

Safety of formoterol in adults and children with asthma: a meta-analysis

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Background: The safety of long-acting β_2 agonists (LABA) for the treatment of persistent asthma remains a topic of ongoing debate.

Objective: To evaluate the risk of serious asthma-related events among patients treated with formoterol, a meta-analysis of all Novartis-sponsored controlled clinical trials was conducted.

Methods: Forty-five randomized, placebo- and active-controlled, parallel-group or crossover studies with formoterol were included. Background inhaled corticosteroid (ICS) use was permitted in all studies; however, in only 2 studies was ICS randomized as study medication. Sub-analyses of the pooled data were performed according to age (5–12; 13–18; >18 years), baseline ICS use, and lung function. Odds ratios (OR) and 95% confidence intervals (CIs) were calculated between formoterol (twice-daily), albuterol (salbutamol) 4 times per day (active control), and placebo.

Results: Patients were randomized to formoterol ($n = 5,367$), placebo ($n = 2,026$), and albuterol ($n = 976$). Two deaths were reported, 1 each in the formoterol (asthma exacerbation) and the placebo (hemorrhagic pancreatitis) groups. No statistically significant differences in serious asthma exacerbations were observed compared with placebo in adolescents and adults. In children, a higher frequency of hospitalizations was observed among patients treated with formoterol compared with placebo (OR 8.4; 95% CI: 1.1–65.3). A trend toward fewer exacerbations was observed among subjects reporting concomitant ICS use at baseline.

Conclusions: This analysis supports current guideline recommendations for the use of LABAs only as add-on therapy to ICS. *Ann Allergy Asthma Immunol.* 2011;107:71–78.

INTRODUCTION

Current treatment guidelines recommend long-term therapy with inhaled corticosteroids (ICS) for the management of patients with persistent asthma.^{1,2} In patients not adequately controlled with ICS alone, add-on therapy with long-acting β_2 -agonists (LABAs) has been demonstrated to improve lung function and asthma symptoms and reduce exacerbations.^{3–5} Despite the well-established treatment benefits with LABAs,^{6–9} controversy continues to surround their role in the management of asthma because of safety concerns, including reports of increased respiratory deaths.^{7,10}

Two well-documented incidents of increased asthma mortality have been attributed to the use of short-acting β_2 -agonists. The first occurred in the 1960s with the introduction of high-dose isoproterenol (isoprenaline forte). The second episode occurred in 1976, in New Zealand; a series of case-controlled studies indicated an increased risk of fatal asthma associated with the use of fenoterol.¹¹ Although the underlying mechanism(s) for the asthma-related deaths are unclear, several hypotheses have been proposed, including (1) higher potency of isoprenaline and fenoterol in comparison with other β_2 -agonists; (2) masking the symptoms of worsening asthma by improved bronchodilation without concomitant anti-inflammatory treatment¹²; or (3) an increase in patients' sensitivity to bronchoconstricting stimuli resulting from the use of β_2 -agonists.

LABAs have been commercially available since 1990. The results of Serevent Nationwide Surveillance (SNS trial, UK)¹³ raised concerns when a nonsignificant increase in asthma-related deaths was described among patients using salmeterol (Serevent 50 μg twice per day) compared with other treatments. After the SNS study results, the US Food and Drug Administration (FDA) requested that the manufacturer of Serevent conduct a postmarketing surveillance study, the Salmeterol Multicenter Asthma Research Trial (SMART) trial, to further investigate the safety of salmeterol. The SMART study was prematurely terminated in 2003 because of adverse outcomes and difficulties with enrollment.¹⁴ Published trial results suggested that patients in the salmeterol-treated group had a significantly elevated relative risk of 4.37 for asthma-related deaths. However, post hoc analyses

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Funding Sources: This study was supported by Novartis Pharma AG, Basel, Switzerland.

Disclosures: J.K. has consulted with Novartis and attended on their behalf, FDA Advisory Meetings on LABAs. He is on the Speakers Bureau for Teva and Merck Pharmaceutical Companies and a Consultant to Inverseon. L.A., Y.W., V.K.T.A., and D.O. are full-time employees of Novartis and hold stock in the company. S.P. was a full-time employee of Novartis at the time of this analysis and holds stock in the company.

Received for publication October 25, 2010; Received in revised form March 11, 2011; Accepted for publication March 15, 2011.

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doi:10.1016/j.anai.2011.03.010

suggested that the risk was significantly lower among patients using background ICS.¹⁵

Formoterol, marketed as Foradil (Novartis AG, Basel, Switzerland), was approved in 2001. An imbalance in asthma-related hospitalizations and intubations was noted in two phase III studies^{16,17} among 1,095 patients. The higher dose of formoterol (24 μ g twice per day) was associated with a higher incidence of serious asthma exacerbations than the lower dose of 12 μ g twice per day. In a 12-month placebo-controlled study in children (5–12 years), an imbalance in asthma-related hospitalizations was observed, with 8 hospitalizations among patients receiving 24 μ g total daily dose (TDD) (the approved dose for children worldwide), 12 asthma-related hospitalizations among patients receiving 48 μ g TDD, and none in the placebo-treated group. To further evaluate the risk of asthma-related hospitalizations associated with formoterol use, a larger safety study was conducted. Two thousand eighty-five subjects were randomized to receive formoterol 48 μ g TDD (24 μ g twice per day), formoterol 24 μ g TDD, placebo or open label formoterol 24 μ g TDD and as needed. In this 16-week trial, the proportion of patients with asthma-related hospitalizations was similar among patients receiving 48 μ g TDD (0.4%, 2 of 527 patients), 24 μ g TDD (0.6%, 3 of 527 patients) and placebo groups (0.2%, 1 of 514 patients) as well as the 24 μ g TDD plus as needed (0.2%, 1 of 517 patients).¹⁸

