Regular treatment with salmeterol and inhaled steroids for chronic asthma: serious adverse events (Review)

Cates CJ, Lasserson TJ, Jaeschke R

This is a reprint of a Cochrane review, prepared and maintained by The Cochrane Collaboration and published in *The Cochrane Library* 2009, Issue 3

http://www.thecochranelibrary.com

TABLE OF CONTENTS

[Intervention Review]

Regular treatment with salmeterol and inhaled steroids for chronic asthma: serious adverse events

Christopher J Cates[1], Toby J Lasserson[1], Roman Jaeschke[2]

[1]Community Health Sciences, St George's, University of London, London, UK. [2]Department of Medicine, McMaster University, Hamilton, Canada

Contact address: Christopher J Cates, Community Health Sciences, St George's, University of London, Cranmer Terrace, London, SW17 0RE, UK. ccates@sgul.ac.uk.

Editorial group: Cochrane Airways Group.
Publication status and date: New, published in Issue 3, 2009.
Review content assessed as up-to-date: 13 April 2009.

Citation: Cates CJ, Lasserson TJ, Jaeschke R. Regular treatment with salmeterol and inhaled steroids for chronic asthma: serious adverse events. *Cochrane Database of Systematic Reviews* 2009, Issue 3. Art. No.: CD006922. DOI: 10.1002/14651858.CD006922.pub2.

ABSTRACT

Background

Epidemiological evidence has suggested a link between beta$_2$-agonists and increased asthma mortality. There has been much debate about possible causal links for this association, and whether regular (daily) long-acting beta$_2$-agonists are safe.

Objectives

The aim of this review is to assess the risk of fatal and non-fatal serious adverse events in trials that randomised patients with chronic asthma to regular salmeterol with inhaled corticosteroids versus the same dose of inhaled corticosteroids alone.

Search methods

Trials were identified using the Cochrane Airways Group Specialised Register of trials. Web sites of clinical trial registers were checked for unpublished trial data and Food and Drug Administration (FDA) submissions in relation to salmeterol were also checked. The date of the most recent search was October 2008.

Selection criteria

Controlled parallel design clinical trials on patients of any age and severity of asthma were included if they randomised patients to treatment with regular salmeterol and inhaled corticosteroids (in separate or combined inhalers), and were of at least 12 weeks duration.

Data collection and analysis

Two authors independently selected trials for inclusion in the review. Outcome data were independently extracted by two authors. Unpublished data on mortality and serious adverse events were obtained from the sponsors, and from FDA submissions.

Main results

The review included 30 studies (10,873 participants) in adults and adolescents, and three studies (1,173 participants) in children. The overall risk of bias was low and data on serious adverse events were obtained from all studies.

Six deaths occurred in 5,710 adults on regular salmeterol with inhaled corticosteroids, and five deaths in 5,163 adults on regular inhaled corticosteroids at the same dose. The difference was not statistically significant (Peto OR 1.05; 95% CI 0.32 to 3.47) and the absolute

difference between groups in risk of death of any cause was 0.00005 (95% CI -0.002 to 0.002). No deaths were reported in 1,173 children, and no deaths were reported to be asthma-related.

Non-fatal serious adverse events of any cause were reported in 134 adults on regular salmeterol with inhaled corticosteroids, compared to 103 adults on regular inhaled corticosteroids; again this was not a significant increase (Peto OR 1.17; 95% CI 0.90 to 1.52). The absolute difference in the risk of non-fatal serious adverse events was 0.003 (95% CI -0.002 to 0.009).

There were three of 586 children with serious adverse events on regular salmeterol with inhaled corticosteroids, compared to four out of 587 on regular inhaled corticosteroids: there was no significant difference between treatments (Peto OR 0.75; 95% CI 0.17 to 3.31).

Asthma-related serious adverse events were reported in 23 and 21 adults in each group respectively, a non-significant difference (Peto OR 0.95; 95% CI 0.52 to 1.73), and only one event was reported in children.

Authors' conclusions

No significant differences have been found in fatal or non-fatal serious adverse events in trials in which regular salmeterol has been randomly allocated with inhaled corticosteroids, in comparison to inhaled corticosteroids at the same dose. Although 10,873 adults and 1,173 children have been included in trials, the number of patients suffering adverse events is too small, and the results are too imprecise to confidently rule out a relative increase in all-cause mortality or non-fatal adverse events. It is therefore not possible to determine whether the increase in all-cause non-fatal serious adverse events reported in the previous meta-analysis on regular salmeterol alone is abolished by the additional use of regular inhaled corticosteroids. The absolute difference between groups in the risk of serious adverse events was small. There were no asthma-related deaths and few asthma-related serious adverse events. Clinical decisions and information for patients regarding regular use of salmeterol have to take into account the balance between known symptomatic benefits of salmeterol and the degree of uncertainty and concern associated with its potential harmful effects.

PLAIN LANGUAGE SUMMARY

Serious adverse events with regular salmeterol and inhaled corticosteroids

There has been some concern raised at the possibility of increased serious adverse events following administration of salmeterol, a long-acting beta$_2$-agonist, to people with asthma. We analysed data from 30 studies in adults and three in children that compared regular salmeterol in addition to inhaled corticosteroids, against the same dose of inhaled corticosteroids. Too few deaths occurred in the trials to gain any conclusive reassurance that regular salmeterol taken with inhaled corticosteroids either reduces the risk of mortality, or in fact does not increase it. Serious adverse events were not significantly increased in adults or children when regular salmeterol was added to inhaled corticosteroids as randomised treatment, but the results are too imprecise to conclude that there is no increased risk.

SUMMARY OF FINDINGS FOR THE MAIN COMPARISON [Explanation]

Regular salmeterol in addition to regular inhaled corticosteroids compared to regular inhaled corticosterods for chronic asthma

Patient or population: patients with chronic asthma
Settings:
Intervention: Regular salmeterol in addition to regular inhaled corticosteroids
Comparison: Regular inhaled corticosterods

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Regular inhaled corticosterods	Regular salmeterol in addition to regular inhaled corticosteroids				
All-cause mortality - Adults and adolescents Follow-up: mean 31 weeks	**1 per 1000**[1]	**1 per 1000** (0 to 3)	**OR 1.05** (0.32 to 3.47)	10873 (30 studies)	⊕⊕⊕◯ **moderate**[2]	
All-cause non-fatal SAE - Adults Follow-up: mean 31 weeks	**20 per 1000**[1]	**23 per 1000** (18 to 30)	**OR 1.17** (0.9 to 1.52)	10873 (30 studies)	⊕⊕⊕◯ **moderate**[2]	
All-cause non-fatal SAE - Children Follow-up: mean 16 weeks	**7 per 1000**[1]	**5 per 1000** (1 to 23)	**OR 0.75** (0.17 to 3.31)	1173 (3 studies)	⊕⊕⊕◯ **moderate**[2]	
Asthma-related SAE - Adults Follow-up: mean 31 weeks	**4 per 1000**[1]	**4 per 1000** (2 to 7)	**OR 0.95** (0.52 to 1.73)	10873 (30 studies)	⊕⊕⊕◯ **moderate**[2]	

Asthma-related SAE - Children Follow-up: mean 16 weeks	**2 per 1000**[1]	**0 per 1000** (0 to 13)	**OR 0.14** (0 to 6.82)	1173 (3 studies)	⊕⊕⊕○ **moderate**[2]

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: Confidence interval; **OR:** Odds ratio;

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

[1] Mean control event rate
[2] Wide confidence intervals due to small number of events

BACKGROUND

When patients with asthma are not controlled by low dose inhaled corticosteroids alone, many asthma guidelines recommend additional long-acting beta$_2$-agonists. Several Cochrane reviews have addressed the efficacy of long-acting beta$_2$-agonists in addition to inhaled corticosteroids (Ni Chroinin 2004; Ni Chroinin 2005), in comparison with placebo (Walters 2007), short-acting beta$_2$-agonists (Walters 2002), leukotriene-receptor antagonists (Ducharme 2006), and increased doses of inhaled corticosteroids (Greenstone 2005). The beneficial effects of long-acting beta$_2$–agonists on lung function, symptoms, quality of life and exacerbations requiring oral steroids have been demonstrated.

However, there is also longstanding controversy over the regular use of beta$_2$-agonists in asthma. Sears 1986 suggested that excessive use of short acting beta$_2$-agonists might have contributed directly or indirectly to increases in asthma deaths in New Zealand between 1960 and 1980. The authors comment that "most deaths were associated with poor assessment, underestimation of severity and inappropriate treatment (over-reliance on bronchodilators and under use of systemic corticosteroids), and delays in obtaining help."

Concern remains that the symptomatic benefit from treatment with long-acting beta$_2$-agonists might lead to underestimation of attack severity in acute asthma, and could lead to an increase in asthma-related deaths. Furthermore, regular treatment with beta$_2$-agonists can lead to tolerance to their bronchodilator effects and this phenomenon may be more marked with longer acting as opposed to shorter acting compounds (Lipworth 1997). A number of molecular mechanisms have been proposed to explain the possible detrimental effect of long-term beta$_2$-agonist use in asthma including receptor down regulation and desensitisation (Giembycz 2006).

A recent meta-analysis of the effect of long-acting beta$_2$-agonists on severe asthma exacerbations and asthma-related deaths (Salpeter 2006) concluded that "long-acting beta-agonists have been shown to increase severe and life-threatening asthma exacerbations, as well as asthma-related deaths". Salpeter 2006 only considered trials that compared long-acting beta$_2$-agonists with placebo, and the review was not able to include 28 trials in the primary analysis (including nearly 6,000 patients) because information was not provided for asthma-related deaths.

Currently there are two long-acting beta$_2$-agonists available, salmeterol and formoterol (also known as eformoterol). These two drugs are known to have differences in receptor activity, and are used in different ways (for example salmeterol has a slower onset of action than salbutamol, and is therefore unsuitable for use as a reliever Beach 1992). 'The Fenoterol Story' is a reminder that all beta$_2$-agonists may not carry the same risks (Pearce 2007), so in view of the potential difference in adverse effects between salmeterol and formoterol, we have revised our original protocol to consider the two drugs separately.

There has been much debate about the interaction between inhaled corticosteroids and long-acting beta$_2$-agonists, in relation to serious adverse events, since the publication of SMART 2006. This study did not randomise patients to inhaled corticosteroids, but nevertheless a subgroup analysis of the results was carried out on the basis of inhaled corticosteroid use at baseline. It is tempting to find reassurance from the fact that there was not a statistically significant increase in asthma-related mortality in the subgroup using inhaled corticosteroids, but this is not the correct way to test for interaction (Altman 2003), and no assessment was carried out during the trial in relation to the actual use of inhaled corticosteroids during the course of the study. There is a need to systematically review all the available data from controlled trials that randomised patients to regular salmeterol in combination with inhaled corticosteroids, and to consider all serious adverse events (fatal and non-fatal), whether or not these are deemed by the investigators to be related to trial medication.

The focus of this review is therefore on regular salmeterol which has been randomised in combination with inhaled corticosteroids, (in a single inhaler or separate inhalers). Due to the difficulty in deciding whether adverse events are asthma-related (particularly in the many studies that do not have independent outcome assessment of adverse events), this review is concerned with studies that capture mortality and serious adverse events, and records both all cause outcomes, and those considered by the trial investigators to be asthma-related events. This approach differs from that of Bateman 2008 where the authors restricted the outcomes to asthma-related events.

Regular salmeterol alone is the subject of a previous review (Cates 2008a), and similarly regular formoterol alone (Cates 2008). In both of these reviews an increase in serious adverse events was demonstrated with regular long-acting beta$_2$-agonists. Formoterol with inhaled corticosteroids has been considered in a further review (Cates 2009).

OBJECTIVES

To assess the risk of mortality and non-fatal serious adverse events in trials which randomised patients with chronic asthma to regular salmeterol and inhaled corticosteroids in comparison to the same dose of inhaled corticosteroids.

METHODS

Criteria for considering studies for this review

Types of studies

Controlled parallel design clinical trials, with or without blinding, in which salmeterol and inhaled corticosteroids were randomly assigned to patients with chronic asthma. Studies on acute asthma and exercise induced bronchospasm were not included.

Types of participants

Patients with a clinical diagnosis of asthma of any age group, unrestricted by disease severity, previous or current treatment.

Types of interventions

Inhaled corticosteroids and salmeterol given regularly for a period of at least 12 weeks, at any daily dose and delivered by any single or separate devices (CFC-MDI, HFA-MDI, DPI). Studies that used comparison groups with the same dose of inhaled corticosteroids were included in this review, and co-intervention with leukotriene receptor antagonists, cromones or oral corticosteroids or theophylline was allowed as long as they were not part of the randomised intervention. Studies that compared different doses of salmeterol, or different delivery devices or propellants (with no placebo arm), or compared salmeterol with formoterol, were not included. Studies in which salmeterol was randomised without an inhaled steroid were excluded from this review, but have been considered in a separate review (Cates 2008).

Types of outcome measures

Primary outcomes

1. All cause mortality
2. All cause non-fatal serious adverse events

Secondary outcomes

1. Asthma-related mortality
2. Asthma-related non-fatal serious adverse events
3. Respiratory-related mortality
4. Respiratory-related non-fatal serious adverse events
5. Cardiovascular-related mortality
6. Cardiovascular-related non-fatal serious adverse events
7. Asthma-related non-fatal life-threatening events (intubation or admission to intensive care)
8. Respiratory-related non-fatal life-threatening events (intubation or admission to intensive care)

Search methods for identification of studies

Electronic searches

Trials were identified using the Cochrane Airways Group Specialised Register of trials, which is derived from systematic searches of bibliographic databases including the Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE, EMBASE, CINAHL, AMED, and PsycINFO, and hand searching of respiratory journals and meeting abstracts. All records in the Specialised Register coded as 'asthma' were searched using the following terms: (((beta* and agonist*) and (long-acting or "long acting")) or ((beta* and adrenergic*) and (long-acting or "long acting")) or (bronchodilat* and (long-acting or "long acting")) or (salmeterol or formoterol or eformoterol or advair or symbicort or serevent or seretide or oxis)) AND (serious or safety or surveillance or mortality or death or intubat* or adverse or toxicity or complications or tolerability)

Searching other resources

Reference lists of all primary studies and review articles were checked for additional references. Web sites of clinical trial registers were checked for unpublished trial data and FDA submissions in relation to salmeterol were also checked.

Data collection and analysis

Selection of studies

Two review authors independently assessed studies identified in the literature searches by examining titles, abstract and keywords fields. Studies that potentially fulfilled the inclusion criteria were obtained in full text. These were independently assessed by CJC and TL for inclusion. Disagreements were resolved by consensus.

Data extraction and management

Data were extracted using a prepared checklist before being entered into Rev Man 5.0 by one reviewer (CJC) with assistance from Susan Hansen, and data on trial characteristics were checked by another reviewer (TL). Outcome data were independently extracted by the third reviewer (RJ) and discrepancies resolved by discussion and correspondence with the sponsors. Data included characteristics of included studies (methods, participants, interventions, outcomes) and results of the included studies. Authors and sponsors of included studies were contacted for unpublished adverse event data, and manufacturers' web sites were searched for further details of adverse events. FDA submissions were also searched. All cause serious adverse events (fatal and non-fatal) were collected, and in view of the difficulty in deciding whether events are asthma related, details of the cause of death and serious adverse events were noted where they were available. The definition of serious adverse events was also recorded, and further information was sought if this was not clear (particularly in relation to hospital admissions and serious adverse events).

Assessment of risk of bias in included studies

One review author (CJC) assessed the included studies for bias protection (including sequence generation for randomisation, allocation concealment, blinding of participants and assessors, loss to follow-up, completeness of outcome assessment and other possible bias prevention), with assistance from Susan Hansen.

Measures of treatment effect

The outcomes of this review were dichotomous, and we recorded the number of participants with one or more outcome events, by allocated treated group.

Unit of analysis issues

We confined our analysis to patients with one or more serious adverse event, rather than the number of events that occurred (as the latter are not independent when one patient suffers multiple events, and are therefore not suitable for meta-analysis).

Assessment of heterogeneity

Heterogeneity was assessed using I^2 to indicate how much of the total heterogeneity was between studies (rather than within studies).

Data synthesis

The outcomes of this review were dichotomous, and we recorded the number of participants with at least one outcome event by allocated treated group. Pooled Odds Ratio (OR) and Risk Difference (RD) were calculated. The Peto Odds Ratio was used for the primary analysis, as no adjustment for zero cells is required. This property was more important than potential problems with unbalanced treatment arms and large effect sizes (in view of the high proportion of zero cells), but the Mantel-Haenszel method was also used for sensitivity analysis. Odds Ratios do not include the large body of evidence coming from the trials with no event in either arm, but such data is included in the analysis of absolute rates using Risk Difference. Funnel plots were inspected to assess publication bias.

Subgroup analysis and investigation of heterogeneity

Subgroup analyses were planned on the basis of age (adults versus children), severity of asthma, dose of salmeterol, and dose of inhaled corticosteroid in the comparison arms. Subgroup comparisons were made using tests for interaction (Altman 2003).

Sensitivity analysis

Sensitivity analysis was carried out to assess the impact of the method used to combine the study events (Risk Difference, Peto Odds Ratio, and Mantel-Haenszel Odds Ratio). The degree of bias protection in the study designs was also part of sensitivity analysis.

RESULTS

Description of studies

See: Characteristics of included studies; Characteristics of excluded studies.

Results of the search

523 abstracts were found from the search of the Cochrane Airways Group Specialised Register of trials in October 2008. For this review 97 abstracts were identified as potentially relevant. Twenty one references to 17 included studies were identified from the search of the specialised register. A further 16 studies were identified from the sponsor's web site and the reference list of a recently published review (Bateman 2008). There were 76 studies that were excluded from the review and full details of the reasons for exclusion are listed in Characteristics of excluded studies.

Included studies

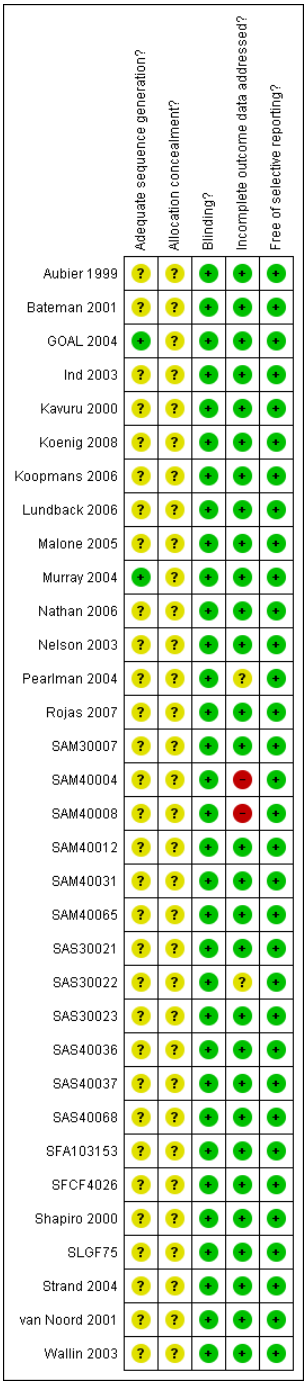
Of the 33 included studies, 30 of these included 10,873 adults and adolescents (over the age of 12, 16 or 18 years according to the Characteristics of included studies). Three studies were in children up to the age of 11 years, and included 1,173 participants. The weighted mean duration was 31 weeks in the adult studies, and 16 weeks in the studies in children.

All studies were sponsored or supported by GlaxoSmithKline and compared fluticasone and salmeterol to fluticasone alone. Most studies used a single inhaler to combine the salmeterol and fluticasone. The dose of salmeterol used was 50 mcg twice daily in all studies except for SAS30021, SAS30022 and SAS30023 in which a once daily dose of 50 mcg was used. The dose of fluticasone varied from 100 to 1000 mcg/day (see Table 1), and some studies stratified patients to different daily doses of fluticasone, but used the same daily dose of fluticasone in each stratum for comparison with additional salmeterol (Koenig 2008; SAM30007; SAM40031; SAM40065).

Risk of bias in included studies

An overview of the risk of bias in individual studies is shown in Figure 1

Figure 1. Methodological quality summary: review authors' judgements about each methodological quality item for each included study.



Allocation

Sequence generation and allocation concealment are not well reported, but correspondence with the sponsors indicates that standard methodology (as required by regulatory authorities), has been used to protect against selection bias in these studies. We therefore regard the risk of selection bias as low.

Blinding

All of the studies were reported as double blind, and double-dummy design was incorporated when the inhaler devices were not the same in each arm.

Selective reporting

Data have been found or provided from the sponsor for all-cause fatal and non-fatal serious adverse events by treatment group for all studies.

Other potential sources of bias

All studies were sponsored by GlaxoSmithKline, the manufacturers of salmeterol and salmeterol/fluticasone inhalers.

Effects of interventions

See: **Summary of findings for the main comparison** Serious adverse events

Primary Outcomes

All cause mortality

Adults and adolescents

In the adult and adolescent studies there were six deaths (out of 5,170 participants) on salmeterol with inhaled corticosteroids and five deaths (out of 5,163 participants) on inhaled corticosteroids alone. The pooled Odds Ratio in adults and adolescents was not statistically significant, (Peto OR 1.05; 95% CI 0.32 to 3.47) and I^2 was zero, but the confidence interval is wide due to the small number of deaths, and still includes the possibility of a three-fold increase in mortality, as well as a three-fold reduction Figure 2. The pooled risk difference from these studies is shown in Figure 3, (RD 0.00005; 95% CI -0.002 to 0.002). In other words, for every 1,000 patients treated with salmeterol and inhaled corticosteroids for 31 weeks, the results are compatible with both a possible increase or decrease of up to two deaths.

Figure 2. Forest plot of comparison: 1 Regular Salmeterol in addition to regular inhaled corticosteroids, outcome: 1.1 All-cause mortality.

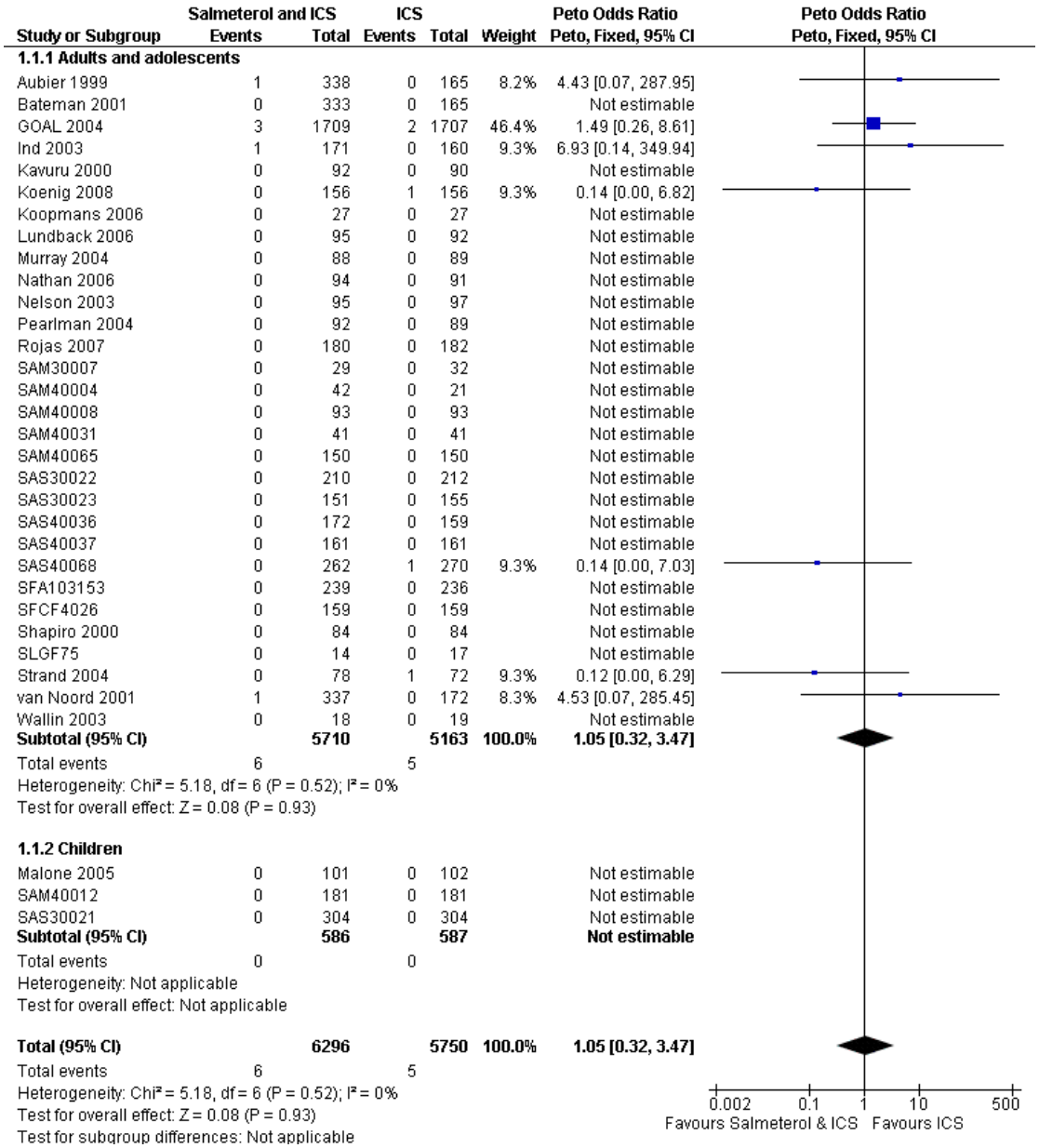
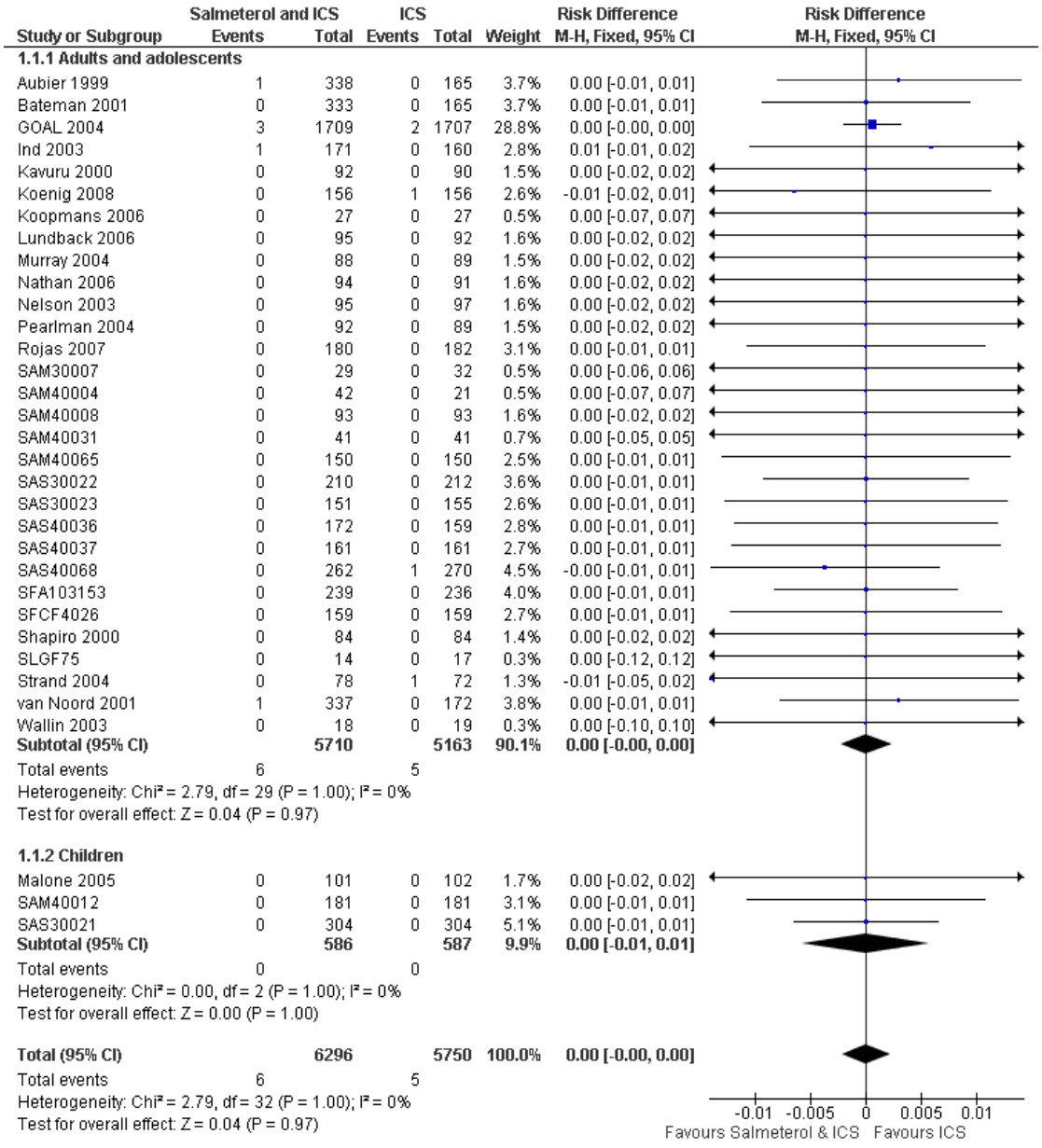


Figure 3. Forest plot of comparison: 1 Regular Salmeterol in addition to regular inhaled corticosteroids, outcome: 1.1 All-cause mortality (Risk Difference)



None of the deaths were reported as being related to asthma. There was one death from bronchial carcinoma in Aubier 1999 in a patient on separate salmeterol and fluticasone inhalers, two deaths from myocardial infarction in each arm of GOAL 2004 and one additional death from pneumonia on salmeterol/fluticasone, one death from pneumothorax in Ind 2003 on separate salmeterol and fluticasone, one death from cardiac arrest and deep vein thrombosis in Koenig 2008 on fluticasone, one death in SAS40068 from ventricular hypertrophy and aortic hypoplasia on fluticasone, one death of unknown cause in Strand 2004 on fluticasone, and one death in van Noord 2001 from leukaemia on combination salmeterol/fluticasone pMDI.

Children

No deaths were reported in the three studies on children (1,173 participants). It is not possible to calculate any Odds Ratios from this data, but the pooled Risk Difference can be assessed with a confidence interval, (RD 0.00; 95% CI -0.006 to 0.006). In other words, for every 1000 patients treated with salmeterol and inhaled corticosteroids for 16 weeks, the 95% confidence interval is compatible with either an increase or decrease of up to a maximum of six deaths.

