

# Meta-analysis: Effects of Adding Salmeterol to Inhaled Corticosteroids on Serious Asthma-Related Events

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**Background:** Recent analyses have suggested an increased risk for serious asthma-related adverse events in patients receiving long-acting  $\beta$ -agonists.

**Purpose:** To examine whether the incidences of severe asthma-related events (hospitalizations, intubations, deaths, and severe exacerbations) differ in persons receiving salmeterol plus inhaled corticosteroids compared with inhaled corticosteroids alone.

**Data Sources:** The GlaxoSmithKline (Research Triangle Park, North Carolina) database, MEDLINE, EMBASE, CINAHL, and the Cochrane Database of Systemic Reviews (1982 to September 2007) were searched without language restriction.

**Study Selection:** Randomized, controlled trials reported in any language that compared inhaled corticosteroids plus salmeterol (administered as fluticasone propionate/salmeterol by means of a single device or concomitant administration of inhaled corticosteroids and salmeterol) versus inhaled corticosteroids alone in participants with asthma.

**Data Extraction:** Three physicians independently reviewed and adjudicated blinded case narratives on serious adverse events that were reported in the GlaxoSmithKline trials.

**Data Synthesis:** Data from 66 GlaxoSmithKline trials involving a total of 20 966 participants with persistent asthma were summa-

rized quantitatively. The summary risk difference for asthma-related hospitalizations from these trials was 0.0002 (95% CI,  $-0.0019$  to  $0.00231$ ;  $P = 0.84$ ) for participants receiving inhaled corticosteroids plus salmeterol ( $n = 35$  events) versus those receiving inhaled corticosteroids alone ( $n = 34$  events). One asthma-related intubation and 1 asthma-related death occurred among participants receiving inhaled corticosteroids with salmeterol; no such events occurred among participants receiving inhaled corticosteroids alone. A subset of 24 trials showed a decreased risk for severe asthma-related exacerbations for inhaled corticosteroids plus salmeterol versus inhaled corticosteroids alone (risk difference,  $-0.025$  [CI,  $-0.036$  to  $-0.014$ ];  $P < 0.001$ ).

**Limitations:** The included trials involved selected patients who received careful follow-up. Only 26 trials were longer than 12 weeks. Few deaths and intubations limited the ability to measure risk for these outcomes.

**Conclusion:** Salmeterol combined with inhaled corticosteroids decreases the risk for severe exacerbations, does not seem to alter the risk for asthma-related hospitalizations, and may not alter the risk for asthma-related deaths or intubations compared with inhaled corticosteroids alone.

*Ann Intern Med.* 2008;149:33-42.

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Asthma is a chronic disease affecting nearly 20 million people in the United States and approximately 300 million people worldwide (1). In response to the growing burden of uncontrolled asthma, evidence-based guidelines were released in the early 1990s to bridge the gap between research and practice, with the objective of improving management. National and international asthma guidelines recommend that all patients with persistent asthma receive regular treatment with anti-inflammatory medication, preferably an inhaled corticosteroid. For patients whose asthma is not controlled by inhaled corticosteroids alone, guidelines recommend adding a long-acting  $\beta$ -agonist (1, 2).

Recently, concern about the role of long-acting  $\beta$ -agonists in asthma management was raised in a randomized, observational study of more than 26 000 patients (3). In this study, salmeterol compared with placebo added to usual therapy showed a small but statistically significant increase in severe asthma-related events, including asthma-related death. In contrast, the largest case-controlled study to date of 532 asthma deaths (4) concluded that use of long-acting  $\beta$ -agonists was not associated with increased risk for asthma-related death compared with other therapies. The Cochrane Airways Group has published several meta-analyses of clinical trials that studied the combination of inhaled corticosteroids and long-acting  $\beta_2$ -agonists and

concluded that exacerbations of asthma were infrequent and occurred at similar or lower rates in participants receiving concurrent long-acting  $\beta$ -agonists and inhaled corticosteroids than in those receiving inhaled corticosteroids alone (5–7).

Salpeter and colleagues (8) performed a meta-analysis examining life-threatening or fatal asthma exacerbations in participants using long-acting  $\beta$ -agonists. Approximately 50% of the participants did not receive concurrent inhaled corticosteroid therapy, and the results showed that, although rare, asthma-related hospitalization and death oc-

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**Context**

Guidelines recommend adding long-acting  $\beta$ -agonists to regimens of patients with asthma that is not controlled on inhaled corticosteroids alone. Is this safe?

**Contribution**

This meta-analysis summarizes 66 GlaxoSmithKline trials involving 20 966 patients with persistent asthma. Trials compared twice-daily salmeterol, 50  $\mu\text{g}$ , plus inhaled corticosteroids with inhaled corticosteroids alone. Combination therapy did not appear to alter risk for asthma-related hospitalizations but did decrease risk for severe exacerbations requiring systemic corticosteroids. The only cases of asthma-related death and intubation occurred in patients receiving combination therapy.

**Caution**

Most trials were short and originally designed to assess lung function rather than clinical outcomes.

—The Editors

occurred more frequently in participants receiving long-acting  $\beta$ -agonists than in those receiving placebo.

Because asthma guidelines clearly state that long-acting  $\beta$ -agonists should be taken concurrently with inhaled corticosteroids (1, 2), we conducted a meta-analysis of published and unpublished GlaxoSmithKline trials that evaluated use of salmeterol and inhaled corticosteroids compared with inhaled corticosteroid monotherapy alone.

**METHODS****Data Sources and Searches**

We reviewed all studies posted as of September 2007 to the GlaxoSmithKline Clinical Trials Registry (<http://ctr.gsk.co.uk/welcome.asp>) for the following GlaxoSmithKline drugs: fluticasone propionate/salmeterol (Advair), salmeterol xinafoate (Serevent), and fluticasone propionate (Flovent). This registry is a repository of data from GlaxoSmithKline-sponsored clinical trials. We also searched MEDLINE, EMBASE, CINAHL, and the Cochrane Database of Systematic Reviews from 1982 to September 2007. These searches were not restricted to studies published in English. Terms included *salmeterol*,  *$\beta$ -agonist*, *long-acting  $\beta$ -agonist*, *inhaled corticosteroids*, *fluticasone propionate*, *budesonide*, *triamcinolone acetonide*, *beclomethasone dipropionate*, *randomized*, *controlled clinical trial*, *asthma*, *Advair*, and *Seretide*. Finally, we supplemented these searches by reviewing references from published reviews.

**Study Selection**

Three reviewers perused the GlaxoSmithKline registry and search outputs (titles and abstracts) to identify randomized, controlled trials that compared the use of inhaled corticosteroids plus salmeterol with inhaled corticosteroids alone in patients with asthma. We selected randomized, dou-

ble-blind, parallel-design, long-term dosing studies (range, 1 to 52 weeks) that used the approved dosage of salmeterol (50  $\mu\text{g}$  twice daily) in the United States and had been completed and analyzed by 30 September 2007. We did not exclude any trials on the basis of language. We excluded uncontrolled, open-label studies; single-dose studies; and crossover studies.

**Data Extraction and Quality Assessment**

One reviewer extracted information about participants, interventions, and comparisons from trials in the GlaxoSmithKline database, registry, or publications, and a second reviewer double-checked this information. One reviewer extracted information about trials that were not sponsored by GlaxoSmithKline.

