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

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ABSTRACT

Background: The safety of long-acting β_2-agonist (LABA) treatment in asthma has been questioned following reported increased respiratory deaths when salmeterol was added to usual pharmacotherapy. We examined whether asthma, cardiac or all-cause mortality or morbidity were increased with formoterol use.

Methods: The analysis included all AstraZeneca randomized, 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.

Results: There were eight asthma-related deaths (0.34 per 1000 patient-years) among 49,906 formoterol-randomized patients (92% using ICS), and two (0.22 per 1000 patient-years) among 18,098 patients (83% using ICS) not randomized to formoterol (RR 1.57, 95% CI 0.31-15.1) which was not statistically significant. Asthma-related SAEs (>90% of which were hospitalizations) were significantly lower among formoterol-randomized patients (0.75% vs. 1.10%; RR 0.68, 95% CI 0.57-0.81). There was no increase in asthma-related SAEs with increased daily doses of formoterol (9 vs 18 vs 36 mcg). There was no statistically significant difference in cardiac mortality (RR 0.34, 95% CI 0.12-1.02) or non-cardiac, non-asthma-related mortality (RR 2.35, 95% 0.69-12.5) in formoterol-randomized when compared to non-LABA-treated patients. All-cause mortality was similar (RR 0.95, 95% CI 0.50-1.92). In

the data set in which all subjects were prescribed ICS at baseline, there were seven asthma-related deaths (0.32 per 1000 patient-years) among 46,003 formoterol-randomized patients and one (0.14 per 1000 patient-years) among 13,905 patients not randomized to formoterol (RR 2.32, 95% CI 0.30-105) which was also not statistically significant.

Conclusions: There were few asthma-related or cardiac-related deaths among patients randomized to formoterol, and all differences were not statistically significant compared with non-LABA-randomized patients. However, despite data on over 68,000 patients, the power is insufficient to conclude no increased mortality with formoterol. Cardiac-related SAEs were not increased, and asthma-related SAEs were significantly reduced with formoterol.

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INTRODUCTION

Safety concerns regarding inhaled adrenergic compounds date back 60 years. Up to five-fold increases in mortality among users of inhaled adrenaline [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 year-long clinical trial showed increased airway responsiveness and worsened asthma control during regular treatment with fenoterol added to usual therapy 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 short-acting β_2-agonists (SABAs) only as needed for symptom relief [14–16].

The introduction of the long-acting β_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 statistically non-significant three-fold excess of asthma-related deaths in patients using regular salmeterol compared with regular salbutamol over 16 weeks [20]. Sixty-nine percent of the studied patients were using ICS at baseline. A controlled study

which employed stepwise reduction of ICS to allow inflammation to gradually increase demonstrated the potential for LABAs to mask clinical evidence of progressive inflammation [21]. In the US, the Food and Drug Administration (FDA) approved salmeterol as monotherapy as well as for use in combination with other therapies, but mandated a post-marketing clinical trial 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 when 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, Basel, 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, randomized, placebo-controlled trial (n=2,085) of Foradil™ found all doses of formoterol associated with fewer exacerbations than placebo, with no indication of any dose–response relationship [24].

Following a safety review of LABAs, the Pulmonary-Allergy Drugs Advisory Committee (PADAC) of the FDA recommended additional safety labelling information in this class [25]. 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 US. However, the AstraZeneca clinical database for formoterol is much larger than that available through Novartis trials. Formoterol Turbuhaler (Oxis®; AstraZeneca, Lund, Sweden) is currently licensed in 82 countries and the combined ICS/LABA budesonide/formoterol (Symbicort®; AstraZeneca) in 101 countries.

This paper 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 as well as all-cause mortality. Three questions were posed of the data:
(a) what are the risks of exposure to formoterol when compared to other treatment regimens that do not include a LABA (non-LABA)?
(b) what are the risks of exposure to formoterol when given in combination with ICS when compared to treatment with non-LABA plus ICS?
(c) what are the risks of exposure to formoterol without ICS when compared with formoterol in combination with ICS?
The use of other treatments (e.g. short-acting β_2-agonists) was not taken into account.

To achieve the largest possible dataset, and mimic a real-life situation where patients may not adhere to guidelines, the primary analysis of this study focused on comparison a). However, given that all guidelines state that LABAs should be used in

asthma management in combination with ICS, and because use of ICS may be regarded as a potential confounder in studies of LABA safety, comparison b) 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 (Figure 1). This large dataset was then subjected to reduction in order to bring more uniformity. The first step excluded trials where treatment was short. Because an adverse effect of treatment on asthma severity may require exposure over many months, the main analysis included all randomized, 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). To focus on adverse effects associated with formoterol in comparison with those of non-LABA regimens, treatment arms involving randomization to the other LABA, salmeterol were excluded from the main analyses (Figure 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 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 randomized patients, are

provided in Tables E-1, E-2, E-3, on-line supplement. After excluding the 4,170 patients randomized to salmeterol, the resulting overall-dataset included 68,004 patients, of whom 49,906 were randomized to formoterol-containing products and 18,098 to non-LABA products (Figure1).

