Eur Respir J 2009; 33: 21–32
DOI: 10.1183/09031936.00145006


# Long-acting β-agonists: a review of formoterol safety data from asthma clinical trials

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**ABSTRACT:** **The safety of long-acting $\beta_2$-agonist (LABA) treatment in asthma has been questioned following reported increased respiratory deaths when salmeterol was added to usual pharmacotherapy. The aim of this study was to examine whether asthma, cardiac or all-cause mortality and morbidity were increased with formoterol use.**

**The analysis included all AstraZeneca randomised controlled parallel-group asthma trials of 3–12-months duration involving formoterol. Risks associated with formoterol use compared with non-LABA treatment, overall and in combination with inhaled corticosteroids (ICS), were assessed using an intention-to-treat analysis of the rates and rate ratios of deaths and serious adverse events (SAEs). The main objective of this study was to compare asthma-related mortality in patients using formoterol and those not using formoterol.**

**There were eight asthma-related deaths (0.34 per 1,000 person-yrs) among 49,906 formoterol-randomised patients (92% using ICS), and two (0.22 per 1,000 person-yrs) among 18,098 patients (83% using ICS) not randomised to formoterol, which was nonsignificant. Asthma-related SAEs (>90% of which were hospitalisations) were significantly fewer among formoterol-randomised patients (0.75 *versus* 1.10%). There was no increase in asthma-related SAEs with increased daily doses of formoterol (9, 18 or 36 μg). There was no significant difference in cardiac mortality or noncardiac nonasthma-related mortality in formoterol-randomised compared to non-LABA-treated patients. All-cause mortality was similar. In the data set in which all subjects were prescribed ICS at baseline, there were seven asthma-related deaths (0.32 per 1,000 person-yrs) among 46,003 formoterol-randomised patients and one (0.14 per 1,000 person-yrs) among 13,905 patients not randomised to formoterol, which was also nonsignificant.**

**There were few asthma-related or cardiac-related deaths among patients randomised to formoterol, and all differences were nonsignificant compared with non-long-acting $\beta_2$-agonist-randomised patients. However, despite data on >68,000 patients, the power was insufficient to conclude that there was no increased mortality with formoterol. Cardiac-related serious adverse events were not increased, and asthma-related serious adverse events were significantly reduced with formoterol.**

**KEYWORDS:** **Asthma, formoterol, long-acting β-agonist, morbidity, mortality, safety**

Safety concerns regarding inhaled adrenergic compounds date back to the late 1940s. Up to five-fold increases in mortality among users of inhaled adrenalin [1] and high-dose isoprenaline [2–4] were reported in 1948 and the 1960s, respectively. A more recent mortality epidemic in New Zealand, beginning in 1976 [5], led to a series of case–control studies [6–8] that indicated an increased risk of fatal asthma associated with prescription of fenoterol. A study in Saskatchewan (Canada) found an increased risk of mortality with increasing use of both fenoterol and salbutamol [9]. Although cardiac adverse events were frequently considered responsible for the increased risk, a 1-yr clinical trial showed increased airway responsiveness and worsened asthma control during regular treatment with fenoterol added to usual therapy

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Received:
November 06 2006
Accepted after revision:
August 24 2008

SUPPORT STATEMENT
M.R. Sears reviewed the trial data, including details of all deaths, and was primarily responsible for writing this article and for the medical content. S. Suissa was responsible for the statistical and pharmacoepidemiological content. A. Ottosson and F. Radner were responsible for extraction, validation and analysis of data from the AstraZeneca trials. All authors read and approved the final manuscript.

STATEMENT OF INTEREST
Statements of interest for all authors of this manuscript can be found at www.erj.ersjournals.com/misc/statements.shtml

**This article has supplementary material accessible from www.erj.ersjournals.com**
**For editorial comments see page 3.**

European Respiratory Journal
Print ISSN 0903-1936
Online ISSN 1399-3003

compared with β-agonist used only as needed for symptom relief [10, 11]. However, subsequent US and UK trials of regular *versus* as needed salbutamol did not detect sustained adverse effects on asthma control [12, 13]. Nevertheless, during the 1990s, consensus guidelines increasingly advocated use of short-acting $\beta_2$-agonists (SABAs) only as needed for symptom relief [14–16].

The introduction of the long-acting $\beta_2$-agonists (LABAs) salmeterol and formoterol prompted questions regarding the possibility of safety issues. Clinical trials showed substantial benefit from adding LABAs to inhaled corticosteroid (ICS) therapy, exceeding that of doubling or even further increasing the dose of ICS [17–19]. At the same time, the Serevent Nationwide Surveillance (SNS) trial in the UK reported a nonsignificant three-fold excess of asthma-related deaths in patients using regular salmeterol compared with regular salbutamol over 16 weeks [20]. Of the patients studied, 69% were using ICS at baseline. A controlled study that employed stepwise reduction of ICS to permit inflammation to gradually increase demonstrated the potential for LABAs to mask clinical evidence of progressive inflammation [21]. In the USA, the Food and Drug Administration (FDA) approved salmeterol as monotherapy, as well as for use in combination with other therapies, but required a post-marketing clinical trial in order to address safety concerns raised by the SNS study. The US study was halted prematurely in 2003, when an interim analysis indicated that addition of salmeterol to usual therapy was associated with an increase in both severe exacerbations and mortality compared with placebo [22]. *Post hoc* subgroup analyses suggested that the increased mortality was confined to patients not prescribed ICS at baseline (nine deaths with salmeterol and none with placebo, compared with four and three deaths, respectively, among patients using ICS at baseline). However the use of ICS was not recorded during the treatment period.

In three placebo-controlled trials (n=1,613) with formoterol (Foradil™; Novartis Pharmaceuticals, Basle, Switzerland), a higher dose (24-μg metered dose twice daily) tended to be associated with more serious asthma exacerbations than a lower dose (12 μg twice daily) [23]. However, a large phase IV, randomised placebo-controlled trial (n=2,085) of Foradil™ found all doses of formoterol to be associated with fewer exacerbations than placebo, with no indication of any dose–response relationship [24].

Following a safety review of LABAs [25], the Pulmonary-Allergy Drugs Advisory Committee (PADAC) of the FDA recommended additional safety labelling information for this class. In November 2005, the FDA directed US manufacturers of salmeterol- and formoterol-containing products to update existing product labels with new warnings [26].

The PADAC review included formoterol data only from Novartis trials, as only that preparation (Foradil™) was then marketed in the USA. However, the AstraZeneca clinical database for formoterol is much larger than that available through Novartis trials. The formoterol Turbuhaler (Oxis®; AstraZeneca, Lund, Sweden) is currently licensed in 82 countries and the combined ICS/LABA budesonide/formoterol Turbuhaler (Symbicort®; AstraZeneca) in 101 countries.

