Cochrane Library

Cochrane Database of Systematic Reviews

Regular treatment with formoterol and an inhaled corticosteroid versus regular treatment with salmeterol and an inhaled corticosteroid for chronic asthma: serious adverse events (Review)

O'Shea O, Stovold E, Cates CJ

O'Shea O, Stovold E, Cates CJ.
Regular treatment with formoterol and an inhaled corticosteroid versus regular treatment with salmeterol and an inhaled corticosteroid for chronic asthma: serious adverse events.
Cochrane Database of Systematic Reviews 2021, Issue 4. Art. No.: CD007694.
DOI: 10.1002/14651858.CD007694.pub3.

www.cochranelibrary.com

WILEY

TABLE OF CONTENTS

[Intervention Review]

Regular treatment with formoterol and an inhaled corticosteroid versus regular treatment with salmeterol and an inhaled corticosteroid for chronic asthma: serious adverse events

Orlagh O'Shea[1], Elizabeth Stovold[2], Christopher J Cates[2]

[1]School of Physiotherapy, Royal College of Surgeons in Ireland, Dublin, Ireland. [2]Cochrane Airways, Population Health Research Institute, St George's, University of London, London, UK

Contact address: Orlagh O'Shea, orlaghoshea@rcsi.com.

Editorial group: Cochrane Airways Group.
Publication status and date: Edited (no change to conclusions), published in Issue 4, 2021.

Citation: O'Shea O, Stovold E, Cates CJ. Regular treatment with formoterol and an inhaled corticosteroid versus regular treatment with salmeterol and an inhaled corticosteroid for chronic asthma: serious adverse events. *Cochrane Database of Systematic Reviews* 2021, Issue 4. Art. No.: CD007694. DOI: 10.1002/14651858.CD007694.pub3.

ABSTRACT

Background

Asthma is characterised by chronic inflammation of the airways and recurrent exacerbations with wheezing, chest tightness, and cough. Treatment with inhaled steroids and bronchodilators can result in good control of symptoms, prevention of further morbidity, and improved quality of life. However, an increase in serious adverse events with the use of both regular formoterol and regular salmeterol (long-acting beta$_2$-agonists) compared with placebo for chronic asthma has been demonstrated in previous Cochrane Reviews. This increase was statistically significant in trials that did not randomise participants to an inhaled corticosteroid, but not when formoterol or salmeterol was combined with an inhaled corticosteroid. The confidence intervals were found to be too wide to ensure that the addition of an inhaled corticosteroid renders regular long-acting beta$_2$-agonists completely safe; few participants and insufficient serious adverse events in these trials precluded a definitive decision about the safety of combination treatments.

Objectives

To assess risks of mortality and non-fatal serious adverse events in trials that have randomised patients with chronic asthma to regular formoterol and an inhaled corticosteroid versus regular salmeterol and an inhaled corticosteroid.

Search methods

We searched the Cochrane Airways Register of Trials, CENTRAL, MEDLINE, Embase, and two trial registries to identify reports of randomised trials for inclusion. We checked manufacturers' websites and clinical trial registers for unpublished trial data, as well as Food and Drug Administration (FDA) submissions in relation to formoterol and salmeterol. The date of the most recent search was 24 February 2021.

Selection criteria

We included controlled clinical trials with a parallel design, recruiting patients of any age and severity of asthma, if they randomised patients to treatment with regular formoterol versus regular salmeterol (each with a randomised inhaled corticosteroid) and were of at least 12 weeks' duration.

Data collection and analysis

Two review authors independently selected trials for inclusion in the review, extracted outcome data from published papers and trial registries, and applied GRADE rating for the results. We sought unpublished data on mortality and serious adverse events from study sponsors and authors. The primary outcomes were all cause mortality and non-fatal serious adverse events. We chose not to calculate an

average result from all the formulations of formoterol and inhaled steroid, as the doses and delivery devices are too diverse to assume a single class effect.

Main results

Twenty-one studies in 11,572 adults and adolescents and two studies in 723 children met the eligibility criteria of the review. No data were available for two studies; therefore these were not included in the analysis. Among adult and adolescent studies, seven compared formoterol and budesonide to salmeterol and fluticasone (N = 7764), six compared formoterol and beclomethasone to salmeterol and fluticasone (N = 1923), two compared formoterol and mometasone to salmeterol and fluticasone (N = 1126), two compared formoterol and fluticasone to salmeterol and fluticasone (N = 790), and one compared formoterol and budesonide to salmeterol and budesonide (N = 229).

In total, five deaths were reported among adults, none of which was thought to be related to asthma. The certainty of evidence for all-cause mortality was low, as there were not enough deaths to permit any precise conclusions regarding the risk of mortality on combination formoterol versus combination salmeterol.

In all, 201 adults reported non-fatal serious adverse events. In studies comparing formoterol and budesonide to salmeterol and fluticasone, there were 77 in the formoterol arm and 68 in the salmeterol arm (Peto odds ratio (OR) 1.14, 95% confidence interval (CI) 0.82 to 1.59; 5935 participants, 7 studies; moderate-certainty evidence). In the formoterol and beclomethasone studies, there were 12 adults in the formoterol arm and 13 in the salmeterol arm with events (Peto OR 0.94, 95% CI 0.43 to 2.08; 1941 participants, 6 studies; moderate-certainty evidence). In the formoterol and mometasone studies, there were 18 in the formoterol arm and 11 in the salmeterol arm (Peto OR 1.02, 95% CI 0.47 to 2.20; 1126 participants, 2 studies; moderate-certainty evidence). One adult in the formoterol and fluticasone studies in the salmeterol arm experienced an event (Peto OR 0.05, 95% CI 0.00 to 3.10; 293 participants, 2 studies; low-certainty evidence). Another adult in the formoterol and budesonide compared to salmeterol and budesonide study in the formoterol arm had an event (Peto OR 7.45, 95% CI 0.15 to 375.68; 229 participants, 1 study; low-certainty evidence).

Only 46 adults were reported to have experienced asthma-related serious adverse events. The certainty of the evidence was low to very low due to the small number of events and the absence of independent assessment of causation.

The two studies in children compared formoterol and fluticasone to salmeterol and fluticasone. No deaths and no asthma-related serious adverse events were reported in these studies. Four all-cause serious adverse events were reported: three in the formoterol arm, and one in the salmeterol arm (Peto OR 2.72, 95% CI 0.38 to 19.46; 548 participants, 2 studies; low-certainty evidence).

Authors' conclusions

Overall, for both adults and children, evidence is insufficient to show whether regular formoterol in combination with budesonide, beclomethasone, fluticasone, or mometasone has a different safety profile from salmeterol in combination with fluticasone or budesonide. Five deaths of any cause were reported across all studies and no deaths from asthma; this information is insufficient to permit any firm conclusions about the relative risks of mortality on combination formoterol in comparison to combination salmeterol inhalers. Evidence on all-cause non-fatal serious adverse events indicates that there is probably little to no difference between formoterol/budesonide and salmeterol/fluticasone inhalers. However events for the other formoterol combination inhalers were too few to allow conclusions. Only 46 non-fatal serious adverse events were thought to be asthma related; this small number in addition to the absence of independent outcome assessment means that we have very low confidence for this outcome.

We found no evidence of safety issues that would affect the choice between salmeterol and formoterol combination inhalers used for regular maintenance therapy by adults and children with asthma.

PLAIN LANGUAGE SUMMARY

Do people with asthma have fewer serious adverse events when taking formoterol and inhaled corticosteroids compared to salmeterol and inhaled corticosteroids?

Background

Asthma is a condition that affects the airways – the small tubes that carry air into and out of the lungs. When a person with asthma comes into contact with an asthma trigger, the airways become irritated and the muscles around the walls of the airways tighten, so that the airways become narrower (bronchoconstriction) and the lining of the airways becomes inflamed and starts to swell. Sometimes, sticky mucus or phlegm builds up, which can further narrow the airways. These reactions cause the airways to become narrower and irritated - making it difficult to breathe, and leading to coughing, wheezing, shortness of breath, and tightness in the chest. People with asthma are generally advised to take inhaled steroids to combat the underlying inflammation, but if asthma is still not controlled, current clinical guidelines for people with asthma recommend the introduction of an additional medication to help. A common strategy in these situations is to use a long-acting beta-agonist: formoterol or salmeterol. A long-acting beta-agonist is an inhaled drug that opens the airways (bronchodilator), making it easier to breathe. Inhaled steroids can be added to these bronchodilators in the same inhaler. A variety of inhaled steroids are used in combined inhalers with either formoterol or salmeterol.

We know from previous Cochrane Reviews that there is a small increase in serious adverse events (such as very severe asthma attacks, as well as other life-threatening events) when regular formoterol or regular salmeterol is taken without inhaled steroids, but this increase was not seen when these drugs were used with an inhaled steroid in a single combined inhaler. This review sought information from trials that compared the two treatments (i.e. when people taking salmeterol with an inhaled corticosteroid were compared directly with people taking formoterol and an inhaled corticosteroid) to see if we could determine which drug was safer.

Study characteristics

We carried out a search for studies in February 2021. In total, we included in this review 23 randomised controlled trials comparing formoterol and inhaled corticosteroids with salmeterol and inhaled corticosteroids. Twenty-one studies with 11,572 participants included adults and adolescents. The lower age in these 21 studies varied from 12 to 16 or 18. Eight of these studies (7730 adults) compared formoterol/budesonide combination inhalers with salmeterol/fluticasone, with smaller numbers (1472, 1126, and 1075 adults) comparing the other formoterol combinations with salmeterol/fluticasone. Only 229 adults were available in studies comparing formoterol/budesonide with salmeterol/budesonide. Two studies of 723 participants included children; the age ranges in these studies were 4 to 12 and 5 to 12; both compared formoterol/fluticasone with salmeterol/fluticasone inhalers.

Key results

No certain differences could be detected between combination formoterol/inhaled corticosteroids and salmeterol/inhaled corticosteroids for all-cause mortality nor for all-cause or asthma-related non-fatal adverse events. No deaths from asthma were reported. The included studies had enough participants to assess the benefits of treatment, but they did not include enough people to determine the comparative safety of these treatments.

Quality of the evidence

In general, the included studies had low levels of bias, but there was a low incidence of mortality and serious adverse events, which reduced the certainty of the evidence for different outcomes. The quality of evidence for all-cause mortality and all-cause non-fatal serious adverse events was graded as low and moderate, respectively. The quality of evidence for asthma-related serious adverse events varied from low to very low due to small numbers of asthma-related events and lack of independent assessment of the causation of events.

