

ORIGINAL ARTICLE

Safety of Adding Salmeterol to Fluticasone Propionate in Children with Asthma

David A. Stempel, M.D., Stanley J. Szeffler, M.D., Søren Pedersen, Dr.Med., Robert S. Zeiger, M.D., Ph.D., Anne M. Yeakey, M.D., Laurie A. Lee, M.D., Andrew H. Liu, M.D., Herman Mitchell, Ph.D., Kenneth M. Kral, M.S., Ibrahim H. Raphiou, Ph.D., Barbara A. Prillaman, M.S., M.A., Kathleen S. Buaron, B.S.N., Suyong Yun Kirby, Ph.D., and Steven J. Pascoe, M.B., B.S., for the VESTRI Investigators*

ABSTRACT

BACKGROUND

From Respiratory Clinical Development (D.A.S., A.M.Y., L.A.L., I.H.R., K.S.B., S.Y.K., S.J.P.) and Research and Development, Clinical Platforms and Sciences, Clinical Statistics (K.M.K.), GlaxoSmithKline, Research Triangle Park, Rho, Chapel Hill (H.M.), and Biostatistics, Parexel International, Durham (B.A.P.) — all in North Carolina; the Department of Pediatrics, Breathing Institute, Pediatric Pulmonary Section, Children's Hospital Colorado and University of Colorado School of Medicine, Aurora (S.J.S., A.H.L.); the Department of Pediatrics, Center Lillebælt, Fredericia and Kolding Hospital, Odense, Denmark (S.P.); and the Department of Allergy and Research and Evaluation, Kaiser Permanente Research, San Diego, CA (R.S.Z.). Address reprint requests to Dr. Stempel at Respiratory Clinical Development, GlaxoSmithKline, 5 Moore Dr., P.O. Box 13398, Research Triangle Park, NC 27709-3398, or at david.a.stempel@gsk.com.

Long-acting beta-agonists (LABAs) have been shown to increase the risk of asthma-related death among adults and the risk of asthma-related hospitalization among children. It is unknown whether the concomitant use of inhaled glucocorticoids with LABAs mitigates those risks. This trial prospectively evaluated the safety of the LABA salmeterol, added to fluticasone propionate, in a fixed-dose combination in children.

METHODS

We randomly assigned, in a 1:1 ratio, children 4 to 11 years of age who required daily asthma medications and had a history of asthma exacerbations in the previous year to receive fluticasone propionate plus salmeterol or fluticasone alone for 26 weeks. The primary safety end point was the first serious asthma-related event (death, endotracheal intubation, or hospitalization), as assessed in a time-to-event analysis. The statistical design specified that noninferiority would be shown if the upper boundary of the 95% confidence interval of the hazard ratio for the primary safety end point was less than 2.675. The main efficacy end point was the first severe asthma exacerbation that led to treatment with systemic glucocorticoids, as assessed in a time-to-event analysis.

RESULTS

Among the 6208 patients, 27 patients in the fluticasone–salmeterol group and 21 in the fluticasone-alone group had a serious asthma-related event (all were hospitalizations); the hazard ratio with fluticasone–salmeterol versus fluticasone alone was 1.28 (95% confidence interval [CI], 0.73 to 2.27), which showed the noninferiority of fluticasone–salmeterol ($P=0.006$). A total of 265 patients (8.5%) in the fluticasone–salmeterol group and 309 (10.0%) in the fluticasone-alone group had a severe asthma exacerbation (hazard ratio, 0.86; 95% CI, 0.73 to 1.01).

CONCLUSIONS

In this trial involving children with asthma, salmeterol in a fixed-dose combination with fluticasone was associated with the risk of a serious asthma-related event that was similar to the risk with fluticasone alone. (Funded by GlaxoSmithKline; VESTRI ClinicalTrials.gov number, NCT01462344.)

*A complete list of the investigators in the VESTRI trial is provided in the Supplementary Appendix, available at NEJM.org.

N Engl J Med 2016;375:840-9.
DOI: 10.1056/NEJMoa1606356
Copyright © 2016 Massachusetts Medical Society.

THE SAFETY OF INHALED BETA-AGONISTS in patients with asthma has been debated since the 1960s.¹⁻⁵ After the introduction of long-acting beta-agonists (LABAs) in the 1990s and the findings of two studies involving adults, attention focused on a potential association of LABAs with an increased risk of asthma-related death.^{6,7} A 2008 meta-analysis conducted by the Food and Drug Administration (FDA) showed a higher risk of asthma-related events (death, intubation, or hospitalization) among patients receiving LABAs than among patients not receiving these medications.⁸ In a subsequent meta-analysis, a higher risk of serious asthma-related events was observed with salmeterol than with non-LABA agents among patients who received no inhaled glucocorticoids and among those who received inhaled glucocorticoids as background maintenance medication or in an inhaler that was separate from the one with salmeterol.⁹ In contrast, there were no asthma-related deaths and the risk of asthma-related hospitalization or intubation was not higher when salmeterol was delivered in a fixed-dose combination with inhaled glucocorticoids than when inhaled glucocorticoids were received alone.⁹ The recent AUSTRI trial involving adolescents and adults showed that the risk of serious asthma-related events was not higher among patients receiving a LABA in a fixed-dose combination with an inhaled glucocorticoid than among those receiving inhaled glucocorticoid monotherapy.¹⁰