A supplementary analysis of all identified AstraZeneca asthma trials, regardless of duration and study design, was also performed to ensure 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 room trials 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 pressurized metered-dose inhaler (pMDI) programme. All identified locally run parallel-group trials in asthmatic patients were also included. There were no exclusions of salmeterol-randomized patients in the supplementary analysis. Results from this supplementary analysis are summarized in this paper and further described in the online supplement.

Outcome events

All deaths and non-fatal 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 categorized 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. In addition, two deaths originally coded to respiratory failure were considered asthma-related.

Cardiac-related events were defined as any event coded using MedDRA v8.0 according to the terms in Table E-4, online supplement.

SAEs (asthma-related and cardiac-related) were defined using the International Conference on Harmonization recommendations, i.e. any adverse event that was immediately life threatening, required inpatient hospitalization or prolongation of existing hospitalization, resulted in persistent or significant disability or incapacity, was a congenital abnormality/birth defect or was an important medical event that may jeopardize 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 person-years of exposure and the rate of fatal outcome events expressed per 1000 person-years computed for each treatment group. The crude rate ratio (RR) associated with formoterol use and its confidence interval (CI) were computed by the exact method (StatXact® version 8.0.0; Cytel® Inc., Cambridge, USA) [27]. For non-fatal events, the crude RR was approximated by the odds ratio obtained from StatXact using the number of randomized patients and the number of patients experiencing at least one event. The adjusted rate ratio, to control for variations in properties of the individual trials, was estimated from the odds ratio computed by conditional logistic regression, adjusting for trial as a covariate. This approach was supplemented with a meta-analysis on the trial level using EXACTMA v 0.3 as described by Martin and Austin [28].

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

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

Analysis of risks of exposure to formoterol vs. non-LABA (question a)

This constituted the primary analysis with asthma mortality being chosen as the primary outcome. The intent-to-treat (ITT) approach for all trials of 3–12 months duration was used to classify patients randomized to: (1) formoterol-containing products, i.e. formoterol only 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. We also assessed the formoterol dose-response effect on the risk of asthma-related SAEs.

Analysis of risks of exposure to formoterol plus ICS vs. non-LABA plus ICS (question b)

Risks were analyzed by comparing outcomes among all patients using or not using ICS at baseline (global-ICS analysis) and then further analysed after excluding patients in the RELIEF trial SD-037-0699 [29] as ICS use during the trial was not

documented after the baseline visit, and patients in trials without a non-LABA comparator, leaving a subset of trials involving both maintenance treatment with ICS and a direct comparison between formoterol and non-LABA treatments (see Fig 1). The ICS-exposed patients in this subset of trials are referred to as the Randomized ICS-dataset.

Analysis of risks of exposure to formoterol without ICS vs. formoterol with ICS (question c).

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

RESULTS

Asthma-related deaths and SAEs

Comparing asthma-related mortality with formoterol vs. non-LABA in the overall-dataset, the a priori primary outcome of this study, there were 8 deaths among 49,906 formoterol-randomized patients and 2 among 18,098 non-LABA randomized patients (rates per 1000 treatment-years, 0.34 vs. 0.22; RR 1.57, 95% CI 0.31-15.1) (Table 1). For asthma-related non-fatal SAEs within the same overall dataset, a significantly lower risk was observed among the formoterol-randomized patients (374 patients with asthma-related SAE [0.75%] vs. 199 [1.10%]; RR 0.68, 95% CI 0.57-0.81) (Table 2).

Comparing asthma-related mortality with formoterol vs. non-LABA among patients prescribed ICS at baseline in the overall dataset (global-ICS analysis), 7 vs 1 asthma

deaths yielded RR 2.32 (95% CI 0.30-105) (Table 1). Within this dataset, analysis of asthma-related non-fatal SAEs showed a significantly lower risk among formoterol patients prescribed ICS at baseline when compared to non-LABA plus ICS (RR 0.63, 95% CI 0.52-0.76) (Table 2).

Comparing asthma-related mortality with formoterol vs. non-LABA among patients all on maintenance treatment with ICS in the Randomized ICS-dataset, there were 3 vs 0 asthma deaths, yielding RR "+ inf" (95% CI 0.29-inf) (Table 1). For asthma-related non-fatal 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 years for formoterol and 18 and 45 years 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-dataset (Table 5). Non-fatal asthma-related SAEs among Black subjects were reported in 8 of 861 formoterol-randomized (0.9%) and 3 of 328 non-LABA-randomized (0.9%) patients. These rates are similar to those in the other small subgroups (Oriental and

Other) and are not notably different to those in Caucasians where non-fatal asthma-related SAEs were reported by 268 of 39,868 formoterol-exposed (0.7%) and 123 of 14,818 non-LABA (0.8%) patients.

Asthma-related SAEs by daily dose of formoterol

There was no increased risk of non-fatal asthma-related SAEs related to increased doses of formoterol by randomized treatment (overall-dataset, Table 6).