Conclusions

We found no safety issues that would affect the choice between salmeterol and formoterol combination inhalers used for regular maintenance therapy in adults and children with asthma.

SUMMARY OF FINDINGS

Summary of findings 1. Adults: formoterol/ICS compared to salmeterol/ICS for chronic asthma: all-cause mortality

Adults formoterol/ICS compared to salmeterol/ICS for chronic asthma: all-cause mortality

Patient or population: adults, chronic asthma: all-cause mortality
Setting: community
Intervention: formoterol/ICS
Comparison: salmeterol/ICS

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№. of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with salmeterol/ICS	Risk with formoterol/ICS				
All-cause mortality - formoterol/budesonide vs salmeterol/fluticasone Follow-up: mean 24 weeks	34 per 100,000	35 per 100,000 (2 to 551)	OR 1.03 (0.06 to 16.44)	5935 (7 RCTs)	⊕⊕⊖⊖ LOW[a]	
All-cause mortality - formoterol/beclomethasone vs salmeterol/fluticasone Follow-up: mean 21 weeks	No deaths		-	1257 (4 RCTs)	N/A	
All-cause mortality - formoterol/mometasone vs salmeterol/fluticasone Follow-up: mean 26 weeks	0 per 100,000	0 per 100,000 (0 to 0)	OR 4.46 (0.23 to 85.40)	1126 (2 RCTs)	⊕⊕⊖⊖ LOW[a]	Zero events on salmeterol prevents calculation of absolute risk
All-cause mortality - formoterol/fluticasone vs salmeterol/fluticasone Follow-up: mean 12 weeks	0 per 100,000	0 per 100,000 (0 to 0)	OR 7.39 (0.15 to 372.38)	270 (2 RCTs)	⊕⊕⊖⊖ LOW[a]	Zero events on salmeterol prevents calculation of absolute risk
All-cause mortality formoterol/budesonide vs salmeterol/budesonide Follow-up: mean 12 weeks	No deaths		-	229 (1 RCT)	N/A	

*__The risk in the intervention group__ (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; N/A: not applicable; OR: odds ratio; RCT: randomised controlled trial.

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]Very wide confidence interval, downgraded by 2 points.

Summary of findings 2. Adults: formoterol/ICS compared to salmeterol/ICS for chronic asthma: all-cause serious adverse events

Adults: formoterol/ICS compared to salmeterol/ICS for chronic asthma: all-cause serious adverse events

Patient or population: adults, chronic asthma: serious adverse events
Setting: community
Intervention: formoterol/ICS
Comparison: salmeterol/ICS

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№. of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with salmeterol/ICS	Risk with formoterol/ICS				
All-cause non-fatal serious adverse events - formoterol/budesonide vs salmeterol/fluticasone Follow-up: mean 24 weeks	2290 per 100,000	2603 per 100,000 (1886 to 3593)	OR 1.14 (0.82 to 1.59)	5935 (7 RCTs)	⊕⊕⊕⊖ MODERATE[a]	
All-cause non-fatal serious adverse events - formoterol/beclomethasone vs salmeterol/fluticasone Follow-up: mean 18 weeks	1325 per 100,000	1247 per 100,000 (574 to 2717)	OR 0.94 (0.43 to 2.08)	1941 (6 RCTs)	⊕⊕⊕⊖ MODERATE[a]	
All-cause non-fatal serious adverse events - formoterol/mometasone vs salmeterol/fluticasone Follow-up: mean 26 weeks	2273 per 100,000	2317 per 100,000 (1081 to 4867)	OR 1.02 (0.47 to 2.20)	1126 (2 RCTs)	⊕⊕⊕⊖ MODERATE[a]	
All-cause non-fatal serious adverse events - formoterol/fluticasone vs salmeterol/fluticasone Follow-up: mean 12 weeks	935 per 100,000	47 per 100,000 (0 to 2841)	OR 0.05 (0.00 to 3.10)	293 (2 RCTs)	⊕⊕⊖⊖ LOW[b]	
All-cause non-fatal serious adverse events - formoterol/budesonide vs salmeterol/budesonide Follow-up: mean 12 weeks	0 per 100,000	0 per 100,000 (0 to 0)	OR 7.45 (0.15 to 375.68)	229 (1 RCT)	⊕⊕⊖⊖ LOW[b]	Zero events on salmeterol prevents calcula-

tion of absolute risk

*The risk in the intervention group (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; RCT: randomised controlled trial.

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]Confidence interval wide, downgraded by 1 point.
[b]Confidence interval very wide, downgraded by 2 points.

Summary of findings 3. Adults: formoterol/ICS compared to salmeterol/ICS for chronic asthma: asthma-related serious adverse events

Adults: formoterol/ICS compared to salmeterol/ICS for chronic asthma: asthma-related serious adverse events

Patient or population: adults, chronic asthma: asthma-related serious adverse events
Setting: community
Intervention: formoterol/ICS
Comparison: salmeterol/ICS

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№. of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with salmeterol/ICS	Risk with formoterol/ICS				
Asthma-related non-fatal serious adverse events - formoterol/budesonide vs salmeterol/fluticasone Follow-up: mean 24 weeks	842 per 100,000	583 per 100,000 (313 to 1059)	OR 0.69 (0.37 to 1.26)	5935 (7 RCTs)	⊕⊕⊖⊖ LOW[a,b]	
Asthma-related non-fatal serious adverse events - formoterol/beclomethasone vs salmeterol/fluticasone Follow-up: mean 19 weeks	131 per 100,000	132 per 100,000 (8 to 2081)	OR 1.01 (0.06 to 16.24)	1510 (5 RCTs)	⊕⊖⊖⊖ VERY LOW[b,c]	
Asthma related non-fatal serious adverse events - formoterol/mometasone v's salmeterol/fluticasone Follow-up: mean 12 weeks	0 per 100,000	0 per 100,000 (0 to 0)	OR 7.00 (0.14 to 353.37)	722 (1 RCT)	⊕⊖⊖⊖ VERY LOW[b,c]	Zero events on salmeterol prevents calcula-

						tion of absolute risk
Asthma-related non-fatal serious adverse events - formoterol/fluticasone vs salmeterol/fluticasone Follow-up: mean 12 weeks	935 per 100,000	47 per 100,000 (0 to 2841)	OR 0.05 (0.00 to 3.10)	293 (2 RCTs)	⊕⊕⊖⊖ VERY LOW[b,c]	
Asthma-related non-fatal serious adverse events - formoterol/budesonide vs salmeterol/budesonide Follow-up: mean 12 weeks	0 per 100,000	0 per 100,000 (0 to 0)	Not estimable	229 (1 RCT)	N/A	No events

*__The risk in the intervention group__ (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; N/A: not applicable; OR: odds ratio; RCT: randomised controlled trial.

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]Confidence interval wide, downgraded by 1 point.
[b]No independent assessment of causation, downgraded by 1 point.
[c]Confidence interval very wide, downgraded by 2 points.

Summary of findings 4. Children: formoterol/fluticasone compared to salmeterol/fluticasone for chronic asthma: serious adverse events

Children: formoterol/fluticasone compared to salmeterol/fluticasone for chronic asthma: serious adverse events

Patient or population: children, chronic asthma: serious adverse events
Setting: community
Intervention: formoterol/fluticasone
Comparison: salmeterol/fluticasone

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№. of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with salmeterol/fluticasone	Risk with formoterol/fluticasone				
All-cause mortality Follow-up: mean 12 weeks	No deaths		-	548 (2 RCTs)	N/A	

All-cause non-fatal serious adverse events Follow-up: mean 12 weeks	365 per 100,000	987 per 100,000 (139 to 6654)	OR 2.72 (0.38 to 19.46)	548 (2 RCTs)	⊕⊕⊖⊖ LOW[a]
Asthma-related non-fatal serious adverse events Follow-up: mean 12 weeks	No asthma-related events		-	548 (2 RCTs)	N/A

*__The risk in the intervention group__ (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; N/A: not applicable; OR: odds ratio; RCT: randomised controlled trial.

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]Very wide confidence interval, downgraded by 2 points.

BACKGROUND

Description of the condition

When asthma is not controlled by low-dose inhaled corticosteroids alone, many asthma guidelines recommend additional long-acting beta$_2$-agonists. Several Cochrane Reviews have addressed the efficacy of long-acting beta$_2$-agonists given with inhaled corticosteroids (Ni Chroinin 2009; Ni Chroinin 2010), in comparison with placebo (Walters 2007), short-acting beta$_2$-agonists (Walters 2002), leukotriene-receptor antagonists (Ducharme 2011), and increased doses of inhaled corticosteroids (Ducharme 2010). The beneficial effects of long-acting beta$_2$-agonists on lung function, symptoms, quality of life, and exacerbations requiring oral steroids have been demonstrated, and a rationale has been put forward for their use in combination with an inhaled corticosteroid (Barnes 2002).

However, a meta-analysis of the effects of long-acting beta$_2$-agonists 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). These review authors considered trials that compared any long-acting beta$_2$-agonists with placebo and were not able to include 28 trials in the primary analysis (including nearly 6000 patients) because information on asthma-related deaths was not provided.

Description of the intervention

Currently, two long-acting beta$_2$-agonists are available for treatment of asthma: formoterol (also known as eformoterol) and salmeterol. These two drugs, which are known to have differences in speed of onset and receptor activity, are used in different ways (e.g. salmeterol has slower onset of action than formoterol; Lotvall 2001). For this reason, we have considered salmeterol and formoterol separately in our previous work. Formoterol is now available in combination inhalers with budesonide, beclomethasone, mometasone, or fluticasone, and salmeterol is available in combination with fluticasone or budesonide.

How the intervention might work

In spite of the benefits noted in people with asthma, concern remains that regular treatment with long-acting beta$_2$-agonists might lead to an increase in asthma-related deaths (as seen in SMART 2006). Regular treatment with beta$_2$-agonists can lead to tolerance to their bronchodilator effects with both long-acting and short-acting compounds (Lipworth 1997); the pharmacology of beta$_2$-agonists is detailed in Appendix 1. A number of 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), as outlined in detail in Appendix 2.

Why it is important to do this review

Two of our published reviews have assessed the risks of fatal and non-fatal serious adverse events with regular salmeterol and formoterol compared to placebo or short-acting beta$_2$-agonists (Cates 2008; Cates 2008a). In comparison to placebo treatment, adults on regular salmeterol and children on regular formoterol demonstrated a significant increase in all-cause non-fatal serious adverse events. Two additional reviews, in which each drug was randomised with an inhaled corticosteroid in comparison to the same dose of the inhaled corticosteroid, have been recently updated following completion of large trials mandated by the Food and Drug Administration (FDA) (Cates 2018; Janjua 2019).

