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Inhaled steroids with and without regular salmeterol for asthma: serious adverse events (Review)

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[Intervention Review]

Inhaled steroids with and without regular salmeterol for asthma: serious adverse events

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ABSTRACT

Background

Epidemiological evidence has suggested a link between use of beta$_2$ -agonists and increased asthma mortality. Much debate has surrounded possible causal links for this association, and whether regular (daily) long-acting beta$_2$ -agonists (LABAs) are safe, particularly when used in combination with inhaled corticosteroids (ICSs). This is an update of a Cochrane Review that now includes data from two large trials including 11,679 adults and 6208 children; both were mandated by the US Food and Drug Administration (FDA).

Objectives

To assess risks of mortality and non-fatal serious adverse events (SAEs) in trials that randomised participants with chronic asthma to regular salmeterol and ICS versus the same dose of ICS.

Search methods

We identified randomised trials using the Cochrane Airways Group Specialised Register of trials. We checked websites of clinical trials registers for unpublished trial data. We also checked FDA submissions in relation to salmeterol. The date of the most recent search was 10 October 2018.

Selection criteria

We included parallel-design randomised trials involving adults, children, or both with asthma of any severity who were randomised to treatment with regular salmeterol and ICS (in separate or combined inhalers) versus the same dose of ICS of at least 12 weeks in duration.

Data collection and analysis

We conducted the review according to standard procedures expected by Cochrane. We obtained unpublished data on mortality and SAEs from the sponsors, from ClinicalTrials.gov, and from FDA submissions. We assessed our confidence in the evidence according to current GRADE recommendations.

Main results

We have included in this review 41 studies (27,951 participants) in adults and adolescents, along with eight studies (8453 participants) in children. We judged that the overall risk of bias was low for all-cause events, and we obtained data on SAEs from all study authors. All except 542 adults (and none of the children) were given salmeterol and fluticasone in the same (combination) inhaler.

Deaths

Eleven of a total of 14,233 adults taking regular salmeterol and ICS died, as did 13 of 13,718 taking regular ICS at the same dose. The pooled Peto odds ratio (OR) was 0.80 (95% confidence interval (CI) 0.36 to 1.78; participants = 27,951; studies = 41; I^2 = 0%; moderate-certainty evidence). In other words, for every 1000 adults treated for 25 weeks, one death occurred among those on ICS alone, and the corresponding risk among those taking salmeterol and ICS was also one death (95% CI 0 to 2 deaths).

No children died, and no adults or children died of asthma, so we remain uncertain about mortality in children and about asthma mortality in any age group.

Non-fatal serious adverse events

A total of 332 adults receiving regular salmeterol with ICS experienced a non-fatal SAE of any cause, compared to 282 adults receiving regular ICS. The pooled Peto OR was 1.14 (95% CI 0.97 to 1.33; participants = 27,951; studies = 41; I^2 = 0%; moderate-certainty evidence). For every 1000 adults treated for 25 weeks, 21 adults on ICS alone had an SAE, and the corresponding risk for those on salmeterol and ICS was 23 adults (95% CI 20 to 27).

Sixty-five of 4229 children given regular salmeterol with ICS suffered an SAE of any cause, compared to 62 of 4224 children given regular ICS. The pooled Peto OR was 1.04 (95% CI 0.73 to 1.48; participants = 8453; studies = 8; I^2 = 0%; moderate-certainty evidence). For every 1000 children treated for 23 weeks, 15 children on ICS alone had an SAE, and the corresponding risk for those on salmeterol and ICS was 15 children (95% CI 11 to 22).

Asthma-related serious adverse events

Eighty and 67 adults in each group, respectively, experienced an asthma-related non-fatal SAE. The pooled Peto OR was 1.15 (95% CI 0.83 to 1.59; participants = 27,951; studies = 41; I^2 = 0%; low-certainty evidence). For every 1000 adults treated for 25 weeks, five receiving ICS alone had an asthma-related SAE, and the corresponding risk among those on salmeterol and ICS was six adults (95% CI 4 to 8).

Twenty-nine children taking salmeterol and ICS and 23 children taking ICS alone reported asthma-related events. The pooled Peto OR was 1.25 (95% CI 0.72 to 2.16; participants = 8453; studies = 8; I^2 = 0%; moderate-certainty evidence). For every 1000 children treated for 23 weeks, five receiving an ICS alone had an asthma-related SAE, and the corresponding risk among those receiving salmeterol and ICS was seven children (95% CI 4 to 12).

Authors' conclusions

We did not find a difference in the risk of death or serious adverse events in either adults or children. However, trial authors reported no asthma deaths among 27,951 adults or 8453 children randomised to regular salmeterol and ICS or ICS alone over an average of six months. Therefore, the risk of dying from asthma on either treatment was very low, but we remain uncertain about whether the risk of dying from asthma is altered by adding salmeterol to ICS.

Inclusion of new trials has increased the precision of the estimates for non-fatal SAEs of any cause. We can now say that the worst-case estimate is that at least 152 adults and 139 children must be treated with combination salmeterol and ICS for six months for one additional person to be admitted to the hospital (compared to treatment with ICS alone). These possible risks still have to be weighed against the benefits experienced by people who take combination treatment.

However more than 90% of prescribed treatment was taken in the new trials, so the effects observed may be different from those seen with salmeterol in combination with ICS in daily practice.

PLAIN LANGUAGE SUMMARY

Inhaled steroids with and without regular salmeterol for asthma: serious adverse events

Review question

Is it safe to add regular salmeterol to inhaled corticosteroid (ICS) for adults or children with asthma?

Background

Another Cochrane Review found that using regular salmeterol without regular ICS for adults with asthma led to an increase in serious adverse events (death or admission to hospital). We wanted to find out if more adverse (harmful) effects occur when people take regular salmeterol in addition to ICS. We looked only at adverse effects - deaths, being admitted to hospital and life-threatening effects. We did not look at the benefits of taking salmeterol for other outcomes. We updated this review in 2018 because of new evidence from large randomised trials of salmeterol in combination with ICS, in 11,679 adults and 6208 children with asthma.

Study characteristics

In total, we have included 41 studies in 27,951 adults and eight studies in 8453 children. Almost all studies used a combination inhaler to deliver salmeterol with ICS and compared this with the same dose of ICS for an average of six months.

Key results

We did not find a difference in the risk of death or serious adverse events in either adults or children.

Eleven of a total of 14,233 adults taking regular salmeterol and ICS died, as did 13 of 13,718 adults taking regular ICS at the same dose. For every 1000 adults treated for 25 weeks, researchers reported one death on ICS alone and a corresponding risk on salmeterol and ICS of one death (95% confidence Interval (CI) 0 to 2 deaths). No deaths in any studies were attributed to asthma, and researchers reported no deaths at all among children.

A non-fatal serious adverse event of any cause occurred in 332 adults on regular salmeterol with ICS compared to 282 adults on regular ICS alone. For every 1000 adults treated for 25 weeks, 21 serious adverse events occurred on ICS alone, and the corresponding risk on salmeterol and ICS was 23 adults (95% CI 20 to 27).

A total of 65 of 4229 children on regular salmeterol with ICS suffered a serious adverse event of any cause compared to 62 of 4224 children on regular ICS alone. For every 1000 children treated for 23 weeks, 15 serious adverse events occurred on ICS alone, and the corresponding risk on salmeterol and ICS was also 15 children (95% CI 11 to 22).

Quality of the evidence

Reviewers assessed the overall risk of bias for all-cause events as low. The two new large studies performed independent assessment to identify the cause of asthma-related serious adverse events. This makes current data on asthma events more reliable than previously reported.

Conclusions

Trials reported no asthma deaths among 27,951 adults or 8453 children randomised to regular salmeterol and ICS or ICS alone over an average of six months. The risk of dying from asthma while receiving either treatment was therefore very low, but we remain uncertain about whether the risk of dying from asthma is altered by adding salmeterol to ICS.

We can now say that the worst-case estimate (safety margin) from this review is that at least 152 adults and 139 children must be treated with combination salmeterol and ICS for six months for one additional person to be admitted to the hospital (compared to ICS alone). These possible risks must be weighed against the benefits experienced by people who take combination treatment.

People monitored in the new trials took over 90% of their prescribed treatment. This is much more than the average amount of medication that people take outside a trial. Therefore the effects shown in trials may be different from the effects experienced by people at home who are not taking their inhalers as prescribed.

Because very few people die of asthma, trials would have to be very large to detect differences in the death rate. Therefore it is probably not feasible to find out if adding salmeterol to ICS causes more deaths among participants in randomised controlled trials - as these trials would be very large, difficult to run, and expensive. It might be better to use case-control studies or to review asthma deaths (e.g. from medical records).

SUMMARY OF FINDINGS FOR THE MAIN COMPARISON [Explanation]

Inhaled steroids with and without regular salmeterol for asthma

Patient or population: adults and children with chronic asthma
Settings: community
Intervention: regular salmeterol in addition to regular inhaled corticosteroid (ICS)
Comparison: regular ICS (at the same dose)

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 ICS	Regular salmeterol in addition to regular ICS				
Adults and adolescents						
All-cause mortality Follow-up: mean 25 weeks	**1 per 1000**[a]	**1 per 1000** (0 to 2)	**OR 0.80** (0.36 to 1.78)	27951 (41)	⊕⊕⊕◯ **moderate**[b]	
All-cause non-fatal SAE[c] Follow-up: mean 25 weeks	**21 per 1000**[a]	**23 per 1000** (20 to 27)	**OR 1.14** (0.97 to 1.33)	27951 (41)	⊕⊕⊕◯ **moderate**[b]	
Asthma-related mortality Follow-up: mean 25 weeks	No deaths due to asthma	No deaths due to asthma	-	27951 (41)	⊕⊕⊕◯ **moderate**[b]	Pooled risk difference zero (95% CI -0.0009 to 0.0009)
Asthma-related non-fatal SAE[c] Follow-up: mean 25 weeks	**5 per 1000**[a]	**6 per 1000** (4 to 8)	**OR 1.15** (0.83 to 1.59)	27951 (41)	⊕⊕◯◯ **low**[b,d]	

Children						
All-cause mortality Follow-up: mean 23 weeks	No deaths	No deaths	-	8453 (8)	⊕⊕⊕◯ **moderate**[b]	Pooled risk difference zero (95% CI -0.0013 to 0.0013)
All-cause non-fatal SAE[c] Follow-up: mean 23 weeks	**15 per 1000**[a]	**15 per 1000** (11 to 22)	**OR 1.04** (0.73 to 1.48)	8453 (8)	⊕⊕⊕◯ **moderate**[b]	
Asthma-related mortality Follow-up: mean 23 weeks	No deaths	No deaths	-	8453 (8)	⊕⊕⊕◯ **moderate**[b]	Pooled risk difference zero (95% CI -0.0013 to 0.0013)
Asthma-related non-fatal SAE[c] Follow-up: mean 23 weeks	**5 per 1000**[a]	**7 per 1000** (4 to 12)	**OR 1.25** (0.72 to 2.16)	8453 (8)	⊕⊕⊕◯ **moderate**[b]	

*The basis for the **assumed risk** is the mean control event rate in the included studies. 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; ICS: inhaled corticosteroid; OR: odds ratio; SAE: serious adverse event

GRADE Working Group grades of evidence.
High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
Very low certainty: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

[a]Mean control event rate.
[b]Imprecision (-1). We regard the upper end of the 95% confidence interval as too high to rule out a potentially important increase. See also Table 3 and Appendix 5.
[c]Non-fatal SAEs were defined as life-threatening adverse events, inpatient hospitalisations or prolongation of existing hospitalisations, persistent or significant disabilities or incapacities, or congenital anomalies or birth defects.
[d]More than half of the events came from trials that did not independently assess the causation of SAEs.

BACKGROUND

Description of the condition

For people whose asthma is not controlled by low-dose inhaled corticosteroids (ICSs) alone, many asthma guidelines recommend adding long-acting beta^2 -agonists (LABAs). Several Cochrane Reviews have addressed the efficacy of LABA in addition to ICS (Ni Chroinin 2004; Ni Chroinin 2005), in comparison with placebo (Walters 2007), short-acting beta^2 -agonists (SABAs; Walters 2002), leukotriene receptor antagonists (LTRAs; Ducharme 2006), and increased doses of ICS (Greenstone 2005). The beneficial effects of LABA on lung function, symptoms, quality of life, and exacerbations requiring oral steroids have been demonstrated.

However, long-standing controversy surrounds the regular use of beta^2 -agonists for people with asthma. Sears 1986 suggested that excessive use of SABAs might have contributed directly or indirectly to an increase in asthma deaths in New Zealand between 1960 and 1980. Study 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 resulting from treatment with LABA 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 become more marked with longer-acting, as opposed to shorter-acting, compounds (Lipworth 1997). Several molecular mechanisms have been proposed to explain the possible detrimental effects of long-term beta^2 -agonist use in asthma, including receptor down-regulation and desensitisation (Giembycz 2006).

A meta-analysis of the effects of LABAs on severe asthma exacerbations and asthma-related deaths 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). However, these researchers considered only trials that compared LABA versus placebo, and 28 of the included trials on 6000 participants did not report asthma-related deaths, reducing certainty in the strength of review author conclusions.

Description of the intervention

Salmeterol and formoterol are examples of LABAs that are available to treat asthma. These two drugs are known to have differences in receptor activity, and they are used in different ways (e.g. salmeterol has a slower onset of action than salbutamol and formoterol, 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 potential differences in adverse effects between salmeterol and formoterol, we have considered the two drugs separately.

How the intervention might work

Since the publication of SMART 2006, much debate has surrounded the interaction between ICS and LABA in relation to serious adverse events (SAEs). This study did not randomise participants to ICS but nevertheless conducted a subgroup analysis of results on the basis of ICS use at baseline. It is tempting to be reassured by the fact that researchers did not find a statistically significant increase in asthma-related mortality in the subgroup using ICS, but this is not the correct way to test for interaction (Altman 2003), and investigators carried out no assessment during the trial in relation to actual use of ICS during the study. There is a need to systematically review all available data from controlled trials that randomised participants to regular salmeterol in combination with ICS, and to consider all SAEs (fatal and non-fatal), whether or not they are deemed by investigators to be related to trial medication.

Why it is important to do this review

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

Regular salmeterol alone is the topic of a previous review (Cates 2008a), as is regular formoterol alone (Cates 2012b). In both of these reviews, review authors demonstrated an increase in SAEs with regular LABA. Another review considered formoterol with ICS (Cates 2009a). Review authors have also provided overviews of the safety of combination therapy in children and in adults (Cates 2012a; Cates 2014, respectively).

Due to ongoing concern over the safety of LABAs, the FDA mandated large trials of salmeterol and ICS in both adults and children. We have included results of these studies in this updated review. The two large new studies were designed to test whether salmeterol was safe when added to ICS; to do this, trial authors

used a safety margin derived from the worst end of the 95% confidence interval of the comparative risk for a combined endpoint in these trials (death, intubation, or hospital admission). In adults, the safety margin was a hazard ratio of 2.0; in children, the hazard ratio was 2.675.

OBJECTIVES

To assess risks of mortality and non-fatal SAEs in trials that randomised participants with chronic asthma to regular salmeterol and ICS versus the same dose of ICS.

METHODS

Criteria for considering studies for this review

Types of studies

We sought randomised controlled trials (RCTs), with or without blinding, in which researchers randomly assigned salmeterol and ICS to participants with chronic asthma.

Types of participants

We included participants of any age with a clinical diagnosis of asthma, unrestricted by disease severity or previous or current treatment. We did not include studies on acute asthma and exercise-induced bronchospasm.

Types of interventions

We searched for trials in which investigators prescribed ICS and salmeterol regularly for a period of at least 12 weeks, at any daily dose, and delivered by any single or separate devices (i.e. chlorofluorocarbon metered dose inhaler (CFC-MDI), hydrofluoroalkane metered dose inhaler (HFA-MDI), or dry powder inhaler (DPI)). We included studies that used comparison groups given the same dose of ICS; co-interventions with LTRAs, cromones, oral corticosteroids (OCSs), or theophylline were allowed as long as they were not part of the randomised intervention. We excluded studies that compared different doses of salmeterol or different delivery devices or propellants (with no placebo arm), or that compared salmeterol versus formoterol. We excluded from this review studies that randomised salmeterol without an inhaled steroid; a separate Cochrane Review has considered these studies (Cates 2008a).

Types of outcome measures

Primary outcomes

- All-cause mortality
- All-cause non-fatal serious adverse events

Secondary outcomes

- Asthma-related mortality
- Asthma-related non-fatal serious adverse events
- Respiratory-related mortality
- Respiratory-related non-fatal serious adverse events
- Cardiovascular-related mortality
- Cardiovascular-related non-fatal serious adverse events
- Asthma-related non-fatal life-threatening events (intubation or admission to intensive care)
- Respiratory-related non-fatal life-threatening events (intubation or admission to intensive care)

Search methods for identification of studies

Electronic searches

We searched the Cochrane Airways Trials Register up to 10 October 2018, with no restrictions on language or type of publication. The Cochrane Airways Trials Register is maintained by the information specialist for Cochrane Airways and contains studies identified from the following sources.

- Monthly searches of the Cochrane Central Register of Controlled Trials (CENTRAL), in the Cochrane Library, through the Cochrane Register of Studies (CRS).
- Weekly searches of MEDLINE Ovid SP.
- Weekly searches of Embase Ovid SP.
- Monthly searches of PsycINFO Ovid SP.
- Monthly searches of the Cumulative Index to Nursing and Allied Health Literature (CINAHL) EBSCO.
- Monthly searches of Allied and Complementary Medicine (AMED) EBSCO.
- Handsearches of the proceedings of major respiratory conferences.

We identified studies contained in the Trials Register using search strategies based on the scope of Cochrane Airways. We have provided details of these strategies, as well as a list of handsearched conference proceedings, in Appendix 3. See Appendix 4 for search terms used to identify studies for this review.

Searching other resources

We checked the reference lists of all primary studies and review articles for additional references. We checked the websites of clinical trial registers for unpublished trial data. We also checked FDA submissions in relation to salmeterol.

Data collection and analysis

Selection of studies

Two review authors independently assessed studies identified via literature searches by examining title, abstract, and keyword fields. We obtained in full text studies that potentially fulfilled the inclusion criteria. CJC and TL independently assessed these for inclusion (CJC, BS, and SW for the 2018 update). We resolved disagreements by consensus.

Data extraction and management

We extracted data using a prepared checklist before one review author (CJC) with assistance from Susan Hansen (information specialist) entered data into RevMan 5.3, and another review author (TL, MF, SS, BS, or SW) checked data on trial characteristics. A third review author (RJ, MF, SS, BS, or SW) independently extracted outcome data and resolved discrepancies by discussion and correspondence with study sponsors. Data included characteristics (methods, participants, interventions, outcomes) and results of included studies. We contacted authors and sponsors of included studies for unpublished adverse event data, and we searched manufacturers' websites for further details of adverse events. We also searched FDA submissions. We collected all-cause SAEs (fatal and non-fatal), and in view of the difficulty involved in deciding whether events were asthma-related, we noted details of the cause of death and SAEs where available. We also recorded the definition of SAEs, and we sought further information if this was not clear (particularly in relation to hospital admissions and SAEs).

Assessment of risk of bias in included studies

Two review authors (of CJC, Susan Hansen, MF, SS, BS, SW) assessed included studies for bias protection (including sequence generation for randomisation, allocation concealment, blinding of participants and assessors, loss to follow-up, and completeness of outcome assessment).

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 participants with one or more SAEs, rather than analysing the number of events that occurred (as the latter are not independent when one participant experiences multiple events and therefore are not suitable for meta-analysis).

Dealing with missing data

When we did not find full data on mortality or SAEs in published papers, we searched the sponsors' trial results sites and clinicaltrials.gov to obtain the missing data.

Assessment of heterogeneity

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

Assessment of reporting biases

We found full data on all-cause mortality and SAEs, so we did not assess reporting biases any further for these outcomes. For asthma-specific SAEs, we looked for evidence of independent outcome assessment in these studies.

Data synthesis

The outcomes of this review are dichotomous, and we recorded the number of participants with at least one outcome event by allocated treatment group. We calculated pooled odds ratios (ORs) and risk differences (RDs). We used the Peto OR 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 we used the Mantel-Haenszel method for sensitivity analysis. ORs do not include the large body of evidence derived from trials with no event in either arm, but we included such data in the analysis of absolute rates using RDs. We inspected funnel plots to assess publication bias.

For the 2018 update, we assessed the safety of adding salmeterol to ICS from the worst-case number needed to treat for an additional harmful outcome (NNTH) for one additional SAE or death to occur. We calculated the NNTH using Visual Rx to transform the upper end of the 95% confidence interval (CI) of the pooled Peto OR, by applying it to the mean event rate in trial control arms (Visual Rx).

Subgroup analysis and investigation of heterogeneity

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

Sensitivity analysis

We carried out sensitivity analysis to assess the impact of the method used to combine study events (Peto OR, Mantel-Haenszel OR, and RD). We included the degree of bias protection in study designs as part of the sensitivity analysis.

'Summary of findings' tables

We assessed the certainty of evidence as high, moderate, low, or very low in accordance with recommendations outlined by the GRADE Working Group for meta-analyses of randomised trials (GRADE website). We have presented these assessments in Summary of findings for the main comparison, alongside the results of our analyses for key outcomes in adults and children (all-cause mortality, all-cause non-fatal SAEs, and asthma-related mortality and SAEs).

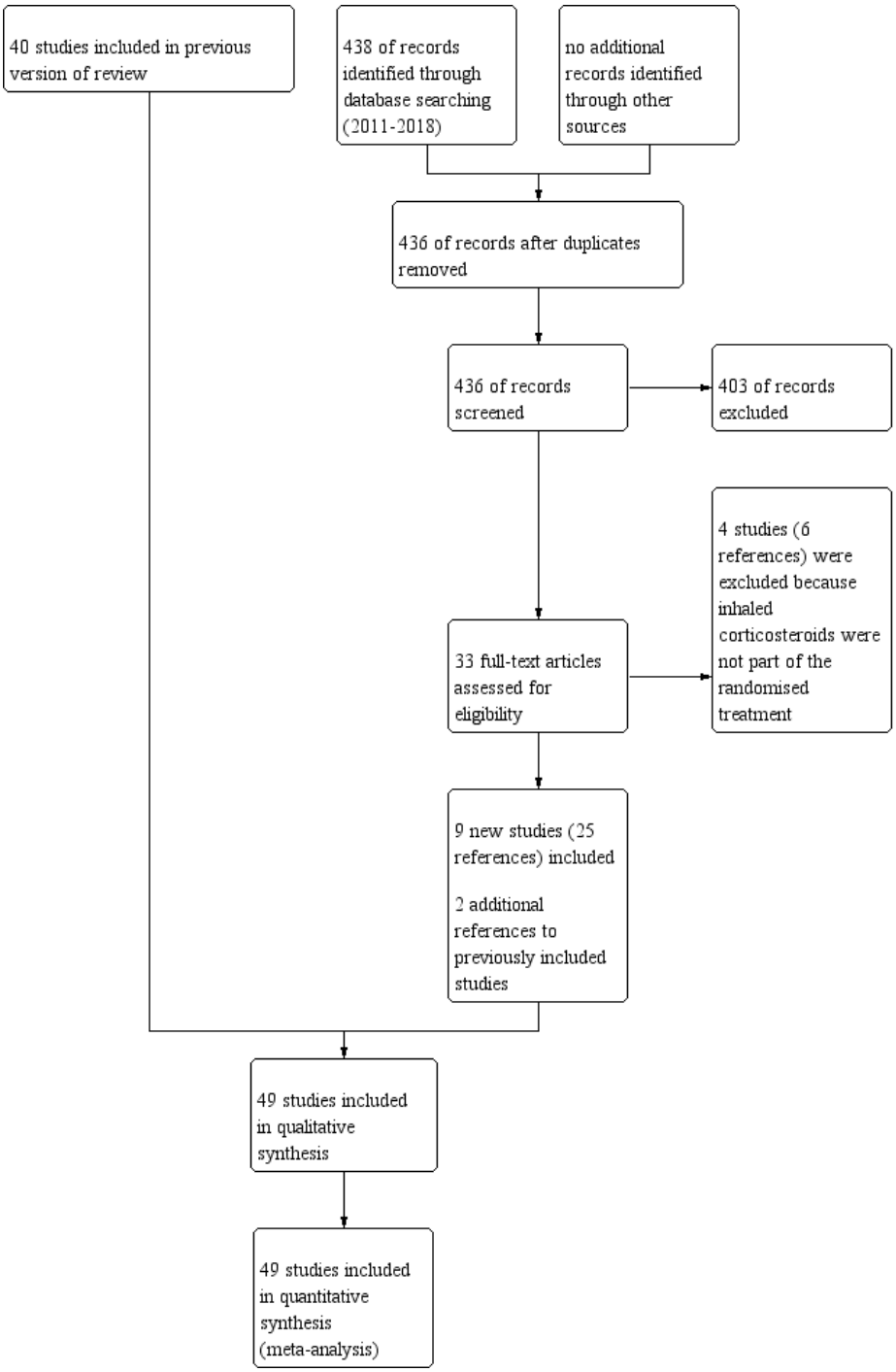
RESULTS

Description of studies

Results of the search

We included 40 studies in the previous version of this review (Cates 2013). The literature search for this review update covered the period from 2011 to October 2018 and yielded 436 references after removal of duplicates. We excluded 403 references on the basis of title and abstract alone, and we selected 33 records for full-text review. We identified nine new studies and two references to previously included studies. Among adults and adolescents, we identified six new studies including 14,504 adult participants (AUSTRI 2016; Bernstein 2017; Mansfield 2017; Raphael 2017; Sher 2017; Slankard 2016), along with three new studies including 6783 child participants (MASCOT 2013; Ploszczuk 2014; VESTRI 2016). We excluded six full-text articles (describing four studies - Bateman 2011; Lotvall 2014; NCT01172808; NCT01172821), as participants used background inhaled corticosteroids, but this was not part of the randomised treatment (Bateman 2011; Casale 2013; Casale 2014; Kerstjens 2014; Kerstjens 2015; Lotvall 2014). The review now includes a total of 49 studies (Figure 1).

Figure 1. Study flow diagram: review update.



Included studies

We included 41 studies in adults and adolescents (27,951 participants) over the age of 12, 16, or 18 years, according to Characteristics of included studies. We included eight studies in children up to the age of 11 years (8453 participants). The weighted mean duration was 25 weeks in adult studies, and 23 weeks in studies in children.

Most studies were sponsored or supported by GlaxoSmithKline and compared combination fluticasone and salmeterol versus fluticasone alone. Teva Pharmaceuticals sponsored Mansfield 2017 and Raphael 2017, and Mundipharma Research Ltd sponsored Ploszczuk 2014. The NIHR Health Technology Assessment programme sponsored MASCOT 2013.

All except 542 adults (and none of the children) randomised to salmeterol were given fluticasone in the same (combination) inhaler (Table 1). The dose of salmeterol used was 50 μg twice daily in most studies (Table 1). The dose of fluticasone varied from 100 to 1000 μg/d (Table 1), and some studies stratified participants to different daily doses of fluticasone but used the same daily dose of fluticasone in each stratum for comparison with additional salmeterol.

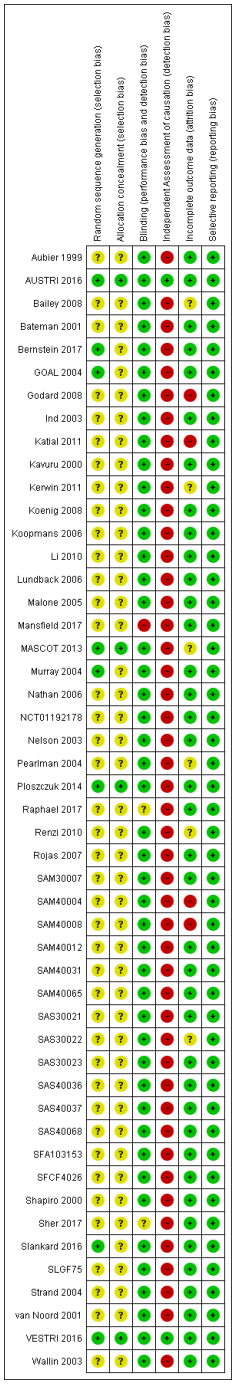
Excluded studies

We excluded 81 studies with reasons described in Characteristics of excluded studies.

Risk of bias in included studies

We have provided an overview of the risk of bias in individual studies in Figure 2. We did not downgrade our certainty in the findings for risk of bias in this update, for the reasons outlined below.

Figure 2. Methodological quality summary: review authors' judgements about each methodological quality item for each included study.



Allocation

Studies did not report clear details of sequence generation and allocation concealment, but we found from correspondence with study sponsors that standard methods (as required by regulatory authorities) had been used to protect against selection bias in these studies. We therefore regarded the risk of selection bias as low, even though sequence generation and allocation concealment are marked as unclear in most studies in Figure 2.

Blinding

All studies were reported as double-blind (with the exception of Mansfield 2017, which was open-label). Researchers incorporated double-dummy design when inhaler devices were not the same in each arm. We therefore assessed risks of performance and detection bias as low for all-cause events.

Indepedent assessment of causation

Previously, no independent assessment had examined the causation of SAEs, so it is possible that asthma-related events were subject to detection bias. However the two large new trials, which contributed 42% of asthma-related events in adults (AUSTRI 2016), as well as 92% in children (VESTRI 2016), used independent panels to assess causation for asthma-related hospitalisation, intubation, or mortality. The risk of bias is therefore reduced for asthma-related events in this update (compared to the previous version of this review).

Incomplete outcome data

Researchers generally reported safety analyses for all randomised participants who had taken at least one dose of treatment. Some studies reported high proportions of withdrawals; these contributed only a small proportion of participants to the meta-analyses, so we did not downgrade the overall quality of evidence for attrition bias.

Selective reporting

Sponsors have not found or provided data for all-cause fatal and non-fatal SAEs by treatment group for all studies, so we regarded the risk of reporting bias as low for the outcomes considered in this review.

Other potential sources of bias

GlaxoSmithKline sponsored or supported most studies, which compared combination fluticasone and salmeterol to fluticasone alone. Teva Pharmaceuticals sponsored Mansfield 2017 and Raphael 2017, and Mundipharma Research Ltd sponsored Ploszczuk 2014. The NIHR Health Technology Assessment programme sponsored MASCOT 2013. However we do not regard sponsorship as necessarily increasing the risk of bias when studies are well designed.

Effects of interventions

See: **Summary of findings for the main comparison** Serious adverse events (SAEs) in adults and children

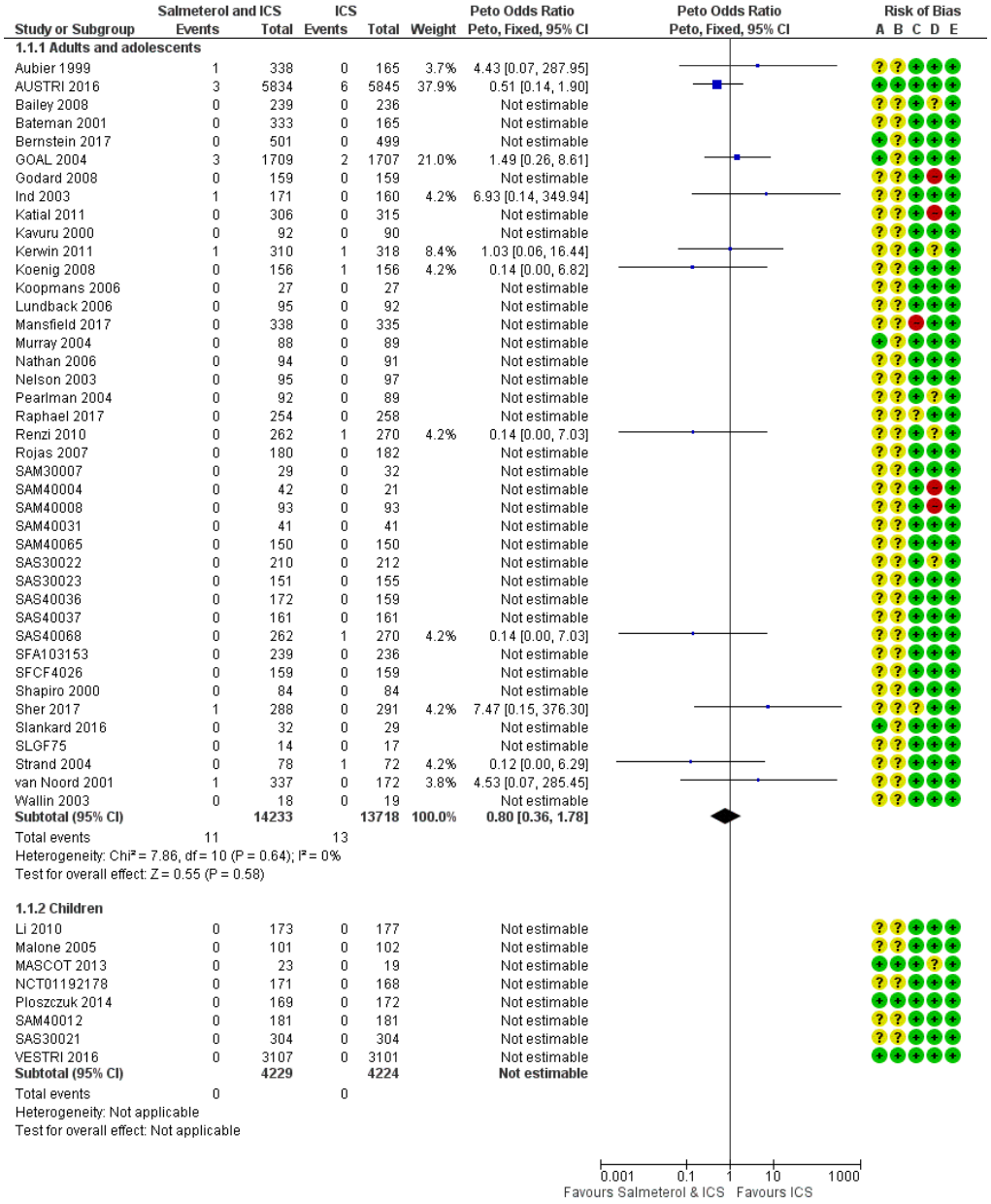
Primary outcomes

All-cause mortality

Adults and adolescents

Eleven deaths occurred in 14,233 adults on regular salmeterol with inhaled corticosteroid (ICS), and 13 deaths in 13,718 adults on regular ICS at the same dose. The pooled odds ratio was Peto OR 0.80 (95% CI 0.36 to 1.78; participants = 27,951; studies = 41; I^2 = 0%; moderate-certainty evidence; Analysis 1.1; Figure 3). In other words, for every 1000 adults treated for 25 weeks, one death occurred on ICS alone, and the corresponding risk for salmeterol and ICS was also one death (95% CI 0 to 2 deaths). We assessed this as moderate-certainty evidence because only 24 deaths in total occurred across all trials (Summary of findings for the main comparison). Moreover, even one extra death per 1000 is not a level of risk that we would regard as acceptable (Appendix 5), so we are unable to conclude with a high level of certainty that regular salmeterol with ICS is as safe as regular ICS alone.

Figure 3. Forest plot of comparison: 1 Regular salmeterol in addition to regular inhaled corticosteroids, outcome: 1.1 All-cause mortality.