Clinical-trial experience regarding the safety of LABAs in children 4 to 11 years of age is limited.¹¹ A review of the 2008 FDA meta-analysis highlights that this age group has the highest risk of serious asthma-related events, primarily hospitalization.^{8,12} This analysis identified that the risk of hospitalization among children was mitigated when LABAs were used concomitantly with inhaled glucocorticoids,⁹ a finding that was similar to the results in studies involving adults. To address the questions raised by the FDA meta-analysis and the limited clinical-trial experience in children, the FDA requested that GlaxoSmithKline, the only U.S. manufacturer of a LABA with a pediatric asthma indication, perform a large safety trial with the primary objective of determining whether fluticasone propionate-salmeterol was noninferior to fluticasone alone with respect to the risk of a serious asthma-related

event among children with persistent asthma and a history of a severe exacerbation. The secondary objective was to assess whether the combination was superior to fluticasone alone in terms of the risk of severe asthma exacerbations.

METHODS

TRIAL DESIGN AND OVERSIGHT

We conducted this international, randomized, double-blind, active-comparator, 26-week trial from November 2011 through November 2015 at 567 trial centers in 32 countries (Fig. S1 in the Supplementary Appendix, available with the full text of this article at NEJM.org). The trial protocol, including the statistical analysis plan, is available at NEJM.org.

A pediatric steering committee reviewed performance standards, a pediatric adjudication committee, whose members were unaware of the treatment assignments, determined the relatedness of end points to asthma, and an independent data and safety monitoring committee reviewed safety data every 6 months, with one planned interim statistical analysis after approximately half the expected 43 events occurred (see the Supplementary Appendix). Scientific oversight was provided by employees of the sponsor (GlaxoSmithKline) who were collectively responsible for the trial design and conduct. The pediatric steering committee and the FDA advised GlaxoSmithKline on the trial design, which was harmonized with that of the AUSTRI trial, the GlaxoSmithKline-sponsored trial that involved adolescents and adults.¹⁰

The initial draft of the manuscript was written by the first and second authors, and all the authors collaborated to prepare the final content for submission. Editorial support was provided by two professional writers, paid by the sponsor. Statistical analyses were performed by employees of GlaxoSmithKline and Parexel International. All the authors had full access to the data and vouch for the accuracy and completeness of all data and analyses and for the fidelity of this report to the protocol. All the authors made the decision to submit the manuscript for publication.

Ethical approval was obtained from the relevant ethics committees and institutional review boards. The trial was conducted in accordance

with Good Clinical Practice guidelines and the provisions of the Declaration of Helsinki.

TRIAL POPULATION

Key inclusion criteria were an age of 4 to 11 years, consistent use of asthma medication during the 4 weeks before enrollment, the Childhood Asthma Control Test (C-ACT)¹³ score (on a scale from 0 to 27, with higher scores indicating better control of asthma¹³; minimally important difference, 1.6 points¹⁴), and a history of asthma exacerbation in the previous 12 months, with no exacerbation occurring during the 30 days before randomization (Table S1 in the Supplementary Appendix). Patients were excluded if they had a history of life-threatening asthma or unstable asthma (see the Supplementary Appendix). Children whose asthma was controlled by inhaled glucocorticoids and a LABA were enrolled on the basis of the U.S. label for fluticasone–salmeterol, which states, “once asthma control is achieved and maintained, assess the patient at regular intervals and step down therapy.”¹⁵ Investigators were instructed to enroll patients only if either treatment option (fluticasone–salmeterol or fluticasone alone) would be appropriate. The parent or legal guardian provided written informed consent. Assent by patients was given as appropriate.

RANDOMIZATION, TREATMENTS, AND BLINDING

Patients were randomly assigned, in a 1:1 ratio, to receive fluticasone–salmeterol or fluticasone alone, on the basis of pretrial medication, C-ACT score, and exacerbation history, to receive one of four treatments: a fixed-dose combination of fluticasone propionate at a dose of 100 μg plus salmeterol at a dose of 50 μg , a fixed-dose combination of fluticasone at a dose of 250 μg plus salmeterol at a dose of 50 μg , fluticasone alone at a dose of 100 μg , or fluticasone alone at a dose of 250 μg (Table S1 in the Supplementary Appendix). Treatment was administered twice daily with the use of Diskus devices (GlaxoSmithKline) that were identical for all regimens to maintain blinding. Treatment was administered in a double-blind manner with respect to the use of salmeterol but not with respect to the dose of fluticasone propionate. Rescue therapy with albuterol (also known as salbutamol) was supplied to all patients by means of a metered-dose inhaler.

TRIAL END POINTS

Safety End Points and Assessments

The primary end point was the first serious asthma-related event (a composite end point that included death, endotracheal intubation, and hospitalization), as assessed in a time-to-event analysis. All intubations and deaths were fully adjudicated. All hospitalizations were screened by one committee member, and those that were deemed to be potentially related to asthma were fully adjudicated. All nonserious adverse events that led to the discontinuation of treatment and all serious adverse events were documented. The vital status of all the patients who received at least one dose of treatment was assessed at the end of the 6-month trial period. Height was measured with the use of standard clinical-office procedures.