Cardiac-related deaths and SAEs

Although cardiac-related death may have a respiratory-related component, all cases of cardiac death had reported terms that motivated their assignment as cardiac-related rather than asthma-related (Table E-5, online supplement). There were eight cardiac-related deaths among 49,906 formoterol-randomized patients (one not using ICS at baseline) and nine among 18,098 patients randomized to non-LABA regimens (three not using ICS at baseline). Rates of cardiac-related death by randomization (deaths per 1000 treatment-years) are included in Table 1. Ages at death ranged from 64–82 years for formoterol-randomized patients and 46–78 years for non-LABA randomized patients. Deaths among the formoterol-randomized patients were reported as due to cardiac arrest (two cases), cardiac failure/myocardial infarction (two cases), myocardial infarction (two cases), cardio-respiratory failure and myocardial ischaemia. Deaths among the non-LABA-randomized patients were reported as due to myocardial infarction (four cases), 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-randomized (0.21%) compared with non-LABA-randomized patients (0.25%); OR 0.83, 95% CI 0.58-1.20) (Table 2).

Analysis of cardiac-related deaths and SAEs in the overall dataset, among patients prescribed ICS at baseline (global-ICS analysis) and in the Randomized-ICS dataset showed no statistically significant differences between treatments (Tables 1-3).

Deaths due to "other" causes

Deaths due to causes other than asthma-related or cardiac-related were numerically more frequent among the formoterol-randomized patients than among the non-LABA randomized (18 deaths among 49,906 patients vs. 3 deaths among 18,098 patients; RR (95% CI) for "other" deaths 2.35 (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 (two cases), brain tumour (two cases), stroke (two cases), suicide (two cases), pulmonary embolism, hepatic carcinoma, peritoneal metastases, ovarian cancer, road accident, carbon monoxide intoxication, typhoid fever and "undefined cause" (three cases) for the 18 formoterol-exposed patients (Table E-6, online supplement). No additional information is available for the four patients who died due to an "undefined cause" (three formoterol-randomized and one non-LABA-randomized 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-randomized patients and 14 (0.08%) among non-LABA-randomized patients (Table 1).

Event rates in the other subsets of trials

Two subsets of trials were not utilized in the analyses of effects of formoterol on patients on maintenance treatment with ICS (the Randomized ICS-dataset, Figure 1). The first subset, trials without a non-LABA comparator group, comprised 28,409 patients all randomized to different treatment regimens of LABA plus ICS, mainly in Symbicort vs Symbicort trials. Table 7 summarizes the event rates from these trials, with two asthma-related deaths (rate 0.16 per 1000 years) 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 [29]. In this trial, ICS could be initiated or withdrawn at any time-point and data for ICS use were collected only at baseline and not during the treatment period which means that treatment with ICS could not be controlled for. Event rates for 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% vs 0.96%, RR 1.63 (95% CI 1.07-2.56). For formoterol similar results were obtained (1.39% vs 0.81%, RR 1.74 (95% CI 1.10-2.85)), suggesting ICS prescription at baseline in RELIEF reflected asthma severity.

Adjusted rate ratios

Adjusted rate ratios 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 show any statistically significant differences between treatments.

Calculation of adjusted rate ratios for asthma mortality utilizes data from only 4 of the 64 trials (the RELIEF trial with three vs. 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 among the formoterol-exposed patients). The remaining 60 trials are not used since the conditional analysis is based only on trials with at least one outcome event and at least one patient in a treatment group (meaning that the 2 deaths in trials with no comparator non-LABA group are excluded from this analysis). All other trials do not contribute information to the estimation of the adjusted rate ratio. Likewise only a small number of trials provide data for cardiac deaths (3 trials), other deaths (6 trials, RR 2.41, 95% CI 0.64-9.04) and all-cause mortality (9 trials, RR 1.39, 95% CI 0.71-2.74), whereas for SAEs more trials contribute 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 [28] gave almost identical results (data not shown).

Overall analysis and actual treatment exposure

Because of the design of the RELIEF study [29], the overall analysis does not completely reflect actual exposure to LABAs. In RELIEF, patients could be on baseline maintenance LABA treatment when randomized 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, online supplement). There was no apparent difference in asthma-related mortality between formoterol as needed and salbutamol as needed, or between different baseline treatments. For cardiac and "other" deaths and for all-cause mortality, there was likewise no clear treatment-related pattern 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 [29]. For the combined formoterol plus salbutamol groups, SAEs were of lowest frequency among those with no ICS at baseline (0.88%), intermediate in those with ICS but no LABA (1.25%) and of highest frequency in those with both ICS and a LABA (1.80%). This apparent paradox likely reflects physician-determined baseline treatment according to perceived severity, with ICS and LABA prescribed for those with more severe asthma (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 (see Methods) added 53 trials to those in the primary analyses, giving 117 trials and 78,339 patients in total. Among these, 54,559 were randomized to formoterol, 4,474 to salmeterol and 20,477 to a non-LABA regimen. Patients in crossover trials have been counted once for each exposed treatment, but only once in the totals column. Numbers of patients per treatment regimen for each of the available trials is presented in Table E-3, online supplement.