Serious Adverse Events (non-fatal all cause)

A serious adverse event is defined as an event that falls in any of the following categories:

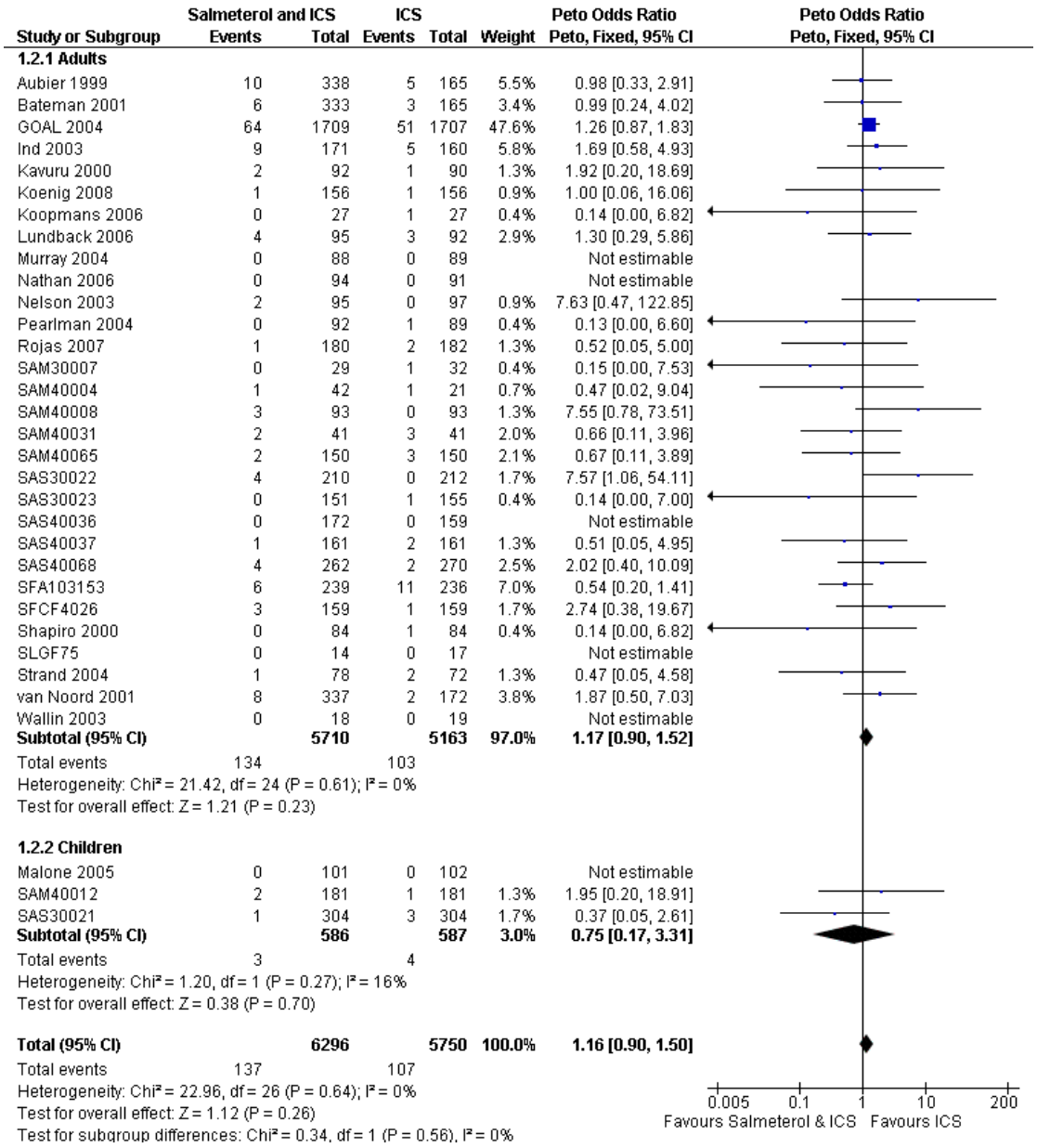
- Results in death,
- Is life-threatening,
- Requires inpatient hospitalization or prolongation of existing hospitalization,
- Results in persistent or significant disability/incapacity, or
- Is a congenital anomaly/birth defect.

This is the definition from the International Conference on Harmonisation (ICH), and we have assumed that this definition was used in the trials (even though this was often not explicitly reported in the papers, it is the standard definition for regulatory trials ICHE2a 1995).

Adults and Adolescents

The number of patients experiencing one or more non-fatal serious adverse events was similar when salmeterol was given with inhaled corticosteroids in comparison to inhaled corticosteroids alone. There were 134 out of 5710 (2.3%) participants on regular salmeterol with ICS and 103 out of 5163 (2.0%) on ICS alone. The Peto Odds Ratio was 1.17 (95% CI 0.90 to 1.52) and I^2 was zero (Figure 4). The pooled RD was 0.003 (95% CI -0.002 to 0.009). For every 1,000 patients treated with salmeterol and inhaled corticosteroids for 31 weeks, the results are compatible with both a possible decrease of up to two patients or an increase of up to nine patients with a serious adverse event.

Figure 4. Forest plot of comparison: 1 Regular Salmeterol in addition to regular inhaled corticosteroids, outcome: 1.2 All-cause non-fatal SAE.



Children

In the trials in children there were three out of 586 (0.5%) participants with serious adverse events on regular salmeterol with ICS and four out of 587 (0.7%) on ICS alone. The Peto Odds Ratio was 0.75 (95% CI 0.17 to 3.31) and I^2 was 16%, and the pooled RD for children was -0.002 (95% CI -0.01 to 0.008). For every 1,000 children treated with salmeterol and inhaled corticosteroids for 16 weeks, the results are compatible with both a possible decrease of up to ten children or an increase of up to eight children with a serious adverse event.

The test for interaction between adults and children did not find a significant impact of age on the treatment effect.

Secondary Outcomes

Mortality by cause of death

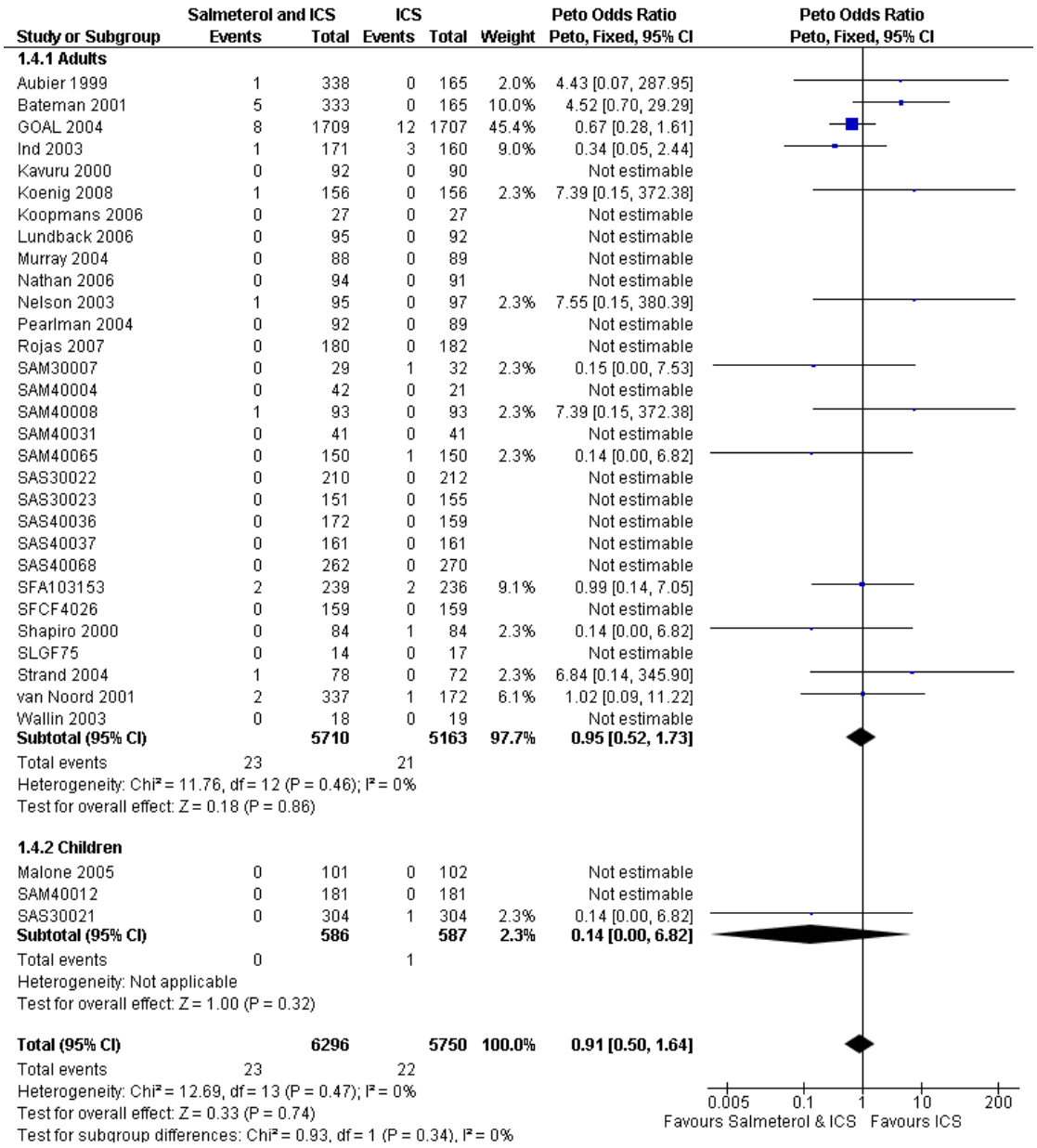
None of the deaths were reported to be due to asthma.

Serious Adverse Events related to Asthma

Adults and Adolescents

The number of patients experiencing one or more asthma related non-fatal serious adverse events was similar when salmeterol was given with inhaled corticosteroids in comparison to inhaled corticosteroids alone. There were 23 out of 5710 (0.4%) participants on regular salmeterol with ICS and 21 out of 5163 (0.4%) on ICS alone. The Peto Odds Ratio was 0.95 (95% CI 0.52 to 1.73) and I^2 was zero (Figure 5). The pooled RD was -0.002 (95% CI -0.003 to 0.003).

Figure 5. Forest plot of comparison: 1 Regular Salmeterol in addition to regular inhaled corticosteroids, outcome: 1.3 Asthma-related SAE.



Children

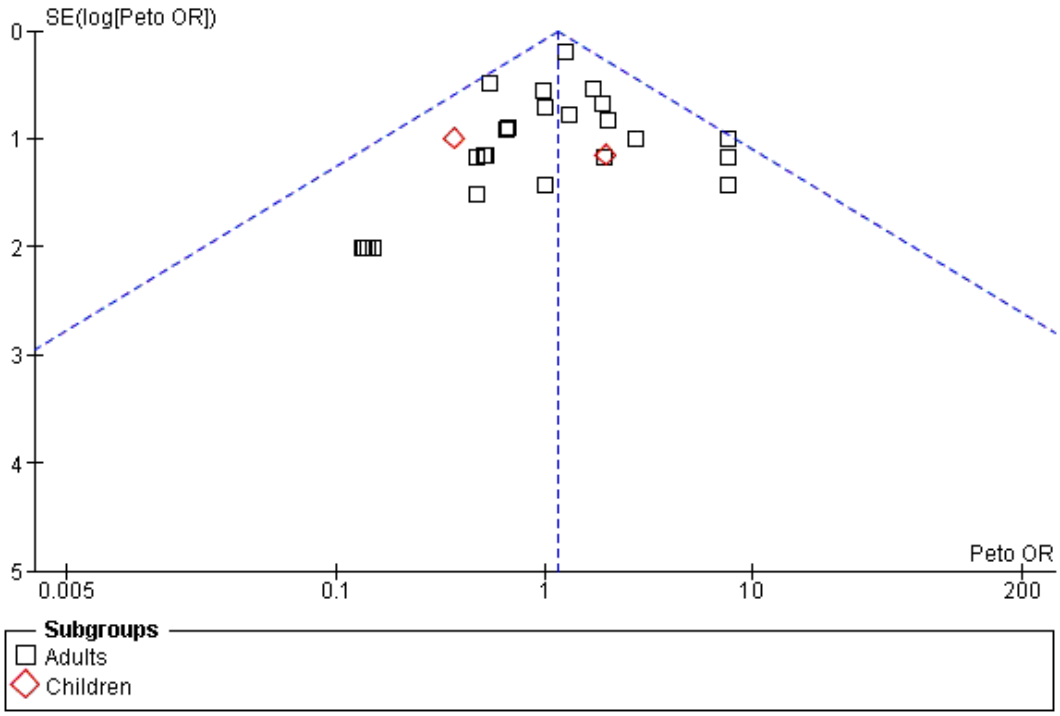
In the trials in patients who were less than 12 years of age none of the children (out of 586) had an asthma-related serious adverse event on regular salmeterol with ICS and one out of 587 (0.2%) on ICS alone. The Peto Odds Ratio showed no significant difference with wide confidence intervals (Peto OR 0.14; 95% CI 0.00 to 6.82). The pooled RD was -0.002 (95% CI -0.008 to 0.005). The difference between children and adults was again not statistically significant. We did not find data to assess the other proposed secondary outcomes (such as ITU admission and intubation).

Sensitivity Analyses

Risk of bias

No unblinded studies were identified. A funnel plot of non-fatal serious adverse events did not suggest obvious publication bias Figure 6.

Figure 6. Funnel plot of comparison: 1 Regular Salmeterol in addition to regular inhaled corticosteroids, outcome: 1.2 All-cause non-fatal SAE.

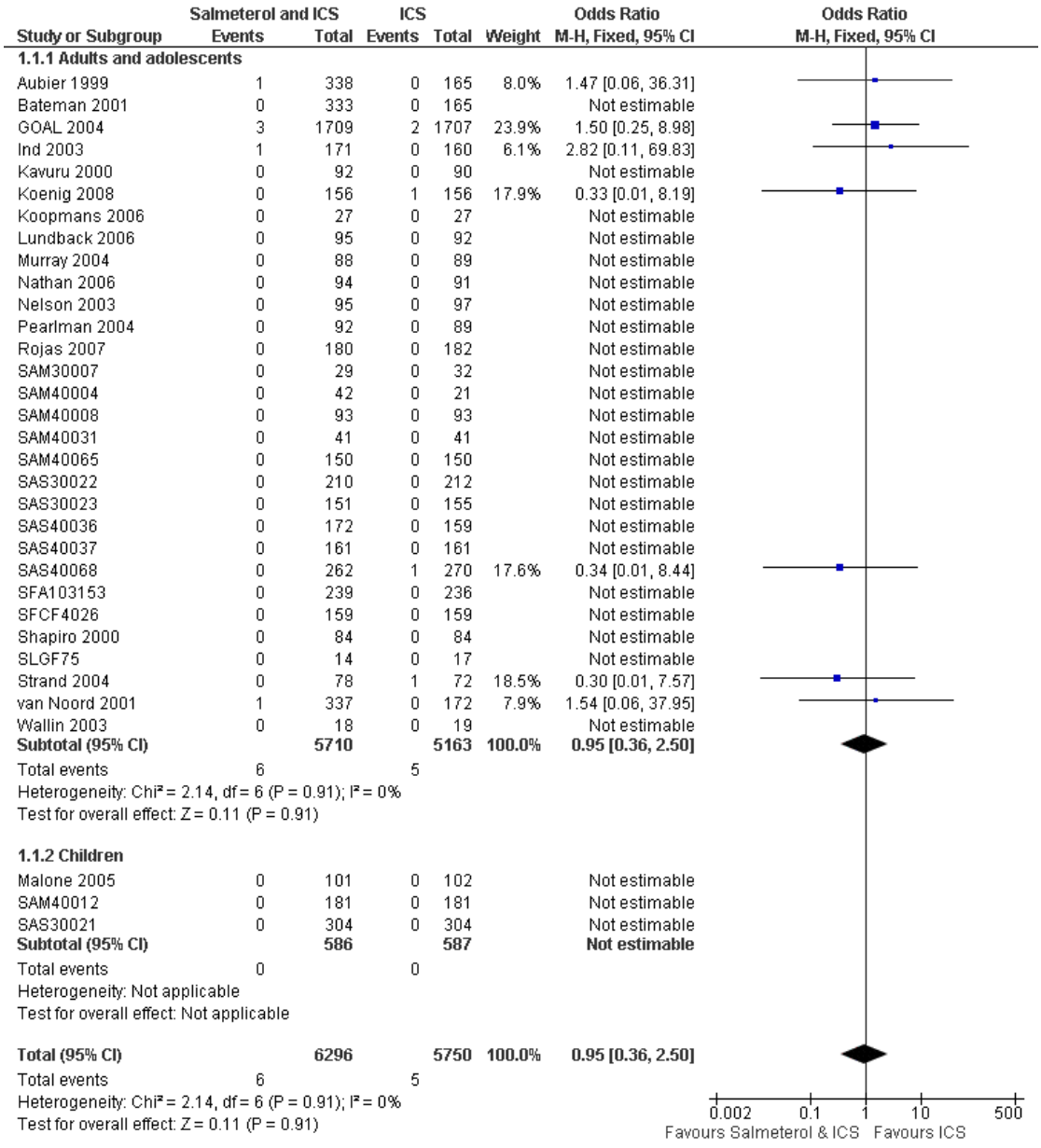


Methods of analysis

The primary outcomes were also analysed using Mantel-Haenszel fixed and random effects models. The results of the fixed effects model for mortality are shown in Figure 7. This method uses a correction for zero cells which is not required for the Peto OR. With this method the addition of 0.5 to all cells when the arms have similar numbers randomised will generate an OR of 3 when there is only one event in the treatment group and none in the control group. When there are very sparse outcomes (such as for mortality), the calculated OR is entirely dependent on the size of the zero cell adjustment, and whether the treatment arms are balanced. Although the direction of effect changes using the Mantel-Haenszel model (OR 0.95; 95% CI 0.36 to 2.50), the confidence

interval is very similar and the results clearly remain non-significant.

Figure 7. Forest plot of comparison: 1 Regular Salmeterol in addition to regular inhaled corticosteroids, outcome: 1.1 All-cause mortality (Mantel-Haenzel Fixed effects)



For non-fatal serious adverse events in adults the Peto method (Peto OR 1.17; 95% CI 0.90 to 1.52) gave almost identical results to Mantel-Haenszel fixed effects model (OR 1.17; 95% CI 0.90 to 1.51) Figure 8 or Mantel-Haenszel random effects (OR 1.14; 95% CI 0.87 to 1.49) Figure 9.

Figure 8. Forest plot of comparison: 1 Regular Salmeterol in addition to regular inhaled corticosteroids, outcome: 1.2 All-cause non-fatal SAE (Mantel-Haenszel fixed effects)

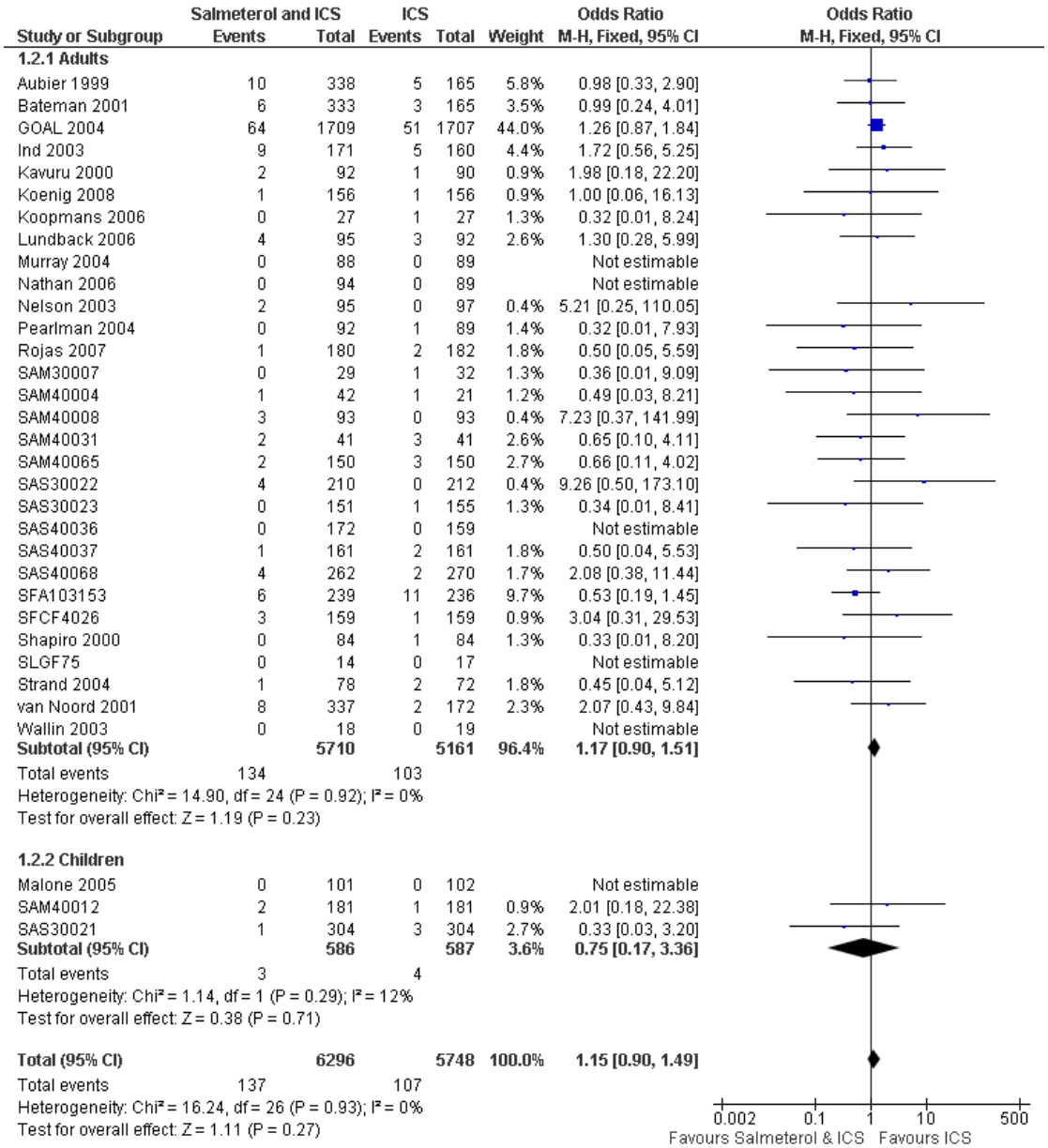
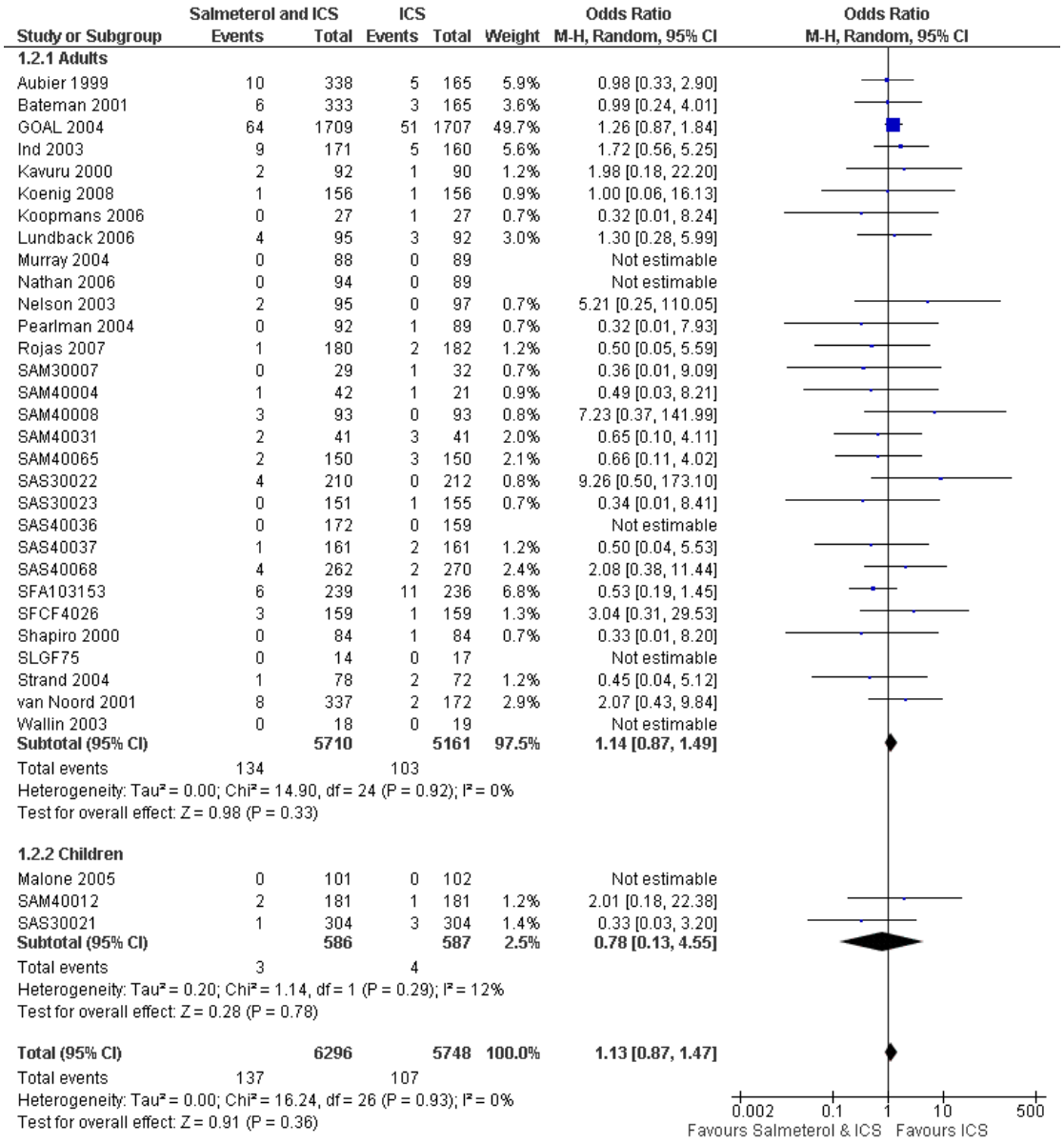
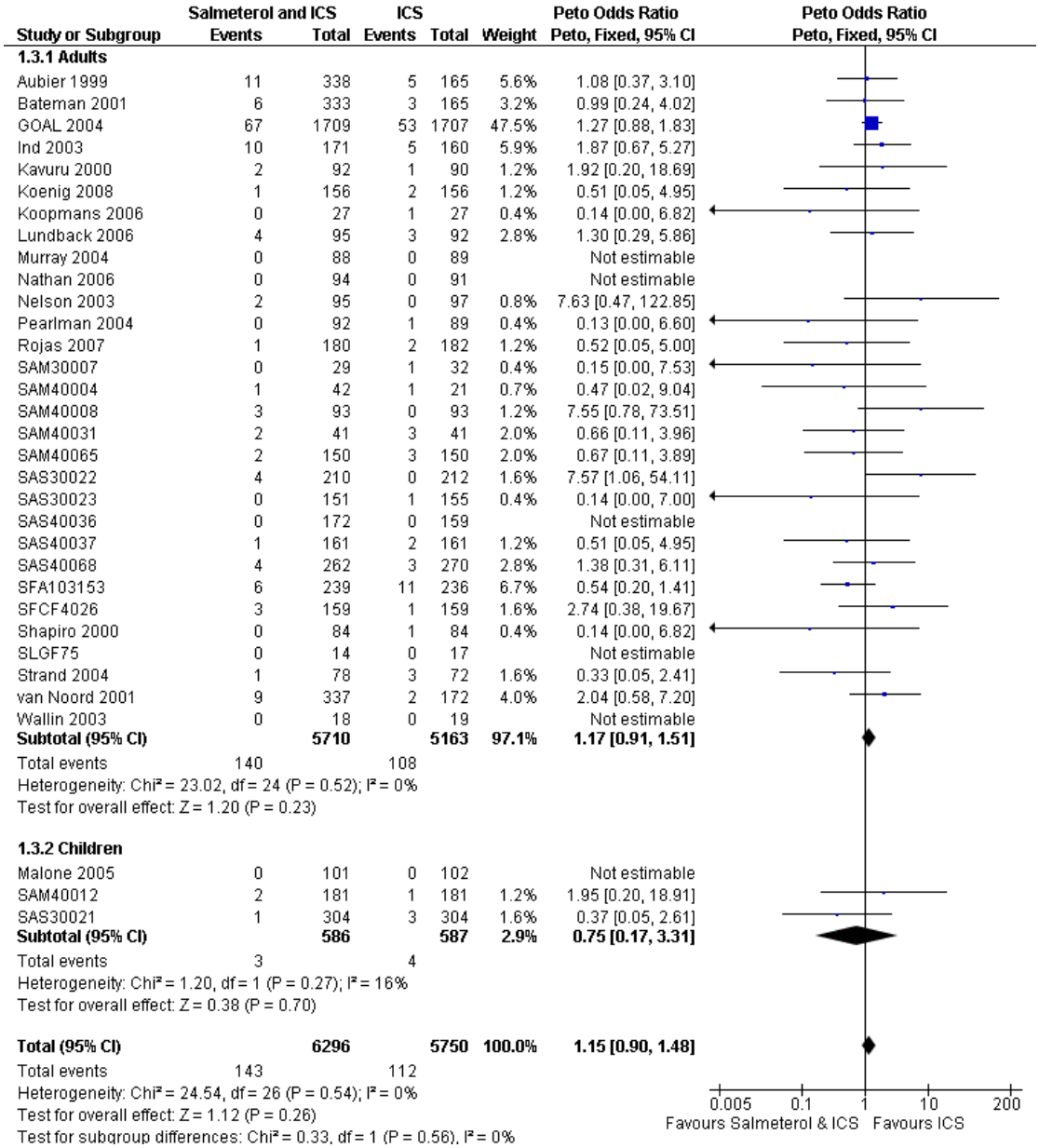


Figure 9. Forest plot of comparison: 1 Regular Salmeterol in addition to regular inhaled corticosteroids, outcome: 1.2 All-cause non-fatal SAE (Mantel-Haenszel random effects)



When fatal and non-fatal serious adverse events were combined the results for adults were almost identical to the pooled result for the non-fatal events in adults (Peto OR 1.17; 95% CI 0.91 to 1.51), and were unchanged in children as there were no deaths in children Figure 10.

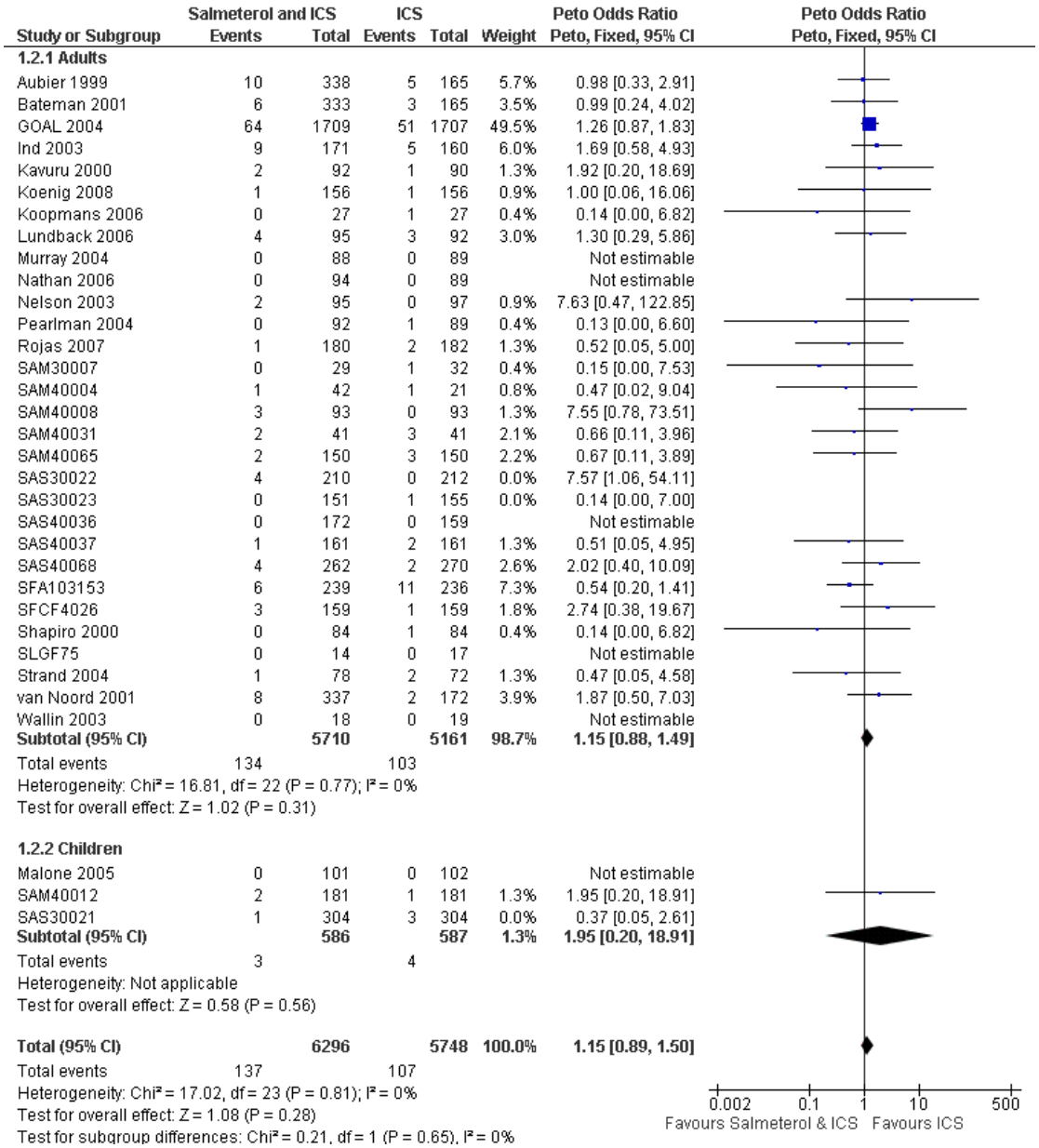
Figure 10. Forest plot of comparison: 1 Regular Salmeterol in addition to regular inhaled corticosteroids, outcome: 1.3 All-cause SAE (fatal and non-fatal)



Dose of salmeterol

The dose of salmeterol used in three studies was less than the usual daily dose of 50 mcg twice daily, so sensitivity analysis was carried out on the primary outcomes excluding these studies (SAS30021; SAS30022; SAS30023). There were no deaths in these studies so mortality results were unaffected. The non-fatal SAE results are shown in Figure 11. The results in adults without these studies in adults (Peto OR 1.15; 95% CI 0.88 to 1.49) are very similar to the full data set, but in children (Peto OR 1.95; 95% CI 0.20 to 18.91) the confidence interval widens when these studies are excluded.

