

Safety of formoterol in patients with asthma: Combined analysis of data from double-blind, randomized controlled trials

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Background: Concerns exist that regular long-acting β_2 -adrenergic agonist (LABA) therapy may increase the risk of serious asthma-related events.

Objective: To assess risks of formoterol-containing versus non-LABA treatment by using a large asthma database.

Methods: This analysis included all blind, parallel-arm, randomized, active-controlled and/or placebo-controlled AstraZeneca-sponsored asthma studies with formoterol-containing and non-LABA comparator arms. Serious adverse events were assessed for inclusion in all-cause death, asthma-related death, asthma-related intubation, and asthma-related hospitalization categories by using blind adjudication. Data were combined across trials; relative risk (RR) was assessed by using Mantel-Haenszel methods.

Results: Data were from 13,542 formoterol-randomized and 9968 non-LABA patients 4 years or older (42 trials), of whom 93% and 89%, respectively, received inhaled corticosteroid as part of randomized treatment or allowed medication. Incidence of all-cause death was low ($n = 3$ and $n = 4$, respectively), with numerically lower all-cause deaths/1000 patient-treatment years in the formoterol-treated group (0.53) versus the non-LABA group (0.82) (RR, 0.64; 95% confidence interval [CI], 0.14-2.92). No asthma-related deaths and 1 asthma-related intubation (formoterol-treated group) occurred. Asthma-related

hospitalizations/1000 patient-treatment years were lower numerically in the formoterol-treated group (12.1) versus the non-LABA group (16.4) (RR, 0.73; 95% CI, 0.54-1.01), with fewer study discontinuations in the formoterol-treated group (12.7% vs 15.4%, respectively; RR, 0.79; 95% CI, 0.74-0.85). Relative to non-LABA, increasing daily formoterol dose (≥ 4.5 , 9, 18, 36 μg) did not increase the rate or incidence of asthma-related hospitalization.

Conclusion: No evidence of increased risk of asthma-related hospitalization, no asthma-related deaths, and a low incidence of all-cause death and asthma-related intubation were seen with formoterol-containing versus non-LABA treatment. (*J Allergy Clin Immunol* 2010;125:390-6.)

Key words: Asthma, formoterol, inhaled corticosteroid, long-acting β_2 -adrenergic agonist, safety, serious adverse events

Inflammation and bronchoconstriction of asthma are addressed by combining an inhaled corticosteroid (ICS) and a long-acting β_2 -adrenergic agonist (LABA), as recommended by asthma management guidelines for patients with persistent asthma not well controlled on ICS alone.^{1,2} The clinical benefits of combining the LABA formoterol and the ICS budesonide have been demonstrated relative to ICS alone in patients with persistent asthma.³⁻¹² However, safety concerns exist with regular LABA therapy use.¹³ Concerns first were raised on the basis of reported associations of salmeterol treatment and an increased risk of asthma-related death.^{14,15} In addition, the incidence of serious asthma events was reported to be higher with regular high-dose formoterol monotherapy (24 μg twice daily) versus placebo.^{16,17} Collectively, these data led to the inclusion of a boxed warning regarding the risk of death and serious asthma exacerbation on products containing LABA.¹⁸

In January 2008, the US Food and Drug Administration (FDA) requested that manufacturers of LABA-containing products provide additional data to evaluate LABA safety further in patients with asthma. This analysis includes all AstraZeneca-sponsored studies of formoterol-containing products that met the specific criteria outlined by the FDA (double-blind, randomized, active-controlled and/or placebo-controlled trials with a formoterol-containing treatment arm and a non-LABA comparator). Products included in the studies were budesonide/formoterol pressurized metered-dose inhaler (Symbicort Inhalation Aerosol; AstraZeneca LP, Wilmington, Del), budesonide/formoterol dry powder inhaler (Symbicort Turbuhaler; AstraZeneca, Lund, Sweden), and formoterol dry powder inhaler (Oxis Turbuhaler; AstraZeneca, Lund, Sweden). Less rigorously controlled postmarketing and open-label studies were excluded, which allowed for a more

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Abbreviations used

FDA: Food and Drug Administration
ICS: Inhaled corticosteroid
LABA: Long-acting β_2 -adrenergic agonist
OSE: Office of Safety and Epidemiology
RR: Relative risk
SAE: Serious adverse event

stringent analysis than a previous analysis of formoterol safety data.¹⁹ The effects of formoterol-containing treatment on the risk of all-cause death, asthma-related death, asthma-related intubation, and asthma-related hospitalization were assessed relative to non-LABA-containing treatment (primary comparison) across studies of patients 4 years or older. This analysis allowed for a systematic investigation of events of interest within patient subgroups of age, formoterol dose, and race.

METHODS

Data source

Inclusion criteria were outlined by the FDA in their request for LABA safety data for their advisory committee meeting held December 10 to 11, 2008.^{20,21} They requested data from blind, parallel-arm, randomized, active-controlled and/or placebo-controlled AstraZeneca-sponsored studies conducted with formoterol (with or without ICS or other adjunctive therapies) in patients with asthma (see this article's Online Repository [Methods](#) section at www.jacionline.org for additional details). Studies were excluded if they were uncontrolled (or had only LABA-containing treatment arms), were designed primarily to obtain clinical pharmacology data, or were performed for an indication other than asthma.

Outcome variables

The current analysis considered all serious adverse events (SAEs) occurring during randomized treatment in all studies that met the inclusion criteria. An SAE (asthma-related and cardiac-related) was defined by using the International Conference on Harmonisation recommendations (ie, any adverse event that was immediately life-threatening, required inpatient hospitalization or prolongation of existing hospitalization, resulted in disability or incapacity, was a congenital abnormality or birth defect, or was an important medical event that could jeopardize the patient or required medical intervention to prevent one of the outcomes listed).