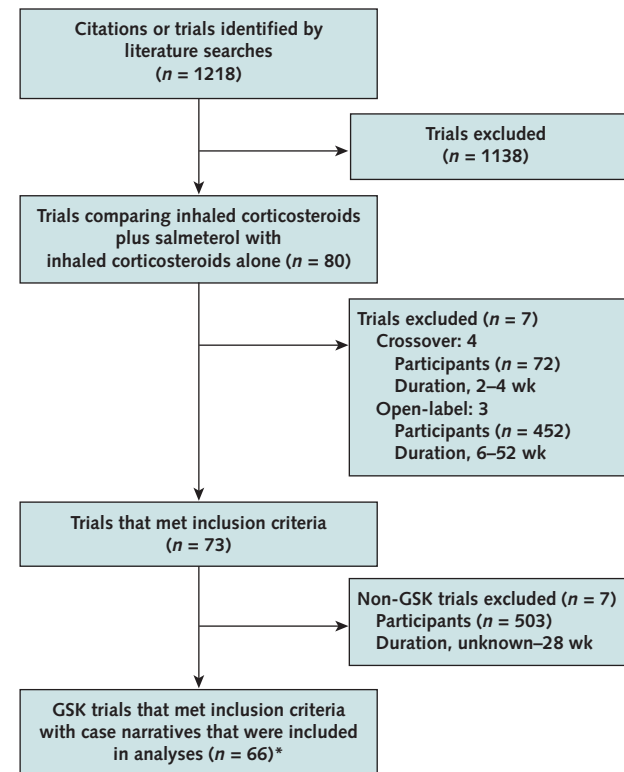
We did not use a specific checklist or scale to assess the quality of the trials: Protocols for the GlaxoSmithKline trials met the International Conference on Harmonisation guidelines. For these trials, a participant could spontaneously report adverse events. Study personnel solicited these participants by regular interviews and asked standardized, open-ended questions about any changes in their health status. The interval for these interviews was defined by the individual protocols but generally did not exceed 4 weeks. All GlaxoSmithKline trials report case narratives of serious adverse events, which include hospitalization, intubation, or death.

We sent case narratives of reported serious adverse events that occurred during the randomized, double-blind phase of the GlaxoSmithKline trials to 3 physicians. These physicians, who were blinded to drug assignment in each case, independently reviewed the narratives and adjudicated the asthma relationship for hospitalization, intubation, and death status of each case. Any disagreements about adjudications were resolved through consensus of the 3 physicians.

**Statistical Analysis**

We used 2 methods to pool GlaxoSmithKline data on asthma-related hospitalizations and severe asthma-related exacerbations that required systemic corticosteroids. First, we calculated risk differences by using data from GlaxoSmithKline trials that met inclusion criteria (even those without events). We applied a treatment group continuity correction for trials in which at least 1 of the treatment groups had no events. In sensitivity analyses, we used 0.01, 0.001, and 0.0001 continuity corrections (9). Second, we used the Peto odds ratio method, which excludes trials with no events and performs reasonably well when imbalance in trial group size is low, the rate of events is low ( $\leq 1\%$ ), and the effect size is small (10, 11). For all estimates, we calculated 95% CIs (12, 13). We used the Cochran  $Q$  test and  $I^2$  to evaluate statistical heterogeneity. All analyses were based on fixed-effects models and were conducted with StatsDirect statistical software, version 2.6.6 (Sale, United Kingdom) (14).

Figure 1. Study flow diagram.



GSK = GlaxoSmithKline.

\*Studies could contribute to more than 1 subanalysis.

### Role of the Funding Source

GlaxoSmithKline sponsored most trials summarized in this review. GlaxoSmithKline also supported data collection, analyses, manuscript preparation, and data interpretation for the review. All authors approved the manuscript for submission.

## RESULTS

Of 1218 reports identified in the combined searches, we found 80 randomized trials that compared salmeterol plus inhaled corticosteroids with inhaled corticosteroids alone (Figure 1). Of these, we excluded 4 short crossover trials that involved a total of 72 participants and 3 open-label trials that included 452 participants. None of the 7 excluded trials reported any asthma-related deaths, intubations, or hospitalizations. One trial (SLGT26) included in the current analysis had 3 groups. We excluded the group that involved 244 participants who were assigned to a dose of salmeterol (100  $\mu$ g twice daily) that exceeded the current recommendation. There were 3 asthma-related hospitalizations but no deaths in this excluded treatment group.

### Trial Characteristics

Seven trials that were not sponsored by GlaxoSmithKline met eligibility criteria. These trials involved a total of

503 participants (15–21). None reported hospitalization, intubation, or death in a participant receiving salmeterol plus inhaled corticosteroids or inhaled corticosteroids alone. Because we did not have access to individual case narratives of adverse events in these trials, we did not include them in the quantitative analyses.

The GlaxoSmithKline registry included 66 eligible trials that involved a total of 20 966 participants (Appendix Table 1, available at [www.annals.org](http://www.annals.org)). In these trials, 10 400 participants received inhaled corticosteroids plus salmeterol and 10 566 received inhaled corticosteroids alone. The median trial duration was 12 weeks (range, 1 to 52 weeks). Sample sizes ranged from 12 to 3416. The mean age of participants was about 38 years. Forty-four percent were men, and 82% were white. Most had moderate to severe persistent asthma. The overall rate of withdrawal for any reason was about 14% among participants receiving inhaled corticosteroids plus salmeterol and about 17% among those receiving inhaled corticosteroids alone.

Most trials used a lung function measure (FEV<sub>1</sub> or peak expiratory flow) as the primary end point. In a few studies, the primary end point was a measure of asthma control, such as exacerbations or symptoms. The largest study (SAM40027) used a composite measure of asthma control that integrated lung function measures as well as symptom control and exacerbations as the primary end point.