Figure 11. Forest plot of comparison: 1 Regular Salmeterol in addition to regular inhaled corticosteroids, outcome: 1.2 All-cause non-fatal SAE (without the lower dose studies)



Subgroup Analyses

Mortality data was too sparse to carry out any sub-group analysis. For non-fatal serious adverse events, tests for interaction between adults and children were all negative, but very few children have been studied, so this result should not be interpreted as excluding important possible differences between adults and children. As only four studies included patients on separate salmeterol and fluticasone inhalers (Aubier 1999 [one of the three study arms]; Ind 2003; SLGF75; Wallin 2003 see Table 1), we did not attempt to make a subgroup comparison between separate and combined inhalers.

DISCUSSION

Summary of main results

All cause mortality

The confidence intervals for all cause mortality in adults and adolescents indicate that for every thousand patients treated with regular salmeterol and inhaled corticosteroids in comparison to the same dose of inhaled corticosteroids are compatible with up to two additional deaths or two less deaths in adults over 31 weeks of treatment, and at most six additional deaths to six less deaths in children over 16 weeks of treatment (the average duration of treatment in the respective trials). The pooled Peto Odds Ratio for adults and adolescents was 1.05 (95% CI 0.32 to 3.47), and could not be calculated for children as there were no deaths in children.

All cause non fatal serious adverse events

For non-fatal serious adverse events the limits of the pooled confidence interval are nine more to two fewer adults and adolescents and eight more to ten fewer children for every thousand treated over the period of time represented in the trials. The Peto Odds Ratio was 1.17 (95% CI 0.90 to 1.52) for adults, and 0.75 (95% CI 0.17 to 3.31) for children.

Overall completeness and applicability of evidence

Two large surveillance studies have been carried out on the use of regular salmeterol (SMART 2006, SNS 1993) without randomised inhaled corticosteroids. No similar size study has been performed to assess the safety of regular salmeterol randomised with inhaled corticosteroids. The results of this review are therefore less precise than those of the previous review on the safety of regular salmeterol randomised without inhaled corticosteroids (Cates 2008a), and very little data are available from studies on children.

Quality of the evidence

Risk of bias was assessed as low in the included studies, as the procedures for randomisation and blinding were appropriate having been designed for regulatory purposes (thereby ensuring common definitions of serious adverse events and minimising the likelihood of selection bias, even though this was not well reported in published papers or trial registers).

Potential biases in the review process

The selection of the best method to combine studies with rare events is contentious when event rates are low, not least because of the corrections required to calculate Odds Ratios with zero events (Sweeting 2004). Since it became apparent in the course of carrying out our reviews that the pooled Odds Ratios were heavily dependent on the zero adjustment used in the Mantel-Haenszel and Inverse Variance methods, we used the Peto Odds Ratio and Risk Differences to report results of this review. The likely bias in using the Peto Odds Ratio is small as only three trials (Aubier 1999; Bateman 2001; van Noord 2001) had any imbalance in the number of patients in each arm (Sweeting 2004). In these studies twice the number patients were randomised to regular salmeterol with inhaled corticosteroids in comparison to inhaled corticosteroids alone.

Similarly the included studies were influenced by the decision to restrict the review to trials that randomised participants to salmeterol and inhaled corticosteroids, but this decision reduces the risk of bias arising from patients discontinuing their usual inhaled steroid medication if they feel better on the randomised treatment. This presupposes a similar risk of SAEs when salmeterol and fluticasone are delivered via one inhaler, and when salmeterol is added to ICS therapy via a separate inhaler, when both are randomised treatments in a controlled trial.

Agreements and disagreements with other studies or reviews

Two existing reviews of the use of salmeterol with inhaled corticosteroids have shown similar results to the findings of this reviews. Bateman 2008 concentrated on asthma-related outcomes,

whilst Jaeschke 2008a considered both salmeterol and formoterol in adults in comparison to the inhaled corticosteroids at the same dose and higher doses. Neither of these reviews showed a significant increase in the risk of serious adverse events, but the results were not precise enough to rule out a clinically important increase or decrease in serious adverse events with regular salmeterol.

It became apparent during the course of preparing this review that there are minor discrepancies between the results recorded in the serious adverse event reports on the GlaxoSmithKline web site and the data used in Bateman 2008 and Jaeschke 2008a. An example of this relates to the death in Aubier 1999, and is related to the question of whether the adverse event was classified as being "on-treatment" (see Aubier Notes in Characteristics of included studies). Overall the magnitude of these differences is small, and mostly relates to an external review of company data and inclusion of reviewed data in some of the analyses; this has not altered the conclusions of the review.

Administration of inhaled corticosteroids

There is no clear difference seen between the point estimate and confidence interval of the Odds Ratio for non-fatal serious adverse events found in this review (Peto OR 1.16; 95% CI 0.90 to 1.50), and those seen in the previous review comparing salmeterol to placebo (Odds Ratio 1.14; 95% CI 1.01 to 1.28) Cates 2008a. However the average non-fatal serious adverse event rate in the control arms of the trials in this review that included randomised inhaled corticosteroids was 2.0% over 31 weeks, in comparison to 3.6% over 28 weeks in SMART 2006 (which accounted for the majority of patients in Cates 2008a).

Combined data from the GSK submission to the FDA (FDA 2008) shows separate outcome data for GSK trials that used inhaled corticosteroids as background treatment, those which randomised patients to inhaled corticosteroids in a separate inhaler and those which randomised patients to a combined salmeterol/fluticasone inhaler. These results are not directly comparable to those included in this review (as higher doses of inhaled corticosteroids may have been used in the control arms), but the breakdown by inhaled corticosteroid use is shown in Figure 12 and Figure 13. These results demonstrate that there was a significantly higher risk of asthma-related hospitalisation in trials where background inhaled corticosteroids were used, but there was no significant difference in trials which randomised patients to inhaled corticosteroids. However smaller numbers of events in the latter groups resulted in wide confidence intervals, so that an increase in adverse events could not be ruled out in trials that randomised patients to regular inhaled corticosteroids with regular salmeterol.

Figure 12. Risk difference (per 10,000 patients) of asthma-related death by use of Inhaled corticosteroids in GSK meta-analysis of trials of regular salmeterol (from FDA submission 2008)

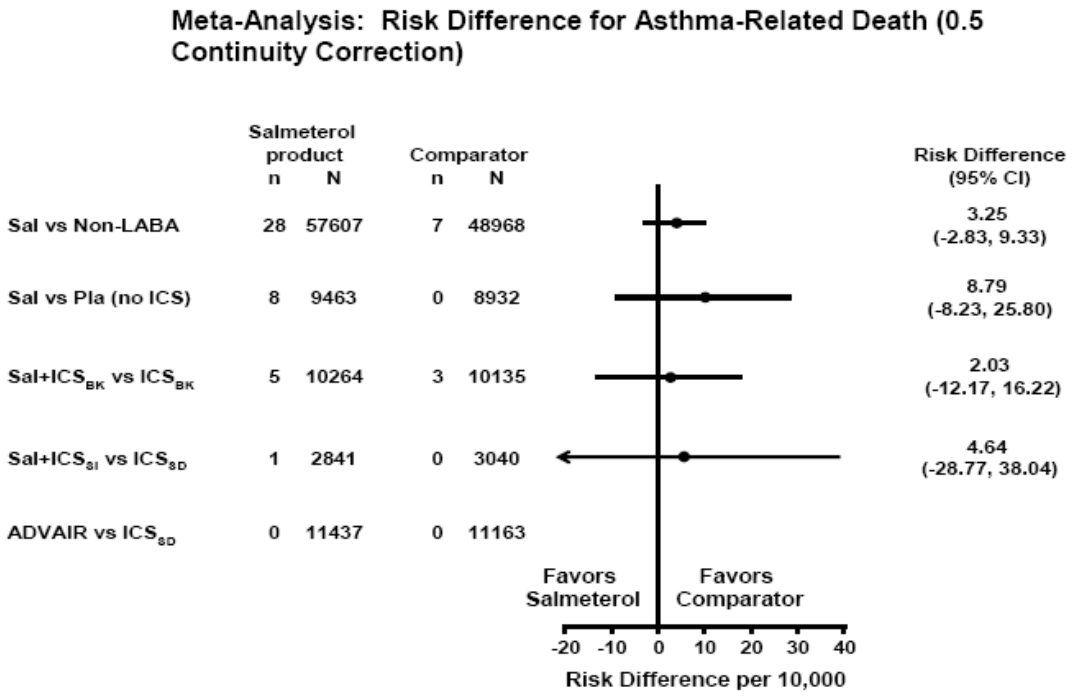
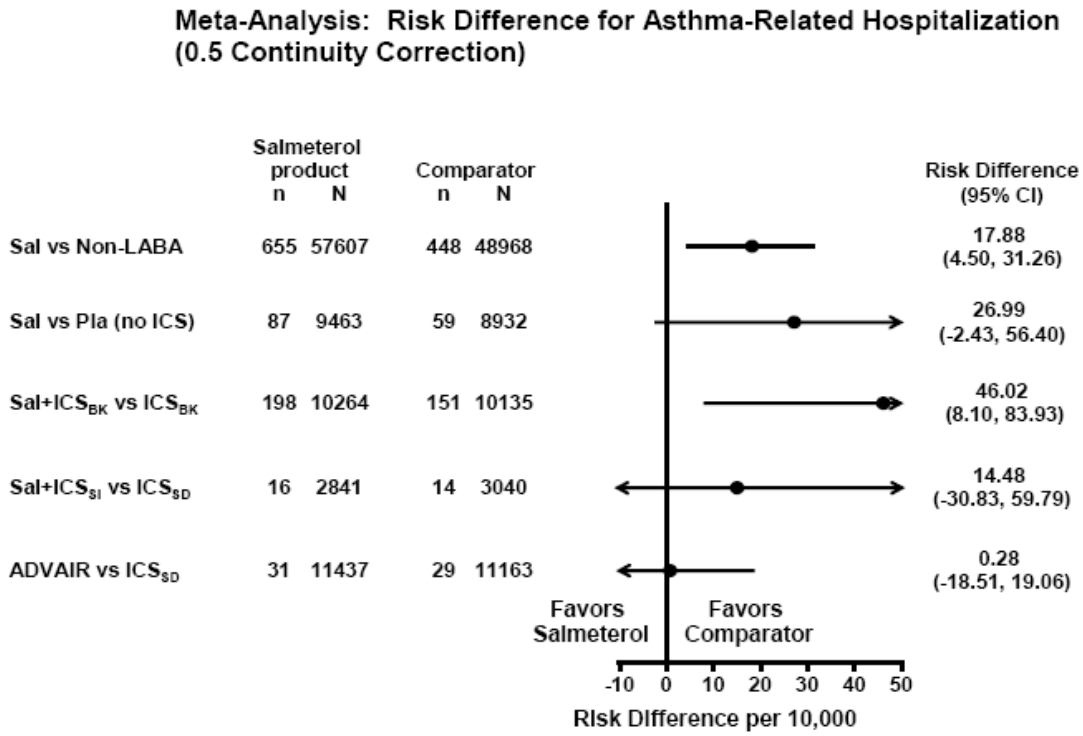


Figure 13. Risk difference (per 10,000 patients) of asthma-related hospitalisation by use of Inhaled corticosteroids in GSK meta-analysis of trials of regular salmeterol (from FDA submission 2008)



It is of interest that the serious adverse event rates in the control arms of these studies are also consistently higher in trials using background inhaled corticosteroids in comparison to those that randomised patients to inhaled corticosteroids. This may reflect a greater asthma severity in those patients who had been started by their own physician on background inhaled corticosteroids (as shown by Sears 2008 in the RELIEF study), but could also be compounded by the known poor adherence to treatment with inhaled corticosteroids in routine practice. This raises uncertainty about the application of the results of patients in clinical trials, which usually include much more intensive monitoring of adherence to therapy. Since we cannot assume that adherence to treatment in trials will be matched in routine practice, care needs to be exercised in both the interpretation and application of the trial results (Weiss 2008).

We were not able to investigate possible difference in trial findings with combined and separate inhalers due to the paucity of patients on separate inhalers included in the trials in this review (less than 300 patients were randomised to separate fluticasone and salmeterol inhalers, see Table 1).

AUTHORS' CONCLUSIONS

Implications for practice

No significant differences have been found in fatal or non-fatal serious adverse events in trials in which regular salmeterol has been randomly allocated with inhaled corticosteroids, in comparison to inhaled corticosteroids at the same dose. Although 10,873 adults and 1,173 children have been included in trials, the number of patients suffering adverse events is too small, and the results are too imprecise to confidently rule out a relative increase in all-cause

mortality or non-fatal adverse events. It is therefore not possible to determine whether the increase in all-cause non-fatal serious adverse events reported in the previous meta-analysis on regular salmeterol alone is abolished by the additional use of inhaled corticosteroids. The absolute difference between groups in the risk of serious adverse events was small. There were no asthma-related deaths and few asthma-related serious adverse events. Clinical decisions and information for patients regarding regular use of salmeterol have to take into account the balance between known symptomatic benefits of salmeterol and the degree of uncertainty and concern associated with its potential harmful effects.

Implications for research

Studies on children are currently lacking in this area. In order to further quantify the risks of regular salmeterol with inhaled corticosteroids a large-scale surveillance study is required. Future research should clearly specify the number of patients with fatal and non-fatal serious adverse events by treatment group and cause, and outcomes should be verified by an independent outcome panel.

ACKNOWLEDGEMENTS

We thank Susan Hansen of the Cochrane Airways Group for assistance in searching for trials and obtaining the abstracts and full reports, and extraction of data on trial characteristics. We also acknowledge the assistance of Matthew Cates in relation to the physiology of beta-agonist receptors and co-writing of protocol. We thank Steve Yancey for providing information from data on file at GlaxoSmithKline.

REFERENCES

References to studies included in this review

Aubier 1999 ***{published data only}***

SFCB3019. http://ctr.gsk.co.uk/Summary/fluticasone_salmeterol/III_SFCB3019.pdf Accessed July 2008.

Aubier M, Pieters WR, Schlösser NJ, Steinmetz KO. Salmeterol/fluticasone propionate (50/500 microg) in combination in a Diskus inhaler (Seretide) is effective and safe in the treatment of steroid-dependent asthma. *Respiratory Medicine* 1999;**93**:876–84.

Bateman 2001 ***{published data only}***

SFCB3022 . http://ctr.gsk.co.uk/Summary/fluticasone_salmeterol/III_SFCB3022.pdf Accessed July 2008.

* Bateman ED, Silins V, Bogolubov M. Clinical equivalence of salmeterol/fluticasone propionate in combination (50/100 micrograms twice daily) when administered via a chlorofluorocarbon-free metered dose inhaler or dry powder inhaler to patients with mild-to-moderate asthma. *Respiratory Medicine* 2001;**95**:136–46.

GOAL 2004 ***{published and unpublished data}***

Anonymous. GSK asthma trial suggests total control is possible. *Pharmaceutical Journal* 2004;**273**(7322):594.

Arthurs R. Gaining optimal asthma control. *Practice Nurse* 2004;**Suppl**:3–8.

Bateman E, Boushey H, Bousquet J, Busse W, Clark T, Pauwels R, Pedersen S. Achieving and maintaining guideline defined asthma control with salmeterol/fluticasone propionate versus fluticasone propionate alone: the results of the GOAL study. *American Journal of Respiratory and Critical Care Medicine* 2004;**169**(7):A87.

Bateman E, Boushey H, Bousquet J, Busse W, Clark T, Pauwels R, Pederson S. Achievement for guideline based asthma control with salmeterol/fluticasone proprioante comapred with fluticasone proprioante alone; Results of Goal study. Triennial World Asthma Meeting, Thailand (16-19 February). 2004.

Bateman E, Pauwels R, Boushey H, Bousquet J, Busse W, Clark T, Pedersen S. Aiming for total control of asthma significantly improves asthma-related quality of life: salmeterol/fluticasone propionate versus fluticasone propionate alone. *Amercian Journal of Respiratory and Critical Care Medicine* 2004;**169**(7):A87.

* Bateman ED, Boushey HA, Bousquet J, Busse WW, Clark TJ, Pauwels RA, Pedersen SE, GOAL Investigators Group. Can guideline-defined asthma control be achieved? The Gaining Optimal Asthma ControL study. *American Journal of Respiratory & Critical Care Medicine* 2004;**170**(8): 836–44.

Bateman ED, Boushey HA, Bousquet J, Busse WW, Clark TJ, Pauwels RA, Pedersen SE, GOAL Investigators Group. Can guideline-defined asthma control be achieved? The Gaining Optimal Asthma ControL study. American Respiratory and Criticial Care Medicine. 2004:Online data supplement.

Bateman ED, Bousquet J, Keech ML, Busse WW, Clark TJ, Pedersen SE. The correlation between asthma control and health status: the GOAL study. European Resspiratory Journal 2006:Epub ahead of print.

Bateman ED, Edin HM, Sondhi S, Gul N. Asthma-related quality of life in the GOAL study: Baseline results. *European Respiratory Journal* 2002;**20**(Suppl 38):46s.

Bons J, Cordier JF, Godard P, Prud'Homme A, Celli I, Bousquet J. Aiming for total control of asthma: the GOAL study design. *Revue Française d'Allergologie et d'Immunologie Clinique* 2004;**44**(367):TT13.

Boushey H, Bateman E, Bousquet J, Busse W, Clark T, Pauwels R, Pedersen S. Improvements in asthma outcomes following 1 year of treatment with salmeterol/

fluticasone or fluticasone alone when stepped up to achieve guideline-defined total control. *Journal Allergy and Clinical Immunology* 2004;**113**(2 (suppl 1)):114s–5s.
Boushey H, Bateman E, Bousquet J, Busse W, Clark T, Pauwels R, Pederson S. Achieving total control of asthma with salmeterol/fluticasone propionate versus fluticasone propionate alone: Goal study results. Triennial World Asthma Meeting, Thailand (16-19 February). 2004.
Boushey HA, Pedersen S, Bateman E, Clark T, Busse W, Bousquet J, Pauwels R. Improved exacerbation rates and asthma control in current and former smokers treated with salmeterol/fluticasone propionate: results of the GOAL study. *Journal of Allergy & Clinical Immunology* 2005;**115** (Suppl 2):S59.
Bousquet J. Is asthma control achievable?. *European Respiratory Review* 2004;**13**(92):102–4.
Bousquet J, Bateman E, Boushey H, Busse W, Clark T, Pauwels R, Pedersen S. The effect of oral corticosteroids and high-dose combination therapy on achieving control of refractory asthma. *Journal Allergy and Clinical Immunology* 2004;**113**(2 (suppl 1)):113s.
Bousquet J, Bons J, Godard P, Cordier JF, Desfougeres JL, Prud'Homme A. Aiming for total control of asthma: the GOAL study results. *Revue Française d'Allergologie et d'Immunologie Clinique* 2004;**44**(367):TT16.
Briggs AH, Bousquet J, Wallace MV, Busse WW, Clark TJH, Pedersen SE, Bateman ED. Cost-effectiveness of asthma control: An economic appraisal of the GOAL study. *Allergy* 2006;**61**(5):531–6.
Busse W, Bateman E, Boushey H, Bousquet J, Clark T, Pauwels R, Pedersen S. Achieving GINA/NIH guideline-based asthma control with salmeterol/fluticasone compared with fluticasone alone: the results of the GOAL study. *Journal of Allergy and Clinical Immunology* 2004;**113**(2 (suppl 1)):114s.
Busse W, Bateman E, Boushey H, Bousquet J, Clark T, Pauwels R, Pederson S. Aiming to achieve total control of asthma with salmeterol/luticaosne proprioante and flutiasone proprioante alone is well tolerated: Goal 1 year safety data. Triennial World Asthma Meeting, Thailand (16-19 February). 2004.
Clark T, Bateman E, Boushey H, Bousquet J, Busse W, Pauwels R, Pedersen S. Salmeterol/fluticasone and fluticasone alone are well tolerated over 1 year of treatment stepped-up to achieve total control: safety results of the GOAL study. *Journal Allergy and Clinical Immunology* 2004;**113**(2 (suppl 1)):115s.
Clark T, Bateman E, Boushey H, Bousquet J, Busse W, Pauwels R, Pedersen S. Time course of achievement of individual clinical goals of asthma treatment: the results of the GOAL study. *Amercian Journal of Respiratory and Critical Care Medicine* 2004;**169**(7):A318.
Clark TJ, Bousquet J, Bateman ED, James MH. GOAL (gaining optimal asthma control): a study to assess asthma control. *European Respiratory Journal* 2001;**18**(Suppl 33): 175–6s.
Clark TJH, Bateman ED, James MH, on behalf of the GOAL Steering Committee. Assessing asthma control using a composite measure based on GINA/NIH guidelines: an analysis of GOAL baseline data. *European Respiratory Journal* 2002;**20**(Suppl 38):47s.
Clark TJH, Bateman ED on behalf of the GOAL Steering Committee. Aiming for Total Control of asthma in ICS-free patients improves traditional outcomes: Results of the Gaining Optimal Asthma controL (GOAL) study [abstract]. 23rd European Academy of Allergology and Clinical Immunology Meeting Abstract Book. June 12-16. Amsterdam, The Netherlands. 2004; Vol. 204:669.
Cordier JF, Bousquet J, Boucot I, Prud'Homme A, Godard P. Which dose for achieving total control of asthma? The results of the GOAL study. *Revue Française d'Allergologie et d'Immunologie Clinique* 2004;**44**(367):TT14.
Godard P, Prud'Homme A, Cordier JF, Sohier B, Bousquet J. Time course of achievement of asthma control: The results of the GOAL study. *Revue Française d'Allergologie et d'Immunologie Clinique* 2004;**44**(367):TT15.
Juniper EF, Bateman ED, Sondhi S, Gul N. Asthma Control Questionnaire (ACQ) differentiates between levels of clinical control in a large scale trial. *Amercian Journal of Respiratory and Critical Care Medicine* 2003;**167**(7):A37.
Pauwels R, Bateman E, Boushey H, Bousquet J, Busse W, Clark T, Pedersen S. Addition of oral corticosteroids to combination therapy has little impact on achieving total control of asthma.. 4th Triennial World Asthma Meeting Abstract Book, Bangkok, Thailand, February 16-19. 2004: 135.
Pauwels R, Bateman E, Boushey H, Bousquet J, Busse W, Clark T, Pedersen S. Aiming for total control of asthma reduces the risk of exacerbations: a comparison of salmeterol/fluticasone propionate versus fluticasone propionate alone. *American Journal of Respiratory and Critical Care Medicine* 2004;**169**(7):A87.
Pauwels R, Bateman E, Boushey H, Bousquet J, Busse W, Clark T, Pedersen S. Can total control of asthma be achieved?: the results of the GOAL study. *Journal of Allergy and Clinical Immunology* 2004;**113**(2 (suppl 1)):114s.
Pedersen SE. Is guideline-defined asthma control achievable? The Gaining Optimal Asthma ControL (GOAL) Study [Er guideline–defineret astmakontrol opnaelig?]. *Ugeskrift for Laeger* 2005;**167**(38):3595–7.
Pedersen SE, Bateman ED on behalf of the GOAL Steering Committee. Aiming for Total Control of asthma in patients taking inhaled corticosteroids improves traditional outcomes: Results of the Gaining Optimal Asthma controL (GOAL) study. [abstract]. 3rd European Academy of Allergology and Clinical Immunology Meeting Abstract Book. June 12-16. Amsterdam, The Netherlands. 2004; Vol. 204:670.
Pederson S, Bateman E, Boushey H, Bousquet J, Busse W, Clark T, Pauwels R. Aiming for guideline defined total control of asthma improves one-year asthma outcomes: Results of Goal study. Triennial World Asthma Meeting, Thailand (16-19 February). 2004.
SAM40027. Gaining Optimal Asthma ControL (GOAL):

A multi-centre, stratified, randomised, double-blind, parallel-group, step-up comparison of the level of asthma control achieved with salmeterol/fluticasone propionate combination DISKUS (ACCUHALER) dry powder inhaler compared with fluticasone propionate DISKUS (ACCUHALER) alone in adults and adolescents. http://www.ctr.gsk.co.uk 2004.

Ind 2003 ***{published data only}***

SLGQ97 (SLGB4010). http://ctr.gsk.co.uk/Summary/salmeterol/IV_SLGB4010.pdf Accessed July 2008.

Ind PW, Dal Negro R, Colman NC, Fletcher CP, Browning D, James MH. Addition of salmeterol to fluticasone propionate treatment in moderate-to-severe asthma. *Respiratory Medicine* 2003;**97**:555–62.

Kavuru 2000 ***{published data only}***

SFCA3002. http://ctr.gsk.co.uk/Summary/fluticasone_salmeterol/III_SFCA3002.pdf Accessed July 2008.

* Kavuru M, Melamed J, Gross G, LaForce C, House K, Prillaman B, et al.Salmeterol and fluticasone propionate combined in a new powder inhalation device for the treatment of asthma: a randomized, double-blind, placebo-controlled trial. *J Allergy Clin Immunol* 2000;**150**(6):1108–16.

Koenig 2008 ***{published data only}***

SAM40086. http://ctr.gsk.co.uk/Summary/fluticasone_salmeterol/IV_SAM40086.pdf Accessed July 31 2008.

Koenig SM, Murray JJ, Wolfe J, Andersen L, Yancey S, Prillaman B, et al.Does measuring BHR add to guideline derived clinical measures in determining treatment for patients with persistent asthma?. *Respiratory Medicine* 2008;**102**:665–73.

Koopmans 2006 ***{published data only}***

SAS30013. http://ctr.gsk.co.uk/Summary/fluticasone_salmeterol/IV_SAS30013.pdf accessed August 11 2008.

Koopmans JG, Lutter R, Jansen HM, van der Zee JS. Adding salmeterol to an inhaled corticosteroid: long term effects on bronchial inflammation in asthma. *Thorax* 2006;**61**:306–12.

Lundback 2006 ***{published data only}***

FAS40008. http://ctr.gsk.co.uk/Summary/fluticasone_salmeterol/IV_FAS40008_1y.pdf accessed August 11th 2008.

Lundbäck B, Rönmark E, Lindberg A, Jonsson AC, Larsson LG, Pétavy F, et al.Control of mild to moderate asthma over 1-year with the combination of salmeterol and fluticasone propionate. *Respiratory Medicine* 2006;**100**:2–10.

Malone 2005 ***{published data only}***

SAS30031. http://ctr.gsk.co.uk/Summary/fluticasone_salmeterol/III_SAS30031.pdf Accessed July 2008.

* Malone R, LaForce C, Nimmagadda S, Schoaf L, House K, Ellsworth A, et al.The safety of twice-daily treatment with fluticasone propionate and salmeterol in pediatric patients with persistent asthma. *Ann Allergy Asthma Immunol* 2005;**96**:66–71.

Murray 2004 ***{published data only}***

SAS30017. http://ctr.gsk.co.uk/Summary/fluticasone_salmeterol/III_SAS30017.pdf Accessed July 2008.

* Murray J, Rosenthal R, Somerville L, Blake K, House K, Baitinger L, et al.Fluticasone propionate and salmeterol administered via Diskus compared with salmeterol or fluticasone propionate alone in patients suboptimally controlled with short-acting beta2-agonists. *Ann Allergy Asthma Immunol. 2004;93:351-9* 2004;**93**:351–9.

Nathan 2006 ***{published and unpublished data}***

Edin HM, Payne E, Herrle MR, Schoaf L, Mather DB, Scott CA, et al.Salmeterol/fluticasone propionate combination via HFA MDI improves quality of life. *Journal of Allergy & Clinical Immunology* 2001;**107**(2):S246.

Nathan RA, Mitchell D, Condemi J, Heller A, Schoaf L, Herrle M, et al.Cardiovascular and hypothalmic-pituitary-adrenal axis safety of fluticasone propionate/salmeterol HFA MDI in adolescent and adult patients with asthma. *American Journal for Respiratory and Critical Care Medicine* 2001;**163**(5):A863.

* Nathan RA, Rooklin A, Schoaf L, Scott C, Ellsworth A, House K, Dorinsky P. Efficacy and tolerability of fluticasone propionate/salmeterol administered twice daily via hydrofluoroalkane 134a metered-dose inhaler in adolescent and adult patients with persistent asthma: a randomized, double-blind, placebo-controlled, 12-week study. *Clinical therapeutics* 2006;**28**(1):73–85.

Pearlman DS, Kent E, Lanz MJ, Peden D, Baitinger L, Herrle M, et al.Fluticasone propionate/salmeterol HFA MDI has a rapid onset of effect in asthmatics treated with short or long-acting beta-agonists (BA) or inhaled corticosteroids (ICS). *Amercian Journal of Respiratory and Critical Care Medicine* 2001;**163**(5):A865.

Rooklin A, Elkayam D, Weiler J, Windom H, Schoaf L, Scott C, et al.The fluticasone propionate/salmeterol HFA MDI is significantly more efficacious in treating asthma than placebo HFA MDI, fluticasone propionate CFC MDI or salmeterol CFC MDI. *Journal of Allergy and Clinicial Immunology* 2001;**107**(2):100s.

SAS30004. A randomized, double-blind, placebo-controlled, parallel-group 12-week trial evaluating the safety and efficacy of the salmeterol/fluticasone propionate combination in GR106642X MDI, 50/250mcg BID, and salmeterol in propellant 11/12 MDI, 50mcg BID, fluticasone propionate in propellant 11/12 MDI, 250mcg BID, and placebo propellant GR106642X MDI in adult and adolescent subjects with asthma. http://ctr.gsk.co.uk 2005.

Nelson 2003 ***{published data only}***

SAS30001. http://ctr.gsk.co.uk/Summary/fluticasone_salmeterol/III_SAS30001.pdf Accessed July 2008.

* Nelson HS, Wolfe JD, Gross G, Greos LS, Baitinger L, Scott C, Dorinsky P. Efficacy and safety of fluticasone

propionate 44mcg/salmeterol 21mcg administered in a hydrofluoroalkane (HFA) metered dose inhaler as an initial asthma maintenance treatment. *Ann Allergy Asthma Immunol* 2003;**91**:263–9.

Pearlman 2004 *{published and unpublished data}*

* Pearlman DS, Peden D, Condemi JJ, Weinstein S, White M, Baitinger L, et al.Efficacy and safety of fluticasone propionate/salmeterol HFA 134A MDI in patients with mild-to-moderate persistent asthma. *Journal of Asthma* 2004;**41**(8):797–806.

SAS30003. A stratified, randomised, double-blind, placebo-controlled, parallel-group, 12-week trial evaluating the safety and efficacy of the salmeterol/fluticasone propionate combination in HFA 134a MDI, 42/88mcg BID, and salmeterol in propellant 11/12 MDI, 42mcg BID, fluticasone propionate in propellant 11/12 MDI, 88mcg BID, and placebo propellant HFA 134a MDI in adult and adolescent subjects with asthma. http://ctr.gsk.co.uk 2005.

Weinstein SF, Pearlman DS, Condemi JJ, Herrle MR, Scott CA, Payne JE, et al.Superior efficacy of the fluticasone propionate/salmeterol 88/42mcg HFA-MDI combination product versus the individual components in asthmatics previously treated with either short- or long-acting beta2-agonists or inhaled corticosteroids. *Journal of Allergy & Clinial Immunology* 2001;**107**(2):S102.

Rojas 2007 *{published data only}*

SAS30039. http://ctr.gsk.co.uk/Summary/fluticasone_salmeterol/III_SAS30039.pdf Accessed July 2008.