As the FDA requested, a blind 3-step adjudication process was performed by AstraZeneca physicians not previously involved in these clinical trials. The adjudication process assessed all SAEs for inclusion in the categories of all-cause death, asthma-related death, asthma-related intubation, or asthma-related hospitalization. At step 1, a drug safety expert blind to treatment assessed all SAEs (868 in 42 trials) and identified those that did not belong to any of the relevant categories (574 SAEs excluded). At step 2, the 294 remaining SAEs were assessed further by 2 AstraZeneca pulmonary specialists who were blind to treatment and not involved previously in any of the trials, resulting in the exclusion of 98 events (evenly distributed between the formoterol-containing and non-LABA groups). At step 3, disagreement between the 2 physicians at step 2 of the adjudication procedure was settled by a third AstraZeneca pulmonary specialist who was blind to treatment and not involved previously in any of the trials (involved 3 events).

Statistical analyses

Overall relative risk (RR) for SAEs and study discontinuation was analyzed by using a stratified Mantel-Haenszel approach adjusted for the time that patients were exposed to study treatment, which allowed for possible differences between trials, thereby reducing bias. Ninety-five percent confidence intervals (CIs) also were provided. A simple pooled analysis of SAE data that did not account for differences between the trials also was performed.

For individual studies, a descriptive 95% credibility interval for the RR was provided by using the method of Barker and Cadwell²² with an uninformative uniform prior (see this article's Online Repository [Methods](#) section at www.jacionline.org).

The primary analysis compared results from the formoterol-containing and non-LABA treatment groups in patients 4 years or older. Overall event rates for formoterol-containing and non-LABA treatments across trials were provided by using the weighted average corresponding to the Mantel-Haenszel estimate of common RR. Because the Mantel-Haenszel analysis for RR included trials with at least 1 event, a supportive Mantel-Haenszel analysis that included all trials (with or without ≥ 1 event) was performed on the event rate differences. In all instances, the analysis of the event rate difference was consistent with the analysis of RR; therefore, only the RR analyses are reported. Time to first asthma-related hospitalization was described for the formoterol-containing and non-LABA treatment groups by using a Kaplan-Meier plot and compared between groups by using a stratified log-rank test.

Secondary analyses of asthma-related hospitalizations also were performed for the formoterol-containing and non-LABA treatment groups and tabulated by cumulative formoterol dose (≥ 4.5 μg , ≥ 9 μg , ≥ 18 μg , ≥ 36 μg) and race. RR of asthma-related hospitalization was evaluated for formoterol at a dose of at least 18 μg (US-approved total daily dose) plus ICS versus ICS treatment alone, formoterol plus ICS as concomitant background therapy versus ICS as concomitant background therapy, and formoterol plus ICS in a free (formoterol + ICS) or fixed (budesonide/formoterol) combination versus ICS treatment alone. Additional RR analyses were performed for formoterol-containing versus non-LABA treatments across age subgroups (4-11 years, 12-17 years, ≥ 18 years).

RESULTS

Fig 1 presents trial exclusions. The resulting dataset included 23,510 patients from 42 trials meeting inclusion criteria (see this article's [Table EI](#), in the Online Repository at www.jacionline.org for individual study details), with 13,542 patients randomized to formoterol-containing products and 9968 patients to non-LABA products ([Table I](#)). Eight percent of patients were not receiving ICS before randomization because they were enrolled in trials in which patients were not allowed to use ICS. Most studies (including 92% of patients) required patients to have unstable asthma at baseline; 99% of these patients were on ICS and the remaining patients were on other asthma medication (mainly sodium cromoglycate) at baseline. Most patients (80%) receiving formoterol-containing products were randomized to ICS treatment. Of the formoterol-treated patients who received concomitant ICS as randomized therapy ($n = 10,852$), 79% received combination therapy in 1 device and 21% received combination therapy via separate inhalers. Among patients not randomized to ICS treatment (2690 formoterol-treated patients; 2659 non-LABA-treated patients), most received ICS as an allowed concomitant medication (65% and 58%, respectively), although compliance to concomitant ICS therapy was not assessed in the studies. Thus, 93% of formoterol-treated and 89% of non-LABA-treated patients received ICS treatment during the study as a component of randomized treatment or as an allowed concomitant medication.

Patient demographic and baseline clinical characteristics were similar in the formoterol-containing ($n = 13,542$) and non-LABA ($n = 9968$) treatment groups in the overall dataset ([Table II](#)). Risk of premature study discontinuation was significantly lower for formoterol-containing versus non-LABA treatment (12.7% vs 15.4%, respectively; RR, 0.79; 95% CI, 0.74-0.85).

Within the 42 included trials, 868 SAEs were identified and adjudicated as being related or not related to asthma. Of these, 672 SAEs were deselected because they did not belong to any of the

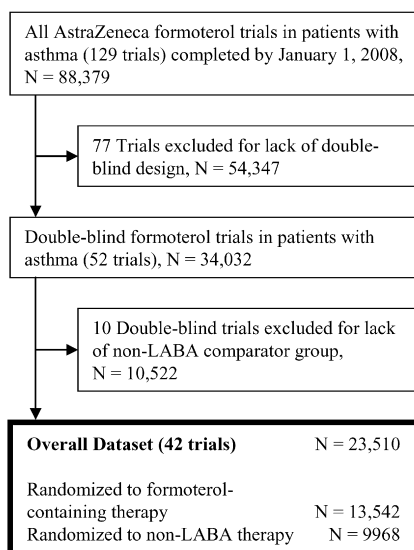


FIG 1. Flow chart of patients with asthma involved in AstraZeneca trials with formoterol.

TABLE I. Overview of dataset (all studies)

Treatment	No. of patients	Total exposure (1000 patient-treatment years)	Daily dosage
FM-containing treatments			
FM DPI*	2690	1.33	9, 18, 36 µg or as needed
BUD (pMDI or DPI) + FM DPI	2328	0.96	Range, 160/9-1280/36 µg
BUD/FM DPI	5861	3.24	Range, 80/4.5-1280/36 µg; maintenance and as needed; or adjustable dosing
BUD/FM pMDI	2663	0.95	Range, 160/9-1280/36 µg
Total	13,542	6.49	
Non-LABA-containing treatments			
BUD (pMDI or DPI)	6913	3.74	Range, 160-1280 µg
Terbutaline*	1285	0.71	2000 µg or as needed
Placebo*	1374	0.43	
Fluticasone propionate	396	0.05	500 µg
Total	9968	4.92	
Total (all treatments)	23,510	11.41	

BUD, Budesonide; DPI, dry powder inhaler; FM, formoterol; pMDI, pressurized metered-dose inhaler.