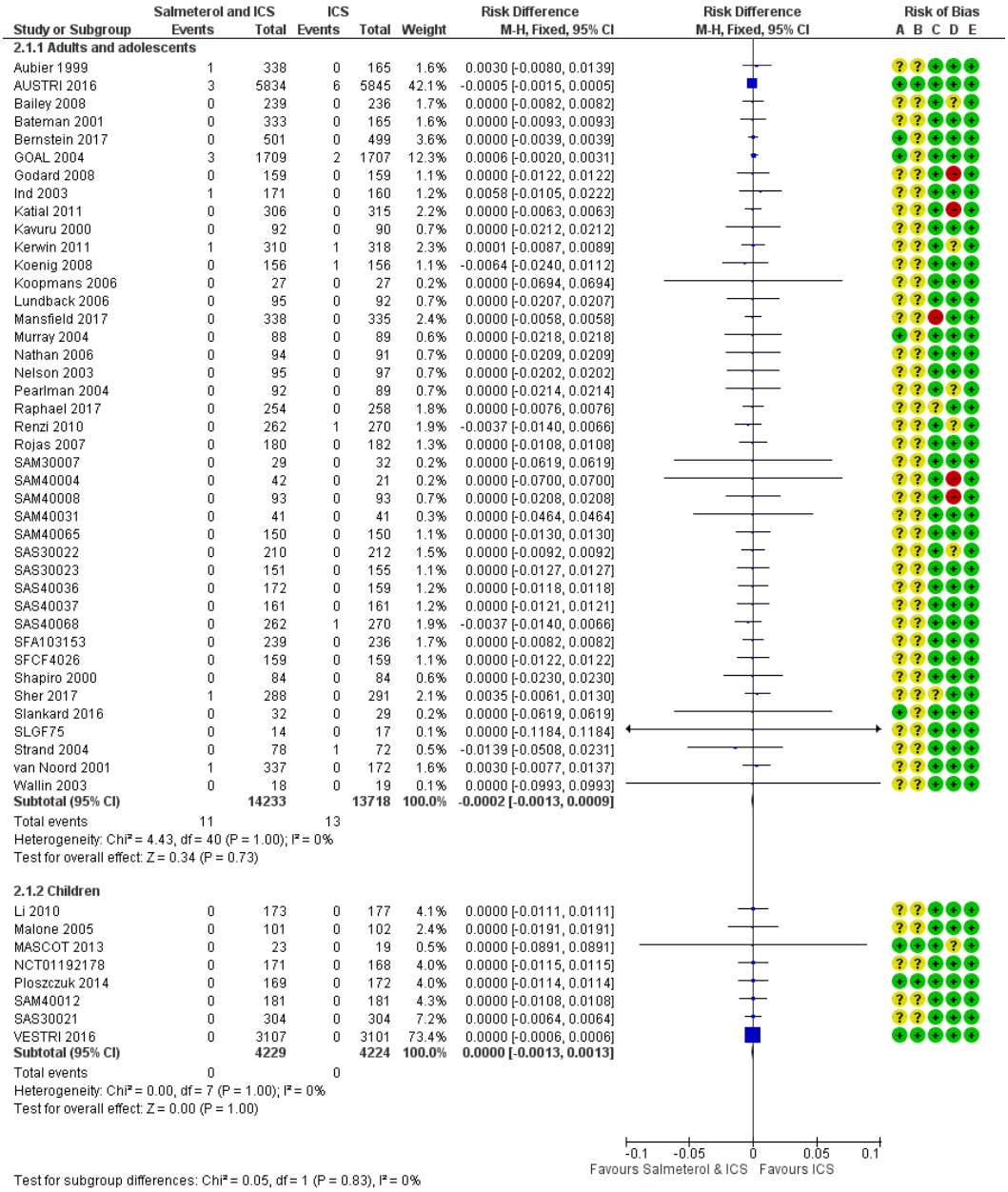


We have listed the causes of death in Table 2. Study authors reported none of the deaths as related to asthma.

Children

Eight studies on children (8453 participants) reported no deaths. It is not possible to calculate any ORs from these data, but the pooled RD can be assessed with a confidence interval (RD 0.0000, 95% CI -0.0013 to 0.0013; Analysis 2.1; Table 3; Figure 4). In other words, for every 1000 children treated with salmeterol and ICS for 23 weeks, the 95% confidence interval is compatible with a possible increase or decrease of one death (Summary of findings for the main comparison). We also assessed this as moderate-certainty evidence because no deaths occurred among children across all trials, and even one extra death per 1000 is not a level of risk that we would regard as acceptable (Summary of findings for the main comparison; Appendix 5).

Figure 4. Forest plot of comparison: 2 Risk difference meta-analysis: regular salmeterol in addition to regular ICS, outcome: 2.1 All-cause mortality.



Serious adverse events (non-fatal all-cause)

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

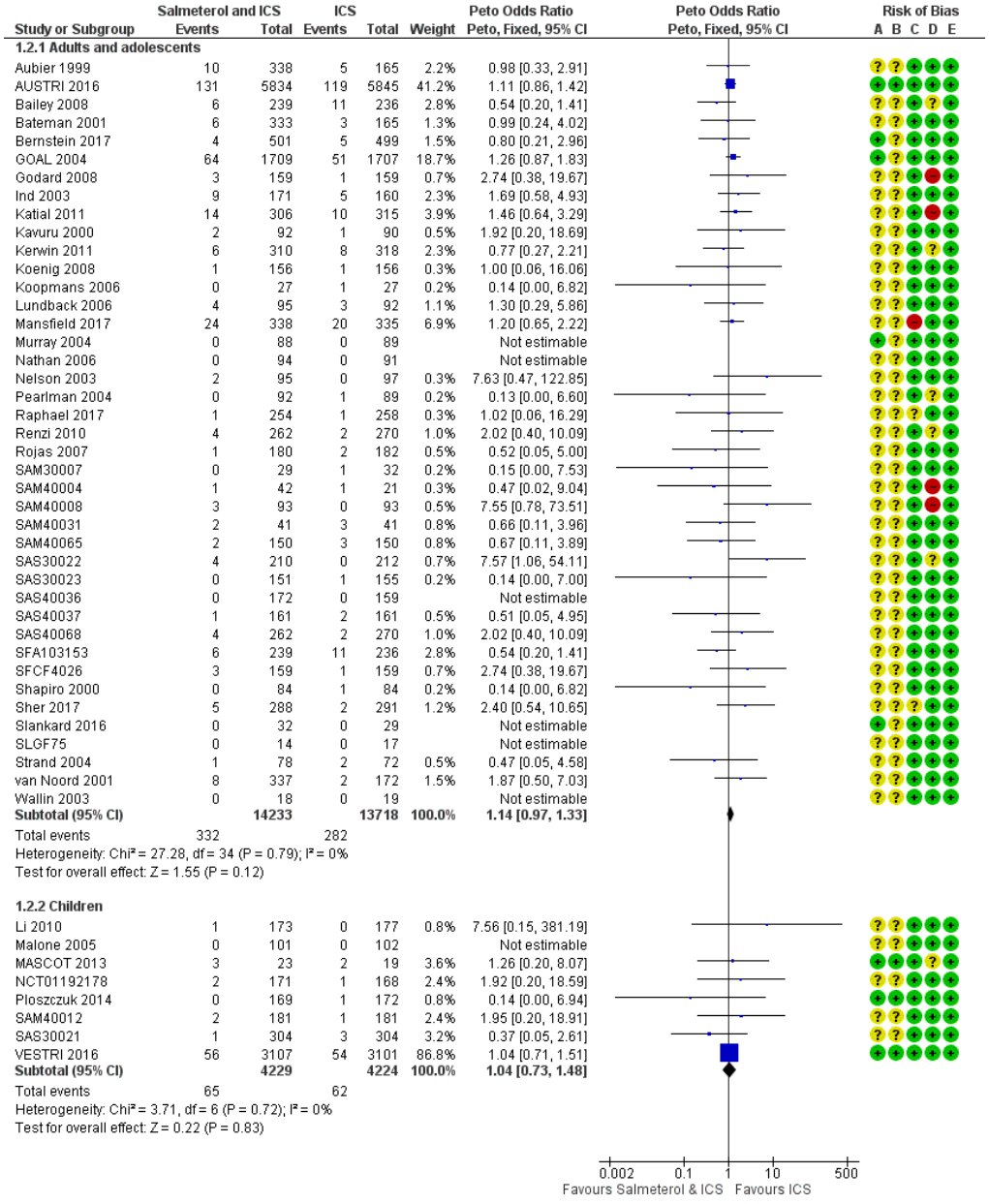
- Results in death.
- Is life-threatening.
- Requires inpatient hospitalisation or prolongation of existing hospitalisation.
- Results in persistent or significant disability/incapacity.
- Is a congenital anomaly/birth defect.

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

Adults and adolescents

Trials reported non-fatal SAEs of any cause in 332 of 14,233 adults on regular salmeterol with ICS compared to 282 of 13,718 adults on regular ICS; the pooled Peto OR was 1.14 (95% CI 0.97 to 1.33; participants = 27,951; studies = 41; I^2 = 0%; moderate-certainty evidence; Figure 5). For every 1000 adults treated for 25 weeks, 21 adults on ICS alone experienced an SAE, and the corresponding risk for salmeterol and ICS was 23 adults (95% CI 20 to 27; Summary of findings for the main comparison).

Figure 5. Forest plot of comparison: 1 Regular salmeterol in addition to regular inhaled corticosteroids, outcome: 1.2 All-cause non-fatal SAE.



We assessed this as moderate-certainty evidence because the upper boundary of the confidence interval for the Peto OR translates into an NNTH of 152 for additional adults to suffer a non-fatal SAE over six months (Table 3). We regarded the upper limit as too high a risk to have a high level of certainty that salmeterol is safe.

Children

Data show 65 of 4229 children with SAEs on regular salmeterol with ICS compared to 62 of 4224 on regular ICS; the pooled odds ratio was Peto OR 1.04 (95% CI 0.73 to 1.48; participants = 8453; studies = 8; I^2 = 0%; moderate-certainty evidence; Figure 5).

For every 1000 children treated for 23 weeks, 15 children experienced an SAE on ICS alone, and the corresponding risk on salmeterol and ICS was also 15 children (95% CI 11 to 22).

We assessed this as moderate-certainty evidence because the upper boundary of the confidence interval for the Peto OR translates into an NNTH of 139 for an additional child to suffer a non-fatal SAE over six months (Table 3). We regarded the upper limit as too high a risk to have a high level of certainty that salmeterol is safe.

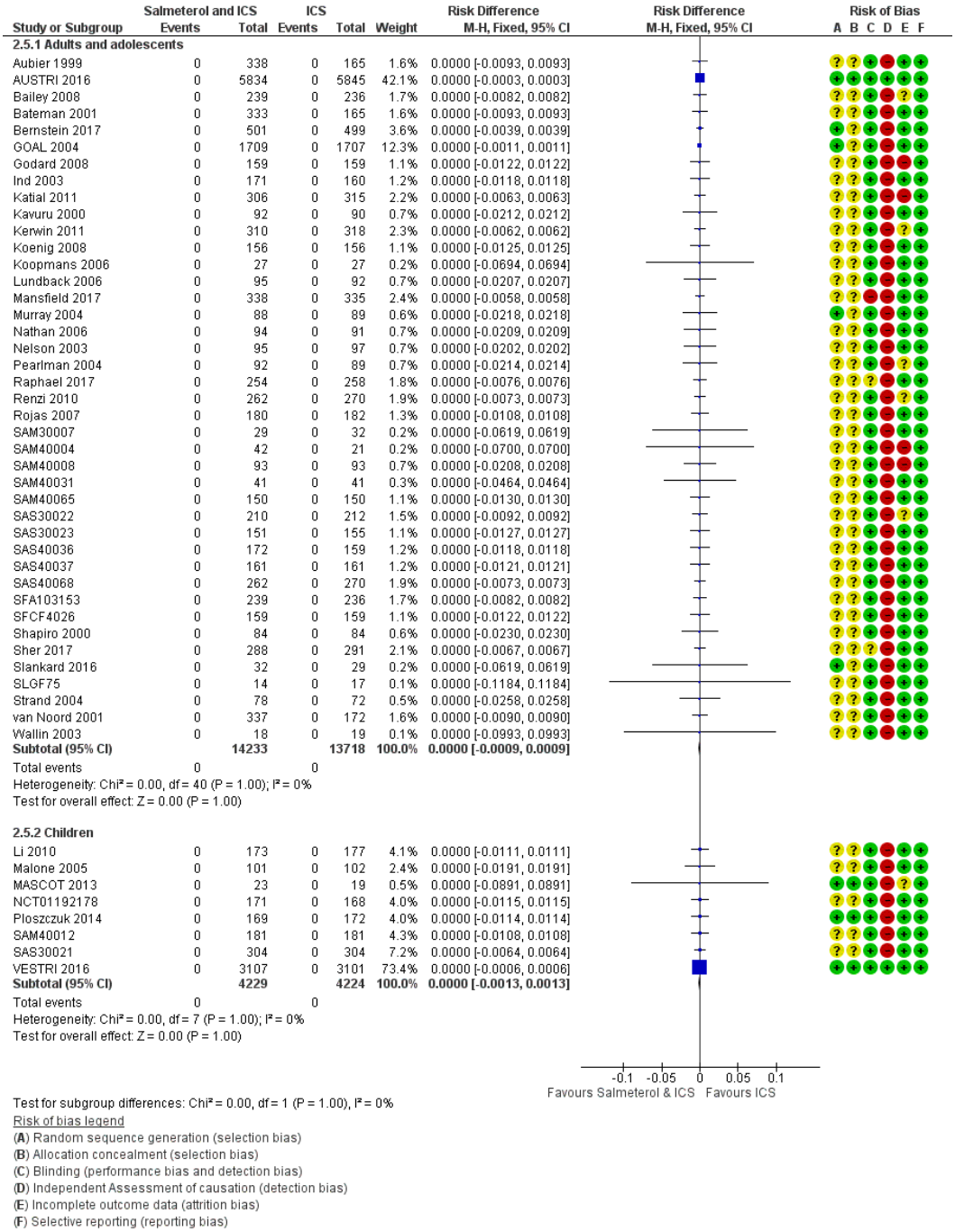
The test for interaction between adults and children did not show a significant impact of age on the treatment effect (Figure 5).

Secondary outcomes

Mortality related to asthma

None of the deaths were reported to be related to asthma. Nevertheless, when all studies were combined in a risk difference meta-analysis, we were able to use this to estimate the maximum increase in asthma deaths that is compatible with the numbers of adults and children included (using the upper end of the 95% confidence interval). For adults, this yields RD 0.0000 (95% CI -0.0009 to 0.0009; participants = 27,951; studies = 41), and for children RD 0.0000 (95% CI -0.0013 to 0.0013; participants = 8453; studies = 8; Table 3; Figure 6). In other words, for both adults and children, the pooled risk difference is compatible with one more or one fewer death per 1000 treated for six months.

Figure 6. Forest plot of comparison: 2 Risk difference meta-analysis: regular salmeterol in addition to regular ICS, outcome: 2.5 Asthma-related mortality.



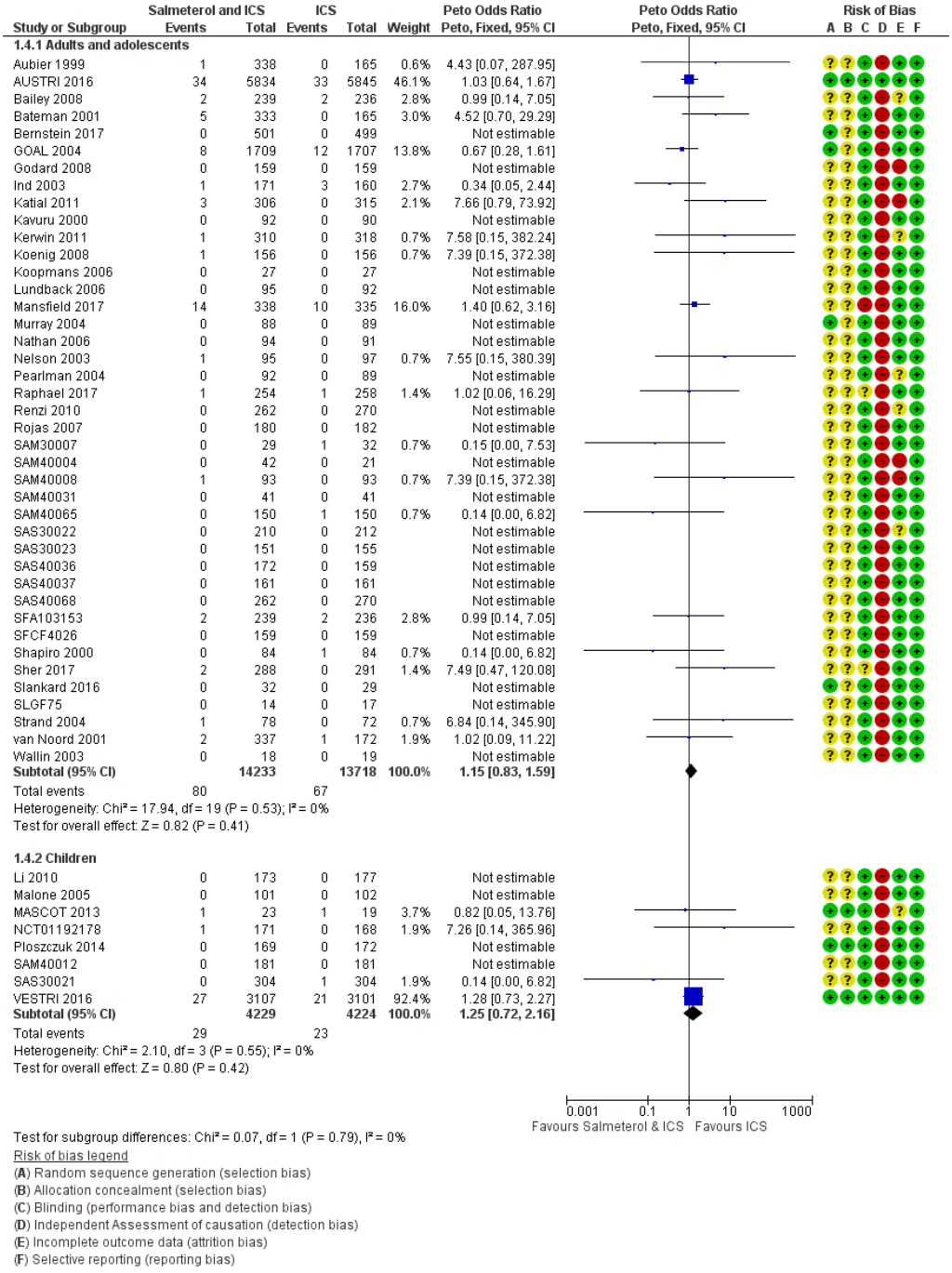
We assessed this as moderate-certainty evidence because no deaths were related to asthma, and even one extra death per 1000 is not a level of risk that we would regard as acceptable (Summary of findings for the main comparison; Appendix 5).

Non-fatal serious adverse events related to asthma

Adults and adolescents

Researchers reported asthma-related SAEs in 80 and 67 adults in each group, respectively, and the pooled odds ratio was Peto OR 1.15 (95% CI 0.83 to 1.59; participants = 27,951; studies = 41; I^2 = 0%; low-certainty evidence; Figure 7).

Figure 7. Forest plot of comparison: 1 Regular salmeterol in addition to regular inhaled corticosteroids, outcome: 1.3 Asthma-related SAE.



For every 1000 adults treated for 25 weeks, five experienced an asthma-related non-fatal SAE on ICS alone, and the corresponding risk on salmeterol and ICS was six adults (95% CI 4 to 8).

We assessed this as low-certainty evidence because the upper boundary of the confidence interval for the Peto OR translates into an NNTH of 351 for an additional adult to suffer a non-fatal asthma-related SAE over six months (Table 3). We also downgraded our certainty in this outcome because more than half of the events occurred during trials that provided no independent assessment of the causation of asthma-related events.

Children

Study results show 29 and 23 children in each treatment group with asthma-related events (Peto OR 1.25, 95% CI 0.72 to 2.16; participants = 8453; studies = 8; I^2 = 0%; moderate-certainty evidence; Figure 7). For every 1000 children treated for 23 weeks, five experienced an asthma-related SAE on ICS alone, and the corresponding risk on salmeterol and ICS was seven children (95% CI 4 to 12).

We assessed this as moderate-certainty evidence because the upper boundary of the confidence interval for the Peto OR translates into an NNTH of 128 for an additional child to suffer a non-fatal asthma-related SAE over six months (Table 3). We regarded this upper limit as too high a risk to have a high level of certainty that salmeterol is safe, but we did not downgrade our certainty in the evidence for detection bias as almost all events occurred in VESTRI 2016 (in which causation was independently assessed).

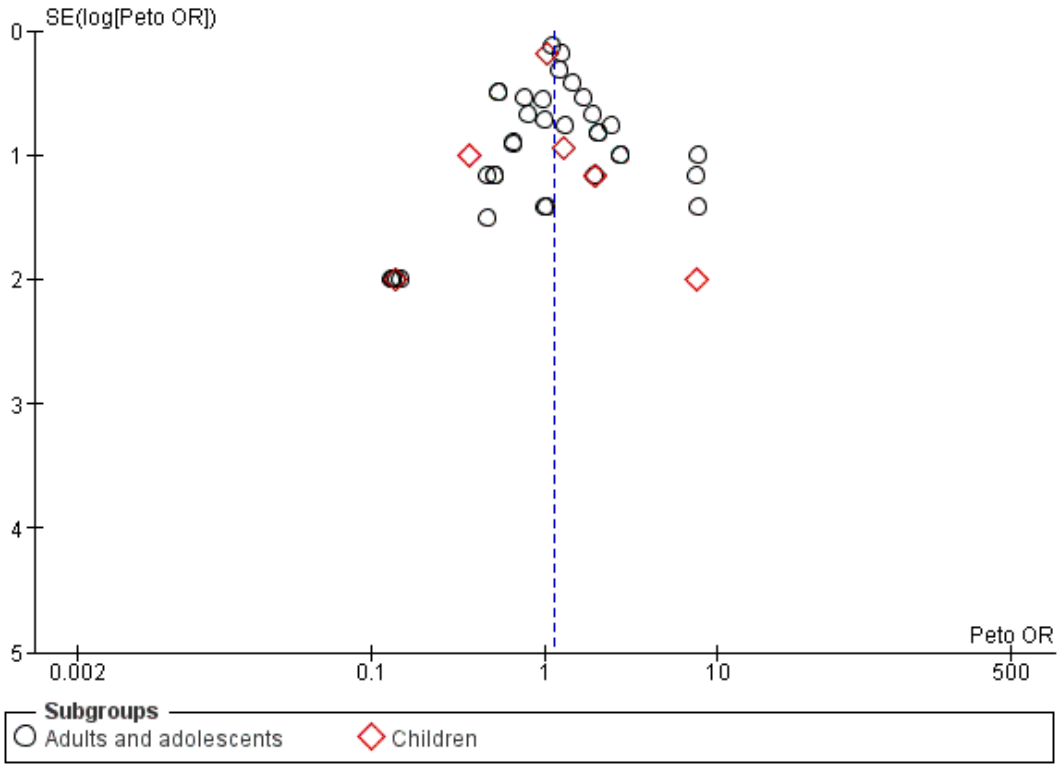
The difference between children and adults again was not statistically significant (Figure 7). We did not find sufficient data to assess the other proposed secondary outcomes (such as intensive care unit admission and intubation).

Sensitivity analyses

Risk of bias

We identified one unblinded study that did not report any deaths (Mansfield 2017); removal of this study for non-fatal SAEs of any cause made very little difference to the pooled Peto OR of 1.13 (95% CI 0.96 to 1.34; participants = 27,278; studies = 41). Removal of the four studies thought to be at high risk of attrition bias also made little difference to the OR of non-fatal SAEs in adults (Peto OR 1.11, 95% CI 0.94 to 1.31; participants = 26,763; studies = 37) (Figure 2). A funnel plot of non-fatal SAEs did not suggest obvious publication bias (Figure 8).

Figure 8. Funnel plot of comparison: 1 Regular salmeterol in addition to regular inhaled corticosteroids, outcome: 1.2 All-cause non-fatal SAE.



Restricting the results for asthma-related SAEs to trials with independent outcome assessment made very little difference to the results in children (OR 1.28, 95% CI 0.73 to 2.27; participants = 6208; studies = 1) but decreased the precision of results in adults (OR 1.03, 95% CI 0.64 to 1.67; participants = 11,679; studies = 1).

Methods of analysis

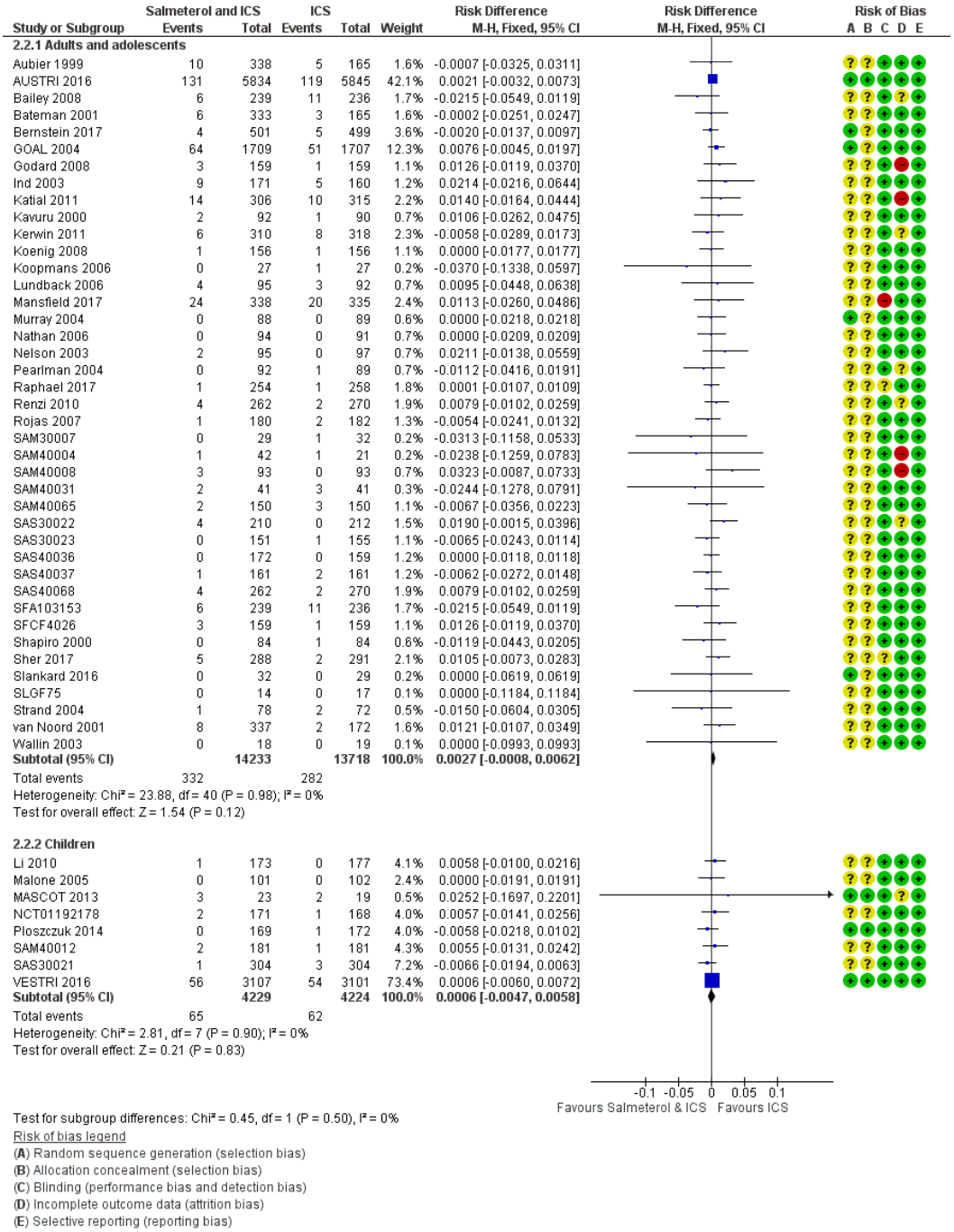
Risk difference

We have summarised the results of using pooled risk differences in Table 4; data show very similar absolute treatment effects to those calculated from the pooled Peto OR in Table 3 and Summary of findings for the main comparison.

For all-cause mortality in adults and adolescents, the pooled RD was -0.0002 (95% CI -0.0013 to 0.0009; Table 4; Figure 4). In other words, for every 1000 adults treated with salmeterol and ICS for 25 weeks, the results are compatible with one more or one fewer death (in comparison with one death on regular ICS alone). In children (with no reported deaths and OR that could not be calculated), the pooled RD for all-cause mortality was 0.0000 (95% CI -0.0013 to 0.0013; Analysis 2.1; Table 4; Figure 4). In other words, for every 1000 children treated with salmeterol and ICS for 23 weeks, the 95% confidence interval of the pooled RD is compatible with a possible increase or decrease of one death (Summary of findings for the main comparison).

For adults and adolescents with a non-fatal SAE of any cause, the pooled RD was 0.0027 (95% CI -0.0008 to 0.0062; Table 4; Figure 9). For children, the pooled RD was 0.0006 (95% CI -0.0047 to 0.0058; Table 4; Figure 9).

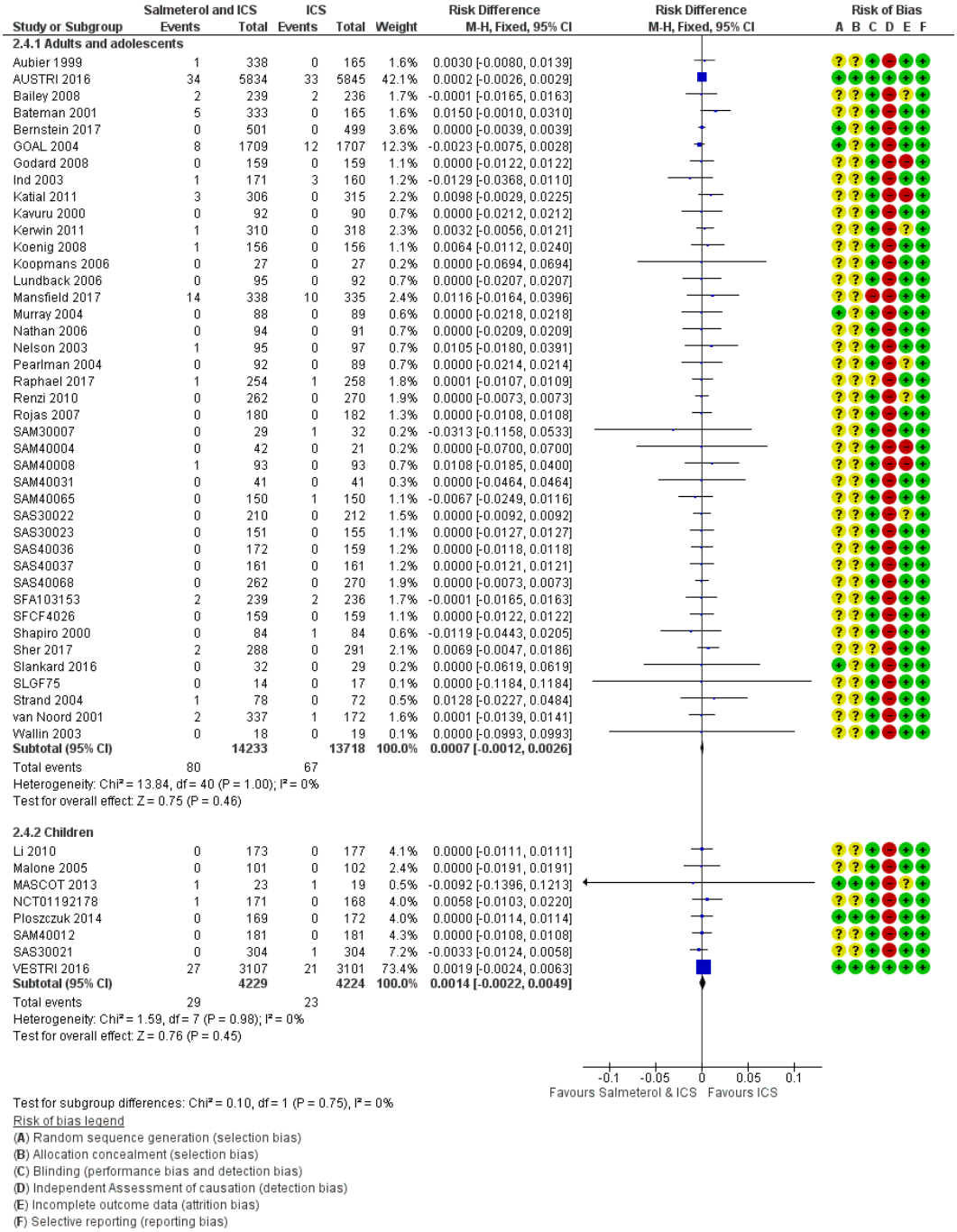
Figure 9. Forest plot of comparison: 2 Risk difference meta-analysis: regular salmeterol in addition to regular ICS, outcome: 2.2 All-cause non-fatal SAE.



When the upper end of the 95% confidence interval is translated into the worst-case NNTH, this yields results very similar to those obtained with the Peto OR and the pooled RD (Table 3; Table 4). For adults, the worst-case NNTH is 152 from the Peto OR and 161 from the RD. Similarly in children, the worst-case NNTH is 139 from the Peto OR and 172 from the RD.

The absolute difference for asthma-related non-fatal SAEs in adults was RD 0.0007 (95% CI -0.0012 to 0.0026). Similarly, the absolute difference for children was RD 0.0014 (95% CI -0.0022 to 0.0049; Table 3; Figure 10). These results are very similar to the absolute differences derived from the Peto OR in Summary of findings for the main comparison.

Figure 10. Forest plot of comparison: 2 Risk difference meta-analysis: regular salmeterol in addition to regular ICS, outcome: 2.4 Asthma-related SAE.



Mantel-Haenszel odds ratio

We analysed primary outcomes using Mantel-Haenszel fixed-effect and random-effects models. The result of the fixed-effect model for mortality in adults was OR 0.80 (95% CI 0.40 to 1.63), and for the random-effects model OR 0.81 (95% CI 0.38 to 1.72); both were very similar to the Peto OR result of 0.80 (95% CI 0.36 to 1.78). The Mantel-Haenszel method uses a correction for zero cells that is not required for the Peto OR. With this method, the addition of 0.5 to all cells when the arms include similar randomised numbers will generate an OR of 3 when only one event occurs in the treatment group, and none in the control group. When outcomes are very sparse (as for mortality), the calculated OR is dependent on the size of the zero cell adjustment and on whether treatment arms are balanced.

For non-fatal serious adverse events in adults, the Peto method (Peto OR 1.14, 95% CI 0.97 to 1.33) yielded almost identical results to the Mantel-Haenszel fixed-effect model (OR 1.13, 95% CI 0.97 to 1.33) or the Mantel-Haenszel random-effects model (OR 1.12, 95% CI 0.95 to 1.32).

Fatal and non-fatal serious adverse events combined

When fatal and non-fatal serious adverse events were combined, the results for adults were almost identical to the pooled result for non-fatal events in adults (Peto OR 1.12, 95% CI 0.96 to 1.31; Analysis 1.3), and results were unchanged in children, as no deaths occurred in children.

Dose of salmeterol

The dose of salmeterol used in seven studies was less than the usual daily dose of 50 μg twice daily, so we carried out sensitivity analysis out on the primary outcomes while excluding these studies (Mansfield 2017; Raphael 2017; SAS30021; SAS30022; SAS30023; Sher 2017; Slankard 2016). Sher 2017 reported one death, and without this event, the pooled odds ratio was Peto OR 0.72 (95% CI 0.32 to 1.65); among studies in children, no deaths occurred, so mortality results were unaffected. Results for an SAE of any cause without these studies in adults (Peto OR 1.11, 95% CI 0.94 to 1.31; participants = 25,398) and in children (Peto OR 1.08, 95% CI 0.75 to 1.54; participants = 7845) are very similar to the full data set.