Barnes N, Rojas R, Palga I, Goldfrad C, Duggan M. Efficacy and safety of fluticasone propionate/salmeterol (250/50ug bd) in a single diskus device compared with fluticasone propionate diskus alone (250ug) as initial maintenance therapy in moderate asthma [Abstract]. American Thoracic Society 2005 International Conference; May 20-25; San Diego, California. 2005:[B35] [Poster: G13].

* Rojas RA, Paluga I, Goldfrad CH, Duggan MT, Barnes N. Initiation of maintenance therapy with salmeterol/fluticasone propionate combination therapy in moderate asthma: a comparison with fluticasone propionate. *J Asthma* 2007;**44**:437–41.

SAM30007 *{published data only}*

SAM30007. http://ctr.gsk.co.uk/Summary/fluticasone_salmeterol/IV_SAM30007.pdf.

SAM40004 *{published data only}*

* SAM40004. http://ctr.gsk.co.uk/Summary/fluticasone_salmeterol/IV_SAM40004.pdf accessed August 19 2008.

SAM40008 *{published data only}*

SAM40008. http://ctr.gsk.co.uk/Summary/fluticasone_salmeterol/IV_SAM40008.pdf.

SAM40012 *{unpublished data only}*

SAM40012. http://ctr.gsk.co.uk/Summary/fluticasone_salmeterol/IV_SAM40012.pdf.

SAM40031 *{published data only}*

SAM40031. http://ctr.gsk.co.uk/Summary/fluticasone_salmeterol/IV_SAM40031.pdf.

SAM40065 *{published data only}*

SAM40065. http://ctr.gsk.co.uk/Summary/fluticasone_salmeterol/IV_SAM40065.pdf accessed august 11th 2008.

SAS30021 *{published data only}*

SAS30021. http://ctr.gsk.co.uk/Summary/fluticasone_salmeterol/III_SAS30021.pdf accessed August 11th 2008.

SAS30022 *{unpublished data only}*

SAS30022. http://ctr.gsk.co.uk/Summary/fluticasone_salmeterol/III_SAS30022.pdf Accessed July 2008.

Kerwin EM, Nathan RA, Meltzer EO, Ortega HG, Yancey SW, Schoaf L, et al.Efficacy and safety of fluticasone propionate/salmeterol 250/50 mcg Diskus administered once daily. Respir Med. 2008/01/22 2008; Vol. 102, issue 4:495–504. [0954–6111: (Print)]

SAS30023 *{published data only}*

SAS30023. http://ctr.gsk.co.uk/Summary/fluticasone_salmeterol/III_SAS30023.pdf accessed August 11 2008.

Boonsawat W, Goryachkina L, Millns H, Balsara S. The efficacy and safety of seretide/advair once daily (50/100 mcg) compared with fluticasone propionate (100mcg) once daily and placebo as initial maintainence therapy in mild asthma [Abstract]. American Thoracic Society 100th International Conference, May 21-26, 2004, Orlando 2004:A37 Poster J82.

SAS40036 *{published data only}*

SAS40036. http://ctr.gsk.co.uk/Summary/fluticasone_salmeterol/IV_SAS40036.pdf accessed August 11th 2008.

SAS40037 *{published data only}*

SAS40037. http://ctr.gsk.co.uk/Summary/fluticasone_salmeterol/IV_SAS40037.pdf accessed August 11 2008.

SAS40068 *{published data only}*

SAS40068. http://ctr.gsk.co.uk/Summary/fluticasone_salmeterol/IV_SAS40068.pdf Accessed August 11 2008.

SFA103153 *{unpublished data only}*

SFA103153. http://ctr.gsk.co.uk/Summary/fluticasone_salmeterol/IV_SFA103153.pdf Accessed July 2008.

Bailey W, Castro M, Matz J, White M, et al.Asthma exacerbations in African Americans treated for 1 year with combination fluticasone proprionate and salmeterol or fluticasone proprionate alone. *Current Medical Research and Opinions* 2008;**24**(6):1669–82.

SFCF4026 *{published data only}*

SFCF4026. http://ctr.gsk.co.uk/Summary/fluticasone_salmeterol/IV_SFCF4026.pdf Accessed August 11 2008.

Shapiro 2000 *{published data only}*

SFCA3003. A Randomized, Double-Blind, Parallel-Group Trial Evaluating Safety and Efficacy of Salmeterol 50mcg BID and Fluticasone Propionate 250mcg BID Individually and in Combination and Placebo in Subjects with Asthma. http://ctr.gsk.co.uk/Summary/fluticasone_salmeterol/III_SFCA3003.pdf 2005.

Shapiro G, Lumry W, Wolfe J, Given J, White M, Woodring A, et al.Combined salmeterol 50mcg and fluticasone propionate 250mcg in the diskus device for the treatment of asthma. *American Journal of Respiratory and Critical Care Medicine* 2000;**161**:527–34.

SLGF75 *{published data only}*

SLGF75. http://ctr.gsk.co.uk/Summary/fluticasone_propionate/IV_SLGF75.pdf Accessed August 11th 2008.

Strand 2004 *{published data only}*

SAM40049. http://ctr.gsk.co.uk/Summary/fluticasone_salmeterol/IV_SAM40049.pdf Accessed July 2008.

Strand AM, Luckow A. Initiation of maintenance treatment of persistent asthma: salmeterol/fluticasone propionate combination treatment is more effective than inhaled steroid alone. *Respiratory Medicine* 2004;**98**:1008–15.

van Noord 2001 *{published data only}*

SFCB3023. http://ctr.glaxowellcome.co.uk/Summary/fluticasone_salmeterol/III_SFCB3023.pdf Accessed July 2008.

* van Noord JA, Lill H, Carrillo Diaz C, Greefhorst AP, Davies P. Clinical equivalence of a salmeterol/fluticasone propionate combination product (50/500 mcg) delivered via a chlorofluorocarbon-free metered-dose inhaler with the Diskus^{TM} in patients with moderate to severe asthma. *Clin Drug Investig 2001;21:243-255.* 2001;**21**:243–55.

Wallin 2003 *{published data only}*

SLGQ98. http://ctr.gsk.co.uk/Summary/salmeterol/IV_SLGQ98.pdf Accessed July 2008.

Wallin A, Sue-Chu M, Bjermer L, Ward J, Sandström T, Lindberg A, et al.Effect of inhaled fluticasone with and without salmeterol on airway inflammation in asthma. *J Allergy Clin Immunol* 2003;**112**:72–8.

References to studies excluded from this review

Adinoff 1998 *{published data only}*

Adinoff AD, Schwartz HJ, Rickard KA, Yancey SW, Swearingen BE. Salmeterol compared with current therapies in chronic asthma.[erratum appears in J Fam Pract 1999 Jan;48(1):67]. Journal of Family Practice 1998; Vol. 47, issue 4:278–84.

Adolfsson 2005 *{published data only}*

Adolfsson LE, Lundgren M, Tilling B, Jern S, Tyren C, Godwood A, et al.Short-term safety and tolerability of double-dose salmeterol/fluticasone propionate in adult asthmatic patients. Clinical Drug Investigation 2005; Vol. 25, issue 4:231–41.

Bateman 1998 *{published data only}*

Bateman ED, Britton M, Carrillo J, Almeida J, Wixon C. Salmeterol/fluticasone combination inhaler. A new, effective and well tolerated treatment for asthma. Clinical Drug Investigation 1998; Vol. 16, issue 3:193–201.

Bateman 2006 *{published data only}*

Bateman ED, Jacques L, Goldfrad C, Atienza T, Mihaescu T, Duggan M. Asthma control can be maintained when fluticasone propionate/salmeterol in a single inhaler is stepped down. Journal of Allergy & Clinical Immunology 2006; Vol. 117, issue 3:563–70.

Baumgarten 2002 *{published data only}*

Baumgarten C, Geldszus R, Behre U, Peslis N, Trautmann M. Initial treatment of symptomatic mild to moderate bronchial asthma with the salmeterol/fluticasone propionate (50/250 microg) combination product (SAS 40023). Eur J Med Res 2002; Vol. 7, issue 1:1–7.

Bergmann 2004 *{published data only}*

Bergmann KC, Lindemann L, Braun R, Steinkamp G. Salmeterol/fluticasone propionate (50/250 microg) combination is superior to double dose fluticasone (500 microg) for the treatment of symptomatic moderate asthma. Swiss Medical Weekly 2004; Vol. 134, issue 3–4:50–8.

Bjermer 2000 *{published data only}*

Bjermer L, Bisgaard H, Bousquet J, Fabbri LM, Greening A, Haahtela T, et al.Montelukast or salmeterol combined with an inhaled steroid in adult asthma: design and rationale of a randomized, double-blind comparative study the IMPACT Investigation of Montelukast as a Partner Agent for Complementary Therapy-trial. Respiratory Medicine 2000; Vol. 94, issue 6:612–21.

Bjermer 2003 *{published data only}*

Bjermer L, Bisgaard H, Bousquet J, Fabbri LM, Greening AP, Haahtela T, et al.Montelukast and fluticasone compared with salmeterol and fluticasone in protecting against asthma exacerbation in adults: one year, double blind, randomised, comparative trial. BMJ 2003; Vol. 327, issue 7420:891.

Bleecker 2006 *{published data only}*

Bleecker ER, Yancey SW, Baitinger LA, Edwards LD, Klotsman M, Anderson WH, et al.Salmeterol response is not affected by beta2-adrenergic receptor genotype in subjects with persistent asthma. Journal of Allergy & Clinical Immunology 2006; Vol. 118, issue 4:809–16.

Bleecker 2007 *{published data only}*

Bleecker E, Yancey S, Ortega H, Anderson W. Arginine 16 genotype does not modulate clinical response to salmeterol in subjects with asthma. Chest 2007; Vol. 132, issue 4:436.

Bleecker 2008 *{published data only}*

Bleecker ER, Postma DS, Lawrance RM, Meyers DA, Ambrose HJ, Goldman M. Effect of ADRB2 polymorphisms on response to long-acting beta2-agonist therapy: a pharmacogenetic analysis of two randomised studies.[see comment]. [Review] [33 refs] Comment in: Lancet. 2008 Dec 22;370(9605):2075-6; PMID: 18156014. LANCET 2008; Vol. 370, issue 9605:2118–25.

Bracamonte 2005 *{published data only}*
Bracamonte T, Schauer U, Emeryk A, Godwood A, Balsara S. Efficacy and safety of salmeterol/fluticasone propionate combination delivered by the Diskus or pressurised metered-dose inhaler in children with asthma. Clinical Drug Investigation 2005; Vol. 25, issue 1:1–11.

Busse 2006 *{published data only}*
Busse W. The effect of salmeterol on eosinophil function. clinicaltrials.gov 2006.

Calhoun 2001 *{published data only}*
Calhoun WJ, Nelson HS, Nathan RA, Pepsin PJ, Kalberg C, Emmett A, et al.Comparison of fluticasone propionate-salmeterol combination therapy and montelukast in patients who are symptomatic on short-acting beta2-agonists alone. American Journal of Respiratory & Critical Care Medicine 2001; Vol. 164, issue 5:759–63.

Chapman 1999 *{published data only}*
Chapman KR, Ringdal N, Backer V, Palmqvist M, Saarelainen S, Briggs M. Salmeterol and fluticasone propionate 50/250 mug administered via combination Diskus inhaler: As effective as when given via separate Diskus inhalers. Canadian Respiratory Journal 1999; Vol. 6, issue 1:45–51.

Condemi 1999 *{published data only}*
Condemi JJ, Goldstein S, Kalberg C, Yancey S, Emmett A, Rickard K. The addition of salmeterol to fluticasone propionate versus increasing the dose of fluticasone propionate in patients with persistent asthma. Salmeterol Study Group. Annals of Allergy, Asthma, & Immunology 1999; Vol. 82, issue 4:383–9.

Cook 1998 *{published data only}*
Cook D, Srebro SH, Rogenes PR, Rickard K, Edwards L, Johnson MC. A comparison of the safety and efficacy of fluticasone, triamcinolone, and fluticasone plus salmeterol in patients with mild to moderate asthma [abstract]. American Journal of Respiratory and Critical Care Medicine 1998; Vol. 157, issue 3 Suppl:A416.

D'Urzo 2001 *{published data only}*
D'Urzo AD, Chapman KR, Cartier A, Hargreave FE, Fitzgerald M, Tesarowski D. Effectiveness and safety of salmeterol in non-specialist practice settings. Chest 2001; Vol. 119, issue 3:714–9.

Del 2001 *{published data only}*
Del Rio-Navarro BE, Sienra-Monge JJL, Alvarez-Amador M, Reyes-Ruiz N, Arevalo-Salas A, Berber A. Serum potassium levels, CPK-MB and ECG in children suffering asthma treated with beclomethasone or beclomethasone-salmeterol. Allergologia et Immunopathologia 2001; Vol. 29, issue 1:16–21.

Deykin 2007 *{published data only}*
Deykin A, Wechsler ME, Boushey HA, Chinchilli VM, Kunselman SJ, Craig TJ, et al.Combination therapy with a long-acting beta-agonist and a leukotriene antagonist in moderate asthma. American Journal of Respiratory & Critical Care Medicine 2007; Vol. 175, issue 3:228–34.

Didier 1997 *{published data only}*
Didier A, Campos OR. A two-month comparison of salmeterol/beclomethasone and slow-release terbutaline/budesonide in moderate asthma management. Clinical Drug Investigation 1997; Vol. 14, issue 1:1–11.

Dorinsky 2004 *{published data only}*
Dorinsky P, Kerwin E, Schoaf L, Ellsworth A, Housse K. Effectiveness and safety of fluticasone propionate / salmeterol 250/50mcg administered once daily to patients with persistent asthma [Abstract]. European Respiratory Journal 2004; Vol. 24, issue Suppl 48:309s.

Faurschou 1994 *{published data only}*
Faurschou P, Engel AM, Haanaes OC. Salmeterol in two different doses in the treatment of nocturnal bronchial asthma poorly controlled by other therapies. Allergy 1994; Vol. 49, issue 10:827–32.

Fish 2001 *{published data only}*
Fish JE, Israel E, Murray JJ, Emmett A, Boone R, Yancey SW, et al.Salmeterol Powder Provides Significantly Better Benefit Than Montelukast in Asthmatic Patients Receiving Concomitant Inhaled Corticosteroid Therapy. Chest 2001; Vol. 120, issue 2:423–30.

Fujimoto 2006 *{published data only}*
Fujimoto K, Komatsu Y, Yasuo M, Urushihata K, Kubo K. Comparison of the clinical efficacy of salmeterol and sustained-release tulobuterol (patch) on inadequately controlled asthma patients on inhaled corticosteroids. Journal of Asthma. 2006; Vol. 43, issue 7:501–7.

GlaxoSmithKline 2004 *{published data only}*
GlaxoSmithKline. A 52-week multicentre, randomised, double-blind, double dummy, placebo-controlled parallel group study to compare the efficacy and tolerability of salmeterol/fluticasone propionate combination (SERETIDE/VIANI/ADVAIR) 50/100 mcg once daily in the morning with fluticasone propionate (FLIXOTIDE/FLOVENT) 100 mcg twice daily and placebo twice daily, all via the DISKUS/ACUHALER as initial maintenance therapy in mild asthmatic subjects. GlaxoSmithKline Clinical Trial Register 2004.

GlaxoSmithKline 2005 *{published data only}*
GlaxoSmithKline. A 12 week, randomized, double-blind, parallel group study to compare the efficacy and safety of salmeterol/fluticasone propionate/GR106642X (25/50 µg x 2 inhalations) bid with fluticasone propionate (125 µg x 2 inhalations) bid in adolescent and adult patients with mild to moderate asthma. GlaxoSmithKline Clinical Trial Register 2005.

GlaxoSmithKline 2005a *{published data only}*
GlaxoSmithKline. Comparison of the efficacy and safety of Seretide and beclomethasone dipropionate plus montelukast in asthma. GlaxoSmithKline Clinical Trial Register 2005.

GlaxoSmithKline 2005c *{published data only}*
GlaxoSmithKline. A multi-centre, randomised, open-label, parallel group clinical trial to assess the efficacy and safety of salmeterol/fluticasone propionate combination product

(2x 25/125µg/actuation, bd) via a hydrofluoroalkane metered-dose inhaler compared with salmeterol/fluticasone propionate accuhaler (50/250µg bd) in adult Chinese patients with mild to moderate asthma. GlaxoSmithKline Clinical Trial Register 2005.

GlaxoSmithKline 2005d *{published data only}*
GlaxoSmithKline. A randomized, double-blind clinical trial comparing the efficacy and safety of salmeterol xinafoate 42mcg bid plus fluticasone propionate 88mcg bid versus fluticasone propionate 220mcg bid alone in subjects with asthma not well controlled on fluticasone propionate 88mcg bid. GlaxoSmithKline Clinical Trial Register 2005.

GlaxoSmithKline 2005e *{published data only}*
GlaxoSmithKline. A repeat dose, randomised, double blind, two-way crossover study to assess the safety and systemic exposure of an investigational formulation compared to concurrent administration of individual fluticasone propionate 50 and salmeterol 50 DISKUS inhalers in subjects aged 18-55 years with mild asthma. GlaxoSmithKline Clinical Trial Register 2005.

Greening 1994 *{published data only}*
Greening AP, Ind PW, Northfield M, Shaw G. Added salmeterol versus higher-dose corticosteroid in asthma patients with symptoms on existing inhaled corticosteroid. Allen & Hanburys Limited UK Study Group. Lancet 1994; Vol. 344, issue 8917:219–24.

Grutters 1999 *{published data only}*
Grutters JC, Brinkman L, Aslander MM, van den Bosch JM, Koenderman L, Lammers JW. Asthma therapy modulates priming-associated blood eosinophil responsiveness in allergic asthmatics. European Respiratory Journal 1999; Vol. 14, issue 4:915–22.

House 2004 *{published data only}*
House K, Dorinsky PM, Stauffer J, Schoaf L, Ellsworth A. The Safety of Fluticasone propionate/Salmeterol Diskus(R) in Pediatric Patients Ages 4 -11 with Asthma [Abstract]. Chest 2004; Vol. 126, issue 4 Suppl:911S–a.

Ilowite 2004 *{published data only}*
Ilowite J, Webb R, Friedman B, Kerwin E, Bird SR, Hustad CM, et al.Addition of montelukast or salmeterol to fluticasone for protection against asthma attacks: a randomized, double-blind, multicenter study. Annals of Allergy, Asthma, & Immunology 2004; Vol. 92, issue 6: 641–8.

Isabelle 2001 *{published data only}*
Isabelle P, Bjamer D, Neuparth N, Desfougeres JL. Efficacy and safety of salmeterol/fluticasone combination 50/100mug bd via two different powder devices in children. Annual Thoracic Society 97th International Conference; San Francisco CA ,May 18-23 2001.

Jarjour 2006 *{published data only}*
SAS40026. http://ctr.gsk.co.uk/Summary/fluticasone_salmeterol/IV_SAS40026.pdf Acessed July 2008.
* Jarjour NN, Wilson SJ, Koenig SM, Laviolette M, Moore WC, Davis WB, et al.Control of airway inflammation maintained at a lower steroid dose with 100/50 microg of fluticasone propionate/salmeterol. *J Allergy Clin Immunol* 2006;**118**:44–52.

Johansson 2001 *{published data only}*
Johansson G, McIvor RA, D'Ambrosio FP, Gratziou C, James MH. Comparison of salmeterol/fluticasone propionate combination with budesonide in patients with mild-to-moderate asthma. Clinical Drug Investigation 2001; Vol. 21, issue 9:633–42.

Juniper 2002 *{published data only}*
Juniper EF, Jenkins C, Price MJ, James MH. Impact of inhaled salmeterol/fluticasone propionate combination product versus budesonide on the health-related quality of life of patients with asthma. American Journal of Respiratory Medicine 2002; Vol. 1, issue 6:435–40.

Kelsen 1999 *{published data only}*
Kelsen SG, Church NL, Gillman SA, Lanier BQ, Emmett AH, Rickard KA, et al.Salmeterol added to inhaled corticosteroid therapy is superior to doubling the dose of inhaled corticosteroids: A randomized clinical trial. Journal of Asthma 1999; Vol. 36, issue 8:703–15.

Koopmans 2005 *{published data only}*
Koopmans JG, Lutter R, Jansen HM, van der Zee JS. Adding salmeterol to an inhaled corticosteroid reduces allergen-induced serum IL-5 and peripheral blood eosinophils. Journal of Allergy & Clinical Immunology 2005; Vol. 116, issue 5:1007–13.

Lazarus 2001 *{published data only}*
Lazarus SC, Boushey HA, Fahy JV, Chinchilli VM, Lemanske RF, Jr, et al.Long-Acting {beta}2-Agonist Monotherapy vs Continued Therapy With Inhaled Corticosteroids in Patients With Persistent Asthma: A Randomized Controlled Trial. JAMA 2001; Vol. 285, issue 20:2583–93.

Lemanske 2001 *{published data only}*
Lemanske RF, Jr, Sorkness CA, Mauger EA, Lazarus SC, Boushey HA, et al.Inhaled Corticosteroid Reduction and Elimination in Patients With Persistent Asthma Receiving Salmeterol: A Randomized Controlled Trial. JAMA 2001; Vol. 285, issue 20:2594–603.

Lotvall *{published data only}*
Lotvall J, Langley S, Woodcock A. Inhaled steroid/long-acting beta2 agonist combination products provide 24 hours improvement in lung function in adult asthmatic patients. Respiratory Research. Vol. 7, 2006. Article Number: 110. Date of Publication: 18 AUG 2006..

Lundback 2000 *{published data only}*
Lundback B, Jenkins C, Price MJ, Thwaites RM. Cost-effectiveness of salmeterol/fluticasone propionate combination product 50/250 microg twice daily and budesonide 800 microg twice daily in the treatment of adults and adolescents with asthma. International Study Group. Respiratory Medicine 2000; Vol. 94, issue 7: 724–32.

Martinat 2003 *{published data only}*
Martinat Y, Desfougeres JL. Fixed-dose fluticasone-salmeterol combination: At least effective and better tolerated than open-dose combinations. [French]. Revue de Pneumologie Clinique 2003; Vol. 59, issue 3:139–48.

Morice 2006 *{published data only}*
Morice A. An open labelled study to compare the systemic side effects of high dose fluticasone/salmeterol with that of high dose ciclesonide/salmeterol in symptomatic asthmatic patients. The North and South Bank Research and Development Consortium 2006; Vol. 1/7/2007:Ongoing.

Murray 1999 *{published data only}*
Murray JJ, Church NL, Anderson WH, Bernstein DI, Wenzel SE, Emmett A, et al.Concurrent use of salmeterol with inhaled corticosteroids is more effective than inhaled corticosteroid dose increases. Allergy & Asthma Proceedings 1999; Vol. 20, issue 3:173–80.

Nan 2004 *{published data only}*
Nan SZ, Zheng JP, Humphries MJ, Xin D. Salmeterol/fluticasone propionate in a single inhaler is superior to budesonide alone in control of Chinese asthmatic adults: An open-label, randomised, 6-week study. Clinical Drug Investigation 2004; Vol. 24, issue 10:583–92.

Nathan 2001 *{published data only}*
Nathan RA, Mitchell D, Condemi J, Heller A, Schoaf L, Herrle M, et al.Cardiovascular and hypthalamic-pituitary-adrenal axis safety of fluticasone propionate/salmeterol hfa mdi in adolescent and adult patients with asthma. Annual Thoracic Society 97th International Conference; San Francisco CA ,May 18-23 2001.

Nelson 2000 *{published data only}*
Nelson HS, Busse WW, Kerwin E, Church N, Emmett A, Rickard K, et al.Fluticasone propionate/salmeterol combination provides more effective asthma control than low-dose inhaled corticosteroid plus montelukast. Journal of Allergy & Clinical Immunology 2000; Vol. 106, issue 6: 1088–95.

Nelson 2001 *{published data only}*
Nelson HS, Nathan RA, Kalberg C, Yancey SW, Rickard KA. Comparison of inhaled salmeterol and oral zafirlukast in asthmatic patients using concomitant inhaled corticosteroids. Medgenmed Computer File: Medscape General Medicine 2001; Vol. 3, issue 4:3.

O'Byrne 2005 *{published data only}*
O'Byrne P. Efficacy of ciclesonide vs fixed combination of fluticasone propionate/salmeterol vs placebo in patients with mild persistent asthma (12 to 75 y). clinicaltrials.gov 2005.

O'Connor 2004 *{published data only}*
O'Connor RD, Nelson H, Borker R, Emmett A, Jhingran P, Rickard K, et al.Cost effectiveness of fluticasone propionate plus salmeterol versus fluticasone propionate plus montelukast in the treatment of persistent asthma. Pharmacoeconomics 2004; Vol. 22, issue 12:815–25.

Pauwels 1998 *{published data only}*
Pauwels RA, Yernault JC, Demedt MG, Geusens P. Safety and efficacy of fluticasone and beclomethasone in moderate to severe asthma. Belgian Multicenter Study Group. American Journal of Respiratory & Critical Care Medicine 1998; Vol. 157, issue 3 Pt 1:827–32.

Pearlman 1999 *{published data only}*
Pearlman DS, Stricker W, Weinstein S, Gross G, Chervinsky P, Woodring A, et al.Inhaled salmeterol and fluticasone: a study comparing monotherapy and combination therapy in asthma. Annals of Allergy, Asthma, & Immunology 1999; Vol. 82, issue 3:257–65.

Peters 2007 *{published data only}*
Peters SP, Anthonisen N, Castro M, Holbrook JT, Irvin CG, Smith LJ, et al.Randomized comparison of strategies for reducing treatment in mild persistent asthma. New England Journal of Medicine 2007; Vol. 356, issue 20:2027–39.

Ringdal 2003 *{published data only}*
Ringdal N, Eliraz A, Pruzinec R, Weber HH, Mulder PG, Akveld M, et al.The salmeterol/fluticasone combination is more effective than fluticasone plus oral montelukast in asthma. Respiratory Medicine 2003; Vol. 97, issue 3: 234–41.

Rosenthal 1999 *{published data only}*
Rosenthal RR, Busse WW, Kemp JP, Baker JW, Kalberg C, Emmett A, et al.Effect of long-term salmeterol therapy compared with as-needed albuterol use on airway hyperresponsiveness. Chest 1999; Vol. 116, issue 3: 595–602.

Russell 1995 *{published data only}*
Russell G, Williams DA, Weller P, Price JF. Salmeterol xinafoate in children on high dose inhaled steroids. Annals of Allergy, Asthma, & Immunology 1995; Vol. 75, issue 5: 423–8.

SAM30002 *{unpublished data only}*
SAM30002. http://ctr.gsk.co.uk/Summary/fluticasone_salmeterol/III_SAM30002.pdf Accessed July 2008.

SAM30013 *{unpublished data only}*
SAM30013. http://ctr.glaxowellcome.co.uk/Summary/fluticasone_salmeterol/III_SAM30013.pdf Accessed July 2008.

SAM40116 *{unpublished data only}*
SAM40116. http://ctr.glaxowellcome.co.uk/Summary/fluticasone_salmeterol/III_SAM40116.pdf Accessed July 2008.

SAS30015 *{unpublished data only}*
SAS30015. http://ctr.gsk.co.uk/Summary/fluticasone_salmeterol/III_SAS30015.pdf Accessed July 2008.

Schermer 2007 *{published data only}*
Schermer TR, Albers JM, Verblackt HW, Costongs RJ, Westers P. Lower inhaled steroid requirement with a fluticasone/salmeterol combination in family practice patients with asthma or COPD. Family Practice 2007; Vol. 24, issue 2:181–8.

Schlosser 1998 *{published data only}*
Schlosser NJJ, Steinmetz KO, Aubier M, Gomez E, Wixon C. Evaluation of long term safety of salmeterol/fluticasone propionate (50/500µg) combination inhaler in patients with reversible airways obstruction. European Respiratory Journal. Supplement. 1998; Vol. 12 Suppl 28:35S.

Scott 2005 *{published data only}*
Scott C, Wu W, Ellsworth A, Crim C. Efficacy and safety of fluticasone propionate/salmeterol DISKUS and fluticasone propionate DISKUS and HFA in children [Abstract]. European Respiratory Journal 2005; Vol. 26, issue Suppl 49:Abstract No. 1057.

SLGA5021 *{published data only}*
SLGA5021. http://ctr.gsk.co.uk/Summary/fluticasone_salmeterol/IV_SLGA5021.pdf Accessed August 11th 2008.

Tonnel 2004 *{published data only}*
Tonnel AB, Desfougeres JL. Efficacy and acceptability of the fixed fluticasone + salmeterol combination in the treatment of acute asthma attacks. Results of a one-year comparative study. [French]. Revue de Pneumologie Clinique 2004; Vol. 60, issue 4:209–16.

Van den 2000 *{published data only}*
Van den Berg NJ, Ossip MS, Hederos CA, Anttila H, Ribeiro BL, Davies PI. Salmeterol/fluticasone propionate 50/100 microg in combination in a Diskus inhaler Seretide is effective and safe in children with asthma. Pediatric Pulmonology 2000; Vol. 30, issue 2:97–105.

Van Noord 1999 *{published data only}*
Van Noord JA, Schreurs AJM, Mol SJM, Mulder PGH. Addition of salmeterol versus doubling the dose of fluticasone propionate in patients with mild to moderate asthma. Thorax 1999; Vol. 54, issue 3:207–12.

Vermetten 1999 *{published data only}*
Vermetten FA, Boermans AJM, Luiten WD, Mulder PGH, Vermue NA. Comparison of salmeterol with beclomethasone in adult patients with mild persistent asthma who are already on low-dose inhaled steroids. Journal of Asthma 1999; Vol. 36, issue 1:97–106.

Woolcock 1996 *{published data only}*
Woolcock A, Lundback B, Ringdal N, Jacques LA. Comparison of addition of salmeterol to inhaled steroids with doubling of the dose of inhaled steroids. American Journal of Respiratory & Critical Care Medicine 1996; Vol. 153, issue 5:1481–8.

You-Ning 2005 *{published data only}*
You-Ning L, Humphries M, Du X, Wang L, Jiang J. Efficacy and safety of salmeterol/fluticasone propionate delivered via a hydrofluoroalkane metered dose inhaler in Chinese patients with moderate asthma poorly controlled with inhaled corticosteroids. International Journal of Clinical Practice 2005; Vol. 59, issue 7:754–9.

Zhong 2002 *{published data only}*
Zhong N. Comparison of the effectiveness and safety in use of salmeterol/fluticasone delivered together in a Seretide Acuhaler or salmeterol and fluticasone delivered separately for patients with moderate or severe asthma. Chinese Journal of Tuberculosis and Respiratory Disease 2002; Vol. 25, issue 6:371.

Zhong 2005 *{published data only}*
Zhong NS, Zheng JP, Cai BQ, Xie CM, Sun TY, Wang DQ, et al.[Evaluation of the clinical efficacy and the safety of salmeterol/fluticasone propionate accuhalar compared to budesonide turbuhalar in the control of adult asthma.]. Zhonghua Jie He He Hu Xi Za Zhi 2005; Vol. 28, issue 4: 233–7.

Additional references

Altman 2003
Altman DG, Bland JM. Statistics Notes: Interaction revisited: the difference between two estimates. *BMJ* 2003; **326**(7382):219.

Anderson 2006
Anderson GP. Current issues with beta(2)-adrenoceptor agonists - Pharmacology and molecular and cellular mechanisms. Clinical Reviews in Allergy & Immunology 2006; Vol. 31, issue 2–3:119–30.

Arnold 1985
Arnold JMO, Oconnor PC, Riddell JG, Harron DWG, Shanks RG, McDevitt DG. Effects of the beta-2-adrenoceptor antagonist ici-118,551 on exercise tachycardia and isoprenaline-induced beta-adrenoceptor responses in man. British Journal of Clinical Pharmacology 1985; Vol. 19, issue 5:619–30.

Barnes 1993
Barnes PJ. Beta-adrenoceptors on smooth-muscle, nerves and inflammatory cells. Life Sciences 1993; Vol. 52, issue 26:2101–9.

Barnes 1995
Barnes PJ. Beta-adrenergic receptors and their regulation. American Journal of Respiratory and Critical Care Medicine 1995; Vol. 152, issue 3:838–60.