In January 2008, the US FDA requested that manufacturers of LABA containing products approved for use in the United States submit data from all randomized, controlled, parallel-group asthma studies of Advair [salmeterol, fluticasone], Foradil [formoterol], Serevent [salmeterol], and Symbicort [formoterol, budesonide]. A meta-analysis of the pooled data was presented at a public advisory committee in December 2008.¹⁹ The primary event under evaluation was a composite endpoint of asthma-related death, intubation, and hospitalization. Among the 60,954 patients included in the analysis, the risk difference between LABA and non-LABA treatments was 2.80 (95% confidence interval [CI]: 1.11–4.49) per 1,000 subjects. However, in trials in which patients received randomized ICS in addition to LABAs, a nonstatistically significant rate of only 0.25 (95% CI: –1.69–2.18) per 1,000 patients was observed. The risk of asthma-related events appeared to decrease with age. In March 2010, a second advisory committee was convened to discuss designs of future safety studies.

The following meta-analysis of all Novartis-sponsored randomized blinded controlled trials was performed in support of the FDA advisory meetings. The analysis includes all trials of the Foradil Aerolizer and Certihaler at all studied dosages.

METHODS

Data Sources

All Novartis-sponsored trials conducted in patients with asthma that included formoterol (Foradil delivered via the inhaler Aerolizer [single-dose dry powder inhaler] or Certihaler [multi-dose dry powder inhaler]) as the investigational

treatment or as an active comparator were evaluated for inclusion. All randomized placebo- and active-controlled, parallel-group or crossover studies in which formoterol was administered either with or without an ICS or other adjunct therapy were included in this analysis. Trials that were uncontrolled, open-label, conducted for indications other than asthma, such as chronic obstructive pulmonary disease or exercise-induced bronchoconstriction, and trials designed primarily to obtain pharmacology data (phase I studies) were excluded from this analysis. Forty-five studies met these criteria and are included in the pooled data set. In adults and adolescents, 25 (14 multiple-dose and 11 single-dose) studies were conducted with Foradil Aerolizer, and 5 (4 multiple-dose and 1 single-dose) with Foradil Certihaler, a multiple-dose dry powder inhaler, as the investigational treatment. In 5 studies (1 multiple-dose and 4 single-dose), Foradil Aerolizer was used as an active comparator. In pediatric patients (5–12 years), 5 (3 multiple-dose and 2 single-dose) studies used Foradil Aerolizer, and 2 (both multiple-dose) used Foradil Certihaler as the investigational treatment. In 1 study, Foradil Aerolizer was used as an active comparator. No studies were conducted in children younger than 5 years of age. Compliance with ICS was not monitored in 43 of the 45 studies.

Treatments

The treatments included in this analysis were formoterol, albuterol (salbutamol), dosed 4 times per day, and placebo. Formoterol administration included the Aerolizer (dry powder capsule device) and the Certihaler (a multi-dose dry powder inhaler); delivered doses from these 2 devices are equivalent. In the included studies, various doses of formoterol were used. All formoterol doses were administered twice per day. For this analysis, formoterol doses were described in terms of TDD, which is the sum of the daily doses; for example, 24 μ g TDD represents a twice-daily dose of 12 μ g or the dose of a single inhalation in single-dose studies. Formoterol treatment was categorized into 4 groups: 12/10 μ g TDD (studies examining a dose of Foradil 6 μ g twice-daily via Aerolizer, Foradil 5 μ g twice daily via Certihaler, or a single dose of Foradil 12 μ g or 10 μ g from the Aerolizer or Certihaler, respectively); 24/20 μ g TDD (studies examining twice-daily doses of Foradil 12 μ g via Aerolizer and 10 μ g via Certihaler); 48 μ g TDD (studies examining twice-daily doses of Foradil 24 μ g via Aerolizer); and other doses (studies examining all other Foradil doses). The 12/10 μ g TDD dose is not approved for use and was used in dose-ranging studies and in early studies as a subtherapeutic dose of 6 μ g twice per day. Regularly dosed albuterol, although no longer the standard of care, was commonly used as an active comparator at the time these studies were conducted. The albuterol treatment group included albuterol doses (TDD) of 400 μ g (8 studies), 800 μ g (6 studies), 1,200 μ g (1 study), and 1,600 μ g (3 studies). In 43 of the 45 trials including the pivotal trials and the large safety study, concomitant ICS use was permitted; however, compliance and adherence were not

monitored. In only 2 studies, Foradil or placebo was randomized to patients receiving protocol-specified ICS (budesonide or beclomethasone).

Outcomes

The outcomes of interest were defined as asthma-related deaths, intubations, and hospitalizations. Individual cases were identified through a blinded physician review of the Novartis clinical and safety databases. The definition of *asthma-related* was based on the asthma-related standardized MedDRA (medical dictionary for regulatory activities) queries (SMQ). The MedDRA 10.1 (the SMQ narrow terms) preferred terms include: *analgesic asthma syndrome*, *asthma*, *asthma exercise induced*, *asthma late onset*, *asthmatic crisis*, *bronchial hyperreactivity*, *bronchospasm*, *infantile asthma*, and *status asthmaticus*. Based on FDA specifications, the search period for inclusion of events was defined as the beginning of treatment to the end of blinded treatment.