These studies did not demonstrate significant increases in serious adverse events, but even with the addition of new trials, the confidence intervals are too wide to ensure that adding an inhaled corticosteroid renders regular long-acting beta$_2$-agonists completely safe. Moreover, indirect comparisons on the relative safety of formoterol and salmeterol based on the results of these existing reviews are subject to confounding due to differences among participants, interventions, comparisons, and outcomes in the trials in each review.

A review comparing the safety of regular formoterol and salmeterol without a randomised inhaled corticosteroid has also been carried out based on trials that have made head-to-head comparisons of the two products (Cates 2012). The trials that were included in Cates 2012 turned out to have used background inhaled corticosteroids for all participants. However, no previous review had compared regular formoterol to regular salmeterol from trials in which an inhaled corticosteroid was a mandatory part of the randomised treatment. We have considered this to be a separate question, as adherence with an inhaled corticosteroid may be better when it is provided as part of the randomised treatment schedule (particularly if a combined inhaler is used).

This review set out to compare the safety of regular formoterol and regular salmeterol when each is used in combination with a randomised inhaled corticosteroid.

OBJECTIVES

To assess risks of mortality and non-fatal serious adverse events in trials that have randomised patients with chronic asthma to regular formoterol and an inhaled corticosteroid versus regular salmeterol and an inhaled corticosteroid.

METHODS

Criteria for considering studies for this review

Types of studies

We included controlled, parallel-design clinical trials, with or without blinding, in which patients with chronic asthma were randomly assigned to regular treatment with formoterol and an inhaled corticosteroid versus salmeterol and an inhaled corticosteroid. We excluded studies on acute asthma and exercise-induced bronchospasm.

Types of participants

We included patients of any age with a clinical diagnosis of asthma, unrestricted by disease severity or previous or current treatment.

Types of interventions

We included trials randomising patients to formoterol versus salmeterol given regularly in combination with an inhaled corticosteroid at any dose and delivered at a fixed dose by any single or separate devices (chlorofluorocarbon metered-dose inhaler (CFC-MDI); hydrofluoroalkane metered-dose inhaler (HFA-MDI); dry powder inhaler (DPI)) for a period of at least 12 weeks.

We excluded studies that used adjustable maintenance dosing and single-inhaler therapy (for maintenance and relief of symptoms).

Types of outcome measures

Primary outcomes

- All-cause mortality
- All-cause non-fatal serious adverse events (see definition below)

Secondary outcomes

- Asthma-related mortality
- Asthma-related non-fatal serious adverse events

We did not subdivide outcomes according to whether trial investigators considered them related to trial medication. We accepted trial investigators' judgement of whether or not serious adverse events were asthma-related.

An assessment of efficacy outcomes (such as exacerbations, symptoms, and lung function) with these drug combinations when co-delivered via the same inhaler has been undertaken and published elsewhere (Lasserson 2008).

Search methods for identification of studies

Electronic searches

The previously published version of this review included searches up to August 2011. For this update, we re-ran the literature search from inception to February 2021 using the following databases and trial registries.

- Cochrane Airways Trials Register (Cochrane Airways 2019), via the Cochrane Register of Studies (all years to 24 February 2021).
- Cochrane Central Register of Controlled Trials (CENTRAL; 2021 Issue 2), in the Cochrane Library, via the Cochrane Register of Studies (all years to 24 February 2021).
- MEDLINE (Ovid SP) (ALL 1946 to 23 February 2021; searched 24 February 2021).
- Embase (Ovid SP) (1974 to week 7 2021; searched 24 February 2021).
- US National Institutes of Health Ongoing Trials Register ClinicalTrials.gov (www.clinicaltrials.gov; all years to 24 February 2021).
- World Health Organization International Clinical Trials Registry Platform (apps.who.int/trialsearch; all years to 9 March 2020). This search was not updated in February 2021 as the platform was inaccessible at that time.

The initial search was conducted on 9 March 2020, and the search was updated on 24 February 2021. Search strategies are presented in Appendix 3. Population search terms were derived from the standard Cochrane Airways search strategy for asthma. Study design search terms are based on those recommended in the *Cochrane Handbook for Systematic Reviews of Interventions* (Lefebvre 2020). The search strategies were developed and searches conducted by the Cochrane Airways Information Specialist (ES). We did not restrict our searches by language or type of publication. We searched for conference abstracts and grey literature using the Cochrane Airways Trials Register, CENTRAL, and Embase.

Searching other resources

We checked the reference lists of all primary studies and review articles for additional references. We checked websites of clinical trial registers for unpublished trial data, and we checked FDA submissions related to salmeterol and formoterol. We searched for errata or retractions from included studies published in full text on PubMed, on 12 October 2020.

Data collection and analysis

Selection of studies

We used Cochrane's Screen4Me workflow to assess the search results. Screen4Me comprises three components: known assessments – a service that matches records in the search results to records that have already been screened in Cochrane Crowd and been labelled as 'RCT' or 'not an RCT'; the RCT classifier – a machine learning model that distinguishes RCTs from non-RCTs; and if appropriate, Cochrane Crowd – Cochrane's citizen science platform whereby the Crowd helps to identify and describe health evidence.

For more information about Screen4Me and the evaluations that have been done, please go to the Screen4Me Web page on the Cochrane Information Specialist's portal (https://community.cochrane.org/organizational-info/resources/resources-groups/information-specialists-portal). In addition, more detailed information regarding evaluations of the Screen4Me components can be found in the following publications: Marshall 2018, Thomas 2017, Noel-Storr 2018, and McDonald 2017.

After completing this initial assessment, we imported the remaining references into Rayyan (Ouzzani 2016), and two review authors (OOS and CJC) independently assessed identified studies by examining titles, abstracts, and keyword fields. We obtained the full text of studies that potentially fulfilled the inclusion criteria. Two review authors (OOS and CJC) independently assessed full-text articles for inclusion. No disagreements occurred.

Data extraction and management

Two review authors (OOS and CJC) extracted data independently using a prepared checklist and cross-checked all data for accuracy. Data were entered by OOS into RevMan 5, and CJC checked entries for accuracy. We extracted data on characteristics (methods, participants, interventions, outcomes) and results of the included studies. We contacted study authors and sponsors of included studies for unpublished adverse event data and searched manufacturers' websites for further details of adverse events. We also searched FDA submissions. We recorded all-cause serious adverse events (fatal and non-fatal), and in view of the difficulty in deciding whether events are asthma-related, noted details of the cause of death. We requested further information when causation was not clear (particularly in relation to serious adverse events).

Assessment of risk of bias in included studies

Two review authors (OOS and CJC) assessed the included studies for bias protection (including sequence generation for randomisation, allocation concealment, blinding of participants and assessors, loss to follow-up, completeness of outcome assessment, and independent assessment of causation of serious adverse events). We judged risk of bias as high, low, or unclear

according to recommendations in the *Cochrane Handbook of Systematic Reviews of Interventions* (Higgins 2011).

Measures of treatment effect

We used the definition of non-fatal serious adverse events as provided by study authors, and given that most trials were carried out for regulatory purposes, we were confident that the following definitions were used.

Definition of serious adverse events

The Expert Working Group (Efficacy) of the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) defines a serious adverse event as follows (ICHE2A):

"a serious adverse event (experience) or reaction is any untoward medical occurrence that at any dose:

- results in death;
- is life-threatening;
- requires inpatient hospitalisation or prolongation of existing hospitalisation;
- results in persistent or significant disability/incapacity; or
- is a congenital anomaly/birth defect.

NOTE: The term "life-threatening" in the definition of "serious" refers to an event in which the patient was at risk of death at the time of the event; it does not refer to an event that hypothetically might have caused death if it were more severe.

Unit of analysis issues

We confined our analysis to patients with one or more serious adverse events rather than to the number of events that occurred (as the latter are not independent when one patient suffers multiple events). Moreover, the same event may be recorded under multiple categories, leading to risk of double-counting of events.

Dealing with missing data

When serious adverse events were not fully reported in the published trial results, we contacted study authors and trial sponsors for further information.

Assessment of heterogeneity

We assessed heterogeneity by using the I^2statisticto determine how much of the total heterogeneity found was between, rather than within, studies.

Assessment of reporting biases

We inspected funnel plots to assess publication bias for outcomes that included 10 or more studies with events.

Data synthesis

The outcomes of this review were dichotomous, and we recorded the numbers of participants with one or more of each outcome event by allocated treated group. We calculated pooled odds ratios (ORs). The Peto odds ratio has advantages when events are rare, as no adjustment for zero cells is required (Higgins 2020). This property was found in previous reviews to be more important than potential problems with unbalanced treatment arms; we therefore calculated the results for serious adverse events in RevMan 5 using the Peto method (with Mantel-Haenszel methods for sensitivity analysis). We did not combine risk differences for this update, as this was not recommended in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2019).

We chose not to calculate an average result from all the formulations of formoterol and inhaled steroid, as the doses and delivery devices are too diverse to assume a single class effect

Subgroup analysis and investigation of heterogeneity

We carried out subgroup analyses on the basis of age (adults versus children) using tests for interaction (Altman 2003). We did not attempt to combine the results from different formoterol combinations and did not carry out formal subgroup tests between them.

Sensitivity analysis

We carried out sensitivity analysis to assess the impact of the methods used to combine study events (Peto odds ratio and Mantel-Haenszel odds ratio). We conducted sensitivity analyses on the degree of bias protection in study designs. When there were discrepant results between published papers and results published in trial registers, we used the data from papers in our primary analysis and carried out a sensitivity analysis using the results from registers. We also carried out a sensitivity analysis to exclude studies that used separate inhalers for formoterol and inhaled corticosteroids.

Summary of findings and assessment of the certainty of the evidence

We created a 'Summary of findings' table using the following outcomes: adults given formoterol and inhaled corticosteroid (ICS) compared to salmeterol and ICS: all-cause mortality; adults given formoterol and ICS compared to salmeterol and ICS: all-cause serious adverse events (SAEs); adults given formoterol and ICS compared to salmeterol and ICS: asthma-related SAEs; and children given formoterol and fluticasone compared to salmeterol and fluticasone. We used the five GRADE considerations (risk of bias, consistency of effect, imprecision, indirectness, and publication bias) to assess the quality of a body of evidence as it relates to studies that contributed data for the pre-specified outcomes. We used the methods and recommendations described in Section 8.5 and Chapter 12 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011), along with GRADEpro software (GRADEpro GDT). We justified all decisions to downgrade the quality of studies by using footnotes, and we made comments to aid the reader's understanding of the review when necessary.