Bateman 2008
Bateman E, Nelson H, Bousquet J, Kral K, Sutton L, Ortega H, et al.Meta-analysis: Effects of Adding Salmeterol to Inhaled Corticosteroids on Serious Asthma-Related Events. Ann Intern Med 2008; Vol. 149, issue 1:33–42.

Beach 1992
Beach JR, Young CL, Stenton SC, Avery AJ, Walters EH, Hendrick DJ. A comparison of the speeds of action of salmeterol and salbutamol in reversing methacholine-induced bronchoconstriction. *Pulm-Pharmacol* 1992;**5**(2): 133–5.

Bennett 1994
Bennett JA, Smyth ET, Pavord ID, Wilding PJ, Tattersfield AE. Systemic effects of salbutamol and salmeterol in patients with asthma. Thorax 1994; Vol. 49, issue 8:771–4.

Brown 1983
Brown MJ, Brown DC, Murphy MB. Hypokalemia from beta-2-receptor stimulation by circulating epinephrine. New England Journal of Medicine 1983; Vol. 309, issue 23:1414–9.

Burgess 1991
Burgess CD, Windom HH, Pearce N, Marshall S, Beasley R, Siebers RWL, et al.Lack of evidence for beta-2 receptor selectivity - a study of metaproterenol, fenoterol, isoproterenol, and epinephrine in patients with asthma. American Review of Respiratory Disease 1991; Vol. 143, issue 2:444–6.

Burggraaf 2001
Burggraaf J, Westendorp RGJ, in't Veen J, Schoemaker RC, Sterk PJ, Cohen AF, et al.Cardiovascular side effects of inhaled salbutamol in hypoxic asthmatic patients. Thorax 2001; Vol. 56, issue 7:567–9.

Cates 2008
Cates Christopher J, Cates Matthew J, Lasserson Toby J. Regular treatment with formoterol for chronic asthma: serious adverse events. *Cochrane Database of Systematic Reviews* 2008, Issue 4. [DOI: 10.1002/14651858.CD006923.pub2; : CD006923]

Cates 2008a
Cates CJ, Cates MJ. Regular treatment with salmeterol for chronic asthma: serious adverse events. *Cochrane Database of Systematic Reviews* 2008, Issue 3. [DOI: 10.1002/14651858.CD006363.pub2; : CD006363]

Cates 2009
Cates CJ, Lasserson TJ, Jaeschke R. Regular treatment with formoterol and inhaled steroids for chronic asthma: serious adverse events. *Cochrane Database of Systematic Reviews* 2009, Issue 2. [DOI: 10.1002/14651858.CD006924.pub2; : CD006924]

Cockcroft 1993
Cockcroft DW, McParland CP, Britto SA, Swystun VA, Rutherford BC. Regular inhaled salbutamol and airway responsiveness to allergen. Lancet 1993; Vol. 342, issue 8875:833–7.

Collins 1969
Collins JM, McDevitt DG, Shanks RG, Swanton JG. Cardio-toxicity of isoprenaline during hypoxia. British Journal of Pharmacology 1969; Vol. 36, issue 1:35–&.

Crane 1989
Crane J, Pearce N, Flatt A, Burgess C, Jackson R, Kwong T, et al.Prescribed fenoterol and death from asthma in New Zealand, 1981-83 - case-control study. Lancet 1989; Vol. 1, issue 8644:917–22.

Ducharme 2006
Ducharme FM, Lasserson TJ, Cates CJ. Long-acting beta-2 agonists versus anti-leukotrienes as add-on therapy to inhaled corticosteroids for chronic asthma (Cochrane Review). *Cochrane Database of Systematic Reviews* 2006, Issue 4. [DOI: 10.1002/14651858.CD003137.pub3; : CD003137]

FDA 2008
GlaxoSmithKline. Benefit Risk Assessment of Salmeterol for the Treatment of Asthma in Adults and Children. www.fda.gov/ohrms/dockets/ac/08/briefing/2008-4398b1-04-GSK.pdf Accessed February 24th 2009.

Giembycz 2006
Giembycz MA, Newton R. Beyond the dogma: novel ß2-adrenoceptor signalling in the airways. *European Respiratory Journal* 2006;**27**(6):1286–1306.

Grainger 1991
Grainger J, Woodman K, Pearce N, Crane J, Burgess C, Keane A, et al.Prescribed fenoterol and death from asthma in New Zealand, 1981-7 - a further case-control study. Thorax 1991; Vol. 46, issue 2:105–11.

Greenstone 2005
Greenstone IR, Ni Chroinin M, Masse V, Danish A, Magdalinos H, Zhang X, et al.Combination of inhaled long-acting beta2-agonists and inhaled steroids versus higher dose of inhaled steroids in children and adults with persistent asthma (Cochrane Review). *Cochrane Database of Systematic Reviews* 2005, Issue 4. [DOI: 10.1002/14651858.CD005533; : CD005533]

Guhan 2000
Guhan AR, Cooper S, Oborne J, Lewis S, Bennett J, Tattersfield AE. Systemic effects of formoterol and salmeterol: a dose-response comparison in healthy subjects. Thorax 2000; Vol. 55, issue 8:650–6.

Hall 1989
Hall JA, Petch MC, Brown MJ. Intracoronary injections of salbutamol demonstrate the presence of functional beta-2-adrenoceptors in the human-heart. Circulation Research 1989; Vol. 65, issue 3:546–53.

Hanania 2002
Hanania NA, Sharfkhaneh A, Barber R, Dickey BF. beta-agonist intrinsic efficacy - Measurement and clinical significance. American Journal of Respiratory and Critical Care Medicine 2002; Vol. 165, issue 10:1353–8.

Hanania 2007
Hanania NA, Moore RH, Zimmerman JL, Miller CT, Bag R, Sharafkhaneh A, et al.The role of intrinsic efficacy in determining response to beta(2)-agonist in acute severe asthma. Respiratory Medicine 2007; Vol. 101, issue 5:1007–14.

Hancox 1999
Hancox RJ, Aldridge RE, Cowan JO, Flannery EM, Herbison GP, McLachlan CR, et al.Tolerance to beta-agonists during acute bronchoconstriction. European Respiratory Journal 1999; Vol. 14, issue 2:283–7.

Hancox 2006
Hancox RJ. Interactions between corticosteroids and beta2-agonists. Clinical Reviews in Allergy & Immunology 2006; Vol. 31, issue 2–3:231–46. [: (Print)]

Haney 2006
Haney S, Hancox RJ. Recovery from bronchoconstriction and bronchodilator tolerance. Clinical Reviews in Allergy & Immunology 2006; Vol. 31, issue 2–3:181–96.

Harvey 1982
Harvey JE, Tattersfield AE. Airway response to salbutamol - effect of regular salbutamol inhalations in normal, atopic, and asthmatic subjects. Thorax 1982; Vol. 37, issue 4:280–7.

ICHE2a 1995
Expert Working Group (Efficacy) of theInternational Conference on Harmonisation of Technical Requirements for Registrationof Pharmaceuticals for Human Use (ICH). Clinical safety data management: Definitions and standards for expedited reporting. http://www.fda.gov/cder/guidance/iche2a.pdf 1995.

Jaeschke 2008
Jaeschke R, O'Byrne PM, Parameswaran N, et al.The safety of formoterol among patients with asthma using inhaled corticosteroids. Systematic review and meta-analysis.. Pol Arch Med Wewn 2008; Vol. 118, issue 11:627–635.

Jaeschke 2008a
Jaeschke R, O'Byrne PM, Mejza F, Nair P, Lesniak W, Brozek J, et al.The Safety of Long-Acting Beta-Agonists among Patients with Asthma Using Inhaled Corticosteroids: Systematic Review and Meta-analysis. Am. J. Respir. Crit. Care Med. 2008; Vol. 178, issue 10:1009–16.

Jones 2001
Jones SL, Cowan JO, Flannery EM, Hancox RJ, Herbison GP, Taylor DR. Reversing acute bronchoconstriction in asthma: the effect of bronchodilator tolerance after treatment with formoterol. European Respiratory Journal 2001; Vol. 17, issue 3:368–73.

Lee 2003
Lee DKC, Jackson CM, Currie GP, Cockburn WJ, Lipworth BJ. Comparison of combination inhalers vs inhaled corticosteroids alone in moderate persistent asthma. British Journal of Clinical Pharmacology 2003; Vol. 56, issue 5:494–500.

Lipworth 1989
Lipworth BJ, Struthers AD, McDevitt DG. Tachyphylaxis to systemic but not to airway responses during prolonged therapy with high-dose inhaled salbutamol in asthmatics. American Review of Respiratory Disease 1989; Vol. 140, issue 3:586–92.

Lipworth 1992
Lipworth BJ, McDevitt DG. Inhaled beta-2-adrenoceptor agonists in asthma - help or hindrance. British Journal of Clinical Pharmacology 1992; Vol. 33, issue 2:129–38.

Lipworth 1997
Lipworth BJ. Airway subsensitivity with long-acting beta 2-agonists: Is there cause for concern?. *Drug Safety* 1997;**16** (5):295–308.

Lipworth 2000
Lipworth BJ, Aziz I. Bronchodilator response to albuterol after regular formoterol and effects of acute corticosteroid administration. Chest 2000; Vol. 117, issue 1:156–62.

McDevitt 1974
McDevitt DG, Shanks RG, Swanton JG. Further observations on cardiotoxicity of isoprenaline during hypoxia. British Journal of Pharmacology 1974; Vol. 50, issue 3:335–44.

Morrison 1993
Morrison KJ, Gao Y, Vanhoutte PM. Beta-adrenoceptors and the epithelial layer in airways. Life Sciences 1993; Vol. 52, issue 26:2123–30.

Nelson 1977
Nelson HS, Raine D, Doner HC, Posey WC. Subsensitivity to bronchodilator action of albuterol produced by chronic administration. American Review of Respiratory Disease 1977; Vol. 116, issue 5:871–8.

Ni Chroinin 2004
Ni Chroinin M, Greenstone IR, Ducharme FM. Addition of inhaled long-acting beta2-agonists to inhaled steroids as first line therapy for persistent asthma in steroid-naive adults (Cochrane Review). *Cochrane Database of Systematic Reviews* 2004, Issue 4. [DOI: 10.1002/14651858.CD005307; : CD005307]

Ni Chroinin 2005
Ni Chroinin M, Greenstone IR, Danish A, Magdolinos H, Masse V, Zhang X, et al.Long-acting beta2-agonists versus placebo in addition to inhaled corticosteroids in children and adults with chronic asthma (Cochrane Review). *Cochrane Database of Systematic Reviews* 2005, Issue 4. [DOI: 10.1002/14651858.CD005535; : CD005535]

Palmqvist 1999
Palmqvist M, Ibsen T, Mellen A, Lotvall J. Comparison of the relative efficacy of formoterol and salmeterol in asthmatic patients. American Journal of Respiratory and Critical Care Medicine 1999; Vol. 160, issue 1:244–9.

Pearce 1990
Pearce N, Grainger J, Atkinson M, Crane J, Burgess C, Culling C, et al.Case-control study of prescribed fenoterol and death from asthma in new-zealand, 1977-81. Thorax 1990; Vol. 45, issue 3:170–5.

Pearce 2007
Pearce N. *Adverse reactions: the Fenoterol story*. 1. Auckland: Auckland University Press, 2007:215. [: 9781869403744]

Salpeter 2006
Salpeter SR, Buckley NS, Ormiston T M, Salpeter EE. Meta-analysis: effect of long-acting beta-agonists on severe asthma exacerbations and asthma-related deaths. *Annals of Internal Medicine* 2006;**144**(12):904–12.

Sears 1986
Sears M, Rea H, Rothwell R, O'Donnell T, Holst P, Gillies A, et al.Asthma mortality: comparison between New Zealand and England. *British Medical Journal* 1986;**293** (6558):1342–5.

Sears 1990
Sears MR, Taylor DR, Print CG, Lake DC, Li QQ, Flannery EM, et al.Regular inhaled beta-agonist treatment in bronchial-asthma. Lancet 1990; Vol. 336, issue 8728: 1391–6.

Sears 2008
Sears MR, Ottosson A, Radner F, Suissa S. Long-acting {beta}-agonists: A review of formoterol safety data from

asthma clinical trials. European Respiratory Journal 2008: 09031936.00145006.

SMART 2006
Nelson HS, Weiss ST, Bleecker ER, Yancey SW, Dorinsky PM, the SMART Study Group. The Salmeterol Multicenter Asthma Research Trial: A Comparison of Usual Pharmacotherapy for Asthma or Usual Pharmacotherapy Plus Salmeterol. *Chest* 2006;**129**:15–26.

SNS 1993
Castle W, Fuller R, Hall J. Serevent nationwide surveillance study:Comparison of salmeterol with salbutamol in asthmatic patients who require regular bronchodilator treatment. *British Medical Journal* 1993;**306**:1034–7.

Speizer 1968
Speizer FE, Doll R, Heaf P. Observations on recent increase in mortality from asthma. British Medical Journal 1968; Vol. 1, issue 5588:335–&.

Sweeting 2004
Sweeting MJ, Sutton AJ, Lambert PC. What to add to nothing? Use and avoidance of continuity corrections in meta-analysis of sparse data. Stat Med. 2004/04/30 2004; Vol. 23, issue 9:1351–75. [0277–6715: (Print)]

van der Woude 2001
van der Woude HJ, Winter TH, Aalbers R. Decreased bronchodilating effect of salbutamol in relieving methacholine induced moderate to severe bronchoconstriction during high dose treatment with long acting beta(2) agonists. Thorax 2001; Vol. 56, issue 7: 529–35.

vanNoord 1996
vanNoord JA, Smeets JJ, Raaijmakers JAM, Bommer AM, Maesen FPV. Salmeterol versus formoterol in patients with moderately severe asthma: Onset and duration of action. European Respiratory Journal 1996; Vol. 9, issue 8:1684–8.

Walters 2002
Walters EH, Walters JAE, Gibson PW. Regular treatment with long acting beta agonists versus daily regular treatment with short acting beta agonists in adults and children with stable asthma (Cochrane Review). *Cochrane Database of Systematic Reviews* 2002, Issue 3. [DOI: 10.1002/14651858.CD003901]

Walters 2007
Walters EH, Gibson PG, Lasserson TJ, Walters JAE. Long-acting beta2-agonists for stable chronic asthma (Cochrane Review). *Cochrane Database of Systematic Reviews* 2007, Issue 1. [DOI: DOI: 10.1002/14651858.CD001385.pub2]

Weber 1982
Weber RW, Smith JA, Nelson HS. Aerosolized terbutaline in asthmatics - development of subsensitivity with long-term administration. Journal of Allergy and Clinical Immunology 1982; Vol. 70, issue 6:417–22.

Weiss 2008
Weiss KB. Drug safety and salmeterol: the controversy continues. Ann Intern Med. 2008/06/05 2008; Vol. 149, issue 1:56–7. [1539–3704: (Electronic)]

Wilson 1981
Wilson JD, Sutherland DC, Thomas AC. Has the change to beta-agonists combined with oral theophylline increased cases of fatal asthma. Lancet 1981; Vol. 1, issue 8232: 1235–7.

Wong 1990
Wong CS, Pavord ID, Williams J, Britton JR, Tattersfield AE. Bronchodilator, cardiovascular, and hypokalaemic effects of fenoterol, salbutamol, and terbutaline in asthma. Lancet 1990; Vol. 336, issue 8728:1396–9.

Yates 1996
Yates DH, Kharitonov SA, Barnes PJ. An inhaled glucocorticoid does not prevent tolerance to the bronchoprotective effect of a long-acting inhaled beta(2)-agonist. American Journal of Respiratory and Critical Care Medicine 1996; Vol. 154, issue 6:1603–7.

* *Indicates the major publication for the study*

CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

Aubier 1999

Methods	A randomized, double-blind, double-dummy, multi centre, parallel-group study over 28 weeks from May 1996 to November 1997 at 55 centres in 3 countries. (Germany, Franceand the Netherlands) Run-in 2 weeks and follow-up 2 weeks
Participants	**Population**: 503 adolescents and adults (12-79) years with asthma. **Baseline Characteristics**: Mean age 48 years. FEV_1 73% predicted. Concomitant inhaled corticosteroids used by 100% of participants **Inclusion Criteria**:At least 12 years old with a documented clinical history of reversible airways disease, and received treatment with any inhaled corticosteroid continuously for 12 weeks prior to run-in. FEV_1 % predicted between 50% to 100%, At the end of the 2-week run-in period were symptomatic (symptom score 2 or more on at least four of the last seven consecutive days), had a mean morning peak expiratory flow rate (PEFR) that was > 50% and < 85% of the maximum PEFR 15 min after administration of inhaled salbutamol 400 ug **Exclusion Criteria**: taking long-acting beta2-agonists
Interventions	1. FSC 500/50 µg BD 2. FP 500 µg + SAL 50 µg BD 3. FP 500 µg BD Delivery was Diskus device
Outcomes	Primary outcome: Mean morning peak expiratory flow rate (PEFR) during Weeks 1-12 The paper reports "The incidence of drug-related adverse events was similar for the three treatments" Full SAE data from web report. One death from bronchial carcinoma on salmeterol and fluticasone (separate inhalers). This death was not included in Jaeschke 2008 as the patient stopped taking study medication to allow for elective surgery and died of surgical complications, but was still in the trial and had intended to restart treatment post-operatively
Notes	

Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	Unclear	Not reported
Allocation concealment?	Unclear	Not reported
Blinding? All outcomes	Yes	Double blind double dummy
Incomplete outcome data addressed? All outcomes	Yes	403/503 (80%) completed the study

Aubier 1999 (*Continued*)

Free of selective reporting?	Yes	Full data on GSK website

Bateman 2001

Methods	A randomized, double-blind, double-dummy, multicenter, parallel-group study over 12 weeks from March 1998 to June 1999 at 69 centers in 10 countries. Run in 2 weeks and 2 weeks follow-up
Participants	**Population**: 497 adolescents and adults (12-79) years with documented clinical history of reversible airways obstruction **Baseline Characteristics**: Mean age 40 years. FEV_1 76% predicted. Concomitant inhaled corticosteroids used by 100% of participants **Inclusion Criteria**:12 years or older with a documented clinical history of reversible airway obstruction, a smoking history of less than 10 pack-years and been using ICS (beclomethasone dipropionate, budesonide or flunisolide 400 -500 µg day or FP 200-250 µg day) for at least 4 weeks before entering the run-in period. FEV_1 % predicted at least 50%. Mean PEF over the last 7 days of the run-in period of between 50% and 85% measured after inhalation of salbutamol (400 mg). Had to be symptomatic, i.e. have a cumulative total symptom score (daytime plus night-time) greater than 8 for the last 7 days of the run-in period, and be taking salbutamol up to 800 µg day. **Exclusion Criteria**: Received a long-acting B_2-agonist or oral B_2-agonist within 2 weeks of the run-in period, changed asthma medication, had a lower respiratory tract infection within 4 weeks of the run-in period or had an acute asthma exacerbation requiring hospitalization within 12 weeks of study entry. Other exclusion criteria included prior treatment with oral, depot or parenteral corticosteroids or combination therapy (containing a B_2-agonist and/or ICS).
Interventions	1. SALM/FP 50/100 µg HFA MDI 2. SALM/FP 50/100 µg Diskus 3. FP 100 µg CFC MDI
Outcomes	Primary efficacy variable was the mean morning PEFR over the 12-week treatment period A serious adverse event was described as any event which was fatal, life-threatening, disabling or incapacitating, or which required or prolonged hospitalisation Paper reports: "During treatment, serious adverse events were reported by three patients (2%) in each group. These included asthma exacerbations (n.5), breast neoplasia (n.1) and events associated with the gastrointestinal system (n.2) and ear, nose and throat (n. 1). The only serious adverse events considered by the investigator to be drug-related were asthma exacerbations in two patients (one each in the SALM/FP MDI and DiskusTM groups)." SFCB3022 reports 5 patients with asthma SAE in SALM/FP groups (333 pts) and none on FP alone (165 pts)
Notes	Bateman reports 4 asthma hospitalisations in SALM/FP groups

Risk of bias

Bateman 2001 (*Continued*)

Item	Authors' judgement	Description
Adequate sequence generation?	Unclear	Not reported
Allocation concealment?	Unclear	Not reported
Blinding? All outcomes	Yes	Double blind, double dummy
Incomplete outcome data addressed? All outcomes	Yes	430/497 (87%) completed the study
Free of selective reporting?	Yes	Full data on GSK website

GOAL 2004

Methods	A randomized, double-blind, multicentre, stratified, parallel-group study over 12 months from December 2000 to December 2002 in 326 centres in Europe, North America, Latin America and Asia Pacific. Run-in 4 weeks
Participants	**Population**: 3416 adolescents and adults (9-83) with uncontrolled asthma. **Baseline Characteristics**: Mean age 40 years. FEV_1 77% predicted. Concomitant inhaled corticosteroids not previously used in stratum 1, low dose in stratum 2 and medium to high dose in stratum 3 at baseline. **Inclusion Criteria**:12 years old or more and less than 80 years old with at least a 6-month history of asthma, bronchodilator reversibility by an increase of at least 15% in FEV_1 over baseline (and 200mL) based on FEV_1 measured pre- and post-inhalation of any short-acting beta2-agonist within the last six months or to demonstrate reversibility at Visit 1, Visit 2, or between Visit 1 and Visit 2 using 200-400mcg of salbutamol/albuterol. Eligible for Stratum 1 of the study if had not received inhaled corticosteroids (ICS) for at least 6 months prior to Visit 1. For Stratum 2, if receiving < or = 500mcg BDP or equivalent daily , Stratum 3, receiving >500 and < 0r = 1000mcg BDP or equivalent daily During two or more of the 4 weeks prior to Visit 2, subjects should have failed to achieve the criteria for 'Well-Controlled' asthma. **Exclusion Criteria**: assessed as having Well-Controlled asthma on more than 3 of the 4 weeks during run-in, change in regular asthma medication; emergency visits due to asthma; treatment with systemic corticosteroids; respiratory tract infection; more than 3 days of morning PEF less than 50% predicted; non-compliance with the diary record card
Interventions	1. FSC 100/50, 250/50 or 500/50 µg BD (by strata) 2. FP 100, 250 or 500 µg BD (by strata) Delivery was Diskus device

GOAL 2004 (*Continued*)

Outcomes	The primary efficacy variable was the proportion of subjects who achieved 'Well-Controlled' asthma with the salmeterol/FP combination compared with FP alone during Phase I of the study Paper states that " Serious adverse events were observed during the double-blind period in 4% and 3% of patients in the salmeterol/fluticasone and fluticasone arms, respectively". Web report gives the number of patients (67 and 53 respectively) Website reports two deaths on FP (both Myocardial Infarction) and three deaths on FPS (two Myocardial infarction and one pneumonia). No asthma-related deaths are reported
Notes	

Risk of bias

Item	**Authors' judgement**	**Description**
Adequate sequence generation?	Yes	Randomization was done telephonically from a computer-generated allocation schedule balanced per stratum and per country
Allocation concealment?	Unclear	Not reported
Blinding? All outcomes	Yes	Double-blind
Incomplete outcome data addressed? All outcomes	Yes	2890/3416 (85%) completed the study
Free of selective reporting?	Yes	Full data on GSK website

Ind 2003

Methods	A randomized, double-blind, double-dummy, multicenter, parallel-group study over 28 weeks from January 1995 to December 1996 at 99 centers in Canada, Denmark, Iceland, Ireland, Italy and the United Kingdom. Run- in 4 weeks
Participants	**Population**: 502 adolescents and adults (16-75) years with asthma poorly controlled on current inhaled corticosteroids. **Baseline Characteristics**: Mean age 45 years. FEV_1 2.3L. Concomitant inhaled corticosteroids used by 100% of participants. **Inclusion Criteria**: Currently receiving inhaled corticosteroids at a dose of 1000 to 1600 mcg daily of inhaled beclomethasone dipropionate (BDP) or equivalent. Asthma poorly controlled (demonstrated by a PEFR of ?85% of maximal achievable PEFR after inhaling 400 mcg salbutamol) and had experienced at least 2 exacerbations of asthma in the last year that required a change in asthma therapy. Therefore, over the last 10 days of the baseline period had to demonstrate an average morning PEFR which was <90% of their maximal achievable PEFR measured at screening and a diurnal variation in PEFR of at least 15%. They also had to have asthma symptoms on at least 4 of the last 7 days or

Ind 2003 (*Continued*)

	nights of the baseline period **Exclusion Criteria**: receiving continuous oral corticosteroids, any serious uncontrolled systemic disease or participation was deemed unsuitable by the physician, had to demonstrate a period variation in PEF of at least 15% (highest evening value-lowest morning value as a percentage of highest PEF) over the last 10 days and/or nights of the run-in period and to have sub-optimal PEF, with average PEF over the last 10 days of the run-in not exceeding 90% of post-bronchodilator PEF (measured at visit 1)
Interventions	1. FP 250 µg + SAL 50 µg BD 2. FP 250 µg BD 3. FP 500 µg BD Delivery was MDI (FP 500 arm not used in this review)
Outcomes	The primary efficacy variables were: mean morning peak expiratory flow rate (PEFR); incidence and severity of asthma exacerbations No SAE information found in paper publication. Full SAE data on web report. One fatal pneumothorax on Salmeterol and Fluticasone (separate inhalers)
Notes	

Risk of bias

Item	**Authors' judgement**	**Description**
Adequate sequence generation?	Unclear	Not reported
Allocation concealment?	Unclear	Not reported
Blinding? All outcomes	Yes	Double blind, double dummy
Incomplete outcome data addressed? All outcomes	Yes	432/502 (86% completed study)
Free of selective reporting?	Yes	Full data on GSK website

Kavuru 2000

Methods	Randomized, double-blind, double-dummy, parallel-group placebo-controlled study over 12 weeks at 42 centers in the U.S. Run in 2 weeks single blind placebo
Participants	**Population**: 356adolescents and adults (12-70) years with asthma. **Baseline Characteristics**: Mean age 37 years. FEV_1 64% predicted. Concomitant inhaled corticosteroids used by 100% of participants in group 1 and 0% of participants in group 2. **Inclusion Criteria**: At least 12 years old and a medical history of asthma, (as defined by the American Thoracic Society) of at least 6 months duration. FEV_1 % predicted

	between 40% to 85%,bronchodilator reversibility by an increase of at least 15% in FEV_1 over baseline 30 minutes after two puffs (180 µg) of inhaled albuterol Stratified into 2 groups according to type of asthma therapy used at enrollment. **Exclusion Criteria**: History of life-threatening asthma; hypersensitivity reaction to sympathomimetic drugs or corticosteroids; smoking within the previous year or a history of >10 pack-years; use of oral, inhaled or injectable corticosteroid therapy within the previous month; use of intranasal corticosteroid therapy except for Flonase (GlaxoWellcome Inc.); use of daily oral corticosteroid treatment within the previous 6 months; use of any other prescription or over-the-counter medication that could have affected the course of asthma or interacted with sympathomimetic amines; abnormal chest x-ray films; clinically significant abnormal 12-lead electrocardiograms (ECGs); or a history of significant concurrent disease (e.g., glaucoma, diabetes, hypertension)
Interventions	1. FSC 100/50 µg BD 2. Fluticasone 100 µg BD Delivery was Diskus inhaler
Outcomes	Mean morning pre-dose Forced Expiratory Volume in 1 second (FEV_1) at endpoint; area under the 12-hour serial FEV_1 curve relative to baseline [AUC(bl)] after I week of treatment (mean FEV_1 AUC); and probability of remaining in the study over time without withdrawal due to lack of efficacy Paper reports no serious drug-related adverse events, and reports two serious adverse events that led to withdrawal. Website records 2 events on FSC and 1 event on FP. (Unclear whether the 2 FSC events were in separate patients, so treated as one patient until further clarification)
Notes	

Risk of bias

Item	**Authors' judgement**	**Description**
Adequate sequence generation?	Unclear	Not reported
Allocation concealment?	Unclear	Not reported
Blinding? All outcomes	Yes	Double blind, double dummy
Incomplete outcome data addressed? All outcomes	Yes	142/182 (78%) completed the study
Free of selective reporting?	Yes	Data on GSK web site

Koenig 2008

Methods	A randomized, double-blind, multicenter, parallel-group study over 40 weeks from February 2003 to October 2004 at 55 sites. (50 in the US, 3 in Latin America, 2 in Latvia). Run-in 2 weeks
Participants	**Population**: 466 adolescents and adults(12-81) with asthma. **Baseline Characteristics**: Mean age 34 years. FEV_1 78% predicted. Concomitant inhaled corticosteroids used by 100% of participants. **Inclusion Criteria**: 12 years of age or older, with a diagnosis of asthma, as defined by the American Thoracic Society (ATS), for at least three months prior to visit 1, must have been treated with a short-acting beta2-agonist, an anticholinergic, or an allowed ICS at a fixed dosing regimen (within an allowed total daily dose) for at least four weeks prior to the screening visit. FEV_1 % predicted between 60% to 95%, bronchodilator reversibility by an increase of at least 12% in FEV_1 over baseline within 30 minutes of inhalation 2 puffs of inhaled albuterol.(180 µg) **Exclusion Criteria**: pregnancy, life-threatening asthma, hospitalization attributable to asthma within the last 6 months, current smoker or a more than10 pack-year history of smoking, a recent (within 2 weeks) upper or lower respiratory tract infection, or significant concurrent diseases. Medications that could confound the evaluation of the study treatments or treatment strategies were prohibited before and throughout the study, including inhaled (up to 250 mcg FP allowed prior to randomization), oral, or parenteral corticosteroids (with the exception of protocol defined use of oral corticosteroids following second consecutive assignment to the highest dose of FP), theophylline or other bronchodilators, leukotriene modifiers, anticholinergics, cromolyn, and nedocromil
Interventions	1. FSC 100/50, 250/50 or 500/50 µg BD (BHR strategy) 2. FP 100, 250 or 500 µg (BHR strategy) 3. FP 100, 250 or 500 µg (Reference strategy) - data was not used from this arm Delivery was Diskus device
Outcomes	Primary efficacy variable was the average inhaled corticosteroid treatment dose over the treatment period Paper reports "There were no non-fatal serious adverse events in any treatment group that were considered to be drug related. One patient in the FP_{BHR} treatment group died due to convulsions and cardiac arrest following deep vein thrombosis." Web report indicates one patient with SAE related to asthma on FSC_{BHR} and one patient with ear infection and sinusitis on FP_{BHR}.
Notes	

Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	Unclear	Not reported
Allocation concealment?	Unclear	Not reported
Blinding? All outcomes	Yes	Double blind

Incomplete outcome data addressed? All outcomes	Yes	321/466 (69%) completed the study
Free of selective reporting?	Yes	Full data on GSK web site

Koopmans 2006

Methods	A randomized, double-blind, single-centre, parallel-group study over 12 months from September 2000 to December 2003 in the Netherlands. Run-in 4 weeks A study to compare the long term effects on airway inflammation of *Seretide* versus *Flixotide* in adult subjects with asthma
Participants	**Population**: 54 adults (19-59) with mild to moderate persistent allergic asthma. **Baseline Characteristics**: Mean age 32 years. FEV_1 89% predicted. Concomitant inhaled corticosteroids used by 100 % of participants (Median dose 600 mcg/day). **Inclusion Criteria**:aged between 18 and 50 years with reversible airways obstruction, informed consent, allergic to house dust mite, PC_{20} histamine < 8 mg/ml, FEV_1 greater than 70% predicted. **Exclusion Criteria**: serious concurrent disease likely to interfere with the study, lower respiratory tract infection, or use of antibiotics in the previous 4 weeks
Interventions	1. FSC 250/50 µg BD 2. FP 250 µg BD Delivery was Diskus device
Outcomes	The primary efficacy variables were the percentage of eosinophils and eosinophil cationic protein (ECP) in induced sputum (baseline and after allergen challenge) at randomisation and 1, 3 6, 9 and 11 months later
Notes	

Risk of bias

Item	**Authors' judgement**	**Description**
Adequate sequence generation?	Unclear	Not reported
Allocation concealment?	Unclear	Not reported
Blinding? All outcomes	Yes	Double blind
Incomplete outcome data addressed? All outcomes	Yes	50/54 (93%) completed the study
Free of selective reporting?	Yes	Data on GSK website