*Patients did not receive concomitant ICSs as randomized therapy.

relevant categories, and 196 SAEs were assigned to 1 of the relevant categories.

Primary analysis (formoterol-containing vs non-LABA treatment)

In the overall dataset, the incidence of all-cause death was low (7/23,510 patients): 3 (0.02%) in the formoterol-containing and 4 (0.04%) in the non-LABA treatment groups. The number of all-cause deaths per 1000 patient-treatment years was lower numerically in the formoterol-containing versus non-LABA

TABLE II. Patient demographic and baseline clinical characteristics (all studies)

Variable	Formoterol-containing therapy (n = 13,542)	Non-LABA therapy (n = 9968)	Total (N = 23,510)
Male, n (%)	6367 (47.0)	4704 (47.2)	11,071 (47.1)
Age (y)			
Mean	33.9	34.8	34.2
Range	4.0-87.0	4.0-87.0	4.0-87.0
Age distribution, n (%)			
4-11 y	2155 (15.9)	1268 (12.7)	3423 (14.6)
12-17 y	1515 (11.2)	1155 (11.6)	2670 (11.4)
≥18 y	9872 (72.9)	7545 (75.7)	17,417 (74.1)
Race, n (%)			
White	11,355 (83.9)	8567 (85.9)	19,922 (84.7)
Asian	1026 (7.6)	678 (6.8)	1704 (7.2)
Other	711 (5.3)	464 (4.7)	1175 (5.0)
Black	436 (3.2)	252 (2.5)	688 (2.9)
Unknown	14 (0.1)	7 (0.1)	21 (0.1)
% Predicted FEV ₁ at baseline	(n = 13,011)	(n = 9537)	(n = 22,548)
Mean	79.9	79.9	79.9
Range	19.0-180.0	18.0-175.0	18.0-180.0
ICS use at baseline, n (%)	11,767 (86.9)	7988 (80.1)	19,755 (84.0)

treatment groups (0.53 vs 0.82, respectively; RR, 0.64; 95% CI, 0.14-2.92). No asthma-related deaths occurred during randomized treatment, and only 1 asthma-related intubation occurred in the formoterol-containing treatment group. The number of asthma-related hospitalizations per 1000 patient-treatment years was lower numerically in the formoterol-containing versus non-LABA treatment groups (12.05 vs 16.40, respectively; RR, 0.73; 95% CI, 0.54-1.01; Fig 2). RR data for asthma-related hospitalizations from the individual studies were consistent with the overall dataset; most of the point estimates appeared to the left of the line of unity, and 95% credibility intervals generally centered on the line of unity, representing no increased risk with formoterol-containing treatment (Fig 2). Time to first asthma-related hospitalization was prolonged in the formoterol-containing versus non-LABA treatment groups ($P = .061$), and this difference between the treatment groups was maintained over time (Fig 3).

Secondary analyses

Analyses by formoterol dose showed that the rate of asthma-related hospitalizations compared with the non-LABA groups did not increase with increasing formoterol dose (Table III). Moreover, the rate of asthma-related hospitalization was lower in the formoterol-containing treatment groups at each dose threshold compared with the non-LABA groups (Table III). An analysis of 17 trials and 7213 patients in which all patients were receiving ICS demonstrated no increased risk of asthma-related hospitalization with the addition of formoterol (at dosages of ≥18 µg/d; approved US dose) to ICS treatment versus ICS alone (RR, 1.01; 95% CI, 0.48-2.09; Fig 4). Individual study results were consistent with the overall dataset, with most of the RR estimates from the individual studies centered on the line of unity.

When all formoterol doses were considered, no evidence of an increased risk of asthma-related hospitalization was seen with the combination of formoterol and an ICS versus ICS alone (Fig 5). Results were similar whether formoterol and ICS

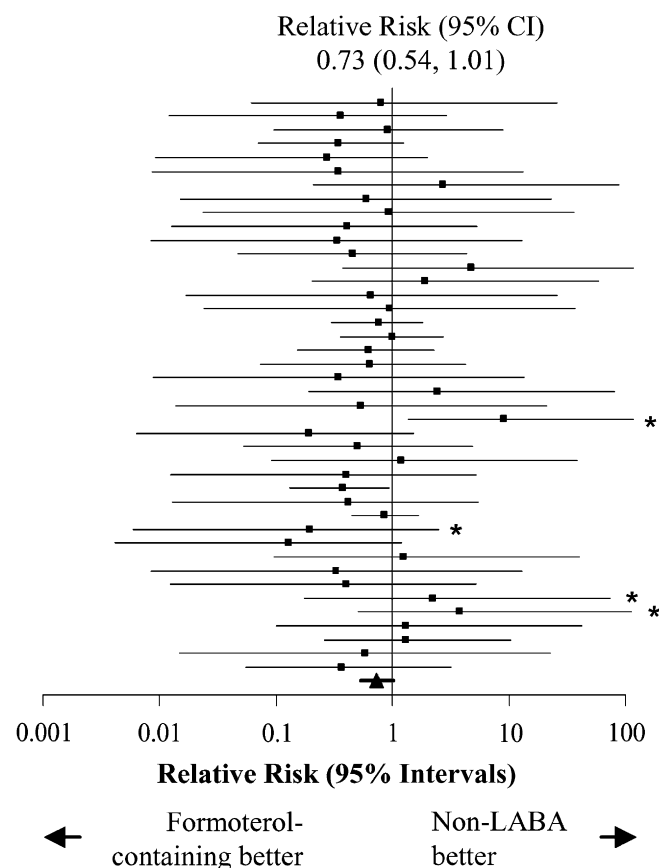


FIG 2. Risk of asthma-related hospitalization with formoterol-containing versus non-LABA therapy: data from 42 individual studies (squares) and combined across studies (triangle; N = 23,510). *A subset of data from only 4 (n = 1270) of 42 (n = 23,510) studies was included in the exploratory analysis conducted by the US Food and Drug Administration Office of Safety and Epidemiology.^{20,21}