Subgroup analyses

Mortality data were too sparse for any subgroup analysis to be performed. For non-fatal SAEs of any cause, tests for interaction between adults and children did not show a significant difference between results according to age group (test for subgroup differences: Chi² = 0.20, df = 1 (P = 0.65); I² = 0%), nor was there a difference in asthma-related events between adults and children (test for subgroup differences: Chi² = 0.07, df = 1 (P = 0.79); I² = 0%). Studies that included patients on separate salmeterol and fluticasone inhalers were too few to permit a subgroup comparison between separate and combined inhalers (Table 1).

DISCUSSION

Summary of main results

The number of adults included in this review has doubled and the number of children quadrupled with the addition of new studies to the 2018 update of this review. As a consequence, estimates of risk of non-fatal serious adverse events have become more precise. The previous upper 95% confidence interval (CI) was Peto odds ratio (OR) 1.44 for adults and 3.91 for children, and is now 1.33 and 1.48, respectively.

However, no deaths in children and no deaths in adults were caused by asthma, so we are not able to draw firm conclusions about the risks of dying from asthma when regular salmeterol is added to inhaled corticosteroid (ICS).

All-cause mortality in adults

Eleven of a total of 14,233 adults on regular salmeterol and ICS died, as did 13 of 13,718 on regular ICS at the same dose. The pooled Peto OR was 0.80 (95% CI 0.36 to 1.78; participants = 27,951; studies = 41; I² = 0%; moderate-certainty evidence). In other words, for every 1000 adults treated for 25 weeks, one death occurred on ICS alone, and the corresponding risk on salmeterol and ICS was also one death (95% CI 0 to 2 deaths).

All-cause non-fatal serious adverse events

A total of 332 adults on regular salmeterol with ICS suffered a non-fatal serious adverse event of any cause compared to 282 adults on regular ICS. The pooled Peto OR was 1.14 (95% CI 0.97 to 1.33; participants = 27,951; studies = 41; I² = 0%; moderate-certainty evidence). For every 1000 adults treated for 25 weeks, 21 adults on ICS alone experienced a serious adverse event, and the corresponding risk on salmeterol and ICS was 23 adults (95% CI 20 to 27).

Sixty-five of 4229 children on regular salmeterol with ICS experienced a serious adverse event of any cause compared to 62 of 4224 on regular ICS. The pooled Peto OR was 1.04 (95% CI

0.73 to 1.48; participants = 8453; studies = 8; I^2 = 0%; moderate-certainty evidence). For every 1000 children treated for 23 weeks, 15 children on ICS alone had a serious adverse event, and the corresponding risk on salmeterol and ICS was also 15 children (95% CI 11 to 22).

Overall completeness and applicability of evidence

Two large surveillance studies examined the use of regular salmeterol without randomised ICS (SMART 2006 SNS 1993). As a result of the increase in serious adverse events reported in these studies, the FDA mandated surveillance studies of regular salmeterol in adults and children. These two large surveillance studies - in adults (AUSTRI 2016 - previously ongoing study NCT01475721) - and in children (VESTRI 2016 - previously ongoing study NCT01462344) - assessed the safety of regular salmeterol in combination with an ICS; these studies have now been published, and the results have been incorporated into this updated review. The two large new studies were designed to test whether salmeterol was safe when added to ICS; to do this, investigators used a safety margin that was derived from the worst end of the 95% confidence interval of the comparative risk for a combined endpoint in these trials (death, intubation, or hospital admission). The FDA pre-defined safety margins for the composite outcomes in these studies of a relative measure of 2.0 in adults and 2.675 in children; confidence intervals of the pooled odds ratios from this review for serious adverse events for adults and children (all-cause and asthma-related) now fall within these margins.

Using the same approach - by transforming the worst-case 95% confidence interval of the pooled odds ratio and the pooled risk difference from all trials in this review - we determined the upper limits of the confidence intervals for both odds ratios and risk differences, and we have presented them in Table 3 and Table 4. We used Visual Rx to convert these upper limits to worst-case numbers needed to treat for an additional harmful effect (NNTH), for one additional person to suffer an event from these upper limits listed in Table 3 and Table 4.

Although the new FDA studies do not exceed their pre-defined safety margins for non-fatal serious adverse events on salmeterol in combination with ICS, the levels of adherence in AUSTRI 2016 (median 95.1%) and VESTRI 2016 (median 94%) were much higher than is usual in day-to-day practice. These trials, as well as many recent trials, also excluded participants with life-threatening asthma. This may limit the applicability of findings from these new studies and from this review.

Almost all studies used combination inhalers; therefore the results of this review do not apply to the use of salmeterol and ICS in separate inhalers.

Quality of the evidence

We assessed risk of bias in the included studies as low for all-cause outcomes, 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). Although we judged most studies to be at high risk of detection bias, we are not concerned about detection bias for asthma-related serious adverse events in children, because most events were reported from the new study VESTRI 2016, which provided independent assessment of causation. However we were more concerned about detection bias affecting the treatment effect in adults because the only study with independent assessment of causation was AUSTRI 2016, which yielded a wider confidence interval when data from this study alone were considered.

We previously assessed our confidence in the evidence as moderate due to statistical imprecision. This reflected the low rates of mortality and non-fatal adverse events across studies included in the review (Summary of findings for the main comparison).

Our confidence in the findings of this review remains moderate. Included studies reported no deaths from asthma and a total of 24 deaths of any cause among adults. Even with additional data for the 2018 update, the upper confidence intervals for all-cause non-fatal serious adverse events remain at a possible NNTH of 152 for adults and 139 for children over six months. We believe that this risk boundary remains too high to grade the evidence with a high level of certainty to show that adding salmeterol to regular ICS was entirely safe.

Potential biases in the review process

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 ORs with zero events (Sweeting 2004). Because it became apparent in the course of carrying out our reviews that the pooled ORs were heavily dependent on the zero adjustment used in Mantel-Haenszel and inverse variance methods, we used the Peto OR and RDs to report results of this review. The likely bias in using the Peto OR is small, as only three trials - Aubier 1999, Bateman 2001, and van Noord 2001 - showed any imbalance in the number of patients in each arm (Sweeting 2004). In these studies, twice the number of patients were randomised to regular salmeterol with ICS in comparison to ICS alone.

Similarly, the included studies were influenced by the decision to restrict the review to trials that randomised participants to salmeterol and ICS, 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 serious adverse events when salmeterol

and fluticasone are delivered via one inhaler, and when salmeterol is added to inhaled corticosteroid therapy via a separate inhaler, when both are randomised treatments in a controlled trial.

Agreements and disagreements with other studies or reviews

An overview of Cochrane Reviews on the safety of regular salmeterol or formoterol in children (with and without combination ICS) does not reveal any significant differences between the safety of regular salmeterol and regular formoterol in children, but the number of children studied remains small in comparison to the number of adults (Cates 2012a Cates 2014). Moreover, no separate safety results are currently available for adolescents who were recruited in the adult and adolescent trials.

Two systematic reviews on the use of salmeterol with ICS have shown results similar to the findings of this review. Bateman 2008 concentrated on asthma-related outcomes, and Jaeschke 2008a considered both salmeterol and formoterol in adults in comparison to ICS at the same dose and at higher doses. Neither of these reviews showed a significant increase in the risk of serious adverse events, but results were not precise enough to rule out a clinically important increase or decrease in serious adverse events with regular salmeterol.

Minor discrepancies between results recorded in serious adverse event reports on the GlaxoSmithKline website and in the data provided by Bateman 2008 and Jaeschke 2008a became apparent during preparation of this review. An example of this is the death in Aubier 1999, which is related to the question of whether the adverse event was classified as being "on-treatment" (see Aubier 1999 notes in Characteristics of included studies). Overall the magnitude of these differences is small, and this relates most often to an external review of company data and inclusion of reviewed data in some analyses; this has not altered the conclusions of this review.

Administration of inhaled corticosteroid (ICS)

No clear difference can be seen between the point estimate and the confidence interval of the OR for non-fatal serious adverse events in adults (Peto OR 1.14, 95% CI 0.97 to 1.33) or children (Peto OR 1.04, 95% CI 0.73 to 1.48) presented in this review, nor in the Peto OR given in the review comparing salmeterol to placebo (OR 1.14, 95% CI 1.01 to 1.28) (Cates 2008a). However the average non-fatal serious adverse event rate in control arms of the trials in this review that included randomised ICS in adults was 2.0% over 25 weeks compared to 3.6% over 28 weeks in SMART 2006 (which accounted for most patients in Cates 2008a).

This may reflect greater asthma severity among patients who had been started by their own physician on background ICS (as shown by Sears 2009 in the RELIEF study), but it could also be compounded by known poor adherence to treatment with ICS in routine practice. This raises uncertainty about application of results reported for patients in clinical trials, which usually include much more intensive monitoring of adherence to therapy. For example, the two new large trials added to this review in 2018 show very high adherence rates; the median level of adherence in AUSTRI 2016 was 95.1%, and in VESTRI 2016 94%. Given that we cannot assume that adherence to treatment in trials will be matched in routine practice, care must be exercised in both interpretation and application of trial results (Weiss 2008).

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

AUTHORS' CONCLUSIONS

Implications for practice

We have now included two large safety trials mandated by the FDA and have provided data from 27,951 adults and 8453 children with asthma. In spite of the large additional studies added for this update, data show no asthma deaths in either age group, so we remain uncertain about the safety of salmeterol and ICS with respect to the risk of dying from asthma.

This additional information has increased the precision of the estimates, such that the upper confidence interval for all-cause non-fatal serious adverse events is the number needed to treat for an additional harmful outcome (NNTH) of 152 for adults and 139 for children over six months for salmeterol in combination with ICS for six months (compared to ICS alone).

Decisions regarding regular use of salmeterol in combination with ICS must take into account the balance between known symptomatic benefits of salmeterol when used in combination with an inhaled corticosteroid and the remaining degree of uncertainty associated with potential harmful effects.

Implications for research

Following publication of the new surveillance studies, we suggest that further randomised trials undertaken to test the safety of salmeterol in combination with inhaled corticosteroids would have to include very large numbers of participants to change the conclusions of this review (particularly in relation to risks of asthma mortality). The increased precision afforded by such large studies may not be worth the substantial costs they would incur. However, there remains a sparsity of evidence from adolescents and from people who have suffered a life-threatening asthma attack, which merits further research through randomised trials, case-control studies, or reviews of asthma deaths.

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John White was the Editor for this review and commented critically on the review.

Sadia Janjua assisted with selection and assessment of the risk of bias in new studies for the 2018 update.

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SAS30039. A 12-week, multi-centre, randomised, double-blind, parallel-group study to compare the efficacy and tolerability of salmeterol/fluticasone propionate combination (SERETIDE™/VIANI™/ADVAIR™) 50/250μg twice-daily with fluticasone propionate 250μg twice-daily, all via the DISKUS®/ACCUHALER® as initial maintenance therapy in moderate persistent asthma. www.gsk-clinicalstudyregister.com/study/SAS30039 (first received 28 September 2008).

SAM30007 *{unpublished data only}*

SAM30007. A multicentre, 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. www.gsk-clinicalstudyregister.com/study/SAM30007 (first received 28 September 2008).

SAM40004 *{unpublished data only}*

* SAM40004. 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 (50/100μg strength) bd via the Accuhaler inhaler, or fluticasone propionate 100μg 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 (50/100μg strength) bd via the Accuhaler inhaler or fluticasone propionate 100μg bd via the Accuhaler inhaler, in adults with reversible airways obstruction (SIRIAS - Seretide in Inflammation and Remodelling In Asthma Study). www.gsk-clinicalstudyregister.com/study/SAM40004 (first received 28 September 2008).

SAM40008 *{unpublished data only}*

SAM40008. 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. www.gsk-clinicalstudyregister.com/study/SAM40008#rs (first received 28 September 2008).

SAM40012 *{unpublished data only}*

SAM40012. A multicentre, 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. www.gsk-clinicalstudyregister.com/study/SAM40012#rs (first received 28 September 2008).

SAM40031 *{unpublished data only}*

SAM40031. A 13 month, randomised, double-blind, parallel-group comparison of the efficacy of Seretide and Flixotide(fluticasone propionate Accuhaler) when down-titrating the inhaled corticosteroid dose in asthmatic adults who have previously received SeretideTM 500/

50 mg twice daily for at least 4 weeks. www.gsk-clinicalstudyregister.com/study/SAM40031 (first received 24 August 2016).

SAM40065 *{unpublished data only}*

SAM40065. A multicenter, randomized, double-blind, parallel group, 40-week comparison of asthma control using bronchial hyperresponsiveness as an additional guide to long-term treatment in adolescents and adults receiving either fluticasone propionate/salmeterol DISKUS twice daily or fluticasone propionate DISKUS twice daily (or placebo twice daily if asymptomatic). www.gsk-clinicalstudyregister.com/study/SAM40065#ps (first received 12 June 2009).

SAS30021 *{unpublished data only}*

SAS30021. A stratified, randomized, double-blind, placebo-controlled, parallel-group, 12 week trial evaluating the safety and efficacy of 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. www.gsk-clinicalstudyregister.com/study/SAS30021 (first received 22 September 2004).

SAS30022 *{unpublished data only}*

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SAS30022. A randomized, double-blind, placebo-controlled, parallel-group, 12 week trial evaluating the safety and efficacy of the fluticasone propionate/salmeterol DISKUS combination product 250/50mcg once daily versus fluticasone propionate 250mcg once daily versus fluticasone propionate/salmeterol 100/50mcg twice daily versus placebo in symptomatic adolescent and adult subjects with asthma that is not controlled on short acting beta agonist therapy. www.gsk-clinicalstudyregister.com/study/SAS30022study&#rs (first received 28 September 2008).

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SAS40036 *{unpublished data only}*

SAS40036. A multicenter, randomized, double-blind, double-dummy, parallel group, 16-week comparison of asthma control in adolescent and adults receiving either fluticasone propionate/salmeterol Diskus combination product 100/50mcg twice daily, fluticasone propionate Diskus 100mcg twice daily, salmeterol xinafoate 50mcg twice daily, or oral montelukast 10mg every day. www.gsk-clinicalstudyregister.com/study/SAS40036?search=study&#rs (first received 28 September 2008).

SAS40037 *{unpublished data only}*

SAS40037. A multicenter, randomized, double-blind, double-dummy, parallel group, 16-week comparison of asthma control in adolescents and adults receiving either fluticasone propionate/salmeterol Diskus combination product 100/50mcg twice daily, fluticasone propionate Diskus 100mcg twice daily, salmeterol xinafoate 50mcg twice daily, or oral montelukast 10mg every day. www.gsk-clinicalstudyregister.com/study/SAS40037#rs (first received 28 September 2008).

SAS40068 *{unpublished data only}*

SAS40068. A 24 week, multicentre, 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. (Program of ADVAIR® control and effectiveness - initial maintenance treatment, PACE - IMT study). https://www.gsk-clinicalstudyregister.com/study/SAS40068 (first received 25 April 2007).

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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. www.gsk-clinicalstudyregister.com/study/SFCA3003#rs (first received 28 September 2008).

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SAM40049. A Danish, multi-centre, comparative, parallel-group study to determine whether initiation of combination treatment with Seretide™ 50/100 mg bd offers better asthma control than monotherapy with Flixotide™ 100 mg bd to adult asthmatic subjects uncontrolled on short-acting bronchodilator alone.. www.gsk-clinicalstudyregister.com/study/SAM40049?search=study&#rs (first received 28 September 2008).

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* *Indicates the major publication for the study*

CHARACTERISTICS OF STUDIES

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

Aubier 1999

Methods	A randomised, 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, France, and the Netherlands). Run-in 2 weeks and follow-up 2 weeks
Participants	**Population:** 503 adolescents and adults (12 to 79 years) with asthma **Baseline characteristics:** mean age 48 years; FEV1 73% predicted Concomitant ICS used by 100% of participants **Inclusion criteria:** at least 12 years old with a documented clinical history of reversible airways disease; received treatment with any inhaled corticosteroid continuously for 12 weeks before run-in; FEV1 % predicted between 50% and 100%. At the end of the 2-week run-in period, symptomatic (symptom score ≥ 2 on at least 4 of the last 7 consecutive days), with mean morning PEF > 50% and < 85% of the maximum PEF 15 minutes after administration of inhaled salbutamol 400 μg **Exclusion criteria:** taking long-acting beta2 -agonists
Interventions	• Fluticasone propionate and salmeterol 500/50 μg twice daily • Fluticasone propionate 500 μg + salmeterol 50 μg twice daily (separate inhalers) • Fluticasone propionate 500 μg twice daily Delivery was by Diskus device
Outcomes	**Primary outcome:** mean morning PEF during weeks 1 to 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 2008b, as the participant stopped taking study medication to allow for elective surgery and died of surgical complications but was still included in the trial and had intended to restart treatment postoperatively
Notes	Sponsored by GSK

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not reported
Allocation concealment (selection bias)	Unclear risk	Not reported
Blinding (performance bias and detection bias) All outcomes	Low risk	Double-blind, double-dummy

Aubier 1999 (*Continued*)

Independent Assessment of causation (detection bias) Asthma-related events	High risk	Causation of SAEs not independently assessed
Incomplete outcome data (attrition bias) All outcomes	Low risk	403/503 (80%) completed the study
Selective reporting (reporting bias)	Low risk	Full data on GlaxoSmithKline website

AUSTRI 2016

Methods	A randomised, double-blind, multi-centre, parallel-group study carried out over 26 weeks
Participants	**Population:** 11,679 adults and older children (> 12 years) with persistent asthma; all participants had a history of severe asthma exacerbation in the past year but no events in the past month **Baseline characteristics:** mean age 43.4 years **Inclusion criteria:** main further inclusion criteria were the following: peak expiratory flow ≥ 50% of predicted normal value, use of daily medication for asthma control and ≥ 1 asthma exacerbation requiring treatment or hospitalisation within 12 months before randomisation **Exclusion criteria:** main exclusion criteria were the following: history of life-threatening asthma, concurrent respiratory disease, > 10-pack-year smoking history, respiratory infection, unstable asthma status
Interventions	• Fluticasone propionate and salmeterol (at a dose of 100 μg of fluticasone and 50 μg of salmeterol, 250 μg and 50 μg, or 500 μg and 50 μg, respectively) twice daily • Fluticasone propionate (at a dose of 100 μg, 250 μg, or 500 μg) twice daily
Outcomes	**Primary outcome:** time until first serious asthma-related adverse outcome
Notes	Sponsored by GSK

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Randomisation was performed with the use of an interactive voice-response system with stratification
Allocation concealment (selection bias)	Low risk	Randomisation was performed with the use of an interactive voice-response system with stratification
Blinding (performance bias and detection bias) All outcomes	Low risk	Double-blind with respect to salmeterol but not dose of fluticasone

AUSTRI 2016 (*Continued*)

Independent Assessment of causation (detection bias) Asthma-related events	Low risk	Independent assessment of safety outcomes
Incomplete outcome data (attrition bias) All outcomes	Low risk	For mortality, the status of all participants who took at least 1 dose of treatment was assessed after 6 months
Selective reporting (reporting bias)	Low risk	Data were extracted for all outcomes of the review

Bailey 2008

Methods	A randomised, double-blind, multi-centre, parallel-group study over 52 weeks from November 2004 to April 2007, at 59 centres in the USA. Run-in 2 weeks on usual ICS, and then 4 weeks on fluticasone 250 μg twice daily
Participants	**Population:** 475 adolescents and adults (12 to 65 years) of African descent with persistent asthma and symptomatic while taking low-dose ICS **Baseline characteristics:** mean age 32 years; FEV_1 85% predicted Concomitant ICS used by 100% of participants **Inclusion criteria:** 12 years of age or older with documented clinical history of persistent asthma for at least 6 months; had been symptomatic when using ICS (fluticasone propionate 200 μg daily or equivalent) for at least 4 weeks before entering the run-in period; FEV_1 % predicted between 60% and 90%, with at least 12% reversibility following 2 to 4 puffs of albuterol **Exclusion criteria:** participants were included in the 52-week study period only if when on the 2-week run-in taking low-dose ICS twice daily, they showed FEV_1 $\geq$ 60% predicted, and in the last 7 days of run-in, they had $\geq$ 4 days of albuterol use or were symptomatic; they were excluded if they had an exacerbation in the 4 weeks on fluticasone 250 μg twice daily
Interventions	• Fluticasone propionate and salmeterol 100/50 μg Diskus twice daily • Fluticasone propionate 100 μg Diskus twice daily alone
Outcomes	**Primary outcome:** rate of asthma exacerbation
Notes	Sponsored by GSK

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Not reported
Allocation concealment (selection bias)	Unclear risk	Not reported

Bailey 2008 (*Continued*)

Blinding (performance bias and detection bias) All outcomes	Low risk	"Double-blind treatment period"
Independent Assessment of causation (detection bias) Asthma-related events	High risk	Causation of SAEs not independently assessed
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	70/239 lost to follow-up on combined treatment, and 85/236 on fluticasone alone
Selective reporting (reporting bias)	Low risk	Full data on GlaxoSmithKline website (SFA103153)

Bateman 2001

Methods	A randomised, double-blind, double-dummy, multi-centre, parallel-group study over 12 weeks from March 1998 to June 1999, at 69 centres in 10 countries. Run-in 2 weeks and 2 weeks' follow-up
Participants	**Population:** 497 adolescents and adults (12 to 79 years) with documented clinical history of reversible airways obstruction **Baseline characteristics:** mean age 40 years; FEV_1 76% predicted Concomitant ICS used by 100% of participants **Inclusion criteria:** 12 years or older with documented clinical history of reversible airway obstruction, smoking history < 10 pack-years, and using ICS (beclomethasone dipropionate, budesonide, or flunisolide 400 to 500 μg/d or fluticasone propionate 200 to 250 μg/d) for $\geq$ 4 weeks before entering the run-in period; FEV_1 % predicted $\geq$ 50%. Mean PEF over last 7 days of run-in period between 50% and 85% measured after inhalation of salbutamol (400 mg); symptomatic (i.e. cumulative total symptom score (daytime plus night-time) > 8 for last 7 days of the run-in period; and taking salbutamol up to 800 μg/d **Exclusion criteria:** received a long-acting $beta_2$ -agonist or an oral $beta_2$ -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 hospitalisation within 12 weeks of study entry. Other exclusion criteria were prior treatment with oral, depot, or parenteral corticosteroids or combination therapy (containing a $beta_2$ -agonist and/or ICS)
Interventions	• Fluticasone propionate and salmeterol 100/50 μg HFA MDI • Fluticasone propionate and salmeterol 100/50 μg Diskus • Fluticasone propionate 100 μg CFC MDI
Outcomes	**Primary efficacy variable:** mean morning PEF over the 12-week treatment period A serious adverse event was described as any event that was fatal, life-threatening, disabling, or incapacitating, or that 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 fluticasone propionate/salmeterol MDI and Diskus groups)" SFCB3022 reports 5 participants with asthma SAE in fluticasone propionate/salmeterol groups (333 participants) and none in the fluticasone propionate alone group (165 participants) Bateman reports 4 asthma hospitalisations in fluticasone propionate/salmeterol groups
Notes	Sponsored by GSK

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Not reported
Allocation concealment (selection bias)	Unclear risk	Not reported
Blinding (performance bias and detection bias) All outcomes	Low risk	Double-blind, double-dummy
Independent Assessment of causation (detection bias) Asthma-related events	High risk	Causation of SAEs not independently assessed
Incomplete outcome data (attrition bias) All outcomes	Low risk	430/497 (87%) completed the study
Selective reporting (reporting bias)	Low risk	Full data on GlaxoSmithKline website

Bernstein 2017

Methods	A randomised, double-blind, double-dummy, parallel-group, 24-week study
Participants	**Population:** intent-to-treat population included 1504 adults and adolescents (aged > 12 years) with an asthma diagnosis for at least 12 weeks who were well controlled on ICS/LABA **Baseline characteristics:** 82% of participants were white; 64% female; mean age 43.5 years. At randomisation, participants had a mean per cent predicted FEV_1 of 90.24% **Inclusion criteria:** required to have $FEV_1 \geq 80\%$ of predicted normal value, and to have received treatment with ICS/LABA (equivalent to fluticasone propionate and salmeterol 250/50 twice daily), either as a fixed-dose combination or through separate inhalers, for at least 12 weeks. Patients had to be able to replace their current SABA with albuterol/salbutamol **Exclusion criteria:** history of life-threatening asthma in previous 5 years; evidence of

	concurrent respiratory disease or other clinically significant medical condition; ongoing respiratory infection within previous 4 weeks; use of tobacco products within previous 3 months or historical use ≥ 10 pack-years; severe milk protein allergy or specific drug allergy; asthma exacerbation that required oral corticosteroids within previous 12 weeks, or that resulted in overnight hospitalisation requiring additional asthma treatment within previous 6 months
Interventions	• Fluticasone furoate and vilanterol 100/25 μg once daily (this arm of the study was not used in the review) • Fluticasone propionate and salmeterol 250/50 μg twice daily • Fluticasone propionate 250 μg twice daily
Outcomes	**Primary outcome:** change from baseline in evening trough FEV_1; safety was also assessed
Notes	Sponsored by GSK

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Eligible patients were randomised 1:1:1 via an interactive voice response system to receive 1 of 3 blinded study treatments
Allocation concealment (selection bias)	Unclear risk	Methods used for allocation concealment were not clearly reported
Blinding (performance bias and detection bias) All outcomes	Low risk	Study authors reported that it was carried out in a double-blind double-dummy manner, and described how this was achieved. Therefore it is unlikely that blinding was broken
Independent Assessment of causation (detection bias) Asthma-related events	High risk	No report of independent assessment of SAEs carried out
Incomplete outcome data (attrition bias) All outcomes	Low risk	Reasons for attrition were given by study authors. Moreover the proportion of withdrawals, in both arms of the study, is relatively small: more than 80% of participants completed the study
Selective reporting (reporting bias)	Low risk	Data were extracted for all outcomes of the review

GOAL 2004

Methods	A randomised, double-blind, multi-centre, stratified, parallel-group study over 12 months from December 2000 to December 2002, at 326 centres in Europe, North America, Latin America, and Asia Pacific. Run-in 4 weeks
Participants	**Population:** 3416 adolescents and adults (9 to 83 years) with uncontrolled asthma **Baseline characteristics:** mean age 40 years; FEV_1 77% predicted; concomitant ICS 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 older but younger than 80 years, with at least a 6-month history of asthma, bronchodilator reversibility by an increase of at least 15% in FEV_1 over baseline (and 200 mL) based on FEV_1 measured pre- and post-inhalation of any short-acting $beta_2$-agonist within last 6 months or to demonstrate reversibility at visit 1, at visit 2, or between visit 1 and visit 2 using 200 to 400 μg of salbutamol/albuterol Eligible for stratum 1 of the study if had not received ICS for at least 6 months before visit 1; for stratum 2, if receiving $\leq$ 500 μg BDP or equivalent daily; for stratum 3, if receiving > 500 and $\leq$ 1000 μg BDP or equivalent daily During 2 or more of the 4 weeks before visit 2, participants 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 < 50% predicted; non-compliance with diary record card
Interventions	• Fluticasone propionate and salmeterol 100/50, 250/50, or 500/50 μg twice daily (by strata) • Fluticasone propionate 100, 250, or 500 μg twice daily (by strata) Delivery was Diskus device
Outcomes	**Primary efficacy variable:** proportion of participants who achieved 'well-controlled' asthma with the fluticasone propionate/salmeterol combination compared with fluticasone propionate alone during phase 1 of the study Paper states: "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 numbers of participants (67 and 53, respectively) Website reports 2 deaths on fluticasone propionate (both myocardial infarction) and 3 deaths on fluticasone propionate/salmeterol (2 myocardial infarction and 1 pneumonia) . No asthma-related deaths were reported
Notes	Sponsored by GSK

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomisation was done telephonically from a computer-generated allocation schedule balanced per stratum and per country

GOAL 2004 (*Continued*)

Allocation concealment (selection bias)	Unclear risk	Not reported
Blinding (performance bias and detection bias) All outcomes	Low risk	Double-blind
Independent Assessment of causation (detection bias) Asthma-related events	High risk	Causation of SAEs not independently assessed
Incomplete outcome data (attrition bias) All outcomes	Low risk	2890/3416 (85%) completed the study
Selective reporting (reporting bias)	Low risk	Full data on GlaxoSmithKline website

Godard 2008

Methods	A randomised, double-blind, 24-week, multi-centre study at 124 centres in France; 8-week open run-in on SFC (50/250 μg twice daily)
Participants	**Population:** 308 adults (18+ years) with asthma controlled on ICS (1000 μg CFC beclomethasone equivalent daily) and LABA **Baseline characteristics:** mean age 44 years; FEV$_1$ 90% predicted Concomitant ICS used by 100% of participants **Inclusion criteria:** currently receiving ICS at a dose of 1000 μg daily of inhaled BDP or equivalent and LABA. Asthma controlled on a stable dose for at least 4 weeks were entered into run-in, and then entered into the full study if asthma was well controlled (as defined in GOAL) in last 2 weeks of 8-week run-in on fluticasone propionate/salmeterol **Exclusion criteria:** excluded from entry into the run-in period if smoking history of $\geq$ 10 pack-years, respiratory tract infection during last 4 weeks before initial clinic visit (V1), acute asthma exacerbation requiring emergency room treatment or hospitalisation within 4 weeks before V1, use of oral/parenteral corticosteroids during last 4 weeks before V1 (12 weeks for depot corticosteroids), any change in asthma maintenance treatment in previous 4 weeks
Interventions	• Fluticasone propionate and salmeterol 250/50 μg twice daily • Fluticasone 250 μg twice daily • Fluticasone propionate/salmeterol 100/50 μg twice daily (not analysed in this review) Delivery device Diskus
Outcomes	**Primary efficacy endpoint:** variation in mean morning PEF over first 12 weeks of the treatment period compared to last 2 weeks of the run-in period (baseline)
Notes	Sponsored by GSK

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**

Godard 2008 (*Continued*)

Random sequence generation (selection bias)	Unclear risk	Not described
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding (performance bias and detection bias) All outcomes	Low risk	"Double-blind randomised 24-week study"
Independent Assessment of causation (detection bias) Asthma-related events	High risk	Causation of SAEs not independently assessed
Incomplete outcome data (attrition bias) All outcomes	High risk	Uneven withdrawals (18/159 on fluticasone propionate/salmeterol and 30/159 on fluticasone)
Selective reporting (reporting bias)	Low risk	Full SAE data reported in paper

Ind 2003

Methods	A randomised, double-blind, double-dummy, multi-centre, parallel-group study over 28 weeks from January 1995 to December 1996, at 99 centres in Canada, Denmark, Iceland, Ireland, Italy, and the United Kingdom. Run-in 4 weeks
Participants	**Population:** 502 adolescents and adults (16 to 75 years) with asthma poorly controlled on current ICS **Baseline characteristics:** mean age 45 years; FEV$_1$ 2.3 L Concomitant ICS used by 100% of participants **Inclusion criteria:** currently receiving ICS at a dose of 1000 to 1600 μg daily of inhaled BDP or equivalent; asthma poorly controlled (demonstrated by PEF < 85% of maximal achievable PEF after inhaling 400 μg 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 PEF < 90% of maximal achievable PEF measured at screening and diurnal variation in PEF $\geq$ 15%; had to have asthma symptoms on $\geq$ 4 of the last 7 days or nights of the baseline period **Exclusion criteria:** receiving continuous OCS; having any serious uncontrolled systemic disease or participation deemed unsuitable by the physician; had to demonstrate a period variation in PEF $\geq$ 15% (highest evening value - lowest morning value as a percentage of highest PEF) over last 10 days and/or nights of the run-in period and to have suboptimal PEF, with average PEF over last 10 days of the run-in not exceeding 90% of post-bronchodilator PEF (measured at visit 1)
Interventions	• Fluticasone propionate 250 μg + salmeterol 50 μg twice daily (in separate inhalers) • Fluticasone propionate 250 μg twice daily • Fluticasone propionate 500 μg twice daily Delivery was MDI (fluticasone propionate 500 arm not used in this review)

Ind 2003 (*Continued*)

Outcomes	**Primary efficacy variables:** mean morning PEF; 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	Sponsored by GSK

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not reported
Allocation concealment (selection bias)	Unclear risk	Not reported
Blinding (performance bias and detection bias) All outcomes	Low risk	Double-blind, double-dummy
Independent Assessment of causation (detection bias) Asthma-related events	High risk	Causation of SAEs not independently assessed
Incomplete outcome data (attrition bias) All outcomes	Low risk	432/502 (86% completed study)
Selective reporting (reporting bias)	Low risk	Full data on GlaxoSmithKline website

Katial 2011

Methods	A 52-week, randomised, double-blind, parallel-group study of fluticasone propionate/salmeterol combination product 250/50 μg twice daily and fluticasone propionate Diskus 250 twice daily in treatment of participants with asthma, at 61 centres in North and South America, Canada, and the Philippines, from May 2007 to May 2009
Participants	**Population:** 621 adults and adolescents (12+ years) with asthma that was not controlled on ICS at low dose (with or without LABA), or at medium dose without LABA; clinical diagnosis of asthma, defined by the ATS, for $\geq$ 6 months before screening **Baseline characteristics:** mean age 38 years; FEV$_1$ 74% predicted Concomitant ICS used by 100% of participants **Inclusion criteria:** participants were required to have treatment with a low to medium dose of ICS or combination ICS/LABA controller medications if the ICS was given at a low dose for $\geq$ 4 weeks before screening; must have reported being symptomatic while taking controller medication in the 4 weeks before screening **Exclusion criteria:** life-threatening asthma in the 12 months before screening; seasonal or exercise-induced asthma without other manifestations of persistent asthma; concurrent respiratory disease or any other significant concurrent condition/disease; patients

	were excluded if they had worsening asthma in the 4 weeks before screening, including an emergency room visit, hospitalisation, or use of oral/ parenteral corticosteroid. Concurrent use of medications that could have affected the course of asthma or interacted with study medication was prohibited
Interventions	• Fluticasone propionate and salmeterol 250/50 μg twice daily • Fluticasone 250 μg twice daily Delivery device Diskus
Outcomes	**Primary outcome:** FEV_1 over a 52-treatment week period. SAE data fully reported in the published paper and in the GlaxoSmithKline Web report (ADA109055)
Notes	Sponsored by GSK. ClinicalTrials.gov identifier NCT00452699 (identical design to Kerwin 2011)

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Not described
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding (performance bias and detection bias) All outcomes	Low risk	"Double-blind"
Independent Assessment of causation (detection bias) Asthma-related events	High risk	Causation of SAEs not independently assessed
Incomplete outcome data (attrition bias) All outcomes	High risk	81/306 on fluticasone propionate/salmeterol and 73/315 on fluticasone propionate withdrew. Of these, 14 and 4, respectively, withdrew due to adverse events or lack of efficacy
Selective reporting (reporting bias)	Low risk	SAE data fully reported

Kavuru 2000

Methods	A randomised, double-blind, double-dummy, parallel-group, placebo-controlled study over 12 weeks at 42 centres in the USA. Run-in 2 weeks single-blind placebo
Participants	**Population:** 356 adolescents and adults (12 to 70 years) with asthma **Baseline characteristics:** mean age 37 years; FEV_1 64% predicted Concomitant ICS used by 100% of participants in group 1 and 0% of participants in

	group 2 **Inclusion criteria:** at least 12 years old with medical history of asthma (as defined by the ATS) of at least 6 months' duration; FEV_1 % predicted between 40% and 85%; bronchodilator reversibility by an increase $\geq$ 15% in FEV_1 over baseline 30 minutes after 2 puffs (180 μg) of inhaled albuterol Stratified into 2 groups according to type of asthma therapy used at enrolment **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 previous month; use of intranasal corticosteroid therapy except for Flonase (GlaxoWellcome Inc.); use of daily oral corticosteroid treatment within 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	• Fluticasone propionate and salmeterol 100/50 μg twice daily • Fluticasone 100 μg twice daily Delivery was Diskus inhaler
Outcomes	Mean morning pre-dose FEV_1 at endpoint; area under 12-hour serial FEV_1 curve relative to baseline after I week of treatment (mean FEV_1 AUC); 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 2 serious adverse events that led to withdrawal. Website records 2 events on fluticasone propionate/salmeterol and 1 event on fluticasone propionate. (Unclear whether the 2 fluticasone propionate/salmeterol events occurred in separate participants, so treated as 1 participant)
Notes	Sponsored by GSK