Lundback 2006

Methods	A randomized, double-blind, parallel-group study over 12 months from August1997 to December 2002 in Sweden. Run-in 2 months An interventional three year study for asthma control - In what way and in what kind of population is it possible to get asthmatic patients free from symptoms, keep the patients in work, restore a normal lung function, diminish hyperreactivity and normalise quality of life?
Participants	**Population**: 282 adults (18-70) with mild to moderate persistent asthma. **Baseline Characteristics**: Mean age 40 years. FEV_1 93% predicted. Concomitant inhaled corticosteroids used by 68% of participants. **Inclusion Criteria**:clinically representative mild to moderate asthma, symptoms, or use of rescue medication at least twice a week, required to have airway hyperreactivity (AHR) demonstrated by methacholine challenge with a PC20 (the concentration required to provoke a 20% reduction in FEV1) <8mg/ml. If AHR was not demonstrated via methacholine challenge then one of the following: diurnal variability in peak expiratory flow (PEF) of at least 20% on >3 days during the last 14 days of the run-in; at least 30% difference between the highest and lowest PEF reading during any 7 days in the run-in period; or an increase of at least 15% in FEV1 or PEF after salbutamol inhalation (0.8 mg). **Exclusion Criteria**: taking daily doses of ICS greater than 1200 µg, had experienced one or more life-threatening exacerbation requiring hospitalisation during the previous 12 months, were hypersensitive to beta-agonists or ICS, were pregnant or lactating or had a respiratory tract infection during the 4 weeks prior to run-in
Interventions	1. FSC 250/50 µg BD 2. FP 250 µg BD 3. Sal 50 µg BD Delivery was Diskus device (arm three was not used in this review)
Outcomes	The primary efficacy variable was the requirement for an increased dose of study medication
Notes	

Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	Unclear	Not reported
Allocation concealment?	Unclear	Not reported
Blinding? All outcomes	Yes	Double blind
Incomplete outcome data addressed? All outcomes	Yes	263/282 (93%) completed the study
Free of selective reporting?	Yes	Data on GSK web site

Malone 2005

Methods	A randomized, double-blind, active-controlled, multicenter, parallel-group study over 12 weeks from April 2002 to January 2003 at 79 centres. (66 in the US and 13 in Canada) . Run-in 2 weeks.
Participants	**Population**: 203 children(4-11) years with persistent asthma. **Baseline Characteristics**: Mean age 8 years. FEV_1 mean 80% predicted. (6-11 y) PEFR mean 87% predicted. (4-5 y) Concomitant inhaled corticosteroids used by 100% of participants. **Inclusion Criteria**:4-11 years of age diagnosed with asthma (ATS definition), who required physician-prescribed treatment for at least 2 months and taking an inhaled corticosteroid for asthma for at least one month prior to visit 1 FEV_1 % predicted between 50% to 95% (6-11 y), am PEFR % predicted between 50% to 95% (4-5 y). Bronchodilator reversibility by an increase of at least 12% in FEV_1 (6-11 yr) or am PEFR (4-5 yr) over baseline within 30 minutes of 2-4 actuations of albuterol (180-360 µg) or to have historical documentation of 12% or greater reversibility within the previous year. **Exclusion Criteria:** history of life-threatening asthma, hospitalization due to asthma twice or more in the previous year, significant concurrent disease (e.g. cystic fibrosis, malignancy or immunologic compromise), recent upper or lower respiratory tract infection, current chickenpox or recent exposure to chickenpox in a nonimmune patient, severe milk protein allergy, hypersensitivity to B_2-agonist, sympathomimetic or corticosteroid therapy, clinically significant abnormal laboratory test results
Interventions	1. FSC 100/50 µg BD 2. FP 100 µg BD Delivery was Diskus device
Outcomes	This was a safety study and no primary efficacy endpoint was identified No SAE occurred in this study.
Notes	

Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	Unclear	Not reported
Allocation concealment?	Unclear	Not reported
Blinding? All outcomes	Yes	Double blind
Incomplete outcome data addressed? All outcomes	Yes	168/203 (83%) completed the study
Free of selective reporting?	Yes	Full data on GSK web site

Murray 2004

Methods	A randomized, double-blind, active-controlled, multicenter, parallel-group study over 12 weeks from November 1999 to September 2000 at 33 centres in the US. Run in 2 weeks single blind placebo
Participants	**Population**: 267 adolescents and adults (12-73) years with persistent asthma. **Baseline Characteristics**: Mean age 34 years. FEV_1 66% predicted. Concomitant inhaled corticosteroids used by 0% of participants. **Inclusion Criteria**:12 years or older with a 6 months history of asthma and must have been treated with as-needed, short-acting, inhaled beta2-agonists alone during the previous month with no oral or inhaled corticosteroid use within one month or long-acting beta-agonist within 72 hours of study entry FEV_1 % predicted between 40% to 85%, bronchodilator reversibility by an increase of at least 15% in FEV_1 over baseline within 30 minutes of inhalation of 2 puffs (180 µg) of albuterol. **Exclusion Criteria**: Pregnancy and/or lactation,life-threatening asthma, hospitalization attributable to asthma twice or more in the last year, current smoker or a more than 10 pack-year history of smoking, significant concurrent diseases including a recent upper or lower respiratory tract infection. Medications prohibited before and throughout the study included inhaled, oral or parenteral corticosteroids, theophylline or other bronchodilators, anticholinergics, leukotriene modifiers, cromolyn and nedocromil
Interventions	1. FSC 100/50 µg BD 2. FP 100 µg BD Delivery Diskus
Outcomes	Two primary efficacy variables were defined: (1) mean change from baseline in AM predose FEV_1 at endpoint for FSC 100/50 compared to SALM 50, (2) area under the serial FEV_1curve at treatment week 12 relative to treatment day 1 baseline for FSC 100/50 compared to FP 100
Notes	

Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	Yes	Treatment assignments were generated in blocks of 6 by a computer-based random codes system
Allocation concealment?	Unclear	Not stated
Blinding? All outcomes	Yes	Double blind
Incomplete outcome data addressed? All outcomes	Yes	228/267 (85%) completed the study
Free of selective reporting?	Yes	Full data on GSK web site

Nathan 2006

Methods	Parallel group Multicentre study over 12 weeks.,
Participants	365 adults and adolescents randomised. Age range: 12-82 years, mean FEV1 68% predicted. Inclusion criteria: FP440-660 mcg/d for at least 3 months prior to study entry; FEV1 40-85%; reversibility >=15%
Interventions	Combination HFA FP/SAL 110/42 BID (220/84) versus CFC SAL 42 BID (84) versus CFC FP 110 BID (220) versus HFA PLA. Inhaler devices: MDI. Run-in: 2 weeks This review only includes data from the salmeterol and placebo arms. Co-interventions: ICS at usual dose was an inclusion criterion, but appears to have been withdrawn in the Salmeterol and Placebo arms of the study
Outcomes	The paper publication mentions one drug-related SAE (an upper GI bleed from the placebo group). Website: SAS30004. No fatal SAE. No SAE on FSC or FP
Notes	

Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	Unclear	Not stated
Allocation concealment?	Unclear	Not stated
Blinding? All outcomes	Yes	Double blind
Incomplete outcome data addressed? All outcomes	Yes	243/365 (67%) completed the study, no SAE events occurred
Free of selective reporting?	Yes	Full data on GSK web site

Nelson 2003

Methods	Randomized, double-blind, active-controlled, parallel-group study over 12 weeks at 33 centres in the U.S. Run in 2 weeks single blind placebo
Participants	**Population**: 283 adolescents and adults (12-77) years with asthma. **Baseline Characteristics**: Mean age 32 years. FEV_1 66% predicted. Concomitant inhaled corticosteroids used by zero percentage of participants. **Inclusion Criteria**: At least 12 years old and a medical history of asthma, (as defined by the American Thoracic Society) requiring asthma pharmacotherapy for at least 6 months, FEV_1 % predicted between 40% to 85%, bronchodilator reversibility by an increase of at least 15% in FEV_1 over baseline within 30 minutes after two inhalations of inhaled albuterol.(180 μg) **Exclusion Criteria**: History of life-threatening asthma; hypersensitivity reaction to sympathomimetic drugs or corticosteroids; smoking within the previous year or a history

Nelson 2003 (*Continued*)

	of >10 pack-years; use of oral, inhaled or injectable corticosteroid therapy within the previous month; use of intranasal corticosteroid therapy except for Flonase (GlaxoWellcome Inc.); use of daily oral corticosteroid treatment within the previous 6 months; use of any other prescription or over-the-counter medication that could have affected the course of asthma or interacted with sympathomimetic amines; abnormal chest x-ray films; clinically significant abnormal 12-lead electrocardiograms (ECGs); or a history of significant concurrent disease (e.g., glaucoma, diabetes, hypertension)
Interventions	1. FSC 88/44 µg HFA BD 2. FP 88 µg CFC BD 3. Salmeterol 42 µg CFC BD (not considered in this review) Delivery was MDI
Outcomes	Primary efficacy measures were area under the serial Forced Expiratory Flow FEV_1 curve for 12 hours following administration of study medication and change from baseline at endpoint in morning pre-dose FEV_1 The paper reports "no serious drug related adverse events".
Notes	

Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	Unclear	Not reported
Allocation concealment?	Unclear	Not reported
Blinding? All outcomes	Yes	Double blind
Incomplete outcome data addressed? All outcomes	Yes	257/283 (91%) completed the study
Free of selective reporting?	Yes	Full data on GSK web site

Pearlman 2004

Methods	Setting: Multicentre study, USA Length of intervention period: 12 weeks Randomisation: yes (method not reported) Allocation concealment: not stated Design: parallel group Masking: double blind Excluded: not stated Withdrawals: not stated (ITT)

Pearlman 2004 (*Continued*)

Participants	N = 360. FPS arm N = 92, FP arm N = 89. Study Population: Males and females 12 years of age or older, with a diagnosis of asthma using the American Thoracic Society definition were screened. All subjects were required to have a FEV1 of 40% to 85% predicted normal and >15% reversibility following 2 puffs of VENTOLIN at Screening. The study population was stratified according to whether or not subjects were treated with inhaled corticosteroids or inhaled beta2-agoinsts at Screening (salmeterol or short-acting beta2-agonists only). Subjects treated with inhaled corticosteroids must have been treated for at least 3 months prior to Visit 1 and receiving a daily dose of: 252-336mcg beclomethasone dipropionate, 600-800mcg triamcinolone acetonide, 1000mcg flunisolide, 400-600mcg budesonide, 176mcg fluticasone propionate inhalation aerosol or 200mcg FP inhalation powder for at least one month prior to Visit 1 with no change in regimen. Eligible subjects using only, as-needed, short-acting beta-agonist therapy were required to have received treatment for at least one week prior to Visit 1 and have a 7 day total symptom score >7 for the 7 days prior to Visit 2. Eligible subjects using salmeterol at baseline were required to have received salmeterol and as-needed, short-acting beta2-agonists only for at least one week prior to Visit 1 No details on distribution between the groups provided. Participants described as symptomatic. Baseline medication: prn SABA alone: 142; SAL: 84; ICS: 134 (37%)
Interventions	1. FSC 88/42 bd 2. Fluticasone 88 bd The other arms were not used for this review.
Outcomes	Paper reports no serious drug-related adverse events. Website:SAS3003. No fatal SAE in the FPS or FP group. One Tachyarrythmia on FP
Notes	

Risk of bias

Item	**Authors' judgement**	**Description**
Adequate sequence generation?	Unclear	Not stated
Allocation concealment?	Unclear	Not stated
Blinding? All outcomes	Yes	Double blind
Incomplete outcome data addressed? All outcomes	Unclear	279/360 (77%) completed study
Free of selective reporting?	Yes	Data on GSK web site

Rojas 2007

Methods	A randomized, double-blind, multicenter, parallel-group study over 12 weeks from February 2003 to September 2003 at 48 centres worldwide. (Argentina (4), Czech Republic (8), France(9), Israel (4), Italy (9), Poland(4), Slovakia (6), Turkey (4) Run in 2 weeks
Participants	**Population**: 362 adolescents and adults (12 - 78) years with moderate persistent asthma **Baseline Characteristics**: Mean age 41 years. FEV_1 72% predicted.Concomitant inhaled corticosteroids used by 0% of participants. **Inclusion Criteria**:12 to 80 years with a documented clinical history of persistent asthma for at least 6 months and currently receiving inhaled short-acting â2-agonists alone. FEV_1 % predicted between 60% and 80%,bronchodilator reversibility by an increase of at least 15% in FEV_1 over baseline after 400µg salbutamol, or a mean morning PEF during the last 7 days of the run-in of less than 85% of the post-bronchodilator value, and a daytime symptom score of at least 2 on at least 4 of the last 7 days of the run-in **Exclusion Criteria**: Taken corticosteroids within 12 weeks, leukotriene receptor antagonists within 4 weeks or long acting inhaled or oral â2-agonists, sodium cromoglycate, nedocromil sodium, ketotifen, methylxanthines, or inhaled anticholinergics within 2 weeks of entering the study, or had an acute asthma exacerbation requiring hospital treatment within 6 weeks, or had a respiratory tract infection within 4 weeks of entering the study, or a smoking history of more than10 pack years
Interventions	1. FSC 250/50 µg BD 2. FP 250 µg BD Delivery was Diskus inhaler
Outcomes	Primary efficacy variable was mean morning PEF. Paper reports: "Only three serious adverse events occurred and none were considered related to study treatment."
Notes	

Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	Unclear	Not reported
Allocation concealment?	Unclear	Not reported
Blinding? All outcomes	Yes	Double blind
Incomplete outcome data addressed? All outcomes	Yes	350/362 (97%) completed the study
Free of selective reporting?	Yes	Full data on GSK web site

SAM30007

Methods	A randomized, double-blind, multi centre, parallel-group study over 30 weeks from September 2000 to May 2002 at 5 centres in Denmark. Run-in 2 weeks A multi centre, randomised, double-blind, controlled, parallel-group, comparative investigation of the corticosteroid-saving potential of the combination therapy fluticasone propionate and salmeterol (SERETIDE) compared with fluticasone propionate alone, given to adult asthmatic subjects, when reducing the inhaled corticosteroid dose from an initially high level of 500 µg bd
Participants	**Population**: 61 adults (18 +) with stable asthma. **Baseline Characteristics**: Mean age 37 years. FEV_1 not reported % predicted. Concomitant inhaled corticosteroids used by 100% of participants. **Inclusion Criteria**: At least18 years old with a clinical diagnosis of stable asthma, treated with 1500-2000µg of budesonide, beclomethasone dipropionate or flunisolide, or 750-1000µg of FP for at least 10 weeks prior to the study. FEV_1 % predicted at least 60%, need to be able to use the data capture method (electronic diary, AM-2) correctly. **Exclusion Criteria**: not reported
Interventions	1. FSC 500/50, 250/50 or 100/50 µg BD 2. FP 500, 250 or 100 µg BD
Outcomes	The primary efficacy endpoint was the minimum dose at which the subject's asthma remained controlled ? the minimum acceptable dose (MAD)
Notes	

Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	Unclear	Not reported
Allocation concealment?	Unclear	Not reported
Blinding? All outcomes	Yes	Double blind
Incomplete outcome data addressed? All outcomes	Yes	55/61 (90%) completed the study
Free of selective reporting?	Yes	Data on GSK web site

SAM40004

Methods	A multi-centre, randomised, double-blind, placebo-controlled parallel group study to compare the effect on airway inflammation and remodelling of treatment with salmeterol/fluticasone propionate combination product (50/100 mcg strength) bd via the *Accuhaler* inhaler, or fluticasone propionate 100 mcg bd via the *Accuhaler* inhaler or placebo via the *Accuhaler* inhaler for 16 weeks, followed by double-blind treatment for 52 weeks with the salmeterol/fluticasone propionate combination product (50/100 mcg strength) bd via the *Accuhaler* inhaler or fluticasone propionate 100 mcg bd via the *Accuhaler* inhaler, in adults with reversible airways obstruction (SIRIAS - Seretide in Inflammation and Remodelling In Asthma Study)
Participants	**Population**: 63 adults (18 - 50) with mild asthma. **Baseline Characteristics**: Mean age 32 years. FEV_1 unknown % predicted. Concomitant inhaled corticosteroids used by unknown % of participants, but all withdrawn during the run-in period. **Inclusion Criteria**: Aged 18 to 50 years with a history of reversible airways obstruction, to have received short-acting $beta_2$- agonist alone or Beclometasone dipropionate or budesonide at a constant daily dose of up to 400 mcg per day (excluding any CFC-free formulation) or FP at a constant daily dose of up to 200 mcg per day via any device for at least four weeks prior to the first visit. In addition subjects were to have had a fall in FEV_1 of at least 20% with a histamine challenge test at the first visit and have a post-bronchodilator FEV_1 of > 60% of predicted normal. To be randomised subjects had to have a fall in FEV_1 of at least 20% with a standardised histamine challenge test, AND at least one of the following criteria: have recorded symptoms on at least 4 of the last seven days of the preventer-free run-in period; have recorded using their inhaled short-acting $beta_2$ -agonist on at least 2 occasions on at least 4 of the last seven days of the preventer-free run-in period; have a period variation of at least 10% over the last seven days of the preventer-free run-in period. **Exclusion Criteria**: not reported
Interventions	1. FSC 100/50 µg BD throughout 2. Placebo initially and then FSC 100/50 µg BD 3. FP100 µg BD throughout Delivery as DPI
Outcomes	Outcome: The primary efficacy endpoint was the level of airway hyper-reactivity (as measured by histamine PC_{20}) and response of the induced airway spasm to bronchodilator (post-bronchodilator forced expiratory volume in one second (FEV_1)) SAE data was used for the 52 week extension period as reported. There were no SAEs reported in the 16 week initial period
Notes	

Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	Unclear	Not reported
Allocation concealment?	Unclear	Not reported

SAM40004 (*Continued*)

Blinding? All outcomes	Yes	Double blind
Incomplete outcome data addressed? All outcomes	No	37/63 (59%) completed the study
Free of selective reporting?	Yes	Data on GSK web site

SAM40008

Methods	A Multicentre, Randomised, Double-Blind, Parallel Group Comparison of the Efficacy of SERETIDE* bd and Fluticasone Propionate bd (Both Via DISKUS*/ACCUHALER*, Inhaler) when Tapering the Inhaled Corticosteroid Dose in Asthmatic Adults Carried out over 26 weeks from May 2000 to July 2001 at 34 centres in 10 countries (Australia, Estonia, Finland, France, Germany, Israel, Latvia, New Zealand, Spain, the United Kingdom)
Participants	**Population**: 186adults (18 +) with persistent asthma. **Baseline Characteristics**: Mean age 50 years. FEV_1 unknown % predicted. Concomitant inhaled corticosteroids used by 100% of participants. **Inclusion Criteria**: 18 years or older with documented evidence of asthma within the previous 2 years and who were receiving 1500-2000mcg/day of BUD or equivalent ICS, excluding FP, for at least 3 months prior to the start of baseline. **Exclusion Criteria**: not reported
Interventions	1. FSC 500/50 µg BD 2. FP 500 µg BD Delivery as DPI
Outcomes	The primary efficacy endpoint was the minimum acceptable daily dose of ICS
Notes	High drop-out rate. Only 8% completed the study

Risk of bias

Item	**Authors' judgement**	**Description**
Adequate sequence generation?	Unclear	Not reported
Allocation concealment?	Unclear	Not reported
Blinding? All outcomes	Yes	Double blind
Incomplete outcome data addressed? All outcomes	No	only 14/186 (8%) completed the study

SAM40008 (*Continued*)

Free of selective reporting?	Yes	Data on GSK web site

SAM40012

Methods	A randomized, double-blind, double-dummy, multi centre, parallel-group study over 24 weeks from June 2000 to June 2001 at 38 centres in 7 countries. (Bulgaria, Hungary, Israel, Poland, Russia, Spain, the United Kingdom) Run-in 2 weeks A multi centre, randomised, double-blind, double-dummy, parallel group comparison of three treatments : 1) salmeterol/fluticasone propionate (SFC) (50/100mcg strength) bd via DISKUS/ACCUHALER inhaler, 2) fluticasone propionate 200mcg bd via DISKUS/ACCUHALER inhaler, 3) fluticasone propionate 100mcg bd via DISKUS/ ACCUHALER inhaler in children aged 4-11 years with asthma
Participants	**Population**: 548 children (4 -11) with asthma. **Baseline Characteristics**: Mean age 8 years. FEV_1 not reported % predicted. Concomitant inhaled corticosteroids used by 100% of participants. **Inclusion Criteria**: Aged 4-11 years, inclusive, with documented evidence of asthma and receiving BDP, BUD or equivalent at a dose of 400-500mcg/day or fluticasone propionate at a dose of 200-250mcg/day for at least 4 weeks before Visit 1. Recorded a symptom score (i.e. total score of daytime and night-time scores) on the electronic daily record card of at least 2 on at least three of the last seven consecutive days of the run-in period and had a mean morning PEF (calculated from the last 7 days of the run-in period) of between 50% and 85% of the PEF measured 15 minutes after administration of 400mcg of salbutamol at the randomisation visit. In addition, subjects had to have recorded at least 70% of data into their electronic daily record cards. **Exclusion Criteria**: not reported
Interventions	1. FSC 100/50 µg BD 2. FP 100 µg BD 3. FP 200 µg BD Delivery was Diskus device (third arm not used in this review)
Outcomes	The primary efficacy endpoint was the percentage of combined symptom-free days and nights during weeks 1-24
Notes	

Risk of bias

Item	**Authors' judgement**	**Description**
Adequate sequence generation?	Unclear	Not reported
Allocation concealment?	Unclear	Not reported
Blinding? All outcomes	Yes	Double blind

SAM40012 (*Continued*)

Incomplete outcome data addressed? All outcomes	Yes	513/548 (94%) completed the study
Free of selective reporting?	Yes	Data on GSK web site

SAM40031

Methods	A 13 month, randomised, double-blind, parallel-group comparison of the efficacy of Seretide (fluticasone propionate/salmeterol combination Accuhaler) and Flixotide(fluticasone propionate Accuhaler) when down-titrating the inhaled corticosteroid dose in asthmatic adults who have previously received Seretide500/50 mcg twice daily for at least 4 weeks A randomized, double-blind, parallel-group study over 52 weeks from March 2002 to February 2006 at 3 centres in Australia
Participants	**Population**: 82 adolescents and adults (18 - 80) with asthma. **Baseline Characteristics**: Mean age 47 years. FEV_1 unknown % predicted. Concomitant inhaled corticosteroids used by 100% of participants. **Inclusion Criteria**: Aged between 18 and 80 years with a clinical diagnosis of asthma according to American Thoracic Society criteria for at least 6 months prior to enrolment, currently receiving FP/SX, either via dry powder inhaler or metered dose inhaler (with or without spacer) at a dose of 500/50 mcg bd or 250/25mc 2 inhalations bd for a minimum of 4 weeks prior to enrolment **Exclusion Criteria**: not reported
Interventions	1. FSC 500/50, 250/50 or 100/50 µg BD (Reduced incrementally) 2. FP 500, 250 or 100 µg BD (Reduced incrementally) Delivery was DPI
Outcomes	The primary efficacy endpoint was the average daily FP dose (mcg/day) from week 0 to completion/withdrawal, including study medication and exacerbation medication
Notes	

Risk of bias

Item	**Authors' judgement**	**Description**
Adequate sequence generation?	Unclear	Not reported
Allocation concealment?	Unclear	Not reported
Blinding? All outcomes	Yes	Double blind
Incomplete outcome data addressed? All outcomes	Yes	60/82 (73%) completed the study

SAM40031 (*Continued*)

Free of selective reporting?	Yes	Data on GSK web site

SAM40065

Methods	A randomized, double-blind, double-dummy, multi centre, parallel-group study for 40 weeks from January 2003 to October 2004 at 44 centres (United States (39), Brazil(3) Bulgaria(2)). Run-in 2 weeks A multicenter, randomized, double-blind, parallel group, 40-week comparison of asthma control using bronchial hyper responsiveness as an additional guide to long-term treatment in adolescents and adults receiving either fluticasone propionate/salmeterol DISKUSTM BID or fluticasone propionate DISKUSTM BID (or placebo BID if asymptomatic)
Participants	**Population**: 449 adults (12 + years) with asthma. **Baseline Characteristics**: Mean age 34 years. FEV_1 not reported % predicted. Concomitant inhaled corticosteroids used by 100% of participants. **Inclusion Criteria**: 12 years of age or older, with a diagnosis of asthma, as defined by the American Thoracic Society (ATS), for at least three months prior to visit 1 and must have been treated with a short-acting $beta_2$-agonist, an anticholinergic, or an allowed ICS at a fixed dosing regimen (within an allowed total daily dose) for at least four weeks prior to the screening visit. FEV_1 % predicted between 60% to 95%, bronchodilator reversibility by an increase of at least 12% in FEV_1 over baseline within 30 minutes following 2 puffs of albuterol inhalation aerosol at the screening visit. Documentation of historical reversibility within 24 months was allowed. **Exclusion Criteria**: history of life-threatening asthma, current unstable asthma, current respiratory tract infection or clinically significant concurrent disease that would put the subject at risk during the study if the condition exacerbated
Interventions	1. FSC 100/50, 250/50 or 500/50 µg BD 2. FP 100, 250 or 500 µg BD (BHR strategy) 3. FP 100, 250 or 500 µg BD (Reference strategy) Delivery was Diskus device (third arm not used in this review)
Outcomes	The primary efficacy endpoint was the average inhaled corticosteroid treatment dose over the treatment period
Notes	SAE data included run-in

Risk of bias

Item	**Authors' judgement**	**Description**
Adequate sequence generation?	Unclear	Not reported
Allocation concealment?	Unclear	Not reported
Blinding? All outcomes	Yes	Double blind

SAM40065 (*Continued*)

Incomplete outcome data addressed? All outcomes	Yes	322/449 (72%) completed the study
Free of selective reporting?	Yes	Data on GSK web site

SAS30021

Methods	A stratified, randomized, double-blind, placebo-controlled, parallel-group study for 12 weeks from November 2001 to February 2004 at 164 centres (United States (153), Latin America(11)) A Stratified, Randomized, Double-Blind, Placebo-Controlled, Parallel-Group, 12-Week Trial Evaluating the Safety and Efficacy of the Fluticasone Propionate/Salmeterol DISKUS Combination Product 100/50mcg Once Daily Versus Fluticasone Propionate DISKUS 100mcg Once Daily and Placebo in Symptomatic Pediatric Subjects (4-11 Years) With Asthma
Participants	**Population**: 908 children(4- 11) with asthma. **Baseline Characteristics**: Mean age 8 years. FEV_1 not reported % predicted. Concomitant inhaled corticosteroids used by 0% of participants. **Inclusion Criteria**: 4-11yrs of age with a diagnosis of asthma for at least 6 months and treated with short-acting beta2-agonists only or non-ICS controller medications for at least one month prior to Screening. FEV_1 % predicted between 50% to 85%, bronchodilator reversibility by an increase of at least 15% in FEV_1 over baseline within 30 minutes following 2 puffs of albuterol at screening. At the Randomisation Visit, subjects were required to demonstrate AM PEF reproducibility of +15% of the Screening Visit pre-albuterol PEF, demonstrate a PM PEF 50-90% of predicted normal, and have either an asthma symptom score of at least 2 on 4 or more days in the week prior to randomisation, or have used albuterol on at least 4 days in the week prior to randomisation **Exclusion Criteria**: Not reported
Interventions	1. FSC 100/50 µg QD 2. FP 100 µg QD Delivery was Diskus device
Outcomes	The primary efficacy endpoint was the change from Baseline in % predicted PM Peak Expiratory Flow (PEF) over Weeks 1-12
Notes	Once daily dose

Risk of bias

Item	**Authors' judgement**	**Description**
Adequate sequence generation?	Unclear	Not reported
Allocation concealment?	Unclear	Not reported

SAS30021 (*Continued*)

Blinding? All outcomes	Yes	Double blind
Incomplete outcome data addressed? All outcomes	Yes	715/908 (79%) completed the study
Free of selective reporting?	Yes	Data on GSK web site

SAS30022

Methods	A randomized, double-blind, placebo-controlled, parallel-group study for 12 weeks from November 2001 to June 2003 at 121 centres. (US (103), Canada (18)) A randomized, double-blind, placebo-controlled, parallel-group, 12-week trial evaluating the efficacy and safety of the fluticasone propionate/salmeterol DISKUS combination product 250/50mcg once daily versus fluticasone propionate/salmeterol DISKUS combination product 100/50mcg twice daily versus fluticasone propionate DISKUS 250mcg once daily versus placebo in symptomatic adolescent and adult subjects with asthma that is not controlled on short acting beta2-agonists alone
Participants	**Population**: 844 adolescents and adults (12 + years) with asthma that was not controlled on short-acting beta2-agonists alone **Baseline Characteristics**: Mean age 33 years. FEV_1 not reported % predicted. Concomitant inhaled corticosteroids used by zero % of participants **Inclusion Criteria**: 12 years of age or older with a diagnosis of asthma for at least 3 months and treated with short-acting beta2-agonists only for at least one month prior to screening. FEV_1 % predicted between 50% to 85%, bronchodilator reversibility by an increase of at least 15% in FEV_1 over baseline within 30 minutes following 2 puffs of albuterol at screening At the Randomization Visit, subjects were required to demonstrate FEV1 reproducibility of ±15% of the Screening Visit pre-VENTOLIN FEV1, demonstrate a PM PEF 50-90% of predicted normal, and have either an asthma symptom score of at least 2 on 4 or more days in the week prior to randomization, or have used VENTOLIN on at least 4 days in the week prior to randomization. **Exclusion Criteria**: not reported
Interventions	1. FSC 250/50 µg QD 2. FSC 100/50 µg BD 3. FP 250 µg QD (Second arm not used in this review)
Outcomes	Primary Outcome/Efficacy Variable was the change from Baseline in % predicted PM peak expiratory flow (PEF) over Weeks 1-12
Notes	

Risk of bias

Item	Authors' judgement	Description

SAS30022 (*Continued*)

Adequate sequence generation?	Unclear	Not reported
Allocation concealment?	Unclear	Not reported
Blinding? All outcomes	Yes	Double blind
Incomplete outcome data addressed? All outcomes	Unclear	698/844 (83%) completed the study
Free of selective reporting?	Yes	Data on GSK web site

SAS30023

Methods	A randomized, double-blind, multi centre, placebo-controlled, parallel-group study over 12 weeks from April 2002 to April 2003 at 69 centres in 9 countries (Australia, France, UK, Hungary, Ukraine, Italy, Philippines, Thailand, Russia) A 12-week multi centre, randomised, double-blind, placebo-controlled parallel group study to compare the efficacy and tolerability of fluticasone propionate/salmeterol combination (SERETIDE/VIANI/ADVAIR) 88/42mcg once daily in the morning with fluticasone propionate 88mcg once daily in the morning and placebo (short-acting ß2-agonist as required only) once daily in the morning, all via the HFA MDI as initial maintenance therapy in mild asthmatic subjects
Participants	**Population**: 464 adolescents and adults (12 - 80) with mild asthma. **Baseline Characteristics**: Mean age 34 years. FEV_1 not reported % predicted. Concomitant inhaled corticosteroids used by zero % of participants. **Inclusion Criteria**: a documented clinical history of asthma for at least 6 months who were currently receiving short-acting ß2-agonists alone **Exclusion Criteria**: Not reported.
Interventions	1. FSC 44/21 µg two puffs once daily 2. FP 44, µg two puffs once daily Delivery was MDI device with HFA propellant
Outcomes	The primary efficacy endpoint was the morning PEF
Notes	

Risk of bias

Item	**Authors' judgement**	**Description**
Adequate sequence generation?	Unclear	Not reported
Allocation concealment?	Unclear	Not reported

SAS30023 (*Continued*)

Blinding? All outcomes	Yes	Double blind
Incomplete outcome data addressed? All outcomes	Yes	433/464 (93%) completed the study
Free of selective reporting?	Yes	Data on GSK web site

SAS40036

Methods	A randomized, double-blind, double-dummy, multicenter, parallel-group study for 16 weeks from October 2001 to May 2003 at 85 centres in the United States. Run-in two weeks
Participants	**Population**: *331* adolescents and adults(15+ years old) with persistent asthma **Baseline Characteristics**: Mean age 41 years. FEV_1 not reported (% predicted). Concomitant inhaled corticosteroids used by 100% of participants. **Inclusion Criteria**: 15 years of age or older, with a diagnosis of asthma, as defined by the American Thoracic Society (ATS), for at least six months prior to visit 1 and must have been treated with an allowed ICS at a fixed dosing regimen (within an allowed total daily dose) for at least four weeks prior to the screening visit. FEV_1 % predicted between 40% to 85%, bronchodilator reversibility by an increase of at least 12% in FEV_1 over baseline within 30 minutes following 2-4 puffs of albuterol inhalation aerosol at the screening visit. Documentation of historical reversibility within 24 months was allowed. **Exclusion Criteria**: Not reported
Interventions	1. FSC 100/50 µg BD 2. FP 100 µg BD Delivery was Diskus device (other arms of trial not considered for this review)
Outcomes	The primary efficacy endpoint was the mean change from baseline at endpoint in morning peak expiratory flow (PEF)
Notes	No SAEs at all reported in double blind phase of the study.