Data Analyses

Both parallel-group and crossover studies were included in the pooled analyses. For crossover studies, only data from the first treatment period were included. Patients were categorized into 3 distinct age groups: children (5–12 years), adolescents (13–18 years), and adults (>18 years). Each age group was further dichotomized into patients receiving (at baseline or during the study) and not receiving ICS. Patients were also categorized according to baseline lung function forced expiratory volume in 1 second (FEV₁) less than 60% of predicted normal, FEV₁ 60% to 80% of predicted normal, and FEV₁ greater than 80% of predicted normal. Fixed-effects meta-analyses, implemented in StatXact,²⁰ were employed to produce combined odds ratio (OR) estimates together with corresponding 95% CIs that compared each of the treatments with placebo. While reporting results, we have used the term *significant* to indicate analyses in which the 95% CIs for the OR excludes 1. For each of the analyses, tests for homogeneity (Breslow-Day and Zelen's) were applied to assess the overall appropriateness of the fixed-effect assumption. The number and percentage of patients with events (incidence) and the number of events per 100 patient treatment exposure years (rate) were also calculated for each patient age group.

Multiple or mixed-treatment comparison methods^{21,22} that extend basic meta-analysis techniques to more than 2 treatment groups and potentially allow comparisons of treatments in which little or no direct evidence is provided by an individual trial, were used to combine the study data from the 3 different treatment groups (formoterol, albuterol, and placebo). As in Cooper et al,²³ a Poisson regression model, estimated using Bayesian Markov Chain Monte Carlo methods with vague priors and including an offset term to account for the total patient years exposure associated with each treatment arm, was used to produce results on the relative risk scale. In terms of meta-analytic assumptions, both fixed effects and random effects were considered for the treatment

contrasts, whereas separate fixed effects were assumed for the baseline parameters (nuisance parameters) associated with each study, using the orthogonal parameterization suggested by Lu and Ades.²¹ To compare the appropriateness of the fixed- and random-effects assumptions, the deviance information criteria were applied.²⁴

RESULTS

Patient Disposition, Demographics, and Baseline Characteristics

Figure 1 shows an overview of the number of patients included in this analysis. Of the 8,369 patients included, 5,367 were randomized to formoterol, 2,026 to placebo, and 976 to albuterol. Most demographic and baseline characteristics were balanced among the treatment groups. In children, however, more placebo patients were enrolled in sites in the United States (73%) compared with 4.2% of the albuterol-treated patients and 58% of the formoterol-treated patients (Table 1). The mean age of all patients included in the study was 37.2 years. Approximately half the subjects in each treatment group were female. Information on race was not available for 45% of the patients in the pooled data set. For those patients whose race was reported, most (>80%) were white. The mean baseline FEV₁ was 2.2 L (68.3% of predicted normal) for all patients combined and was balanced across the treatment groups. Approximately 70% of the patients ($n = 5,682$) reported using ICS either at baseline or as concomitant treatment during the course of the trials.

To assess the appropriateness of combining effects across studies, using fixed-effect meta-analysis, a test for homogeneity was conducted. This showed little evidence of between-study heterogeneity ($P > .1$) that could not be attributed to chance alone. However, such tests have limited power in the meta-analyses of rare events.

Asthma-Related and All-Cause Mortality

Among the 8,369 patients across all 45 trials, 2 deaths were reported, 1 patient receiving Foradil and 1 patient receiving albuterol. A 66-year-old woman with a 46-year history of asthma and baseline FEV₁ of 1.55 L (62% of predicted normal) died of asthma exacerbation 19 days after randomization to formoterol 48 μ g TDD. She did not report using concomitant ICS. A 26-year-old woman receiving albuterol died of hemorrhagic pancreatitis.

Serious Asthma Exacerbations (Asthma-Related Deaths, Intubations, and Hospitalizations)

Although the event of interest represents a composite endpoint of asthma-related death, intubation, and hospitalization, most events were hospitalizations, with only 1 death described in a patient receiving 48 μ g TDD formoterol (as described, this patient was also intubated) and 7 intubations: 4 occurring among patients receiving formoterol 48 μ g TDD and 3 among patients receiving formoterol 24 μ g TDD. The OR of a patient experiencing a serious asthma exacerbation with formoterol 24/20 μ g (the only dose approved for use in