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Not reported
Allocation concealment (selection bias)	Unclear risk	Not reported
Blinding (performance bias and detection bias) All outcomes	Low risk	Double-blind, double-dummy
Independent Assessment of causation (detection bias) Asthma-related events	High risk	Causation of SAEs not independently assessed
Incomplete outcome data (attrition bias) All outcomes	Low risk	142/182 (78%) completed the study

Kavuru 2000 (*Continued*)

Selective reporting (reporting bias)	Low risk	Data available on GlaxoSmithKline website

Kerwin 2011

Methods	A 52-week, randomised, double-blind, parallel-group study of fluticasone propionate/salmeterol combination product (fluticasone propionate/salmeterol) 250/50 μg twice daily and fluticasone propionate Diskus 250 twice daily in treatment of people with asthma, at 76 centres in North and South America, Canada, and the Philippines, from May 2007 to April 2009
Participants	**Population:** 628 adults and adolescents (12+ years) with asthma that was not controlled on ICS at low dose (with or without LABA), or at medium dose without LABA; clinical diagnosis of asthma, defined by the ATS, for $\geq$ 6 months before screening **Baseline characteristics:** mean age 40 years; FEV_1 74% predicted Concomitant ICS used by 100% of participants **Inclusion criteria:** required to have received treatment with a low to medium dose of ICS or combination inhaled corticosteroid/long-acting $beta_2$-agonist (ICS/LABA) controller medications, if ICS was at a low dose, for $\geq$ 4 weeks before screening; must have reported being symptomatic while taking fluticasone propionate/salmeterol Diskus 100 μg twice daily in the 4 weeks before screening **Exclusion criteria:** life-threatening asthma in the 12 months before screening; seasonal or exercise-induced asthma without other manifestations of persistent asthma, concurrent respiratory disease, or any other significant concurrent condition/disease; patients were excluded if they had worsening asthma in the 4 weeks before screening including an emergency room visit, hospitalisation, or use of oral/ parenteral corticosteroid. Concurrent use of medications that could have affected the course of asthma or interacted with study medication was prohibited
Interventions	• Fluticasone propionate and salmeterol 250/50 μg twice daily • Fluticasone 250 μg twice daily Delivery device Diskus
Outcomes	**Primary outcome:** FEV_1 over a 52-treatment-week period; SAE data fully reported in the published paper and in the GlaxoSmithKline Web report (ADA109057)
Notes	Sponsored by GSK. ClinicalTrials.gov identifier NCT00452348 (identical in design to Katial 2011)

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not described
Allocation concealment (selection bias)	Unclear risk	Not described

Kerwin 2011 (*Continued*)

Blinding (performance bias and detection bias) All outcomes	Low risk	"Double-blind therapy"
Independent Assessment of causation (detection bias) Asthma-related events	High risk	Causation of SAEs not independently assessed
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	79/310 on fluticasone propionate/salmeterol and 84/318 on fluticasone withdrew, but withdrawals were balanced for adverse events and lack of efficacy
Selective reporting (reporting bias)	Low risk	Full SAE data reported in paper and in the GlaxoSmithKline Web report

Koenig 2008

Methods	A randomised, double-blind, multi-centre, parallel-group study over 40 weeks from February 2003 to October 2004, at 55 sites (50 in the USA, 3 in Latin America, 2 in Latvia). Run-in 2 weeks
Participants	**Population:** 466 adolescents and adults (12 to 81 years) with asthma **Baseline characteristics:** mean age 34 years; FEV 78% predicted Concomitant ICS used by 100% of participants **Inclusion criteria:** 12 years of age or older, with a diagnosis of asthma, as defined by the ATS, for ≥ 3 months before visit 1; must have been treated with a short-acting beta -agonist, an anticholinergic, or an allowed ICS at a fixed dosing regimen (within an allowed total daily dose) for at least 4 weeks before screening visit; FEV % predicted between 60% and 95%; bronchodilator reversibility by an increase of ≥ 12% in FEV over baseline within 30 minutes of inhalation of 2 puffs of inhaled albuterol (180 μg) **Exclusion criteria:** pregnancy, life-threatening asthma, hospitalisation attributable to asthma within the last 6 months, current smoker or > 10-pack-year history of smoking, recent (within 2 weeks) upper or lower respiratory tract infection or significant concurrent disease. Medications that could confound evaluation of study treatments or treatment strategies were prohibited before and throughout the study, including inhaled (up to 250 μg fluticasone propionate allowed before randomisation), oral, or parenteral corticosteroids (with the exception of protocol-defined use of oral corticosteroids following second consecutive assignment to highest dose of fluticasone propionate/salmeterol), theophylline or other bronchodilators, leukotriene modifiers, anticholinergics, cromolyn, and nedocromil
Interventions	• Fluticasone propionate and salmeterol 100/50, 250/50, or 500/50 μg twice daily (BHR strategy) • Fluticasone propionate 100, 250, or 500 μg (BHR strategy) • Fluticasone propionate 100, 250, or 500 μg (reference strategy) - data from this arm not used Delivery was Diskus device

Koenig 2008 (*Continued*)

Outcomes	**Primary efficacy variable:** 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 fluticasone propionate$_{BHR}$ treatment group died due to convulsions and cardiac arrest following deep vein thrombosis" Web report indicates 1 participant with SAE related to asthma on fluticasone propionate/salmeterol$_{BHR}$ and 1 with ear infection and sinusitis on fluticasone propionate$_{BHR}$
Notes	Sponsored by GSK

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not reported
Allocation concealment (selection bias)	Unclear risk	Not reported
Blinding (performance bias and detection bias) All outcomes	Low risk	Double-blind
Independent Assessment of causation (detection bias) Asthma-related events	High risk	Causation of SAEs not independently assessed
Incomplete outcome data (attrition bias) All outcomes	Low risk	321/466 (69%) completed the study
Selective reporting (reporting bias)	Low risk	Full data on GlaxoSmithKline website

Koopmans 2006

Methods	A randomised, double-blind, single-centre, parallel-group study over 12 months from September 2000 to December 2003, in the Netherlands. Run-in 4 weeks Study conducted to compare long-term effects on airway inflammation of seretide vs flixotide in adult patients with asthma
Participants	**Population:** 54 adults (19 to 59 years) with mild to moderate persistent allergic asthma **Baseline characteristics:** mean age 32 years; FEV$_1$ 89% predicted Concomitant ICS used by 100% of participants (median dose 600 μg/d) **Inclusion criteria:** between 18 and 50 years of age with reversible airways obstruction, informed consent, allergic to house dust mite, PC20 histamine < 8 mg/mL, FEV$_1$ > 70% predicted **Exclusion criteria:** serious concurrent disease likely to interfere with the study, lower respiratory tract infection, use of antibiotics in the previous 4 weeks

Koopmans 2006 (*Continued*)

Interventions	• Fluticasone propionate and salmeterol 250/50 μg twice daily • Fluticasone propionate 250 μg twice daily Delivery was Diskus device
Outcomes	**Primary efficacy variables:** 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	Sponsored by GSK

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Not reported
Allocation concealment (selection bias)	Unclear risk	Not reported
Blinding (performance bias and detection bias) All outcomes	Low risk	Double-blind
Independent Assessment of causation (detection bias) Asthma-related events	High risk	Causation of SAEs not independently assessed
Incomplete outcome data (attrition bias) All outcomes	Low risk	50/54 (93%) completed the study
Selective reporting (reporting bias)	Low risk	Data available on GSK website

Li 2010

Methods	A randomised, double-blind, double-dummy, 12-week, parallel-group study evaluating the safety of fluticasone propionate/salmeterol 100/50 μg HFA (2 inhalations of 50/25 μg) twice daily compared with fluticasone propionate 100 μg HFA (2 inhalations of 50 μg) twice daily in patients 4 to 11 years of age with persistent asthma. Ran from February 2007 to February 2008, at 25 centres in North America, 13 centres in Latin America, and 18 centres in Europe
Participants	**Population:** 350 children (age 4 to 11 years) with persistent asthma who were symptomatic on an ICS **Baseline characteristics:** 22% were aged 4 to 5 years, and 78% 6 to 11 years. Spacers were used by 78% of children at baseline **Inclusion criteria:** male and female patients 4 to 11 years of age with a diagnosis of asthma requiring ICS for control of asthma symptoms for at least 1 month before

	screening. Patients 6 to 11 years of age were required to have FEV$_1$ ≥ 60% of predicted value, and those 4 and 5 years of age were required to have a clinic AM PEF ≥ 60% of predicted value at the screening visit. Patients also had to demonstrate reversibility ≥ 12% to albuterol over baseline or to have historical documentation of ≥ 12% reversibility within 24 months before the screening visit **Exclusion criteria:** life-threatening asthma or hospitalisation for asthma twice or more often in the past year
Interventions	• Fluticasone propionate and salmeterol 100/50 μg HFA (administered as 2 inhalations of 50/25 μg ex-valve strength via HFA MDI) twice daily • Fluticasone propionate 100 μg HFA ex-valve strength, HFA (administered as 2 inhalations ex-valve strength of 50 μg via HFA MDI) twice daily Delivery was via MDI (with spacer if inhalation technique was not well co-ordinated)
Outcomes	Adverse events and serious adverse events on treatment. No fatal events occurred, and 1 participant on fluticasone propionate/salmeterol had a head injury after a fall (reported on the GSK website 25 September 2008, study ID SFA106484, but not found in the paper publication)
Notes	Sponsored by GSK

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Not stated
Allocation concealment (selection bias)	Unclear risk	Not stated
Blinding (performance bias and detection bias) All outcomes	Low risk	"Double-blind, double-dummy"
Independent Assessment of causation (detection bias) Asthma-related events	High risk	Causation of SAEs not independently assessed
Incomplete outcome data (attrition bias) All outcomes	Low risk	93% completed
Selective reporting (reporting bias)	Low risk	Data on GSK website

Lundback 2006

Methods	A randomised, double-blind, parallel-group study over 12 months from August 1997 to December 2002, in Sweden. Run-in 2 months An interventional 3-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 patients at work, restore normal lung function, diminish hyperreactivity, and normalise quality of life?
Participants	**Population:** 282 adults (18 to 70 years) with mild to moderate persistent asthma **Baseline characteristics:** mean age 40 years; FEV_1 93% predicted Concomitant ICS 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 FEV_1) < 8 mg/mL. If AHR was not demonstrated via methacholine challenge, then one of the following: diurnal variability in PEF ≥ 20% on more than 3 days during the last 14 days of the run-in; at least 30% difference between highest and lowest PEF readings during any 7 days in the run-in period; increase ≥ 15% in FEV_1 or PEF after salbutamol inhalation (0.8 mg) **Exclusion criteria:** taking daily doses of ICS > 1200 μg, had experienced ≥ 1 life-threatening exacerbation requiring hospitalisation during previous 12 months, were hypersensitive to beta-agonists or ICS, were pregnant or lactating, had a respiratory tract infection during the 4 weeks before run-in
Interventions	• Fluticasone propionate and salmeterol 250/50 μg twice daily • Fluticasone propionate 250 μg twice daily • Salmeterol 50 μg twice daily Delivery was Diskus device (arm 3 was not used in this review)
Outcomes	**Primary efficacy variable:** requirement for an increased dose of study medication
Notes	Sponsored by GSK

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Not reported
Allocation concealment (selection bias)	Unclear risk	Not reported
Blinding (performance bias and detection bias) All outcomes	Low risk	Double-blind
Independent Assessment of causation (detection bias) Asthma-related events	High risk	Causation of SAEs not independently assessed

Lundback 2006 (*Continued*)

Incomplete outcome data (attrition bias) All outcomes	Low risk	263/282 (93%) completed the study
Selective reporting (reporting bias)	Low risk	Data on GSK website

Malone 2005

Methods	A randomised, double-blind, active-controlled, multi-centre, parallel-group study over 12 weeks from April 2002 to January 2003, at 79 centres (66 in the USA and 13 in Canada). Run-in 2 weeks
Participants	**Population:** 203 children (4 to 11 years) with persistent asthma **Baseline characteristics:** mean age 8 years; FEV$_1$ mean 80% predicted (6 to 11 years); PEF mean 87% predicted (4 to 5 years) Concomitant ICS used by 100% of participants **Inclusion criteria:** 4 to 11 years of age with diagnosis of asthma (ATS definition), who required physician-prescribed treatment for at least 2 months and were taking an inhaled corticosteroid for asthma for at least 1 month before visit 1; FEV$_1$ % predicted between 50% and 95% (6 to 11 years), AM PEF % predicted between 50% and 95% (4 to 5 years). Bronchodilator reversibility by an increase $\geq$ 12% in FEV$_1$ (6 to 11 years) or AM PEF (4 to 5 years) over baseline within 30 minutes of 2 to 4 actuations of albuterol (180 to 360 μg), or with historical documentation of $\geq$ 12% reversibility within the previous year **Exclusion criteria:** history of life-threatening asthma; hospitalisation due to asthma twice or more often in the previous year; significant concurrent disease (e.g. cystic fibrosis, malignancy, immunological compromise); recent upper or lower respiratory tract infection; current chickenpox or recent exposure to chickenpox in a non-immune patient; severe milk protein allergy; hypersensitivity to beta$_2$ -agonist, sympathomimetic, or corticosteroid therapy; clinically significant abnormal laboratory test results
Interventions	• Fluticasone propionate and salmeterol 100/50 μg twice daily • Fluticasone propionate 100 μg twice daily Delivery was Diskus device.
Outcomes	This was a safety study, and no primary efficacy endpoint was identified No SAEs occurred in this study
Notes	Sponsored by GSK

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Not reported
Allocation concealment (selection bias)	Unclear risk	Not reported

Malone 2005 (*Continued*)

Blinding (performance bias and detection bias) All outcomes	Low risk	Double-blind
Independent Assessment of causation (detection bias) Asthma-related events	High risk	Causation of SAEs not independently assessed
Incomplete outcome data (attrition bias) All outcomes	Low risk	168/203 (83%) completed the study
Selective reporting (reporting bias)	Low risk	Full data on GSK website

Mansfield 2017

Methods	A 26-week, open-label, randomised, active drug-controlled trial with a 14-day run-in period
Participants	**Population:** 758 participants with persistent asthma were enrolled **Baseline characteristics:** mean age ranged from 38.4 to 46.1 years; mean baseline FEV$_1$ ranged from 2.31 to 2.70 L **Inclusion criteria:** those with FEV$_1$ > 40% of relevant predicted value, those already on an established treatment regimen of SABA for use as needed and either a mid- or high-dose ICS or ICS/LABA combination as preventive therapy for over 8 weeks, those with demonstrated reversibility of FEV$_1$ > 12% within 30 minutes after short-acting beta-agonist administration **Exclusion criteria:** treatment with low-dose ICS without LABA, history of life-threatening asthma exacerbation, asthma exacerbation within 30 days of screening, hospitalisation for asthma 2 months before screening, use of immunosuppressive medications 4 weeks before screening, documented or suspected bacterial or viral infection within 2 weeks of screening, any illness that in the judgement of investigators would put the patient at risk during the study, current smokers and those with a 10-pack-year smoking history, patients who used tobacco products within the past year
Interventions	• Fluticasone propionate and salmeterol given as a multi-dose dry powder inhaler at doses of 100 μg/12.5 μg or 200 μg/12.5 μg twice daily, or via a dry powder inhaler at doses of 250 μg/50 μg or 500 μg/50 μg twice daily • Fluticasone propionate given as a multi-dose dry powder inhaler at doses of 100 μg or 200 μg twice daily, or in a hydrofluoroalkane inhaler at doses of 220 μg or 440 μg twice daily
Outcomes	**Primary outcome:** change from baseline in morning trough FEV$_1$ over the 26-week treatment period
Notes	Sponsored by Teva Pharmaceuticals
Risk of bias	

Mansfield 2017 (*Continued*)

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Methods used for sequence generation were not clearly reported - only that participants were randomised
Allocation concealment (selection bias)	Unclear risk	Methods used for allocation concealment were not clearly reported
Blinding (performance bias and detection bias) All outcomes	High risk	This was an open-label study
Independent Assessment of causation (detection bias) Asthma-related events	High risk	No report of independent assessment of SAEs
Incomplete outcome data (attrition bias) All outcomes	Low risk	Attrition was below 80%, and all participants randomised were available for the safety study, even if they did not complete the full study
Selective reporting (reporting bias)	Low risk	Data were extracted for all outcomes of the review

MASCOT 2013

Methods	A prospective, controlled, double-blind, multi-centre, randomised clinical trial lasting 48 weeks, with a 4-week open run-in
Participants	**Population:** 63 children aged 6 to 14 years with asthma uncontrolled on low-dose ICSs were randomised **Baseline characteristics:** average age of children included was 10.39 years; 63.5% were male **Inclusion criteria:** children who required frequent short-acting beta$_2$ -agonist relief therapy: $\geq$ 7 puffs in the past 7 days; children with symptoms of asthma (i.e. wheeze, shortness of breath but not cough alone) that resulted in (I) nocturnal wakening in the last week and/or (ii) interference with usual activities in the last week and/or (iii) exacerbations, defined as a short course of oral corticosteroids, an unscheduled general practitioner or accident and emergency (A&E) department visit, or a hospital admission within the past 6 months **Exclusion criteria:** children who received long-acting beta$_2$ -agonists, leukotriene receptor antagonists, regular theophylline therapy, or high-dose ICSs (> 1000 μg) and unlicensed beclomethasone dipropionate or equivalent (at the discretion of the investigator); also children with other respiratory diseases, cystic fibrosis, cardiac disease, or immunological disorders

Interventions	During the 4-week run-in period, all patients were commenced on fluticasone propionate inhalers (Flixotide, GSK) at 200 μg per day (100 μg twice daily). Children who remained symptomatic at the end of the run-in period were randomised to 1 of 3 double-blind treatment regimens. • Inhaled fluticasone propionate 100 μg and salmeterol 50 μg twice daily (combination inhaler) plus placebo tablet once daily • Inhaled fluticasone propionate 100 μg twice daily plus placebo tablet once daily • Inhaled fluticasone propionate 100 μg twice daily plus montelukast 5-mg tablet once daily (this arm was not used in the review)
Outcomes	**Primary outcome:** number of asthma exacerbations requiring treatment with oral corticosteroids over the planned 48-week study period **Secondary outcomes:** number of hospital admissions due to respiratory problems and adverse events
Notes	Funded by NIHR Health Assessment Technology Programme

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomisation code lists were generated (by an individual at the MCRN CTU who was not involved with the MASCOT trial) with the software package Stata (Release 9, StataCorp LP, College Station, TX, USA) using block randomisation with variable block length, stratified by secondary care centre, with allocation to the 3 treatment arms in the ratio 1:1:1
Allocation concealment (selection bias)	Low risk	The pharmacy at each secondary care centre held the randomisation list for that centre, with treatment allocations labelled A, B, and C. After determining a participant's treatment allocation from the list, the pharmacist selected an appropriate treatment pack and removed a serrated label showing A, B, or C before dispensing to the participant
Blinding (performance bias and detection bias) All outcomes	Low risk	Study drugs were identical in appearance and were identically packaged, with all patients, clinicians, and trial personnel blinded to treatment allocation throughout
Independent Assessment of causation (detection bias) Asthma-related events	High risk	Independent assessment of causation was not clearly described

Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Early trial closure due to difficulty in recruiting makes the effect of attrition bias due to the small sample size unclear
Selective reporting (reporting bias)	Low risk	Adverse events and hospitalisations were reported

Murray 2004

Methods	A randomised, double-blind, active-controlled, multi-centre, parallel-group study over 12 weeks from November 1999 to September 2000, at 33 centres in the USA. Run-in 2 weeks, single-blind placebo
Participants	**Population:** 267 adolescents and adults (12 to 73 years) with persistent asthma **Baseline characteristics:** mean age 34 years; FEV1 66% predicted Concomitant ICS used by 0% of participants **Inclusion criteria:** 12 years of age or older with a 6-month history of asthma; must have been treated with as-needed SABA alone during the previous month with no oral or ICS use within 1 month, or LABA within 72 hours of study entry; FEV1 % predicted between 40% and 85%; bronchodilator reversibility by an increase ≥ 15% in FEV1 over baseline within 30 minutes of inhalation of 2 puffs (180 μg) of albuterol **Exclusion criteria:** pregnancy and/or lactation, life-threatening asthma, hospitalisation attributable to asthma twice or more in the last year, current smoker or > 10-pack-year history of smoking, significant concurrent disease 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	• Fluticasone propionate and salmeterol 100/50 μg twice daily • Fluticasone propionate 100 μg twice daily Delivery Diskus
Outcomes	**Primary efficacy variables:** mean change from baseline in AM predose FEV1 at endpoint for fluticasone propionate/salmeterol 100/50 compared to salmeterol 50; area under the serial FEV1 curve at treatment week 12 relative to treatment day 1; baseline for fluticasone propionate/salmeterol 100/50 compared to fluticasone propionate 100
Notes	Sponsored by GSK

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Treatment assignments were generated in blocks of 6 by a computer-based random codes system

Murray 2004 (*Continued*)

Allocation concealment (selection bias)	Unclear risk	Not stated
Blinding (performance bias and detection bias) All outcomes	Low risk	Double-blind
Independent Assessment of causation (detection bias) Asthma-related events	High risk	Causation of SAEs not independently assessed
Incomplete outcome data (attrition bias) All outcomes	Low risk	228/267 (85%) completed the study
Selective reporting (reporting bias)	Low risk	Full data on GSK website

Nathan 2006

Methods	A parallel-group, multi-centre study over 12 weeks
Participants	365 adults and adolescents randomised **Age range:** 12 to 82 years; mean FEV_1 68% predicted **Inclusion criteria:** fluticasone propionate 440 to 660 μg/d for $\geq$ 3 months before study entry; FEV_1 40% to 85%; reversibility $\geq$ 15%
Interventions	Fluticasone propionate and salmeterol HFA 110/42 twice daily (220/84) vs CFC salmeterol 42 twice daily (84) vs CFC fluticasone 110 twice daily (220) vs HFA placebo **Inhaler devices:** MDI **Run-in:** 2 weeks This review includes only data from the fluticasone propionate and salmeterol and fluticasone arms **Co-interventions:** ICS at usual dose was an inclusion criterion, but it appears to have been withdrawn in the salmeterol and placebo arms of the study
Outcomes	The paper publication mentions 1 drug-related SAE (an upper gastrointestinal bleed from the placebo group) **Website:** SAS30004 No fatal SAE. No SAE on fluticasone propionate/salmeterol or fluticasone propionate
Notes	Sponsored by GSK

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Not stated
Allocation concealment (selection bias)	Unclear risk	Not stated

Nathan 2006 (*Continued*)

Blinding (performance bias and detection bias) All outcomes	Low risk	Double-blind
Independent Assessment of causation (detection bias) Asthma-related events	High risk	Causation of SAEs not independently assessed
Incomplete outcome data (attrition bias) All outcomes	Low risk	243/365 (67%) completed the study; no SAEs occurred
Selective reporting (reporting bias)	Low risk	Full data on GSK website

NCT01192178

Methods	A randomised, double-blind, 16-week, parallel-group study in paediatric patients from 2 August 2010 to 16 December 2010, at 39 centres in the USA
Participants	**Population:** 339 children (4 to 11 years) with persistent asthma who were symptomatic on an ICS **Baseline characteristics:** 22% aged 4 to 5 years; 78% 6 to 11 years. Spacers were used by 78% of children at baseline **Inclusion criteria:** male and female children 4 to 11 years of age with diagnosis of asthma requiring an ICS for control of asthma. Patients were required to have an AM PEF $\geq$ 70% of predicted value at the screening visit. Patients also had to have a history of $\geq$ 1 exacerbation of asthma during the previous respiratory viral season that required use of outpatient systemic corticosteroids or an urgent care visit, an emergency room visit, or hospitalisation **Exclusion criteria:** life-threatening asthma, unstable asthma, evidence of concurrent respiratory disease, history of any upper or lower respiratory tract infection within 4 weeks of randomisation that required use of an antibiotic or was accompanied by worsening asthma, other clinically significant medical conditions
Interventions	• Fluticasone propionate and salmeterol Diskus 100/50 μg, 1 inhalation twice daily • Fluticasone propionate Diskus 100 μg, 1 inhalation twice daily, for 16 weeks
Outcomes	**Primary outcome:** number of exacerbations of asthma during the double-blind period. No deaths were reported; 2 children suffered SAEs on fluticasone propionate/salmeterol (1 was status asthmaticus) and 1 child suffered an SAE (syncope) on fluticasone propionate
Notes	Sponsored by GSK

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**

NCT01192178 (*Continued*)

Random sequence generation (selection bias)	Unclear risk	Not stated
Allocation concealment (selection bias)	Unclear risk	Not stated
Blinding (performance bias and detection bias) All outcomes	Low risk	"Double-blind"
Independent Assessment of causation (detection bias) Asthma-related events	High risk	Causation of SAEs not independently assessed
Incomplete outcome data (attrition bias) All outcomes	Low risk	86% in both groups completed treatment
Selective reporting (reporting bias)	Low risk	Full data on GSK website

Nelson 2003

Methods	A randomised, double-blind, active-controlled, parallel-group study over 12 weeks, at 33 centres in the USA. Run-in 2 weeks (run-in was single-blind placebo)
Participants	**Population:** 283 adolescents and adults (12 to 77 years) with asthma **Baseline characteristics:** mean age 32 years; FEV$_1$ 66% predicted Concomitant ICS used by 0% of participants **Inclusion criteria:** at least 12 years old with medical history of asthma (as defined by the ATS) requiring asthma pharmacotherapy for at least 6 months; FEV$_1$ % predicted between 40% and 85%; bronchodilator reversibility by an increase $\geq$ 15% in FEV$_1$ over baseline within 30 minutes after 2 inhalations of inhaled albuterol (180 μg) **Exclusion criteria:** history of life-threatening asthma; hypersensitivity reaction to sympathomimetic drugs or corticosteroids; smoking within previous year or history of > 10 pack-years; use of oral, inhaled, or injectable corticosteroid therapy within previous month; use of intranasal corticosteroid therapy except for Flonase (GlaxoWellcome Inc.); use of daily oral corticosteroid treatment within 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 history of significant concurrent disease (e.g. glaucoma, diabetes, hypertension)
Interventions	• Fluticasone propionate and salmeterol 100/50 μg HFA twice daily • Fluticasone propionate 100 μg CFC twice daily • Salmeterol 502 μg CFC twice daily (not considered in this review) Delivery was MDI
Outcomes	**Primary efficacy measures:** area under the serial FEV$_1$ curve for 12 hours following administration of study medication; change from baseline at endpoint in morning predose FEV$_1$

Nelson 2003 (*Continued*)

	The paper reports: "no serious drug related adverse events"
Notes	Sponsored by GSK

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not reported
Allocation concealment (selection bias)	Unclear risk	Not reported
Blinding (performance bias and detection bias) All outcomes	Low risk	Double-blind
Independent Assessment of causation (detection bias) Asthma-related events	High risk	Causation of SAEs not independently assessed
Incomplete outcome data (attrition bias) All outcomes	Low risk	257/283 (91%) completed the study
Selective reporting (reporting bias)	Low risk	Full data on GSK website

Pearlman 2004

Methods	A randomised, double-blind, active-controlled, parallel-group study over 12 weeks, at 36 centres in the USA and 1 centre in Puerto Rico
Participants	N = 360. Fluticasone propionate/salmeterol arm n = 92, fluticasone propionate arm n = 89 **Population:** males and females 12 years of age or older with a diagnosis of asthma, using the ATS definition, were screened. All patients were required to have FEV1 40% to 85% predicted normal and > 15% reversibility following 2 puffs of ventolin at screening. Study population was stratified according to whether or not participants were treated with ICS or inhaled beta2 -agonists at screening (salmeterol or short-acting beta2 -agonists only). Patients treated with ICS must have been treated for at least 3 months before visit 1 and must have been receiving a daily dose of 252 to 336 μg beclomethasone dipropionate, 600 to 800 μg triamcinolone acetonide, 1000 μg flunisolide, 400 to 600 μg budesonide, 176 μg fluticasone propionate inhalation aerosol, or 200 μg fluticasone propionate inhalation powder for at least 1 month before visit 1 with no change in regimen. Eligible patients using only as-needed short-acting beta-agonist therapy were required to have received treatment for at least 1 week before visit 1 with a 7-day total symptom score > 7 for the 7 days before visit 2. Eligible patients using salmeterol at baseline were required to have received only salmeterol and as-needed, short-acting beta2 -agonists for at least 1 week before visit 1. No details were provided on distribution between groups.

Pearlman 2004 (*Continued*)

	Participants were described as symptomatic. Baseline medication included prn SABA alone - 142; salmeterol - 84; and ICS - 134 (37%)
Interventions	• Fluticasone propionate and salmeterol 100/50 μg twice daily • Fluticasone 100 μg twice daily The other treatment arms were not used for this review
Outcomes	Paper reports no serious drug-related adverse events **Website:** SAS3003. No fatal SAEs in the fluticasone propionate/salmeterol or fluticasone propionate group. One tachyarrhythmia on fluticasone propionate
Notes	Sponsored by GSK

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Not stated
Allocation concealment (selection bias)	Unclear risk	Not stated
Blinding (performance bias and detection bias) All outcomes	Low risk	Double blind
Independent Assessment of causation (detection bias) Asthma-related events	High risk	Causation of SAEs not independently assessed
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	279/360 (77%) completed the study
Selective reporting (reporting bias)	Low risk	Data on GSK website

Ploszczuk 2014

Methods	A randomised, double-blind, parallel-group, multi-centre study over 12 weeks from March 2012 to November 2013, across multiple sites (Bulgaria, Czech Republic, Hungary, India, Poland, Romania, Russian Federation, Ukraine). Run in 2 to 4 weeks of ICS
Participants	**Population:** 512 children 5 to < 12 years of age with asthma **Baseline characteristics:** 66% males, 33% females included in the study **Inclusion criteria:** male and female children 5 to < 12 years of age with a known history of moderate to severe persistent reversible asthma for $\geq$ 6 months before screening visit, FEV_1 $\geq$ 60% to $\leq$ 90% predicted during the screening period followed by appropriate withholding of asthma medications (no LABA within 12 hours and/or no SABA within 6 hours of PFT; no ICS on the day of screening), documented reversibility $\geq$ 15% FEV

	in the screening period, current ICS use at a stable dose for ≥ 4 weeks before screening, inadequate asthma control on ICS alone at ≤ 500 µg fluticasone equivalents per day or controlled asthma on ICS-LABA combination at ICS dose ≤ 200 µg fluticasone equivalents per day, demonstrated satisfactory pMDI and spacer technique, adequate spirometry performed, willing and able to add information in electronic diary with help of parent or guardian, attending all study visits, willing and able to substitute pre-study inhaler medication for entire study duration; if female post menarche, a urine pregnancy test may be undertaken at the discretion of the investigator and parents/legal representative (test must be negative); written informed consent and assent obtained as per national law **Exclusion criteria:** near fatal or life-threatening asthma within past year (including intubation), hospitalisation or emergency visit for asthma within past 6 months, history of systemic (injectable/oral) corticosteroid medication within 1 month of screening visit, current or prior non-response or partial response only to ICS/LABA combination, evidence of clinically unstable disease (determined by medical history, clinical laboratory tests, physical examination), clinically significant upper and lower respiratory infection within 4 weeks before screening, significant non-reversible active pulmonary disease, known HIV positive status, current smoking history within 12 months before screening, current alcohol//substance abuse within 12 months before screening, beta-blocking agents, tricyclic antidepressants, monoamine oxidase inhibitors, astemizole (Hismanal) , quinidine-type antiarrhythmics, or potent CYP 3A4 inhibitors such as ketoconazole within 1 week before screening; current use of medications that may affect outcomes of study; hypersensitivity/idiosyncratic reactions to test medications/components; investigational medicinal product within 30 days of screening; current participation in a clinical study
Interventions	• Fluticasone propionate and salmeterol 100/50 µg twice daily (total 200/100 µg/d) • Fluticasone propionate 100 µg twice daily (total 200 µg/d) • Fluticasone propionate /formoterol 100/10 µg twice daily (total 200/20 µg/d); this arm was not used in the analysis of this review
Outcomes	**Primary efficacy variables:** change from baseline in pre-dose to 2 hour post-dose FEV over 12 weeks Safety and tolerability profiles were reported to be similar in all treatment groups, but data were not reported
Notes	This is a conference abstract that was also published in another journal (Ploszczuk 2014a) This trial was published at clinicatrials.gov and EudraCT websites. Sponsored by Mundipharma Research Ltd

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Not clearly reported but trial was conducted for regulatory purposes
Allocation concealment (selection bias)	Low risk	Randomisation schedule was filed securely by Interactive response technology

Ploszczuk 2014 (*Continued*)

Blinding (performance bias and detection bias) All outcomes	Low risk	Blinding was properly maintained throughout the study. Each participant received 2 inhalers (double-dummy)
Independent Assessment of causation (detection bias) Asthma-related events	High risk	No independent assessment of causation was reported
Incomplete outcome data (attrition bias) All outcomes	Low risk	All participants who took at least 1 dose of treatment were included in the safety analysis
Selective reporting (reporting bias)	Low risk	Serious adverse events were reported on the EU Clinical Trials register

Raphael 2017

Methods	A randomised, double-blind, multi-centre, parallel-group, placebo-controlled phase 3 study carried out over 12 weeks
Participants	**Population:** 787 adults and older children (> 12 years old) with persistent asthma previously treated with low- or mid-dose inhaled corticosteroids (ICSs) or ICS/long-acting beta-agonists were enrolled in this study; 647 were randomised **Baseline characteristics:** mean age was 41.5 years; 71% of participants were receiving inhaled glucocorticoids at baseline, and 29% were receiving combined ICS/LABA; 44% of the cohort was male and 80% white **Inclusion criteria:** at the screening visit, patients were required to have FEV$_1$ 40% and 85% of predicted value for age, height, sex, and race, as per National Health and Nutrition Examination Survey III reference values. Previous treatment had to include low- or mid-dose ICS or ICS/LABA for at least 1 month before consent was obtained (those taking ICS/LABA were required to have a pre-screening visit to change to a comparable dose of ICS monotherapy). All patients were required to be able to replace their current SABA with albuterol/salbutamol HFA MDI inhalation aerosol at the screening visit for use as required for the duration of the study. Participants were to withhold all inhaled SABA bronchodilators for at least 6 hours before all study visits. In addition, participants had to demonstrate reversibility of disease (15% reversibility (all participants) and 200-mL increase (participants 18 years old) from baseline FEV$_1$) within 30 minutes following SABA administration at the screening visit **Exclusion criteria:** history of life-threatening asthma exacerbation; asthma exacerbation requiring systemic corticosteroids 30 days before the screening visit, any hospitalisation for asthma 2 months before the screening visit
Interventions	• Fluticasone propionate and salmeterol (50 or 100 fluticasone propionate/12.5 μg salmeterol) twice daily • Fluticasone propionate (50 or 100 μg) twice daily A novel inhalation-driven device (multi-dose dry powder inhaler (MDPI); Teva Pharmaceuticals, Inc., Frazer, PA) was used to administer all doses of the interventions