Efficacy End Points

The primary efficacy end point was the first severe asthma exacerbation, as assessed in a time-to-event analysis; a severe asthma exacerbation was defined as asthma deterioration leading to the use of systemic glucocorticoids for at least 3 days or a depot injection of glucocorticoids, according to the physician’s clinical judgment (see the Supplementary Appendix). The main objective with respect to efficacy was to determine whether fluticasone–salmeterol was superior to fluticasone alone in terms of the first severe asthma exacerbation. Asthma exacerbations were recorded independently of adverse events, and withdrawal from the trial was at the discretion of the investigator. Secondary efficacy end points included the number of rescue therapy-free days and the number of asthma-control days.

STATISTICAL ANALYSIS

The primary safety end point was assessed by a stratified Cox proportional-hazards regression model, with terms for randomized treatment (fluticasone–salmeterol or fluticasone alone) and randomization stratum. If the resulting estimate of the upper boundary of the 95% confidence interval for the hazard ratio for the first serious asthma-related event in the time-to-event analysis (fluticasone–salmeterol as compared with fluticasone alone) was less than 2.675, noninferiority was concluded. The noninferiority margin was based on the event rate observed in the meta-analysis of LABA-containing products conducted in 2008⁸ and also factored in the sample

size and time period that were required to complete the trial. The main efficacy objective — to determine whether fluticasone–salmeterol was superior to fluticasone alone in terms of the first severe asthma exacerbation — was tested with the use of a Cox proportional-hazards regression model.

Within each treatment group, data from the two dose subgroups were combined (fluticasone–salmeterol 100/50 μg and 250/50 μg ; fluticasone alone 100 μg and 250 μg). The trial was not powered to allow the formal statistical comparison or evaluation of fluticasone–salmeterol versus fluticasone alone in subgroups. Descriptive analyses were performed for the subgroups of age and race, with results expressed as hazard ratios and 95% confidence intervals.

In calculating the sample size for the primary safety end point, we assumed a rate of 0.007 patients with an event in the fluticasone-alone group over the 26-week trial period. The sample size was adjusted to accommodate one interim statistical analysis, which was to be conducted when approximately half the expected number of composite end points had occurred. The Haybittle–Peto method was used for managing the alpha-spending function over the interim analysis and the final analysis.^{16,17} We calculated that a sample of 6202 patients would allow the observation of 43 patients having a composite end-point event, which would provide the trial with 90% power to show the noninferiority of fluticasone–salmeterol to fluticasone alone with the use of a log-rank test, at a one-sided alpha level of 0.025, and to reject the null hypothesis that the risk associated with fluticasone–salmeterol versus fluticasone alone was greater than the noninferiority margin.

The intention-to-treat population, which included all the patients who underwent randomization and received at least one dose of trial medication, was used for the analysis of the primary end point. Events were included in the analysis during the entire 6-month trial period even if the treatment was discontinued early or until 7 days after the last dose of treatment, whichever was the longer interval from randomization. A modified intention-to-treat population was used for efficacy analyses, which included only data collected up to 7 days after each patient stopped the trial medication. Four efficacy subgroups were determined on the basis

of asthma control at baseline, exacerbation history, and previous asthma therapy (Table S2 in the Supplementary Appendix).

RESULTS

TRIAL POPULATION

The intention-to-treat population included 3107 patients in the fluticasone–salmeterol group and 3101 in the fluticasone-alone group (Fig. 1). The characteristics of age, sex, race, baseline C-ACT score, and season of enrollment (season of enrollment was analyzed post hoc) were similar in the two overall treatment groups (Table 1, and Table S3 in the Supplementary Appendix). The median rate of adherence to the trial regimen, as determined by the dose counter in the Diskus S4 in the Supplementary Appendix).