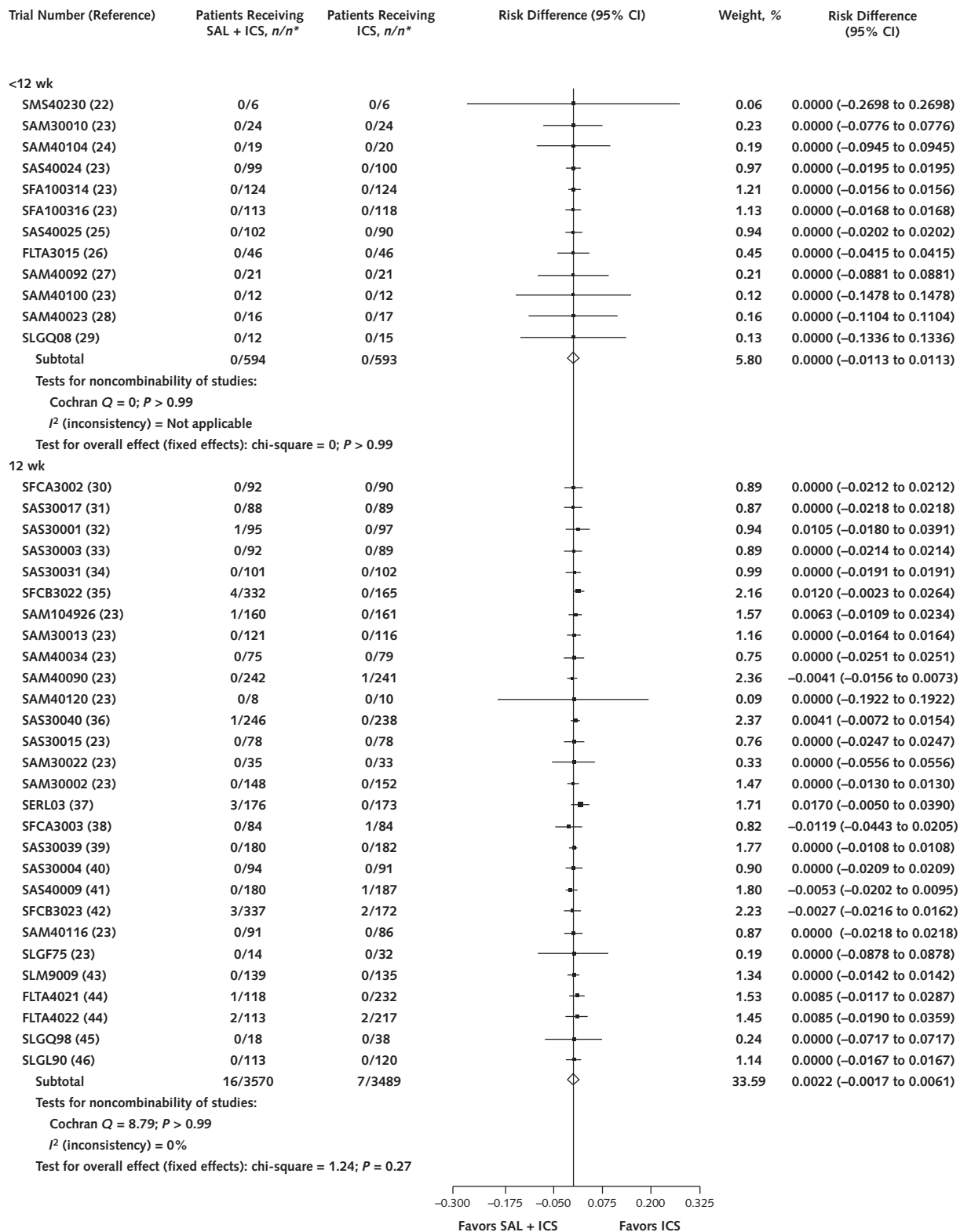
### Asthma-Related Hospitalizations

Overall, 35 and 34 events occurred among participants receiving an inhaled corticosteroid plus salmeterol or an inhaled corticosteroid alone, respectively. In 40 of the 66 trials, no asthma-related hospitalizations occurred. The summary risk difference for asthma-related hospitalization attributed to inhaled corticosteroids plus salmeterol versus inhaled corticosteroids alone was 0.0002 (95% CI, -0.0019 to 0.0023;  $P = 0.84$ ) (Figures 2 and 3). Sensitivity analyses with different continuity corrections yielded similar results and conclusions (Appendix Table 2, available at [www.annals.org](http://www.annals.org)). The summary odds ratio for asthma-related hospitalization was 1.07 (CI, 0.66 to 1.73;  $P = 0.79$ ) for inhaled corticosteroids plus salmeterol (in a single device or 2 separate devices) compared with inhaled corticosteroids alone.

### Asthma-Related Intubations

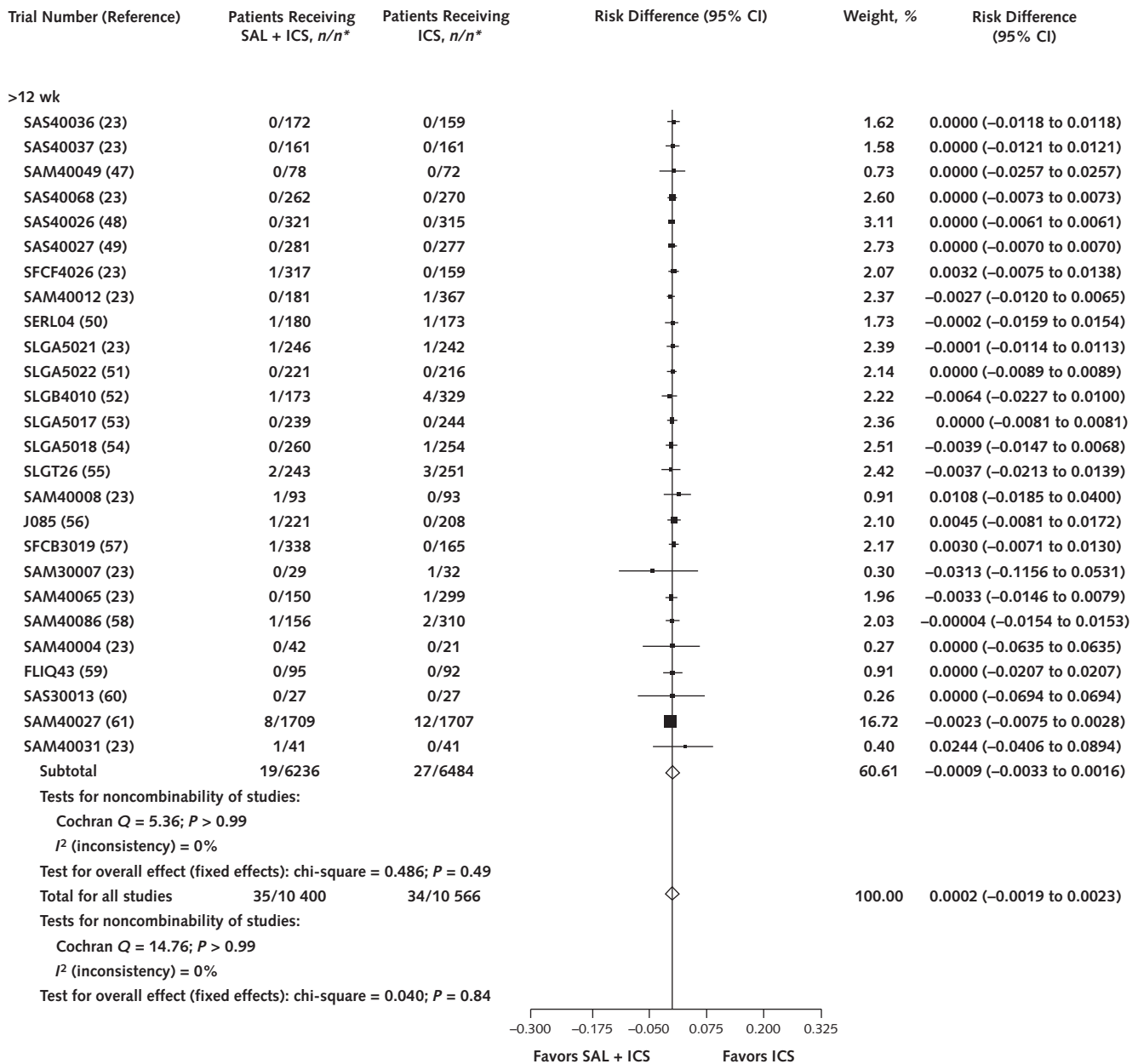
One event occurred in a participant receiving blinded treatment with beclomethasone dipropionate plus salmeterol. A 24-year-old woman had worsening asthma 6 days after beginning treatment with beclomethasone dipropionate plus salmeterol. She was also receiving concurrent treatment with inhaled open-label beclomethasone dipropionate and theophylline. She presented to the emergency department 4 hours after onset of symptoms. She was intubated and ventilated and treated with intravenous steroids, theophylline, and

Figure 2. Salmeterol (SAL) plus inhaled corticosteroids (ICS) versus ICS alone: risk difference for asthma-related hospitalization.



\*Number of events/total population.

Figure 2—Continued



albuterol. She was successfully extubated the following day, and the event fully resolved.

### Asthma-Related Deaths

One asthma-related death occurred while a participant was receiving blinded study treatment. Approximately 3 months after beginning study treatment with inhaled salmeterol, 50  $\mu\text{g}$  twice daily, and inhaled fluticasone propionate, 250  $\mu\text{g}$  twice daily (by means of separate devices), a 25-year-old man was admitted to the hospital in respiratory arrest. The patient was cyanotic and asystolic, and cardiopulmonary resuscitation was in progress on arrival at the hospital. Aspirated stomach content was suctioned

from the lungs. He was given atropine and adrenaline but died shortly after admission. An autopsy confirmed that the cause of death was anoxia secondary to status asthmaticus and pneumothorax.

Six deaths (all-cause) among participants receiving inhaled corticosteroids plus salmeterol (4 using a single device and 2 using separate devices) and 6 deaths (all-cause) among participants receiving inhaled corticosteroids alone (1 receiving triamcinolone and 5 receiving fluticasone propionate) occurred. The death described in the previous paragraph was the 1 person among the 6 participants who received inhaled corticosteroids plus salmeterol.