The present article reports a comprehensive review of safety data obtained in completed AstraZeneca trials (up to December 2006) involving formoterol with respect to the risks of asthma-related and cardiac-related death and serious adverse events (SAEs), as well as all-cause mortality. Three questions were posed of the data. 1) What are the risks of exposure to formoterol compared to other treatment regimens that do not include a LABA (non-LABA)? 2) What are the risks of exposure to formoterol when given in combination with ICS compared to treatment with non-LABA plus ICS? 3) What are the risks of exposure to formoterol without ICS compared with formoterol in combination with ICS? The use of other treatments (*e.g.* SABAs) was not taken into account.

In order to achieve the largest possible data set, and mimic a real-life situation in which patients may not adhere to guidelines, the primary analysis of the present study focused on question 1. However, given that all guidelines state that LABAs should be used in asthma management in combination with ICS, and as use of ICS may be regarded as a potential confounder in studies of LABA safety, question 2 was added as a *post hoc* analysis to determine risks associated with the addition of LABA to treatment with ICS *versus* non-LABA with ICS.

## METHODS

### *Data source*

All AstraZeneca trials (completed by December 2006) in patients with asthma involving the use of formoterol either alone as maintenance or reliever therapy or in combination with budesonide were identified through the company database. This consisted of 78,339 patients participating in 117 trials (fig. 1). This large data set was then subjected to reduction in order to bring about more uniformity. The first step excluded trials in which treatment was short. Since an adverse effect of treatment on asthma severity may require exposure over many months, the main analysis included all randomised controlled trials with durations of 3–12 months, performed either as centrally run trials or trials run by marketing companies in different countries (locally run). In order to focus on adverse effects associated with formoterol in comparison with those of non-LABA regimens, treatment arms involving randomisation to the other LABA, salmeterol, were excluded from the main analyses (fig. 1). The remaining trials included those from the centrally run AstraZeneca clinical development programmes for formoterol Turbuhaler (14 trials), budesonide/formoterol Turbuhaler (19 trials) and budesonide/formoterol pressurised metered-dose inhaler (pMDI; 11 trials), and 20 trials conducted by local AstraZeneca marketing companies with formoterol Turbuhaler or budesonide/formoterol Turbuhaler. Details of these 64 trials, involving 72,174 randomised patients, are provided in tables E-1–E-3 of the supplementary material. After excluding the 4,170 patients randomised to salmeterol, the resulting overall data set included 68,004 patients, of whom 49,906 were randomised to formoterol-containing products and 18,098 to non-LABA products (fig. 1).

A supplementary analysis of all identified AstraZeneca asthma trials, regardless of duration or study design, was also performed in order to ensure that no important safety signals were missed by selecting only trials of 3–12 months' duration. These included all centrally run trials in asthmatic patients, including long-term safety studies, emergency department trials

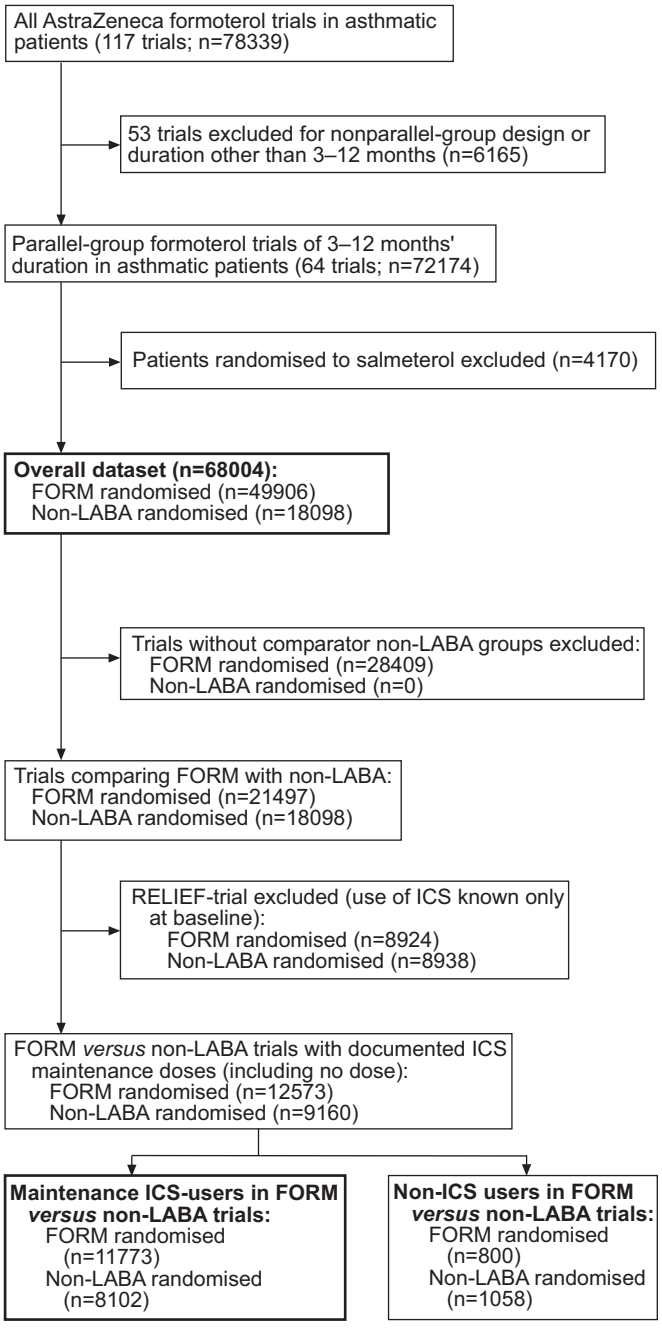


**FIGURE 1.** Flow chart showing all patients involved in AstraZeneca trials with formoterol (FORM). LABA: long-acting $\beta_2$-agonist; RELIEF: Real life effectiveness of Oxis Turbuhaler as needed in asthmatic patients during six months; ICS: inhaled corticosteroid.

in acute severe asthma, pharmacokinetic and high-dose tolerance studies, methacholine-induced bronchoconstriction studies and trials in a prematurely terminated (due to device malfunction) formoterol pMDI programme. All identified locally run parallel-group trials in asthmatic patients were also included. There were no exclusions of salmeterol-randomised patients in the supplementary analysis. Results from this supplementary analysis are summarised in the present article and further described in the supplementary material.

### *Outcome events*

All deaths and nonfatal SAEs were evaluated at the time by the original investigators involved in each study, and prior to unblinding in blinded trials. All fatalities in all trials were reassessed by the present authors, and categorised as asthma-related, cardiac-related or due to other reasons. Asthma-related events were defined as any event coded to the preferred terms asthma, status asthmaticus or bronchospasm according to the *Medical Dictionary for Regulatory Activities* (MedDRA) Version 8.0 [27]. In addition, two deaths originally coded to respiratory failure were considered asthma-related. Cardiac-related events were defined as any event coded using MedDRA according to the terms in table E-4 of the supplementary material.