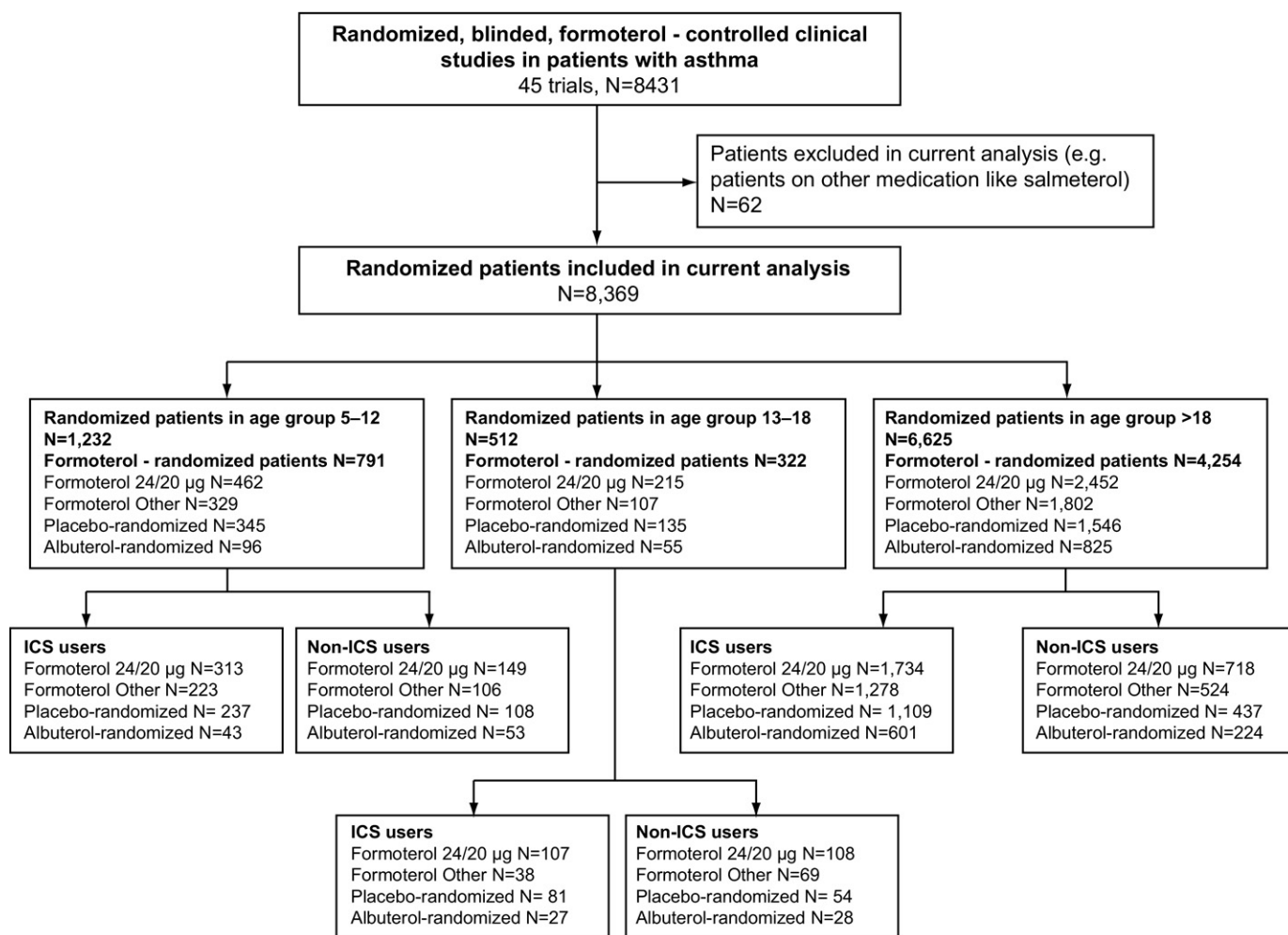


Figure 1. Distribution of patients included in the analysis.

children and the most widely used dose for all ages) and albuterol in the 5 to 12, 13 to 18, and older than 18 years age groups versus placebo are shown in Figure 2. Among patients of all ages, the number of serious asthma exacerbations among patients randomized to formoterol and albuterol was significantly higher compared with those receiving placebo. The rate of events per 100 patient treatment exposure years was 2.7 among patients treated with formoterol 24/20 µg TDD (22 events among 3,129 subjects) as compared with 1.4 for placebo (8 events among 2,026 subjects) and 4.5 for albuterol (10 events among 976 subjects) (Table 2). In children, the OR of serious asthma exacerbations was higher among patients treated with formoterol compared with placebo (OR 8.4; 95% CI: 1.1–65.3). No significant differences were seen in the rate of serious asthma exacerbations compared with placebo among adolescents (OR 0.3; 95% CI: 0.03–3.5) and adults (OR 1.3; 95% CI: 0.4–3.7).

When applying the Bayesian Markov Chain Monte Carlo modeling, across all age-group classifications, similar model

performance in terms of the deviance information criteria²³ occurred for both the fixed- and random-effects models. The posterior median relative risk estimates and 95% CIs from the fixed-effects model are presented in Table 3. The application of the random-effects model (results not presented) resulted in very similar posterior median estimates but wider 95% CIs, reflecting the additional between-study variability.

Serious Asthma Exacerbations in Patients Classified According to Formoterol Dose

Several trials contributing data to the pooled analyses included treatment arms in which subjects received formoterol at doses below the approved doses. Five hundred eighty-five (585) subjects in the pooled group were treated with 12 µg TDD formoterol. All trials incorporating this treatment arm were conducted outside the United States, and many were single-dose trials.