Risk of bias

Item	**Authors' judgement**	**Description**
Adequate sequence generation?	Unclear	Not reported
Allocation concealment?	Unclear	Not reported
Blinding? All outcomes	Yes	Double blind, double dummy
Incomplete outcome data addressed? All outcomes	Yes	243/331 (73%) completed the study

SAS40036 (*Continued*)

Free of selective reporting?	Yes	Data on GSK web site

SAS40037

Methods	A randomized, double-blind, double-dummy, multicenter, parallel-group study for 16 weeks from October 2001 to May 2003 at 87 centres in the United States. Run-in two weeks
Participants	**Population**: *331* adolescents and adults(15+ years old) with persistent asthma **Baseline Characteristics**: Mean age 41 years. FEV_1 not reported (% predicted). Concomitant inhaled corticosteroids used by 100% of participants. **Inclusion Criteria**: 15 years of age or older, with a diagnosis of asthma, as defined by the American Thoracic Society (ATS), for at least six months prior to visit 1 and must have been treated with an allowed ICS at a fixed dosing regimen (within an allowed total daily dose) for at least four weeks prior to the screening visit. FEV_1 % predicted between 40% to 85%, bronchodilator reversibility by an increase of at least 12% in FEV_1 over baseline within 30 minutes following 2-4 puffs of albuterol inhalation aerosol at the screening visit. Documentation of historical reversibility within 24 months was allowed. **Exclusion Criteria**: diagnosed with life-threatening asthma, hospitalised for asthma within the previous 6 months, had a concurrent respiratory disease, or had intermittent or seasonal asthma alone, had a respiratory tract infection or used antibiotics for the treatment of a suspected or diagnosed respiratory tract infection within 14 days of Visit 1
Interventions	1. FSC 100/50 µg BD 2. FP 100 µg BD Delivery was Diskus device (other arms of trial not considered for this review)
Outcomes	The primary efficacy endpoint was the mean change from baseline at endpoint in morning peak expiratory flow (PEF)
Notes	

Risk of bias

Item	**Authors' judgement**	**Description**
Adequate sequence generation?	Unclear	Not reported
Allocation concealment?	Unclear	Not reported
Blinding? All outcomes	Yes	double blind, double dummy
Incomplete outcome data addressed? All outcomes	Yes	230/322 (71%) completed the study

SAS40037 (*Continued*)

Free of selective reporting?	Yes	Data on GSK web site

SAS40068

Methods	A randomized, double-blind, multicenter, parallel-group study for 24 weeks from October 2002 to February 2004 at 58 centres in Canada A 24 week, multi centre, randomized, double-blind, parallel group trial to compare the efficacy and tolerability of salmeterol/fluticasone propionate (*ADVAIR) DISKUS* inhalation device 50/100 mcg bid with fluticasone propionate DISKUS inhalation device 100 mcg bid as initial maintenance treatment in adult and adolescent subjects with symptomatic, persistent asthma not controlled on short-acting bronchodilators alone
Participants	**Population**: 532 adolescents and adults(12+ years) with symptomatic, persistent asthma. **Baseline Characteristics**: Mean age 35 years. FEV_1 not reported % predicted. Concomitant inhaled corticosteroids used by 0% of participants. **Inclusion Criteria**: 12 years of age or older with symptomatic, persistent mild asthma (defined as FEV_1 at least 80% predicted and over the last 7 consecutive days of run-in, had an asthma symptom score of 2, or more on at least 3 days or disruptions of normal sleep patterns on 2 or more occasions, or had used rescue bronchodilator medication on 4 or more days), and treated with inhaled short-acting bronchodilators alone **Exclusion Criteria**: taken any other asthma therapy (e.g. inhaled corticosteroids, leukotriene modifiers, inhaled long-acting beta2-agonists) within 1 month prior to screening, had a smoking history of 10 pack years or more, or had an acute asthma exacerbation requiring emergency room treatment within the last 6 weeks or hospitalization within the last 12 weeks prior to screening
Interventions	1. FSC 100/50 µg BD 2. FP 100 µg BD Delivery was Diskus device
Outcomes	The primary efficacy endpoint was the change from baseline in daily record card (DRC) mean morning peak expiratory flow (PEF) over 24 weeks One death due to aorta hypoplasia and ventricular hypertrophy on Fluticasone
Notes	

Risk of bias

Item	**Authors' judgement**	**Description**
Adequate sequence generation?	Unclear	Not reported
Allocation concealment?	Unclear	Not reported
Blinding? All outcomes	Yes	Double blind

SAS40068 (*Continued*)

Incomplete outcome data addressed? All outcomes	Yes	433/532 (81%) completed the study
Free of selective reporting?	Yes	Data in GSK web site

SFA103153

Methods	A randomized, double-blind,multicenter, parallel-group study for 52 weeks from November 2004 to April 2007 at 59 centres in the United States. Run-in 4 weeks
Participants	**Population**: 475 adolescents and adults(12 - 65) of African descent with persistent asthma **Baseline Characteristics**: Mean age 32 years. FEV_1 78% predicted. Concomitant inhaled corticosteroids used by 100% of participants. **Inclusion Criteria**: Subjects were of African descent, 12 to 65 years of age with persistent asthma, and were symptomatic while taking an ICS **Exclusion Criteria**: Not reported
Interventions	1. FSC 100/50 µg BD 2. FP 100 µg BD Delivery was Diskus device
Outcomes	The primary efficacy endpoint was asthma exacerbation rate per subject per year
Notes	

Risk of bias

Item	**Authors' judgement**	**Description**
Adequate sequence generation?	Unclear	Not reported
Allocation concealment?	Unclear	Not reported
Blinding? All outcomes	Yes	Double blind
Incomplete outcome data addressed? All outcomes	Yes	320/475 (67%) completed the study
Free of selective reporting?	Yes	Data on GSK web site

SFCF4026

Methods	A randomized, double-blind, multicenter, parallel-group study for 24 weeks from May 2002 to November 2003 at 124 centres in France. Run-in 8 weeks Maintenance of asthma control in adults: comparison of three therapeutic strategies in patients whose asthma is controlled by a medium dose of inhaled corticosteroid and a long-acting inhaled beta2-agonist
Participants	**Population**: 476 adolescents and adults(18+ years) with asthma. **Baseline Characteristics**: Mean age 45 years. FEV_1 not reported % predicted. Concomitant inhaled corticosteroids used by 100% of participants **Inclusion Criteria**: 18 years of age or older with a documented history of asthma (for at least 6 months) and whose asthma was controlled with the current treatment (inhaled corticosteroid at a dose of 1000mcg of CFC beclomethasone dipropionate or equivalent and a long-acting beta2-agonist at recommended dose) at stable dose for at least 4 weeks prior to the run-in period. Randomized if fulfilled the following criteria: at least 2 of the following: diurnal symptoms at least 2 days per week, use of rescue short-acting bronchodilator no more than 2 days per week and no more than 4 occasions per week, PEF at least 80 % predicted every day. Plus all the following criteria: no night-time awakenings due to asthma, no exacerbations, no emergency visits, no treatment related adverse events enforcing a change in asthma therapy. **Exclusion Criteria**: for entry in the run in period:smoking history of ten pack-years or more, respiratory tract infection during the last 4 weeks prior to visit 1 (the last 2 weeks after amendment number 1), acute asthma exacerbation requiring emergency room treatment or hospitalization within 4 weeks prior to visit 1, use of oral/parenteral corticosteroids during the last 4 weeks prior to visit 1 or any change in maintenance treatment, use of depot corticosteroid within 12 weeks of visit 1. For entry into the treatment period: changes in asthma medication (excluding study rescue medication), use of oral/parenteral or depot corticosteroids, respiratory tract infection, insufficient asthma control, according to daily record card, asthma control questionnaire and investigator's judgement to allow a reduction in maintenance treatment
Interventions	1. FSC 250/50 µg BD 2. FSC 100/50 µg BD 3. FP 250 µg BD Delivery was Diskus device (arm two not used in this review)
Outcomes	The primary efficacy endpoint was the morning peak expiratory flow (PEF) over the first 12 weeks of the treatment period
Notes	

Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	Unclear	Not reported
Allocation concealment?	Unclear	Not reported

SFCF4026 (*Continued*)

Blinding? All outcomes	Yes	Double blind
Incomplete outcome data addressed? All outcomes	Yes	413/476 (87%) completed the study
Free of selective reporting?	Yes	Data on GSK web site

Shapiro 2000

Methods	Setting: multi centre study, USA
Participants	349 adults and adolescents randomised (four treatment arm study; FPS: 84; FP: 84. Data from 13 participants excluded from the analysis due to poor procedure at one site) Inclusion criteria: >/=12 years; ATS defined asthma of >/=6 mo duration requiring pharmacotherapy for at least 6 months; FEV1 between 40 and 85% predicted; >/=15% increase in FEV1 30 mins after 2 puffs of albuterol; use of ICS 12 weeks prior to the study Exclusion criteria: Females with negative pregnancy tests; life-threatening asthma; hypersensitivity to sympathomimetic drugs/steroids; smoking within previous year; smoking history of >10 pack years; use of oral/injectable steroid therapy within 1 month of study; use of daily oral steroids within 6 months prior to the study; use of any prescription or over the counter medication that could have affected asthma or course of treatment; abnormal CXR; clinically significant abnormal 12-lead ECGs history of concurrent disease
Interventions	1. FSC 250/50 bd 2. Fluticasone 250 bd Third arm not used in this review
Outcomes	83% completed study in FPS arm and 73% in FP arm. Paper reports "no serious drug-related adverse events. Two patients treated with salmeterol withdrew from the study because of adverse events; however, these adverse events were considered by the investigator to be unrelated to study drug (bilateral subcapsular cataracts and postsurgical infection)." Website SFCA3003: no fatal adverse events. No serious adverse events in FPS arm; one in FP arm (Asthma exacerbation)
Notes	

Risk of bias

Item	**Authors' judgement**	**Description**
Adequate sequence generation?	Unclear	Not stated
Allocation concealment?	Unclear	Not stated

Shapiro 2000 (*Continued*)

Blinding? All outcomes	Yes	Double blind
Incomplete outcome data addressed? All outcomes	Yes	131/168 (78%) completed the study
Free of selective reporting?	Yes	Full data on GSK web site

SLGF75

Methods	A randomized, double-blind, multicenter, parallel-group study for 12 weeks from January 1998 to December 1998 at 7 centres in Italy. Run-in 4 weeks, follow-up 2 weeks Salmeterol plus low-dose fluticasone propionate (FP) versus high-dose fluticasone propionate (FP) in naive patients with mild to moderate asthma: effects on pulmonary function, and inflammatory markers of induced sputum
Participants	**Population**: 46 adolescents and adults(16 - 65) with mild to moderate asthma **Baseline Characteristics**: Mean age 39 years. FEV_1 unreported % predicted. Concomitant inhaled corticosteroids used by 0% of participants. **Inclusion Criteria**: performed on three study visits. Pre-study visit: all subjects with asthma disease for at least 6 months, Visit 2: 16-65 years old with asthma at moderate level (score of severity at least 6), did not use anti-inflammatory drugs for last month before visit 1, FEV_1 % predicted at least 60%, eosinophils at least 5% in induced sputum. Visit 4: bronchial asthma assessed up to 6 (severity classes value) and with persistence of eosinophils at least 5% (or at least 3% in sites where an amendment was applicable) in induced sputum **Exclusion Criteria**: inhaled steroids or cromones in last 3 months, more than one short course of oral steroids in last 3 months or one short course of oral steroids in last month before pre-study visit; respiratory tract infection in the last 1 month pre-study visit, with lung or other important disease, or on Beta-blocker therapy; hypersensitivity to Beta 2-agonist and suspected to abuse drug or alcohol
Interventions	1. FP 100 + SAL 50 µg BD 2. FP 100 µg BD 3. FP 250 µg BD Delivery was Diskus (third arm not used in this review)
Outcomes	The primary efficacy endpoint was the daily morning peak expiratory flow (PEF)
Notes	

Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	Unclear	Not reported

SLGF75 (*Continued*)

Allocation concealment?	Unclear	Not reported
Blinding? All outcomes	Yes	Double blind
Incomplete outcome data addressed? All outcomes	Yes	42/46 (91%) completed the study
Free of selective reporting?	Yes	Data on GSK web site

Strand 2004

Methods	A randomized, double-blind, comparative, multicenter, parallel-group study over 12 weeks from May 2001 to September 2002 at 45 centres in Denmark. Run-in 2 weeks
Participants	**Population**: 150 adults with persistent asthma **Baseline Characteristics**: Mean age 39 years. PEF 80% predicted. Concomitant inhaled corticosteroids used by 0% of participants. **Inclusion Criteria**:At least 18 years old and an asthma medical history of at least 3 months, either diurnal PEF variation ?20% on at least 2 days or one of the following must have been determined within 3 years prior to baseline: forced expiratory volume in 1 second (FEV_1) reversibility ?15% in response to bronchodilator, provocative concentration of methacholine causing a 20% fall in FEV_1 (PC_{20}) less than 4 mg/mL, diurnal PEF variation at least 20%; mean relief medication (albuterol) use at least 1 episode/week; and day or night symptom score 1 or more at least once/week. **Exclusion Criteria**: Upper or lower respiratory tract infection or middle ear infection within 1 month prior to visit 1; other lung diseases than asthma; known or suspected other diseases or situations likely to affect the outcome of the study results; known serious cardiovascular disease, diabetes mellitus, untreated hypokalaemia, or thyrotoxicosis; use of long-acting bronchodilators, inhaled corticosteroids, or other long-acting asthma medication within 2 months prior to visit 1; use of daily oral corticosteroid treatment within 2 months of visit 1 or oral corticosteroid therapy within 1 month prior to visit
Interventions	1. FSC 100/50 µg BD 2. FP 100 µg BD
Outcomes	The primary efficacy variable was symptom-free days and nights "1 patient in the S/FP group and 2 patients in the FP group had a serious adverse event. None of these serious adverse events was considered related to the study drug." One death reported on the web site in the FP arm but no cause given
Notes	

Risk of bias

Item	**Authors' judgement**	**Description**
Adequate sequence generation?	Unclear	Not reported

Strand 2004 (*Continued*)

Allocation concealment?	Unclear	Not reported
Blinding? All outcomes	Yes	Double blind
Incomplete outcome data addressed? All outcomes	Yes	126/150 completed study
Free of selective reporting?	Yes	Full data from GSK web site

van Noord 2001

Methods	A randomized, double-blind, double-dummy, multicenter, placebo-controlled, parallel-group study over 3 months from December 1997 to March 1999 at 61 centres in 13 countries. Run in 2 weeks
Participants	**Population**: 509 adolescents and adults (12-82) years with moderate to severe asthma **Baseline Characteristics**: Mean age 47 years. FEV_1 72% predicted. Concomitant inhaled corticosteroids used by 100% of participants **Inclusion Criteria:**12 years old or more with a documented clinical history of reversible airways obstruction and symptomatic on ICS therapy (beclomethasone dipropionate, budesonide or flunisolide at a dose of 1500-2000µg/day or FP 750 to 1000 µg day) for at least four weeks before the start of the study. FEV_1 % predicted between 50% to 100%. During the last seven days of the run-in period, required to have had a mean morning PEFR of > 50% and < 85% of PEFR measured 15 minutes after administration of 400µg of salbutamol at the randomisation visit, and a cumulative total symptom score (daytime plus night-time) in the daily record card of at least 8. **Exclusion Criteria**: Received a long-acting B_2-agonist or oral B_2-agonist with 2 weeks of the run-in period, changed asthma medication, had a lower respiratory tract infection in the 4 weeks preceding the run-in period or had an acute asthma exacerbation requiring hospitalisation in the 12 weeks preceding study entry.
Interventions	1. FSC 500/50 µg HFA BD via MDI 2. FSC 500/50 µg HFA BD via Diskus 3. FP 500 µg CFC BD via MDI
Outcomes	Primary efficacy variable was the mean morning PEF over the 12-week treatment period Paper reports eight patients with SAE in FPS groups and 2 on FP. These included 3 asthma exacerbations. Web report indicates that 2 of these were on FPS and one on FP One death report on FSC via MDI due to Leukaemia
Notes	

Risk of bias

Item	**Authors' judgement**	**Description**
Adequate sequence generation?	Unclear	Not stated

van Noord 2001 (*Continued*)

Allocation concealment?	Unclear	Not stated
Blinding? All outcomes	Yes	Double-blind, double-dummy
Incomplete outcome data addressed? All outcomes	Yes	447/509 (88%) completed the study
Free of selective reporting?	Yes	Full data on GSK website

Wallin 2003

Methods	A randomized, double-blind, parallel-group study over 12 weeks. Run-in 2 to 4 weeks
Participants	**Population**: 56 asthmatics, previously not well-controlled on inhaled corticosteroids **Baseline Characteristics**: Mean age 42 years. FEV_1 88% predicted. Concomitant inhaled corticosteroids used by 100% of participants. **Inclusion Criteria**:asthma symptoms on six or more days or four or more nights; need for rescue salbutamol on six or more days or four or more nights; greater than 20% variation between AM and PM PEF on four or more days; pulmonary function, one or more of: at least 15% increase in FEV_1 15 mins after inhalation of 400-800 µg salbutamol, at least 15% increase in PEF 15 mins after inhalation of 400-800 µg salbutamol compared to the mean AM PEF values in the preceding week, more than 20% variation between AM and PM PEF on at least 4 consecutive days, PC_{20} methacholine < 4 mg/ml **Exclusion Criteria**: not reported as such
Interventions	1. FP 200 + SAL 50 µg BD 2. FP 200 µg BD 3. FP 500 µg BD (not used in this review) Delivery was Discus device
Outcomes	Primary end points were submucosal eosinophil and mast cell counts No information in paper but zero SAEs reported on GSK website
Notes	

Risk of bias

Item	**Authors' judgement**	**Description**
Adequate sequence generation?	Unclear	Not stated
Allocation concealment?	Unclear	Not stated
Blinding? All outcomes	Yes	Double blind

Wallin 2003 (*Continued*)

Incomplete outcome data addressed? All outcomes	Yes	46/56 (82%) completed the study
Free of selective reporting?	Yes	SAE data on GSK website

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Adinoff 1998	Not randomised to ICS
Adolfsson 2005	Dose response study
Bateman 1998	Device comparison
Bateman 2006	Higher dose ICS in control arm
Baumgarten 2002	4 week study
Bergmann 2004	Higher dose ICS in control arm
Bjermer 2000	Salmeterol versus LRTA
Bjermer 2003	Salmeterol versus LRTA
Bleecker 2006	Salmeterol versus Salmeterol/Fluticasone
Bleecker 2007	Review
Bleecker 2008	Salmeterol versus LRTA
Bracamonte 2005	Device comparison
Busse 2006	Cross-over study
Calhoun 2001	Salmeterol versus LRTA
Chapman 1999	Device comparison
Condemi 1999	Higher dose ICS in control arm
Cook 1998	Higher dose ICS in control arm
D'Urzo 2001	6 week duration

(*Continued*)

Del 2001	Salmeterol versus LRTA
Deykin 2007	Comparison between different combined inhalers
Didier 1997	No ICS control arm
Dorinsky 2004	Comparison between different combined inhalers
Faurschou 1994	3 week cross-over study
Fish 2001	Salmeterol versus LRTA
Fujimoto 2006	Salmeterol versus tolobuterol
GlaxoSmithKline 2004	Higher dose ICS in control arm
GlaxoSmithKline 2005	Higher dose ICS in control arm
GlaxoSmithKline 2005a	Salmeterol versus LRTA
GlaxoSmithKline 2005c	Device comparison
GlaxoSmithKline 2005d	Higher dose ICS in control arm
GlaxoSmithKline 2005e	Cross-over study
Greening 1994	Higher dose ICS in control arm
Grutters 1999	8 week duration
House 2004	2 week duration
Ilowite 2004	Salmeterol versus LRTA
Isabelle 2001	Device comparison
Jarjour 2006	FPS compared to higher dose FP
Johansson 2001	Different ICS in control arm
Juniper 2002	Different ICS in control arm
Kelsen 1999	Higher dose ICS in control arm
Koopmans 2005	Single dose study
Lazarus 2001	Not randomised to ICS

(*Continued*)

Lemanske 2001	Not randomised to ICS
Lotvall	Single dose study
Lundback 2000	Different ICS in control arm
Martinat 2003	Device comparison
Morice 2006	Comparison between two different combined inhalers
Murray 1999	Higher dose ICS in control arm
Nan 2004	Different ICS in control arm
Nathan 2001	Review of SAS30003 and SAS30004
Nelson 2000	Salmeterol versus LRTA
Nelson 2001	Salmeterol versus LRTA
O'Byrne 2005	Different ICS in control arm
O'Connor 2004	Salmeterol versus LRTA
Pauwels 1998	Different ICS in control arm and salmeterol given in both groups
Pearlman 1999	4 week study
Peters 2007	Higher dose ICS in control arm
Ringdal 2003	Salmeterol versus LRTA
Rosenthal 1999	No randomisation to ICS
Russell 1995	No randomisation to ICS
SAM30002	FPS compared to Budesonide at higher dose
SAM30013	FPS compared with higher dose fluticasone
SAM40116	Patients with asthma and COPD compared to higher dose fluticasone
SAS30015	FPS compared to BDP
Schermer 2007	Higher dose ICS in control arm
Schlosser 1998	Device comparison

(*Continued*)

Scott 2005	Device comparison
SLGA5021	FPS comparison with higher dose fluticasone
Tonnel 2004	Device comparison in acute asthma
Van den 2000	Device comparison
Van Noord 1999	Higher dose ICS in control arm
Vermetten 1999	Higher dose ICS in control arm
Woolcock 1996	Higher dose ICS in control arm
You-Ning 2005	Device comparison
Zhong 2002	Device comparison
Zhong 2005	Comparison to different ICS in control arm

DATA AND ANALYSES

Comparison 1. Regular Salmeterol in addition to regular inhaled corticosteroids

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 All-cause mortality	33	12046	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.05 [0.32, 3.47]
1.1 Adults and adolescents	30	10873	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.05 [0.32, 3.47]
1.2 Children	3	1173	Peto Odds Ratio (Peto, Fixed, 95% CI)	Not estimable
2 All-cause non-fatal SAE	33	12046	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.16 [0.90, 1.50]
2.1 Adults	30	10873	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.17 [0.90, 1.52]
2.2 Children	3	1173	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.75 [0.17, 3.31]
3 All-cause SAE (fatal and non-fatal)	33	12046	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.15 [0.90, 1.48]
3.1 Adults	30	10873	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.17 [0.91, 1.51]
3.2 Children	3	1173	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.75 [0.17, 3.31]
4 Asthma-related SAE	33	12046	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.91 [0.50, 1.64]
4.1 Adults	30	10873	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.95 [0.52, 1.73]
4.2 Children	3	1173	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.14 [0.00, 6.82]

Analysis 1.1. Comparison 1 Regular Salmeterol in addition to regular inhaled corticosteroids, Outcome 1 All-cause mortality.

Review: Regular treatment with salmeterol and inhaled steroids for chronic asthma: serious adverse events

Comparison: 1 Regular Salmeterol in addition to regular inhaled corticosteroids

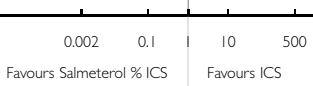
Outcome: 1 All-cause mortality

Study or subgroup	Salmeterol and ICS n/N	ICS n/N	Peto Odds Ratio Peto,Fixed,95% CI	Peto Odds Ratio Peto,Fixed,95% CI
1 Adults and adolescents				
Aubier 1999	1/338	0/165		4.43 [0.07, 287.95]
Bateman 2001	0/333	0/165		0.0 [0.0, 0.0]
GOAL 2004	3/1709	2/1707		1.49 [0.26, 8.61]
Ind 2003	1/171	0/160		6.93 [0.14, 349.94]
Kavuru 2000	0/92	0/90		0.0 [0.0, 0.0]
Koenig 2008	0/156	1/156		0.14 [0.00, 6.82]
Koopmans 2006	0/27	0/27		0.0 [0.0, 0.0]
Lundback 2006	0/95	0/92		0.0 [0.0, 0.0]
Murray 2004	0/88	0/89		0.0 [0.0, 0.0]
Nathan 2006	0/94	0/91		0.0 [0.0, 0.0]
Nelson 2003	0/95	0/97		0.0 [0.0, 0.0]
Pearlman 2004	0/92	0/89		0.0 [0.0, 0.0]
Rojas 2007	0/180	0/182		0.0 [0.0, 0.0]
SAM30007	0/29	0/32		0.0 [0.0, 0.0]
SAM40004	0/42	0/21		0.0 [0.0, 0.0]
SAM40008	0/93	0/93		0.0 [0.0, 0.0]
SAM40031	0/41	0/41		0.0 [0.0, 0.0]
SAM40065	0/150	0/150		0.0 [0.0, 0.0]
SAS30022	0/210	0/212		0.0 [0.0, 0.0]
SAS30023	0/151	0/155		0.0 [0.0, 0.0]
SAS40036	0/172	0/159		0.0 [0.0, 0.0]
SAS40037	0/161	0/161		0.0 [0.0, 0.0]
SAS40068	0/262	1/270		0.14 [0.00, 7.03]
SFA103153	0/239	0/236		0.0 [0.0, 0.0]

(*Continued* . . .)

(. . . *Continued*)

Study or subgroup	Salmeterol and ICS n/N	ICS n/N	Peto Odds Ratio Peto,Fixed,95% CI	Peto Odds Ratio Peto,Fixed,95% CI
SFCF4026	0/159	0/159		0.0 [0.0, 0.0]
Shapiro 2000	0/84	0/84		0.0 [0.0, 0.0]
SLGF75	0/14	0/17		0.0 [0.0, 0.0]
Strand 2004	0/78	1/72		0.12 [0.00, 6.29]
van Noord 2001	1/337	0/172		4.53 [0.07, 285.45]
Wallin 2003	0/18	0/19		0.0 [0.0, 0.0]
Subtotal (95% CI)	**5710**	**5163**		**1.05 [0.32, 3.47]**
Total events: 6 (Salmeterol and ICS), 5 (ICS)				
Heterogeneity: Chi² = 5.18, df = 6 (P = 0.52); I² =0.0%				
Test for overall effect: Z = 0.08 (P = 0.93)				
2 Children				
Malone 2005	0/101	0/102		0.0 [0.0, 0.0]
SAM40012	0/181	0/181		0.0 [0.0, 0.0]
SAS30021	0/304	0/304		0.0 [0.0, 0.0]
Subtotal (95% CI)	**586**	**587**		**0.0 [0.0, 0.0]**
Total events: 0 (Salmeterol and ICS), 0 (ICS)				
Heterogeneity: Chi² = 0.0, df = 0 (P<0.00001); I² =0.0%				
Test for overall effect: Z = 0.0 (P < 0.00001)				
Total (95% CI)	**6296**	**5750**		**1.05 [0.32, 3.47]**
Total events: 6 (Salmeterol and ICS), 5 (ICS)				
Heterogeneity: Chi² = 5.18, df = 6 (P = 0.52); I² =0.0%				
Test for overall effect: Z = 0.08 (P = 0.93)				
Test for subgroup differences: Not applicable				

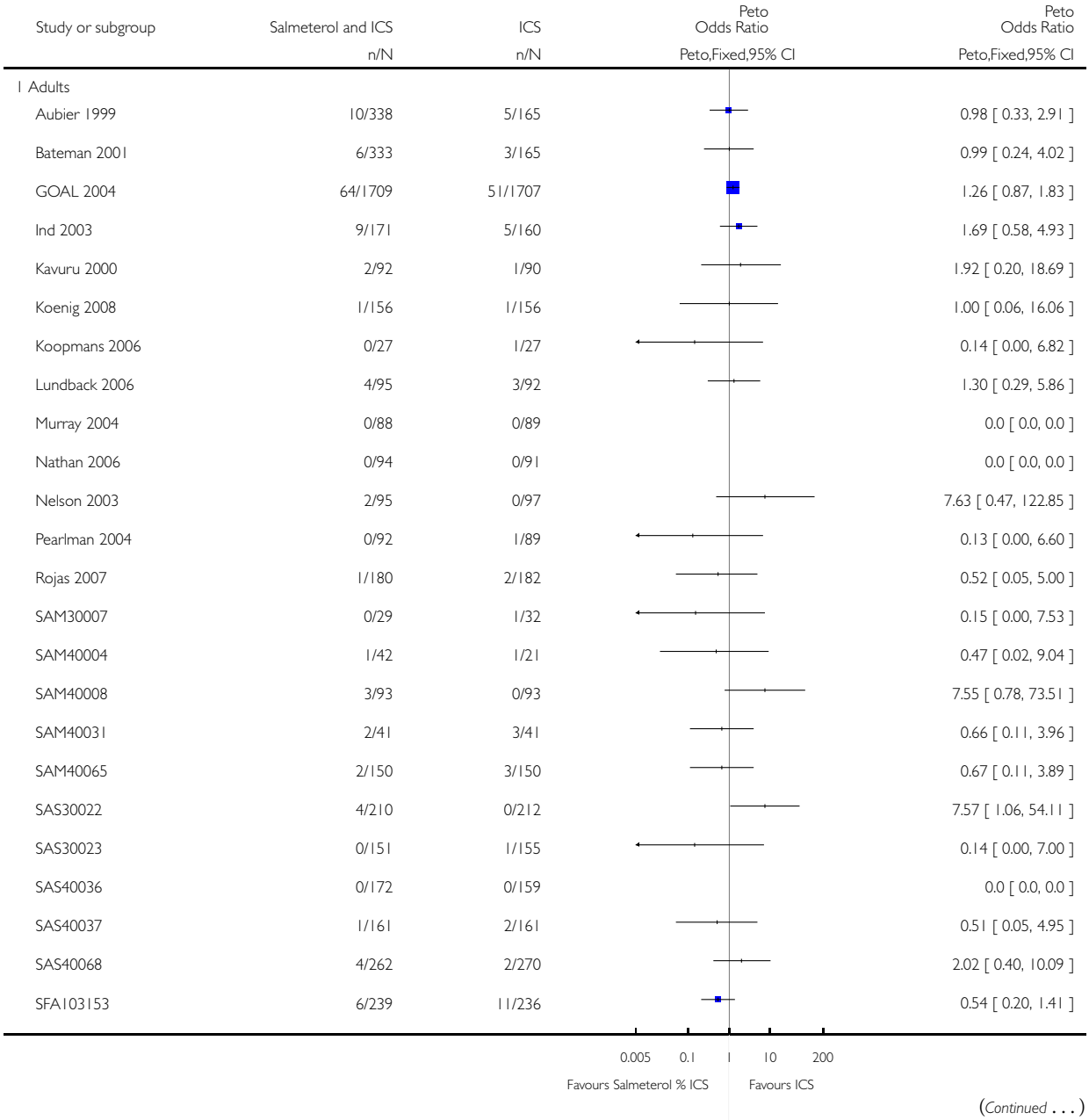


Analysis 1.2. Comparison 1 Regular Salmeterol in addition to regular inhaled corticosteroids, Outcome 2 All-cause non-fatal SAE.

Review: Regular treatment with salmeterol and inhaled steroids for chronic asthma: serious adverse events

Comparison: 1 Regular Salmeterol in addition to regular inhaled corticosteroids

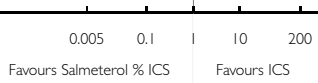
Outcome: 2 All-cause non-fatal SAE



(*Continued* . . .)