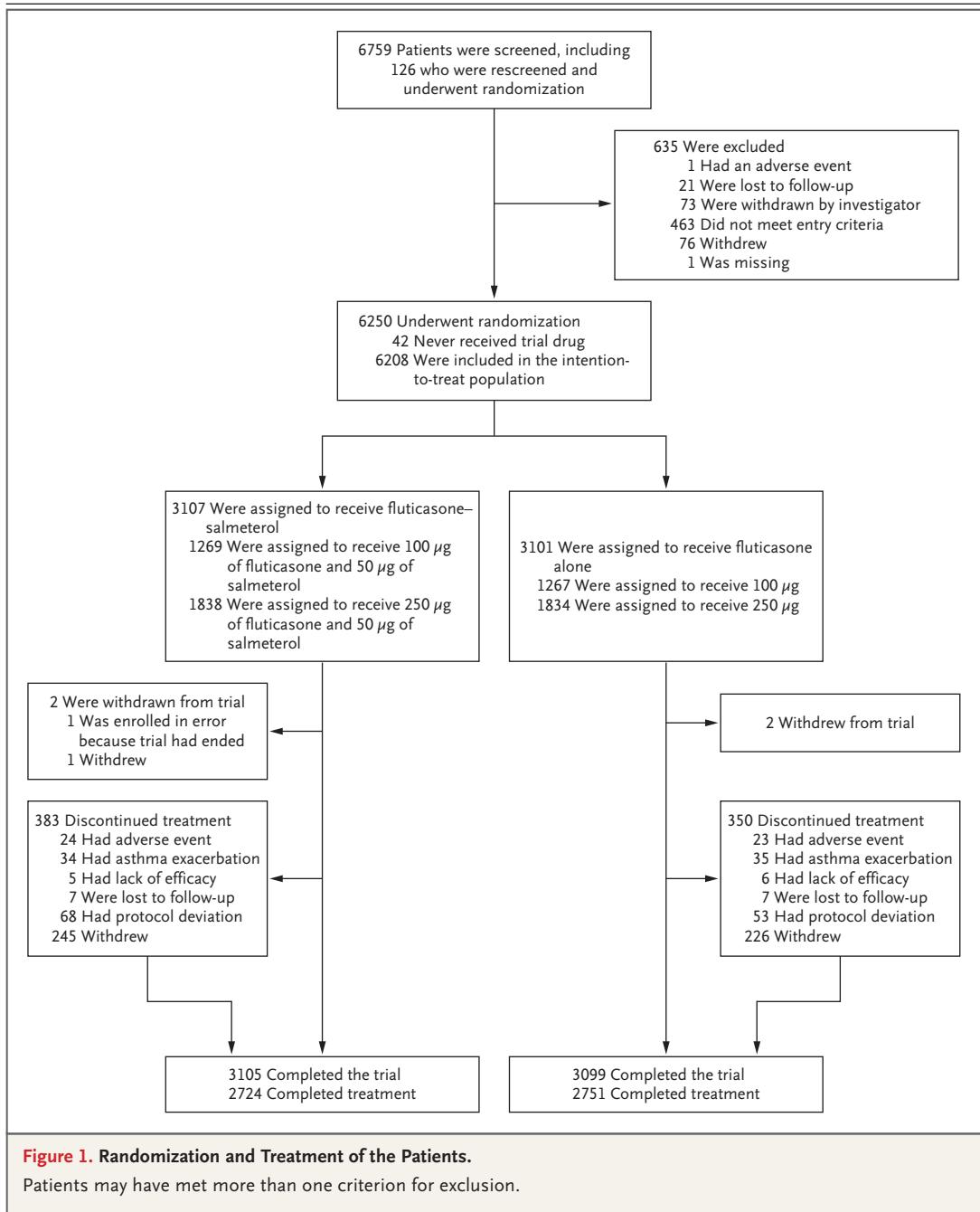
SAFETY

Prespecified Primary Safety End Point

Of the 6208 patients in the intention-to-treat population, 48 had a serious asthma-related event (27 patients in the fluticasone–salmeterol group and 21 in the fluticasone-alone group) (Table 2). Only asthma-related hospitalizations were reported; there were no deaths or asthma-related endotracheal intubations in either treatment group (Table 2). The hazard ratio for a serious asthma-related event (fluticasone–salmeterol vs. fluticasone alone) was 1.28 (95% confidence interval [CI], 0.73 to 2.27). The upper boundary of the 95% confidence interval was less than 2.675, which showed the noninferiority of fluticasone–salmeterol to fluticasone alone ($P=0.006$). The Kaplan–Meier curves for the first event of the composite end point in the time-to-event analysis are shown in Figure 2. The event rates in subgroups defined according to age, race, and sex were all less than 2% of the defined populations for each treatment group (Table 2).

Other Safety End Points

A total of 34 children (1.1%) in the fluticasone–salmeterol group and 35 (1.1%) in the fluticasone-alone group withdrew owing to an asthma exacerbation. A total of 56 patients (1.8%) in the fluticasone–salmeterol group and 54 (1.7%) in the fluticasone-alone group had a serious adverse event (Table S5 in the Supplementary Appendix).



The growth velocity was 2.712 cm per 6 months in the subgroup that received 100 µg of fluticasone and 2.657 cm per 6 months in the subgroup that received 250 µg of fluticasone (difference, -0.055 cm per 6 months; 95% CI, -0.190 to 0.079).

PRESPECIFIED EFFICACY END POINTS

Primary End Point

A total of 265 patients (8.5%) in the fluticasone-salmeterol group and 309 (10.0%) in the fluticasone-alone group had one or more severe asthma exacerbations (Table 3). The hazard ratio in

the time-to-event analysis of the first severe asthma exacerbation with fluticasone–salmeterol versus fluticasone alone was 0.86 (95% CI, 0.73 to 1.01) when age was included as a covariate. Among black patients, 6.7% of the patients in the fluticasone–salmeterol group and 8.4% of those in the fluticasone-alone group had a severe exacerbation (hazard ratio, 0.80; 95% CI, 0.51 to 1.24). There was no apparent between-group difference in the number of patients who had a severe exacerbation in each of the age groups (4 to 6 years and 7 to 11 years) (Table 3).

Prespecified Secondary Efficacy End Points

For further insight into the efficacy of the LABA, we compared four prespecified subgroups that included 86.3% of the trial population to reflect changes from baseline therapy (addition, maintenance, or withdrawal of the LABA) (Table 3); 13.7% of the patients did not meet the criteria for the prespecified subgroups. Among patients in subgroup 1, who entered the trial with asthma controlled by combined inhaled glucocorticoid and LABA therapy, fewer patients who continued to take combination therapy had a severe exacerbation than those who had LABA withdrawn (i.e., who were treated with fluticasone alone) (7.5% vs. 9.9%; hazard ratio, 0.75; 95% CI, 0.57 to 0.98). In subgroup 2, patients entered the trial with asthma that was uncontrolled by low-dose glucocorticoid and LABA therapy and had their dose of inhaled glucocorticoid increased. Fewer patients in this group who were treated with fluticasone–salmeterol had a severe exacerbation than those who had the LABA withdrawn and were treated with fluticasone alone at a dose of 250 μg (11.3% vs. 15.2%; hazard ratio, 0.73; 95% CI, 0.52 to 1.03). Among patients in subgroup 3, who had uncontrolled asthma and entered the trial while taking an inhaled glucocorticoid only, the addition of the LABA to fluticasone at a dose of 250 μg resulted in 7.2% having a severe exacerbation, as compared with 8.0% with a severe exacerbation among those who were treated with fluticasone alone at a dose of 250 μg (hazard ratio, 0.91; 95% CI, 0.62 to 1.33). Among patients in subgroup 4, who entered the trial with asthma that was controlled by inhaled glucocorticoid treatment only and who had had two or more exacerbations in the previ-