Among patients of all ages, a higher OR of serious asthma exacerbations versus placebo is found for subjects treated

Table 1. Demographics and Baseline Disease Characteristics of Patients Included in the Analysis Summarized by Treatment and Age Groups

	Formoterol 24/20 μg TDD	Placebo	Albuterol
Age group: 5–12 years			
Age, mean (SD)	9.4 (2.00)	9.6 (2.03)	9.3 (1.99)
Sex, % (M/F)	67.1/32.9	63.8/36.2	62.5/37.5
Location, % (US/Non-US)	58.2/41.8	73.0/27.0	4.2/95.8
Race, n (%)			
White	289 (78.7)	273 (80.3)	3 (75.0)
Black	48 (13.1)	35 (10.3)	1 (25.0)
Asian	2 (0.5)	4 (1.2)	0 (0.0)
Other	28 (7.6)	28 (8.2)	0 (0.0)
Baseline FEV ₁ , mean (L/% predicted)	1.6/74.3	1.6/72.4	1.6/80.3
Concomitant ICS use, %	67.7 (n=462)	68.7 (n=345)	44.8
BMI at baseline, mean	18.7	20.0	17.3
Age group: 13–18 years			
Age, mean (SD)	15.0 (1.70)	15.3 (1.71)	15.2 (1.80)
Sex, % (M/F)	67.0/33.0	63.0/37.0	54.5/45.5
Location, % (US/Ex-US)	88.4/11.6	89.6/10.4	89.1/10.9
Race, n (%)			
White	159 (79.5)	101 (80.2)	44 (89.8)
Black	20 (10.0)	13 (10.3)	3 (6.1)
Asian	6 (3.0)	2 (1.6)	0 (0.0)
Other	15 (7.5)	10 (7.9)	2 (4.1)
Baseline FEV ₁ , mean (L/% predicted)	2.7/70.9	2.7/72.8	2.4/68.8
Concomitant ICS use, %	49.8	60.0	49.1
BMI at baseline, mean	22.7	22.5	24.2
Age group: >18 years			
Mean age (SD)	44.2 (15.13)	42.3 (14.31)	45.0 (16.04)
Sex, % (M/F)	47.6/52.4	42.7/57.3	43.3/56.7
Location, % (US/Non-US)	51.8/48.2	53.6/46.4	46.8/53.2
Race, n (%)			
White	1,245 (81.0)	804 (82.0)	332 (86.0)
Black	152 (9.9)	91 (9.3)	22 (5.7)
Asian	24 (1.6)	18 (1.8)	3 (0.8)
Other	116 (7.5)	68 (6.9)	29 (7.5)
Mean FEV ₁ , % predicted, (L/% predicted)	2.2/66.7	2.3/68.4	2.1/66.1
Concomitant ICS use, %	70.7	71.7	72.8
Mean BMI	25.9	26.4	26.3

Abbreviations: ICS, inhaled corticosteroids; FEV₁, forced expiratory volume in 1 second; BMI, body mass index; TDD, total daily dose.

with 12/10 μg TDD and 48/40 μg TDD compared with subjects treated with the most commonly used dose of 24/20 μg TDD. For formoterol 12 μg TDD, the OR versus placebo was 3.9 (95% CI 1.5–10.3) and for 48 μg formoterol the OR versus placebo was 2.9 (95% CI 1.2–6.6). As discussed in previous sections, the OR versus placebo was 1.8 (95% CI 0.8–4.0) for patients randomized to formoterol 24 μg TDD. The same pattern was observed in the pediatric and adult age groups.

Serious Asthma Exacerbations in Patients Using ICS

Approximately 70% of the patients ($n = 5,682$) reported using ICS either at baseline or as concomitant treatment during the trials. Among adults who reported using concomitant ICS at baseline, a trend toward fewer serious asthma exacerbations was seen in those receiving formoterol as compared with placebo (13–18 years: OR 0.8; 95% CI 0.05–12.3; >18 years: OR 0.6, 95% CI 0.2–2.2). In

patients 5 to 12 years of age, the impact of concomitant use of ICS appeared to be less (OR 7.8, 95% CI 1.0–61.3). The limited number of adolescents in the analyses precludes meaningful subanalyses. In the 2 studies in which ICS were randomized study treatments, 4 hospitalizations were reported, all occurring in the non-formoterol treatment group.

Serious Asthma Exacerbations in Patients Classified According to Baseline Lung Function

Baseline lung function data were available for 6,106 patients. Of these, 1,725 patients had baseline FEV₁ less than 60% of predicted normal, 3,286 had baseline FEV₁ 60% to 80% of predicted normal, and 1,095 had baseline FEV₁ greater than 80% of predicted normal. No clear association was seen between serious asthma exacerbations and baseline lung function (data not shown).

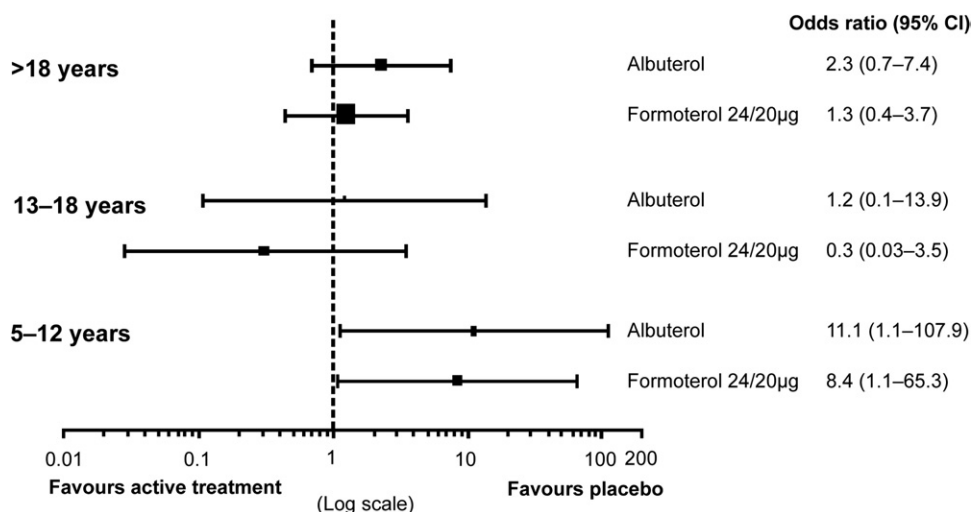


Figure 2. Odds ratios (95% CIs) for serious asthma exacerbations in asthma patients summarized by treatment group and age.