RESULTS

Description of studies

Results of the search

We carried out the updated search for relevant studies up to February 2021 and identified a total of 1367 search results after duplicates were removed. In assessing these studies, we used Cochrane's Screen4Me workflow to help identify potential reports of randomised trials. The results of Screen4Me assessments can be seen in Figure 1. We then assessed the remaining 906 records, and

we obtained 51 abstracts as full articles. See Figure 2 for the PRISMA study flow diagram.

Figure 1. Screen4Me assessments, March 2020.

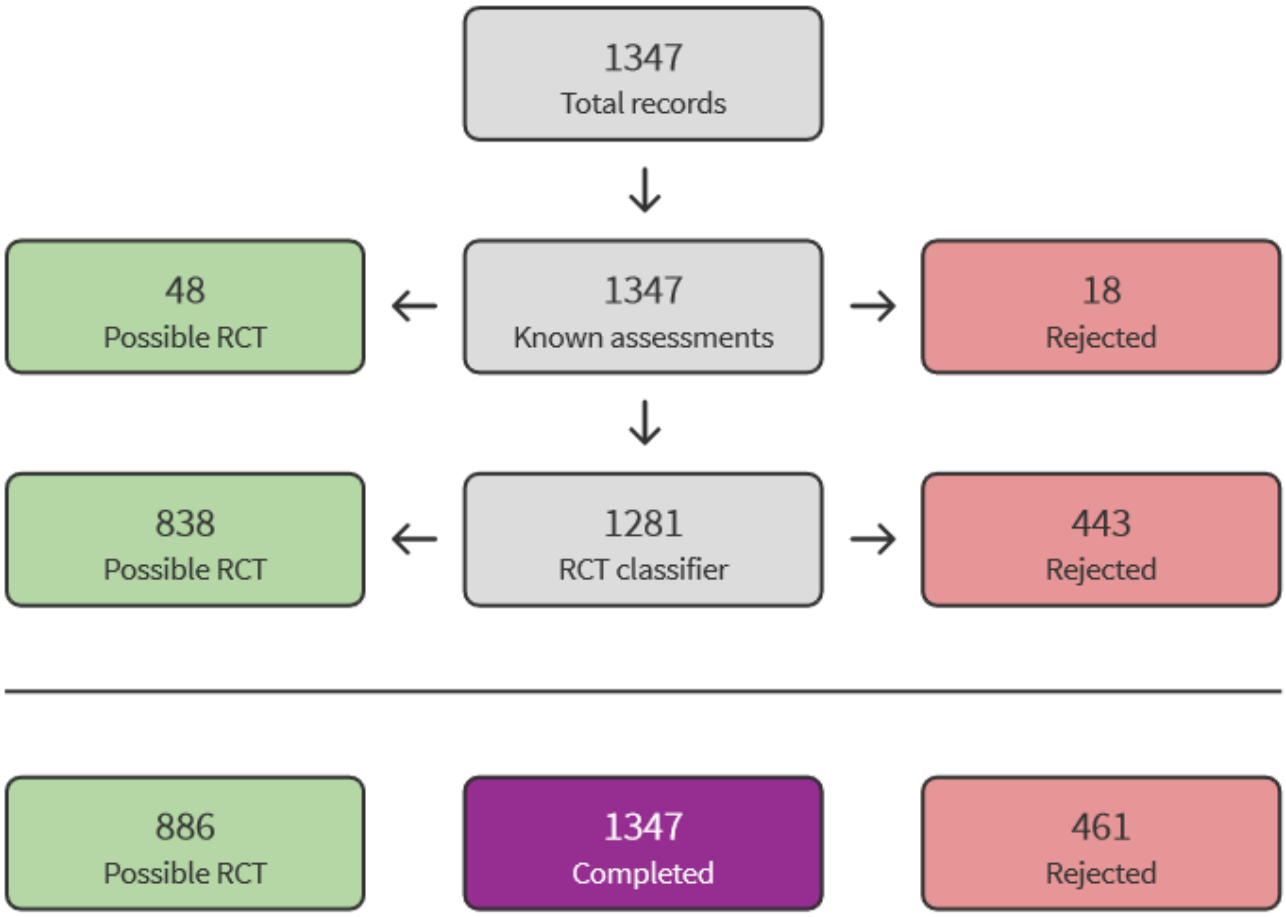


Figure 2. Study flow diagram.

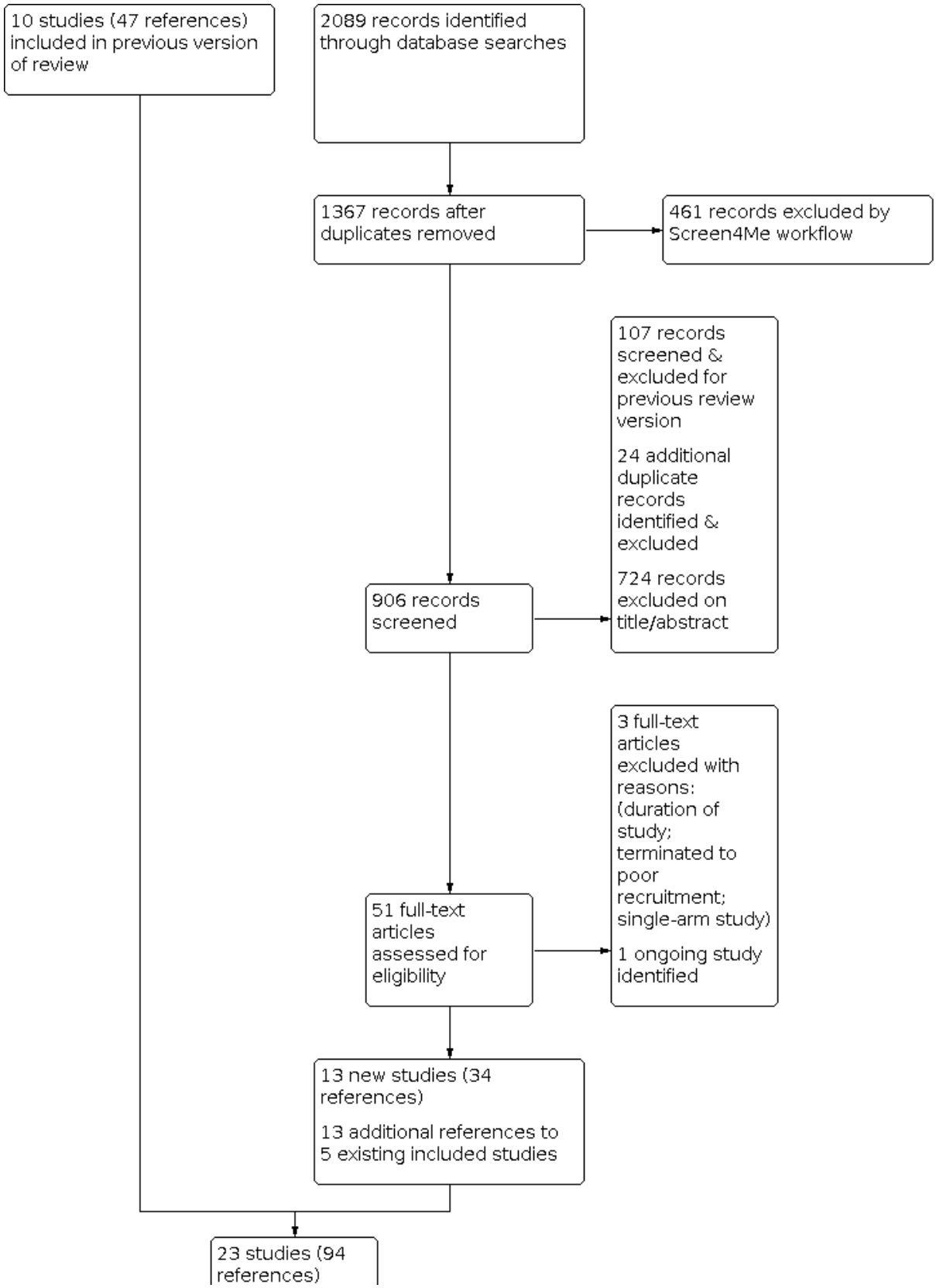
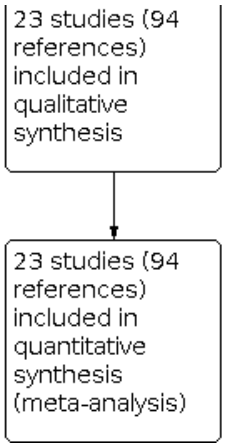


Figure 2. (Continued)



We included 34 abstracts related to 13 new studies (Akamatsu 2014; Bernstein 2011; Emeryk 2016; EUCTR-002587-99-CZ; EUCTR-003449-17-IT; EUCTR-004833-70-BG; Hsieh 2013; NCT00901368; Papi 2012; Ploszczuk 2014; Scichilone 2010; Usmani 2017; Woo 2020). We included as additional references 13 abstracts related to five existing studies (Busse 2008; Bodzenta-Lukaszyk 2011; Kuna 2007; Maspero 2010; Papi 2007). We excluded three articles and provided reasons for their exclusion under Characteristics of excluded studies (NCT02491970; Rani 2016; UMIN000006572). We identified one study as ongoing (NCT03387241).

The review now includes a total of 23 studies. Twenty-one studies included adults and adolescents; we refer to these hereafter as studies in adults. Two studies identified for the update included children only (Emeryk 2016; Ploszczuk 2014).

Included studies

We consider each combination of formoterol with a different inhaled corticosteroid in a separate subgroup; the details of dose and type of medication are summarised in Table 1.

Adults

Overall in eight studies, 7730 adults were randomised to formoterol and budesonide versus salmeterol and fluticasone (Aalbers 2004; Akamatsu 2014; Busse 2008; Dahl 2006; Kuna 2007; Ringdal 2002; SAM 40010; SAM 40048); in seven studies, 1472 adults were randomised to formoterol and extra-fine beclomethasone versus salmeterol and fluticasone (EUCTR-002587-99-CZ; EUCTR-003449-17-IT; Hsieh 2013; NCT00901368; Papi 2007; Papi 2012; Scichilone 2010); in three studies, 1015 adults were randomised to formoterol and fluticasone or salmeterol and fluticasone (Bodzenta-Lukaszyk 2011; Usmani 2017; Woo 2020); and in two studies, 1126 adults were randomised to formoterol and mometasone or salmeterol and fluticasone (Bernstein 2011; Maspero 2010). One study randomised 229 adults to formoterol and budesonide versus salmeterol and budesonide (EUCTR-004833-70-BG).