SAEs (asthma-related and cardiac-related) were defined using the International Conference on Harmonisation recommendations, *i.e.* any adverse event that was immediately life-threatening, required inpatient hospitalisation or prolongation of existing hospitalisation, resulted in persistent or significant disability or incapacity, was a congenital abnormality/birth defect or was an important medical event that may jeopardise the subject or require medical intervention to prevent one of the outcomes listed above.

### *Data analyses*

For each patient, the person-time of follow-up in the trial was measured and cumulated to obtain exposure in person-yrs and the rate of fatal outcome events, expressed per 1,000 person-yrs, for each treatment group was computed. The crude rate ratio (RR) associated with formoterol use and its confidence interval (CI) were computed using the exact method as described in the manual for StatXact® [28]. For nonfatal events, the crude RR was approximated by the odds ratio (OR) using the number of randomised patients and the number of patients experiencing at least one event. The adjusted RR, to control for variations in properties of the individual trials, was estimated from the OR computed by conditional logistic regression, adjusting for trial as a covariate. This approach was supplemented with a meta-analysis at the trial level as described by MARTIN and AUSTIN [29].

For RRs and ORs, differences were considered significant when the 95% CI excluded 1.00.

Formoterol doses were expressed as delivered doses. Formoterol delivered doses of 9, 18 and 36 μg correspond to metered doses of 12, 24 and 48 μg, respectively. Ethnicity was classified as Caucasian, Oriental, Black (including African American) and other.

### *Analysis of risks of exposure to formoterol* versus *non-LABA (question 1)*

This constituted the primary analysis, with asthma mortality being chosen as the primary outcome. The intent-to-treat approach for all trials of 3–12 months' duration was used to classify patients randomised to: 1) formoterol-containing products, *i.e.* formoterol alone or formoterol combined with budesonide (two inhalers or in a single device); or 2) non-LABA products, including ICS (budesonide/fluticasone), SABA (terbutaline/salbutamol) and placebo.

Additional stratified analyses were performed by age, sex and ethnicity. The formoterol dose–response effect on the risk of asthma-related SAEs was also assessed.

### *Analysis of risks of exposure to formoterol plus ICS versus non-LABA plus ICS (question 2)*

Risks were analysed by comparing outcomes among all patients using or not using ICS at baseline (global ICS analysis). A further analysis excluded patients in trials without a non-LABA comparator and patients in the Real life effectiveness of Oxis Turbuhaler as needed in asthmatic patients during six months (RELIEF; SD-037-0699) trial [30] since ICS use during this trial was not documented after the baseline visit. This leaves a subset of trials involving a direct comparison between formoterol and non-LABA treatment in patients with documented maintenance treatment with ICS during the trial, including no dose (fig. 1). The ICS-exposed patients in this subset of trials are referred to as the randomised ICS data set.

### *Analysis of risks of exposure to formoterol without ICS versus formoterol with ICS (question 3)*

Only trials with at least one treatment arm with formoterol combined with ICS and one treatment arm with formoterol without ICS could be utilised for this analysis.

## RESULTS

### *Asthma-related deaths and SAEs*

Comparing asthma-related mortality with formoterol *versus* non-LABA in the overall dataset, the *a priori* primary outcome of the present study, there were eight deaths among 49,906 formoterol-randomised patients and two among 18,098 non-LABA-randomised patients (0.34 *versus* 0.22 per 1,000 treatment-yrs; RR 1.57; 95% CI 0.31–15.1; table 1). For asthma-related nonfatal SAEs within the same overall dataset, a significantly lower risk was observed among the formoterol-randomised patients (374 (0.75%) patients with asthma-related SAEs *versus* 199 (1.10%); RR 0.68; 95% CI 0.57–0.81; table 2).

Comparing asthma-related mortality with formoterol *versus* non-LABA among patients prescribed ICS at baseline in the overall data set (global ICS analysis), seven *versus* one asthma death yielded an RR of 2.32 (95% CI 0.30–105; table 1). Within this data set, analysis of asthma-related nonfatal SAEs showed a significantly lower risk among formoterol patients prescribed ICS at baseline compared to those prescribed non-LABA plus ICS (RR 0.63; 95% CI 0.52–0.76; table 2).

Comparing asthma-related mortality with formoterol *versus* non-LABA among patients all on maintenance treatment with ICS in the randomised ICS data set, there were three *versus* no asthma deaths, yielding an RR of ∞ (95% CI 0.29–∞; table 3). For asthma-related nonfatal SAEs, there was, again, a significantly lower risk among patients treated with formoterol plus ICS compared to non-LABA plus ICS (OR 0.69; 95% CI 0.49–0.96; table 3).

### *Asthma-related deaths and SAEs by age, sex and ethnicity*

The patients' ages at death were 13, 35, 43, 44, 55, 56, 65 and 67 yrs for formoterol and 18 and 45 yrs for non-LABA regimens. Review of the asthma-related deaths, including age, sex, race, concomitant medication, duration of trial, duration of formoterol exposure before death, daily formoterol dose and certified cause of death, revealed no consistent patterns among any of these variables (table 4). There were no deaths among the small number (n=1,189) of Black subjects.

There was no evidence of increased risk of asthma-related SAEs associated with formoterol in any subgroup of patients by age, sex or ethnicity in the overall data set (table 5). Nonfatal asthma-related SAEs among Black subjects were reported in eight out of 861 (0.9%) formoterol-randomised and three out of 328 (0.9%) non-LABA-randomised patients. These rates are similar to those in the other small subgroups (Oriental and other), and are not notably different from those in Caucasians, in whom nonfatal asthma-related SAEs were reported by 268 out of 39,868 (0.7%) formoterol-exposed and 123 out of 14,818 (0.8%) non-LABA patients.

### *Asthma-related SAEs by daily dose of formoterol*

There was no increased risk of nonfatal asthma-related SAEs related to increased doses of formoterol by randomised treatment (overall data set; table 6).

### *Cardiac-related deaths and SAEs*

Although cardiac-related death may have a respiratory-related component, all cases of cardiac death had terms reported that motivated their assignment as cardiac-related rather than asthma-related (table E-5 of supplementary material). There were eight cardiac-related deaths among 49,906 formoterol-randomised patients (one not using ICS at baseline) and nine among 18,098 patients randomised to non-LABA regimens (three not using ICS at baseline). Rates of cardiac-related death by randomisation (deaths per 1,000 treatment-yrs) are included in table 1. Ages at death ranged 64–82 yrs for formoterol-randomised patients and 46–78 yrs for non-LABA-randomised patients. Deaths among the formoterol-randomised patients were reported as due to cardiac arrest (n=2), cardiac failure/myocardial infarction (n=2), myocardial infarction (n=2), cardio-respiratory failure and myocardial ischaemia. Deaths among the non-LABA-randomised patients were reported as due to myocardial infarction (n=4), cardiac failure, cardiac arrest, sudden cardiac death, aortic stenosis and cardiomyopathy.

The percentage of patients reporting at least one cardiac-related SAE was similar for formoterol-randomised (0.21%) compared with non-LABA-randomised (0.25%) patients (OR 0.83; 95% CI 0.58–1.20; table 2).