combination therapy was administered via separate inhalers (formoterol + ICS) or via 1 inhaler (budesonide/formoterol; Fig 5). No increased risk of asthma-related hospitalization in patients randomized to receive formoterol and allowed to take ICS as a concomitant background medication versus patients who received non-LABA therapy and were allowed ICS as background therapy (RR, 0.71; 95% CI, 0.36-1.40) was evident. In addition, no evidence of an increased risk of asthma-related hospitalization was seen in the formoterol-containing versus non-LABA treatment groups, regardless of age (children, RR, 1.22; 95% CI, 0.62-2.37; adolescents, RR, 0.77; 95% CI, 0.37-1.62; adults, RR, 0.59; 95% CI, 0.38-0.90; see this article's Figs E1-E3 in the Online Repository at www.jacionline.org), although numerical point estimates of RR increased with decreasing age. In children, the numerical imbalance in RR against the formoterol-containing treatment was contributed to by a high number of patients (n = 7) with asthma-related hospitalizations who were receiving a subtherapeutic dose of budesonide/formoterol (80/4.5 μ g once daily) in 1 study. As suggested by 1 reviewer of the article, we have conducted an analysis excluding patients in that subtherapeutic dosing arm from the combined analysis of children (n = 3302), and the RR was 1.02 (95% CI, 0.51-2.04). The incidence of asthma-related hospitalizations did not differ between the formoterol-containing and non-LABA treatment

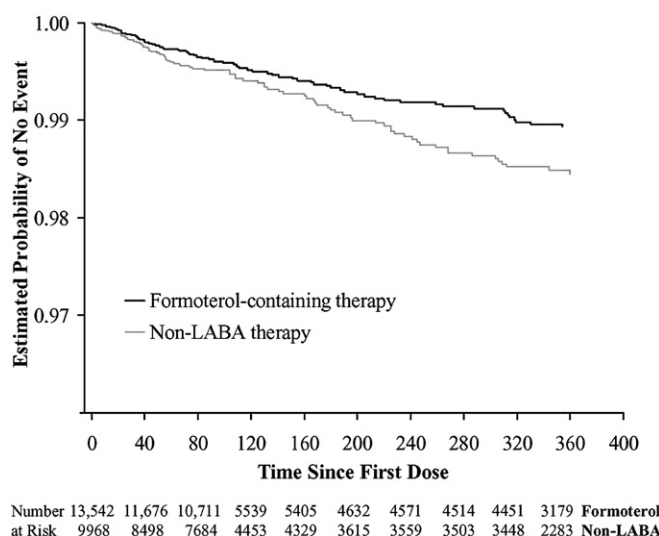


FIG 3. Kaplan-Meier probability curve for the time to first asthma-related hospitalization with formoterol-containing treatment versus non-LABA therapy (combined data from all studies; N = 23,510).

TABLE III. Asthma-related hospitalizations by daily formoterol dosage threshold

Treatment	No. of patients	Patients reporting ≥ 1 asthma-related hospitalization, n (%)	Hospitalization per 1000 patient-treatment years
Formoterol ≥ 4.5 μ g	12,522	67 (0.54)	11.59
Non-LABA	8945	69 (0.77)	16.16
Formoterol ≥ 9 μ g	12,285	60 (0.49)	10.71
Non-LABA	8945	69 (0.77)	16.16
Formoterol ≥ 18 μ g	5653	25 (0.44)	13.81
Non-LABA	4160	18 (0.43)	15.25
Formoterol ≥ 36 μ g	1088	1 (0.09)	1.89
Non-LABA	561	2 (0.36)	9.52

arms by race (see this article's Online Repository, Results and Table EII, at www.jacionline.org).

DISCUSSION

The current analysis is the most stringent assessment of formoterol safety data to date, including only double-blind, randomized, controlled trials with a formoterol-containing treatment arm and a non-LABA comparator arm. The primary purpose was to identify any serious asthma-related safety signals associated with formoterol-containing treatments in a large asthma dataset. The results of this comprehensive analysis showed a numerically reduced risk of asthma-related hospitalization with formoterol-containing treatment versus non-LABA therapy in patients with asthma. No asthma-related deaths were observed, and the incidence of all-cause death and asthma-related intubation was low in both the formoterol-containing and non-LABA treatment groups.

A previous analysis of formoterol safety data (N = 68,004) in patients with asthma differed from the current analysis because it included a broader set of randomized trials with open-label designs or without a non-LABA comparator arm and did not

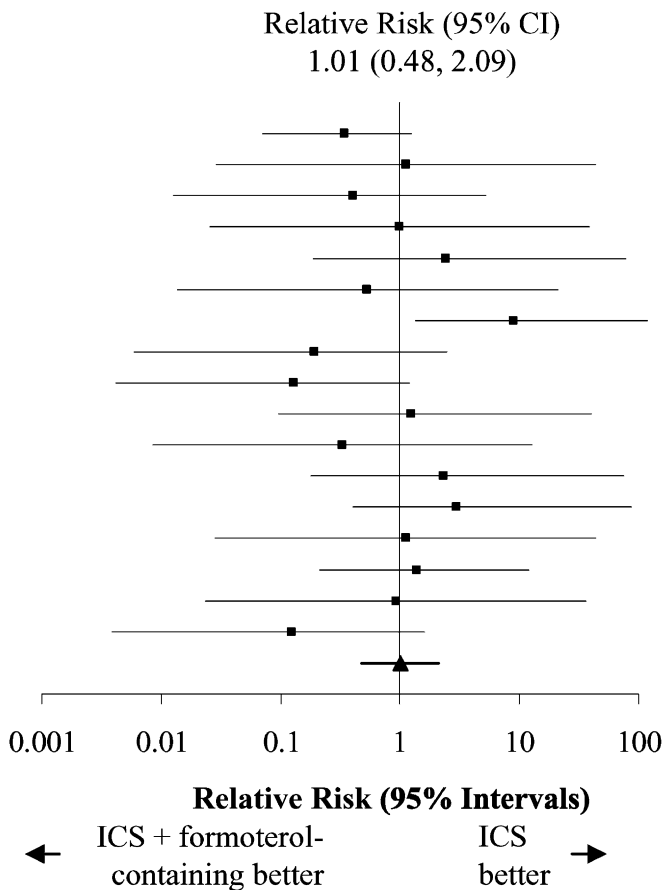


FIG 4. Risk of asthma-related hospitalization with formoterol ($\geq 18 \mu\text{g/d}$) + ICS compared with ICS: data from 17 individual studies (squares) and combined across studies (triangle; $N = 7213$).