**Table. Severe Asthma Exacerbations Requiring Systemic Corticosteroids\***

| Drug   | Patients, n | Patients with an Exacerbation, n (%) | Risk Difference (95% CI)  | P Value | Peto Odds Ratio (95% CI) | P Value |
|--|-------------|--------------------------------------|---------------------------|---------|--------------------------|---------|
| Salmeterol + inhaled corticosteroids (by means of a single or separate device) | 3541        | 175 (4.9)                            | -0.025 (-0.036 to -0.014) | <0.001  | 0.65 (0.54 to 0.79)      | <0.001  |
| Inhaled corticosteroids  | 4008        | 334 (8.3)                            |                           |         |                          |         |
| Salmeterol + fluticasone propionate (by means of a single device)              | 2298        | 67 (2.9)                             | -0.012 (-0.023 to -0.002) | 0.025   | 0.71 (0.53 to 0.96)      | 0.026   |
| Inhaled corticosteroids  | 2556        | 144 (5.6)                            |                           |         |                          |         |
| Salmeterol + inhaled corticosteroids (by means of a separate device)           | 1243        | 108 (8.7)                            | -0.048 (-0.071 to -0.024) | <0.001  | 0.61 (0.48 to 0.78)      | <0.001  |
| Inhaled corticosteroids  | 1452        | 190 (13.1)                           |                           |         |                          |         |

\*Results from 24 studies reporting severe exacerbations.

### Subgroup Analyses of Asthma-Related Hospitalizations

Six trials involved children (*n* = 1575) age 4 to 17 years. Two participants (1 in each treatment group) had an asthma-related hospitalization.

Twelve trials were less than 12 weeks in duration, 28 were 12 weeks in duration, and 26 were more than 12 weeks in duration. No asthma-related hospitalizations in either treatment group occurred in studies less than 12 weeks in duration (*n* = 1187 participants). Sixteen events among participants receiving inhaled corticosteroids plus salmeterol and 7 events among participants receiving inhaled corticosteroids alone occurred in studies that were 12 weeks in duration (*n* = 7059 participants). Nineteen events among participants receiving inhaled corticosteroids plus salmeterol and 27 events among participants receiving inhaled corticosteroids alone occurred (*n* = 12 720 participants) in studies longer than 12 weeks.

Forty-one trials involving a total of 11 859 participants used a similar dose of inhaled corticosteroids in the groups that received inhaled corticosteroids plus salmeterol and that received inhaled corticosteroids alone. In these trials, 22 events occurred in the group receiving inhaled corticosteroids plus salmeterol and 21 events occurred in the group receiving a similar dose of inhaled corticosteroids alone. Thirty-one trials involving 9696 participants compared a higher dose (generally a double dose) of inhaled corticosteroids alone with salmeterol plus corticosteroids. In these trials, 14 events occurred in the group receiving inhaled corticosteroids plus salmeterol and 13 events occurred in the group receiving the higher dose of inhaled corticosteroids alone.

Studies were also grouped by fluticasone propionate plus salmeterol administered in a single device versus inhaled corticosteroids alone (49 trials and 15 995 participants) and by inhaled corticosteroids plus salmeterol administered in separate devices compared with inhaled corticosteroids alone (18 trials and 5136 participants). Twenty-six events occurred in the group receiving fluticasone propionate plus salmeterol in a single device compared with 23 for the group receiving inhaled corticoste-

roids alone. There were 9 events among participants receiving inhaled corticosteroids plus salmeterol with separate devices and 11 events among participants receiving inhaled corticosteroids alone.

### Severe Asthma-Related Exacerbations

Twenty-four trials conducted in the United States involving 7549 participants provided information on the number of severe asthma exacerbations that required systemic corticosteroids (Table). The summary risk difference for a severe asthma-related exacerbation for inhaled corticosteroids plus salmeterol in a single or separate device versus inhaled corticosteroids alone was -0.025 (CI, -0.036 to -0.014; *P* < 0.001). Risk differences for comparisons of delivery of corticosteroids and salmeterol by means of single or separate devices were similar.

### DISCUSSION

These results, derived primarily from 66 GlaxoSmith-Kline trials in 20 966 participants, suggest that the addition of salmeterol to inhaled corticosteroids does not alter the risk for asthma-related hospitalization compared with inhaled corticosteroids alone. Furthermore, addition of salmeterol may not alter the risk for asthma-related intubation and death in patients with moderate to severe persistent asthma; however, with only 2 intubation or death events, it is difficult to draw firm conclusions. The risk difference for asthma-related hospitalization attributed to inhaled corticosteroids plus salmeterol compared with inhaled corticosteroids alone was within the range of 19 of 10 000 patients, having some benefit for 23 of 10 000 patients at risk. Therapy with salmeterol plus inhaled corticosteroids prevented some severe asthma exacerbations: About 5% of participants receiving salmeterol plus inhaled corticosteroid had a severe exacerbation requiring systemic steroids compared with about 8% of participants receiving inhaled corticosteroids alone. Furthermore, only 1 asthma-related death and 1 asthma-related intubation were seen in 20 966 participants. The low incidence of hospitalizations and intubations is reassuring because hospital admission is

a recognized risk factor for asthma mortality and an important cause of severe morbidity (54–56).

The Cochrane Airways Group has reported 3 separate meta-analyses for studies including participants receiving inhaled corticosteroids plus long-acting  $\beta$ -agonists compared with those receiving inhaled corticosteroids alone. Two meta-analyses showed that asthma exacerbations were infrequent and occurred at a similar rate between the comparison treatment groups (5, 6). The most recent review reported fewer major exacerbations in participants receiving long-acting  $\beta$ -agonists compared with placebo with or without the presence of inhaled corticosteroids (odds ratio = 0.73 [CI, 0.64 to 0.84]) (7). Additional meta-analyses by Masoli and colleagues (65) and Shrewsbury and colleagues (66) reported fewer exacerbations for participants receiving inhaled corticosteroids plus salmeterol compared with higher doses of inhaled corticosteroids alone. Our analysis, which is larger than these previously published meta-analyses, confirms that treatment with long-acting  $\beta$ -agonists and inhaled corticosteroids, compared with inhaled corticosteroids alone, decreases risk for some severe exacerbations but may not alter the risk for asthma-related hospitalization, intubation, or death.

Other studies have reported disparate findings on the use of long-acting  $\beta$ -agonists and the incidence of asthma-related exacerbations, hospitalizations, and death. The Salmeterol Multicenter Asthma Research Trial (SMART) showed an increased number of asthma deaths and life-threatening experiences associated with the use of long-acting  $\beta$ -agonists (3). In addition, recent meta-analyses by Salpeter and colleagues (8) (of which SMART comprised 80% of the weight) reported that use of long-acting  $\beta$ -agonists compared with placebo resulted in a higher incidence of asthma-related, life-threatening exacerbations or deaths (8). In SMART, patients had to have a diagnosis of asthma. Baseline peak flow without withholding bronchodilators was 84% of predicted. In the current meta-analysis, all participants had to have a diagnosis of asthma without coexistent lung disease, such as chronic obstructive pulmonary disease, and a mean baseline percentage of predicted FEV<sub>1</sub> of approximately 70% after withholding bronchodilators. Perhaps a more important differentiator between our meta-analysis and the meta-analyses by Salpeter and colleagues (8), including SMART, is that the studies in their analysis did not require use of inhaled corticosteroids as a study treatment; as a result, only about half of the participants in these studies reported using inhaled corticosteroids.

It is important to understand the role of inhaled corticosteroids in trials with long-acting  $\beta$ -agonists. For example, 16 asthma-related deaths were reported in SMART. For patients receiving salmeterol or placebo without reported baseline use of inhaled corticosteroids, 9 and 0 asthma-related deaths were reported, respectively. In contrast, for patients reporting use of inhaled corticosteroids at baseline, 4 and 3 asthma-related deaths occurred in the salme-

terol and placebo groups, respectively. The results from the analysis by Salpeter and colleagues (8) are heavily influenced by the outcomes for patients receiving long-acting  $\beta$ -agonists without concurrent inhaled corticosteroids and subsequently influenced the authors' speculation: 4000 of 5000 theoretical asthma deaths in the United States would be due to the use of long-acting  $\beta$ -agonists. However, national statistics reported by the Centers for Disease Control and Prevention on asthma deaths and the reported use of long-acting  $\beta$ -agonist-containing products do not support this estimate. In fact, the number of asthma-related deaths has declined steadily since 1996 in the United States since salmeterol (1994) and then salmeterol plus fluticasone propionate in a single device (2001) have been available (67, 68).