Analysis of cardiac-related deaths and SAEs in the overall data set, among patients prescribed ICS at baseline (global ICS analysis) and in the randomised ICS data set showed no significant differences between treatments (tables 1–3).

### *Deaths due to other causes*

Deaths due to causes other than asthma-related or cardiac-related causes were numerically more frequent among the formoterol-randomised patients than among the non-LABA-randomised (18 deaths among 49,906 patients *versus* three deaths among 18,098 patients; RR 2.35; 95% CI 0.69–12.5; table 1). The deaths were reported as stroke, liver cirrhosis and an undefined cause for the three non-LABA-exposed patients, and as lung cancer (n=2), brain tumour (n=2), stroke (n=2), suicide (n=2), pulmonary embolism, hepatic carcinoma,

**TABLE 1** Rates and rate ratios (RRs) of cause-specific death across randomised controlled trials stratified by any inhaled corticosteroid (ICS) use at baseline

| | Formoterol | | | | No Formoterol | | | | RR (95% CI)# |
|---|---|---|---|---|---|---|---|---|---|
| | Patients n | Follow-up TPY | Deaths n | Rate per TTY | Patients n | Follow-up TPY | Deaths n | Rate per TTY | |
| **Asthma-related death** | | | | | | | | | |
| All subjects | 49906 | 23.6 | 8 | 0.34 | 18098 | 9.2 | 2 | 0.22 | 1.57 (0.31–15.1) |
| With ICS | 46003 | 21.7 | 7 | 0.32 | 13905 | 7.2 | 1 | 0.14 | 2.32 (0.30–105) |
| No ICS | 3903 | 1.9 | 1 | 0.54 | 4193 | 2.1 | 1 | 0.48 | 1.13 (0.014–88) |
| **Cardiac-related death** | | | | | | | | | |
| All subjects | 49906 | 23.6 | 8 | 0.34 | 18098 | 9.2 | 9¶ | 0.97 | 0.35 (0.12–1.02) |
| With ICS | 46003 | 21.7 | 7 | 0.32 | 13905 | 7.2 | 6 | 0.84 | 0.38 (0.11–1.39) |
| No ICS | 3903 | 1.9 | 1 | 0.54 | 4193 | 2.1 | 3 | 1.44 | 0.38 (0.0071–4.7) |
| **Other deaths** | | | | | | | | | |
| All subjects | 49906 | 23.6 | 18 | 0.76 | 18098 | 9.2 | 3 | 0.32 | 2.35 (0.69–12.5) |
| With ICS | 46003 | 21.7 | 17 | 0.78 | 13905 | 7.2 | 2 | 0.28 | 2.82 (0.67–25) |
| No ICS | 3903 | 1.9 | 1 | 0.54 | 4193 | 2.1 | 1 | 0.48 | 1.13 (0.014–88) |
| **Total deaths** | | | | | | | | | |
| All subjects | 49906 | 23.6 | 34 | 1.44 | 18098 | 9.2 | 14 | 1.52 | 0.95 (0.50–1.92) |
| With ICS | 46003 | 21.7 | 31 | 1.43 | 13905 | 7.2 | 9 | 1.26 | 1.14 (0.53–2.73) |
| No ICS | 3903 | 1.9 | 3 | 1.61 | 4193 | 2.1 | 5 | 2.41 | 0.68 (0.11–3.47) |

CI: confidence interval; TPY: 1,000 person-yrs; TTY: 1,000 treatment-yrs. #: for asthma, cardiac, ''other'' or any death for formoterol *versus* non-long-acting $\beta_2$-agonist (non-LABA) [28]. ¶: two salbutamol as needed randomised patients in the Real life effectiveness of Oxis Turbuhaler as needed in asthmatic patients during 6 months (SD-037-0699) trial who suffered a cardiac-related death actually were exposed to formoterol as needed: one erroneously received formoterol instead of salbutamol at start of treatment, and one used salbutamol for 5 weeks and then exchanged medication with a formoterol-randomised patient and died 2 days later; the physician could not determine which drug was used before death. When applying a worst-case approach and reassigning these two deaths to formoterol, the resulting 10 *versus* seven cardiac deaths give rates of 0.43 *versus* 0.76 per TTY and a RR (95% CI) for cardiac death of 0.56 (0.19–1.73) for formoterol *versus* non-LABA, as calculated using StatXact 8.0.0 (Cytel® Inc., Cambridge, MA, USA) [27].

peritoneal metastases, ovarian cancer, road accident, carbon monoxide intoxication, typhoid fever and undefined cause (n=3) for the 18 formoterol-exposed patients (table E-6 of supplementary material). No additional information is available for the four patients who died due to an undefined cause (three formoterol-randomised and one non-LABA-randomised patient, *i.e.* the same incidence of 0.006%).

### *All-cause mortality*

All-cause mortality was similar between treatments, with 48 deaths reported in total, 34 (0.07%) among formoterol-randomised patients and 14 (0.08%) among non-LABA-randomised patients (table 1).

### *Event rates in the other subsets of trials*

Two subsets of trials were not utilised in the analyses of effects of formoterol on patients receiving maintenance treatment with ICS (the randomised ICS data set; fig. 1). The first subset, trials without a non-LABA comparator group, comprised 28,409 patients, all randomised to different treatment regimens of LABA plus ICS, mainly in Symbicort *versus* Symbicort trials. Table 7 summarises the event rates from these trials, with two asthma-related deaths (rate 0.16 per 1,000 treatment-yrs) and a low rate of asthma-related SAEs (incidence 0.67%).

The second subset consisted of a single large open-label trial, RELIEF, which compared as needed use of formoterol with as needed salbutamol, both given in addition to regular asthma treatment [30]. In this trial, ICS could be initiated or withdrawn at any time point, and data on ICS use were collected only at baseline and not during the treatment period, meaning that treatment with ICS could not be controlled for. Event rates in the RELIEF trial population are also presented in table 7, together with rates by ICS prescription at baseline. The incidence of asthma-related SAEs for non-LABA with ICS at baseline was significantly higher than for non-LABA without ICS prescription at baseline (1.55 *versus* 0.96%; RR 1.63; 95% CI 1.07–2.56). For formoterol, similar results were obtained (1.39 *versus* 0.81%; RR 1.74; 95% CI 1.10–2.85), suggesting that ICS prescription at baseline in the RELIEF trial reflected asthma severity.

### *Adjusted RRs*

Adjusted RRs controlling for trial effect were also calculated. The adjusted RRs were somewhat higher than the crude RRs for the most rare events, *e.g.* asthma death (RR 2.68; 95% CI 0.53–13.5), cardiac death (RR 0.75; 95% CI 0.28–2.02) and all-cause mortality (RR 1.39; 95% CI 0.71–2.74), whereas the results were similar for the more frequent events, such as SAEs. None of the adjusted comparisons showed any significant differences between treatments.