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

Across all available trials there were 56 deaths, of which 10 were asthma-related (all in trials included in the overall-dataset). In addition to the 17 cardiac-related deaths in the overall-dataset, another three were reported in these additional trials (Table E-5), 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-dataset (Table E-6), 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-randomized, 0.07% for non-LABA-randomized and 0.07% for salmeterol-randomized patients.

Non-fatal asthma-related and cardiac-related SAEs

Across all trials in the supplementary analyses, there were 403 (0.7%) patients among the 54,559 formoterol-randomized 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-randomized 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-4, online supplement.

DISCUSSION

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

When analyzing 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, and 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 patient-years of formoterol exposure in the overall dataset yielded a mortality rate of 0.34 per 1000 patient-years. The risk for asthma-related death comparing all formoterol-exposed patients to all non-LABA-exposed patients in the overall analysis was 1.57 (95% CI 0.31-15.1). The other

question posed in this analysis was 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 1,2) showed an RR of 2.32, but this was also not statistically significant and was associated with wide confidence intervals. This included all patients using ICS at least at baseline but it also included both the RELIEF trial [29], 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-randomized patients. Hence the global analysis could be viewed as less appropriate despite the larger number of patients. The analysis based on the smaller Randomized ICS-dataset (Table 3) which retained all patients with known ICS exposure during treatment and a non-LABA comparator arm had 3 asthma-related deaths in 11,773 formoterol-randomized patients compared to zero among the non-LABA randomized patients. Mortality risk cannot be accurately estimated with only three deaths, albeit all in the formoterol arm, and the calculated rate ratio becomes infinite. However, the absolute rate of asthma-mortality is low (0.48 per 1000 treatment years). The significantly lower risk for asthma-SAEs for formoterol vs non-LABA added to ICS-treatment is similar to the findings of a recent meta-analysis by Jaeschke et al [30].

We explored the dataset to assess the relative risk of using formoterol alone. However, the data were insufficiently large to address this, our third, question. Ideally this question would be addressed by examining trials in which patients were randomized to formoterol with ICS vs. formoterol without ICS. The only AstraZeneca trials using this design were those performed in the United States where monotherapy with individual components of combination therapy is mandated by the

FDA. However, the 384 patients randomized to formoterol without ICS in these trials are too few to analyse with any meaning. Overall, less than 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 dataset, no increased risks for 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 Randomized-ICS method, there was no increased risk of cardiac SAEs with regimens of formoterol with ICS versus non-LABA with ICS (Table 2-3).

Hospital admission is a recognised marker of risk of asthma mortality [31,32]. While these were not analysed separately, the significant reduction of asthma-related SAEs with formoterol, over 90% of which were hospitalisations, speaks against a relationship between formoterol and increased asthma mortality.

The main limitation of this study is the lack of sufficient power to make a definitive conclusion about the risk of death for patients treated with formoterol. While use of formoterol largely with ICS is not associated with a statistically significant increased risk of asthma-related deaths, the power is too low to conclude no association with formoterol, even with data on over 68,000 patients. Given the observed asthma mortality rate of around 0.3 per 1000 patient-years and the overall sample sizes in our study of formoterol-exposed (49,006) and non-exposed patients (18,098), corresponding to 23,600 and 9,200 treatment-years, respectively, our study had 42%, 70% and 88% power to detect three-fold, four-fold and five-fold increases in the risk.

The study was also unable to address adequately the issue of age, gender and ethnicity factors which have 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.

This report also does not provide the same weight of evidence as would a large, randomized, controlled trial of formoterol safety. The report is compiled as an observational study, using data from randomized controlled trials. Several factors need to be considered with respect to their potential for introducing bias into these findings. Data are derived from formoterol arms of numerous trials, and comparator data come from arms in the same or different trials. Many trials do not have non–LABA arms or non-ICS arms. There may be differences in asthma severity and indications for ICS treatment in 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 need for oral corticosteroid; it is not possible to know to what extent these entry criteria may have selected a population at lower risk for 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 datasets are difficult because of differences in study design and selection criteria including severity of disease and treatment. A further criticism of this study is that it did not include all trials involving formoterol. We did not include Novartis formoterol trials in this review as the primary data for their published and unpublished trials were not available to the authors. Furthermore, possible differences

in formulation and delivery of the two preparations of formoterol could confound or invalidate the analyses. The dose-related increase in non-fatal 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. On the other hand, the data from this 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 [29].

The findings reported here contrast with the report of Salpeter et al. [33], who undertook a meta-analysis of LABA trials with durations of 3 months or longer in which LABA was compared with placebo therapy. They concluded that there was significantly increased mortality and morbidity associated with both LABAs. However, their analyses included only one of the trials [34] included in our primary analysis and one additional trial [35] included in our supplementary analysis, out of a total of 117 AstraZeneca trials in our review, and specifically excluded many relevant trials, as noted in several responses [36] to the original report of Salpeter et al. One single trial (the Salmeterol Multicenter Asthma Research Trial [SMART]) accounted for more than 26,000 patients (78%) included in their meta-analysis, while the two AstraZeneca trials that were included contributed only 753 patients (2%). In a critique of the paper, Chinchilli commented: “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" [37].