Table 2. Summary of Serious Asthma Exacerbations (%) by Treatment Group and Age (Approved and Unapproved Doses of Formoterol)

	Formoterol TDD			Placebo	Albuterol QID
	12/10 µg	20/24 µg	48 µg		
All patients, N	585	3129	1515	2026	976
Serious exacerbations, n (%)	9 (1.5)	22 (0.7)	17 (1.1)	8 (0.4)	10 (1.0)
Serious exacerbations/100 patient years	10.8	2.7	3.8	1.4	4.5
Odds ratio vs placebo	3.9	1.8	2.9	—	2.6
(95% CI)	(1.5, 10.3)	(0.8, 4.0)	(1.2, 6.6)	—	(1.0, 6.6)
5–12 years inclusive, N	103	462	188	345	96
Serious exacerbations, n (%)	5 (4.9)	11 (2.4)	8 (4.3)	1 (0.3)	3 (3.1)
Serious exacerbations/100 patient years	28.7	5.4	5.8	0.6	16.2
Odds ratio vs placebo	17.6	8.4	15.3	—	11.1
(95% CI)	(2.0, 152.0)	(1.1, 65.3)	(1.9, 123.2)	—	(1.1, 107.9)
13–18 years inclusive, N	6	215	101	135	55
Serious exacerbations, n (%)	0	1 (0.5)	0	2 (1.5)	1 (1.8)
Serious exacerbations/100 patient years	0	1.8	0	6.1	8.4
Odds ratio vs placebo	—	0.3	—	—	1.2
(95% CI)	—	(0.03, 3.5)	—	—	(0.1, 13.9)
>18 years, N	476	2452	1226	1546	825
Serious exacerbations, n (%)	4 (0.8)	10 (0.4)	9 (0.7)	5 (0.3)	6 (0.7)
Serious exacerbations/100 patient years	6.2	1.9	3.1	1.4	3.1
Odds ratio vs placebo	2.6	1.3	2.3	—	2.3
(95% CI)	(0.7, 9.8)	(0.4, 3.7)	(0.8, 6.8)	—	(0.7, 7.4)

Serious Asthma Exacerbations in Patients Classified According to Race

Insufficient numbers of nonwhite subjects were available to assess the effect of race on the risk of serious asthma exacerbations. Eight serious asthma exacerbations occurred among the 1,693 white patients (0.5%) randomized to formoterol, compared with 3 in the 1,178 subjects (0.3%) randomized to placebo and 3 in the 379 subjects (0.8%) randomized to albuterol. Three black subjects experienced serious asthma exacerbations (1.4%); all of them were randomized to formoterol. No serious asthma exacerbations were reported among subjects describing their race as Asian or Other.

DISCUSSION

Evidence-based guidelines recommend the use of LABAs, leukotriene antagonists, and theophylline² as adjuvant therapy in children, adolescents, and adults who complain of asthma-related symptoms or increased impairment despite receiving ICS. Multiple clinical trials have shown that the concomitant use of an LABA and an ICS provides greater improvement in lung function and other measures of asthma control as compared with doubling the dose of ICS or adding theophylline or leukotriene antagonists.^{10,25,26} Based on this evidence, LABAs are recommended in the guidelines as add-on treatment in children, adolescents, and adults not adequately controlled on

Table 3. Comparative Analyses of Serious Asthma Exacerbations: Bayesian Markov Chain Monte Carlo Modeling (Fixed Effects Model Results)

Relative risk	Posterior median	Confidence interval		
		2.50%	97.50%	
5–12 years				
Formoterol/placebo	17.29	2.65	634.80	
Albuterol/placebo	7.31	0.68	287.52	
Albuterol/formoterol	0.41	0.09	1.55	
13–18 years				
Formoterol/placebo	0.61	0.01	21.84	
Albuterol/placebo	2.14	0.05	155.92	
Albuterol/formoterol	3.52	0.07	330.61	
>18 years				
Formoterol/placebo	1.52	0.56	4.92	
Albuterol/placebo	3.50	0.79	17.66	
Albuterol/formoterol	2.24	0.58	9.04	
All				
Formoterol/placebo	2.14	1.00	5.19	
Albuterol/placebo	2.07	0.70	6.24	
Albuterol/formoterol	0.96	0.40	2.24	

low- and medium-dose ICS alone. The Best Add on Therapy Giving Effective Responses study showed that children with uncontrolled asthma, despite using low-dose ICS, were more likely to have a best response by adding an LABA than by increasing the dose of ICS or adding a leukotriene-receptor antagonist. However, the study also showed that the best response in a number of children was to ICS or leukotriene-receptor antagonist step-up therapy, indicating that regular monitoring and individual dose adjustments are needed during therapy.²⁶

This meta-analysis of data from 45 Novartis-sponsored randomized, double-blind placebo- and active-controlled studies evaluated the safety of formoterol in asthma patients. In 43 of the 45 trials, including the pivotal trials and the large safety study, concomitant ICS use was permitted; however, compliance and adherence were not monitored.