use a blind adjudication procedure for assessing all SAEs.¹⁹ Despite these differences, the results from the current analysis of 23,510 patients with asthma generally were consistent with the analysis by Sears et al,¹⁹ in which a lower incidence of asthma-related SAEs ($>90\%$ were hospitalizations) and a similar incidence of all-cause death were reported for formoterol-treated patients versus the non-LABA groups, with no evidence of an increase in asthma-related SAEs with increasing formoterol dose. However, Sears et al¹⁹ reported asthma-related deaths in 8 of 49,906 formoterol-treated patients (0.34 per 1000 patient-treatment years) and 2 of 18,098 non-LABA-treated patients (0.22 per 1000 patient-treatment years). This result differs from the 0 asthma-related deaths in the current analysis because the 10 asthma-related deaths occurred in open-label trials or trials without a non-LABA comparator group ($n = 7$), occurred after the end of the randomized treatment period ($n = 1$), or were adjudicated in this analysis as all-cause death rather than asthma-related ($n = 2$: septic shock, respiratory failure [per death certificate; originally reported by the investigator as subarachnoid hemorrhage]) and were excluded from the analysis. A recent meta-analysis²³ identified 1 asthma-related death in the formoterol monotherapy group (Foradil; Novartis, Basel, Switzerland; $n = 2783$) versus none in the placebo group ($n = 1739$; odds ratio, 1.55; 95% CI, 0.06-38.21); this study was not included in the current analysis of AstraZeneca-conducted studies. The relationship to treatment of the asthma-related deaths in these analyses is

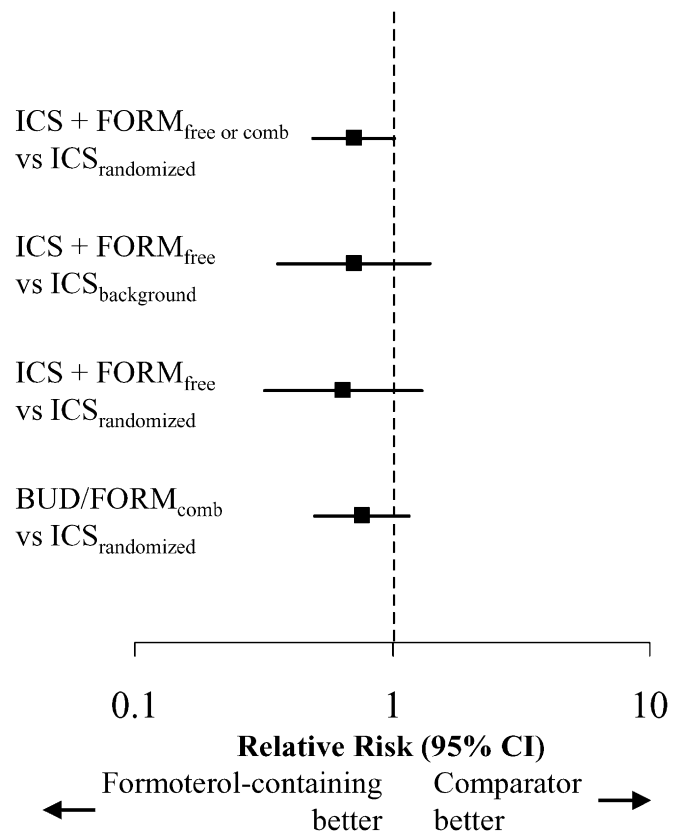


FIG 5. Risk of asthma-related hospitalization with formoterol + ICS (free and/or fixed-combination) compared with ICS: combined data. (*The individual analyses are not mutually exclusive.) BUD/FORM_{comb}, Budesonide and formoterol administered together in 1 inhaler (Symbicort Inhalation Aerosol or Symbicort Turbuhaler); ICS_{background}, ICS as concomitant therapy (nonrandomized); ICS_{randomized}, ICS as randomized therapy; ICS + FORM_{free}, ICS and formoterol administered together in separate inhalers as a free combination; ICS + FORM_{free or comb}, ICS and formoterol administered together in a free or fixed combination.

difficult to assess because of the rarity of these events. However, if asthma-related deaths and asthma-related hospitalizations are correlated in the sense that they both represent different degrees of severe asthma worsening, the trend toward reduced risk of asthma-related hospitalization with formoterol-containing versus non-LABA therapy in the current analysis and that of Sears et al¹⁹ may argue against a causal relationship.

In contrast with the current analysis, an exploratory analysis of LABA safety data prepared by the US FDA Office of Safety and Epidemiology (OSE) showed a nonsignificant increased risk of asthma-related hospitalization (risk difference, 7.49 per 1000 subjects; 95% CI, -1.47 to 16.44)^{20,21} in patients receiving budesonide/formoterol versus non-LABA treatment. However, the OSE analysis^{20,21} excluded data for non-US-approved doses and ages (4-11 years for AstraZeneca formoterol-containing products). Thus, only a subset of data from 4 ($n = 1270$) of the 42 trials ($N = 23,510$) included in the present analysis (5% of the AstraZeneca data provided to the FDA) was included in the OSE analysis. Chance selection likely accounts for the difference in risk between the 2 analyses because the 95% CIs broadly overlap. The well accepted standard for safety analyses is to begin with as broad an assessment as possible, including all age groups

and all doses, especially those higher than the approved dosage.²⁴ Moreover, large sample sizes are critical for detecting rare events and accurately estimating event incidence. Therefore, the current analysis provides a more complete and robust assessment of formoterol safety compared with the OSE analysis.

Overall, the current analysis of combined data stratified by trial was generally consistent with individual trial results and secondary analyses by formoterol dose threshold, age subgroup, and race. Although the point estimate for the RR of asthma-related hospitalization for formoterol-containing versus non-LABA treatment increased with decreasing age, the adolescent and pediatric subgroups had lower patient numbers and wider CIs than adults, limiting interpretation. It also should be noted that an exploratory study arm of budesonide/formoterol 80/4.5 $\mu\text{g} \times 1$ inhalation once daily, a dosage that proved subtherapeutic for the population studied,²⁵ contributed substantially to the higher point estimate of RR for pediatric patients. When the patients in the subtherapeutic once-daily budesonide/formoterol 80/4.5- μg arm of that study were excluded from the current analysis, the RR for children aged 4 to 11 years was more consistent with that observed for adolescents and adults.