The conclusion of Salpeter et al. also differs markedly from that of two recent Cochrane analyses on this topic [38,39]. 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 [40] examined trials of LABAs for chronic asthma in adults and children where 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., and affirmed the safety of LABA used in conjunction with ICS [41].

In summary, this is the largest analysis to date of trials involving the LABA, formoterol. Numerous studies have shown the benefit of adding a LABA when compared with doubling or further increasing the dose of ICS [18,19,35] and the greater benefits to most outcomes of adding a LABA compared with adding a leukotriene antagonist [42]. International asthma treatment guidelines and the FDA now emphasize that LABA should not be used as monotherapy but always used together with an ICS in asthma [43]. The reduction in asthma-related SAEs associated with use of formoterol when compared with non-LABA, and the lack of any dose-response relation with SAEs,

provides some reassurance regarding safety of formoterol used largely with ICS, but given the infrequency of deaths, the power of our study is insufficient to conclude with confidence that there is no association between formoterol and mortality. Further studies of mortality in asthma will be needed to enable a better assessment of risks so that these can be compared against the widely accepted benefits that LABAs have brought to the management of patients with asthma.

COMPETING INTERESTS

Malcolm Sears has served as a consultant or advisory board member for, or received research funding from, Altana (Nycomed), AstraZeneca, GlaxoSmithKilne, Merck Frosst Canada, Merck Sharp Dohme, Novartis and Schering-Plough, and holds an endowed chair in Respiratory Epidemiology jointly endowed by AstraZeneca and McMaster University. Anders Ottosson and Finn Radner are full-time employees at AstraZeneca R&D, Lund, Sweden. Samy Suissa has served as a consultant or advisory board member for AstraZeneca, Boehringer Ingelheim and GlaxoSmithKline.

AUTHORS CONTRIBUTIONS

Malcolm Sears reviewed the trial data, including details of all deaths, and was primarily responsible for writing the paper and for the medical content. Samy Suissa was responsible for the statistical and pharmacoepidemiological content. Anders Ottosson and Finn Radner were responsible for extraction, validation and analysis of data from the AstraZeneca trials. All authors read and approved the final manuscript.

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FIGURE 1. FLOW CHART OF ALL PATIENTS INVOLVED IN ASTRAZENECA TRIALS WITH FORMOTEROL