In addition, retrospective observational studies using large administrative medical and pharmacy claims databases have shown that clinical outcomes (albuterol use and asthma-related emergency department visits or hospitalizations) and adherence to inhaled corticosteroids are improved when inhaled corticosteroids and long-acting  $\beta$ -agonists are administered in 1 device compared with inhaled corticosteroids and long-acting  $\beta$ -agonists in separate devices or with inhaled corticosteroids alone (69–73). Our meta-analysis, the independent Cochrane meta-analyses, and observational studies all support the premise that inhaled corticosteroid use mitigates the risk for untoward asthma-related events that may be associated with use of long-acting  $\beta$ -agonists.

Epidemiologic studies provide an alternative methodology to randomized, controlled trials to characterize rare safety events. Studies involving more than 68 000 participants across 7 observational studies designed to explore serious respiratory and asthma-related events have not shown an association between salmeterol use and serious asthma events, including death (4, 74–79). Of these, the most comprehensive was a population-based study that evaluated salmeterol use and risk for asthma death (4). Anderson and colleagues (4) evaluated a sample (532 asthma deaths; age <71 years) with date-, age-, and geographic area-matched control participants with a hospital admission for acute asthma. Recent or past use of salmeterol was not associated with an increased risk for asthma death. Furthermore, in a sensitivity analysis restricted to participants with more severe disease (122 pairs), defined as case-patients and matched-control participants with at least 1 hospital admission due to asthma in the year before the index date, salmeterol use was not associated with an increased risk for asthma death.

The clinical trials included in our meta-analysis represent all studies conducted by GlaxoSmithKline comparing inhaled corticosteroids plus salmeterol with similar-dose or higher-dose inhaled corticosteroids alone. Our meta-analysis is unique because of the unrestricted access to case narratives for all events. In contrast, independent researchers conducting meta-analyses generally extract data from

public sources. However, not all clinical studies are published in peer-reviewed public sources, and information for all serious adverse events in published sources may be abbreviated. As a result of the unrestricted access, accounting for all asthma-related hospitalizations is complete. The paucity of asthma-related deaths or intubations limits the ability to fully characterize these outcomes, but the scarcity of these severe outcomes is reassuring.

Inclusion in our meta-analysis is limited to studies conducted by GlaxoSmithKline. Generalizability may be limited because the randomized, controlled clinical trials involved selected participants who received careful follow-up. However, the number of participants providing data for severe asthma-related events and asthma-related hospitalizations for the treatments of interest is greater than any previous meta-analysis reported to date (to our knowledge). Furthermore, the studies are not limited to specific geographic or ethnic groups because nearly 40% of the studies are from the United States, but the remainder are from other countries worldwide. In our analysis, only 26 trials were longer than 12 weeks. The inclusion of shorter-term studies may limit the ability to detect untoward changes if longer-term use of the medications is needed before serious asthma-related outcomes manifest due to either an unknown pharmacologic mechanism or changes in patient behaviors and subsequent medication misuse. However, review of events from longer-term studies, some up to 1 year, did not show an increase in events for participants receiving long-acting  $\beta$ -agonists plus inhaled corticosteroids compared with inhaled corticosteroids alone. In addition, the only asthma-related intubation occurred within 1 week of initiating study treatment, and the only death occurred after less than 12 weeks of treatment. Thus, if we had limited this analysis to longer-term studies, we would have omitted reporting these 2 events.

In summary, we found that the use of salmeterol combined with inhaled corticosteroids does not alter the risk for asthma-related hospitalizations, may not affect risk for asthma-related deaths or asthma-related intubations, and reduces the risk for severe asthma exacerbations when compared with inhaled corticosteroids alone in patients with persistent asthma. This analysis involving 20 966 participants provides reassuring safety data about the use of salmeterol combined with inhaled corticosteroids and supports national and international asthma treatment guidelines, which recommend that long-acting  $\beta$ -agonists always be used with concurrent inhaled corticosteroids.

From University of Cape Town, Cape Town, South Africa; National Jewish Medical and Research Center, Denver, Colorado; Hôpital Arnaud de Villeneuve, Montpellier, France; and GlaxoSmithKline, Research Triangle Park, North Carolina.

**Note:** Drs. Bateman, Nelson, and Bousquet did the blinded adjudication of serious adverse events in this analysis.

**Grant Support:** By GlaxoSmithKline.

**Potential Financial Conflicts of Interest:** *Employment:* K. Kral (GlaxoSmithKline), L. Sutton (GlaxoSmithKline), H. Ortega (GlaxoSmithKline), S. Yancey (GlaxoSmithKline). *Consultancies:* E. Bateman (Roche, Almirall, GlaxoSmithKline, AstraZeneca, Merck, Boehringer Ingelheim, Pfizer, Altana), H. Nelson (GlaxoSmithKline), J. Bousquet (GlaxoSmithKline). *Honoraria:* E. Bateman (GlaxoSmithKline, Boehringer Ingelheim, Altana, Pfizer, AstraZeneca), H. Nelson (GlaxoSmithKline), J. Bousquet (GlaxoSmithKline). *Stock ownership or options (other than mutual funds):* L. Sutton (GlaxoSmithKline), H. Ortega (GlaxoSmithKline), S. Yancey (GlaxoSmithKline). *Expert testimony:* E. Bateman (GlaxoSmithKline). *Grants received:* E. Bateman (GlaxoSmithKline, Chiesi, AstraZeneca, Boehringer Ingelheim, Altana, Pfizer, Sanofi-Aventis, Almirall, Schering-Plough, Lilly), H. Nelson (GlaxoSmithKline).

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**Appendix Table 1. Included Studies**