Outcomes	Safety was assessed by monitoring of vital signs, physical and oropharyngeal examinations, ECGs, concomitant medication usage, and adverse events (AEs). All AEs were coded using the *Medical Dictionary for Research Activities,* version 17.10, preferred terms. Participants who demonstrated oropharyngeal signs consistent with oral candidiasis were to have a culture to confirm the diagnosis. SAEs were defined as an AE occurring at any dose that resulted in death, a life-threatening AE, inpatient hospitalisation or prolongation of existing hospitalisation, persistent or significant disability or incapacity, or a congenital anomaly or birth defect. Asthma exacerbations, defined as any worsening of asthma requiring an emergency department visit or hospitalisation, were documented
Notes	Sponsored by Teva Pharmaceuticals

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Study states: "At the randomisation visit, patients were randomized to one of the five treatment groups in equal proportions" but does not specify how they were assigned to each treatment group"
Allocation concealment (selection bias)	Unclear risk	No details
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Reported to be carried out in a double-blind manner, but further information detailing how this was maintained throughout the study was not readily available in this publication It appears that blinding was maintained throughout the intervention and follow-up period, but again it is unclear how this was done
Independent Assessment of causation (detection bias) Asthma-related events	High risk	No clearly documented independent assessment of causation
Incomplete outcome data (attrition bias) All outcomes	Low risk	Reasons for participant withdrawal were clearly stated and discussed in the Results section: "AEs were the most frequent reason for study withdrawal, occurring in 12 patients overall, including six patients in the placebo group. Another 10 patients withdrew due to disease progression or lack of efficacy, including six in the placebo group" with overall attrition rates relatively low in both arms of the study - 6.5% for

		fluticasone propionate and 4.2% for FS, respectively, from a relatively large population (N = 787). Safety data were reported for all included participants bar 6 people, with details as to why they were not reported made clear
Selective reporting (reporting bias)	Low risk	Study was registered with an NCT number and had clearly prespecified primary and secondary outcomes. Data for safety outcomes were clearly reported and were easily accessible

Renzi 2010

Methods	A 24-week, multi-centre, randomised, double-blind, parallel-group trial to compare the efficacy and tolerability of salmeterol/fluticasone propionate (ADVAIR®) Diskus inhalation device 50/100 μg twice daily vs fluticasone propionate Diskus inhalation device 100 μg twice daily as initial maintenance treatment in adult and adolescent patients with symptomatic persistent asthma not controlled on short-acting bronchodilators alone
Participants	**Population:** 532 adults and adolescents (12+ years) with a documented history of asthma treated with SABA only **Inclusion criteria:** male and female patients ≥ 12 years of age with a documented history of asthma treated with SABA only and with FEV ≥ 80% predicted were eligible for recruitment to the 2-week run-in period. They were recruited to the trial if they were symptomatic for the last 7 days of run-in on SABA alone **Exclusion criteria:** key exclusion criteria were use of asthma controller medications in the previous month or systemic corticosteroids in the previous 12 weeks; exacerbations requiring emergency room treatment in the previous 6 weeks or hospitalisation in the previous 12 weeks; smoking history of ≥ 10 pack-years
Interventions	• Fluticasone propionate and salmeterol 100/50 μg twice daily • Fluticasone 100 μg twice daily Delivery device Diskus
Outcomes	Change in morning PEF over 24 weeks; SAEs fully reported in paper and in GSK Web report (SAS40068)
Notes	Sponsored by GSK

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Not described

Renzi 2010 (*Continued*)

Allocation concealment (selection bias)	Unclear risk	Not described
Blinding (performance bias and detection bias) All outcomes	Low risk	"Double-blind"
Independent Assessment of causation (detection bias) Asthma-related events	High risk	Causation of SAEs not independently assessed
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	53/262 on fluticasone propionate/salmeterol and 46/270 on fluticasone propionate lost to follow-up (withdrawn due to adverse events, 6 and 11, respectively)
Selective reporting (reporting bias)	Low risk	SAEs fully reported in paper and in GSK Web report (SAS40068)

Rojas 2007

Methods	A randomised, double-blind, multi-centre, 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 to 78 years) with moderate persistent asthma **Baseline characteristics:** mean age 41 years; FEV1 72% predicted Concomitant ICS used by 0% of participants **Inclusion criteria:** 12 to 80 years with documented clinical history of persistent asthma for at least 6 months and currently receiving inhaled short-acting beta2 -agonists alone. FEV1 % predicted between 60% and 80%, bronchodilator reversibility by an increase of at least 15% in FEV1 over baseline after 400 μg salbutamol, or a mean morning PEF during the last 7 days of the run-in of < 85% of post-bronchodilator value, and a daytime symptom score $\geq$ 2 on at least 4 of the last 7 days of the run-in **Exclusion criteria:** taken corticosteroids within 12 weeks; LTRA within 4 weeks or long-acting inhaled or oral beta2 -agonists, sodium cromoglycate, nedocromil sodium, ketotifen, methylxanthines, or inhaled anticholinergics within 2 weeks of entering the study; had an acute asthma exacerbation requiring hospital treatment within 6 weeks; had a respiratory tract infection within 4 weeks of entering the study or a smoking history of > 10 pack-years
Interventions	• Fluticasone propionate and salmeterol 250/50 μg twice daily • Fluticasone propionate 250 μg twice daily Delivery was Diskus inhaler
Outcomes	**Primary efficacy variable:** mean morning PEF Paper reports: "Only three serious adverse events occurred and none were considered related to study treatment"

Rojas 2007 (*Continued*)

Notes	Sponsored by GSK	
Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Not reported
Allocation concealment (selection bias)	Unclear risk	Not reported
Blinding (performance bias and detection bias) All outcomes	Low risk	Double blind
Independent Assessment of causation (detection bias) Asthma-related events	High risk	Causation of SAEs not independently assessed
Incomplete outcome data (attrition bias) All outcomes	Low risk	350/362 (97%) completed the study
Selective reporting (reporting bias)	Low risk	Full data on GSK website

SAM30007

Methods	A randomised, 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 comparative investigation of the corticosteroid-saving potential of the combination therapy fluticasone propionate and salmeterol (SERETIDE) vs fluticasone propionate alone, given to adults with asthma, when the ICS dose was reduced from an initially high level of 500 μg twice daily
Participants	**Population:** 61 adults (18+ years) with stable asthma **Baseline characteristics:** mean age 37 years; FEV not reported % predicted Concomitant ICS used by 100% of participants **Inclusion criteria:** at least 18 years old with a clinical diagnosis of stable asthma; treated with 1500 to 2000 μg of budesonide, beclomethasone dipropionate, or flunisolide, or 750 to 1000 μg of fluticasone propionate, for at least 10 weeks before the study; FEV % predicted $\geq$ 60%; had to be able to use the data capture method (electronic diary, AM-2) correctly **Exclusion criteria:** not reported
Interventions	• Fluticasone propionate and salmeterol 500/50, 250/50, or 100/50 μg twice daily • Fluticasone propionate 500, 250, or 100 μg twice daily
Outcomes	**Primary efficacy endpoint:** minimum dose at which the participant's asthma remained controlled - the minimum acceptable dose (MAD)

SAM30007 (*Continued*)

Notes	Sponsored by GSK	
Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Not reported
Allocation concealment (selection bias)	Unclear risk	Not reported
Blinding (performance bias and detection bias) All outcomes	Low risk	Double-blind
Independent Assessment of causation (detection bias) Asthma-related events	High risk	Causation of SAEs not independently assessed
Incomplete outcome data (attrition bias) All outcomes	Low risk	55/61 (90%) completed the study
Selective reporting (reporting bias)	Low risk	Data on GSK website

SAM40004

Methods	A multi-centre, randomised, double-blind, placebo-controlled, parallel-group study to compare effects on airway inflammation and remodelling of treatment with salmeterol/fluticasone propionate combination product (50/100 μg strength) twice daily via the *Accuhaler* inhaler, or fluticasone propionate 100 μg twice daily 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 μg strength) twice daily via the *Accuhaler* inhaler, or fluticasone propionate 100 μg twice daily via the *Accuhaler* inhaler, in adults with reversible airways obstruction (SIRIAS - Seretide in Inflammation and Remodelling In Asthma Study)
Participants	**Population:** 63 adults (18 to 50 years) with mild asthma. **Baseline characteristics:** mean age 32 years; FEV$_1$ unknown % predicted; concomitant ICS 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; received short-acting beta$_2$-agonist alone or beclomethasone dipropionate or budesonide at a constant daily dose of up to 400 μg per day (excluding any CFC-free formulation), or fluticasone propionate at a constant daily dose of up to 200 μg per day via any device for at least 4 weeks before the first visit. In addition, patients had to have had a fall in FEV$_1$ $\geq$ 20% with a histamine challenge test at the first visit and a post-bronchodilator FEV$_1$ > 60% of predicted normal. To be randomised, participants had to have a fall in FEV$_1$ $\geq$ 20% with a standardised histamine challenge test, and at least 1 of the following criteria: recorded symptoms on at least 4 of the last 7 days of the preventer-free run-in

	period; recorded using their inhaled short-acting beta$_2$ -agonist on at least 2 occasions on at least 4 of the last 7 days of the preventer-free run-in period; have a period variation $\geq$ 10% over the last 7 days of the preventer-free run-in period **Exclusion criteria:** not reported
Interventions	• Fluticasone propionate and salmeterol 100/50 μg twice daily throughout • Placebo initially, and then fluticasone propionate/salmeterol 100/50 μg twice daily • Fluticasone propionate 100 μg twice daily throughout Delivery as DPI
Outcomes	**Primary efficacy endpoint:** level of airway hyperreactivity (as measured by histamine PC20); response of induced airway spasm to bronchodilator (post-bronchodilator FEV$_1$) SAE data were used for the 52-week extension period, as reported. No SAEs were reported in the 16-week initial period
Notes	Sponsored by GSK

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Not reported
Allocation concealment (selection bias)	Unclear risk	Not reported
Blinding (performance bias and detection bias) All outcomes	Low risk	Double-blind
Independent Assessment of causation (detection bias) Asthma-related events	High risk	Causation of SAEs not independently assessed
Incomplete outcome data (attrition bias) All outcomes	High risk	37/63 (59%) completed the study
Selective reporting (reporting bias)	Low risk	Data on GSK website

SAM40008

Methods	A multi-centre, randomised, double-blind, parallel-group comparison of the efficacy of SERETIDE* twice daily and fluticasone propionate twice daily (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, United Kingdom)
Participants	**Population:** 186 adults (18+ years) with persistent asthma **Baseline characteristics:** mean age 50 years; FEV_1 unknown % predicted Concomitant ICS used by 100% of participants **Inclusion criteria:** 18 years of age or older with documented evidence of asthma within previous 2 years who were receiving 1500 to 2000 μg/d of BUD or equivalent ICS, excluding fluticasone propionate, for at least 3 months before the start of baseline **Exclusion criteria:** not reported
Interventions	• Fluticasone propionate and salmeterol 500/50 μg twice daily • Fluticasone propionate 500 μg twice daily Delivery as DPI
Outcomes	**Primary efficacy endpoint:** minimum acceptable daily dose of ICS
Notes	Sponsored by GSK. High dropout rate. Only 8% completed the study

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Not reported
Allocation concealment (selection bias)	Unclear risk	Not reported
Blinding (performance bias and detection bias) All outcomes	Low risk	Double-blind
Independent Assessment of causation (detection bias) Asthma-related events	High risk	Causation of SAEs not independently assessed
Incomplete outcome data (attrition bias) All outcomes	High risk	Only 14/186 (8%) completed the study
Selective reporting (reporting bias)	Low risk	Data on GSK website

SAM40012

Methods	A randomised, 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, United Kingdom). Run-in 2 weeks Comparison of 3 treatments: (1) salmeterol/fluticasone propionate (SFC) (50/100 μg strength) twice daily via Diskus/ACCUHALER inhaler, (2) fluticasone propionate 200 μg twice daily via Diskus/ACCUHALER inhaler, (3) fluticasone propionate 100 μg twice daily via Diskus/ACCUHALER inhaler in children aged 4 to 11 years with asthma
Participants	**Population:** 548 children (4 to 11 years) with asthma **Baseline characteristics:** mean age 8 years; FEV1 not reported % predicted Concomitant ICS used by 100% of participants **Inclusion criteria:** aged 4 to 11 years, inclusive, with documented evidence of asthma and receiving BDP, BUD, or equivalent at a dose of 400 to 500 μg/d or fluticasone propionate at a dose of 200 to 250 μg/d for at least 4 weeks before visit 1. Recorded symptom score (i.e. total score of daytime and night-time scores) of at least 2 on the electronic daily record card on at least 3 of the last 7 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 400 μg of salbutamol at the randomisation visit. In addition, patients had to have recorded at least 70% of data into their electronic daily record cards **Exclusion criteria:** not reported
Interventions	• Fluticasone propionate and salmeterol 100/50 μg twice daily • Fluticasone propionate 100 μg twice daily • Fluticasone propionate 200 μg twice daily Delivery was Diskus device (third arm not used in this review)
Outcomes	**Primary efficacy endpoint:** percentage of combined symptom-free days and nights during weeks 1 to 24
Notes	Sponsored by GSK

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not reported
Allocation concealment (selection bias)	Unclear risk	Not reported
Blinding (performance bias and detection bias) All outcomes	Low risk	Double-blind
Independent Assessment of causation (detection bias) Asthma-related events	High risk	Causation of SAEs not independently assessed

SAM40012 (*Continued*)

Incomplete outcome data (attrition bias) All outcomes	Low risk	513/548 (94%) completed the study
Selective reporting (reporting bias)	Low risk	Data on GSK website

SAM40031

Methods	A 1-year, randomised, double-blind, parallel-group comparison of the efficacy of Seretide (fluticasone propionate/salmeterol combination Accuhaler) and Flixotide (fluticasone propionate Accuhaler) when ICS dose is down-titrated in adults with asthma who have previously received Seretide 500/50 μg twice daily for at least 4 weeks Study conducted over 52 weeks from March 2002 to February 2006, at 3 centres in Australia
Participants	**Population:** 82 adolescents and adults (18 to 80 years) with asthma **Baseline characteristics:** mean age 47 years; FEV$_1$ unknown % predicted Concomitant ICS used by 100% of participants **Inclusion criteria:** between 18 and 80 years of age with clinical diagnosis of asthma according to ATS criteria for at least 6 months before enrolment; currently receiving fluticasone propionate/salmeterol via dry powder inhaler or metered dose inhaler (with or without spacer) at a dose of 500/50 μg twice daily or 250/25 μg 2 inhalations twice daily for a minimum of 4 weeks before enrolment **Exclusion criteria:** not reported
Interventions	• Fluticasone propionate and salmeterol 500/50, 250/50, or 100/50 μg twice daily (reduced incrementally) • Fluticasone propionate 500, 250, or 100 μg twice daily (reduced incrementally) Delivery was DPI
Outcomes	**Primary efficacy endpoint:** average daily fluticasone propionate dose (μg/d) from week 0 to completion/withdrawal, including study medication and exacerbation medication
Notes	SAE data included run-in

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Not reported
Allocation concealment (selection bias)	Unclear risk	Not reported
Blinding (performance bias and detection bias) All outcomes	Low risk	Double-blind

SAM40031 (*Continued*)

Independent Assessment of causation (detection bias) Asthma-related events	High risk	Causation of SAEs not independently assessed
Incomplete outcome data (attrition bias) All outcomes	Low risk	60/82 (73%) completed the study
Selective reporting (reporting bias)	Low risk	Data on GSK website

SAM40065

Methods	A randomised, 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 Comparison of asthma control using bronchial hyperresponsiveness as an additional guide to long-term treatment in adolescents and adults receiving fluticasone propionate/ salmeterol Diskus twice daily or fluticasone propionate Diskus twice daily (or placebo twice daily if asymptomatic)
Participants	**Population:** 449 adults (12+ years) with asthma **Baseline characteristics:** mean age 34 years; FEV_1 not reported % predicted Concomitant ICS used by 100% of participants **Inclusion criteria:** 12 years of age or older with diagnosis of asthma, as defined by the ATS, for at least 3 months before visit 1; must have been treated with a SABA, an anticholinergic, or an allowed ICS at a fixed dosing regimen (within an allowed total daily dose) for at least 4 weeks before the screening visit; FEV_1 % predicted between 60% and 95%; bronchodilator reversibility by an increase $\geq$ 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 patient at risk during the study if the condition was exacerbated
Interventions	• Fluticasone propionate and salmeterol 100/50, 250/50, or 500/50 μg twice daily • Fluticasone propionate 100, 250, or 500 μg twice daily (BHR strategy) • Fluticasone propionate 100, 250, or 500 μg twice daily (reference strategy) Delivery was Diskus device (third arm not used in this review)
Outcomes	**Primary efficacy endpoint:** average ICS treatment dose over the treatment period; SAE data included run-in
Notes	Sponsored by GSK

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**

SAM40065 (*Continued*)

Random sequence generation (selection bias)	Unclear risk	Not reported
Allocation concealment (selection bias)	Unclear risk	Not reported
Blinding (performance bias and detection bias) All outcomes	Low risk	Double-blind
Independent Assessment of causation (detection bias) Asthma-related events	High risk	Causation of SAEs not independently assessed
Incomplete outcome data (attrition bias) All outcomes	Low risk	322/449 (72%) completed the study
Selective reporting (reporting bias)	Low risk	Data on GSK website

SAS30021

Methods	A stratified, randomised, 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, randomised, double-blind, placebo-controlled, parallel-group, 12-week trial evaluating the safety and efficacy of the fluticasone propionate/salmeterol Diskus combination product 100/50 μg once daily vs fluticasone propionate Diskus 100 μg once daily and placebo in symptomatic paediatric subjects (4 to 11 years) with asthma
Participants	**Population:** 908 children (4 to 11 years) with asthma **Baseline characteristics:** mean age 8 years; FEV_1 not reported % predicted Concomitant ICS used by 0% of participants **Inclusion criteria:** 4 to 11 years of age with diagnosis of asthma for at least 6 months and treated with SABA only or non-ICS controller medications for at least 1 month before screening; FEV_1 % predicted between 50% and 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, participants were required to demonstrate AM PEF reproducibility of +15% of the screening visit pre-albuterol PEF, to demonstrate a PM PEF 50% to 90% of predicted normal, and to have an asthma symptom score of at least 2 on 4 or more days in the week before randomisation, or to have used albuterol on at least 4 days in the week before randomisation **Exclusion criteria:** not reported
Interventions	• Fluticasone propionate and salmeterol 100/50 μg once daily • Fluticasone propionate 100 μg once daily Delivery was Diskus device
Outcomes	**Primary efficacy endpoint:** change from baseline in % predicted PM PEF over weeks 1 to 12

SAS30021 (*Continued*)

Notes	Sponsored by GSK	
Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Not reported
Allocation concealment (selection bias)	Unclear risk	Not reported
Blinding (performance bias and detection bias) All outcomes	Low risk	Double blind
Independent Assessment of causation (detection bias) Asthma-related events	High risk	Causation of SAEs not independently assessed
Incomplete outcome data (attrition bias) All outcomes	Low risk	715/908 (79%) completed the study
Selective reporting (reporting bias)	Low risk	Data on GSK website

SAS30022

Methods	A randomised, double-blind, placebo-controlled, parallel-group study for 12 weeks from November 2001 to June 2003, at 121 centres (US (103), Canada (18)) A trial evaluating the efficacy and safety of the fluticasone propionate/salmeterol Diskus combination product 250/50 μg once daily vs fluticasone propionate/salmeterol Diskus combination product 100/50 μg twice daily vs fluticasone propionate Diskus 250 μg once daily vs placebo in symptomatic adolescent and adult patients with asthma that is not controlled on short-acting beta$_2$ -agonists alone
Participants	**Population:** 844 adolescents and adults (12+ years) with asthma that was not controlled on SABA alone **Baseline characteristics:** mean age 33 years; FEV$_1$ not reported % predicted Concomitant ICS used by 0% of participants **Inclusion criteria:** 12 years of age or older with diagnosis of asthma for at least 3 months and treated with short-acting beta$_2$ -agonists only for at least 1 month before screening; FEV$_1$ % predicted between 50% and 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, participants were required to demonstrate FEV$_1$ reproducibility of ±15% of the screening visit pre-ventolin FEV$_1$, to demonstrate a PM PEF 50% to 90% of predicted normal, and to have an asthma symptom score $\geq$ 2 on $\geq$ 4 days in the week before randomisation or to have used ventolin on $\geq$ 4 days in the week before randomisation **Exclusion criteria:** not reported

SAS30022 (*Continued*)

Interventions	• Fluticasone propionate and salmeterol 250/50 μg once daily • Fluticasone propionate and salmeterol 100/50 μg twice daily • Fluticasone propionate 250 μg once daily (second arm not used in this review)
Outcomes	**Primary outcome/efficacy variable:** change from baseline in % predicted PM PEF over weeks 1 to 12
Notes	Sponsored by GSK

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Not reported
Allocation concealment (selection bias)	Unclear risk	Not reported
Blinding (performance bias and detection bias) All outcomes	Low risk	Double-blind
Independent Assessment of causation (detection bias) Asthma-related events	High risk	Causation of SAEs not independently assessed
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	698/844 (83%) completed the study
Selective reporting (reporting bias)	Low risk	Data on GSK website

SAS30023

Methods	A randomised, 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) Study to compare the efficacy and tolerability of fluticasone propionate/salmeterol combination (SERETIDE/VIANI/ADVAIR) 88/42 μg once daily in the morning with fluticasone propionate 88 μg once daily in the morning and placebo (short-acting beta $_2$ -agonist as required only) once daily in the morning, all via the HFA MDI as initial maintenance therapy in mild asthmatic patients
Participants	**Population:** 464 adolescents and adults (12 to 80 years) with mild asthma **Baseline characteristics:** mean age 34 years; FEV_1 not reported % predicted Concomitant ICS used by 0% of participants **Inclusion criteria:** documented clinical history of asthma for $\geq$ 6 months who were currently receiving short-acting beta$_2$ -agonists alone

SAS30023 (*Continued*)

	Exclusion criteria: not reported
Interventions	• Fluticasone propionate and salmeterol 50/25 μg 2 puffs once daily • Fluticasone propionate 50 μg 2 puffs once daily Delivery was MDI device with HFA propellant
Outcomes	**Primary efficacy endpoint:** morning PEF
Notes	No SAEs at all were reported in the double-blind phase of the study

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Not reported
Allocation concealment (selection bias)	Unclear risk	Not reported
Blinding (performance bias and detection bias) All outcomes	Low risk	Double-blind
Independent Assessment of causation (detection bias) Asthma-related events	High risk	Causation of SAEs not independently assessed
Incomplete outcome data (attrition bias) All outcomes	Low risk	433/464 (93%) completed the study
Selective reporting (reporting bias)	Low risk	Data on GSK website

SAS40036

Methods	A randomised, double-blind, double-dummy, multi-centre, parallel-group study for 16 weeks from October 2001 to May 2003, at 85 centres in the United States. Run-in 2 weeks
Participants	**Population:** 331 adolescents and adults (15+ years) with persistent asthma **Baseline characteristics:** mean age 41 years; FEV$_1$ not reported (% predicted) Concomitant ICS used by 100% of participants **Inclusion criteria:** 15 years of age or older with diagnosis of asthma, as defined by the ATS, for at least 6 months before visit 1; must have been treated with an allowed ICS at a fixed dosing regimen (within an allowed total daily dose) for at least 4 weeks before the screening visit; FEV$_1$ % predicted between 40% and 85%; bronchodilator reversibility by an increase of $\geq$ 12% in FEV$_1$ over baseline within 30 minutes following 2 to 4 puffs of albuterol inhalation aerosol at the screening visit. Documentation of historical reversibility within 24 months was allowed

SAS40036 (*Continued*)

	Exclusion criteria: not reported
Interventions	• Fluticasone propionate and salmeterol 100/50 μg twice daily • Fluticasone propionate 100 μg twice daily Delivery was Diskus device (other arms of trial not considered for this review)
Outcomes	**Primary efficacy endpoint:** mean change from baseline at endpoint in morning PEF. No SAEs at all were reported in the double-blind phase of the study
Notes	Sponsored by GSK

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Not reported
Allocation concealment (selection bias)	Unclear risk	Not reported
Blinding (performance bias and detection bias) All outcomes	Low risk	Double-blind, double-dummy
Independent Assessment of causation (detection bias) Asthma-related events	High risk	Causation of SAEs not independently assessed
Incomplete outcome data (attrition bias) All outcomes	Low risk	243/331 (73%) completed the study
Selective reporting (reporting bias)	Low risk	Data on GSK website

SAS40037

Methods	A randomised, double-blind, double-dummy, multi-centre, parallel-group study for 16 weeks from October 2001 to May 2003, at 87 centres in the United States. Run-in 2 weeks
Participants	**Population:** 331 adolescents and adults (15+ years) with persistent asthma **Baseline characteristics:** mean age 41 years; FEV_1 not reported (% predicted) Concomitant ICS used by 100% of participants **Inclusion criteria:** 15 years of age or older with diagnosis of asthma, as defined by the ATS, for at least 6 months before visit 1; must have been treated with an allowed ICS at a fixed dosing regimen (within an allowed total daily dose) for at least 4 weeks before the screening visit; FEV_1 % predicted between 40% and 85%; bronchodilator reversibility by an increase of $\geq$ 12% in FEV_1 over baseline within 30 minutes following 2 to 4 puffs of albuterol inhalation aerosol at the screening visit. Documentation of historical

SAS40037 (*Continued*)

	reversibility within 24 months was allowed **Exclusion criteria:** diagnosis of life-threatening asthma, hospitalised for asthma within previous 6 months, concurrent respiratory disease or intermittent or seasonal asthma alone, respiratory tract infection or used antibiotics for treatment of a suspected or diagnosed respiratory tract infection within 14 days of visit 1
Interventions	• Fluticasone propionate and salmeterol 100/50 μg twice daily • Fluticasone propionate 100 μg twice daily Delivery was Diskus device (other arms of trial not considered for this review)
Outcomes	**Primary efficacy endpoint:** mean change from baseline at endpoint in morning PEF
Notes	Sponsored by GSK

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Not reported
Allocation concealment (selection bias)	Unclear risk	Not reported
Blinding (performance bias and detection bias) All outcomes	Low risk	Double-blind, double-dummy
Independent Assessment of causation (detection bias) Asthma-related events	High risk	Causation of SAEs not independently assessed
Incomplete outcome data (attrition bias) All outcomes	Low risk	230/322 (71%) completed the study
Selective reporting (reporting bias)	Low risk	Data on GSK website

SAS40068

Methods	A randomised, double-blind, multi-centre, parallel-group study for 24 weeks from October 2002 to February 2004, at 58 centres in Canada Trial to compare the efficacy and tolerability of salmeterol/fluticasone propionate (*ADVAIR)* Diskus inhalation device 50/100 μg twice daily with fluticasone propionate Diskus inhalation device 100 μg twice daily as initial maintenance treatment in adult and adolescent patients with symptomatic persistent asthma not controlled on short-acting bronchodilators alone

SAS40068 (*Continued*)

Participants	**Population:** 532 adolescents and adults (12+ years) with symptomatic persistent asthma **Baseline characteristics:** mean age 35 years; FEV_1 not reported % predicted Concomitant ICS used by 0% of participants **Inclusion criteria:** 12 years of age or older with symptomatic persistent mild asthma (defined as FEV_1 $\geq$ 80% predicted over the last 7 consecutive days of run-in, asthma symptom score $\geq$ 2 on $\geq$ 3 days, disruptions of normal sleep patterns on $\geq$ 2 occasions, or had used rescue bronchodilator medication on $\geq$ 4 days) treated with inhaled short-acting bronchodilators alone **Exclusion criteria:** taken any other asthma therapy (e.g. ICS, leukotriene modifiers, inhaled long-acting $beta_2$ -agonists) within 1 month before screening, smoking history $\geq$ 10 pack-years, acute asthma exacerbation requiring emergency room treatment within last 6 weeks, or hospitalisation within last 12 weeks before screening
Interventions	• Fluticasone propionate and salmeterol 100/50 μg twice daily • Fluticasone propionate100 μg twice daily Delivery was Diskus device
Outcomes	**Primary efficacy endpoint:** change from baseline in daily record card (DRC) mean morning PEF over 24 weeks One death due to aorta hypoplasia and ventricular hypertrophy on fluticasone
Notes	Sponsored by GSK

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Not reported
Allocation concealment (selection bias)	Unclear risk	Not reported
Blinding (performance bias and detection bias) All outcomes	Low risk	Double blind
Independent Assessment of causation (detection bias) Asthma-related events	High risk	Causation of SAEs not independently assessed
Incomplete outcome data (attrition bias) All outcomes	Low risk	433/532 (81%) completed the study
Selective reporting (reporting bias)	Low risk	Data in GSK website

SFA103153

Methods	A randomised, double-blind, multi-centre, 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 to 65 years) of African descent with persistent asthma **Baseline characteristics:** mean age 32 years; FEV_1 78% predicted Concomitant ICS used by 100% of participants **Inclusion criteria:** patients 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	• Fluticasone propionate and salmeterol 100/50 μg twice daily • Fluticasone propionate 100 μg twice daily Delivery was Diskus device
Outcomes	**Primary efficacy endpoint:** asthma exacerbation rate per patient per year
Notes	Sponsored by GSK

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Not reported
Allocation concealment (selection bias)	Unclear risk	Not reported
Blinding (performance bias and detection bias) All outcomes	Low risk	Double-blind
Independent Assessment of causation (detection bias) Asthma-related events	High risk	Causation of SAEs not independently assessed
Incomplete outcome data (attrition bias) All outcomes	Low risk	320/475 (67%) completed the study
Selective reporting (reporting bias)	Low risk	Data on GSK website

SFCF4026

Methods	A randomised, double-blind, multi-centre, 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 3 therapeutic strategies in patients whose asthma was controlled by a medium dose of inhaled corticosteroid and a long-acting inhaled beta$_2$ -agonist
Participants	**Population:** 476 adolescents and adults (18+ years) with asthma **Baseline characteristics:** mean age 45 years; FEV_1 not reported % predicted Concomitant ICS 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 with asthma controlled by current treatment (inhaled corticosteroid at a dose of 1000 μg of CFC beclomethasone dipropionate or equivalent and a long-acting beta$_2$ -agonist at recommended dose) at a stable dose for $\geq$ 4 weeks before the run-in period. Randomised if fulfilled the following criteria: $\geq$ 2 of the following: diurnal symptoms $\geq$ 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 $\geq$ 80% predicted every day. Plus all of 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 into the run-in period: smoking history of $\geq$ 10 pack-years, respiratory tract infection during the last 4 weeks before visit 1 (the last 2 weeks after amendment number 1), acute asthma exacerbation requiring emergency room treatment or hospitalisation within 4 weeks before visit 1, use of oral/parenteral corticosteroids during the last 4 weeks before 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	• Fluticasone propionate and salmeterol 250/50 μg twice daily • Fluticasone propionate and salmeterol 100/50 μg twice daily • Fluticasone propionate 250 μg twice daily Delivery was Diskus device (arm 2 not used in this review)
Outcomes	**Primary efficacy endpoint:** morning PEF over first 12 weeks of the treatment period
Notes	Sponsored by GSK

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Not reported
Allocation concealment (selection bias)	Unclear risk	Not reported

SFCF4026 (*Continued*)

Blinding (performance bias and detection bias) All outcomes	Low risk	Double-blind
Independent Assessment of causation (detection bias) Asthma-related events	High risk	Causation of SAEs not independently assessed
Incomplete outcome data (attrition bias) All outcomes	Low risk	413/476 (87%) completed the study
Selective reporting (reporting bias)	Low risk	Data on GSK website

Shapiro 2000

Methods	Multi-centre study, USA
Participants	349 adults and adolescents randomised (4-treatment arm study; fluticasone propionate/salmeterol: 84; fluticasone propionate: 84). Data from 13 participants excluded from analysis due to poor procedure at 1 site **Inclusion criteria:** ≥ 12 years of age; ATS-defined asthma of ≥ 6 months' duration requiring pharmacotherapy for ≥ 6 months; FEV_1 between 40% and 85% predicted; ≥ 15% increase in FEV_1 30 minutes after 2 puffs of albuterol; use of ICS 12 weeks before the study **Exclusion criteria:** females with positive pregnancy tests; life-threatening asthma; hypersensitivity to sympathomimetic drugs/steroids; smoking within previous year; smoking history > 10 pack-years; use of oral/injectable steroid therapy within 1 month of study; use of daily OCS within 6 months before the study; use of any prescription or over-the-counter medication that could have affected asthma or course of treatment; abnormal chest x-ray; clinically significant abnormal 12-lead electrocardiogram; history of concurrent disease
Interventions	• Fluticasone propionate and salmeterol 250/50 μg twice daily • Fluticasone 250 μg twice daily Third arm not used in this review
Outcomes	83% in the fluticasone propionate/salmeterol arm and 73% in the fluticasone propionate arm completed the study 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 fluticasone propionate/salmeterol arm; 1 in fluticasone propionate arm (asthma exacerbation)
Notes	Sponsored by GSK
Risk of bias	

Shapiro 2000 (*Continued*)

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not stated
Allocation concealment (selection bias)	Unclear risk	Not stated
Blinding (performance bias and detection bias) All outcomes	Low risk	Double blind
Independent Assessment of causation (detection bias) Asthma-related events	High risk	Causation of SAEs not independently assessed
Incomplete outcome data (attrition bias) All outcomes	Low risk	131/168 (78%) completed the study
Selective reporting (reporting bias)	Low risk	Full data on GSK website

Sher 2017

Methods	A randomised, double-blind, multi-centre, parallel-group study carried out over 12 weeks
Participants	**Population:** 728 adults and older children (> 12 years) with persistent asthma who previously took an ICS with or without a LABA **Baseline characteristics:** mean age was 44.7 years; 45% were receiving inhaled glucocorticoids at baseline and 55% were on combined IC/LABA; 40% of the cohort were male and 81% were white **Inclusion criteria:** patients were eligible if they had FEV_1 of 40% and 85% of predicted value for age, height, sex, and race per National Health and Nutrition Examination Survey III reference values; 15 exhibited 15% reversibility in FEV_1 (all patients) and 200-mL increase in FEV_1 from baseline (patients 12 years of age) within 30 minutes of exposure to a short-acting agonist, and had a treatment regimen that included albuterol or salbutamol for use as needed for 8 weeks before screening and an ICS (either ICS monotherapy or ICS/LABA) at a qualifying dose of fluticasone DPI 200 g/d or equivalent for 1 month. Patients who received ICS/LABA therapy had a pre-screening visit to change to a comparable dose of ICS monotherapy **Exclusion criteria:** history of life-threatening asthma exacerbation, asthma exacerbation that required systemic corticosteroids within 30 days before screening, any hospitalisation for asthma within 2 months before screening
Interventions	• Fluticasone propionate and salmeterol (100 or 200 μg/12.5 μg salmeterol) twice daily • Fluticasone propionate (100 or 200 μg) twice daily A novel, inhalation-driven, multi-dose dry powder inhaler (RespiClick MDPI; Teva Pharmaceuticals, Inc., Frazer, PA) was used in all arms of the study

Outcomes	Safety was assessed by monitoring of vital signs, physical and oropharyngeal examinations, electrocardiograms, concomitant medication usage, and AEs. An SAE was defined as an AE that occurred at any dose and resulted in death, a life-threatening AE, inpatient hospitalisation or prolongation of existing hospitalisation, persistent or significant disability or incapacity, congenital anomaly, or a birth defect. An asthma exacerbation was defined as worsening asthma that required any significant treatment other than study medication or rescue albuterol/salbutamol, including systemic corticosteroids, urgent care and/or emergency department visit, or hospitalisation. An asthma exacerbation was considered an AE only if it met the criteria for an SAE
Notes	Sponsored by Teva Pharmaceuticals