In our analyses, formoterol did not appear to increase the risk of asthma-related mortality in patients. A single death occurred (a 66-year-old woman) after formoterol treatment in this pooled data set. No deaths among children and adolescent patients were reported.

The number of asthma-related hospitalizations was increased among patients randomized to formoterol or regularly dosed albuterol compared with those receiving placebo. Albuterol, administered regularly, was associated with a rate of hospitalization that was similar to formoterol, suggesting that any increased risk of hospitalization is related to beta-agonist use as a class and not to the drug's duration of action. Although a more prolonged effect can be observed with a LABA, the use of a short-acting β_2 -agonist regimen also may mask the significant underlying inflammation similar to the LABAs, as shown by McIvor et al.¹²

A total of 7 intubations occurred, all with patients older than 18 years of age receiving formoterol. Only 1 patient was treated with a dose and formulation approved in the United States.

In adults and adolescents, the risk of serious asthma exacerbation after the administration of formoterol was small and not statistically significant. In children, however, the rate of asthma-related hospitalizations among patients treated with formoterol was significantly higher than the rate among patients treated with placebo (OR 8.4, 95% CI 1.1–65.3). This could be because most of the pediatric data are from a 12-month placebo-controlled study conducted by Bensch et al²⁷ between 1996 and 1998 when the standard of care for the treatment of asthma differed from current treatment standards (LABAs were used without concomitant ICS). In that study, 8 serious asthma exacerbations were reported among patients randomized to formoterol 24 μ g TDD and 12 among those randomized to 48 μ g TDD, whereas no patients receiving placebo experienced a serious asthma exacerbation. The percentages of discontinuations were 23% (placebo), 22% (formoterol 24 μ g TDD), and 19% (formoterol 48 μ g TDD). The high withdrawal rates and lack of follow-up for early drop-outs may have contributed to the absence of serious asthma exacerbations with placebo treatment in this trial. The absence of any asthma hospitalizations in the placebo group is also unusual based on the expected rate of hospitalizations in patients of this age from health survey data and clinical trials. In the Childhood Asthma Management Program Research Group study, a 4- to 6-year study of 1,041 children (5–12 years), patients receiving placebo reported 4.4 hospitalizations per 100 treatment years, whereas those treated with budesonide experienced only 2.5 hospitalizations.²⁸

Recently, published analyses of other formoterol formulations have not demonstrated differences in the rate of serious asthma exacerbations between children treated with formoterol and those treated with placebo if ICS is administered concomitantly. The frequency of asthma-related hospitalizations among 5,481 children between 4 and 11 years was 1.1% (38/3,316) among those treated with formoterol versus 1.1% (23/2,165) among patients randomized to the non-LABA treatment arm.²⁹ Among adults, the concomitant use of an LABA with an ICS appears to reduce asthma-related exacerbations associated with the use of formoterol as compared with non-LABA therapies.³⁰ Similar results were also reported by Jaeschke et al.³¹ The trend toward fewer exacerbations observed in this analysis may be influenced by the use of ICS either at baseline or as concomitant treatment during the course of the trials by approximately 70% of the subjects. In patients with asthma using ICS, formoterol decreased the risk of asthma-related hospitalizations.³¹

This meta-analysis supports current asthma treatment guidelines recommending LABAs as chronic therapy in conjunction with an ICS for adult and adolescent patients whose disease is not controlled by ICS alone. The analyses confirm data from other asthma studies and meta-analyses suggesting

that the use of LABAs in the absence of concomitant ICS increases the risk of asthma-related hospitalizations.

ACKNOWLEDGMENTS

The authors acknowledge Shaik Asma Sultana, professional medical writer (Novartis), and Gerald Dodson (Novartis) for assistance in the preparation of this manuscript.