The calculation of adjusted RRs for asthma mortality utilised data from only four of the 64 trials (the RELIEF trial, with three *versus* two asthma-related deaths in formoterol-exposed *versus* non-LABA-exposed patients, and SD-037-0345, SD-037-0003 and SD-039-0673, with one asthma-related death per trial

**TABLE 2** Asthma-related and cardiac-related serious adverse events (SAEs) across randomised controlled trials stratified by any inhaled corticosteroid (ICS) use at baseline

| | Formoterol | | | No Formoterol | | | RR (95% CI)# |
|---|---|---|---|---|---|---|---|
| | Patients n | Follow-up TPY | Patients with SAEs¶ n (%) | Patients n | Follow-up TPY | Patients with SAEs n (%) | |
| **Asthma-related SAEs** | | | | | | | |
| All subjects | 49906 | 23.6 | 374 (0.75) | 18098 | 9.2 | 199 (1.10) | 0.68 (0.57–0.81) |
| With ICS | 46003 | 21.7 | 346 (0.75) | 13905 | 7.2 | 166 (1.19) | 0.63 (0.52–0.76) |
| No ICS | 3903 | 1.9 | 28 (0.72) | 4193 | 2.1 | 33 (0.79) | 0.91 (0.53–1.56) |
| **Cardiac-related SAEs** | | | | | | | |
| All subjects | 49906 | 23.6 | 103 (0.21) | 18098 | 9.2 | 45 (0.25) | 0.83 (0.58–1.20) |
| With ICS | 46003 | 21.7 | 95 (0.21) | 13905 | 7.2 | 38 (0.27) | 0.76 (0.51–1.13) |
| No ICS | 3903 | 1.9 | 8 (0.20) | 4193 | 2.1 | 7 (0.17) | 1.23 (0.39–3.98) |

SAEs defined using International Conference on Harmonisation recommendations. RR: rate ratio; CI: confidence interval; TPY: 1,000 person-yrs. #: for the odds ratio for asthma-related and cardiac-related SAEs (for formoterol *versus* non-long-acting $\beta_2$-agonist) [28], as calculated using StatXact 8.0.0 (Cytel® Inc., Cambridge, MA, USA) [27]; ¶: at least one nonfatal SAE per patient.

among the formoterol-exposed patients). The remaining 60 trials were not used since the conditional analysis was based only on trials with at least one outcome event and at least one patient in a treatment group (meaning that the two deaths in trials with no comparator non-LABA group were excluded from this analysis). No other trials contributed information to the estimation of the adjusted RR. Likewise, only a small number of trials provided data for cardiac deaths (three trials), other deaths (six trials; RR 2.41; 95% CI 0.64–9.04) and all-cause mortality (nine trials; RR 1.39; 95% CI 0.71–2.74), whereas, for SAEs, more trials contributed information (30 trials for asthma-related SAEs; RR 0.84; 95% CI 0.69–1.03, and 13 for cardiac-related SAEs; RR 0.81; 95% CI 0.53–1.24). Meta-analyses according to MARTIN and AUSTIN [29] gave almost identical results (data not shown).

**TABLE 3** Rates and rate ratios (RRs) of cause-specific deaths and serious adverse events (SAEs) across randomised controlled trials comparing formoterol with non-long-acting $\beta_2$-agonist (non-LABA) stratified by known maintenance inhaled corticosteroid (ICS) use#

| | Formoterol | | | | | No Formoterol | | | | | RR (95%CI)+ |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | Patients n | Follow-up TPY | Deaths/ SAEs¶ n | Death rate per TTY | SAEs % | Patients n | Follow-up TPY | Deaths/ SAEs¶ n | Death rate per TTY | SAEs % | |
| **Asthma-related death** | | | | | | | | | | | |
| Maintenance ICS | 11773 | 6.2 | 3 | 0.48 | | 8102 | 4.4 | 0 | 0 | | ∞ (0.29–∞) |
| No ICS | 800 | 0.4 | 0 | 0 | | 1058 | 0.6 | 0 | 0 | | |
| **Cardiac-related death** | | | | | | | | | | | |
| Maintenance ICS | 11773 | 6.2 | 1 | 0.16 | | 8102 | 4.4 | 2 | 0.45 | | 0.34 (0.058–6.61) |
| No ICS | 800 | 0.4 | 0 | 0 | | 1058 | 0.6 | 0 | 0 | | |
| **Asthma-related SAEs** | | | | | | | | | | | |
| Maintenance ICS | 11773 | 6.2 | 76 | | 0.65 | 8102 | 4.4 | 76 | | 0.94 | 0.69 (0.49–0.96) |
| No ICS | 800 | 0.4 | 3 | | 0.38 | 1058 | 0.6 | 3 | | 0.28 | 1.32 (0.18–9.9) |
| **Cardiac-related SAEs** | | | | | | | | | | | |
| Maintenance ICS | 11773 | 6.2 | 21 | | 0.18 | 8102 | 4.4 | 15 | | 0.19 | 0.96 (0.47–2.01) |
| No ICS | 800 | 0.4 | 1 | | 0.13 | 1058 | 0.6 | 0 | | 0 | NC |

CI: confidence interval; TPY: 1,000 person-yrs; TTY: 1,000 treatment-yrs; NC: not computable. #: all trials except Real life effectiveness of Oxis Turbuhaler as needed in asthmatic patients during 6 months trial (ICS treatment during the trial not recorded) and trials without a non-LABA comparator; ¶: at least one nonfatal SAE per patient; +: as calculated using StatXact 8.0.0 (Cytel® Inc., Cambridge, MA, USA) [27].

**TABLE 4** Details of all asthma-related deaths

| Case no. | Randomised treatment | Study ref. | Duration[#] days | Daily randomised treatment dose | Age/sex/race | Duration of randomised treatment days | Time in study until onset/death[¶] days | Baseline drug other than randomised treatment[+] | | Patient considered ICS-exposed | Cause of death |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | | LABA | ICS | | |
| **1** | Form | SD-037-0345/181/30801 | 365 | 9 μg Form + 160 μg Bud | 35/F/X | 241[§] | 237/247 | NP | NP | Yes | Status asthmaticus; septic shock |
| **2** | Form | SD-039-0673/448/1488 | 365 | 9/160 μg Form/Bud + Terb *p.r.n.* | 65/F/O | 299 | 300/300 | NP | NP | Yes | Asthma |
| **3** | Form | SD-039-0735/110/76 | 180 | 9/320 μg Form/Bud + Form/Bud *p.r.n.* | 55/M/C | 159[ƒ] | 166/198 | NP | NP | Yes | Respiratory failure |
| **4** | Form | SD-037-0699/26069/261384 | 180 | Form *p.r.n.* | 56/F/C | 2[##] | 2/2 | Salm | Flut | Yes | Asthma |
| **5** | Form | SD-037-0699/45304/451773 | 180 | Form *p.r.n.* | 43/F/O | 69 | 69/69 | NR | BDP | Yes | Asthma |
| **6** | Form | SD-037-0699/45218/451990 | 180 | Form *p.r.n.* | 44/M/O | 15 | 15/15 | NR | NR | No | Asthma |
| **7** | Non-LABA | SD-037-0699/45224/452193 | 180 | Salb *p.r.n.* | 45/F/O | 92 | 92/92 | NR | NR | No | Asthma |
| **8** | Non-LABA | SD-037-0699/71029/710030 | 180 | Salb *p.r.n.* | 18/M/C | 91 | 91/91 | NR | BDP | Yes | Asthma |
| **9** | Form | SD-037-0003/34/3403 | 90 | 18 μg Form | 13/M/C | 26 | 27/28 | NP | BDP | Yes | Respiratory failure |
| **10** | Form | AD-039-0001/9199/919901 | 180 | 9/160 μg Form/Bud | 67/F/C | 28 | 28/31 | NP | NP | Yes | Asthma |