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	"For the double-blind treatment period, the patients were randomized in a 1:1:1:1:1 ratio to one of five double-blind treatment groups"; how they were assigned to each was not specified
Allocation concealment (selection bias)	Unclear risk	No details
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Reported to be carried out in a double-blind manner, but further information detailing how this was maintained throughout the study was not readily available in the publication
Independent Assessment of causation (detection bias) Asthma-related events	High risk	No clear documentation of independent assessment of causation
Incomplete outcome data (attrition bias) All outcomes	Low risk	Clear reasons for participant withdrawal were detailed in the study report: "Overall, 78 patients (11%) discontinued the study, most frequently from the placebo group and most commonly due to disease progression (n=24 [3%]) or lack of efficacy (n 9 [1%])" With attrition rates of 0.3% in the fluticasone propionate treatment arm and 1% in the fluticasone propionate and salmeterol arm in a population of 583 Safety outcomes were reported in all included participants apart from 8 patients, including 2 (1.4%) in the placebo group and 6 (1.0%) in the

Sher 2017 (*Continued*)

		active treatment groups who discontinued due to AEs
Selective reporting (reporting bias)	Low risk	Study was registered with an NCT number and had clearly pre-specified primary and secondary outcomes. All safety-related outcomes were reported and were easily attainable

Slankard 2016

Methods	A randomised, double-blind, multi-centre study conducted in patients with moderate to severe asthma who were being treated with combined inhaled corticosteroids/LABA over 16 weeks
Participants	**Population:** 61 (67 randomised) participants age 18 years or older with physician-diagnosed moderate or severe persistent asthma who were receiving treatment with combined ICS/LABA **Baseline characteristics:** mean age of participants with Arg/Arg genotype (n = 28) was 47.2, and for those with Gly/Gly genotype (n = 33) 43.1. 23% of the Arg/Arg subgroup and 24% of the Gly/Gly subgroup were female. 15% (Arg/Arg) and 17% (Gly/Gly) were of white ethnic origin, and 8% (Arg/Arg) and 10% (Arg/Arg) were of African American origin **Inclusion criteria:** after providing informed consent, all potential study participants underwent genetic screening for beta$_2$ -adrenergic receptor genotype, and those homozygous for the arginine or glycine variant at the 16th amino acid position (Arg/Arg or Gly/Gly) were eligible to participate **Exclusion criteria:** pregnancy at the time of enrolment, active tobacco use or > 10-pack-year history of tobacco use, history of intubation for asthma within past 10 years, FEV_1 < 60% of predicted on screening spirometry before the run-in or < 70% predicted at the randomisation visit, major comorbidity (symptomatic coronary artery disease, ongoing treatment for malignancy, poorly controlled diabetes)
Interventions	• Fluticasone propionate and salmeterol (Advair HFAR, 45 μg, 115 μg, or 230 μg of fluticasone propionate with 21 μg of salmeterol, 2 puffs every 12 hours) • Fluticasone propionate (Flovent HFAR, 44 μg, 110 μg, or 220 μg) twice daily Advair HFA devices were used to deliver ICS/LABA fixed dose and Flovent HFA for fluticasone propionate alone
Outcomes	Participants who experienced more than 2 exacerbations during the course of the study were withdrawn according to pre-determined safety parameters. (Exacerbation is defined in Selected Methods of the Supplementary Appendix.) Adverse events were defined as any untoward events or symptoms reported by the participant, whether related or not related to the study drug
Notes	

Risk of bias

Slankard 2016 (*Continued*)

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"Randomization was carried out by the Columbia University Research Pharmacy using the Microsoft Excel random number generator"
Allocation concealment (selection bias)	Unclear risk	Further details regarding allocation concealment were not described, but it appears that participants were blinded to their allocation
Blinding (performance bias and detection bias) All outcomes	Low risk	"Investigators and research staff were kept blinded to the genotype and study drug assignment. HFA devices were blinded and distributed by the Columbia University Research Pharmacy"
Independent Assessment of causation (detection bias) Asthma-related events	High risk	Independent assessment of causation was not clearly documented
Incomplete outcome data (attrition bias) All outcomes	Low risk	Attrition rates were quite high due to the small overall sample size (N = 90), but most withdrawals occurred following initial (genotype) screening, whereas the level of attrition was much lower following treatment allocations, suggesting this was less likely to influence subsequent outcomes. Furthermore, reasons for withdrawal were clearly detailed in the trial flow chart (Fig. 2 of the paper)
Selective reporting (reporting bias)	Low risk	Study was registered with an NCT number and had clearly pre-specified primary and secondary outcomes. All safety-related outcomes were reported and were easily attainable

SLGF75

Methods	A randomised, double-blind, multi-centre, 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 vs high-dose fluticasone propionate in naive patients with mild to moderate asthma: effects on pulmonary function and inflammatory markers of induced sputum

SLGF75 (*Continued*)

Participants	**Population:** 46 adolescents and adults (16 to 65 years) with mild to moderate asthma **Baseline characteristics:** mean age 39 years; FEV_1 unreported % predicted Concomitant ICS used by 0% of participants **Inclusion criteria:** performed on 3 study visits: • Pre-study visit: all patients with asthma disease for ≥ 6 months • Visit 2: 16 to 65 years old with asthma at moderate level (score of severity ≥ 6), did not use anti-inflammatory drugs for last month before visit 1, FEV_1 % predicted ≥ 60%, eosinophils ≥ 5% in induced sputum • Visit 4: bronchial asthma assessed up to 6 (severity classes value) and with persistence of eosinophils ≥ 5% (or ≥ 3% in sites where an amendment was applicable) in induced sputum **Exclusion criteria:** inhaled steroids or cromones in last 3 months, more than 1 short course of OCS in last 3 months or 1 short course of OCS 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	• Fluticasone propionate 100 + salmeterol 50 μg twice daily • Fluticasone propionate 100 μg twice daily • Fluticasone propionate 250 μg twice daily Delivery was Diskus (third arm not used in this review)
Outcomes	**Primary efficacy endpoint:** daily morning PEF
Notes	Sponsored by GSK

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Not reported
Allocation concealment (selection bias)	Unclear risk	Not reported
Blinding (performance bias and detection bias) All outcomes	Low risk	Double-blind
Independent Assessment of causation (detection bias) Asthma-related events	High risk	Causation of SAEs not independently assessed
Incomplete outcome data (attrition bias) All outcomes	Low risk	42/46 (91%) completed the study
Selective reporting (reporting bias)	Low risk	Data on GSK website

Strand 2004

Methods	A randomised, double-blind, comparative, multi-centre, 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 ICS used by 0% of participants **Inclusion criteria:** at least 18 years old with asthma medical history ≥ 3 months, either diurnal PEF variation 20% on at least 2 days or 1 of the following must have been determined within 3 years before baseline: FEV$_1$ reversibility > 15% in response to bronchodilator, provocative concentration of methacholine causing a 20% fall in FEV$_1$ (PC20) < 4 mg/mL, diurnal PEF variation ≥ 20%; mean relief medication (albuterol) use ≥ 1 episode/week; and daytime or night-time symptom score ≥ 1 at least once per week **Exclusion criteria:** upper or lower respiratory tract infection or middle ear infection within 1 month before visit 1; lung disease other than asthma; known or suspected other diseases or situations likely to affect outcomes or study results; known serious cardiovascular disease, diabetes mellitus, untreated hypokalaemia, or thyrotoxicosis; use of long-acting bronchodilators, ICS, or other long-acting asthma medication within 2 months before visit 1; use of daily oral corticosteroid treatment within 2 months of visit 1 or oral corticosteroid therapy within 1 month before the visit
Interventions	• Fluticasone propionate and salmeterol 100/50 μg twice daily • Fluticasone propionate 100 μg twice daily
Outcomes	**Primary efficacy variable:** symptom-free days and nights "1 patient in the fluticasone propionate/salmeterol group and 2 patients in the fluticasone propionate group had a serious adverse event. None of these serious adverse events was considered related to the study drug" One death reported on the website in the fluticasone propionate/arm but no cause given
Notes	Sponsored by GSK

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not reported
Allocation concealment (selection bias)	Unclear risk	Not reported
Blinding (performance bias and detection bias) All outcomes	Low risk	Double-blind
Independent Assessment of causation (detection bias) Asthma-related events	High risk	Causation of SAEs not independently assessed

Strand 2004 (*Continued*)

Incomplete outcome data (attrition bias) All outcomes	Low risk	126/150 completed the study
Selective reporting (reporting bias)	Low risk	Full data from GSK website

van Noord 2001

Methods	A randomised, double-blind, double-dummy, multi-centre, 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 to 82 years) with moderate to severe asthma **Baseline characteristics:** mean age 47 years; FEV_1 72% predicted Concomitant ICS used by 100% of participants **Inclusion criteria:** 12 years old or older with documented clinical history of reversible airways obstruction and symptomatic on ICS therapy (beclomethasone dipropionate, budesonide, or flunisolide at a dose of 1500 to 2000 μg/d or fluticasone propionate 750 to 1000 μg d) for at least 4 weeks before the start of the study. FEV_1 % predicted between 50% and 100% During the last 7 days of the run-in period, required to have had a mean morning PEF > 50% and < 85% of PEF measured 15 minutes after administration of 400 μg of salbutamol at the randomisation visit, and a cumulative total symptom score (daytime plus night-time) in the daily record card $\geq$ 8 **Exclusion criteria:** received a LABA or an oral $beta_2$ -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, had an acute asthma exacerbation requiring hospitalisation in the 12 weeks preceding study entry
Interventions	• Fluticasone propionate and salmeterol 500/50 μg HFA twice daily via MDI • Fluticasone propionate and salmeterol 500/50 μg HFA twice daily via Diskus • Fluticasone propionate 500 μg CFC twice daily via MDI
Outcomes	**Primary efficacy variable:** mean morning PEF over the 12-week treatment period Paper reports 8 participants with SAE in fluticasone propionate/salmeterol groups and 2 on fluticasone propionate. These included 3 asthma exacerbations. Web report indicates that 2 of these were on fluticasone propionate/salmeterol and 1 on fluticasone propionate One death reported on fluticasone propionate/salmeterol via MDI due to leukaemia
Notes	Sponsored by GSK

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Not stated
Allocation concealment (selection bias)	Unclear risk	Not stated

van Noord 2001 (*Continued*)

Blinding (performance bias and detection bias) All outcomes	Low risk	Double-blind, double-dummy
Independent Assessment of causation (detection bias) Asthma-related events	High risk	Causation of SAEs not independently assessed
Incomplete outcome data (attrition bias) All outcomes	Low risk	447/509 (88%) completed the study
Selective reporting (reporting bias)	Low risk	Full data on GSK website

VESTRI 2016

Methods	A randomised, double-blind, multi-centre, parallel-group study carried out over 26 weeks
Participants	**Population:** 6208 boys or girls aged 4 to 11 attending daycare or school, with persistent asthma and a history of asthma exacerbation in the previous 12 months, with no exacerbation occurring during the 30 days before randomisation **Baseline characteristics:** mean age was 7.6 years; 61.8% were male and 64.3% were white **Inclusion criteria:** consistent use of asthma medication during the 4 weeks before enrolment, and a history of 1 to 4 asthma exacerbations in the past 12 months **Exclusion criteria:** history of life-threatening asthma or unstable asthma; taking high-dose ICS or ICS/LABA; concurrent respiratory disease, respiratory infection, exercise-induced asthma as the only asthma-related diagnosis; asthma exacerbation in previous 4 weeks or > 4 exacerbations in previous 12 months; asthma hospitalisation in previous 4 weeks or > 2 asthma hospitalisations in previous 12 months; clinically significant uncontrolled disease; neurological or psychiatric disease or drug or alcohol abuse (in the patient or the parent/guardian); use of investigational medication; drug allergy; severe hypersensitivity to cow's milk proteins; concomitant medications that could significantly affect the course of asthma; use of potent cytochrome P450 3A4 inhibitors; affiliation with investigator's site; child in care
Interventions	• Fluticasone propionate (100 or 250 μg) twice daily via Diskus • Fluticasone propionate and salmeterol (a fixed-dose combination of 100 μg fluticasone propionate plus salmeterol at a dose of 50 μg or a fixed-dose combination of fluticasone at a dose of 250 μg plus salmeterol at a dose of 50 μg) twice daily via Diskus
Outcomes	**Primary endpoint:** first serious asthma-related event (defined as hospitalisation, intubation, or death)
Notes	Sponsored by GSK

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**

VESTRI 2016 (*Continued*)

Random sequence generation (selection bias)	Low risk	Central randomisation procedure
Allocation concealment (selection bias)	Low risk	Centralised Registration and Medication Ordering System (RAMOS-NG)
Blinding (performance bias and detection bias) All outcomes	Low risk	Double-blind with respect to salmeterol but not to dose of ICS
Independent Assessment of causation (detection bias) Asthma-related events	Low risk	Independent adjudication committee for asthma outcomes
Incomplete outcome data (attrition bias) All outcomes	Low risk	Only 2 children in each group failed to complete the trial
Selective reporting (reporting bias)	Low risk	Data were extracted for all review outcomes

Wallin 2003

Methods	A randomised, double-blind, parallel-group study over 12 weeks. Run-in 2 to 4 weeks
Participants	**Population:** 56 patients, previously not well controlled on ICS **Baseline characteristics:** mean age 42 years; FEV$_1$ 88% predicted Concomitant ICS used by 100% of participants **Inclusion criteria:** asthma symptoms on ≥ 6 days or ≥ 4 nights; need for rescue salbutamol on ≥ 6 days or ≥ 4 nights; > 20% variation between AM and PM PEF on ≥ 4 days; pulmonary function, ≥ 1 of the following: ≥ 15% increase in FEV$_1$ 15 minutes after inhalation of 400 to 800 μg salbutamol, ≥ 15% increase in PEF 15 minutes after inhalation of 400 to 800 μg salbutamol compared to mean AM PEF values in the preceding week, > 20% variation between AM and PM PEF on ≥ 4 consecutive days, PC20 methacholine < 4 mg/mL **Exclusion criteria:** not reported as such
Interventions	• Fluticasone propionate 200 + salmeterol 50 μg twice daily • Fluticasone propionate 200 μg twice daily • Fluticasone propionate 500 μg twice daily (not used in this review) Delivery was Diskus device
Outcomes	**Primary endpoints:** submucosal eosinophil and mast cell counts No information in the paper, but no SAEs reported on the GSK website
Notes	Sponsored by GSK

Risk of bias

Wallin 2003 (*Continued*)

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not stated
Allocation concealment (selection bias)	Unclear risk	Not stated
Blinding (performance bias and detection bias) All outcomes	Low risk	Double-blind
Independent Assessment of causation (detection bias) Asthma-related events	High risk	Causation of SAEs not independently assessed
Incomplete outcome data (attrition bias) All outcomes	Low risk	46/56 (82%) completed the study
Selective reporting (reporting bias)	Low risk	SAE data on GSK website

ACQ: Asthma Control Questionnaire; AE: adverse event; ATS: American Thoracic Society; AUC: area under the curve; BDP: beclomethasone dipropionate; BHR: bronchial hyperresponsiveness; BUD: budesonide; CFC: chlorofluorocarbon; DPI: dry powder inhaler; DRC: daily record card; ECG: electrocardiogram; ECP: eosinophil cationic protein; FEV_1 : forced expiratory volume in one second; GSK: GlaxoSmithKline; HFA: hydrofluoroalkane; ICS: inhaled corticosteroid; LABA: long-acting $beta_2$ -agonist; LTRA: leukotriene receptor antagonist; MAD: minimum acceptable dose; MDI: metered dose inhaler; NCT: National Clinical Trial; OCS: oral corticosteroid; PC20: concentration needed to produce a 20% fall in FEV_1 ; PEF: peak expiratory flow; SABA: short-acting $beta_2$ -agonist; SAE: serious adverse event.

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
Bateman 2011	ICS was not a randomised treatment

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Baumgarten 2002	4-week study
Bergmann 2004	Higher-dose ICS in control arm
Bjermer 2000	Salmeterol vs LTRA
Bjermer 2003	Salmeterol vs LTRA
Bleecker 2006	Salmeterol vs salmeterol/fluticasone
Bleecker 2007	Review
Bleecker 2008	Salmeterol vs LTRA
Bracamonte 2005	Device comparison
Busse 2006	Cross-over study
Calhoun 2001	Salmeterol vs LTRA
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
Del 2001	Salmeterol vs LTRA
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 vs LTRA
Fujimoto 2006	Salmeterol vs tulobuterol
GlaxoSmithKline 2004	Higher-dose ICS in control arm
GlaxoSmithKline 2005a	Salmeterol vs LTRA
GlaxoSmithKline 2005b	Higher-dose ICS in control arm

(*Continued*)

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 vs LTRA
Isabelle 2001	Device comparison
Jarjour 2006	FSC 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
Kerstjens 2015	ICS was not a randomised treatment
Koopmans 2005	Single-dose study
Lazarus 2001	Not randomised to ICS
Lemanske 2001	Not randomised to ICS
Lotvall 2006	Single-dose study
Lotvall 2014	ICS was not a randomised treatment
Lundback 2000	Different ICS in control arm
Martinat 2003	Device comparison
Murray 1999	Higher-dose ICS in control arm
Nan 2004	Different ICS in control arm
Nathan 2001	Review of SAS30003 and SAS30004
NCT01172808	ICS was not a randomised treatment

(*Continued*)

NCT01172821	ICS was not a randomised treatment
Nelson 2000	Salmeterol vs LTRA
Nelson 2001	Salmeterol vs LTRA
O'Byrne 2005	Different ICS in control arm
O'Connor 2004	Salmeterol vs LTRA
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
Reddel 2010	Down-titration study designed to allow uneven fluticasone dose between the 2 arms of the trial
Ringdal 2003	Salmeterol vs LTRA
Rosenthal 1999	No randomisation to ICS
Russell 1995	No randomisation to ICS
SAM30002	FSC compared to budesonide at higher dose
SAM30013	FSC compared with higher-dose fluticasone
SAM40116	Patients with asthma and COPD given higher-dose fluticasone
SAS30015	FSC compared to BDP
Schermer 2007	Higher-dose ICS in control arm
Schlosser 1998	Device comparison
Scott 2005	Device comparison
SLGA5021	FSC 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

(*Continued*)

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

BDP: beclomethasone dipropionate; COPD: chronic obstructive pulmonary disease; FP: fluticasone propionate; FSC: fluticasone propionate/salmeterol; ICS: inhaled corticosteroid; LTRA: leukotriene receptor antagonist.

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

NCT02980133

Trial name or title	A 12-week, randomized, double-blind, placebo-controlled, efficacy and safety study of fluticasone propionate multidose dry powder inhaler compared with fluticasone propionate/salmeterol multidose dry powder inhaler in patients aged 4 through 11 years with persistent asthma
Methods	Parallel-arm randomised trial
Participants	Children aged 4 to 11 with persistent asthma
Interventions	Fluticasone propionate/salmeterol multidose dry powder inhaler
Outcomes	Fluticasone propionate multidose dry powder inhaler
Starting date	16 December 2016
Contact information	Teva
Notes	

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	49		Peto Odds Ratio (Peto, Fixed, 95% CI)	Subtotals only
1.1 Adults and adolescents	41	27951	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.80 [0.36, 1.78]
1.2 Children	8	8453	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.0 [0.0, 0.0]
2 All-cause non-fatal SAE	49		Peto Odds Ratio (Peto, Fixed, 95% CI)	Subtotals only
2.1 Adults and adolescents	41	27951	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.14 [0.97, 1.33]
2.2 Children	8	8453	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.04 [0.73, 1.48]
3 All-cause SAE (fatal and non-fatal)	49		Peto Odds Ratio (Peto, Fixed, 95% CI)	Subtotals only
3.1 Adults and adolescents	41	27951	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.12 [0.96, 1.31]
3.2 Children	8	8453	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.04 [0.73, 1.48]
4 Asthma-related SAE	49		Peto Odds Ratio (Peto, Fixed, 95% CI)	Subtotals only
4.1 Adults and adolescents	41	27951	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.15 [0.83, 1.59]
4.2 Children	8	8453	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.25 [0.72, 2.16]

Comparison 2. Risk difference meta-analysis: regular salmeterol in addition to regular ICS

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 All-cause mortality	49		Risk Difference (M-H, Fixed, 95% CI)	Subtotals only
1.1 Adults and adolescents	41	27951	Risk Difference (M-H, Fixed, 95% CI)	-0.00 [-0.00, 0.00]
1.2 Children	8	8453	Risk Difference (M-H, Fixed, 95% CI)	0.0 [-0.00, 0.00]
2 All-cause non-fatal SAE	49		Risk Difference (M-H, Fixed, 95% CI)	Subtotals only
2.1 Adults and adolescents	41	27951	Risk Difference (M-H, Fixed, 95% CI)	0.00 [-0.00, 0.01]
2.2 Children	8	8453	Risk Difference (M-H, Fixed, 95% CI)	0.00 [-0.00, 0.01]
3 All-cause SAE (fatal and non-fatal)	49		Risk Difference (M-H, Fixed, 95% CI)	Subtotals only
3.1 Adults and adolescents	41	27951	Risk Difference (M-H, Fixed, 95% CI)	0.00 [-0.00, 0.01]
3.2 Children	8	8453	Risk Difference (M-H, Fixed, 95% CI)	0.00 [-0.00, 0.01]
4 Asthma-related SAE	49		Risk Difference (M-H, Fixed, 95% CI)	Subtotals only
4.1 Adults and adolescents	41	27951	Risk Difference (M-H, Fixed, 95% CI)	0.00 [-0.00, 0.00]
4.2 Children	8	8453	Risk Difference (M-H, Fixed, 95% CI)	0.00 [-0.00, 0.00]
5 Asthma-related mortality	49		Risk Difference (M-H, Fixed, 95% CI)	Subtotals only
5.1 Adults and adolescents	41	27951	Risk Difference (M-H, Fixed, 95% CI)	0.0 [-0.00, 0.00]
5.2 Children	8	8453	Risk Difference (M-H, Fixed, 95% CI)	0.0 [-0.00, 0.00]

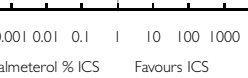
Analysis 1.1. Comparison 1 Regular salmeterol in addition to regular inhaled corticosteroids, Outcome 1 All-cause mortality.

Review: Inhaled steroids with and without regular salmeterol for 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	Weight	Peto Odds Ratio Peto,Fixed,95% CI
1 Adults and adolescents					
Aubier 1999	1/338	0/165		3.7 %	4.43 [0.07, 287.95]
AUSTRI 2016	3/5834	6/5845		37.9 %	0.51 [0.14, 1.90]
Bailey 2008	0/239	0/236			Not estimable
Bateman 2001	0/333	0/165			Not estimable
Bernstein 2017	0/501	0/499			Not estimable
GOAL 2004	3/1709	2/1707		21.0 %	1.49 [0.26, 8.61]
Godard 2008	0/159	0/159			Not estimable
Ind 2003	1/171	0/160		4.2 %	6.93 [0.14, 349.94]
Katial 2011	0/306	0/315			Not estimable
Kavuru 2000	0/92	0/90			Not estimable
Kerwin 2011	1/310	1/318		8.4 %	1.03 [0.06, 16.44]
Koenig 2008	0/156	1/156		4.2 %	0.14 [0.00, 6.82]
Koopmans 2006	0/27	0/27			Not estimable
Lundback 2006	0/95	0/92			Not estimable
Mansfield 2017	0/338	0/335			Not estimable
Murray 2004	0/88	0/89			Not estimable
Nathan 2006	0/94	0/91			Not estimable
Nelson 2003	0/95	0/97			Not estimable
Pearlman 2004	0/92	0/89			Not estimable
Raphael 2017	0/254	0/258			Not estimable
Renzi 2010	0/262	1/270		4.2 %	0.14 [0.00, 7.03]
Rojas 2007	0/180	0/182			Not estimable
SAM30007	0/29	0/32			Not estimable
SAM40004	0/42	0/21			Not estimable



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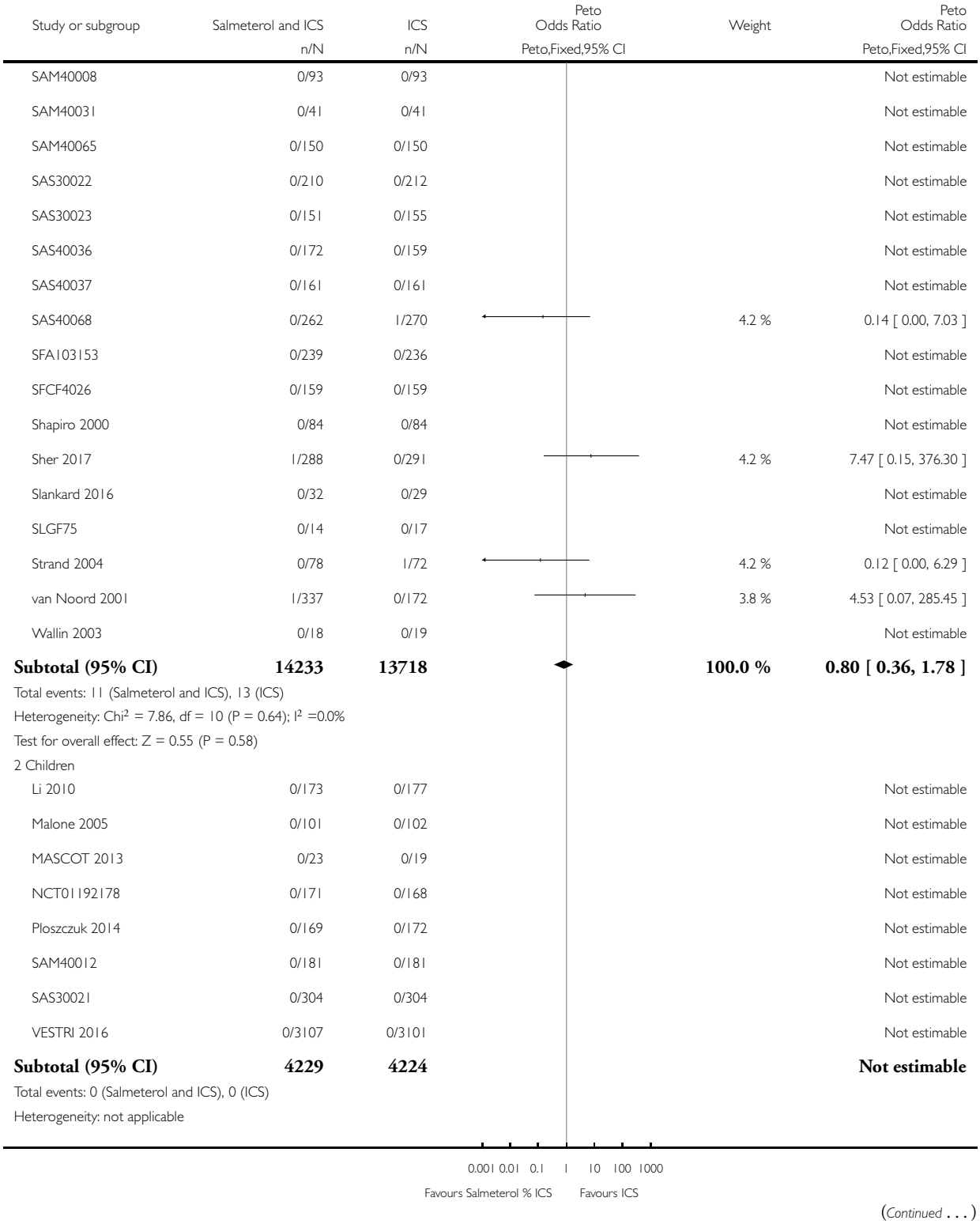

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Study or subgroup	Salmeterol and ICS n/N	ICS n/N	Peto Odds Ratio Peto,Fixed,95% CI	Weight	Peto Odds Ratio Peto,Fixed,95% CI
Test for overall effect: not applicable					

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

Review: Inhaled steroids with and without regular salmeterol for asthma: serious adverse events

Comparison: 1 Regular salmeterol in addition to regular inhaled corticosteroids

Outcome: 2 All-cause non-fatal SAE

Study or subgroup	Salmeterol and ICS n/N	ICS n/N	Peto Odds Ratio Peto,Fixed,95% CI	Weight	Peto Odds Ratio Peto,Fixed,95% CI
1 Adults and adolescents					
Aubier 1999	10/338	5/165		2.2 %	0.98 [0.33, 2.91]
AUSTRI 2016	131/5834	119/5845		41.2 %	1.11 [0.86, 1.42]
Bailey 2008	6/239	11/236		2.8 %	0.54 [0.20, 1.41]
Bateman 2001	6/333	3/165		1.3 %	0.99 [0.24, 4.02]
Bernstein 2017	4/501	5/499		1.5 %	0.80 [0.21, 2.96]
GOAL 2004	64/1709	51/1707		18.7 %	1.26 [0.87, 1.83]
Godard 2008	3/159	1/159		0.7 %	2.74 [0.38, 19.67]
Ind 2003	9/171	5/160		2.3 %	1.69 [0.58, 4.93]
Katial 2011	14/306	10/315		3.9 %	1.46 [0.64, 3.29]
Kavuru 2000	2/92	1/90		0.5 %	1.92 [0.20, 18.69]
Kerwin 2011	6/310	8/318		2.3 %	0.77 [0.27, 2.21]
Koenig 2008	1/156	1/156		0.3 %	1.00 [0.06, 16.06]
Koopmans 2006	0/27	1/27		0.2 %	0.14 [0.00, 6.82]

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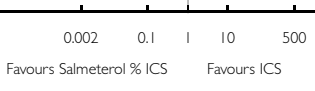
Study or subgroup	Salmeterol and ICS n/N	ICS n/N	Peto Odds Ratio Peto,Fixed,95% CI	Weight	Peto Odds Ratio Peto,Fixed,95% CI
Lundback 2006	4/95	3/92		1.1 %	1.30 [0.29, 5.86]
Mansfield 2017	24/338	20/335		6.9 %	1.20 [0.65, 2.22]
Murray 2004	0/88	0/89			Not estimable
Nathan 2006	0/94	0/91			Not estimable
Nelson 2003	2/95	0/97		0.3 %	7.63 [0.47, 122.85]
Pearlman 2004	0/92	1/89		0.2 %	0.13 [0.00, 6.60]
Raphael 2017	1/254	1/258		0.3 %	1.02 [0.06, 16.29]
Renzi 2010	4/262	2/270		1.0 %	2.02 [0.40, 10.09]
Rojas 2007	1/180	2/182		0.5 %	0.52 [0.05, 5.00]
SAM30007	0/29	1/32		0.2 %	0.15 [0.00, 7.53]
SAM40004	1/42	1/21		0.3 %	0.47 [0.02, 9.04]
SAM40008	3/93	0/93		0.5 %	7.55 [0.78, 73.51]
SAM40031	2/41	3/41		0.8 %	0.66 [0.11, 3.96]
SAM40065	2/150	3/150		0.8 %	0.67 [0.11, 3.89]
SAS30022	4/210	0/212		0.7 %	7.57 [1.06, 54.11]
SAS30023	0/151	1/155		0.2 %	0.14 [0.00, 7.00]
SAS40036	0/172	0/159			Not estimable
SAS40037	1/161	2/161		0.5 %	0.51 [0.05, 4.95]
SAS40068	4/262	2/270		1.0 %	2.02 [0.40, 10.09]
SFA103153	6/239	11/236		2.8 %	0.54 [0.20, 1.41]
SFCF4026	3/159	1/159		0.7 %	2.74 [0.38, 19.67]
Shapiro 2000	0/84	1/84		0.2 %	0.14 [0.00, 6.82]
Sher 2017	5/288	2/291		1.2 %	2.40 [0.54, 10.65]
Slankard 2016	0/32	0/29			Not estimable
SLGF75	0/14	0/17			Not estimable
Strand 2004	1/78	2/72		0.5 %	0.47 [0.05, 4.58]
van Noord 2001	8/337	2/172		1.5 %	1.87 [0.50, 7.03]
Wallin 2003	0/18	0/19			Not estimable
Subtotal (95% CI)	**14233**	**13718**		**100.0 %**	**1.14 [0.97, 1.33]**
Total events: 332 (Salmeterol and ICS), 282 (ICS)					
Heterogeneity: Chi^2 = 27.28, df = 34 (P = 0.79); I^2 =0.0%					
Test for overall effect: Z = 1.55 (P = 0.12)					



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Study or subgroup	Salmeterol and ICS n/N	ICS n/N	Peto Odds Ratio Peto,Fixed,95% CI	Weight	Peto Odds Ratio Peto,Fixed,95% CI
2 Children					
Li 2010	1/173	0/177		0.8 %	7.56 [0.15, 381.19]
Malone 2005	0/101	0/102			Not estimable
MASCOT 2013	3/23	2/19		3.6 %	1.26 [0.20, 8.07]
NCT01192178	2/171	1/168		2.4 %	1.92 [0.20, 18.59]
Ploszczuk 2014	0/169	1/172		0.8 %	0.14 [0.00, 6.94]
SAM40012	2/181	1/181		2.4 %	1.95 [0.20, 18.91]
SAS30021	1/304	3/304		3.2 %	0.37 [0.05, 2.61]
VESTRI 2016	56/3107	54/3101		86.8 %	1.04 [0.71, 1.51]
Subtotal (95% CI)	**4229**	**4224**		**100.0 %**	**1.04 [0.73, 1.48]**
Total events: 65 (Salmeterol and ICS), 62 (ICS)					
Heterogeneity: Chi^2 = 3.71, df = 6 (P = 0.72); I^2 =0.0%					
Test for overall effect: Z = 0.22 (P = 0.83)					
Test for subgroup differences: Chi^2 = 0.20, df = 1 (P = 0.65), I^2 =0.0%					

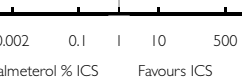
Analysis 1.3. Comparison 1 Regular salmeterol in addition to regular inhaled corticosteroids, Outcome 3 All-cause SAE (fatal and non-fatal).