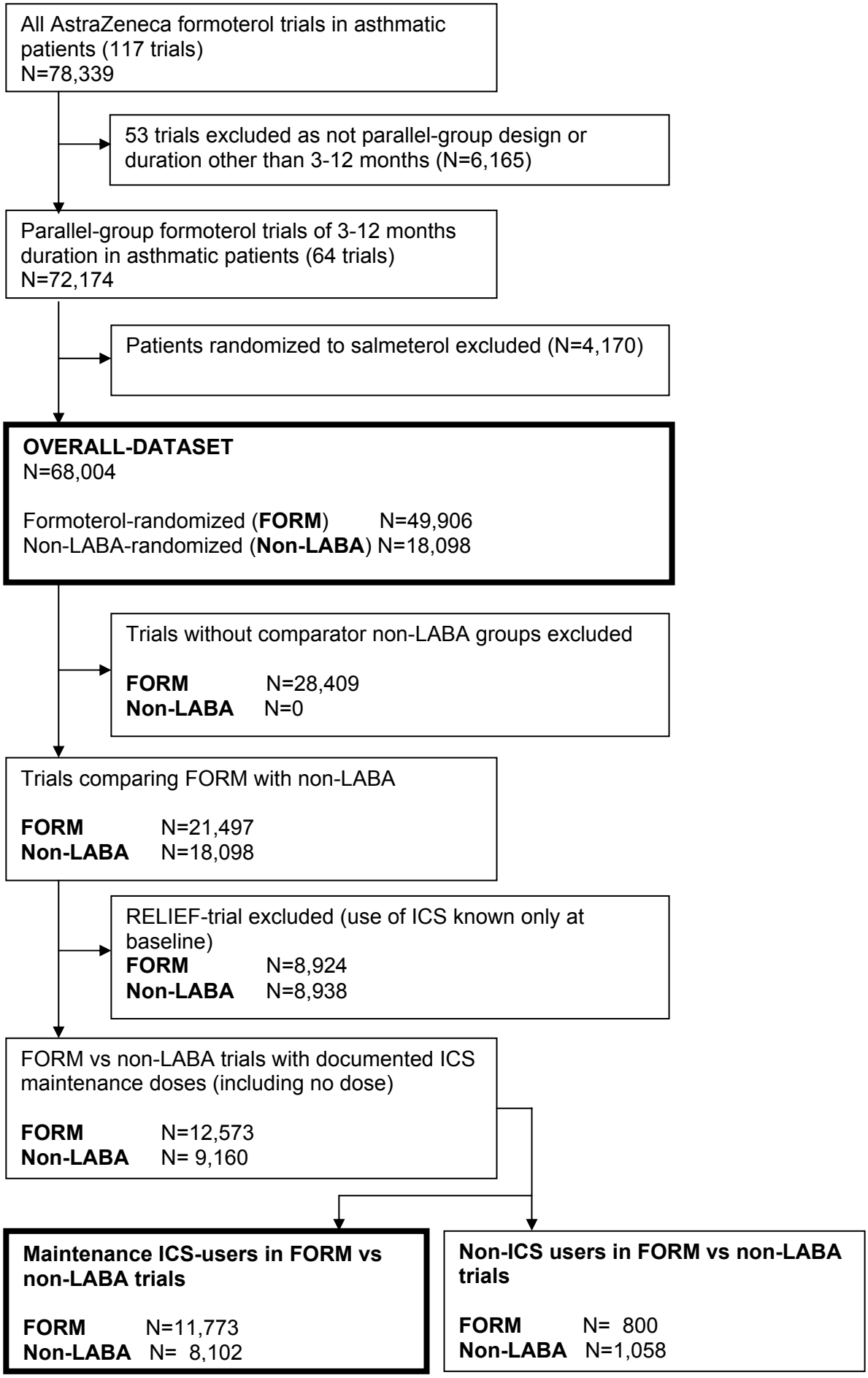

TABLE 1. RATES AND RATE RATIOS OF CAUSE-SPECIFIC DEATH ACROSS RANDOMIZED CONTROLLED TRIALS, STRATIFIED BY ANY ICS USE AT BASELINE

	Formoterol				No Formoterol				
	Patients (n)	Person years (1000)	Deaths	Rate per TTY	Patients (n)	Person-years (1000)	Deaths	Rate per TTY	Rate ratio (95%CI)*
Asthma-related death									
All subjects	49,906	23.6	8	0.34	18,098	9.2	2	0.22	1.57 (0.31-15.1)
With ICS	46,003	21.7	7	0.32	13,905	7.2	1	0.14	2.32 (0.30-105)
No ICS	3,903	1.9	1	0.54	4,193	2.1	1	0.48	1.13 (0.014-88)
Cardiac-related death									
All subjects	49,906	23.6	8	0.34	18,098	9.2	9†	0.97	0.35 (0.12-1.02)
With ICS	46,003	21.7	7	0.32	13,905	7.2	6	0.84	0.38 (0.11-1.39)
No ICS	3,903	1.9	1	0.54	4,193	2.1	3	1.44	0.38 (0.0071-4.7)
Other deaths									
All subjects	49,906	23.6	18	0.76	18,098	9.2	3	0.32	2.35 (0.69-12.5)
With ICS	46,003	21.7	17	0.78	13,905	7.2	2	0.28	2.82 (0.67-25)
No ICS	3,903	1.9	1	0.54	4,193	2.1	1	0.48	1.13 (0.014-88)
Total deaths									
All subjects	49,906	23.6	34	1.44	18,098	9.2	14	1.52	0.95 (0.50-1.92)
With ICS	46,003	21.7	31	1.43	13,905	7.2	9	1.26	1.14 (0.53-2.73)
No ICS	3,903	1.9	3	1.61	4,193	2.1	5	2.41	0.68 (0.11-3.47)

* Rate ratio and exact confidence intervals for asthma, cardiac ,"other" or any death (for formoterol vs. non-LABA) as calculated using StatXact 8.0.0 (Cytel® Inc., Cambridge, USA) [27].

† Two salbutamol as needed-randomized patients in the RELIEF study (SD-037-0699) 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 then exchanged medication with a formoterol-randomized patient and died 2 days later; the physician could not determine which drug was used before death. When applying a worst-case approach and re-assigning these two deaths to formoterol, the resulting 10 vs. 7 cardiac-deaths gives rates per TTY of 0.43 vs. 0.76 and a rate ratio (95% CI) for cardiac death of 0.56 (0.19-1.73) for formoterol vs. non-LABA.

ICS = inhaled corticosteroid; LABA = long-acting β_2-agonist; TTY = 1,000 treatment-years; SABA = short-acting β_2-agonist

TABLE 2 NUMBERS AND PERCENT OF ASTHMA-RELATED AND CARDIAC-RELATED SERIOUS ADVERSE EVENTS (SAEs) ACROSS RANDOMIZED CONTROLLED TRIALS, STRATIFIED BY ANY ICS USE AT BASELINE

	Formoterol				No Formoterol				
	Patients (n)	**Person-years (1000)**	**SAEs¤**	**%**	**Patients (n)**	**Person-years (1000)**	**SAEs**	**%**	**Rate ratio (95%CI)***
Asthma-related SAEs									
All subjects	49,906	23.6	374	0.75	18,098	9.2	199	1.10	0.68 (0.57-0.81)
With ICS	46,003	21.7	346	0.75	13,905	7.2	166	1.19	0.63 (0.52-0.76)
No ICS	3,903	1.9	28	0.72	4,193	2.1	33	0.79	0.91 (0.53-1.56)
Cardiac-related SAEs									
All subjects	49,906	23.6	103	0.21	18,098	9.2	45	0.25	0.83 (0.58-1.20)
With ICS	46,003	21.7	95	0.21	13,905	7.2	38	0.27	0.76 (0.51-1.13)
No ICS	3,903	1.9	8	0.20	4,193	2.1	7	0.17	1.23 (0.39-3.98)

¤ Number of patients reporting at least one non-fatal SAE

* Rate ratio and exact confidence intervals for the odds ratio for asthma-related and cardiac-related SAE (for formoterol vs. non-LABA) as calculated using StatXact 8.0.0 (Cytel® Inc., Cambridge, USA) [27].