ICS: inhaled corticosteroids; LABA: long-acting $\beta_2$-agonist; Form: formoterol; Bud: budesonide; F: female; X: other (*i.e.* other than Caucasian, Oriental or Black); Terb: terbutaline; O: Oriental; M: male; C: Caucasian; Salm: salmeterol; Flut: fluticasone; BDP: beclomethasone dipropionate; Salb: salbutamol; NR: none reported; NP: none permitted; *p.r.n.*: as needed. [#]: from clinical study protocol; [¶]: first day of randomised treatment to day of onset of event leading to death/day of death; [+]: taken in addition to study drug as maintenance therapy; [§]: patient developed pneumonia and septic shock during a hospital admission for asthma, the probable immediate cause of death was septic shock; [ƒ]: patient hospitalised for asthma, discontinued trial on day 159, remained at hospital and developed respiratory insufficiency that progressed into respiratory failure with fatal outcome; [##]: patient randomised on day of severe asthma attack and took one dose of formoterol in the evening, death was pronounced the following evening.

**TABLE 5** Nonfatal asthma-related serious adverse events (SAEs) by age, sex and ethnicity (overall data set)

| | Formoterol-containing products | Non-LABA-containing products | Total |
|---|---|---|---|
| **Age group** | | | |
| 4–11 yrs | 39/3264 (1.2) | 25/2165 (1.2) | 64/5429 (1.2) |
| 12–17 yrs | 24/4556 (0.5) | 17/1889 (0.9) | 41/6445 (0.6) |
| 18–64 yrs | 270/37882 (0.7) | 136/12596 (1.1) | 404/50478 (0.8) |
| ⩾65 yrs | 43/4162 (1.0) | 21/1448 (1.5) | 64/5610 (1.1) |
| Unknown | 0/42 (0) | 0/0 (0) | 0/42 (0) |
| **Sex** | | | |
| Male | 146/22057 (0.7) | 72/8068 (0.9) | 218/30125 (0.7) |
| Female | 228/27800 (0.8) | 127/10030 (1.3) | 355/37830 (0.9) |
| Unknown | 0/49 (0) | 0/0 (0) | 0/49 (0) |
| **Ethnicity** | | | |
| Caucasian | 268/39868 (0.7) | 123/14818 (0.8) | 391/54686 (0.7) |
| Black | 8/861 (0.9) | 3/328 (0.9) | 11/1189 (0.9) |
| Oriental | 70/4065 (1.7) | 53/1916 (2.8) | 123/5981 (2.1) |
| Other | 25/2170 (1.2) | 20/1036 (1.9) | 45/3206 (1.4) |
| Unknown | 3/2942 (0.1) | 0/0 (0) | 3/2942 (0.1) |
| **Total** | 374/49906 (0.7) | 199/18098 (1.1) | 573/68004 (0.8) |

Data are presented as n/N (%) of patients reporting at least one asthma-related nonfatal SAE (defined using International Conference on Harmonisation recommendations). LABA: long-acting $\beta_2$-agonist.

### *Overall analysis and actual treatment exposure*

The design of the RELIEF study [30] means that the overall analysis did not completely reflect actual exposure to LABAs. In the RELIEF trial, patients could be on baseline maintenance LABA treatment when randomised to formoterol or salbutamol as needed. A separate analysis examined treatment-related differences for asthma-related and cardiac-related events according to baseline treatment, namely no ICS, ICS without LABA, and ICS plus LABA (tables E-7 and E-8 of supplementary material). There was no apparent difference in asthma-related mortality between formoterol as needed and salbutamol as needed, or between different baseline treatments. Likewise, for cardiac and other deaths and for all-cause mortality, no clear treatment-related pattern was apparent. Examining asthma-related and cardiac-related SAEs from the RELIEF trial by baseline ICS and LABA use, for all within-baseline-medication-group safety comparisons, formoterol as needed was associated with a similar or lower risk than salbutamol as needed.

There was a relationship between the overall frequency of asthma-related SAEs and baseline medication in the RELIEF trial [30]. For the combined formoterol plus salbutamol groups, SAEs were of lowest frequency among those receiving no ICS at baseline (0.88%), intermediate in those receiving ICS but no LABA (1.25%) and of highest frequency in those receiving both ICS and a LABA (1.80%). This apparent paradox probably reflects physician-determined baseline treatment according to perceived severity, with ICS and LABA prescribed for those with more severe asthma (and hence more susceptible to SAEs), an example of confounding by severity.

### *Supplementary analysis*

#### Numbers of trials and patients

The supplementary analyses, which included all available trials in asthmatic patients irrespective of duration and design, added 53 trials to those in the primary analyses, giving 117 trials and 78,339 patients in total. Among these, 54,559 were randomised to formoterol, 4,474 to salmeterol and 20,477 to a non-LABA regimen. Patients in crossover trials were counted once for each treatment to which they were exposed, but only once in the totals column. The number of patients per treatment regimen for each of the available trials is presented in table E-3 of the supplementary material.

#### Asthma-related, cardiac-related and all-cause mortality

Across all of the available trials, there were 56 deaths, of which 10 were asthma-related (all in trials included in the overall data set). In addition to the 17 cardiac-related deaths in the overall data set, another three were reported in the additional trials (table E-5 of the supplementary material), two in formoterol-exposed patients in a long-term safety trial and one in a salmeterol-exposed patient. Five additional deaths from other causes were added to the 21 deaths included in the overall data set (table E-6 of the supplementary material), two in formoterol-exposed patients, one in a non-LABA-exposed patient and two in salmeterol-exposed patients. All-cause mortality across all available trials was 0.07% for formoterol-randomised, 0.07% for non-LABA-randomised and 0.07% for salmeterol-randomised patients.