Administration of formoterol with an ICS versus ICS alone produced results similar to the overall primary analysis, regardless of whether the combination was administered in separate inhalers or in 1 inhaler. Likewise, no increased risk of asthma-related hospitalization with formoterol plus background ICS therapy versus background ICS alone was evident. Formoterol is a rapid-onset, full agonist of the β_2 -adrenergic receptor. At the December 2008 FDA advisory committee meeting,²⁶ data were reported for the slower-onset partial agonist salmeterol ($n = 12,658$), which showed no evidence of an increased risk of asthma-related hospitalization with fluticasone/salmeterol in 1 inhaler versus ICS (odds ratio, 1.01; 95% CI, 0.60-1.69).²⁷ These results, along with results from previous studies¹⁴⁻¹⁷ in which the coadministration of ICS in combination with a LABA was questionable and potentially suboptimal, suggest that the most important mechanism behind the previously observed increase in asthma-related events may be the undertreatment of the inflammatory component of asthma. The increased incidence of serious exacerbations associated with a high-dose formoterol treatment reported by Mann et al¹⁶ was not confirmed by the results from the substantially larger and more robust dataset included in the current analysis, in which maintenance ICS therapy was coadministered in a large majority of the patients.

Methodologic difficulties may complicate the interpretation of results when investigating the occurrence of very rare events, particularly disease-related and treatment-related events. Potential biases can arise even in well-controlled clinical trials. Even if populations are comparable at randomization, differences in treatment efficacy can lead to changes in population characteristics during the treatment phase because of differential withdrawal rates. Thus, it is possible for disease severity in the various treatment arms to become increasingly dissimilar as the study progresses, especially if the study has a long duration or has preset discontinuation criteria related to the disease under study. In this analysis, a difference was seen in study withdrawals between the formoterol-containing and non-LABA treatment groups, with a greater risk of early study withdrawals in the non-LABA group. A higher incidence of study withdrawals was evident particularly in the placebo arms of studies in the current analysis that used sensitive discontinuation criteria.^{3,9} These results suggest that the

current findings may underestimate the risk of an asthma-related event in the non-LABA comparator groups. In addition, the grouping of disease-related and treatment-related events into 1 category (ie, asthma-related events) may be limiting because a similar incidence of a combined event (eg, hospitalization) could have resulted from differential effects of formoterol-containing and non-LABA therapies on the cause of the event (disease or treatment-related). However, this distinction may not be clinically important if the treatment under evaluation (ie, formoterol-containing) is of clinical benefit to the patient without increasing the risk of the asthma-related event (whether disease-related or treatment-related).

In summary, results from this analysis of data from 23,510 patients in 42 controlled, randomized, blind, parallel-group trials showed no evidence of an increased risk of all-cause death or asthma-related death, intubation, or hospitalization with formoterol-containing versus non-LABA treatment in patients with asthma. The consistency of data among the primary combined analysis, individual trials, and secondary analyses based on formoterol dose, age, race, and concomitant ICS administration support the overall findings. However, because of the rarity of events, such as asthma-related deaths or intubations, even this large and stringent dataset is not sufficient to refute definitively the signal of a potential risk generated by previous studies. This analysis does not address the safety of formoterol-containing products on the basis of real-life use. However, the results from the current analysis, together with the clinical benefits that have been demonstrated with the combination of formoterol and the ICS budesonide in studies of patients with persistent asthma,³⁻⁸ support the recommendations in the National Asthma Education and Prevention Program and Global Initiative for Asthma guidelines for use of ICS/LABA combination therapy, such as budesonide/formoterol, in patients whose asthma is not controlled with an ICS alone.

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Clinical implications: This article assessed the effects of formoterol-containing treatment on risk of all-cause death, asthma-related death, asthma-related intubation, and asthma-related hospitalization relative to non-LABA-containing treatment in patients age ≥ 4 years.

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METHODS

For studies containing a randomized, blind phase followed by an open-label phase, only data from the blind phase were requested by the FDA for inclusion. For randomized, double-blind crossover studies, only data from the first crossover period were requested for inclusion. In addition, studies had to be completed with unblinded and locked data available by January 1, 2008.

With regard to the descriptive 95% CI for the RR for individual studies, the median of the posterior distribution was used to provide a point estimate for the RR.

RESULTS

Among white patients, the percentage of patients with at least 1 asthma-related hospitalization was lower numerically in the formoterol-containing treatment group compared with the non-LABA group (Table E2). The number of patients in the black, Asian, and other racial subgroups was low; however, no indication of an increased incidence of asthma-related hospitalizations was seen in the formoterol-containing treatment group compared with the non-LABA group.

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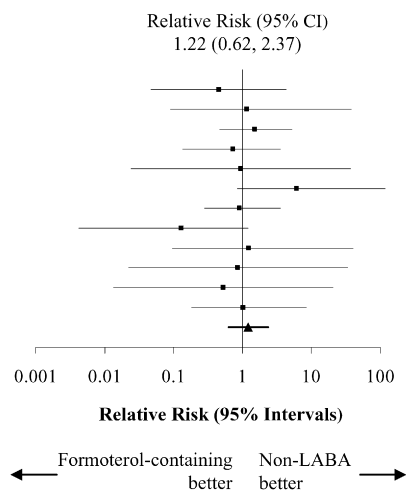


FIG E1. Risk of asthma-related hospitalization with formoterol-containing treatment versus non-LABA therapy in patients aged 4 to 11 years: data presented from 12 individual studies (*squares*) and combined across studies (*triangle*; $n = 3417$). *The numerical imbalance in RR against the formoterol-containing treatment in the combined analysis was contributed to by a high number of patients ($n = 7$) with asthma-related hospitalizations who were receiving a subtherapeutic dose of budesonide/formoterol (80/4.5 μg once daily) in 1 study. ^{E26}

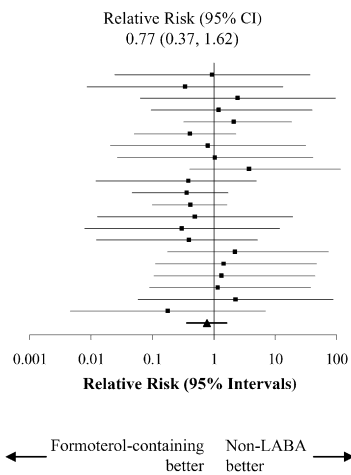


FIG E2. Risk of asthma-related hospitalization with formoterol-containing treatment versus non-LABA therapy in patients age 12 to 17 years: data presented from 21 individual studies (*squares*) and combined across studies (*triangle*; n = 2670).