ICS = inhaled corticosteroid; ITT = intention to treat; LABA = long-acting β_2-agonist; SABA = short-acting β_2-agonist; SAE = serious adverse event (defined using the International Conference on Harmonization recommendations)

TABLE 3. RATES AND RATE RATIOS OF CAUSE-SPECIFIC DEATHS AND SAEs ACROSS RANDOMIZED CONTROLLED TRIALS COMPARING FORMOTEROL WITH NON-LABA, STRATIFIED BY KNOWN MAINTENANCE ICS USE*

	Formoterol					No Formoterol					
	Patients	1000 person -years	Deaths or SAEs**	Death rate per TTY	% SAE	Patients	(1000 person -years)	Deaths or SAEs	Death rate per TTY	% SAE	Rate ratio (95%CI)***
Asthma-related death											
Maintenance ICS-users	11,773	6.2	3	0.48		8,102	4.4	0	0		+Inf (0.29-+inf)
Non-ICS users	800	0.4	0	0		1,058	0.6	0	0		-
Cardiac-related death											
Maintenance ICS-users	11,773	6.2	1	0.16		8,102	4.4	2	0.45		0.34 (0.058-6.61)
Non-ICS users	800	0.4	0	0		1,058	0.6	0	0		-
Asthma-related SAEs											
Maintenance ICS-users	11,773	6.2	76		0.65%	8,102	4.4	76		0.94%	0.69 (0.49-0.96)
Non-ICS users	800	0.4	3		0.38%	1,058	0.6	3		0.28%	1.32 (0.18-9.9)
Cardiac-related SAEs											
Maintenance ICS-users	11,773	6.2	21		0.18%	8,102	4.4	15		0.19%	0.96 (0.47-2.01)
Non-ICS users	800	0.4	1		0.13%	1,058	0.6	0		0	nc

* All trials except RELIEF (ICS treatment during the trial not recorded) and trials without a non-LABA comparator

** Number of patients reporting at least one non-fatal SAE

*** Rate ratio and exact confidence intervals as calculated using StatXact 8.0.0 (Cytel® Inc., Cambridge, USA) [27].

ICS = inhaled corticosteroid; LABA = long-acting β_2-agonist; TTY = 1,000 treatment-years; nc= not computable

TABLE 4. DETAILS OF ALL ASTHMA-RELATED DEATHS

Case no.	Randomized treatment	Study ref.	Duration[‡]	Daily dose of randomized treatment[*]	Age/sex/ race[†]	Number of days on randomized treatment	Days in study until onset/ Death[§]	Baseline LABA and/or ICS other than randomized treatment[‖]		Considered as ICS-exposed patient?	Cause of death
1	Formoterol	SD-037-0345/ 181/30801	365	9 μg FORM + 160 μg BUD	35/F/X	241**	213/247	x	x	Yes	Status asthmaticus; septic shock
2	Formoterol	SD-039-0673/ 448/1488	365	9/160 μg FORM/BUD plus TERB prn	65/F/O	299	300/300	x	x	Yes	Asthma
3	Formoterol	SD-039-0735/ 110/76	180	9/320 μg FORM/BUD plus FORM/BUD prn	55/M/C	159***	166/198	x	x	Yes	Respiratory failure
4	Formoterol	SD-037-0699/ 26069/261384	180	FORM prn	56/F/C	2[††]	2/2	SALM	FLUT	Yes	Asthma
5	Formoterol	SD-037-0699/ 45304/451773	180	FORM prn	43/F/O	69	69/69	–	BDP	Yes	Asthma
6	Formoterol	SD-037-0699/ 45218/451990	180	FORM prn	44/M/O	15	15/15	–	–	No	Asthma
7	Non-LABA	SD-037-0699/ 45224/452193	180	SALB prn	45/F/O	92	92/92	–	–	No	Asthma
8	Non-LABA	SD-037-0699/ 71029/710030	180	SALB prn	18/M/C	91	91/91	–	BDP	Yes	Asthma
9	Formoterol	SD-037-0003/ 34/3403	90	18 μg FORM	13/M/C	26	26/26	x	BDP	Yes	Respiratory failure
10	Formoterol	AD-039-0001/ 9199/919901	180	9/160 μg FORM/BUD	67/F/C	28	28/31	x	x	Yes	Asthma

* Randomized treatment: BUD = budesonide; FLUT = fluticasone; FORM = formoterol; prn = as needed; SALB = salbutamol; TERB = terbutaline.
† Sex: M = male; F = female. Race: C = Caucasian; O = Oriental; X = Other (other than Caucasian, Oriental and Black).
‡ Duration in days from clinical study protocol.
§ Days from first day of randomized treatment to day of onset of event leading to death/day of death.
‖ Medications taken in addition to the study drug as maintenance therapy: BDP = beclomethasone dipropionate; FLUT = fluticasone; SALM = salmeterol; – = none reported; x = none allowed.
** The patient developed pneumonia and septic shock during a hospital admission for asthma. Probable immediate cause of death was septic shock.
*** The patient was hozpitalized for asthma, discontunued the trial on day 159, remained at the hospital, developed respiratory insuffiency which progressed into respiratory failure with fatal outcome
†† The patient was randomized on day of a severe asthma attack and took one dose of formoterol in the evening. Death was pronounced the following evening.