(. . . *Continued*)

Study or subgroup	Salmeterol and ICS n/N	ICS n/N	Peto Odds Ratio Peto,Fixed,95% CI	Peto Odds Ratio Peto,Fixed,95% CI
SFCF4026	3/159	1/159		2.74 [0.38, 19.67]
Shapiro 2000	0/84	1/84		0.14 [0.00, 6.82]
SLGF75	0/14	0/17		0.0 [0.0, 0.0]
Strand 2004	1/78	2/72		0.47 [0.05, 4.58]
van Noord 2001	8/337	2/172		1.87 [0.50, 7.03]
Wallin 2003	0/18	0/19		0.0 [0.0, 0.0]
Subtotal (95% CI)	**5710**	**5163**		**1.17 [0.90, 1.52]**
Total events: 134 (Salmeterol and ICS), 103 (ICS)				
Heterogeneity: Chi² = 21.42, df = 24 (P = 0.61); I² =0.0%				
Test for overall effect: Z = 1.21 (P = 0.23)				
2 Children				
Malone 2005	0/101	0/102		0.0 [0.0, 0.0]
SAM40012	2/181	1/181		1.95 [0.20, 18.91]
SAS30021	1/304	3/304		0.37 [0.05, 2.61]
Subtotal (95% CI)	**586**	**587**		**0.75 [0.17, 3.31]**
Total events: 3 (Salmeterol and ICS), 4 (ICS)				
Heterogeneity: Chi² = 1.20, df = 1 (P = 0.27); I² =16%				
Test for overall effect: Z = 0.38 (P = 0.70)				
Total (95% CI)	**6296**	**5750**		**1.16 [0.90, 1.50]**
Total events: 137 (Salmeterol and ICS), 107 (ICS)				
Heterogeneity: Chi² = 22.96, df = 26 (P = 0.64); I² =0.0%				
Test for overall effect: Z = 1.12 (P = 0.26)				
Test for subgroup differences: Chi² = 0.34, df = 1 (P = 0.56), I² =0.0%				



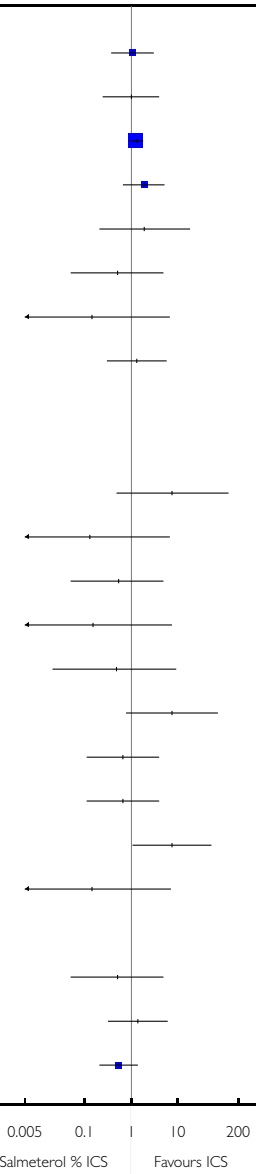
Analysis 1.3. Comparison 1 Regular Salmeterol in addition to regular inhaled corticosteroids, Outcome 3 All-cause SAE (fatal and non-fatal).

Review: Regular treatment with salmeterol and inhaled steroids for chronic asthma: serious adverse events

Comparison: 1 Regular Salmeterol in addition to regular inhaled corticosteroids

Outcome: 3 All-cause SAE (fatal and non-fatal)

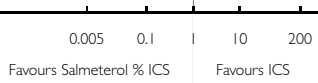
Study or subgroup	Salmeterol and ICS n/N	ICS n/N	Peto Odds Ratio Peto,Fixed,95% CI	Peto Odds Ratio Peto,Fixed,95% CI
1 Adults				
Aubier 1999	11/338	5/165		1.08 [0.37, 3.10]
Bateman 2001	6/333	3/165		0.99 [0.24, 4.02]
GOAL 2004	67/1709	53/1707		1.27 [0.88, 1.83]
Ind 2003	10/171	5/160		1.87 [0.67, 5.27]
Kavuru 2000	2/92	1/90		1.92 [0.20, 18.69]
Koenig 2008	1/156	2/156		0.51 [0.05, 4.95]
Koopmans 2006	0/27	1/27		0.14 [0.00, 6.82]
Lundback 2006	4/95	3/92		1.30 [0.29, 5.86]
Murray 2004	0/88	0/89		0.0 [0.0, 0.0]
Nathan 2006	0/94	0/91		0.0 [0.0, 0.0]
Nelson 2003	2/95	0/97		7.63 [0.47, 122.85]
Pearlman 2004	0/92	1/89		0.13 [0.00, 6.60]
Rojas 2007	1/180	2/182		0.52 [0.05, 5.00]
SAM30007	0/29	1/32		0.15 [0.00, 7.53]
SAM40004	1/42	1/21		0.47 [0.02, 9.04]
SAM40008	3/93	0/93		7.55 [0.78, 73.51]
SAM40031	2/41	3/41		0.66 [0.11, 3.96]
SAM40065	2/150	3/150		0.67 [0.11, 3.89]
SAS30022	4/210	0/212		7.57 [1.06, 54.11]
SAS30023	0/151	1/155		0.14 [0.00, 7.00]
SAS40036	0/172	0/159		0.0 [0.0, 0.0]
SAS40037	1/161	2/161		0.51 [0.05, 4.95]
SAS40068	4/262	3/270		1.38 [0.31, 6.11]
SFA103153	6/239	11/236		0.54 [0.20, 1.41]



(*Continued . . .*)

(. . . *Continued*)

Study or subgroup	Salmeterol and ICS n/N	ICS n/N	Peto Odds Ratio Peto,Fixed,95% CI	Peto Odds Ratio Peto,Fixed,95% CI
SFCF4026	3/159	1/159		2.74 [0.38, 19.67]
Shapiro 2000	0/84	1/84		0.14 [0.00, 6.82]
SLGF75	0/14	0/17		0.0 [0.0, 0.0]
Strand 2004	1/78	3/72		0.33 [0.05, 2.41]
van Noord 2001	9/337	2/172		2.04 [0.58, 7.20]
Wallin 2003	0/18	0/19		0.0 [0.0, 0.0]
Subtotal (95% CI)	**5710**	**5163**		**1.17 [0.91, 1.51]**
Total events: 140 (Salmeterol and ICS), 108 (ICS)				
Heterogeneity: Chi² = 23.02, df = 24 (P = 0.52); I² =0.0%				
Test for overall effect: Z = 1.20 (P = 0.23)				
2 Children				
Malone 2005	0/101	0/102		0.0 [0.0, 0.0]
SAM40012	2/181	1/181		1.95 [0.20, 18.91]
SAS30021	1/304	3/304		0.37 [0.05, 2.61]
Subtotal (95% CI)	**586**	**587**		**0.75 [0.17, 3.31]**
Total events: 3 (Salmeterol and ICS), 4 (ICS)				
Heterogeneity: Chi² = 1.20, df = 1 (P = 0.27); I² =16%				
Test for overall effect: Z = 0.38 (P = 0.70)				
Total (95% CI)	**6296**	**5750**		**1.15 [0.90, 1.48]**
Total events: 143 (Salmeterol and ICS), 112 (ICS)				
Heterogeneity: Chi² = 24.54, df = 26 (P = 0.54); I² =0.0%				
Test for overall effect: Z = 1.12 (P = 0.26)				
Test for subgroup differences: Chi² = 0.33, df = 1 (P = 0.56), I² =0.0%				

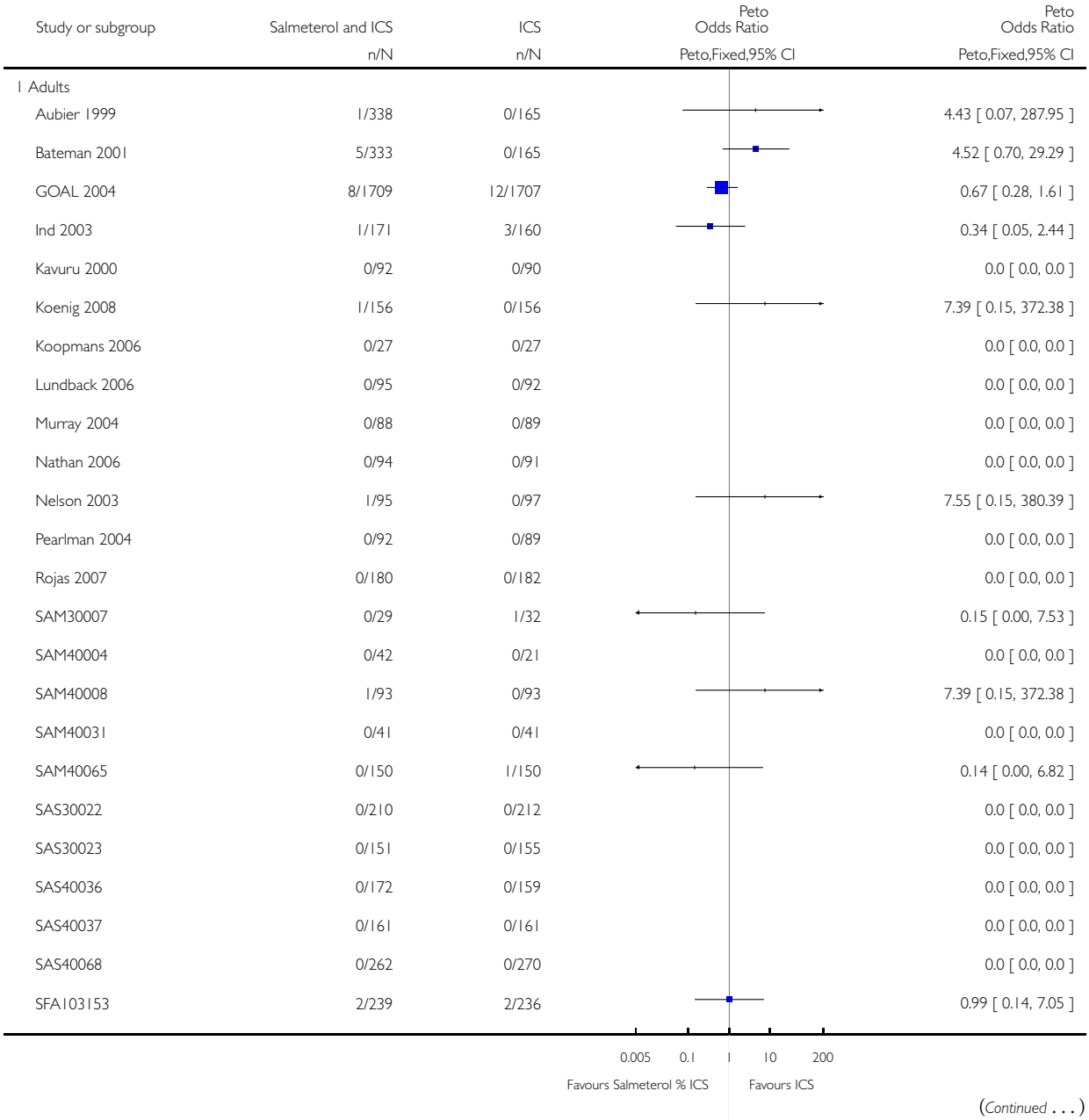


Analysis 1.4. Comparison 1 Regular Salmeterol in addition to regular inhaled corticosteroids, Outcome 4 Asthma-related SAE.

Review: Regular treatment with salmeterol and inhaled steroids for chronic asthma: serious adverse events

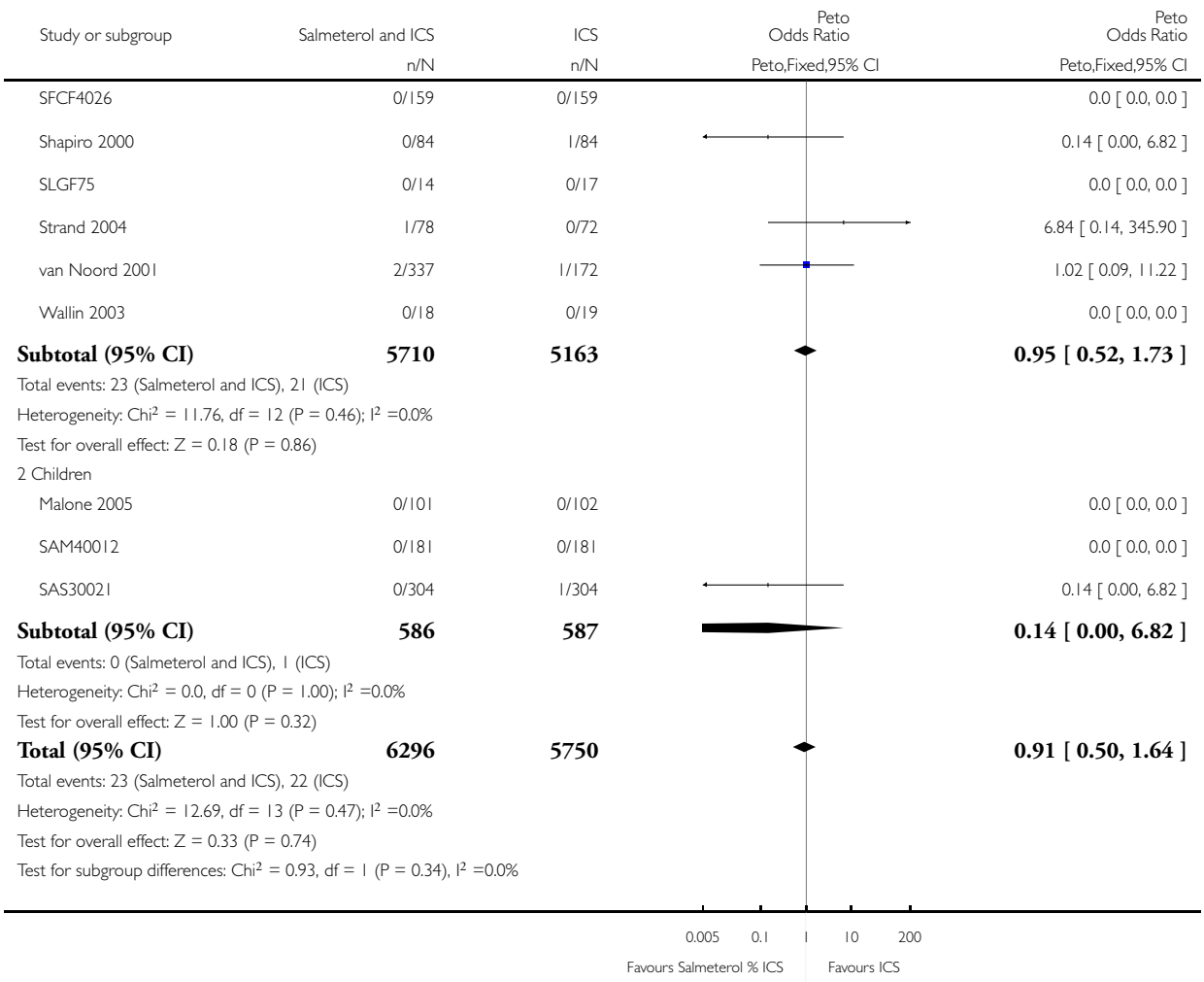
Comparison: 1 Regular Salmeterol in addition to regular inhaled corticosteroids

Outcome: 4 Asthma-related SAE



(*Continued* . . .)

(. . . *Continued*)



ADDITIONAL TABLES

Table 1. Dose of Salmeterol and Fluticasone

Study ID	Age of Participants (Years)	Daily dose of Fluticasone (mcg)	Daily dose of Salmeterol (mcg)	Combined Inhaler	Separate Inhalers
Aubier 1999	12+	1000	100	√	√
Bateman 2001	12+	200	100	√	
GOAL 2004	12+	200/500/1000	100	√	

Table 1. Dose of Salmeterol and Fluticasone (*Continued*)

Ind 2003	16+	500	100		√
Kavuru 2000	12+	200	100	√	
Koenig 2008	12+	200/500/1000	100	√	
Koopmans 2006	18+	500	100	√	
Lundback 2006	18+	500	100	√	
Malone 2005	4 to 11	200	100	√	
Murray 2004	12+	200	100	√	
Nathan 2006	12+	220	100	√	
Nelson 2003	12+	200	100	√	
Pearlman 2004	12+	200	100	√	
Rojas 2007	12+	500	100	√	
SAM30007	18+	200/500/1000	100	√	
SAM40004	18+	200	100	√	
SAM40008	18+	1000	100	√	
SAM40012	4 to 11	200	100	√	
SAM40031	18+	200/500/1000	100	√	
SAM40065	12+	200/500/1000	100	√	
SAS30021	4 to 11	100	50	√	
SAS30022	12+	500	50	√	
SAS30023	12+	100	50	√	
SAS40036	15+	200	100	√	
SAS40037	15+	200	100	√	
SAS40068	12+	200	100	√	
SFA103153	12+	200	100	√	

Table 1. Dose of Salmeterol and Fluticasone (*Continued*)

SFCF4026	18+	500	100	√	
Shapiro 2000	12+	500	100	√	
SLGF75	16+	200	100		√
Strand 2004	18+	200	100	√	
van Noord 2001	12+	1000	100	√	
Wallin 2003	12+	400	100		√

APPENDICES

Appendix 1. Pharmacology of beta$_2$-agonists

-agonists are thought to cause bronchodilation primarily through binding beta$_2$-adrenoceptors on airways smooth muscle (ASM), with subsequent activation of both membrane-bound potassium channels and a signalling cascade involving enzyme activation and changes in intracellular calcium levels following a rise in cyclic adenosine monophosphate (cAMP) (Barnes 1993). However, beta$_2$-adrenoceptors are also expressed on a wide range of cell types where beta$_2$-agonists may have a clinically significant effect including airway epithelium (Morrison 1993), mast cells, post capillary venules, sensory and cholinergic nerves and dendritic cells (Anderson 2006). Beta$_2$-agonists will also cross-react to some extent with other beta-adrenoceptors including beta$_1$-adrenoceptors on the heart. The *in vivo* effect of any beta$_2$-agonist will depend on a number of factors relating to both the drug and the patient. The degree to which a drug binds to one receptor over another is known as *selectivity,* which can be defined as absolute binding ratios to different receptors *in vitro*, whilst *functional selectivity* is measured from downstream effects of drugs in different tissue types *in vitro* or *in vivo.* All of the beta$_2$-agonists described thus far are more beta$_2$ selective than their predecessor isoprenaline *in vitro*. However, because attempts to differentiate selectivity between the newer agents are confounded by so many factors, it is difficult to draw conclusions about *in vitro* selectivity studies and probably best to concentrate on specific adverse side-effects in human subjects at doses which cause the same degree of bronchodilatation. The *potency* of a drug refers to the concentration that achieves half the maximal receptor activation of which that drug is capable but it is not very important clinically as for each drug, manufacturers will alter the dose to try to achieve a therapeutic ratio of desired to undesired effects. In contrast *efficacy* refers to the ability of a drug to activate its receptor independent of drug concentration. Drugs that fully activate a receptor are known as full agonists and those that partially activate a receptor are known as partial agonists. Efficacy also is very much dependent on the system in which it is being tested and is affected by factors including the number of receptors available and the presence of other agonists and antagonists. Thus whilst salmeterol acts as a partial agonist *in vitro* it causes a similar degree of bronchodilation to the strong agonist formoterol in stable asthmatic patients (vanNoord 1996), presumably because there are an abundance of well-coupled beta$_2$-adrenoceptors available with few downstream antagonising signals. In contrast, with repetitive dosing formoterol is significantly better than salmeterol at preventing methacholine-induced bronchoconstriction (Palmqvist 1999). These differences have led to attempts to define the "intrinsic efficacy" of a drug independent of tissue conditions (Hanania 2002), as shown in Table 1. The clinical significance of intrinsic efficacy remains unclear.

Appendix 2. Possible mechanisms of increased asthma mortality with beta-agonists

Direct toxicity

This hypothesis states that direct adverse effects of $beta_2$-agonists are responsible for an associated increase in mortality and most research in the area has concentrated on effects detrimental to the heart. Whilst it is often assumed that cardiac side-effects of $beta_2$-agonists are due to cross-reactivity with $beta_1$-adrenoceptors (i.e. poor selectivity), it is worth noting that human myocardium also contains an abundance of $beta_2$-adrenoceptors capable of triggering positive chronotropic and inotropic responses (Lipworth 1992). Indeed, there is good evidence that cardiovascular side-effects of isoprenaline (Arnold 1985) and other $beta_2$-agonists including salbutamol (Hall 1989) are mediated predominantly via cardiac $beta_2$-adrenoceptors thus making the concept of *in vitro* selectivity less relevant. Generalised $beta_2$-adrenoceptor activation can also cause hypokalaemia (Brown 1983) and it has been proposed that, through these and other actions $beta_2$-agonists may predispose to life-threatening dysrhythmias or cause other adverse cardiac effects.

During the 1960s epidemic most deaths occurred in patients with severe asthma and it was originally assumed that asthma and its sequelae, including hypoxia, were the primary cause of death. However, mucus plugging and hypoxia does not preclude a cardiac event as the final cause of death, and one might expect those with severe asthma to take more doses of a prescribed inhaler. As noted by Speizer and Doll most deaths in the 1960s were in the 10-19 age group and "at these ages children have begun to act independently and may be particularly prone to misuse a self-administered form of treatment" (Speizer 1968). If toxicity were related to increasing doses of $beta_2$-agonists one might expect most deaths to occur in hospital where high doses are typically used and this was not the case. One possible explanation for this anomaly was provided by animal experiments in which large doses of isoprenaline caused little ill effect in anaesthetised dogs with normal arterial oxygenation whereas much smaller doses caused fatal cardiac depression and asystole (although no obvious dysrhythmia) when hypoxic (Collins 1969; McDevitt 1974). It has been hypothesised therefore that such events would be less likely in hospital where supplemental oxygen is routinely given. The clinical relevance of these studies remains unclear although there is some evidence of a synergistic effect between hypoxia and salbutamol use in asthmatic patients in reducing total peripheral vascular resistance (Burggraaf 2001) - another $beta_2$ mediated effect which could be detrimental to the heart during an acute asthma attack through a reduction in diastolic blood pressure. Other potential mechanisms of isoprenaline toxicity include a potential increase in mucous plugging and worsening of ventilation perfusion mismatch despite bronchodilation (Pearce 1990).

Further concerns about a possible toxic effect of $beta_2$-agonists were raised during the New Zealand epidemic in the 1970s. In 1981 Wilson et al who first reported the epidemic reviewed 22 fatal cases of asthma and noted "In 16 patients death was seen to be sudden and unexpected. Although all were experiencing respiratory distress, most were not cyanosed and the precipitate nature of their death suggested a cardiac event, such as an arrest, inappropriate to the severity of their respiratory problem" (Wilson 1981). In humans, fenoterol causes significantly greater chronotropic, inotropic and electrocardiographic side-effects than salbutamol in asthmatic patients (Wong 1990). Interestingly, across the same parameters fenoterol also causes more side-effects than isoprenaline (Burgess 1991).

In patients with mild asthma and without a bronchoconstrictor challenge, salmeterol and salbutamol cause a similar degree of near maximal bronchodilation at low doses (Bennett 1994). However, whilst as a one off dose salbutamol is typically used at 2-4 times the concentration of salmeterol, the dose equivalences for salmeterol versus salbutamol in increasing heart rate and decreasing potassium concentration and diastolic blood pressure were 17.7, 7.8 and 7.6 respectively (i.e. salmeterol had a greater effect across all parameters). Given the lower intrinsic efficacy of salmeterol (Table 2), these results highlight the importance of *in vivo* factors; one possible explanation for the difference is the increased lipophilicity of salmeterol compared to salbutamol contributing to higher systemic absorption (Bennett 1994).

When comparing increasing actuations of standard doses of formoterol and salmeterol inhalers in stable asthmatic patients, relatively similar cardiovascular effects are seen at lower doses (Guhan 2000). However, at the highest doses (above those recommended by the manufacturers) there were trends towards an increase in systolic blood pressure with formoterol; in comparison there was a trend towards a decrease in diastolic blood pressure and an increase in QTc interval with salmeterol although no statistical analysis of the difference was performed. In contrast in asthmatic patients with methacholine-induced bronchoconstriction there was no significant difference between salmeterol and formoterol in causing increased heart rate and QTc interval although formoterol caused significantly greater bronchodilation and hypokalaemia (Palmqvist 1999). Whilst there is good evidence of cardiovascular and metabolic side-effects with increasing doses of $beta_2$-agonists, it is a little difficult to envisage serious adverse effects of this nature when using LABAs at manufacturer-recommended preventative doses. However, it is possible that some patients choose to use repeated doses of LABAs during exacerbations.

Tolerance

In this setting, the term *tolerance* refers to an impaired response to beta$_2$-agonists in patients who have been using regular beta$_2$-agonist treatment previously (Haney 2006). Tolerance is likely to result from a combination of reduced receptor numbers secondary to receptor internalisation and reduced production and also uncoupling of receptors to downstream signalling pathways following repeated activation (Barnes 1995). This phenomenon is likely to explain the beneficial reduction in systemic side effects seen with regular use of beta$_2$-agonists including salbutamol after 1-2 weeks (Lipworth 1989). However, the same effect on beta$_2$-adrenoceptors in the lung might be expected to produce a diminished response to the bronchodilating activity of beta$_2$-agonists following regular use. In patients with stable asthma, whilst there is some evidence of tolerance to both salbutamol (Nelson 1977) and terbutaline (Weber 1982) other studies have been less conclusive (Harvey 1982; Lipworth 1989). However, evidence of tolerance to short and long-acting beta$_2$-agonists in both protecting against and reducing bronchoconstriction is much stronger in the setting of an acute bronchoconstrictor challenge with chemical, allergen and 'natural' stimuli (Haney 2006; Lipworth 1997).

Studies comparing salmeterol and formoterol have shown that both cause tolerance compared to placebo but there was no significant difference between the drugs (van der Woude 2001). There also appears to be little difference in the tolerance induced by regular formoterol and regular salbutamol treatment (Hancox 1999; Jones 2001). To the authors' knowledge no studies have looked specifically at the degree of tolerance caused by isoprenaline and fenoterol in the setting of acute bronchoconstriction. Tolerance to bronchodilation has been shown to clearly occur with addition of inhaled corticosteroids to salmeterol and formoterol (Lee 2003) and terbutaline (Yates 1996). There is conflicting evidence as to whether high dose steroids can reverse tolerance in the acute setting (Lipworth 2000; Jones 2001).

At first glance the toxicity and tolerance hypotheses might appear incompatible as systemic and cardiovascular tolerance ought to protect against toxicity in the acute setting and there is good evidence that such tolerance occurs in stable asthmatic patients (Lipworth 1989). However, whilst this study showed that changes in heart rate and potassium levels were blunted by previous beta$_2$-agonist use, they were not abolished; furthermore, at the doses studied these side-effects appear to follow an exponential pattern (Lipworth 1989). In contrast, in the presence of bronchoconstrictor stimuli the bronchodilator response to beta$_2$-agonists follows a flatter curve (Wong 1990; Hancox 1999) and as previously discussed this curve is shifted downwards by previous beta$_2$-agonist exposure (Hancox 1999). Thus, it is theoretically possible that in the setting of an acute asthmatic attack and strong bronchoconstricting stimuli, bronchodilator tolerance could lead to repetitive beta$_2$-agonist use and ultimately more systemic side-effects than would otherwise have occurred. Of course, other sequelae of inadequate bronchodilation including airway obstruction will be detrimental in this setting.

Whilst the tolerance hypothesis is often cited as contributing towards the asthma mortality epidemics it is difficult to argue that reduced efficacy of a drug can cause increased mortality relative to a time when that drug was not used at all. However, tolerance to the bronchodilating effect of endogenous circulating adrenaline is theoretically possible and there is also evidence of rebound bronchoconstriction when stopping fenoterol (Sears 1990), which may be detrimental. Furthermore, it appears that regular salbutamol treatment can actually increase airway responsiveness to allergen (Cockcroft 1993) a potentially important effect that could form a variant of the toxicity hypothesis. Differences between beta$_2$-agonists in this regard are unclear, but the combination of rebound hyperresponsiveness and tolerance of the bronchodilator effect with regular beta$_2$-agonist exposure has been recently advocated as a possible mechanism to explain the association between beta$_2$-agonists and asthma mortality (Hancox 2006).

Other explanations

Confounding by severity

Historically, this hypothesis has been used extensively to try to explain the association between mortality and the use of fenoterol during the 1970s New Zealand epidemic (see Pearce 2007) and is still quoted today. The hypothesis essentially relies on the supposition that patients with more severe asthma are more likely to take either higher doses of beta$_2$-agonists or a particular beta$_2$-agonist (such as fenoterol) thereby explaining the association. This hypothesis was carefully ruled out in the three case-control studies by comparing the association between fenoterol and mortality in patients with varying severity of disease (Crane 1989; Pearce 1990; Grainger 1991). Furthermore, the hypothesis cannot explain the overall increase in mortality in the 1960s and 1970s nor can it explain any significant increase in mortality (whether taking inhaled steroids or not) from randomised controlled trial data.

The delay hypothesis

This hypothesis accepts that beta$_2$-agonists or a particular beta$_2$-agonist cause an increased risk of mortality but indirectly by causing patients to delay before getting medical help and further treatments including high dose steroids and oxygen. There is evidence that

both salmeterol and formoterol can reduce awareness of worsening underlying inflammation (Bijl-Hofland 2001; McIvor 1998). It is difficult to rule out the delay hypothesis in either explaining or contributing towards both the asthma mortality epidemics and an association with regular use of LABAs. There is evidence that beta$_2$-agonists with higher intrinsic efficacy are more effective at relieving bronchoconstriction in the acute setting (Hanania 2007) and could paradoxically cause patients to delay seeking medical help for longer. For the delay hypothesis to explain the increase in mortality during the 1960s and 1970s one has to imply that hospital treatment of asthma when mortality rates were low during the earlier years of the 20^{th} century was effective. It is difficult to say exactly how effective such treatment is likely to have been.

Reduced corticosteroid treatment

A slight but significant variation of the delay hypothesis suggests that patients who have separate beta$_2$-agonists and corticosteroid inhalers may choose to take less corticosteroid because of better symptom control from the inhaled beta$_2$-agonists and it is reduced corticosteroid treatment that contributes to a rise in mortality. It is rather difficult to see how this hypothesis explains the epidemics of asthma deaths in the 1960s and 1970s relative to the 1920s and 30s, given that corticosteroids were not used for the treatment of asthma in the earlier decades. If this hypothesis were to explain increased mortality from more recent randomised controlled trial data one would not expect to see an increase in mortality in those taking LABAs alone.

HISTORY

Protocol first published: Issue 1, 2008

Review first published: Issue 3, 2009

CONTRIBUTIONS OF AUTHORS

CJC: Conception of the idea and co-writing of protocol with MJC.

TL: Co-writing of the protocol, trial selection, data extraction and co-writing the review.

RJ: Trial selection, data extraction and co-writing the review.

DECLARATIONS OF INTEREST

In the past three years, Dr Jaeschke received honoraria for lectures from Boehringer Ingelheim (2006; 4000 US $) and GlaxoSmithKline (2007; 2000 Euros) and travel support from Boehringer Ingelheim and GlaxoSmithKline (2006 and 2007; up to 1000 US $).

SOURCES OF SUPPORT

Internal sources

- NHS R&D, UK.

External sources

- No sources of support supplied

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

Although the protocol originally included studies comparing salmeterol and ICS with higher doses of ICS, we restricted this review to studies randomising patients to the same dose of ICS with and without salmeterol. Due to problems with fixed continuity corrections for zero cells we have used the Peto OR as the primary metric for analysis of relative measures, and the risk difference for absolute measures. Subgroup analysis was not attempted on the basis of asthma severity or dose of ICS.

INDEX TERMS

Medical Subject Headings (MeSH)

Adolescent; Adrenal Cortex Hormones [administration & dosage; *adverse effects]; Adrenergic beta-Agonists [administration & dosage; *adverse effects]; Albuterol [administration & dosage; adverse effects; *analogs & derivatives]; Anti-Asthmatic Agents [administration & dosage; *adverse effects]; Asthma [drug therapy; *mortality]

MeSH check words

Adult; Child; Humans; Young Adult