| Trial Number (Reference)  | Study Duration, wk | Study Group      | Patients Randomized, n | Mean Age, (SD or Range), y | Men, % | White, % | Withdrawn, %* | Patient-Years of Exposure | Comments   |
|---------------------------|--------------------|------------------|------------------------|----------------------------|--------|----------|---------------|---------------------------|--|
| <b>&lt;12-wk duration</b> |                    |                  |                        |                            |        |          |               |                           |  |
| SMS40230 (22)             | 1                  | BDP 500 + SAL 50 | 6                      | 20 (17–30)                 | 83     | NR       | 0             | 0.1                       | –  |
|                           |                    | BDP 500          | 6                      | 20 (17–30)                 | 83     | NR       | 0             | 0.1                       | –  |
| SAM30010 (23)             | 2                  | FSC 250/50       | 24                     | 50 (16.2)                  | 67     | 0        | 0             | 0.9                       | All participants were Asian  |
|                           |                    | FP 250           | 24                     | 47 (16.8)                  | 58     | 0        | 8             | 0.9                       |  |
| SAM40104 (24)             | 4                  | FSC 100/50       | 19                     | 38 (9.8)                   | 47     | 100      | 5             | 1.4                       | –  |
|                           |                    | FP 100           | 20                     | 42 (14.7)                  | 40     | 95       | 5             | 1.6                       | –  |
| SAS40024 (23)†            | 4                  | FSC 100/50       | 99                     | 28 (9.9)                   | 36     | 81       | 2             | 8.0                       | –  |
|                           |                    | FP 100           | 100                    | 27 (10.5)                  | 45     | 70       | 9             | 7.9                       | –  |
| SFA100314 (23)†           | 4                  | FSC 100/50       | 124                    | 11 (3.3)                   | 60     | 65       | 10            | 9.7                       | –  |
|                           |                    | FP 100           | 124                    | 11 (3.6)                   | 60     | 65       | 18            | 9.4                       | –  |
| SFA100316 (23)†           | 4                  | FSC 100/50       | 113                    | 11 (3.4)                   | 58     | 55       | 6             | 8.8                       | –  |
|                           |                    | FP 100           | 118                    | 12 (3.4)                   | 56     | 52       | 8             | 9.3                       | –  |
| SAS40025 (25)†            | 4                  | FSC 250/50       | 102                    | 29 (11.0)                  | 36     | 75       | 4             | 8.2                       | –  |
|                           |                    | FP 250           | 90                     | 29 (11.4)                  | 42     | 69       | 3             | 7.4                       | –  |
| FLTA3015 (26)†            | 4                  | FP 88 + SAL 42   | 25                     | 33 (2.6)                   | 40     | 84       | 8             | 3.6‡                      | FP and FP + SAL doses were combined for meta-analysis                  |
|                           |                    | FP 220 + SAL 42  | 21                     | 26 (2.4)                   | 67     | 81       | 0             |                           |  |
|                           |                    | FP 88            | 23                     | 27 (2.1)                   | 74     | 100      | 4             | 3.6‡                      |  |
|                           |                    | FP 220           | 23                     | 33 (2.6)                   | 57     | 91       | 4             |                           |  |
| SAM40092 (27)             | 6                  | FSC 100/50       | 21                     | 42 (36–48)                 | 52     | 100      | 0             | 2.4                       | –  |
|                           |                    | FP 100           | 21                     | 39 (33–45)                 | 38     | 100      | 0             | 2.4                       | –  |
| SAM40100 (23)             | 6                  | FSC 100/50       | 12                     | 7 (2.5)                    | 58     | 75       | 8             | 1.3                       | –  |
|                           |                    | FP 200           | 12                     | 8 (1.9)                    | 42     | 92       | 8             | 1.3                       | –  |
| SAM40023 (28)             | 6                  | FP 250 + SAL 50  | 16                     | 26 (7.0)                   | 44     | NR       | 13            | 1.8                       | –  |
|                           |                    | FP 250           | 17                     | 28 (6.2)                   | 41     | NR       | 6             | 2.0                       | –  |
| SLGQ08/SLM8905 (29)       | 8                  | BDP 400 + SAL 50 | 12                     | 27 (20.8)                  | 50     | NR       | NR            | 1.8                       | –  |
|                           |                    | BDP 400          | 15                     | 26 (19.4)                  | 53     | NR       | NR            | 2.3                       | –  |
| <b>12-wk duration</b>     |                    |                  |                        |                            |        |          |               |                           |  |
| SFCA3002 (30)†            | 12                 | FSC 100/50       | 92                     | 38 (14.7)                  | 59     | 84       | 18            | 19.5                      | –  |
|                           |                    | FP 100           | 90                     | 39 (14.3)                  | 52     | 83       | 26            | 17.9                      | –  |
| SAS30017 (31)†            | 12                 | FSC 100/50       | 88                     | 36 (13.8)                  | 47     | 72       | 14            | 18.5                      | –  |
|                           |                    | FP 100           | 89                     | 32 (13.1)                  | 51     | 84       | 12            | 19.4                      | –  |
| SAS30001 (32)†            | 12                 | FSC 88/42 (HFA)  | 95                     | 29 (12.7)                  | 52     | 80       | 9             | 21.1                      | –  |
|                           |                    | FP 88            | 97                     | 34 (13.5)                  | 53     | 77       | 8             | 21.5                      | –  |
| SAS30003 (33)†            | 12                 | FSC 88/42 (HFA)  | 92                     | 33 (12.0)                  | 38     | 73       | 8             | 20.6                      | –  |
|                           |                    | FP 88            | 89                     | 35 (15.9)                  | 42     | 83       | 16            | 19.2                      | –  |
| SAS30031 (34)†            | 12                 | FSC 100/50       | 101                    | 8 (2.2)                    | 68     | 67       | 19            | 20.8                      | –  |
|                           |                    | FP 100           | 102                    | 8 (2.2)                    | 59     | 72       | 16            | 22.1                      | –  |
| SFCB3022 2001 (35)        | 12                 | FSC 100/50 (HFA) | 165                    | 41 (18.6)                  | 44     | 92       | 12            | 71.0‡                     | Both FSC groups were combined for meta-analysis                        |
|                           |                    | FSC 100/50       | 167                    | 39 (17.3)                  | 47     | 94       | 13            |                           |  |
|                           |                    | FP 100           | 165                    | 40 (17.6)                  | 41     | 93       | 15            | 34.8                      |  |
| SAM104926 (23)            | 12                 | FSC 100/50       | 160                    | 8 (2.00)                   | 65     | 96       | 2             | 37.6                      | –  |
|                           |                    | FP 200           | 161                    | 8 (2.01)                   | 64     | 95       | 4             | 37.6                      | –  |
| SAM30013 (23)             | 12                 | FSC 100/50       | 121                    | 38 (14.1)                  | 30     | 89       | 3             | 27.7                      | –  |
|                           |                    | FP 250           | 116                    | 36 (14.9)                  | 40     | 91       | 6             | 25.9                      | –  |
| SAM40034 (23)             | 12                 | FSC 100/50       | 75                     | 37 (11.6)                  | 36     | NR       | 5             | 17.2                      | –  |
|                           |                    | FP 250           | 79                     | 37 (11.0)                  | 42     | NR       | 6             | 18.2                      | –  |
| SAM40090 (23)             | 12                 | FSC 100/50       | 242                    | 38 (14.9)                  | 40     | 83       | 18            | 50.7                      | –  |
|                           |                    | FP 250           | 241                    | 40 (15.0)                  | 43     | 84       | 17            | 51.0                      | –  |
| SAM40120 (23)             | 12                 | FSC 100/50       | 8                      | 52 (10.0)                  | 50     | 100      | 25            | 1.8                       | –  |
|                           |                    | FP 250           | 10                     | 59 (10.0)                  | 60     | 100      | 10            | 2.3                       | –  |
| SAS30040 (36)             | 12                 | FSC 100/50       | 246                    | 40 (15.9)                  | 39     | 70       | 2             | 56.8                      | –  |
|                           |                    | FP 250           | 238                    | 41 (15.1)                  | 42     | 70       | 2             | 55.3                      | –  |
| SAS30015 (23)             | 12                 | FSC 100/50 (HFA) | 78                     | 34 (14.2)                  | 54     | NR       | 12            | 16.8                      | –  |
|                           |                    | BDP 200          | 78                     | 36 (15.6)                  | 55     | NR       | 22            | 15.9                      | –  |
| SAM30022 (23)             | 12                 | FSC 100/50 (HFA) | 35                     | 48 (15.9)                  | 46     | 97       | 29            | 6.7                       | –  |
|                           |                    | BDP 400          | 33                     | 38 (17.6)                  | 55     | 100      | 30            | 6.6                       | –  |
| SAM30002 (23)             | 12                 | FSC 100/50       | 148                    | 38 (14.0)                  | 36     | 0        | 13.5          | 34.0                      | All participants were Asian; device used is not commercially available |
|                           |                    | BUD 400          | 152                    | 37 (14.0)                  | 41     | 0        | 13.8          | 35.0                      |  |
| SAS40007/SERL03 (37)      | 12                 | FSC 100/50       | 176                    | 36 (16.0)                  | 38     | 94       | 13            | 37.                       | –  |
|                           |                    | BUD 400          | 173                    | 36 (17.0)                  | 48     | 94       | 9             | 38.3                      | –  |