TABLE 5. NON-FATAL ASTHMA-RELATED SERIOUS ADVERSE EVENTS BY AGE, SEX AND ETHNICITY (OVERALL DATASET)

	Number (%) of patients reporting at least one asthma-related non-fatal SAE											
	Formoterol-containing products				Non-LABA-containing products				Total			
Age group (years)												
4–11	39	of	3,264	1.2%	25	of	2,165	1.2%	64	of	5,429	1.2%
12–17	24	of	4,556	0.5%	17	of	1,889	0.9%	41	of	6,445	0.6%
18–64	270	of	37,882	0.7%	136	of	12,596	1.1%	404	of	50,478	0.8%
>65	43	of	4,162	1.0%	21	of	1,448	1.5%	64	of	5,610	1.1%
Unknown	0	of	42	0.0%	0	of	0	0.0%	0	of	42	0.0%
Sex												
Male	146	of	22,057	0.7%	72	of	8,068	0.9%	218	of	30,125	0.7%
Female	228	of	27,800	0.8%	127	of	10,030	1.3%	355	of	37,830	0.9%
Unknown	0	of	49	0.0%	0	of	0	0.0%	0	of	49	0.0%
Ethnicity												
Caucasian	268	of	39,868	0.7%	123	of	14,818	0.8%	391	of	54,686	0.7%
Black	8	of	861	0.9%	3	of	328	0.9%	11	of	1,189	0.9%
Oriental	70	of	4,065	1.7%	53	of	1,916	2.8%	123	of	5,981	2.1%
Other	25	of	2,170	1.2%	20	of	1,036	1.9%	45	of	3,206	1.4%
Unknown	3	of	2,942	0.1%	0	of	0	0.0%	3	of	2,942	0.1%
Total	374	of	49,906	0.7%	199	of	18,098	1.1%	573	of	68,004	0.8%

LABA = long-acting β_2-agonist; SAE = serious adverse event (defined using the International Conference on Harmonization recommendations)

TABLE 6. NUMBER OF NON-FATAL ASTHMA-RELATED SERIOUS ADVERSE EVENTS BY DAILY DOSE OF FORMOTEROL (OVERALL DATASET)

Daily dose of formoterol	Patients, n	Mean duration, days	Number (%) of patients reporting at least one asthma-related non-fatal SAE	
9 µg*	5,306	218	57	1.07%
18 µg	15,923	131	92	0.58%
36 µg	909	239	4	0.44%
As-needed use or adjustable dosing	27,768	185	221	0.80%
Total – all trials combined	49,906	173	374	0.75%

* Includes the children who received 80/4.5 µg once daily + terbutaline as-needed in trial SD-039-0673.

SAE = serious adverse event (defined using the International Conference on Harmonization recommendations)

TABLE 7. EVENT RATES IN ADDITIONAL SUBGROUPS

	Formoterol								
	Patients (n)	**Person years** (1000)	Deaths	Rate per TTY	SAEs*	Percent SAEs	**Patients** (n)	**Person years** (1000)	De
Trials without non-LABA comparator groups									
Asthma-related events	28,409	12,7	2	0.16	189	0.67%	-		
Cardiac-related events	28,409	12,7	1	0.08	61	0.21%	-		
Other deaths	28,409	12,7	9	0.71	-	-	-		
Total deaths	28,409	12,7	12	0.94	-	-	-		
RELIEF trial, overall results									
Asthma-related events	8,924	4.3	3	0.70	106	1.19%	8,938	4.3	
Cardiac-related events	8,924	4.3	6	1.40	20	0.22%	8,938	4.3	
Other deaths	8,924	4.3	4	0.93	-	-	8,938	4.3	
Total deaths	8,924	4.3	13	3.02	-	-	8,938	4.3	
RELIEF trial, ICS-users at baseline									
Asthma-related events	5,821	2.8	2	0.72	81	1.39%	5,803	2.8	
Cardiac-related events	5,821	2.8	5	1.80	13	0.22%	5,803	2.8	
Other deaths	5,821	2.8	3	1.08	-	-	5,803	2.8	
Total deaths	5,821	2.8	10	3.60	-	-	5,803	2.8	
RELIEF trial, non- ICS-users at baseline									
Asthma-related events	3,103	1.5	1	0.67	25	0.81%	3,135	1.5	
Cardiac-related events	3,103	1.5	1	0.67	7	0.23%	3,135	1.5	
Other deaths	3,103	1.5	1	0.67	-	-	3,135	1.5	
Total deaths	3,103	1.5	3	2.03	-	-	3,135	1.5	

* Number of patients reporting at least one non-fatal SAE

SAE = serious adverse event (defined using the International Conference on Harmonization recommendations)