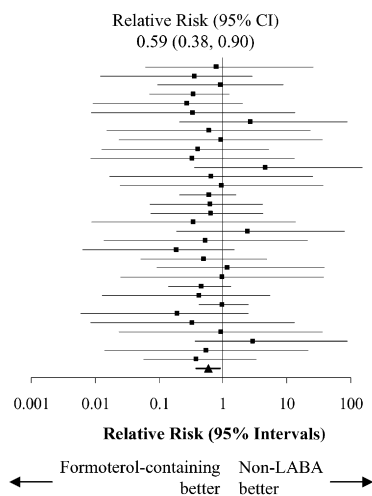


FIG E3. Risk of asthma-related hospitalization with formoterol-containing treatment versus non-LABA therapy in patients 18 years or older: data presented from 33 individual studies (*squares*) and combined across studies (*triangle*; n = 17,417).

TABLE E1. Studies included in this analysis*

Study identifier	Formoterol treatment	Non-LABA comparator	Study duration	No. of patients
37-3002 ^{E1}	Formoterol DPI 4.5, 9, 18 µg bid	Placebo	4 wk	221†
37-3006 ^{E2}	Formoterol DPI 9 µg bid	Placebo	12 wk	343
		Terbutaline 500 µg qid		
37-3008 ^{E3}	Formoterol DPI 18 µg bid	Placebo	6 mo	239
37-3018 ^{E4}	Formoterol DPI 9 µg bid + budesonide DPI 80 or 320 µg bid	Budesonide 80 or 320 µg DPI bid	12 mo	853
37-3026 ^{E5}	Formoterol DPI 4.5 µg bid	Placebo	12 wk	396
		Terbutaline 500 µg qid		
37-3027† ^{E6}	Formoterol DPI 4.5, 9, 18 µg bid	Placebo	7 d	165
37-3041 ^{E6}	Formoterol DPI 9 µg bid + budesonide DPI 80 µg bid	Budesonide 320 µg bid	12 mo	60
39-3002-1†	Formoterol DPI 9 µg bid	Budesonide 160 µg bid	4 wk	21
	Formoterol DPI 9 µg bid + budesonide DPI 160 µg bid			
BU-543-0681A ^{E7}	Formoterol DPI 9 µg bid + budesonide DPI 320 µg bid	Budesonide DPI 320 µg bid	4 wk	663
DC-037-0002 ^{E8}	Formoterol DPI 4.5, 9 µg bid	Placebo	3 mo	301
	Continued previous ICS therapy	Continued previous ICS therapy		
SD-004-0216†	Formoterol DPI 9 µg bid + budesonide DPI 160 µg bid	Budesonide DPI 160 µg bid + placebo Budesonide DPI 160 µg + zafirlukast 20 mg bid	8 wk	352
SD-037-0003 ^{E9}	Formoterol DPI 4.5, 9 µg bid	Placebo	3 mo	248
SD-037-0011 ^{E10}	Formoterol DPI 4.5, 18 µg bid or 9 µg qd	Placebo	2 wk	72
		Terbutaline 500 µg qid		
SD-037-0345 ^{E11}	Formoterol DPI 4.5 µg + budesonide DPI 80, 160 µg bid	Placebo	12 mo	1970
		Budesonide DPI 80, 160 µg bid		
SD-037-0745†	Formoterol DPI 4.5, 9, 18 µg bid	Placebo	1 mo	282
SD-037-0123 ^{E12}	Formoterol DPI 4.5 µg as needed (up to 54 µg)	Terbutaline 500 µg as needed (up to 6 mg)	12 wk	362
SD-037-0695 ^{E13}	Formoterol 4.5 µg as needed Continued previous ICS therapy	Terbutaline 250 µg as needed Continued previous ICS therapy	6 mo	552
SD-037-0714 ^{E14}	Formoterol 4.5 µg as needed	Terbutaline 500 µg as needed	12 mo	455
SD-037-0716 ^{E14}	Formoterol 4.5 µg as needed	Terbutaline 500 µg as needed	12 mo	674
BA-039-0001 ^{E15}	Budesonide/formoterol DPI 160/4.5 µg bid (adjustable dosing: 2 inh wk 1-4, up to 4 inh after wk 5)	Budesonide DPI 320 µg bid (adjustable dosing: 2 inh wk 1-4, up to 4 inh after wk 5)	4 mo	133
SD-039-0348 ^{E16}	Budesonide/formoterol DPI 80/4.5 µg bid	Budesonide DPI 160 µg bid	12 wk	467
SD-039-0349 ^{E17}	Budesonide/formoterol DPI 160/4.5 µg × 2 inh bid Formoterol DPI 4.5 µg × 2 inh + budesonide DPI 160 µg × 2 inh bid	Budesonide 160 µg × 2 inh bid	12 wk	362
SD-039-0353 ^{E18}	Budesonide/formoterol DPI 80/4.5 µg × 2 inh bid	Budesonide DPI 80 µg × 2 inh bid	12 wk	286
SD-039-0618 ^{E19}	Budesonide/formoterol DPI 160/4.5 µg × 1 inh bid	Fluticasone DPI 250 µg × 1 inh bid	12 wk	344
SD-039-0665 ^{E20}	Budesonide/formoterol DPI 80/4.5 µg × 2 inh qd Budesonide/formoterol DPI 80/4.5 µg × 1 inh bid	Budesonide DPI 160 µg × 1 inh qd	12 wk	616
SD-039-0666 ^{E21}	Budesonide/formoterol DPI 160/4.5 µg × 2 inh qd Budesonide/formoterol DPI 160/4.5 µg × 1 inh bid	Budesonide DPI 320 µg × 1 inh qd	12 wk	523
SD-039-0667 ^{E22}	Budesonide/formoterol DPI 80/4.5 µg × 2 inh qd and as needed	Budesonide 160 µg × 2 inh qd + terbutaline 400 µg as needed	6 mo	696
SD-039-0668 ^{E23}	Budesonide/formoterol DPI 160/4.5 µg × 2 inh qd and as needed	Budesonide 160 µg × 2 inh qd + terbutaline 400 µg as needed	12 mo	1890
SD-039-0671 ^{E24}	Budesonide/formoterol DPI 80/4.5 µg bid	Fluticasone DPI 250 µg bid	2 wk	438