Continued on following page

Appendix Table 1—Continued

| Trial Number (Reference)  | Study Duration, wk | Study Group            | Patients Randomized, n | Mean Age, (SD or Range), y | Men, % | White, % | Withdrawn, %* | Patient-Years of Exposure | Comments  |
|---------------------------|--------------------|------------------------|------------------------|----------------------------|--------|----------|---------------|---------------------------|---|
| SFCA3003 (38)†            | 12                 | FSC 250/50             | 84                     | 38 (14.3)                  | 48     | 73       | 17            | 18.1                      | —   |
|                           |                    | FP 250                 | 84                     | 40 (15.6)                  | 54     | 89       | 27            | 16.2                      |   |
| SAS30039 (39)             | 12                 | FSC 250/50             | 180                    | 40 (15.4)                  | 43     | 78       | 3             | 41.7                      | —   |
|                           |                    | FP 250                 | 182                    | 41 (14.7)                  | 42     | 80       | 4             | 42.3                      |   |
| SAS30004 (40)†            | 12                 | FSC 220/42 (HFA)       | 94                     | 39 (14.8)                  | 39     | 78       | 14            | 20.2                      | —   |
|                           |                    | FP 220                 | 91                     | 39 (15.7)                  | 37     | 82       | 22            | 18.6                      |   |
| SAS40009 (41)             | 12                 | FSC 250/50             | 180                    | 50 (14.2)                  | 47     | NR       | 7.3           | 41.4                      | —   |
|                           |                    | FP 500                 | 187                    | 49 (13.9)                  | 41     | NR       | 6.4           | 43.0                      |   |
| SFCB3023 (42)             | 12                 | FSC 250/50 (HFA)       | 176                    | 48 (14.9)                  | 40     | 93       | 12            | 72.9‡                     | Both FSC groups were combined for meta-analysis   |
|                           |                    | FSC 250/50             | 161                    | 47 (14.8)                  | 40     | 92       | 12            |                           |   |
|                           |                    | FP 500                 | 172                    | 46 (15.6)                  | 42     | 93       | 13            | 37.2                      |   |
| SAM40116 (23)             | 12                 | FSC 100/50 or 250/50   | 91                     | 48 (16.1)                  | 44     | NR       | 5             | 20.9                      | Treatment assignment based on baseline severity; FSC and FP doses were combined for meta-analysis |
|                           |                    | FP 250 or 500          | 86                     | 48 (17.2)                  | 37     | NR       | 5             | 19.8                      |   |
| SLGF75/FLIC14 (23)        | 12                 | FP 100 + SAL 50        | 14                     | 42 (16.3)                  | 36     | 100      | 2             | 3.2                       | FP doses were combined for meta-analysis  |
|                           |                    | FP 100                 | 17                     | 42 (10.6)                  | 71     | 100      | 2             | 7.4‡                      |   |
|                           |                    | FP 250                 | 15                     | 33 (13.1)                  | 60     | 100      | 0             |                           |   |
| SMS40081/SLM9009 (43)     | 12                 | FP 200 or 500 + SAL 50 | 139                    | 46 (15)                    | 47     | NR       | 4             | 32.0                      | —   |
|                           |                    | FP 400 or 1000         | 135                    | 47 (14)                    | 50     | NR       | 7             | 31.0                      |   |
| FLTA4021 (44)†            | 12                 | FP 100 + SAL 50        | 118                    | 40 (15.2)                  | 41     | 89       | 8             | 26.5                      | FP and TAA doses were combined for meta-analysis; data published with FLTA4022                    |
|                           |                    | FP 250                 | 114                    | 40 (12.8)                  | 36     | 79       | 6             | 51.7‡                     |   |
|                           |                    | TAA 600                | 118                    | 39 (11.9)                  | 37     | 88       | 12            |                           |   |
| FLTA4022 (44)†            | 12                 | FP 100 + SAL 50        | 113                    | 42 (14.9)                  | 42     | 85       | 6             | 25.5                      | FP and TAA doses were combined for meta-analysis; data published with FLTA4021                    |
|                           |                    | FP 250                 | 109                    | 39 (14.6)                  | 41     | 88       | 6             | 49.3‡                     |   |
|                           |                    | TAA 600                | 108                    | 41 (12.5)                  | 32     | 90       | 6             |                           |   |
| SLGQ98 (45)               | 12                 | FP 200 + SAL 50        | 18                     | 43 (16)                    | 61     | NR       | 22            | 4.1                       | FP doses were combined for meta-analysis  |
|                           |                    | FP 200                 | 19                     | 42 (12)                    | 42     | NR       | 16            | 8.7‡                      |   |
|                           |                    | FP 500                 | 19                     | 40 (15)                    | 47     | NR       | 16            |                           |   |
| SLM9021B/SLGL90 (46)      | 12                 | BDP 200 + SAL 50       | 113                    | 42 (14.0)                  | 53     | 91       | 13            | 26.0                      | —   |
|                           |                    | BDP 400                | 120                    | 42 (14.0)                  | 38     | 96       | 13            | 27.6                      |   |
| <b>&gt;12-wk duration</b> |                    |                        |                        |                            |        |          |               |                           |   |
| SAS40036 (23)†            | 16                 | FSC 100/50             | 172                    | 40 (13.4)                  | 39     | 88       | 17            | 47.8                      | —   |
|                           |                    | FP 100                 | 159                    | 42 (14.5)                  | 43     | 87       | 37            | 37.8                      |   |
| SAS40037 (23)†            | 16                 | FSC 100/50             | 161                    | 41 (14.4)                  | 36     | 83       | 24            | 43.3                      | —   |
|                           |                    | FP 100                 | 161                    | 40 (14.5)                  | 42     | 85       | 34            | 39.3                      |   |
| SAM40049 (47)             | 24                 | FSC 100/50             | 78                     | 39 (15.4)                  | 49     | NR       | 14            | 32.9                      | —   |
|                           |                    | FP 100                 | 72                     | 38 (15.1)                  | 38     | NR       | 18            | 29.9                      |   |
| SAS40068 (23)             | 24                 | FSC 100/50             | 262                    | 35 (14.3)                  | 14     | 89       | 20            | 120.5                     | —   |
|                           |                    | FP 100                 | 270                    | 34 (14.2)                  | 13     | 90       | 17            | 124.2                     |   |
| SAS40026 (48)†            | 24                 | FSC 100/50             | 321                    | 40 (15.1)                  | 40     | 88       | 14            | 95.7                      | —   |
|                           |                    | FP 250                 | 315                    | 39 (14.9)                  | 35     | 90       | 21            | 83.0                      |   |
| SAS40027 (49)†            | 24                 | FSC 100/50             | 281                    | 38 (13.9)                  | 41     | 90       | 16            | 91.9                      | —   |
|                           |                    | FP 250                 | 277                    | 39 (14.2)                  | 43     | 88       | 19            | 89.0                      |   |
| SFCF4026/SAM40088 (23)    | 24                 | FSC 250/50             | 159                    | 45 (16.0)                  | 50     | NR       | 11.3          | 145.8‡                    | Both FSC groups were combined for meta-analysis   |
|                           |                    | FSC 100/50             | 158                    | 45 (16.0)                  | 53     | NR       | 9.6           |                           |   |
|                           |                    | FP 250                 | 159                    | 45 (16.0)                  | 47     | NR       | 18.9          | 73.1                      |   |
| SAM40012 (23)             | 24                 | FSC 100/50             | 181                    | 8 (2.0)                    | 70     | 100      | 2             | 81.4                      | —   |
|                           |                    | FP 100                 | 181                    | 8 (2.2)                    | 64     | 100      | 6             | 162.8‡                    |   |
|                           |                    | FP 200                 | 186                    | 8 (2.2)                    | 69     | 100      | 3             |                           |   |
| SAS40006/SERLO4 (50)      | 24                 | FSC 250/50             | 180                    | 45 (15.0)                  | 50     | 94       | 16            | 76.1                      | —   |
|                           |                    | BUD 800                | 173                    | 48 (16.0)                  | 50     | 95       | 17            | 71.9                      |   |
| SLGA5021 (23)†            | 24                 | FP 100 + SAL 50        | 246                    | 38 (12–78)                 | 50     | 94       | 13            | 106.2                     | —   |
|                           |                    | FP 250                 | 242                    | 37 (12–76)                 | 50     | 93       | 14            | 102.5                     |   |
| SLGA5022 (51)†            | 24                 | FP 100 + SAL 50        | 221                    | 37 (12–75)                 | 38     | 86       | 9             | 99.0                      | —   |
|                           |                    | FP 250                 | 216                    | 37 (12–71)                 | 40     | 83       | 14            | 93.0                      |   |