Review: Inhaled steroids with and without regular salmeterol for 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	Weight	Peto Odds Ratio Peto,Fixed,95% CI
1 Adults and adolescents					
Aubier 1999	11/338	5/165		2.2 %	1.08 [0.37, 3.10]
AUSTRI 2016	134/5834	125/5845		41.1 %	1.08 [0.84, 1.38]
Bailey 2008	6/239	11/236		2.7 %	0.54 [0.20, 1.41]
Bateman 2001	6/333	3/165		1.3 %	0.99 [0.24, 4.02]
Bernstein 2017	4/501	5/499		1.4 %	0.80 [0.21, 2.96]
GOAL 2004	67/1709	53/1707		18.8 %	1.27 [0.88, 1.83]
Godard 2008	3/159	1/159		0.6 %	2.74 [0.38, 19.67]
Ind 2003	10/171	5/160		2.3 %	1.87 [0.67, 5.27]
Katial 2011	14/306	10/315		3.8 %	1.46 [0.64, 3.29]
Kavuru 2000	2/92	1/90		0.5 %	1.92 [0.20, 18.69]
Kerwin 2011	7/310	9/318		2.5 %	0.79 [0.29, 2.14]
Koenig 2008	1/156	2/156		0.5 %	0.51 [0.05, 4.95]
Koopmans 2006	0/27	1/27		0.2 %	0.14 [0.00, 6.82]
Lundback 2006	4/95	3/92		1.1 %	1.30 [0.29, 5.86]
Mansfield 2017	24/338	20/335		6.7 %	1.20 [0.65, 2.22]
Murray 2004	0/88	0/89			Not estimable
Nathan 2006	0/94	0/91			Not estimable
Nelson 2003	2/95	0/97		0.3 %	7.63 [0.47, 122.85]
Pearlman 2004	0/92	1/89		0.2 %	0.13 [0.00, 6.60]
Raphael 2017	1/254	1/258		0.3 %	1.02 [0.06, 16.29]
Renzi 2010	4/262	3/270		1.1 %	1.38 [0.31, 6.11]
Rojas 2007	1/180	2/182		0.5 %	0.52 [0.05, 5.00]
SAM30007	0/29	1/32		0.2 %	0.15 [0.00, 7.53]
SAM40004	1/42	1/21		0.3 %	0.47 [0.02, 9.04]



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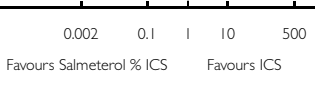
Study or subgroup	Salmeterol and ICS n/N	ICS n/N	Peto Odds Ratio Peto,Fixed,95% CI	Weight	Peto Odds Ratio Peto,Fixed,95% CI
SAM40008	3/93	0/93		0.5 %	7.55 [0.78, 73.51]
SAM40031	2/41	3/41		0.8 %	0.66 [0.11, 3.96]
SAM40065	2/150	3/150		0.8 %	0.67 [0.11, 3.89]
SAS30022	4/210	0/212		0.6 %	7.57 [1.06, 54.11]
SAS30023	0/151	1/155		0.2 %	0.14 [0.00, 7.00]
SAS40036	0/172	0/159			Not estimable
SAS40037	1/161	2/161		0.5 %	0.51 [0.05, 4.95]
SAS40068	4/262	3/270		1.1 %	1.38 [0.31, 6.11]
SFA103153	6/239	11/236		2.7 %	0.54 [0.20, 1.41]
SFCF4026	3/159	1/159		0.6 %	2.74 [0.38, 19.67]
Shapiro 2000	0/84	1/84		0.2 %	0.14 [0.00, 6.82]
Sher 2017	6/288	2/291		1.3 %	2.78 [0.69, 11.21]
Slankard 2016	0/32	0/29			Not estimable
SLGF75	0/14	0/17			Not estimable
Strand 2004	1/78	3/72		0.6 %	0.33 [0.05, 2.41]
van Noord 2001	9/337	2/172		1.6 %	2.04 [0.58, 7.20]
Wallin 2003	0/18	0/19			Not estimable
Subtotal (95% CI)	**14233**	**13718**		**100.0 %**	**1.12 [0.96, 1.31]**
Total events: 343 (Salmeterol and ICS), 295 (ICS)					
Heterogeneity: Chi^2 = 29.13, df = 34 (P = 0.71); I^2 =0.0%					
Test for overall effect: Z = 1.41 (P = 0.16)					
2 Children					
Li 2010	1/173	0/177		0.8 %	7.56 [0.15, 381.19]
Malone 2005	0/101	0/102			Not estimable
MASCOT 2013	3/23	2/19		3.6 %	1.26 [0.20, 8.07]
NCT01192178	2/171	1/168		2.4 %	1.92 [0.20, 18.59]
Ploszczuk 2014	0/169	1/172		0.8 %	0.14 [0.00, 6.94]
SAM40012	2/181	1/181		2.4 %	1.95 [0.20, 18.91]
SAS30021	1/304	3/304		3.2 %	0.37 [0.05, 2.61]
VESTRI 2016	56/3107	54/3101		86.8 %	1.04 [0.71, 1.51]
Subtotal (95% CI)	**4229**	**4224**		**100.0 %**	**1.04 [0.73, 1.48]**
Total events: 65 (Salmeterol and ICS), 62 (ICS)					
Heterogeneity: Chi^2 = 3.71, df = 6 (P = 0.72); I^2 =0.0%					



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Study or subgroup	Salmeterol and ICS n/N	ICS n/N	Peto Odds Ratio Peto,Fixed,95% CI	Weight	Peto Odds Ratio Peto,Fixed,95% CI
Test for overall effect: Z = 0.22 (P = 0.83)					
Test for subgroup differences: Chi^2 = 0.15, df = 1 (P = 0.70), I^2 =0.0%					

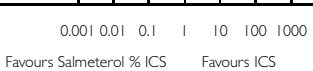
Analysis 1.4. Comparison 1 Regular salmeterol in addition to regular inhaled corticosteroids, Outcome 4 Asthma-related SAE.

Review: Inhaled steroids with and without regular salmeterol for asthma: serious adverse events

Comparison: 1 Regular salmeterol in addition to regular inhaled corticosteroids

Outcome: 4 Asthma-related SAE

Study or subgroup	Salmeterol and ICS n/N	ICS n/N	Peto Odds Ratio Peto,Fixed,95% CI	Weight	Peto Odds Ratio Peto,Fixed,95% CI
1 Adults and adolescents					
Aubier 1999	1/338	0/165		0.6 %	4.43 [0.07, 287.95]
AUSTRI 2016	34/5834	33/5845		46.1 %	1.03 [0.64, 1.67]
Bailey 2008	2/239	2/236		2.8 %	0.99 [0.14, 7.05]
Bateman 2001	5/333	0/165		3.0 %	4.52 [0.70, 29.29]
Bernstein 2017	0/501	0/499			Not estimable
GOAL 2004	8/1709	12/1707		13.8 %	0.67 [0.28, 1.61]
Godard 2008	0/159	0/159			Not estimable
Ind 2003	1/171	3/160		2.7 %	0.34 [0.05, 2.44]
Katial 2011	3/306	0/315		2.1 %	7.66 [0.79, 73.92]
Kavuru 2000	0/92	0/90			Not estimable
Kerwin 2011	1/310	0/318		0.7 %	7.58 [0.15, 382.24]
Koenig 2008	1/156	0/156		0.7 %	7.39 [0.15, 372.38]
Koopmans 2006	0/27	0/27			Not estimable



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Study or subgroup	Salmeterol and ICS n/N	ICS n/N	Peto Odds Ratio Peto,Fixed,95% CI	Weight	Peto Odds Ratio Peto,Fixed,95% CI
Lundback 2006	0/95	0/92			Not estimable
Mansfield 2017	14/338	10/335		16.0 %	1.40 [0.62, 3.16]
Murray 2004	0/88	0/89			Not estimable
Nathan 2006	0/94	0/91			Not estimable
Nelson 2003	1/95	0/97		0.7 %	7.55 [0.15, 380.39]
Pearlman 2004	0/92	0/89			Not estimable
Raphael 2017	1/254	1/258		1.4 %	1.02 [0.06, 16.29]
Renzi 2010	0/262	0/270			Not estimable
Rojas 2007	0/180	0/182			Not estimable
SAM30007	0/29	1/32		0.7 %	0.15 [0.00, 7.53]
SAM40004	0/42	0/21			Not estimable
SAM40008	1/93	0/93		0.7 %	7.39 [0.15, 372.38]
SAM40031	0/41	0/41			Not estimable
SAM40065	0/150	1/150		0.7 %	0.14 [0.00, 6.82]
SAS30022	0/210	0/212			Not estimable
SAS30023	0/151	0/155			Not estimable
SAS40036	0/172	0/159			Not estimable
SAS40037	0/161	0/161			Not estimable
SAS40068	0/262	0/270			Not estimable
SFA103153	2/239	2/236		2.8 %	0.99 [0.14, 7.05]
SFCF4026	0/159	0/159			Not estimable
Shapiro 2000	0/84	1/84		0.7 %	0.14 [0.00, 6.82]
Sher 2017	2/288	0/291		1.4 %	7.49 [0.47, 120.08]
Slankard 2016	0/32	0/29			Not estimable
SLGF75	0/14	0/17			Not estimable
Strand 2004	1/78	0/72		0.7 %	6.84 [0.14, 345.90]
van Noord 2001	2/337	1/172		1.9 %	1.02 [0.09, 11.22]
Wallin 2003	0/18	0/19			Not estimable
Subtotal (95% CI)	**14233**	**13718**		**100.0 %**	**1.15 [0.83, 1.59]**
Total events: 80 (Salmeterol and ICS), 67 (ICS)					
Heterogeneity: Chi² = 17.94, df = 19 (P = 0.53); I² =0.0%					
Test for overall effect: Z = 0.82 (P = 0.41)					

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Study or subgroup	Salmeterol and ICS n/N	ICS n/N	Peto Odds Ratio Peto,Fixed,95% CI	Weight	Peto Odds Ratio Peto,Fixed,95% CI
2 Children					
Li 2010	0/173	0/177			Not estimable
Malone 2005	0/101	0/102			Not estimable
MASCOT 2013	1/23	1/19		3.7 %	0.82 [0.05, 13.76]
NCT01192178	1/171	0/168		1.9 %	7.26 [0.14, 365.96]
Ploszczuk 2014	0/169	0/172			Not estimable
SAM40012	0/181	0/181			Not estimable
SAS30021	0/304	1/304		1.9 %	0.14 [0.00, 6.82]
VESTRI 2016	27/3107	21/3101		92.4 %	1.28 [0.73, 2.27]
Subtotal (95% CI)	**4229**	**4224**		**100.0 %**	**1.25 [0.72, 2.16]**
Total events: 29 (Salmeterol and ICS), 23 (ICS)					
Heterogeneity: Chi^2 = 2.10, df = 3 (P = 0.55); I^2 =0.0%					
Test for overall effect: Z = 0.80 (P = 0.42)					
Test for subgroup differences: Chi^2 = 0.07, df = 1 (P = 0.79), I^2 =0.0%					

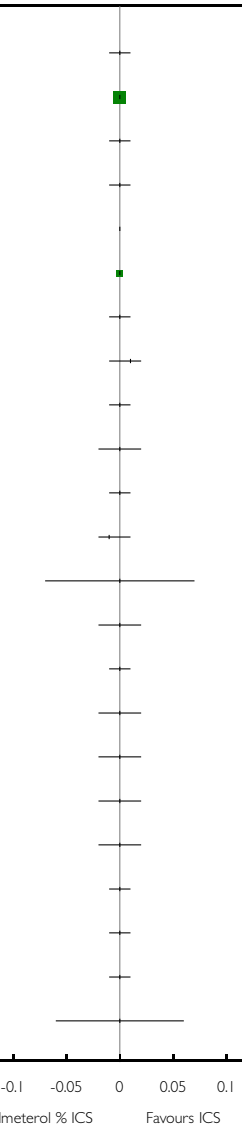
Analysis 2.1. Comparison 2 Risk difference meta-analysis: regular salmeterol in addition to regular ICS, Outcome 1 All-cause mortality.

Review: Inhaled steroids with and without regular salmeterol for asthma: serious adverse events

Comparison: 2 Risk difference meta-analysis: regular salmeterol in addition to regular ICS

Outcome: 1 All-cause mortality

Study or subgroup	Salmeterol and ICS n/N	ICS n/N	Risk Difference M-H,Fixed,95% CI	Weight	Risk Difference M-H,Fixed,95% CI
1 Adults and adolescents					
Aubier 1999	1/338	0/165		1.6 %	0.00 [-0.01, 0.01]
AUSTRI 2016	3/5834	6/5845		42.1 %	0.00 [0.00, 0.00]
Bailey 2008	0/239	0/236		1.7 %	0.0 [-0.01, 0.01]
Bateman 2001	0/333	0/165		1.6 %	0.0 [-0.01, 0.01]
Bernstein 2017	0/501	0/499		3.6 %	0.0 [0.00, 0.00]
GOAL 2004	3/1709	2/1707		12.3 %	0.00 [0.00, 0.00]
Godard 2008	0/159	0/159		1.1 %	0.0 [-0.01, 0.01]
Ind 2003	1/171	0/160		1.2 %	0.01 [-0.01, 0.02]
Katial 2011	0/306	0/315		2.2 %	0.0 [-0.01, 0.01]
Kavuru 2000	0/92	0/90		0.7 %	0.0 [-0.02, 0.02]
Kerwin 2011	1/310	1/318		2.3 %	0.00 [-0.01, 0.01]
Koenig 2008	0/156	1/156		1.1 %	-0.01 [-0.02, 0.01]
Koopmans 2006	0/27	0/27		0.2 %	0.0 [-0.07, 0.07]
Lundback 2006	0/95	0/92		0.7 %	0.0 [-0.02, 0.02]
Mansfield 2017	0/338	0/335		2.4 %	0.0 [-0.01, 0.01]
Murray 2004	0/88	0/89		0.6 %	0.0 [-0.02, 0.02]
Nathan 2006	0/94	0/91		0.7 %	0.0 [-0.02, 0.02]
Nelson 2003	0/95	0/97		0.7 %	0.0 [-0.02, 0.02]
Pearlman 2004	0/92	0/89		0.7 %	0.0 [-0.02, 0.02]
Raphael 2017	0/254	0/258		1.8 %	0.0 [-0.01, 0.01]
Renzi 2010	0/262	1/270		1.9 %	0.00 [-0.01, 0.01]
Rojas 2007	0/180	0/182		1.3 %	0.0 [-0.01, 0.01]
SAM30007	0/29	0/32		0.2 %	0.0 [-0.06, 0.06]



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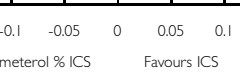
Study or subgroup	Salmeterol and ICS n/N	ICS n/N	Risk Difference M-H,Fixed,95% CI	Weight	Risk Difference M-H,Fixed,95% CI
SAM40004	0/42	0/21		0.2 %	0.0 [-0.07, 0.07]
SAM40008	0/93	0/93		0.7 %	0.0 [-0.02, 0.02]
SAM40031	0/41	0/41		0.3 %	0.0 [-0.05, 0.05]
SAM40065	0/150	0/150		1.1 %	0.0 [-0.01, 0.01]
SAS30022	0/210	0/212		1.5 %	0.0 [-0.01, 0.01]
SAS30023	0/151	0/155		1.1 %	0.0 [-0.01, 0.01]
SAS40036	0/172	0/159		1.2 %	0.0 [-0.01, 0.01]
SAS40037	0/161	0/161		1.2 %	0.0 [-0.01, 0.01]
SAS40068	0/262	1/270		1.9 %	0.00 [-0.01, 0.01]
SFA103153	0/239	0/236		1.7 %	0.0 [-0.01, 0.01]
SFCF4026	0/159	0/159		1.1 %	0.0 [-0.01, 0.01]
Shapiro 2000	0/84	0/84		0.6 %	0.0 [-0.02, 0.02]
Sher 2017	1/288	0/291		2.1 %	0.00 [-0.01, 0.01]
Slankard 2016	0/32	0/29		0.2 %	0.0 [-0.06, 0.06]
SLGF75	0/14	0/17		0.1 %	0.0 [-0.12, 0.12]
Strand 2004	0/78	1/72		0.5 %	-0.01 [-0.05, 0.02]
van Noord 2001	1/337	0/172		1.6 %	0.00 [-0.01, 0.01]
Wallin 2003	0/18	0/19		0.1 %	0.0 [-0.10, 0.10]
Subtotal (95% CI)	**14233**	**13718**		**100.0 %**	**0.00 [0.00, 0.00]**
Total events: 11 (Salmeterol and ICS), 13 (ICS)					
Heterogeneity: Chi^2 = 4.43, df = 40 (P = 1.00); I^2 =0.0%					
Test for overall effect: Z = 0.34 (P = 0.73)					
2 Children					
Li 2010	0/173	0/177		4.1 %	0.0 [-0.01, 0.01]
Malone 2005	0/101	0/102		2.4 %	0.0 [-0.02, 0.02]
MASCOT 2013	0/23	0/19		0.5 %	0.0 [-0.09, 0.09]
NCT01192178	0/171	0/168		4.0 %	0.0 [-0.01, 0.01]
Ploszczuk 2014	0/169	0/172		4.0 %	0.0 [-0.01, 0.01]
SAM40012	0/181	0/181		4.3 %	0.0 [-0.01, 0.01]
SAS30021	0/304	0/304		7.2 %	0.0 [-0.01, 0.01]
VESTRI 2016	0/3107	0/3101		73.4 %	0.0 [0.00, 0.00]
Subtotal (95% CI)	**4229**	**4224**		**100.0 %**	**0.0 [0.00, 0.00]**
Total events: 0 (Salmeterol and ICS), 0 (ICS)					



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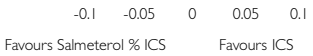
Study or subgroup	Salmeterol and ICS n/N	ICS n/N	Risk Difference M-H,Fixed,95% CI	Weight	Risk Difference M-H,Fixed,95% CI
Heterogeneity: Chi² = 0.0, df = 7 (P = 1.00); I² =0.0%					
Test for overall effect: Z = 0.0 (P = 1.0)					
Test for subgroup differences: Chi² = 0.05, df = 1 (P = 0.83), I² =0.0%					



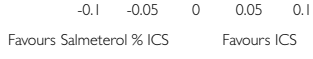
Analysis 2.2. Comparison 2 Risk difference meta-analysis: regular salmeterol in addition to regular ICS, Outcome 2 All-cause non-fatal SAE.

Review: Inhaled steroids with and without regular salmeterol for asthma: serious adverse events

Comparison: 2 Risk difference meta-analysis: regular salmeterol in addition to regular ICS

Outcome: 2 All-cause non-fatal SAE

Study or subgroup	Salmeterol and ICS n/N	ICS n/N	Risk Difference M-H,Fixed,95% CI	Weight	Risk Difference M-H,Fixed,95% CI
1 Adults and adolescents					
Aubier 1999	10/338	5/165		1.6 %	0.00 [-0.03, 0.03]
AUSTRI 2016	131/5834	119/5845		42.1 %	0.00 [0.00, 0.01]
Bailey 2008	6/239	11/236		1.7 %	-0.02 [-0.05, 0.01]
Bateman 2001	6/333	3/165		1.6 %	0.00 [-0.03, 0.02]
Bernstein 2017	4/501	5/499		3.6 %	0.00 [-0.01, 0.01]
GOAL 2004	64/1709	51/1707		12.3 %	0.01 [0.00, 0.02]
Godard 2008	3/159	1/159		1.1 %	0.01 [-0.01, 0.04]
Ind 2003	9/171	5/160		1.2 %	0.02 [-0.02, 0.06]
Katial 2011	14/306	10/315		2.2 %	0.01 [-0.02, 0.04]
Kavuru 2000	2/92	1/90		0.7 %	0.01 [-0.03, 0.05]
Kerwin 2011	6/310	8/318		2.3 %	-0.01 [-0.03, 0.02]
Koenig 2008	1/156	1/156		1.1 %	0.0 [-0.02, 0.02]



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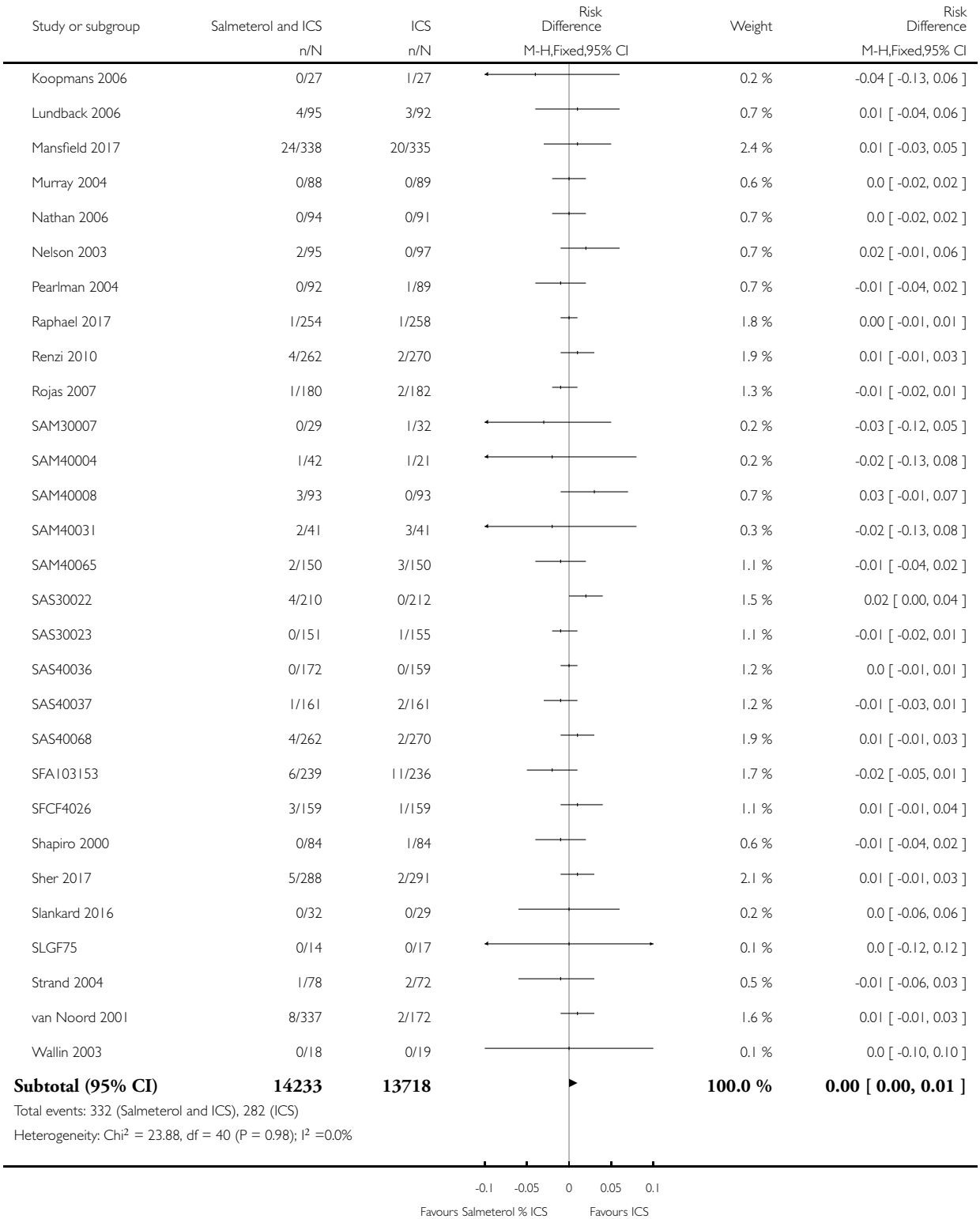

Study or subgroup	Salmeterol and ICS n/N	ICS n/N	Risk Difference M-H,Fixed,95% CI	Weight	Risk Difference M-H,Fixed,95% CI
Koopmans 2006	0/27	1/27		0.2 %	-0.04 [-0.13, 0.06]
Lundback 2006	4/95	3/92		0.7 %	0.01 [-0.04, 0.06]
Mansfield 2017	24/338	20/335		2.4 %	0.01 [-0.03, 0.05]
Murray 2004	0/88	0/89		0.6 %	0.0 [-0.02, 0.02]
Nathan 2006	0/94	0/91		0.7 %	0.0 [-0.02, 0.02]
Nelson 2003	2/95	0/97		0.7 %	0.02 [-0.01, 0.06]
Pearlman 2004	0/92	1/89		0.7 %	-0.01 [-0.04, 0.02]
Raphael 2017	1/254	1/258		1.8 %	0.00 [-0.01, 0.01]
Renzi 2010	4/262	2/270		1.9 %	0.01 [-0.01, 0.03]
Rojas 2007	1/180	2/182		1.3 %	-0.01 [-0.02, 0.01]
SAM30007	0/29	1/32		0.2 %	-0.03 [-0.12, 0.05]
SAM40004	1/42	1/21		0.2 %	-0.02 [-0.13, 0.08]
SAM40008	3/93	0/93		0.7 %	0.03 [-0.01, 0.07]
SAM40031	2/41	3/41		0.3 %	-0.02 [-0.13, 0.08]
SAM40065	2/150	3/150		1.1 %	-0.01 [-0.04, 0.02]
SAS30022	4/210	0/212		1.5 %	0.02 [0.00, 0.04]
SAS30023	0/151	1/155		1.1 %	-0.01 [-0.02, 0.01]
SAS40036	0/172	0/159		1.2 %	0.0 [-0.01, 0.01]
SAS40037	1/161	2/161		1.2 %	-0.01 [-0.03, 0.01]
SAS40068	4/262	2/270		1.9 %	0.01 [-0.01, 0.03]
SFA103153	6/239	11/236		1.7 %	-0.02 [-0.05, 0.01]
SFCF4026	3/159	1/159		1.1 %	0.01 [-0.01, 0.04]
Shapiro 2000	0/84	1/84		0.6 %	-0.01 [-0.04, 0.02]
Sher 2017	5/288	2/291		2.1 %	0.01 [-0.01, 0.03]
Slankard 2016	0/32	0/29		0.2 %	0.0 [-0.06, 0.06]
SLGF75	0/14	0/17		0.1 %	0.0 [-0.12, 0.12]
Strand 2004	1/78	2/72		0.5 %	-0.01 [-0.06, 0.03]
van Noord 2001	8/337	2/172		1.6 %	0.01 [-0.01, 0.03]
Wallin 2003	0/18	0/19		0.1 %	0.0 [-0.10, 0.10]
Subtotal (95% CI)	**14233**	**13718**		**100.0 %**	**0.00 [0.00, 0.01]**
Total events: 332 (Salmeterol and ICS), 282 (ICS)					
Heterogeneity: Chi^2 = 23.88, df = 40 (P = 0.98); I^2 =0.0%					

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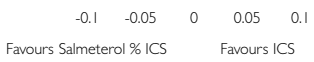
Study or subgroup	Salmeterol and ICS n/N	ICS n/N	Risk Difference M-H,Fixed,95% CI	Weight	Risk Difference M-H,Fixed,95% CI
Test for overall effect: Z = 1.54 (P = 0.12)					
2 Children					
Li 2010	1/173	0/177		4.1 %	0.01 [-0.01, 0.02]
Malone 2005	0/101	0/102		2.4 %	0.0 [-0.02, 0.02]
MASCOT 2013	3/23	2/19		0.5 %	0.03 [-0.17, 0.22]
NCT01192178	2/171	1/168		4.0 %	0.01 [-0.01, 0.03]
Ploszczuk 2014	0/169	1/172		4.0 %	-0.01 [-0.02, 0.01]
SAM40012	2/181	1/181		4.3 %	0.01 [-0.01, 0.02]
SAS30021	1/304	3/304		7.2 %	-0.01 [-0.02, 0.01]
VESTRI 2016	56/3107	54/3101		73.4 %	0.00 [-0.01, 0.01]
Subtotal (95% CI)	**4229**	**4224**		**100.0 %**	**0.00 [0.00, 0.01]**
Total events: 65 (Salmeterol and ICS), 62 (ICS)					
Heterogeneity: Chi^2 = 2.81, df = 7 (P = 0.90); I^2 =0.0%					
Test for overall effect: Z = 0.21 (P = 0.83)					
Test for subgroup differences: Chi^2 = 0.45, df = 1 (P = 0.50), I^2 =0.0%					



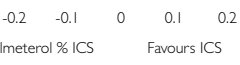
Analysis 2.3. Comparison 2 Risk difference meta-analysis: regular salmeterol in addition to regular ICS, Outcome 3 All-cause SAE (fatal and non-fatal).

Review: Inhaled steroids with and without regular salmeterol for asthma: serious adverse events

Comparison: 2 Risk difference meta-analysis: regular salmeterol in addition to regular ICS

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

Study or subgroup	Salmeterol and ICS n/N	ICS n/N	Risk Difference M-H,Fixed,95% CI	Weight	Risk Difference M-H,Fixed,95% CI
1 Adults and adolescents					
Aubier 1999	11/338	5/165		1.6 %	0.00 [-0.03, 0.03]
AUSTRI 2016	134/5834	125/5845		42.1 %	0.00 [0.00, 0.01]
Bailey 2008	6/239	11/236		1.7 %	-0.02 [-0.05, 0.01]
Bateman 2001	6/333	3/165		1.6 %	0.00 [-0.03, 0.02]
Bernstein 2017	4/501	5/499		3.6 %	0.00 [-0.01, 0.01]
GOAL 2004	67/1709	53/1707		12.3 %	0.01 [0.00, 0.02]
Godard 2008	3/159	1/159		1.1 %	0.01 [-0.01, 0.04]
Ind 2003	10/171	5/160		1.2 %	0.03 [-0.02, 0.07]
Katial 2011	14/306	10/315		2.2 %	0.01 [-0.02, 0.04]
Kavuru 2000	2/92	1/90		0.7 %	0.01 [-0.03, 0.05]
Kerwin 2011	7/310	9/318		2.3 %	-0.01 [-0.03, 0.02]
Koenig 2008	1/156	2/156		1.1 %	-0.01 [-0.03, 0.02]
Koopmans 2006	0/27	1/27		0.2 %	-0.04 [-0.13, 0.06]
Lundback 2006	4/95	3/92		0.7 %	0.01 [-0.04, 0.06]
Mansfield 2017	24/338	20/335		2.4 %	0.01 [-0.03, 0.05]
Murray 2004	0/88	0/89		0.6 %	0.0 [-0.02, 0.02]
Nathan 2006	0/94	0/91		0.7 %	0.0 [-0.02, 0.02]
Nelson 2003	2/95	0/97		0.7 %	0.02 [-0.01, 0.06]
Pearlman 2004	0/92	1/89		0.7 %	-0.01 [-0.04, 0.02]
Raphael 2017	2/254	2/258		1.8 %	0.00 [-0.02, 0.02]
Renzi 2010	4/262	3/270		1.9 %	0.00 [-0.02, 0.02]
Rojas 2007	1/180	2/182		1.3 %	-0.01 [-0.02, 0.01]
SAM30007	0/29	1/32		0.2 %	-0.03 [-0.12, 0.05]



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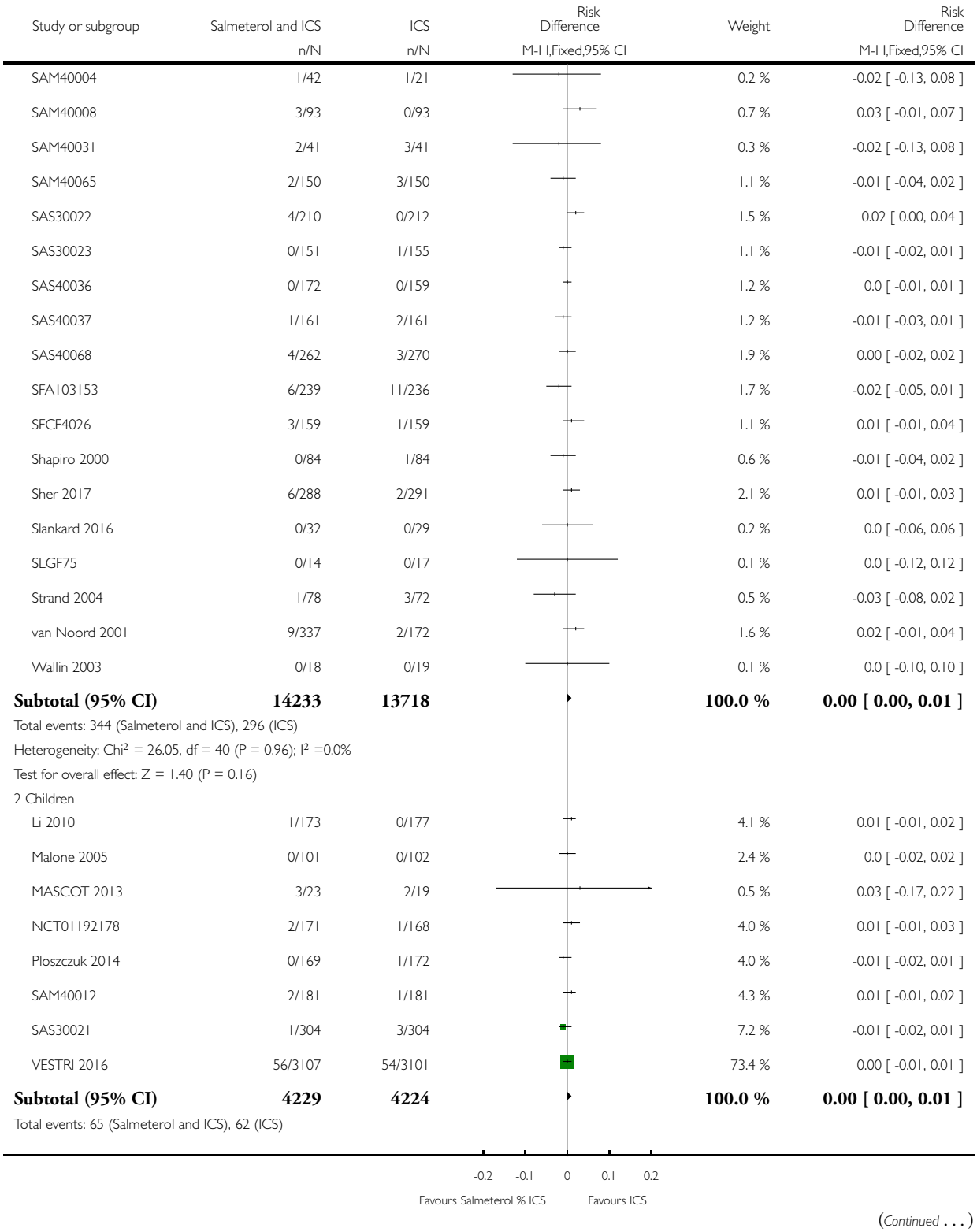

Study or subgroup	Salmeterol and ICS n/N	ICS n/N	Risk Difference M-H,Fixed,95% CI	Weight	Risk Difference M-H,Fixed,95% CI
SAM40004	1/42	1/21		0.2 %	-0.02 [-0.13, 0.08]
SAM40008	3/93	0/93		0.7 %	0.03 [-0.01, 0.07]
SAM40031	2/41	3/41		0.3 %	-0.02 [-0.13, 0.08]
SAM40065	2/150	3/150		1.1 %	-0.01 [-0.04, 0.02]
SAS30022	4/210	0/212		1.5 %	0.02 [0.00, 0.04]
SAS30023	0/151	1/155		1.1 %	-0.01 [-0.02, 0.01]
SAS40036	0/172	0/159		1.2 %	0.0 [-0.01, 0.01]
SAS40037	1/161	2/161		1.2 %	-0.01 [-0.03, 0.01]
SAS40068	4/262	3/270		1.9 %	0.00 [-0.02, 0.02]
SFA103153	6/239	11/236		1.7 %	-0.02 [-0.05, 0.01]
SFCF4026	3/159	1/159		1.1 %	0.01 [-0.01, 0.04]
Shapiro 2000	0/84	1/84		0.6 %	-0.01 [-0.04, 0.02]
Sher 2017	6/288	2/291		2.1 %	0.01 [-0.01, 0.03]
Slankard 2016	0/32	0/29		0.2 %	0.0 [-0.06, 0.06]
SLGF75	0/14	0/17		0.1 %	0.0 [-0.12, 0.12]
Strand 2004	1/78	3/72		0.5 %	-0.03 [-0.08, 0.02]
van Noord 2001	9/337	2/172		1.6 %	0.02 [-0.01, 0.04]
Wallin 2003	0/18	0/19		0.1 %	0.0 [-0.10, 0.10]
Subtotal (95% CI)	**14233**	**13718**		**100.0 %**	**0.00 [0.00, 0.01]**
Total events: 344 (Salmeterol and ICS), 296 (ICS)					
Heterogeneity: Chi² = 26.05, df = 40 (P = 0.96); I² =0.0%					
Test for overall effect: Z = 1.40 (P = 0.16)					
2 Children					
Li 2010	1/173	0/177		4.1 %	0.01 [-0.01, 0.02]
Malone 2005	0/101	0/102		2.4 %	0.0 [-0.02, 0.02]
MASCOT 2013	3/23	2/19		0.5 %	0.03 [-0.17, 0.22]
NCT01192178	2/171	1/168		4.0 %	0.01 [-0.01, 0.03]
Ploszczuk 2014	0/169	1/172		4.0 %	-0.01 [-0.02, 0.01]
SAM40012	2/181	1/181		4.3 %	0.01 [-0.01, 0.02]
SAS30021	1/304	3/304		7.2 %	-0.01 [-0.02, 0.01]
VESTRI 2016	56/3107	54/3101		73.4 %	0.00 [-0.01, 0.01]
Subtotal (95% CI)	**4229**	**4224**		**100.0 %**	**0.00 [0.00, 0.01]**
Total events: 65 (Salmeterol and ICS), 62 (ICS)					

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Study or subgroup	Salmeterol and ICS n/N	ICS n/N	Risk Difference M-H,Fixed,95% CI	Weight	Risk Difference M-H,Fixed,95% CI
Heterogeneity: Chi² = 2.81, df = 7 (P = 0.90); I² =0.0%					
Test for overall effect: Z = 0.21 (P = 0.83)					
Test for subgroup differences: Chi² = 0.37, df = 1 (P = 0.54), I² =0.0%					

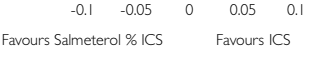
Analysis 2.4. Comparison 2 Risk difference meta-analysis: regular salmeterol in addition to regular ICS, Outcome 4 Asthma-related SAE.