Children

Two studies randomised 723 children to formoterol and fluticasone or salmeterol and fluticasone (Emeryk 2016; Ploszczuk 2014).

Doses and delivery devices

Details of delivery devices and doses of medication in each trial are given in Table 1. All studies used combination inhalers, except Ringdal 2002, in which formoterol and budesonide were administered in separate inhalers. We judged the dose of inhaled corticosteroid in each arm to be equivalent, except in Ringdal 2002 (higher-dose budesonide) and SAM 40048 (higher-dose fluticasone) (see Table 1). Although most studies compared 12 µg formoterol twice daily with 50 µg salmeterol twice daily, SAM 40010 and SAM 40048 compared 6 µg formoterol with 50 µg salmeterol twice daily. Usmani 2017 compared 20 µg formoterol twice daily with 50 µg salmeterol twice daily.

Run-in period

Most studies continued their previous treatment with ICS alone during the run-in period (those previously on long-acting beta$_2$-agonist (LABA) were excluded or discontinued LABA treatment), and patients were enrolled in the study if they were symptomatic at the end of run-in. Busse 2008 allowed ICS and LABA/ICS to be continued during run-in, but participants still had to be symptomatic to be enrolled into the study. Bodzenta-Lukaszyk 2011 did not specify treatment details for the screening phase of 4 to 10 days to evaluate eligibility, and Maspero 2010 kept participants on their previous medication during screening. Akamatsu 2014 and Papi 2012 were step-down studies in which participants continued combination treatment during the 8-week run-in.

In the studies included for the 2020 update, nearly all participants had been using a LABA/ICS before randomisation. EUCTR-004833-70-BG, Hsieh 2013, Ploszczuk 2014, and Scichilone 2010 did not include a run-in period in which participants used a LABA nor specify that participants had been using a LABA before randomisation. In Emeryk 2016, most participants (83.8% and 86.8% in each group) had been using a LABA before randomisation.

Age of participants

In adult studies, the lower age limit varied from 12 years old in Aalbers 2004, SAM 40010, SAM 40048, Kuna 2007, Busse 2008 and Maspero 2010, to 16 or 18 years old in Ringdal 2002, Dahl 2006, Papi 2007 and Bodzenta-Lukaszyk 2011.

In studies of children, participant age ranged from 4 to 12 years and from 5 to 12 years, respectively - in Ploszczuk 2014 and Emeryk 2016.

Sponsorship and location

Almost all included studies were sponsored by one of the manufacturers of combined inhalers, and the duration and locations of studies are shown in Table 2. Sponsorship for Akamatsu 2014 is not known.

Excluded studies

We listed the excluded studies under Characteristics of excluded studies along with reasons for exclusion.

Risk of bias in included studies

Figure 3 shows an overview of the potential risks of bias in each study.

Figure 3. Methodological quality summary: review authors' judgements about each methodological quality item for each included study.

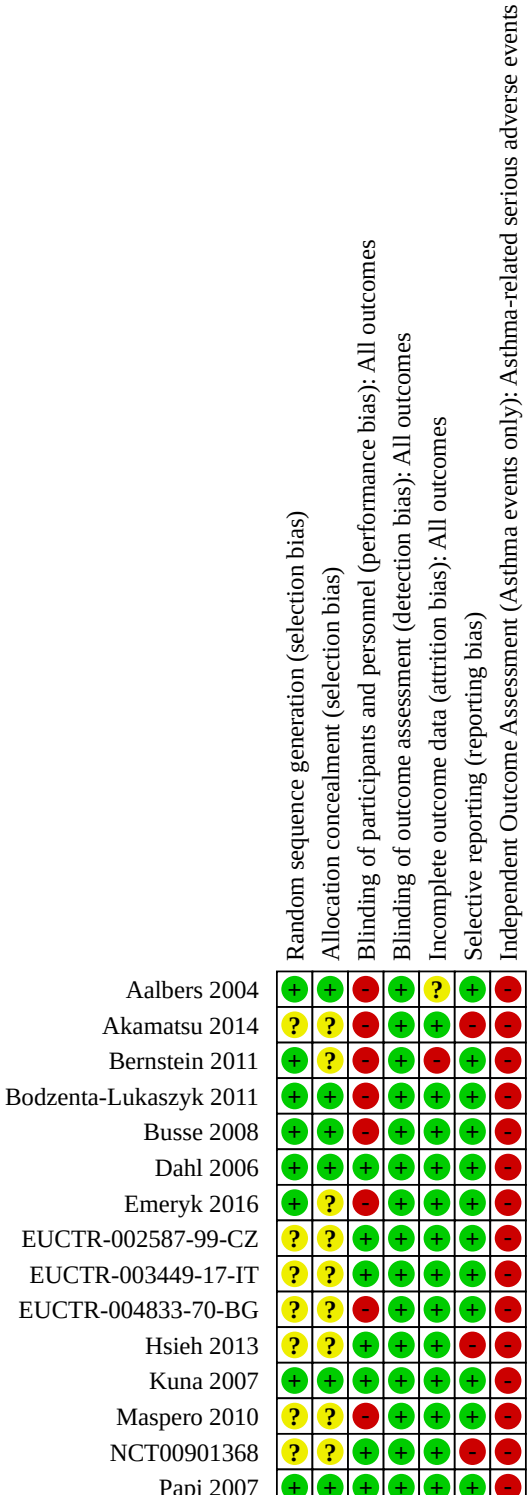
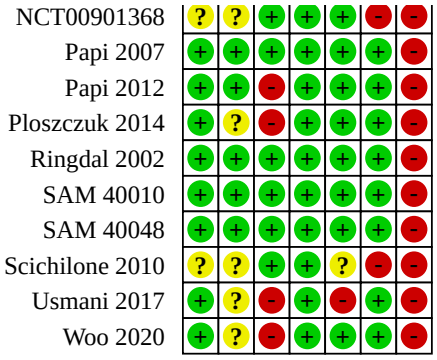


Figure 3. (Continued)



Allocation

We judged sequence generation and allocation concealment to be adequate in 10 studies (Aalbers 2004; Bodzenta-Lukaszyk 2011; Busse 2008; Dahl 2006; Emeryk 2016; Kuna 2007; Papi 2007; Papi 2012; Ploszczuk 2014; Ringdal 2002). Methods used were not clearly reported in the other studies, but we regarded it as likely that this was a reporting issue, as sponsored studies tended to be at low risk of selection bias.

Blinding

Eleven studies had well-reported methods of blinding (Dahl 2006; EUCTR-002587-99-CZ; EUCTR-003449-17-IT; Hsieh 2013; Kuna 2007; NCT00901368; Papi 2007; Ringdal 2002; SAM 40010; SAM 40048; Scichilone 2010), and 12 studies were open-label (Aalbers 2004; Akamatsu 2014; Bernstein 2011; Bodzenta-Lukaszyk 2011; Busse 2008; Emeryk 2016; EUCTR-004833-70-BG; Maspero 2010; Papi 2012; Ploszczuk 2014; Usmani 2017; Woo 2020), but one study reported evaluator blinding (Maspero 2010). All studies were judged to be at low risk of bias with regard to detection bias for all-cause events, regardless of blinding, because blinding did not impact the assessment of all-cause outcomes.

Incomplete outcome data

All studies, with the exception of Aalbers 2004 Bernstein 2011, and Scichilone 2010, reported that at least 80% of participants completed the study, and in most cases, the completion rate was 90% or above (see Characteristics of included studies for details of individual studies). Usmani 2017 was judged to have high risk of bias with regard to attrition bias due to the discrepancy in dropouts between the two groups (88.7% and 98.6% completion, respectively). Bernstein 2011 was also judged to have high risk of bias with regard to attrition bias, as > 40% dropouts were reported across the two groups (41% and 42%, respectively).

Selective reporting

Following correspondence with study authors and funders, we obtained full data on all-cause SAEs from all studies, with the exception of Akamatsu 2014, Scichilone 2010, Hsieh 2013, and NCT00901368.

Other potential sources of bias

Almost all studies have been sponsored by manufacturers of combined long-acting beta$_2$-agonists and ICS inhalers. None of the studies had an independent assessment of the cause of SAEs, which we regard as having high risk of bias when asthma-related events (rather than all-cause events) are considered.

Effects of interventions

See: **Summary of findings 1** Adults: formoterol/ICS compared to salmeterol/ICS for chronic asthma: all-cause mortality; **Summary of findings 2** Adults: formoterol/ICS compared to salmeterol/ICS for chronic asthma: all-cause serious adverse events; **Summary of findings 3** Adults: formoterol/ICS compared to salmeterol/ICS for chronic asthma: asthma-related serious adverse events; **Summary of findings 4** Children: formoterol/fluticasone compared to salmeterol/fluticasone for chronic asthma: serious adverse events