Table 1. Characteristics of the Patients at Baseline.*

Characteristic	Fluticasone–Salmeterol (N=3107)	Fluticasone Alone (N=3101)
Male sex — no. (%)	1920 (61.8)	1874 (60.4)
Age		
Mean — yr	7.6 \pm 2.2	7.6 \pm 2.2
Distribution — no. (%)		
4–6 yr	1096 (35.3)	1114 (35.9)
7–11 yr	2011 (64.7)	1987 (64.1)
Race — no. (%) [†]		
White	1998 (64.3)	2032 (65.5)
Black	539 (17.3)	511 (16.5)
Other	570 (18.3)	558 (18.0)
Geographic region — no. (%)		
North America	1439 (46.3)	1433 (46.2)
Latin America	335 (10.8)	322 (10.4)
Europe	774 (24.9)	789 (25.4)
Africa	350 (11.3)	349 (11.3)
Asia–Pacific	209 (6.7)	208 (6.7)
Asthma duration — yr	4 \pm 2.8	4 \pm 2.7

* Plus–minus values are means \pm SD. The analysis was performed in the intention-to-treat population, which included all the patients who had undergone randomization and received at least one dose of fluticasone–salmeterol or fluticasone alone. There were no imbalances in the characteristics at baseline between the treatment groups.

[†] Race was self-reported.

ous year, 12.5% of those who had the LABA added had a severe exacerbation, as compared with 9.7% who continued taking fluticasone alone (hazard ratio, 1.35; 95% CI, 0.81 to 2.25) (Table 3).

Rescue Therapy–free Days and Asthma Control

The mean percentage of rescue therapy–free days was similar in the fluticasone–salmeterol group and the fluticasone-alone group (83.0% and 81.9%, respectively), as was the mean percentage of days with asthma controlled (74.8% and 73.4%, respectively) (Table S6 in the Supplementary Appendix). The C-ACT score showed that 53.1% of all patients had asthma controlled at baseline and that 88.1% of the patients in the fluticasone–salmeterol group and 88.5% of those in the fluticasone-alone group had asthma controlled at the end of the trial.

Table 2. Composite Safety End Points and Hospitalizations, According to Age, Race, and Sex, in the Intention-to-Treat Population.

Safety End Point	Fluticasone–Salmeterol (N=3107)	Fluticasone Alone (N=3101)
Composite safety end point — no. (%)	27 (0.9)	21 (0.7)
Asthma-related death	0	0
Asthma-related intubation	0	0
Asthma-related hospitalization	27 (0.9)	21 (0.7)
Total no. of asthma-related hospitalizations*	28	22
Patients hospitalized — no./total no. (%)		
According to age		
4–6 yr	11/1096 (1.0)	10/1114 (0.9)
7–11 yr	16/2011 (0.8)	11/1987 (0.6)
According to race		
White	11/1998 (0.6)	13/2032 (0.6)
Black	6/539 (1.1)	3/511 (0.6)
Other	10/570 (1.8)	5/558 (0.9)
According to sex		
Female	12/1187 (1.0)	4/1227 (0.3)
Male	15/1920 (0.8)	17/1874 (0.9)

* One patient in each treatment group was not withdrawn from the trial after the first hospitalization and was hospitalized a second time.