Review: Inhaled steroids with and without regular salmeterol for asthma: serious adverse events

Comparison: 2 Risk difference meta-analysis: regular salmeterol in addition to regular ICS

Outcome: 4 Asthma-related SAE

Study or subgroup	Salmeterol and ICS n/N	ICS n/N	Risk Difference M-H,Fixed,95% CI	Weight	Risk Difference M-H,Fixed,95% CI
1 Adults and adolescents					
Aubier 1999	1/338	0/165		1.6 %	0.00 [-0.01, 0.01]
AUSTRI 2016	34/5834	33/5845		42.1 %	0.00 [0.00, 0.00]
Bailey 2008	2/239	2/236		1.7 %	0.00 [-0.02, 0.02]
Bateman 2001	5/333	0/165		1.6 %	0.02 [0.00, 0.03]
Bernstein 2017	0/501	0/499		3.6 %	0.0 [0.00, 0.00]
GOAL 2004	8/1709	12/1707		12.3 %	0.00 [-0.01, 0.00]
Godard 2008	0/159	0/159		1.1 %	0.0 [-0.01, 0.01]
Ind 2003	1/171	3/160		1.2 %	-0.01 [-0.04, 0.01]
Katial 2011	3/306	0/315		2.2 %	0.01 [0.00, 0.02]
Kavuru 2000	0/92	0/90		0.7 %	0.0 [-0.02, 0.02]
Kerwin 2011	1/310	0/318		2.3 %	0.00 [-0.01, 0.01]
Koenig 2008	1/156	0/156		1.1 %	0.01 [-0.01, 0.02]



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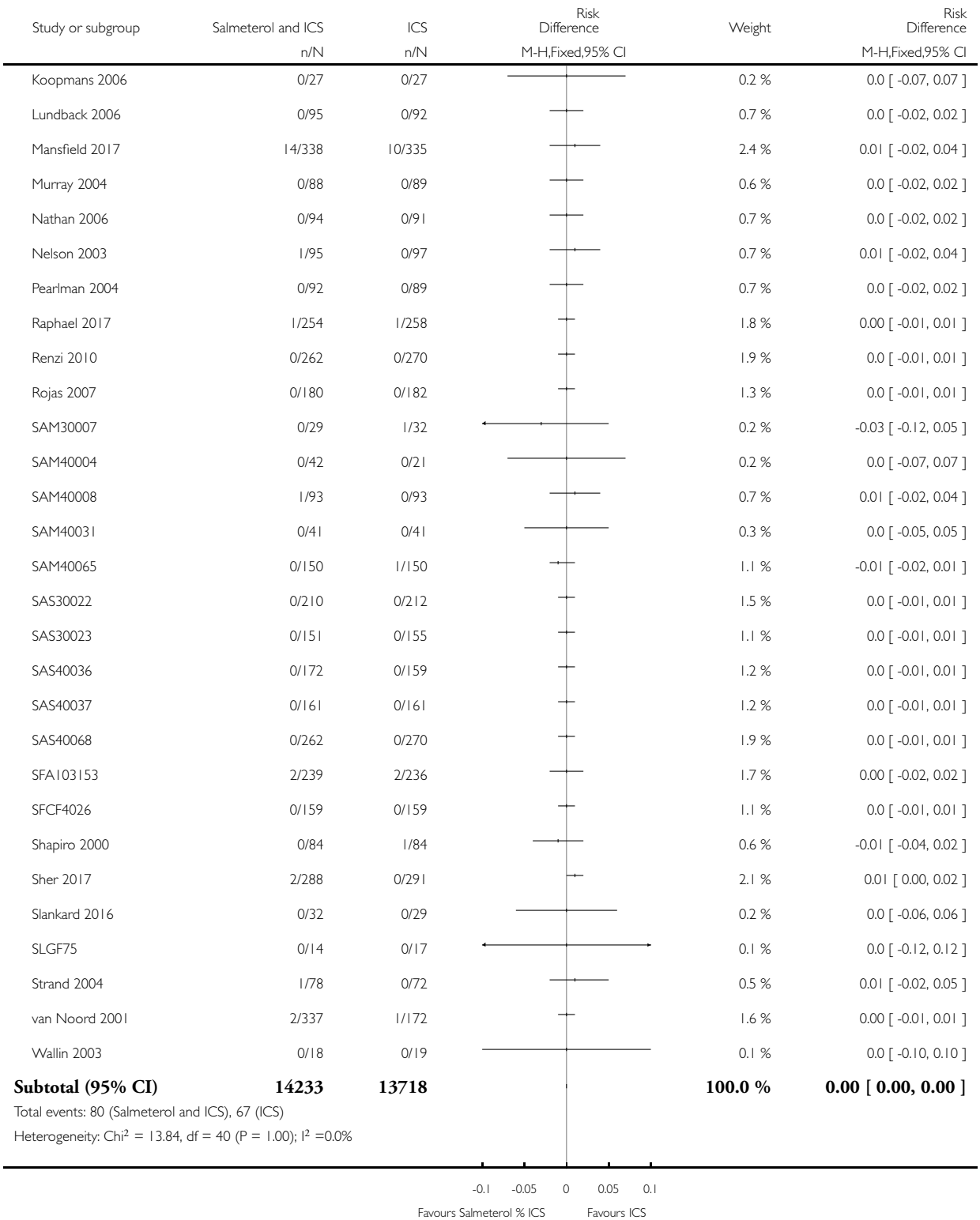

Study or subgroup	Salmeterol and ICS n/N	ICS n/N	Risk Difference M-H,Fixed,95% CI	Weight	Risk Difference M-H,Fixed,95% CI
Koopmans 2006	0/27	0/27		0.2 %	0.0 [-0.07, 0.07]
Lundback 2006	0/95	0/92		0.7 %	0.0 [-0.02, 0.02]
Mansfield 2017	14/338	10/335		2.4 %	0.01 [-0.02, 0.04]
Murray 2004	0/88	0/89		0.6 %	0.0 [-0.02, 0.02]
Nathan 2006	0/94	0/91		0.7 %	0.0 [-0.02, 0.02]
Nelson 2003	1/95	0/97		0.7 %	0.01 [-0.02, 0.04]
Pearlman 2004	0/92	0/89		0.7 %	0.0 [-0.02, 0.02]
Raphael 2017	1/254	1/258		1.8 %	0.00 [-0.01, 0.01]
Renzi 2010	0/262	0/270		1.9 %	0.0 [-0.01, 0.01]
Rojas 2007	0/180	0/182		1.3 %	0.0 [-0.01, 0.01]
SAM30007	0/29	1/32		0.2 %	-0.03 [-0.12, 0.05]
SAM40004	0/42	0/21		0.2 %	0.0 [-0.07, 0.07]
SAM40008	1/93	0/93		0.7 %	0.01 [-0.02, 0.04]
SAM40031	0/41	0/41		0.3 %	0.0 [-0.05, 0.05]
SAM40065	0/150	1/150		1.1 %	-0.01 [-0.02, 0.01]
SAS30022	0/210	0/212		1.5 %	0.0 [-0.01, 0.01]
SAS30023	0/151	0/155		1.1 %	0.0 [-0.01, 0.01]
SAS40036	0/172	0/159		1.2 %	0.0 [-0.01, 0.01]
SAS40037	0/161	0/161		1.2 %	0.0 [-0.01, 0.01]
SAS40068	0/262	0/270		1.9 %	0.0 [-0.01, 0.01]
SFA103153	2/239	2/236		1.7 %	0.00 [-0.02, 0.02]
SFCF4026	0/159	0/159		1.1 %	0.0 [-0.01, 0.01]
Shapiro 2000	0/84	1/84		0.6 %	-0.01 [-0.04, 0.02]
Sher 2017	2/288	0/291		2.1 %	0.01 [0.00, 0.02]
Slankard 2016	0/32	0/29		0.2 %	0.0 [-0.06, 0.06]
SLGF75	0/14	0/17		0.1 %	0.0 [-0.12, 0.12]
Strand 2004	1/78	0/72		0.5 %	0.01 [-0.02, 0.05]
van Noord 2001	2/337	1/172		1.6 %	0.00 [-0.01, 0.01]
Wallin 2003	0/18	0/19		0.1 %	0.0 [-0.10, 0.10]
Subtotal (95% CI)	**14233**	**13718**		**100.0 %**	**0.00 [0.00, 0.00]**
Total events: 80 (Salmeterol and ICS), 67 (ICS)					
Heterogeneity: Chi² = 13.84, df = 40 (P = 1.00); I² =0.0%					

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Study or subgroup	Salmeterol and ICS n/N	ICS n/N	Risk Difference M-H,Fixed,95% CI	Weight	Risk Difference M-H,Fixed,95% CI
Test for overall effect: Z = 0.75 (P = 0.46)					
2 Children					
Li 2010	0/173	0/177		4.1 %	0.0 [-0.01, 0.01]
Malone 2005	0/101	0/102		2.4 %	0.0 [-0.02, 0.02]
MASCOT 2013	1/23	1/19		0.5 %	-0.01 [-0.14, 0.12]
NCT01192178	1/171	0/168		4.0 %	0.01 [-0.01, 0.02]
Ploszczuk 2014	0/169	0/172		4.0 %	0.0 [-0.01, 0.01]
SAM40012	0/181	0/181		4.3 %	0.0 [-0.01, 0.01]
SAS30021	0/304	1/304		7.2 %	0.00 [-0.01, 0.01]
VESTRI 2016	27/3107	21/3101		73.4 %	0.00 [0.00, 0.01]
Subtotal (95% CI)	**4229**	**4224**		**100.0 %**	**0.00 [0.00, 0.00]**
Total events: 29 (Salmeterol and ICS), 23 (ICS)					
Heterogeneity: Chi^2 = 1.59, df = 7 (P = 0.98); I^2 =0.0%					
Test for overall effect: Z = 0.76 (P = 0.45)					
Test for subgroup differences: Chi^2 = 0.10, df = 1 (P = 0.75), I^2 =0.0%					

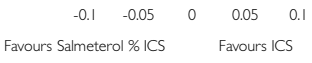
Analysis 2.5. Comparison 2 Risk difference meta-analysis: regular salmeterol in addition to regular ICS, Outcome 5 Asthma-related mortality.

Review: Inhaled steroids with and without regular salmeterol for asthma: serious adverse events

Comparison: 2 Risk difference meta-analysis: regular salmeterol in addition to regular ICS

Outcome: 5 Asthma-related mortality

Study or subgroup	Salmeterol and ICS n/N	ICS n/N	Risk Difference M-H,Fixed,95% CI	Weight	Risk Difference M-H,Fixed,95% CI
1 Adults and adolescents					
Aubier 1999	0/338	0/165		1.6 %	0.0 [-0.01, 0.01]
AUSTRI 2016	0/5834	0/5845		42.1 %	0.0 [0.00, 0.00]
Bailey 2008	0/239	0/236		1.7 %	0.0 [-0.01, 0.01]
Bateman 2001	0/333	0/165		1.6 %	0.0 [-0.01, 0.01]
Bernstein 2017	0/501	0/499		3.6 %	0.0 [0.00, 0.00]
GOAL 2004	0/1709	0/1707		12.3 %	0.0 [0.00, 0.00]
Godard 2008	0/159	0/159		1.1 %	0.0 [-0.01, 0.01]
Ind 2003	0/171	0/160		1.2 %	0.0 [-0.01, 0.01]
Katial 2011	0/306	0/315		2.2 %	0.0 [-0.01, 0.01]
Kavuru 2000	0/92	0/90		0.7 %	0.0 [-0.02, 0.02]
Kerwin 2011	0/310	0/318		2.3 %	0.0 [-0.01, 0.01]
Koenig 2008	0/156	0/156		1.1 %	0.0 [-0.01, 0.01]
Koopmans 2006	0/27	0/27		0.2 %	0.0 [-0.07, 0.07]
Lundback 2006	0/95	0/92		0.7 %	0.0 [-0.02, 0.02]
Mansfield 2017	0/338	0/335		2.4 %	0.0 [-0.01, 0.01]
Murray 2004	0/88	0/89		0.6 %	0.0 [-0.02, 0.02]
Nathan 2006	0/94	0/91		0.7 %	0.0 [-0.02, 0.02]
Nelson 2003	0/95	0/97		0.7 %	0.0 [-0.02, 0.02]
Pearlman 2004	0/92	0/89		0.7 %	0.0 [-0.02, 0.02]
Raphael 2017	0/254	0/258		1.8 %	0.0 [-0.01, 0.01]
Renzi 2010	0/262	0/270		1.9 %	0.0 [-0.01, 0.01]
Rojas 2007	0/180	0/182		1.3 %	0.0 [-0.01, 0.01]
SAM30007	0/29	0/32		0.2 %	0.0 [-0.06, 0.06]



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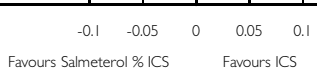
Study or subgroup	Salmeterol and ICS n/N	ICS n/N	Risk Difference M-H,Fixed,95% CI	Weight	Risk Difference M-H,Fixed,95% CI
SAM40004	0/42	0/21		0.2 %	0.0 [-0.07, 0.07]
SAM40008	0/93	0/93		0.7 %	0.0 [-0.02, 0.02]
SAM40031	0/41	0/41		0.3 %	0.0 [-0.05, 0.05]
SAM40065	0/150	0/150		1.1 %	0.0 [-0.01, 0.01]
SAS30022	0/210	0/212		1.5 %	0.0 [-0.01, 0.01]
SAS30023	0/151	0/155		1.1 %	0.0 [-0.01, 0.01]
SAS40036	0/172	0/159		1.2 %	0.0 [-0.01, 0.01]
SAS40037	0/161	0/161		1.2 %	0.0 [-0.01, 0.01]
SAS40068	0/262	0/270		1.9 %	0.0 [-0.01, 0.01]
SFA103153	0/239	0/236		1.7 %	0.0 [-0.01, 0.01]
SFCF4026	0/159	0/159		1.1 %	0.0 [-0.01, 0.01]
Shapiro 2000	0/84	0/84		0.6 %	0.0 [-0.02, 0.02]
Sher 2017	0/288	0/291		2.1 %	0.0 [-0.01, 0.01]
Slankard 2016	0/32	0/29		0.2 %	0.0 [-0.06, 0.06]
SLGF75	0/14	0/17		0.1 %	0.0 [-0.12, 0.12]
Strand 2004	0/78	0/72		0.5 %	0.0 [-0.03, 0.03]
van Noord 2001	0/337	0/172		1.6 %	0.0 [-0.01, 0.01]
Wallin 2003	0/18	0/19		0.1 %	0.0 [-0.10, 0.10]
Subtotal (95% CI)	**14233**	**13718**		**100.0 %**	**0.0 [0.00, 0.00]**
Total events: 0 (Salmeterol and ICS), 0 (ICS)					
Heterogeneity: Chi^2 = 0.0, df = 40 (P = 1.00); I^2 =0.0%					
Test for overall effect: Z = 0.0 (P = 1.0)					
2 Children					
Li 2010	0/173	0/177		4.1 %	0.0 [-0.01, 0.01]
Malone 2005	0/101	0/102		2.4 %	0.0 [-0.02, 0.02]
MASCOT 2013	0/23	0/19		0.5 %	0.0 [-0.09, 0.09]
NCT01192178	0/171	0/168		4.0 %	0.0 [-0.01, 0.01]
Ploszczuk 2014	0/169	0/172		4.0 %	0.0 [-0.01, 0.01]
SAM40012	0/181	0/181		4.3 %	0.0 [-0.01, 0.01]
SAS30021	0/304	0/304		7.2 %	0.0 [-0.01, 0.01]
VESTRI 2016	0/3107	0/3101		73.4 %	0.0 [0.00, 0.00]
Subtotal (95% CI)	**4229**	**4224**		**100.0 %**	**0.0 [0.00, 0.00]**
Total events: 0 (Salmeterol and ICS), 0 (ICS)					



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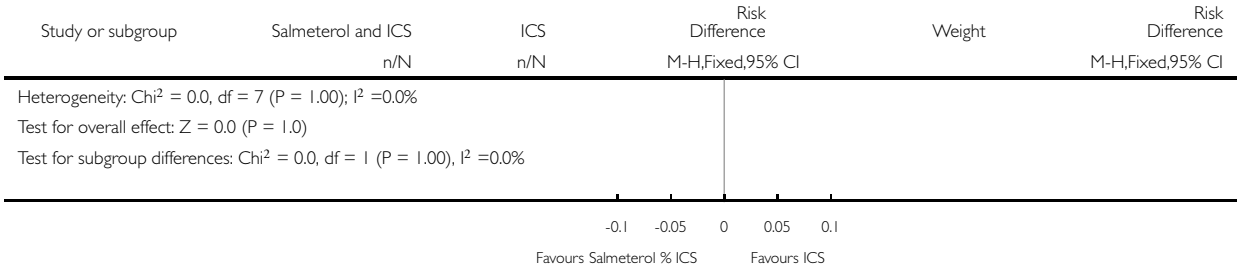

ADDITIONAL TABLES

Table 1. Dose of salmeterol and fluticasone

Study ID	Age of participants (Years)	N on FSC	N on ICS	Daily dose of fluticasone (μg)	Daily dose of salmeterol (μg)	Combined inhaler	Separate inhalers	Duration (weeks)
Aubier 1999	12+	338	165	1000	100	√	√	28
AUSTRI 2016	12+	5834	5845	200/500/1000	100	√		26
Bailey 2008	12+	239	236	200	100	√		52
Bateman 2001	12+	333	165	200	100	√		52
Bernstein 2017	12+	501	499	500	100	√		24
GOAL 2004	12+	1709	1707	200/500/1000	100	√		12
Godard 2008	18+	159	159	500	100	√		24
Ind 2003	16+	171	160	500	100		√	28
Katial 2011	12+	306	315	500	100	√		52
Kavuru 2000	12+	92	90	200	100	√		52

Table 1. Dose of salmeterol and fluticasone (*Continued*)

Kerwin 2011	12+	310	318	500	100	√		12
Koenig 2008	12+	156	156	200/500/1000	100	√		40
Koopmans 2006	18+	27	27	500	100	√		12
Li 2010	4 to 11	173	177	200	100	√		12
Lundback 2006	18+	95	92	500	100	√		12
Malone 2005	4 to 11	101	102	200	100	√		12
Mansfield 2017	12+	338	335	200/400/500/1000	25/100	√		26
MASCOT 2013	4 to 11	23	19	200	100	√		48
Murray 2004	12+	88	89	200	100	√		12
Nathan 2006	12+	94	91	220	100	√		16
NCT0119217	4 to 11	171	168	200	100	√		16
Nelson 2003	12+	95	97	200	100	√		12
Pearlman 2004	12+	92	89	200	100	√		12
Ploszczuk 2014	2 to 11	169	172	200	100	√		12
Raphael 2017	12+	254	258	100/200	25	√		12
Renzi 2010	12+	262	270	200	100	√		24
Rojas 2007	12+	180	182	500	100	√		12
SAM30007	18+	29	32	200/500/1000	100	√		30

Table 1. Dose of salmeterol and fluticasone (*Continued*)

SAM40004	18+	42	21	200	100	√		52
SAM40008	18+	93	93	1000	100	√		26
SAM40012	4 to 11	181	181	200	100	√		24
SAM40031	18+	41	41	200/500/1000	100	√		52
SAM40065	12+	150	150	200/500/1000	100	√		40
SAS30021	4 to 11	304	304	100	50	√		12
SAS30022	12+	210	212	500	50	√		12
SAS30023	12+	151	155	100	50	√		12
SAS40036	15+	172	159	200	100	√		16
SAS40037	15+	161	161	200	100	√		16
SAS40068	12+	262	270	200	100	√		24
SFA103153	12+	239	236	200	100	√		52
SFCF4026	18+	159	159	500	100	√		24
Shapiro 2000	12+	84	84	500	100	√		12
Sher 2017	12+	288	291	200/400	25	√		12
Slankard 2016	18+	32	29	88/220/440	42	√		16
SLGF75	16+	14	17	200	100		√	12
Strand 2004	18+	78	72	200	100	√		12
van Noord 2001	12+	337	172	1000	100	√		12
VESTRI 2016	4 to 11	3107	3101	200/500	100	√		26
Wallin 2003	12+	18	19	400	100		√	12

FSC: salmeterol/fluticasone; ICS: inhaled corticosteroid.

Table 2. Mortality

Study ID	Treatment arm	Cause of death in adults (n)
AUSTRI 2016	salmeterol and fluticasone	Heroin overdose (1), stroke (1), and dyspnoea due to metastatic hepatic carcinoma (1)
AUSTRI 2016	fluticasone	Aortic dissection (1), sudden cardiac death (1), gastroenteritis (1) , sepsis (1), and stroke (2)
Aubier 1999	salmeterol and fluticasone (separate inhalers)	Bronchial carcinoma (1)
GOAL 2004	salmeterol and fluticasone	Myocardial infarction (2) and pneumonia (1)
GOAL 2004	fluticasone	Myocardial infarction (2)
Ind 2003	salmeterol and fluticasone (separate inhalers)	Pneumothorax (1)
Kerwin 2011	salmeterol and fluticasone	Cardiac disease (1)
Kerwin 2011	fluticasone	Breast cancer (1)
Koenig 2008	fluticasone	Cardiac arrest and deep vein thrombosis (1)
Renzi 2010	fluticasone	Cardiac arrest (1)
SAS40068	fluticasone	Ventricular hypertrophy and aortic hypoplasia (1)
Sher 2017	salmeterol and fluticasone	A female patient developed severe jaundice on day 30, which led to withdrawal of the study drug, and she died 6 weeks later. She had begun taking an herbal supplement before the onset of jaundice and then declined recommended interventions and investigations into her condition. The death was considered not related to study treatment
Strand 2004	fluticasone	Unknown cause (1)
van Noord 2001	salmeterol and fluticasone	Leukaemia (1)

Table 3. Summary of pooled odds ratios

Peto OR meta-analysis: regular salmeterol in addition to regular ICS vs ICS alone								
All-cause mortality	**Events Rx**	**Total Rx**	**Events control**	**Total control**	**Peto OR**	**CI start**	**CI end**	**Worst-case NNTH[a] (from OR CI end)**
Adults and adolescents	11	14,233	13	13,718	0.80	0.36	1.78	1661
Children	0	4229	0	4224	-	-	-	-
All cause non-fatal SAE								
Adults and adolescents	332	14,233	282	13,718	1.14	0.97	1.33	152
Children	65	4229	62	4224	1.04	0.73	1.48	139
Asthma-related mortality								
Adults and adolescents	0	14,233	0	13,718	-	-	-	-
Children	0	4229	0	4224	-	-	-	-
Asthma-related SAE								
Adults and adolescents	80	14,233	67	13,718	1.15	0.83	1.59	351
Children	29	4229	23	4224	1.25	0.72	2.16	128

[a]NNTH (number needed to treat for an additional harmful outcome) calculated using Visual Rx to transform the upper end of the 95% confidence interval of the Peto OR, respectively.

Table 4. Summary of pooled risk difference

Risk difference meta-analysis: regular salmeterol in addition to regular ICS vs ICS alone								
All-cause mortality	**Events Rx**	**Total Rx**	**Events control**	**Total control**	**Risk difference**	**CI start**	**CI end**	**Worst-case NNTH[a] (from RD 95% CI end)**

Table 4. Summary of pooled risk difference (*Continued*)

Adults and adolescents	11	14,233	13	13,718	-0.0002	-0.0013	0.0009	1099
Children	0	4229	0	4224	0.0000	-0.0013	0.0013	763
All-cause non-fatal SAE								
Adults and adolescents	333	14,233	283	13,718	0.0027	-0.0008	0.0062	161
Children	65	4229	62	4224	0.0006	-0.0047	0.0058	172
Asthma-related mortality								
Adults and adolescents	0	14,233	0	13,718	0.0000	-0.0009	0.0009	1099
Children	0	4229	0	4224	0.0000	-0.0013	0.0013	763
Asthma-related non-fatal SAE								
Adults and adolescents	82	14,233	67	13,718	0.0007	-0.0012	0.0026	385
Children	29	4229	23	4224	0.0014	-0.0022	0.0049	205

[a] NNTH (number needed to treat for an additional harmful outcome) calculated from the inverse of the upper end of the 95% confidence interval (CI end) of the risk difference.

APPENDICES

Appendix 1. Pharmacology of beta$_2$-agonists

Beta$_2$-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 is probably best to concentrate on specific adverse side effects in human subjects at doses that 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 is 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 in 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 may 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 do 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 seen in the 10 to 19-year 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 hospitals, 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 hospitals, 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 for reducing total

peripheral vascular resistance (Burggraaf 2001) - another beta$_2$-mediated effect that 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 mucus 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 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 to 4 times the concentration of salmeterol, dose equivalencies 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, 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 increasing actuations of standard doses of formoterol and salmeterol inhalers are compared 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 LABAs are used at manufacturer-recommended preventative doses. However, it is possible that some patients may 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 to 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 show no significant differences 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 review 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 (Jones 2001; Lipworth 2000).

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, although 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 (Hancox 1999; Wong 1990), 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 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 fenoterol is stopped (Sears 1990), which may be detrimental. Furthermore, it appears that regular salbutamol treatment can actually increase airway responsiveness to allergen (Cockcroft 1993); this is 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 it 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; Grainger 1991; Pearce 1990). 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 can cause 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 explaining or contributing towards both 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 in relieving bronchoconstriction in the acute setting (Hanania 2007), and that they could paradoxically cause patients to delay longer in seeking medical help. 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 20th 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 1930s, given that corticosteroids were not used for the treatment of asthma in 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 among those taking LABAs alone.

Appendix 3. Sources and search methods for the Cochrane Airways Group Specialised Register (CAGR)

Electronic searches: core databases

Database	Dates searched	Frequency of search
CENTRAL (via the Cochrane Register of Studies (CRS))	From inception	Monthly
MEDLINE (Ovid)	1946 onwards	Weekly
Embase (Ovid)	1974 onwards	Weekly
PsycINFO (Ovid)	1967 onwards	Monthly
CINAHL (EBSCO)	1937 onwards	Monthly
AMED (EBSCO)	From inception	Monthly

Handsearches: core respiratory conference abstracts

Conference	Years searched
American Academy of Allergy, Asthma and Immunology (AAAAI)	2001 onwards
American Thoracic Society (ATS)	2001 onwards
Asia Pacific Society of Respirology (APSR)	2004 onwards
British Thoracic Society Winter Meeting (BTS)	2000 onwards
Chest Meeting	2003 onwards
European Respiratory Society (ERS)	1992, 1994, 2000 onwards
International Primary Care Respiratory Group Congress (IPCRG)	2002 onwards
Thoracic Society of Australia and New Zealand (TSANZ)	1999 onwards

MEDLINE search strategy used to identify trials for the CAGR

Asthma search

1. exp Asthma/
2. asthma$.mp.
3. (antiasthma$ or anti-asthma$).mp.
4. Respiratory Sounds/
5. wheez$.mp.
6. Bronchial Spasm/
7. bronchospas$.mp.
8. (bronch$ adj3 spasm$).mp.
9. bronchoconstrict$.mp.
10. exp Bronchoconstriction/
11. (bronch$ adj3 constrict$).mp.
12. Bronchial Hyperreactivity/
13. Respiratory Hypersensitivity/
14. ((bronchial$ or respiratory or airway$ or lung$) adj3 (hypersensitiv$ or hyperreactiv$ or allerg$ or insufficiency)).mp.
15. ((dust or mite$) adj3 (allerg$ or hypersensitiv$)).mp.
16. or/1-15

Filter to identify RCTs

1. exp "clinical trial [publication type]"/
2. (randomised or randomised).ab,ti.
3. placebo.ab,ti.
4. dt.fs.
5. randomly.ab,ti.
6. trial.ab,ti.
7. groups.ab,ti.
8. or/1-7
9. Animals/
10. Humans/
11. 9 not (9 and 10)
12. 8 not 11

The MEDLINE strategy and RCT filter are adapted to identify trials in other electronic databases.

Appendix 4. Search strategy to identify relevant trials from the Cochrane Airways Trials Register

#1 AST:MISC1
#2 MeSH DESCRIPTOR Asthma Explode All
#3 asthma*:ti,ab
#4 #1 or #2 or #3
#5 MeSH DESCRIPTOR Adrenergic beta-2 Receptor Agonists
#6 (long-acting or "long acting") NEAR ((beta* NEAR3 (agonist* OR adrenergic*)) OR bronchodilat*)
#7 LABA:TI,AB
#8 MESH DESCRIPTOR Salmeterol Xinafoate
#9 salmeterol:ti,ab,kw
#10 MESH DESCRIPTOR Formoterol Fumarate
#11 formoterol:ti,ab,kw
#12 eformoterol:ti,ab,kw
#13 (Advair OR Symbicort OR Serevent OR Foradil OR Oxis):ti,ab,kw
#14 #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13

#15 #4 AND #14
#16 MESH DESCRIPTOR Drug-Related Side Effects and Adverse Reactions EXPLODE ALL
#17 MESH DESCRIPTOR Drug Monitoring
#18 MESH DESCRIPTOR Adverse Drug Reaction Reporting Systems
#19 MESH DESCRIPTOR Product Surveillance, Postmarketing EXPLODE ALL
#20 MESH DESCRIPTOR Mortality EXPLODE ALL
#21 serious or safety or surveillance or mortality or death or intubat* or adverse or toxic* or complication* or tolerability or harm*
#22 #16 OR #17 OR #18 OR #19 OR #20 OR #21
#23 #15 AND #22
#24 INREGISTER
#25 #23 AND #24

Appendix 5. Quality of life considerations

To compare outcomes measured in different units has been always a challenge. To address this problem, economists developed quality-adjusted life years (QALYs), which allow us to balance fatal and not fatal results of a specific intervention. Regarding treatment with salmeterol and inhaled corticosteroids, we can assume that the number of QALYs lost by one death could never be greater than the number of QALYs gained with the benefits in health-related quality of life. First, since the QALYs lost by one person's death depend on his or her age, we have selected as potential scenarios the two asthma-related deaths that occurred in the budesonide-formoterol group of the recent safety trial of formoterol and inhaled steroids (Peters 2016). The death of a 22-year-old woman equates to 59.998 QALYs, and the death of a 68-year-old woman equals to 11.480 QALYs, considering life expectancy at birth of women in OECD (84 years) and English population norms of EQ-5D index (Janssen 2014). Second, the average QALY gained for each patient receiving salmeterol/fluticasone propionate fixed combination within one year ranges from 0.01 to 0.0152 (GOAL 2004 Ismaila 2014). Third, it is therefore necessary that 6000-3960 patients-year benefit from treatment to compensate the death of the 22-year-old woman (60 QALYs), and it is necessary that 1150-759 patients-year benefit from treatment to compensate the death of a 68-year-old woman (11.5 QALYs). Thus, translating these estimates to the current systematic review, a death over six months on salmeterol would need from two to ten thousand people to benefit from the treatment.

WHAT'S NEW

Date	Event	Description
10 October 2018	New search has been performed	New literature search was run
10 October 2018	New citation required and conclusions have changed	We added 6 additional studies including 14,504 adults (AUSTRI 2016; Bernstein 2017; Mansfield 2017; Raphael 2017; Sher 2017; Slankard 2016), as well as 3 additional studies including 6591 children (MASCOT 2013; Ploszczuk 2014; VESTRI 2016). The 2 large ongoing studies identified at the last update (NCT01462344; NCT01475721) are now included as AUSTRI 2016 and VESTRI 2016 Roman Jaeschke stepped down as an author of the review, and Sam Waterson and Ben Sayer joined as review authors

HISTORY

Protocol first published: Issue 1, 2008

Review first published: Issue 3, 2009

Date	Event	Description
1 August 2012	New search has been performed	New literature search was run
1 August 2012	New citation required but conclusions have not changed	The 2012 update identified 5 additional studies including 2574 adults and adolescents (Bailey 2008; Godard 2008; Katial 2011; Kerwin 2011; Renzi 2010), along with 2 additional studies including 689 children (Li 2010; NCT01192178). Also identified were 2 large ongoing studies, which aim to recruit 6000 children and 11,000 adults. They were expected to report results in 2017 (NCT01462344; NCT01475721) Current evidence is insufficient to show that regular salmeterol in combination with fluticasone is safe for use in adults or children

CONTRIBUTIONS OF AUTHORS

CJC: conception of the idea and co-writing of the protocol (Cates 2009). First author for data extraction and co-writing of both updates

MF and SS: data extraction and co-writing the 2013 and 2018 updates.

BS and SW: trial selection, data extraction, and co-writing of the 2018 update.

Previous versions

Toby Lasserson: co-writing of the protocol (Cates 2009), trial selection, data extraction, and co-writing of the original review (Cates 2009b).
Roman Jaeschke: trial selection, data extraction, and co-writing of the original review (Cates 2009b), as well as the update (Cates 2013).
Matthew J Cates: co-writing of the protocol, data extraction, and co-writing of the original review (Cates 2009b).

DECLARATIONS OF INTEREST

CJC: joint co-ordinating editor of the Cochrane Airways Group.

SS: none known.

MF: none known.

BS: none known.

SW: none known.

Previous versions

Roman Jaeschke received honoraria for lectures from Boehringer Ingelheim (2006; USD4000) and GlaxoSmithKline (2007; EUR2000), as well as travel support from Boehringer Ingelheim and GlaxoSmithKline (2006 and 2007; up to USD1000). This occurred more than five years before publication of the review.
Mattthew Cates and Toby Lasserson: none known.

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DIFFERENCES BETWEEN PROTOCOL AND REVIEW

Although the protocol originally included studies comparing salmeterol and ICS versus higher doses of ICS (Cates 2009), we restricted this review and update to studies randomising participants to the same dose of ICS with and without salmeterol. Due to problems with fixed continuity corrections for zero cells, we used the Peto OR as the primary metric for analysis of relative measures, and the risk difference for absolute measures. We did not attempt subgroup analysis on the basis of asthma severity or dose of ICS.

For the 2018 update, we assessed the safety of adding salmeterol to ICS from the worst case number needed to treat for an additional harmful outcome (NNTH) for one additional serious adverse event or death to occur. We calculated the NNTH using Visual Rx to transform the upper end of the 95% CI of the pooled Peto OR, by applying it to the mean event rate in control arms of the trials.

INDEX TERMS

Medical Subject Headings (MeSH)

Adrenal Cortex Hormones [administration & dosage; *adverse effects]; Adrenergic beta-2 Receptor Agonists [administration & dosage; *adverse effects]; Albuterol [administration & dosage; adverse effects; *analogs & derivatives]; Anti-Asthmatic Agents [administration & dosage; *adverse effects]; Asthma [drug therapy; *mortality]; Randomized Controlled Trials as Topic; Salmeterol Xinafoate

MeSH check words

Adolescent; Adult; Child; Humans; Young Adult