Appendix Table 1—Continued

| Trial Number (Reference)  | Study Duration, wk | Study Group  | Patients Randomized, n | Mean Age, (SD or Range), y | Men, % | White, % | Withdrawn, %* | Patient-Years of Exposure | Comments  |
|---------------------------|--------------------|--|------------------------|----------------------------|--------|----------|---------------|---------------------------|---|
| SLGQ97/SLGB4010/J121 (52) | 24                 | FP 250 + SAL 50                                    | 173                    | 45 (15.6)                  | 40     | NR       | 16            | 69.9                      | FP doses were combined for meta-analysis  |
|                           |                    | FP 250   | 162                    | 46 (15.2)                  | 48     | NR       | 9             |                           |   |
|                           |                    | FP 500   | 167                    | 44 (14.9)                  | 49     | NR       | 13            |                           |   |
| SLGA5017 (53)†            | 24                 | BDP 200 + SAL 50                                   | 239                    | 42 (13.9)                  | 43     | 90       | 20            | 97.4                      | –   |
| SLGA5018 (54)†            | 24                 | BDP 200 + SAL 50                                   | 260                    | 42 (12.9)                  | 41     | 86       | 19            | 106.5                     | –   |
|                           |                    | BDP 400  | 254                    | 42 (14.3)                  | 45     | 85       | 22            | 101.5                     | –   |
| SMS30045/SLGT26 (55)      | 24                 | BDP 500 + SAL 50                                   | 243                    | 44 (18–79)                 | 51     | 95       | 10            | 106.5                     | –   |
|                           |                    | BDP 1000   | 251                    | 42 (17–72)                 | 54     | 92       | 14            | 108.8                     | –   |
| SAM40008 (23)             | 26                 | FSC 500/50   | 93                     | 48 (15.1)                  | 52     | 100      | 92            | 17.5                      | Withdrawals based on protocol-defined measures of asthma control  |
|                           |                    | FP 500   | 93                     | 51 (16.1)                  | 43     | 98       | 92            | 15.7                      |   |
| SLGQ85/J085 (56)          | 26                 | BDP 400 + SAL 50                                   | 221                    | 48 (15.0)                  | 46     | NA       | 32            | 110.1                     | –   |
|                           |                    | BDP 1000   | 208                    | 47 (15.0)                  | 41     | NA       | 32            | 103.6                     |   |
| SFCB3019 (57)§            | 28                 | FSC 500/50   | 167                    | 46 (15.0)                  | 57     | 95       | 19            | 163.9‡                    | FSC and FP + SAL groups were combined for meta-analysis   |
|                           |                    | FP 500 + SAL 50                                    | 171                    | 48 (15.1)                  | 50     | 98       | 16            |                           |   |
|                           |                    | FP 500   | 165                    | 50 (15.1)                  | 53     | 96       | 25            | 75.4                      |   |
| SAM30007 (23)             | 30                 | FSC 500/50, 250/50, or 100/50                      | 29                     | 38 (11.4)                  | 52     | 100      | 10            | 8.8                       | All participants initiated therapy with FSC or FP 500 with protocol-defined downward titration allowed; FSC and FP doses were combined for meta-analysis      |
|                           |                    | FP 500, 250, or 100                                | 32                     | 36 (11.8)                  | 53     | 97       | 9             | 10.2                      |   |
| SAM40065 (23)†            | 40                 | FSC 100/50, 250/50, or 500/50                      | 150                    | 35 (15.2)                  | 35     | 77       | 25            | 93.5                      | Upward and downward dose titration allowed based on BHR or clinical judgment (reference treatment strategy); FSC and FP doses were combined for meta-analysis |
|                           |                    | FP 100, 250, or 500 BHR                            | 150                    | 34 (13.9)                  | 37     | 77       | 33            | 180.7‡                    |   |
|                           |                    | FP 100, 250, or 500 (reference treatment strategy) | 149                    | 34 (13.3)                  | 38     | 83       | 26            |                           |   |
| SAM40086 (58)†            | 40                 | FSC 100/50, 250/50, or 500/50                      | 156                    | 35 (14.4)                  | 38     | 79       | 30            | 91.7                      | Upward and downward dose titration allowed based on BHR or clinical judgment (reference treatment strategy); FSC and FP doses were combined for meta-analysis |
|                           |                    | FP 100, 250, or 500 BHR                            | 156                    | 35 (14.4)                  | 36     | 77       | 33            | 183.4‡                    |   |
|                           |                    | FP 100, 250, or 500 (reference treatment strategy) | 154                    | 33 (15.5)                  | 49     | 81       | 31            |                           |   |
| SAM40004 (23)             | 52                 | FSC 100/50   | 22                     | 31 (8.6)                   | 64     | 95       | 27            | 20.5‡                     | Both FSC groups were combined for meta-analysis; 1 group received FSC for 52 wk, the other initiated FSC 17 wk into the study                                 |
|                           |                    | FSC 100/50   | 20                     | 33 (10.5)                  | 60     | 95       | 50            |                           |   |
|                           |                    | FP 100   | 21                     | 32 (7.0)                   | 62     | 100      | 48            | 6.1                       |   |
| FAS40008/FLIQ43 (59)      | 52                 | FSC 250/50   | 95                     | 40 (11.9)                  | 34     | NR       | 9             | 86.4                      | –   |
|                           |                    | FP 250   | 92                     | 39 (12.0)                  | 42     | NR       | 5             | 79.6                      |   |
| SAS30013 (60)             | 52                 | FSC 250/50   | 27                     | 32 (21–59)                 | 37     | 100      | 0             | 22.8                      | –   |
|                           |                    | FP 250   | 27                     | 32 (19–57)                 | 30     | 100      | 14.8          | 22.8                      |   |

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**Appendix Table 1—Continued**

| Trial Number (Reference) | Study Duration, wk | Study Group                   | Patients Randomized, n | Mean Age, (SD or Range), y | Men, % | White, % | Withdrawn, %* | Patient-Years of Exposure | Comments   |
|--------------------------|--------------------|-------------------------------|------------------------|----------------------------|--------|----------|---------------|---------------------------|--|
| SAM40027 (61)            | 52                 | FSC 100/50, 250/50, or 500/50 | 1709                   | 40 (16.3)                  | 43     | 71       | 14            | 1590.9                    | Study allowed upward titration to achieve asthma control; FSC and FP doses were combined for meta-analysis   |
|                          |                    | FP 100, 250, or 500           | 1707                   | 40 (16.2)                  | 41     | 71       | 17            | 1549.1                    |  |
| SAM40031 (23)            | 52                 | FSC 500/50, 250/50, or 100/50 | 41                     | 45 (15.0)                  | 49     | 93       | 19.5          | 18.0                      | All participants initiated therapy with FSC or FP 500 with protocol-defined downward titration allowed; FSC and FP doses were combined for meta-analysis |
|                          |                    | FP 500, 250, or 100           | 41                     | 49 (17.0)                  | 41     | 95       | 34.1          | 16.5                      |  |

BDP = beclomethasone dipropionate; BHR = bronchial hyperreactivity; BUD = budesonide; FP = fluticasone propionate; FSC = fluticasone propionate/salmeterol; HFA = hydrofluoroalkane; ICS = inhaled corticosteroids; NA = not available; NR = not reported; SAL = salmeterol; TAA = triamcinolone acetonide.

\* Values represent all patient withdrawals from the studies, whether due to a serious adverse event, loss to follow-up, or the patient's or investigator's discretion.

† Study included in subanalysis for severe exacerbations requiring oral corticosteroid use.

‡ For studies containing 2 similar groups (e.g., ICS, ICS + SAL, or FSC) at differing doses, groups were combined to determine patient-years of exposure.

§ Only study with an ICS + SAL group represented in both a single device and separate devices in direct comparison with ICS alone.

**Appendix Table 2. Sensitivity Analyses for Asthma-Related Hospitalizations with Differing Continuity Corrections**

| Continuity Correction | Risk Difference (95% CI)        | P Value |
|-----------------------|---------------------------------|---------|
| 0.01                  | 0.00212 (−0.001324 to 0.001749) | 0.787   |
| 0.001                 | 0.00213 (−0.001312 to 0.001737) | 0.785   |
| 0.0001                | 0.00212 (−0.00131 to 0.001735)  | 0.785   |