DISCUSSION

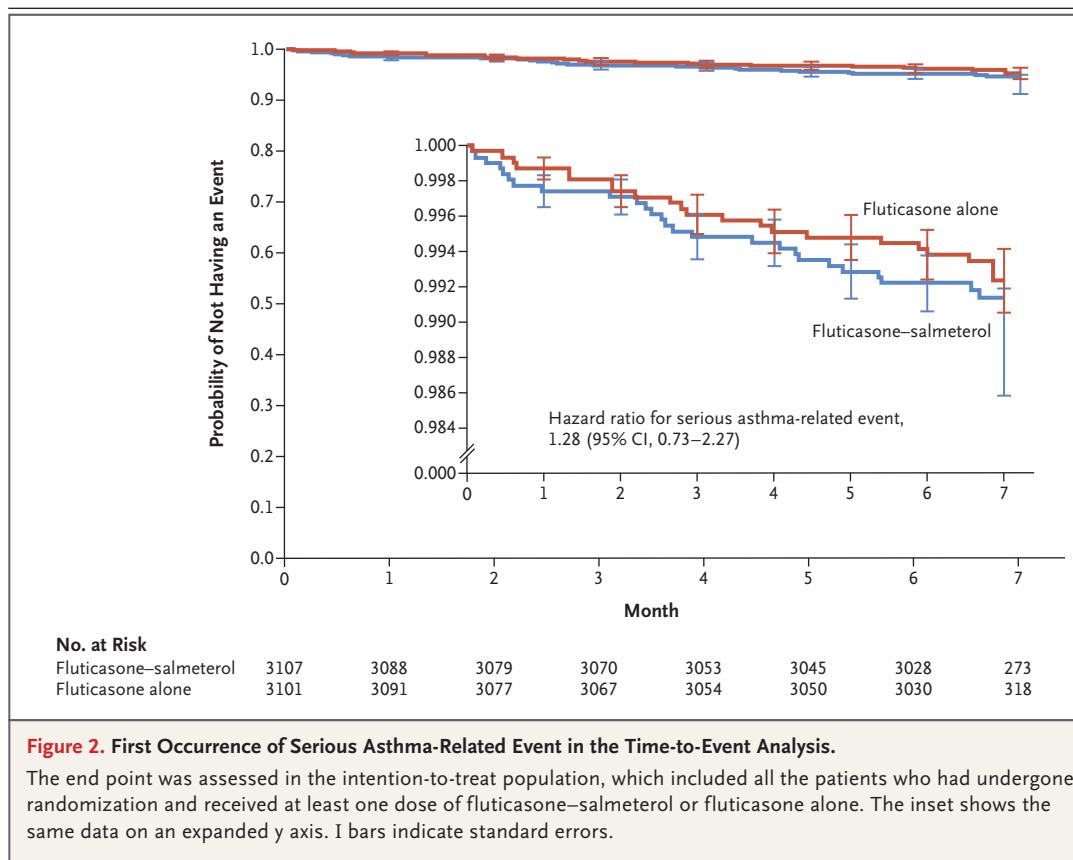
The VESTRI trial was conducted to detect whether there is excess risk associated with the addition of a LABA to maintenance inhaled glucocorticoids among children with asthma. The observed end points fell within the prespecified noninferiority margin with respect to the risk of serious asthma-related events associated with salmeterol delivered in a fixed-dose combination with fluticasone propionate, as compared with equipotent doses of fluticasone alone. The safety findings in this trial concur with those of previous meta-analyses that compared a fixed-dose combination of a LABA with inhaled glucocorticoids and with the results of the AUSTRI trial, which involved 11,751 adolescents and adults and which was similar in design to the current trial.^{8,9,10}

Asthma-related deaths are uncommon in children, and no association with LABAs has been reported previously.^{8,12} No deaths or asthma-related intubations occurred in our trial. The hospitalization rate in our trial was approximately 1.5 hospitalizations per 100 patient-years with each treatment, which is consistent with the in-

cidence observed by the U.S. National Surveillance of Asthma among children 5 to 14 years of age.¹⁸ The low event rate precluded meaningful interpretation of differences in numbers of events in subgroups according to age, race, or sex. These safety comparisons were not powered to detect noninferiority and the event rates were numerically consistent with data in the AUSTRI trial, including data from adolescents.¹⁰

The entry criteria in our trial were selected primarily for the safety analysis. More than half the patients entered the study with a C-ACT score that showed asthma control, and there was no pretreatment run-in phase to establish baseline medication requirements. Given the variability in the baseline characteristics, efficacy subgroups were prespecified to address differences in asthma control and previous medication use. We found that the number of patients who had a severe asthma exacerbation was 14% lower among children receiving fluticasone–salmeterol than among those receiving fluticasone alone — a nonsignificant difference.

Of the overall trial population, 54.9% of the patients were in efficacy subgroups 1 and 2



(Table 3) and entered the trial while taking combination treatment with an inhaled glucocorticoid and a LABA. The number of patients who had a severe asthma exacerbation was 25% lower among children who continued taking fluticasone-salmeterol than among those who switched to fluticasone alone. This finding suggests the need to understand better the appropriate clinical variables that need to be assessed before patients step down from combination therapy. Patients in subgroup 3 had uncontrolled asthma at baseline and had differing baseline medications, and the addition of a LABA had no significant effect. In subgroup 4, the number of children who had a severe exacerbation was not significantly lower among children whose asthma was controlled with the use of low- or medium-dose inhaled glucocorticoid monotherapy and who had salmeterol added than among those who continued glucocorticoid monotherapy; this finding supports present asthma guidelines that do not recommend adjunctive therapy for patients whose asthma is adequately controlled with the use of inhaled glucocorticoids.^{19,20}

The evidence supporting the role of LABAs in children whose asthma is uncontrolled by low-dose inhaled glucocorticoids is limited by the fact that few clinical trials involving children have had efficacy as a primary end point. Two studies that included children 4 to 11 years of age whose asthma was inadequately controlled by inhaled glucocorticoids showed an improvement in lung function and a resolution or abatement of symptoms with the addition of a LABA.^{21,22} Another study showed that the addition of salmeterol to fluticasone was equivalent to doubling the dose of fluticasone in children whose asthma was inadequately controlled by a moderate dose of inhaled glucocorticoids.²³ The Best Add-on Therapy Giving Effective Responses (BADGER) study, which compared three step-up treatment options in children whose asthma was poorly controlled by low-dose inhaled glucocorticoids, showed that the addition of a LABA to the inhaled glucocorticoid was the best treatment option among the three options studied (the other options were increasing the dose of the inhaled glucocorticoid and adding a leukotriene antagonist).²⁴