(Continued)

TABLE EI. (Continued)

Study identifier	Formoterol treatment	Non-LABA comparator	Study duration	No. of patients
SD-039-0673 ^{E25,E26}	Budesonide/formoterol DPI 80/4.5 µg qd or bid and as needed Budesonide/formoterol DPI 80/4.5 µg qd or bid and terbutaline 400 µg as needed	Budesonide DPI 320 µg qd or bid + terbutaline 400 µg as needed	12 mo	2753
SD-039-0688 ^{E27}	Budesonide/formoterol DPI 80/4.5 µg × 2 inh bid Budesonide DPI 80 µg × 2 inh + formoterol DPI 4.5 µg × 2 inh bid	Budesonide DPI 80 × 2 inh µg bid	12 wk	630
SD-039-0689 ^{E28}	Budesonide/formoterol DPI 320/9 µg × 2 inh bid (wk 1-24) Budesonide DPI 320 µg + formoterol DPI 9 µg × 2 inh bid (wk 1-24)	Budesonide 320 µg × 2 inh bid (wk 1-12)	3/6 mo	456
SD-039-0714 [‡]	Budesonide/formoterol DPI 160/4.5 µg bid	Budesonide DPI 160 µg bid	12 wk	270
SD-039-0716 (NCT00651651) ^{E29}	Budesonide/formoterol pMDI 80/4.5 µg × 2 inh bid Formoterol DPI 4.5 µg × 2 inh bid	Placebo Budesonide pMDI 80 µg × 2 inh bid	12 wk	511
SD-039-0717 (NCT00652002) ^{E30}	Budesonide/formoterol pMDI 160/4.5 µg × 2 inh bid Budesonide pMDI 160 µg + formoterol DPI 4.5 µg × 2 inh bid Formoterol DPI 4.5 µg × 2 inh bid	Placebo Budesonide pMDI 160 µg × 2 inh bid	12 wk	596
SD-039-0718 (NCT00651547) ^{E31}	Budesonide/formoterol pMDI 40/4.5 µg × 2 inh bid Formoterol DPI 4.5 µg × 2 inh bid	Budesonide pMDI 40 µg × 2 inh bid	12 wk	411
SD-039-0725 (NCT00646321) ^{E32}	Budesonide/formoterol pMDI 40/4.5 µg × 2 inh bid Budesonide/formoterol pMDI 80/4.5 µg × 2 inh qd	Budesonide pMDI 80 µg × 2 inh qd	12 wk	521
SD-039-0726 (NCT00652392) ^{E33}	Budesonide/formoterol pMDI 80/4.5 µg × 2 inh qd Budesonide/formoterol pMDI 160/4.5 µg × 2 inh qd Budesonide/formoterol pMDI 80/4.5 µg × 2 inh bid	Budesonide pMDI 160 µg × 2 inh qd Placebo	12 wk	751
SD-039-0728 (SD-039-0728) ^{E34}	Budesonide/formoterol pMDI 160/4.5 µg × 2 inh bid Budesonide/formoterol pMDI 320/4.5 µg × 2 inh bid	Budesonide pMDI 320 × 2 inh bid	52 wk	708
D5896C00001 (NCT00646516) ^{E35}	Budesonide/formoterol pMDI 80/4.5 µg × 2 inh qd Budesonide/formoterol pMDI 160/4.5 µg × 2 inh qd Budesonide/formoterol pMDI 80/4.5 µg × 2 inh bid	Budesonide pMDI 160 µg × 2 inh qd	12 wk	618
SD-039-0681 ^{E36}	Budesonide/formoterol pMDI 160/4.5 µg × 2 inh bid Budesonide/formoterol DPI 160/4.5 µg × 2 inh bid	Budesonide CFC pMDI 160 µg × 2 inh bid	12 wk	679
SD-039-0682 ^{E37}	Budesonide/formoterol HFA pMDI 80/4.5 µg × 2 inh bid Budesonide/formoterol DPI 80/4.5 µg × 2 inh bid	Budesonide CFC pMDI 80 µg × 2 inh bid	12 wk	622

bid, Twice daily; *CFC*, chlorofluorocarbon; *DPI*, dry powder inhaler; *HFA*, hydrofluoroalkane; *inh*, inhalation; *pMDI*, pressurized metered-dose inhaler; *qd*, once daily; *qid*, 4 times daily.

*Delivered dose presented for formoterol (6 µg metered = 4.5 µg delivered; 12 µg metered = 9 µg delivered; 24 µg metered = 18 µg delivered) and budesonide (100 µg metered = 80 µg delivered; 200 µg metered = 160 µg delivered; 400 µg metered = 320 µg delivered).

†Represents safety population for each study.

‡Unpublished data.

TABLE EII. Percentage of patients reporting ≥ 1 asthma-related hospitalization by race

Treatment	No. of patients	No. (%) of patients with ≥ 1 asthma-related hospitalization
White		
Formoterol-treated	11,311	58 (0.51)
Non-LABA	8540	68 (0.80)
Black		
Formoterol-treated	436	2 (0.46)
Non-LABA	252	3 (1.19)
Asian		
Formoterol-treated	1026	9 (0.88)
Non-LABA	678	7 (1.03)
Other		
Formoterol-treated	711	9 (1.27)
Non-LABA	463	5 (1.08)
Unknown		
Formoterol-treated	58	0
Non-LABA	35	0