REFERENCES

1. GINA. Global Initiative for Asthma. Global strategy for asthma management and prevention. Available at <http://www.ginasthma.com>. Accessed January 2010.
2. NHLBI. National Heart, Lung, and Blood Institute National Asthma Education and Prevention Program Expert Panel Report 3: Guidelines for the Diagnosis and Management of Asthma. NIH Publication No. 07-4051. Available at <http://www.nhlbi.nih.gov/guidelines/asthma/asthgdln.pdf>. Accessed: July 2009.
3. Shrewsbury S, Pyke S, Britton M. Meta-analysis of increased dose of inhaled steroid or addition of salmeterol in symptomatic asthma (MI-ASMA). *BMJ*. 2000;320:1368–1373.
4. Kips JC, Pauwels RA. Long-acting inhaled beta (2)-agonist therapy in asthma. *Am J Respir Crit Care Med*. 2001;164:923–932.
5. O'Byrne P, Bateman ED, Bousquet J, et al. From the 2006 Revision: GINA Report Global strategy for asthma management and prevention. Available at <http://www.ginasthma.com>. Accessed March 2007.
6. Greening AP, Wind P, Northfield M, Shaw G. Added salmeterol versus higher-dose corticosteroid in asthma patients with symptoms on existing inhaled corticosteroid. *Lancet*. 1994;344:219–224.
7. Fahy JV, Boushey HA. Controversies involving inhaled beta-agonists and inhaled corticosteroids in the treatment of asthma. *Clin Chest Med*. 1995;16:715–733.
8. Woolcock A, Lundback B, Ringdal N, Jacques LA. Comparison of addition of salmeterol to inhaled steroids with doubling of the dose of inhaled steroids. *Am J Respir Crit Care Med*. 1996;153:1481–1488.
9. Pauwels RA, Löfdahl CG, Postma DS, et al. Effect of inhaled formoterol and budesonide on exacerbations of asthma. *N Engl J Med*. 1997;337:1405–1411. Erratum in: *N Engl J Med*. 1998;338:139.
10. Taylor DR, Sears MR, Cockcroft DW. The beta-agonist controversy. *Med Clin North Am*. 1996;80:719–748.
11. Pearce N, Beasley R, Crane J, Burgess C, Jackson R. End of the New Zealand asthma mortality epidemic. *Lancet*. 1995;345:41–44.
12. McIvor RA, Pizzichini E, Turner MO, Hussack P, Hargreave FE, Sears MR. Potential masking effects of salmeterol on airway inflammation in asthma. *Am J Respir Crit Care Med*. 1998;158:924–930.
13. 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;306:1034–1037.
14. U.S. Food and Drug Administration. Study of asthma-drug halted. FDA Talk Paper. 2003:T03-06.
15. Nelson HS, Weiss ST, Bleecker ER, Yancey SW, Dorinsky PM. SMART Study Group. The Salmeterol Multicenter Asthma Research Trial: a comparison of usual pharmacotherapy for asthma or usual pharmacotherapy plus salmeterol. *Chest*. 2006;129:15–26. Erratum in: *Chest*. 2006;129:1393.
16. Bensch G, Lapidus RJ, Levine BE, et al. A randomized, 12-week, double-blind, placebo-controlled study comparing formoterol dry powder inhaler with albuterol metered-dose inhaler. *Ann Allergy Asthma Immunol*. 2001;86:19–27.
17. Pleskow W, LaForce CF, Yegen U, Matos D, Cioppa GD. Formoterol delivered via the dry powder Aerolizer inhaler versus albuterol MDI and placebo in mild-to-moderate asthma: a randomized, double-blind, double-dummy trial. *J Asthma*. 2003;40:505–514.
18. Wolfe J, Laforce C, Friedman B, et al. Formoterol, 24 microg bid, and serious asthma exacerbations: similar rates compared with formoterol, 12 microg bid, with and without extra doses taken on demand, and placebo. *Chest*. 2006;129:27–38.
19. Levenson M. Long-acting beta-agonists and adverse asthma events meta-analysis: statistical briefing package for joint meeting of the Pulmonary-Allergy Drugs Advisory Committee, Drug Safety and Risk Management Advisory Committee, and Pediatric Advisory Committee on December 10–11, 2008. Available at <http://www.fda.gov/ohrms/dockets/ac/08/briefing/2008-4398b1-01-FDA.pdf>. Accessed March 2009.
20. StatXact 7 PROCs for SAS Users. Cytel Software Corporation. Cambridge, MA, USA. 2005.
21. Lu G, Ades A. Combination of direct and indirect evidence in mixed treatment comparisons. *Stats Med*. 2004;23:3105–3124.
22. Caldwell DM, Ades AE, Higgins JPT. Simultaneous comparison of multiple treatments: combining direct and indirect evidence. *BMJ*. 2005;331:897–900.
23. Cooper NJ, Sutton AJ, Lu G, Khunt K. Mixed comparison of stroke prevention treatments in individuals with nonrheumatic atrial fibrillation. *Arch Intern Med*. 2006;166:1269–1275.
24. Spiegelhalter DJ, Best NG, Carlin BP, van der Linde A. Bayesian measures of model complexity and fit. *J R Stat Soc Ser B*. 2002;64:1–34.
25. Bateman ED, Boushey HA, Bousquet J, et al. Can guideline-defined asthma control be achieved? The Gaining Optimal Asthma Control study. *Am J Respir Crit Care Med*. 2004;170:836–844.
26. Lemanske RF, Mauger DT, Sorkness CA, et al. Step up therapy for children with uncontrolled asthma while receiving ICS. *N Engl J Med*. 2010;362:975–985.
27. Bensch G, Berger WE, Blokhin BM, et al. One-year efficacy and safety of inhaled formoterol dry powder in children with persistent asthma. *Ann Allergy Asthma Immunol*. 2002;89:180–190.
28. CAMP. The Childhood Asthma Management Program Research Group. Long-term effects of budesonide or nedocromil in children with asthma. *N Engl J Med*. 2000;343:1054–1063.
29. Price J, Radner F, Lenney W, Lindberg B. Safety of formoterol in children and adolescents: experience from asthma clinical trials. *Arch Dis Child*. 2010;95:1047–1053.
30. Sears MR, Ottosson A, Radner F, Suissa S. Long-acting β -agonists: a review of formoterol safety data from asthma clinical trials. *Eur Respir J* 2009;33:21–32.
31. Jaeschke R, O'Byrne PM, Mejza F, et al. The safety of long acting beta agonists among patients with asthma using inhaled corticosteroids. *Am J Respir Crit Care Med* 2008;178:1009–1016.

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