Table 3. First Severe Asthma Exacerbation in the Time-to-Event Analysis, According to Overall Population Subgroup, in the Modified Intention-to-Treat Population.*

Subgroup	Fluticasone–Salmeterol <i>no. of patients with exacerbation/ no. of patients (%)</i>	Fluticasone Alone <i>no. of patients with exacerbation/ no. of patients (%)</i>	Hazard Ratio (95% CI)
Overall population	265/3107 (8.5)	309/3101 (10.0)	0.86 (0.73–1.01)
Black race	36/539 (6.7)	43/511 (8.4)	0.80 (0.51–1.24)
Age			
4–6 yr	100/1096 (9.1)	118/1114 (10.6)	0.84 (0.65–1.10)
7–11 yr	165/2011 (8.2)	191/1987 (9.6)	0.87 (0.71–1.07)
Efficacy subgroup†			
Subgroup 1: Maintenance of combination LABA–glucocorticoid therapy vs. glucocorticoid monotherapy in patients with controlled asthma	90/1208 (7.5)	120/1208 (9.9)	0.75 (0.57–0.98)
Subgroup 2: Maintenance of LABA therapy and increased dose of inhaled glucocorticoid vs. increased dose of inhaled glucocorticoid	56/497 (11.3)	75/494 (15.2)	0.73 (0.52–1.03)
Subgroup 3: Addition of LABA to medium-dose inhaled glucocorticoid vs. medium-dose inhaled glucocorticoid monotherapy in patients with uncontrolled asthma	51/709 (7.2)	57/711 (8.0)	0.91 (0.62–1.33)
Subgroup 4: Addition of LABA to inhaled glucocorticoid vs. inhaled glucocorticoid monotherapy in patients with controlled asthma	33/264 (12.5)	26/268 (9.7)	1.35 (0.81–2.25)

* Severe exacerbations were recorded from the start of treatment until 7 days after the stopping of the treatment (modified intention-to-treat population). CI denotes confidence interval, and LABA long-acting beta-agonist.

† The four efficacy subgroups, which included 86.3% of the trial population, were formed to reflect changes from baseline therapy (addition, maintenance, or withdrawal of LABA).

The limitations of this trial include the short (6-month) duration and the infrequent occurrence of serious asthma-related events. Other limitations include the following: first, the trial excluded patients with multiple previous asthma-related hospitalizations and intubations, and its findings may not be applicable to children with very severe asthma. The trial was designed with FDA guidance to assess a composite end point of serious asthma-related events. However, only asthma-related hospitalizations were observed. Second, it is not known whether the results of this trial are applicable to other combinations of inhaled glucocorticoids and LABAs. Third, potential concomitant risk factors such as allergen sensitivity were not addressed in this analysis. Fourth, the adherence to the medication regimen was higher than that seen in clinical practice; however, adherence is important when testing the risk associated with a drug to ensure that patients have maximal exposure to the drug.²⁵ Fifth, because of the small number of patients (48) who were hospitalized, we were unable to

test differences according to race, age, or sex. Finally, height data did not include growth velocity at baseline, a stadiometer was not used, and the data were not limited to prepubescent children.

This trial extends the safety findings of the AUSTRI trial to the pediatric age group.¹⁰ In conclusion, the results of the VESTRI trial showed that salmeterol given in combination with fluticasone propionate did not result in a higher risk of severe asthma events among children 4 to 11 years of age than fluticasone alone.

Supported by GlaxoSmithKline.

Dr. Stempel, Dr. Yeakey, Dr. Lee, Dr. Raphiou, Ms. Buaron, Dr. Yun Kirby, and Dr. Pascoe are employees of and hold stock in GlaxoSmithKline. Mr. Kral and Ms. Prillaman are former employees of and hold stock in GlaxoSmithKline; Mr. Kral now works at GlaxoSmithKline on contract, and Ms. Prillaman is a current employee of Parexel International working on behalf of GlaxoSmithKline. Dr. Szeffler reports receiving consulting fees, paid to his institution, from Roche, AstraZeneca, Aerocrine, Daiichi-Sankyo, Boehringer Ingelheim, grant support from GlaxoSmithKline, serving on an advisory panel for Merck, participating in manuscript preparation and advisory boards for a study funded by Genentech, and participating in the development of a study funded by Novartis; Dr. Pedersen, receiving con-

sulting fees from Boehringer Ingelheim and AstraZeneca and lecture fees from Boehringer Ingelheim, AstraZeneca, and San-doz; Dr. Zeiger, receiving fees for serving on a steering committee from GlaxoSmithKline, consulting fees from AstraZeneca, Genentech, GlaxoSmithKline, Novartis, and Teva Pharmaceuticals, and grant support to his institution from AstraZeneca, Aerocrine, MedImmune, Genentech, Merck, and GlaxoSmithKline; and Dr. Liu, receiving lecture fees from Merck. No other potential conflict of interest relevant to this article was reported.

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

We thank Gillian Groeger and Alex Lowe, of Fishawack India, for editorial assistance with an earlier version of the manuscript (in the form of writing assistance, assembling tables and figures, collating author comments, grammatical editing, and referencing); the external committee members of the pediatric steering committee, the data and safety monitoring committee, and the pediatric adjudication committee; Shannon Gooding and Anna Speight for assistance during the protocol design and data analysis; and Robert Strunk (deceased), the chair of the pediatric adjudication committee, for major contributions to the advancement of the study of asthma in children.