Adults

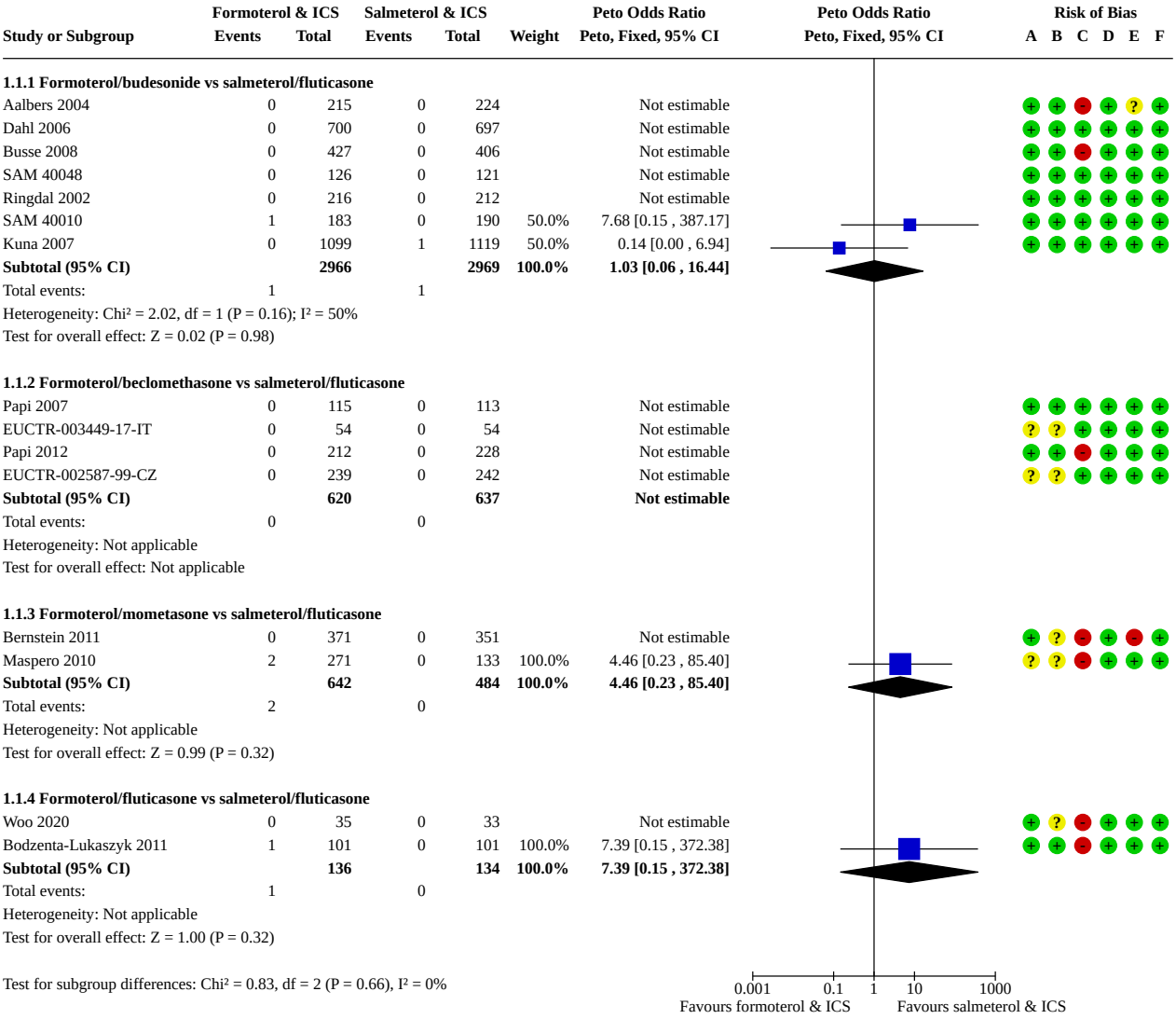
No asthma-related deaths were reported in any of the included studies, and not enough deaths were considered as cardiovascular-related mortality (which was a secondary outcome in our protocol). Therefore, we analysed all-cause mortality and listed the recorded causation of each death narratively in the text.

Formoterol/budesonide versus salmeterol/fluticasone

Mortality

Two deaths were reported in 5935 adult and adolescent participants; neither was asthma-related. In SAM 40010, there was one death in the formoterol/budesonide group due to gastrointestinal obstruction, cardiac failure, and septic shock. In Kuna 2007, one death in the salmeterol/fluticasone group was due to cardiac failure. Pooled results show there may be little to no difference in all-cause mortality between groups (Peto odds ratio (OR) 1.03; 95% confidence interval (CI) 0.06 to 16.44; I^2 = 50%; see Figure 4); however this is low-certainty evidence, as the confidence intervals are very wide.

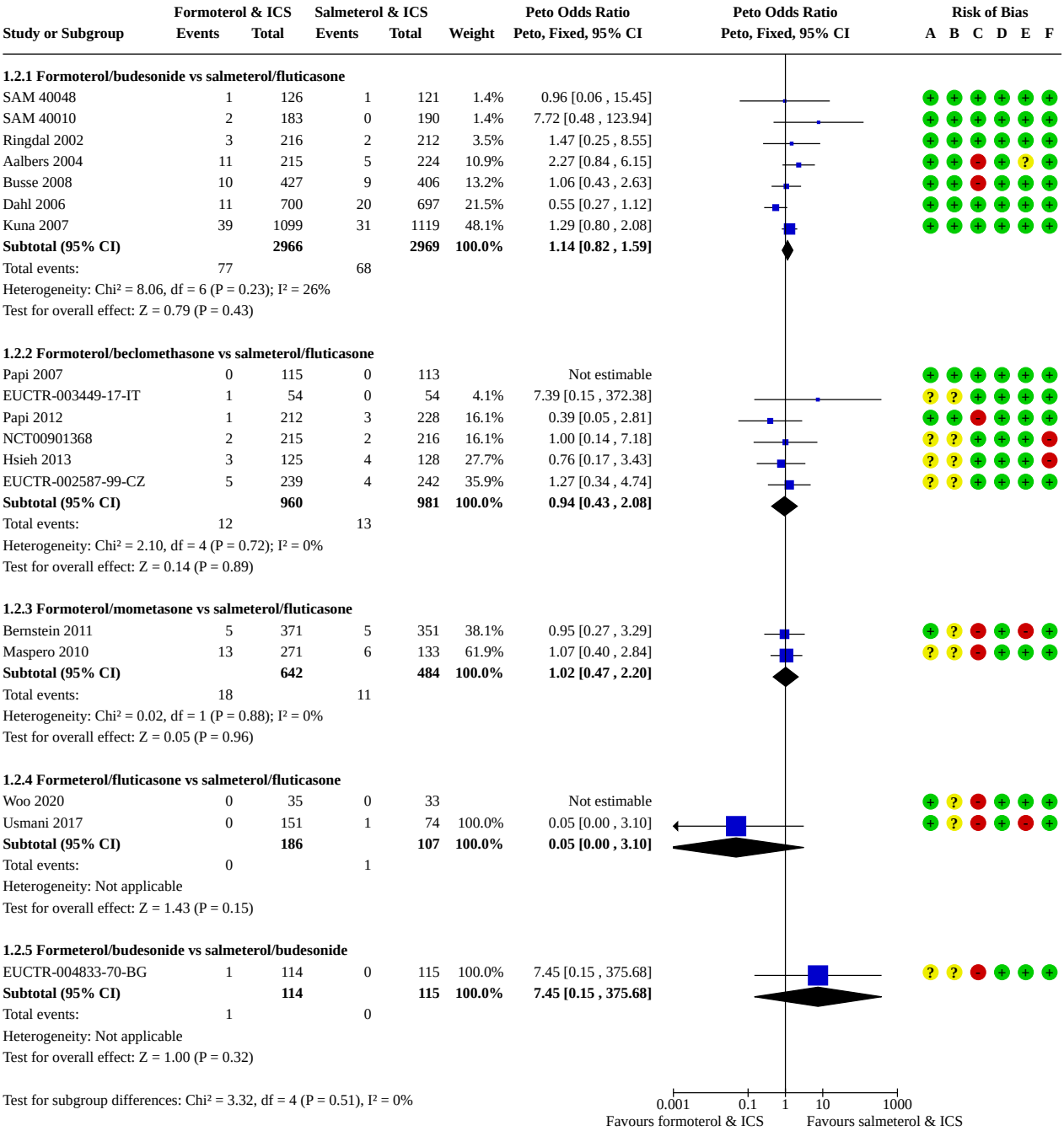
Figure 4. Forest plot of comparison: 1 Fixed-dose formoterol/ICS versus salmeterol/fluticasone, outcome: 1.1 All-cause mortality.



All-cause non-fatal serious adverse events

In all, 77 out of 2966 adults and adolescents on formoterol and budesonide suffered one or more SAEs, compared to 68 out of 2969 patients on salmeterol and fluticasone. There is probably little to no difference in SAEs between groups (Peto OR 1.14, 95% CI 0.82 to 1.59; I^2 = 26%; see Figure 5); however the confidence interval is too wide to conclude that risks are the same for each treatment.

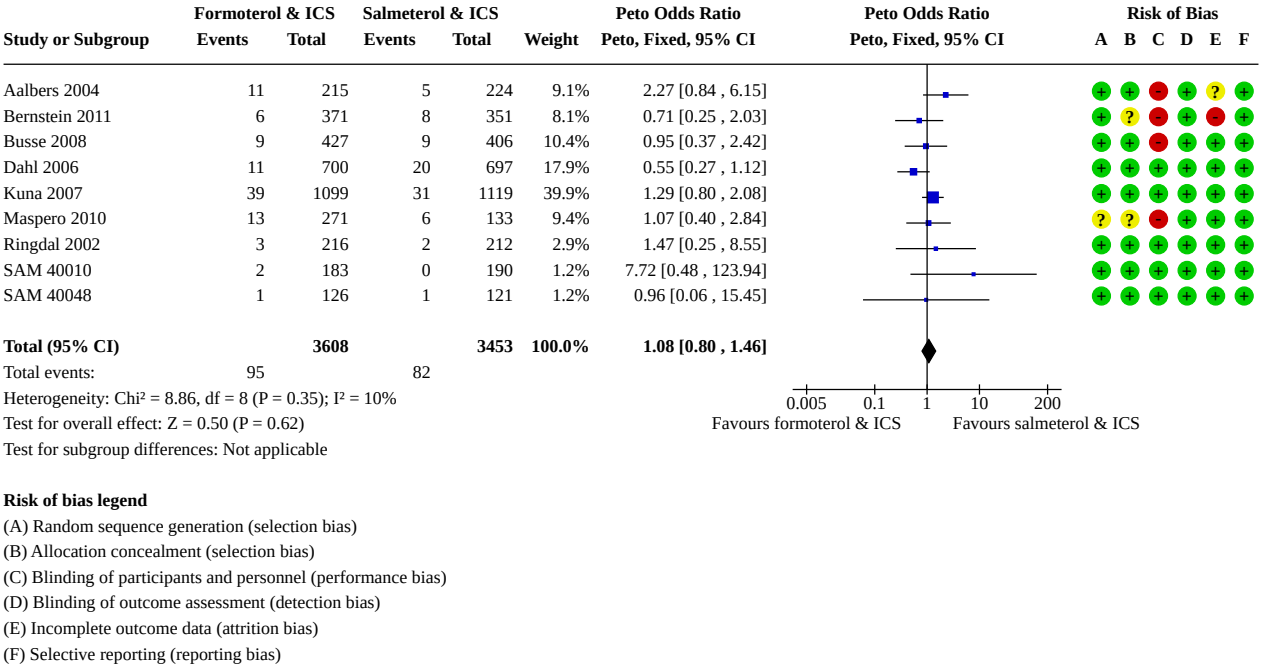
Figure 5. Forest plot of comparison: 1 Fixed-dose formoterol/ICS versus salmeterol/fluticasone, outcome: 1.2 All-cause non-fatal serious adverse events.