**TABLE 6** Nonfatal asthma-related serious adverse events (SAEs)[#] by daily dose of formoterol (overall data set)

| Daily dose of formoterol | Patients n | Mean duration days | Patients reporting SAEs[¶] n (%) |
|---|---|---|---|
| **9 μg**[+] | 5306 | 218 | 57 (1.07) |
| **18 μg** | 15923 | 131 | 92 (0.58) |
| **36 μg** | 909 | 239 | 4 (0.44) |
| **As-needed use/adjustable dosing** | 27768 | 185 | 221 (0.80) |
| **Total**[§] | 49906 | 173 | 374 (0.75) |

[#]: defined using International Conference on Harmonisation recommendations; [¶]: at least one asthma-related nonfatal SAE per patient; [+]: includes children who received 80/4.5 μg budesonide/formoterol once daily plus terbutaline as needed in trial SD-039-0673; [§]: all trials combined.

**TABLE 7** Event rates in additional subgroups

| Trial | Formoterol | | | | | No Formoterol | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | Patients n | Follow-up TPY | Deaths n | Death rate per TTY | Patients with SAEs# n (%) | Patients n | Follow-up TPY | Deaths n | Death rate per TTY | Patients with SAEs# n (%) |
| **No LABA comparator groups** | | | | | | | | | | |
| Asthma-related events | 28409 | 12.7 | 2 | 0.16 | 189 (0.67) | | | | | |
| Cardiac-related events | 28409 | 12.7 | 1 | 0.08 | 61 (0.21) | | | | | |
| Other deaths | 28409 | 12.7 | 9 | 0.71 | | | | | | |
| Total deaths | 28409 | 12.7 | 12 | 0.94 | | | | | | |
| **RELIEF: overall results** | | | | | | | | | | |
| Asthma-related events | 8924 | 4.3 | 3 | 0.70 | 106 (1.19) | 8938 | 4.3 | 2 | 0.47 | 120 (1.34) |
| Cardiac-related events | 8924 | 4.3 | 6 | 1.40 | 20 (0.22) | 8938 | 4.3 | 7 | 1.63 | 30 (0.38) |
| Other deaths | 8924 | 4.3 | 4 | 0.93 | | 8938 | 4.3 | 2 | 0.47 | |
| Total deaths | 8924 | 4.3 | 13 | 3.02 | | 8938 | 4.3 | 11 | 2.56 | |
| **RELIEF: BL ICS use** | | | | | | | | | | |
| Asthma-related events | 5821 | 2.8 | 2 | 0.72 | 81 (1.39) | 5803 | 2.8 | 1 | 0.36 | 90 (1.55) |
| Cardiac-related events | 5821 | 2.8 | 5 | 1.80 | 13 (0.22) | 5803 | 2.8 | 4 | 1.43 | 23 (0.40) |
| Other deaths | 5821 | 2.8 | 3 | 1.08 | | 5803 | 2.8 | 1 | 0.36 | |
| Total deaths | 5821 | 2.8 | 10 | 3.60 | | 5803 | 2.8 | 6 | 2.15 | |
| **RELIEF: no BL ICS use** | | | | | | | | | | |
| Asthma-related events | 3103 | 1.5 | 1 | 0.67 | 25 (0.81) | 3135 | 1.5 | 1 | 0.67 | 30 (0.96) |
| Cardiac-related events | 3103 | 1.5 | 1 | 0.67 | 7 (0.23) | 3135 | 1.5 | 3 | 1.99 | 7 (0.22) |
| Other deaths | 3103 | 1.5 | 1 | 0.67 | | 3135 | 1.5 | 1 | 0.67 | |
| Total deaths | 3103 | 1.5 | 3 | 2.03 | | 3135 | 1.5 | 5 | 3.32 | |

TPY: 1,000 person-yrs; TTY: 1,000 treatment-yrs; SAEs: serious adverse events; LABA: long-acting $\beta_2$-agonist; RELIEF: Real life effectiveness of Oxis Turbuhaler as needed in asthmatic patients during 6-month trial; BL: baseline; ICS: inhaled corticosteroid. #: at least one nonfatal SAE per patient (defined using International Conference on Harmonisation recommendations).

### Nonfatal asthma-related and cardiac-related serious adverse events

Across all trials in the supplementary analyses, there were 402 (0.7%) patients among the 54,559 formoterol-randomised patients with at least one asthma-related SAE and 113 (0.2%) with at least one cardiac-related SAE. Among the 20,477 non-LABA-randomised patients, the corresponding numbers were 207 (1.0%) and 46 (0.2%). These results do not differ from those of the primary analysis. The results are presented in table E-3 of the supplementary material.

## DISCUSSION

The primary purpose of the present analysis was to determine whether or not use of formoterol was associated with an increased risk of asthma mortality in the largest possible data set from clinical trials, including some patients not on regular treatment with ICS. The present analysis involved 68,004 patients from the AstraZeneca clinical trial programme for formoterol and budesonide/formoterol, providing ~23,600 person-yrs of exposure to formoterol. Although an RR of 1.57 did not show a significantly increased risk of death, mortality is a rare event in such trials and estimates of risk should be interpreted with caution given that the trials were not powered on these events. More confidence can be placed in the rates for SAEs, for which the numbers of events were substantially greater. The use of formoterol was associated with a significant reduction in asthma-related nonfatal SAEs among both patients in the whole data set and those prescribed ICS at baseline (global ICS analysis), with the RRs being 0.68 and 0.63, respectively.

When analysing the safety of LABAs, two questions are important. What is the overall risk of death if patients are given a LABA regardless of other therapy? What is the relative risk when a LABA, such as formoterol, is added to standard treatment with ICS? Eight asthma-related deaths in 23,600 person-yrs of formoterol exposure in the overall data set yielded a mortality rate of 0.34 per 1,000 person-yrs. The risk of asthma-related death comparing all formoterol-exposed patients with all non-LABA-exposed patients in the overall analysis was 1.57 (95% CI 0.31–15.1). The other question posed in the present analysis regarded the risk of formoterol compared with non-LABA when both were used with concomitant ICS, as per international asthma guidelines. The global ICS analysis (tables 1 and 2) showed an RR of 2.32, but this was also not significant and was associated with wide CIs. This included all patients using ICS at least at baseline, but it also included both the RELIEF trial [30], in which use of ICS after trial entry was not documented (ICS could be discontinued or started), and trials comparing different strategies of using combination ICS/LABA therapies in which there were no non-LABA-randomised patients. Hence the global analysis could be viewed as less appropriate despite the larger number of patients. The analysis based on the smaller randomised ICS

data set (table 3), which retained all patients with known ICS exposure during treatment and a non-LABA comparator arm, had three asthma-related deaths in 11,773 formoterol-randomised patients compared to none among the non-LABA-randomised patients. Mortality risk cannot be accurately estimated with only three deaths, albeit all in the formoterol arm, and the calculated RR becomes infinite. However, the absolute rate of asthma mortality is low (0.48 per 1,000 treatment-yrs). The significantly lower risk found for asthma SAEs for formoterol *versus* non-LABA added to ICS treatment is similar to the findings of a recent meta-analysis by JAESCHKE *et al.* [31].