REFERENCES

- Speizer FE, Doll R, Heaf P. Observations on recent increase in mortality from asthma. *Br Med J* 1968;1:335-9.
- Crane J, Pearce N, Flatt A, et al. Prescribed fenoterol and death from asthma in New Zealand, 1981-83: case-control study. *Lancet* 1989;1:917-22.
- Spitzer WO, Suissa S, Ernst P, et al. The use of beta-agonists and the risk of death and near death from asthma. *N Engl J Med* 1992;326:501-6.
- Ernst P, Habbick B, Suissa S, et al. Is the association between inhaled beta-agonist use and life-threatening asthma because of confounding by severity? *Am Rev Respir Dis* 1993;148:75-9.
- Suissa S, Ernst P, Boivin JF, et al. A cohort analysis of excess mortality in asthma and the use of inhaled beta-agonists. *Am J Respir Crit Care Med* 1994;149:604-10.
- Castle W, Fuller R, Hall J, Palmer J. Serevent nationwide surveillance study: comparison of salmeterol with salbutamol in asthmatic patients who require regular bronchodilator treatment. *BMJ* 1993;306:1034-7.
- Nelson HS, Weiss ST, Bleecker ER, Yancey SW, Dorinsky PM. The Salmeterol Multicenter Asthma Research Trial: a comparison of usual pharmacotherapy for asthma or usual pharmacotherapy plus salmeterol. *Chest* 2006;129:15-26.
- Levenson M. Long-acting beta-agonists and adverse asthma events meta-analysis. Silver Spring, MD: Food and Drug Administration, November 2008 (<http://www.fda.gov/ohrms/dockets/ac/08/briefing/2008-4398b1-01-FDA.pdf>).
- Weatherall M, Wijesinghe M, Perrin K, Harwood M, Beasley R. Meta-analysis of the risk of mortality with salmeterol and the effect of concomitant inhaled corticosteroid therapy. *Thorax* 2010;65:39-43.
- Stempel DA, Raphiou IH, Kral KM, et al. Serious asthma events with fluticasone plus salmeterol versus fluticasone alone. *N Engl J Med* 2016;374:1822-30.
- Drazen JM, O'Byrne PM. Risks of long-acting beta-agonists in achieving asthma control. *N Engl J Med* 2009;360:1671-2.
- McMahon AW, Levenson MS, McEvoy BW, Mosholder AD, Murphy D. Age and risks of FDA-approved long-acting β_2 -adrenergic receptor agonists. *Pediatrics* 2011;128(5):e1147-54.
- Liu AH, Zeiger R, Sorkness C, et al. Development and cross-sectional validation of the Childhood Asthma Control Test. *J Allergy Clin Immunol* 2007;119:817-25.
- Voorend-van Bergen S, Vaessen-Verberne AA, Landstra AM, et al. Monitoring childhood asthma: web-based diaries and the asthma control test. *J Allergy Clin Immunol* 2014;133(6):1599-605.e2.
- Prescribing information for Advair Diskus. Research Triangle Park, NC: GlaxoSmithKline, April 2014 (https://www.gsksource.com/pharma/content/dam/GlaxoSmithKline/US/en/Prescribing_Information/Advair_Diskus/pdf/ADV AIR-DISKUS-PI-MG.PDF).
- Cytel East 5 user manual. Cambridge, MA: Cytel 2007.
- Jennison CTB. Group sequential methods with applications to clinical trials. London: Chapman and Hall/CRC, 2000.
- Moorman JE, Akinbami LJ, Bailey CM, et al. National surveillance of asthma: United States, 2001-2010. *Vital Health Stat* 3 2012;1-58.
- Guidelines for the diagnosis and management of asthma (EPR-3). Bethesda, MD: National Institutes of Health, July 2007 (<http://www.nhlbi.nih.gov/health-pro/guidelines/current/asthma-guidelines/>).
- Global Initiative for Asthma (GINA). Global strategy for asthma management and prevention, 2016 (<http://ginasthma.org/2016-gina-report-global-strategy-for-asthma-management-and-prevention/>).
- Russell G, Williams DA, Weller P, Price JF. Salmeterol xinafoate in children on high dose inhaled steroids. *Ann Allergy Asthma Immunol* 1995;75:423-8.
- Zimmerman B, D'Urzo A, Bérubé D. Efficacy and safety of formoterol Turbuhaler when added to inhaled corticosteroid treatment in children with asthma. *Pediatr Pulmonol* 2004;37:122-7.
- Vaessen-Verberne AA, van den Berg NJ, van Nierop JC, et al. Combination therapy salmeterol/fluticasone versus doubling dose of fluticasone in children with asthma. *Am J Respir Crit Care Med* 2010;182:1221-7.
- Lemanske RF Jr, Mauger DT, Sorkness CA, et al. Step-up therapy for children with uncontrolled asthma receiving inhaled corticosteroids. *N Engl J Med* 2010;362:975-85.
- Bauman LJ, Wright E, Leickly FE, et al. Relationship of adherence to pediatric asthma morbidity among inner-city children. *Pediatrics* 2002;110(1):e6.

Copyright © 2016 Massachusetts Medical Society.

RECEIVE THE JOURNAL'S TABLE OF CONTENTS EACH WEEK BY E-MAIL

To receive the table of contents of the *Journal* by e-mail every Wednesday evening, sign up at NEJM.org.