Busse 2008 reported that nine participants suffered an SAE in each arm of the trial (Table S4 of the paper), but one additional participant on formoterol/budesonide was admitted to hospital on treatment for an episode that was judged to have started during run-in. Another participant had an SAE after the last dose of randomised treatment, but correspondence with the sponsors revealed that this participant had already suffered an SAE on treatment, and so was already included. We therefore decided to

enter 10 participants for the formoterol/budesonide arm of this trial. We carried out a sensitivity analysis to assess the impact of excluding the additional patient in the formoterol/budesonide arm, and results show very little difference in the odds ratio (Peto OR 1.08, 95% CI 0.80 to 1.46; see Figure 6).

Figure 6. Forest plot of comparison: 3 Sensitivity analysis, outcome: 3.1 Busse SAE sensitivity analysis.



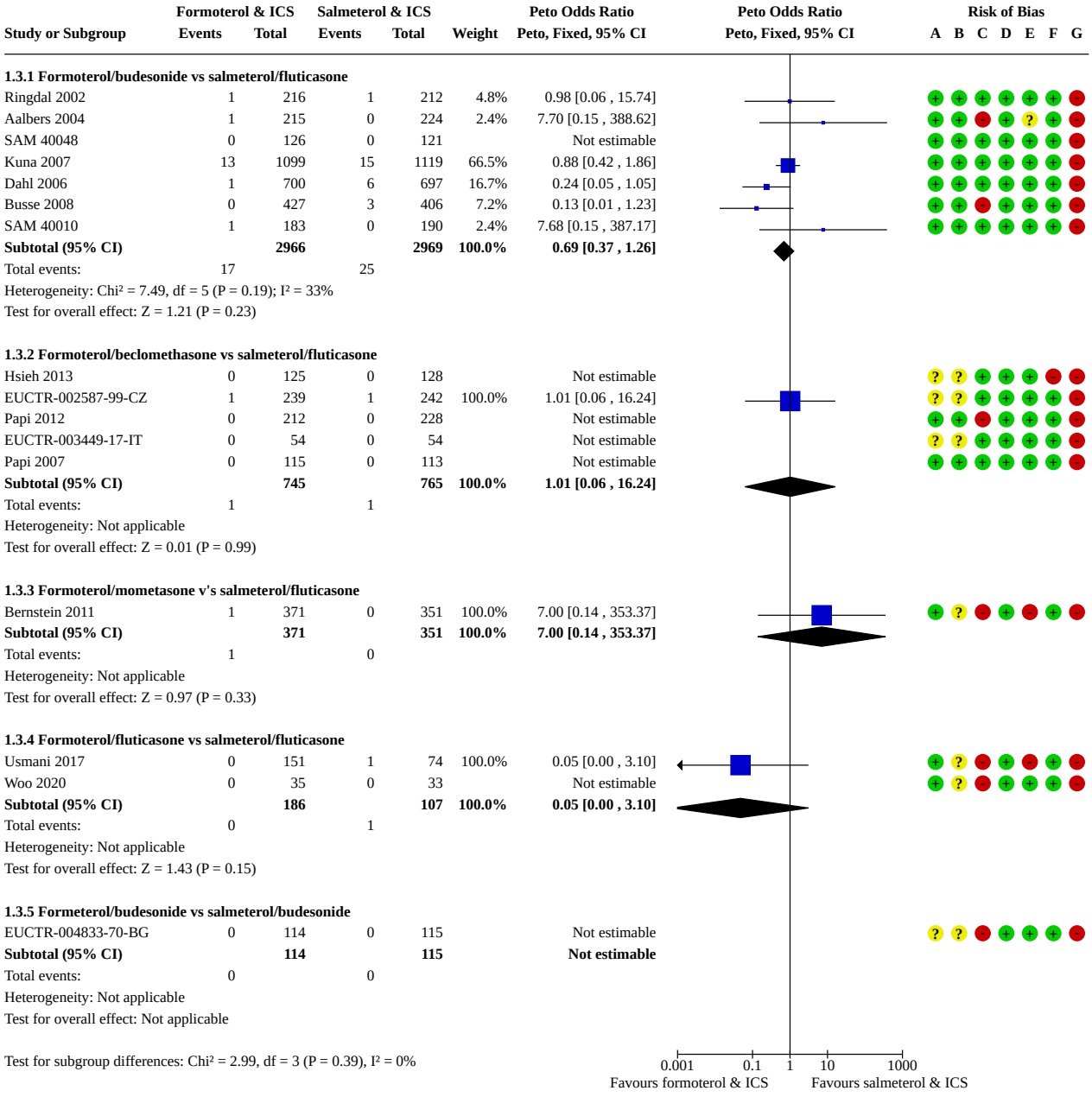
Risk of bias legend

(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)

Asthma-related non-fatal serious adverse events

For two studies, we were not able to find published reports on the number of patients who had experienced one or more asthma-related SAEs, but we were able to obtain this information from the sponsor (Busse 2008; Kuna 2007). Overall 17 adults and adolescents out of 2966 on formoterol and budesonide had asthma-related SAEs, as did 25 out of 2969 on salmeterol and fluticasone. Risk of asthma-related events may be numerically lower with formoterol/budesonide (Peto OR 0.69, 95% CI 0.37 to 1.26; I^2 = 33%; see Figure 7), but no independent outcome assessment was performed and the confidence interval is wide, so we regard this as low-certainty evidence.

Figure 7. Forest plot of comparison: 1 Fixed-dose formoterol/ICS versus salmeterol/fluticasone, outcome: 1.3 Asthma-related non-fatal serious adverse events.



Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Independent Outcome Assessment (Asthma events only): Asthma-related serious adverse events

The number of patients in Dahl 2006 admitted to hospital on salmeterol and fluticasone was recorded as four, which is lower than the six patients recorded as having asthma-related SAEs in this review. The reason for this difference has been clarified following correspondence with GlaxoSmithKline and is related to one patient who experienced acute bronchospasm but was not admitted to hospital, and a second patient who was admitted to hospital but had an exacerbation that had started during the run-in period.

Formoterol/beclomethasone versus salmeterol/fluticasone

Mortality

No deaths were reported in four studies; Scichilone 2010, NCT00901368, and Hsieh 2013 did not provide any data on mortality.

All-cause non-fatal serious adverse events

A total of 12 all-cause non-fatal SAEs were reported among 960 adolescent and adult participants in the formoterol group, and 13 all-cause non-fatal SAEs among 981 adolescent and adult participants in the salmeterol group. In the formoterol arm, there was one all-cause non-fatal SAE in EUCTR-003449-17-IT (bronchopneumonia), one in Papi 2012, two in NCT00901368, three in Hsieh 2013, and five in EUCTR-002587-99-CZ (fractured neck of femur, atrial fibrillation, anaemia, calculus urinary, and one asthma-related). In the salmeterol arm, there were three all-cause non-fatal SAEs in Papi 2012, four in Hsieh 2013, and four in EUCTR-002587-99-CZ. Scichilone 2010 did not provide any data on all-cause non-fatal SAEs. There is probably little to no difference in SAEs between groups (Peto OR 0.94, 95% CI 0.43 to 2.08; see Figure 5), but again, the confidence interval is too wide to conclude that risks are same for each treatment.

Asthma-related non-fatal serious adverse events

There were two asthma-related SAEs: one in 533 adolescent and adult participants in the formoterol arm, and one in 537 adolescent and adult participants the salmeterol arm. Both of these occurred in EUCTR-002587-99-CZ. NCT00901368 and Scichilone 2010 did not provide any data on asthma-related SAEs. There may be little to no difference in non-fatal SAEs between groups (Peto OR 1.01, 95% CI 0.06 to 16.24; see Figure 7), but as there were only two events and no independent outcome assessment, the evidence is very uncertain.

Formoterol/mometasone versus salmeterol/fluticasone

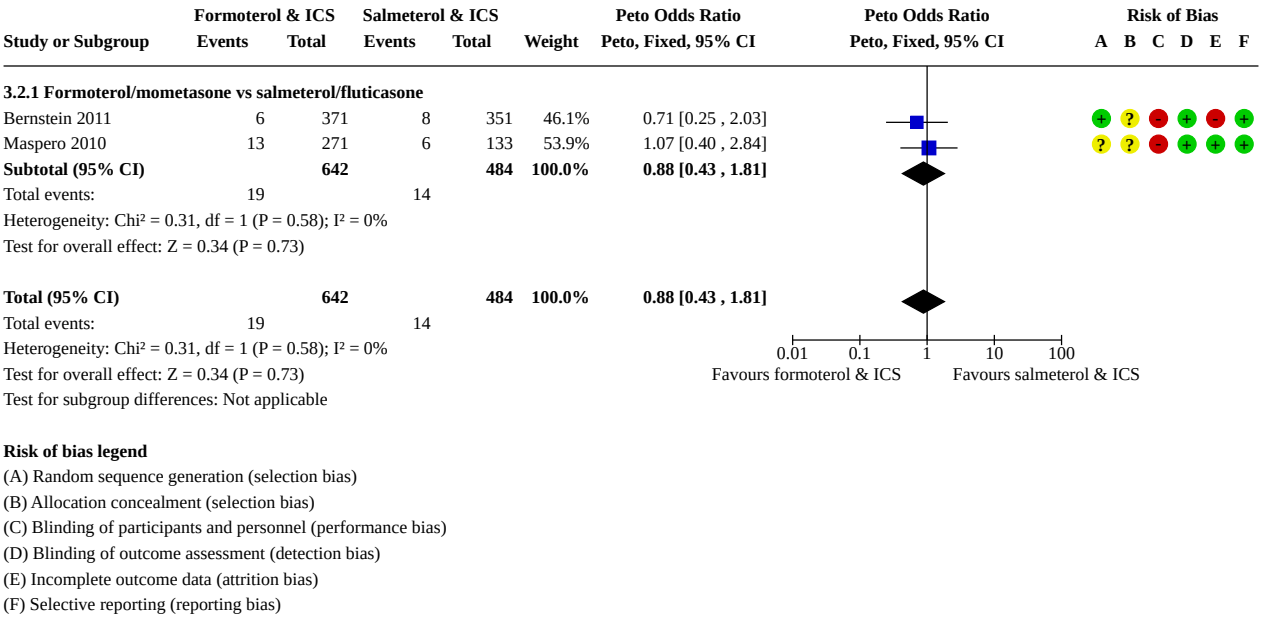
Mortality

Two deaths occurred in the formoterol/mometasone arm of Maspero 2010 (see Figure 4). One death was due to electrocution, and one due to gastric cancer. No deaths occurred in Bernstein 2011. Treatment with formoterol/mometasone may involve greater risk (Peto OR 4.46, 95% CI 0.23 to 85.40; see Figure 4), but with only two deaths in total, this is low-certainty evidence with a very wide confidence interval.