The data set was explored to assess the relative risk of using formoterol alone. However, the data were insufficient to address this, the third, question. Ideally, this question would be addressed by examining trials in which patients were randomised to formoterol with ICS *versus* formoterol without ICS. The only AstraZeneca trials using this design were those performed in the USA, where monotherapy with individual components of combination therapy is required by the FDA. However, the 384 patients randomised to formoterol without ICS in these trials were too few to analyse with any meaning. Overall, <8% of all formoterol-treated patients in AstraZeneca asthma trials were not exposed to ICS.

When comparing all formoterol-exposed patients to all non-LABA-exposed patients in the overall data set, no increased risks of cardiac-related deaths (table 1) or cardiac-related non-fatal SAEs (table 2) were observed. Similarly, when examined by ICS use by either the global ICS or randomised ICS method, there was no increased risk of cardiac SAEs with regimens of formoterol with ICS *versus* non-LABA with ICS (tables 2 and 3).

Hospital admission is a recognised marker of risk of asthma mortality [32, 33]. Although these were not analysed separately, the significant reduction in asthma-related SAEs with formoterol, >90% of which were hospitalisations, speaks against a relationship between formoterol and increased asthma mortality.

The main limitation of the present study was the lack of sufficient power to form a definitive conclusion regarding the risk of death for patients treated with formoterol. Although use of formoterol, largely with ICS, was not associated with a significantly increased risk of asthma-related deaths, the power was too low to conclude that there was no association with formoterol, even with data on >68,000 patients. Given the observed asthma mortality rate of ~0.3 per 1,000 person-yrs and the overall sample sizes in the present study of formoterol-exposed (49,906) and non-exposed patients (18,098), corresponding to 23,600 and 9,200 treatment-yrs, respectively, the present study had a 42, 70 and 88% power for detecting three-, four- and five-fold increases in the risk. The study was also unable to adequately address the issue of age, sex and ethnicity factors, which could be important in modifying the risk of death. The AstraZeneca database lacks sufficient numbers to specifically address the risk in the formoterol-exposed Black population, but no increase in mortality or incidence of asthma-related SAEs was seen in the small numbers of Black subjects.

The present report also does not provide the same weight of evidence as would a large randomised controlled trial of formoterol safety. The report was compiled as an observational study, using data from randomised controlled trials. Several factors need to be considered with respect to their potential for introducing bias into these findings. Data were derived from formoterol arms of numerous trials, and comparator data from arms in the same or different trials. Many trials did not have non-LABA arms or non-ICS arms. There may have been differences in asthma severity and indications for ICS treatment in the different trials, impacting outcomes. Patients entered into most of these trials were required to be in a relatively stable condition with no recent exacerbation or requirement for oral corticosteroid; it is not possible to know to what extent these entry criteria may have selected a population at lower risk of SAEs from treatment. Some deaths and SAEs were assessed and coded as asthma-related or cardiac-related in open trials in which the assigned treatment was known.

Analyses of multiple trial data sets are difficult because of differences in study design and selection criteria, including severity of disease and treatment. A further criticism of the present study is that it did not include all trials involving formoterol. Novartis formoterol trials were not included in the present review as the primary data from their published and unpublished trials were not available to the present authors. Furthermore, possible differences in the formulation and delivery of the two preparations of formoterol could confound or invalidate the analyses. The dose-related increase in nonfatal asthma-related SAEs observed in the Novartis phase III formoterol programme [23] was not confirmed in their phase IV trial comprising 2,085 patients [24], nor in the present review of almost 50,000 formoterol-treated patients. On the contrary, the risk of SAEs in the AstraZeneca trials decreased with higher formoterol doses, an effect that may also be attributable to the higher dose of concomitant ICS generally used with higher doses of formoterol. Conversely, the data from the present study reflect the full breadth of experience with formoterol in AstraZeneca trials in many different populations and situations, including one very large trial (RELIEF), in which formoterol could be used freely as reliever medication and also in addition to maintenance formoterol in some patients [30].

The findings reported here contrast with the report of SALPETER *et al.* [34], who undertook a meta-analysis of LABA trials with durations of ⩾3 months in which LABA was compared with placebo therapy. They concluded that significantly increased mortality and morbidity were associated with both LABAs. However, their analyses included only one of the trials [35] included in the present primary analysis and one additional trial [36] included in the present supplementary analysis, out of a total of 117 AstraZeneca trials in the present review, and specifically excluded many relevant trials, as noted in several responses [37] to the original report of SALPETER *et al.* [34]. One single trial, the Salmeterol Multicenter Asthma Research Trial (SMART), accounted for >26,000 (78%) patients included in their meta-analysis, whereas the two AstraZeneca trials that were included contributed only 753 (2%) patients. In a critique of the paper, CHINCHILLI [38] made the following comment: ''Given the domination by the SMART trial, however, it may be incorrect to claim that this constitutes a systematic overview to investigate the risks of LABAs on asthma-related deaths''.

The conclusion of SALPETER *et al.* [34] also differs markedly from that of two recent Cochrane analyses on this topic [39, 40].

These analyses included trials in which ICS was uniformly used by all patients, and concluded that add-on LABA was both effective and safe. A more recent Cochrane analysis [41] examined trials of LABAs for chronic asthma in adults and children in which the background therapy contained varied or no ICS, and excluded those in which patients were uniformly taking ICS. In this latter review of 67 trials, a median of only 62% were taking ICS. The benefits of add-on LABA on asthma control were seen both with and without ICS therapy, but the authors identified potential safety issues with LABA without ICS, again based almost exclusively on the trial of NELSON *et al.* [22], in which excess mortality was seen among patients without ICS at baseline. The Asthma Guidelines Committee of the Canadian Thoracic Society carefully reviewed the meta-analysis of SALPETER *et al.* [34], and affirmed the safety of LABA used in conjunction with ICS [42].

In summary, the present study is the largest analysis to date of trials involving the long-acting $\beta_2$-agonist formoterol. Numerous studies have shown the benefit of adding a long-acting $\beta_2$-agonist compared with doubling or further increasing the dose of inhaled corticosteroid [18, 19, 36] and the greater benefits to most outcomes of adding a long-acting $\beta_2$-agonist compared with adding a leukotriene antagonist [43]. International asthma treatment guidelines and the US Food and Drug Administration now emphasise that long-acting $\beta_2$-agonist should not be used as monotherapy in asthma but always together with an inhaled corticosteroid [44]. The reduction in asthma-related serious adverse events associated with use of formoterol compared with non-long-acting $\beta_2$-agonist, and the lack of any dose–response relation with serious adverse events, provides some reassurance regarding the safety of formoterol used largely with inhaled corticosteroid, but, given the infrequency of deaths, the power of the present study is insufficient to conclude with confidence that there is no association between formoterol and mortality. Further studies of mortality in asthma are required in order to permit better assessment of risks so that these can be compared against the widely accepted benefits that long-acting $\beta_2$-agonists have brought to the management of patients with asthma.

## ACKNOWLEDGEMENTS

The authors are grateful to the reviewers of this article for their detailed consideration of the complex issues involved and their helpful suggestions regarding data presentation.

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