All-cause non-fatal serious adverse events

Similar proportions of participants with non-fatal SAEs of any cause were reported for both formoterol/mometasone (n = 18 participants) and salmeterol/fluticasone (n = 11 participants). Available evidence shows there is probably little to no difference in non-fatal SAEs between formoterol and salmeterol (Peto OR 1.02, 95% CI 0.47 to 2.20; see Figure 5), but the confidence intervals are too wide to conclude that the safety of the two products is equivalent. Similarly, Bernstein 2011 reported five non-fatal SAEs in each arm of the trial; however EU Clinical Trials (EUCT) and National Clinical Trial (NCT) websites report six and eight SAEs per group. We carried out a sensitivity analysis to assess the impact of excluding the additional SAEs reported at EUCT and NCT websites, which showed a similar odds ratio (Peto OR 0.88, 95% CI 0.43 to 1.81; see Figure 8).

Figure 8. Forest plot of comparison: 3 Sensitivity analysis, outcome: 3.2 Bernstein SAE sensitivity analysis.



Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)

Asthma-related serious adverse events

One asthma-related SAE was reported in Bernstein 2011 among 371 participants in the formoterol arm (Peto OR 7.00, 95% CI 0.14 to 353.37; see Figure 7). With only one event, the evidence on differences between groups in risk of asthma-related SAEs is very uncertain.

Formoterol/fluticasone versus salmeterol/fluticasone

Mortality

One death from haemorrhagic stroke and cardiac arrest occurred in the formoterol arm with 101 participants in Bodzenta-Lukaszyk 2011. No deaths occurred in Woo 2020, and Usmani 2017 did not provide any data on mortality. With only a single death, evidence on differences between groups in risk of death is uncertain (Peto OR 7.39, 95% CI 0.15 to 372.38; see Figure 4).

All-cause non-fatal serious adverse events

One all-cause non-fatal SAE (pneumonia) was reported in the salmeterol arm of Usmani 2017, with 74 participants. None occurred in Woo 2020, and Bodzenta-Lukaszyk 2011 did not provide any data on this. Again with a single event, the evidence on differences between groups in risk of all-cause non-fatal SAEs is uncertain (Peto OR 0.05, 95% CI 0.00 to 3.10; see Figure 5).

Asthma-related serious adverse events

One asthma non-fatal SAE (pneumonia) was reported in the salmeterol arm of Usmani 2017, with 74 participants. None occurred in Woo 2020, and Bodzenta-Lukaszyk 2011 did not provide any data on this. With a single event and no independent outcome assessment, the evidence on differences in risk between groups is very uncertain (Peto OR 0.05, 95% CI 0.00 to 3.10; see Figure 7).

Formoterol/budesonide versus salmeterol/budesonide

No deaths occurred and one all-cause non-fatal SAE was reported in the formoterol arm among 114 participants (EUCTR-004833-70-BG). This non-fatal SAE was not thought to be asthma-related (Peto OR 7.45, 95% CI 0.15 to 375.68; see Figure 5). As only a single event was reported, we are unable to make any meaningful comparison of the relative safety of the two treatments.

Children

Formoterol/fluticasone versus salmeterol/fluticasone

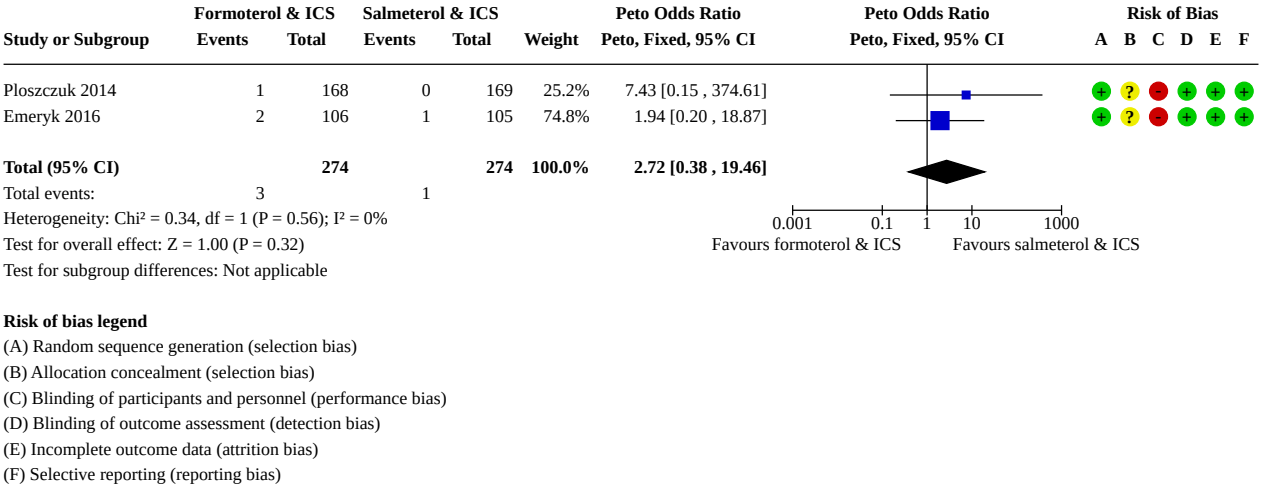
Mortality

No deaths were reported in either of the children's studies (Emeryk 2016; Ploszczuk 2014).

All-cause non-fatal serious adverse events

Three all-cause non-fatal SAEs were reported in the formoterol arm among 274 participants: two appendicitis (Emeryk 2016), and one bronchitis (Ploszczuk 2014). One all-cause non-fatal SAE was reported in the salmeterol group among 274 participants. One case of pneumonia occurred in Emeryk 2016. Although risk of SAE may be higher in children on formoterol/fluticasone (Peto OR 2.72, 95% CI 0.38 to 19.46; 548 participants, 2 studies; I^2 = 0%; see Figure 9), the very wide confidence intervals mean that this is low-certainty evidence.

Figure 9. Forest plot of comparison: 2 Children formoterol/fluticasone versus salmeterol/fluticasone, outcome: 2.2 All-cause non-fatal serious adverse events.



Asthma-related serious adverse events

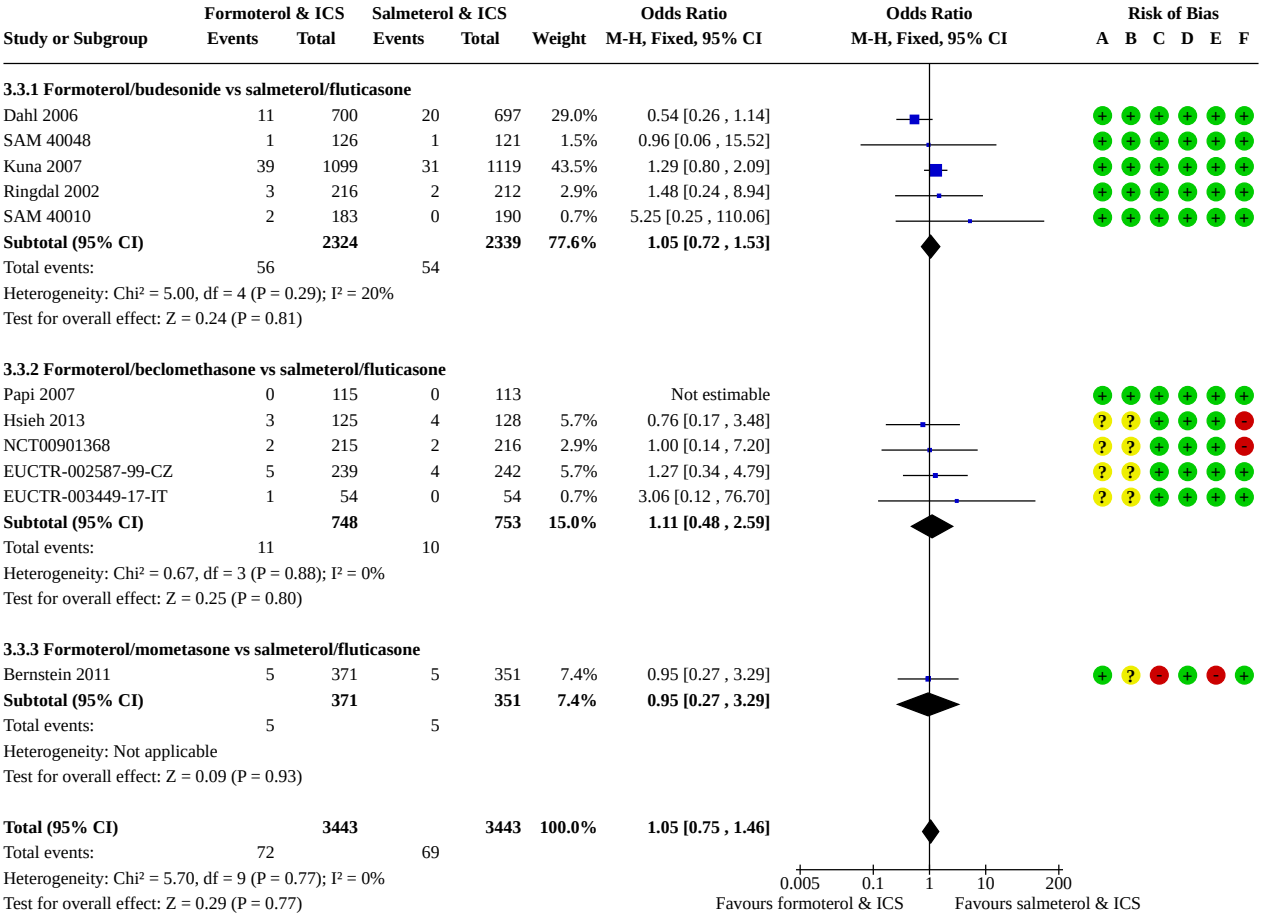
No asthma-related SAEs were reported in either of the children's studies (Emeryk 2016; Ploszczuk 2014).

Sensitivity analysis

We carried out sensitivity analysis while excluding the single study that used separate inhalers for formoterol and ICS (Ringdal 2002); this made little difference in all-cause non-fatal SAEs (Peto OR 1.08, 95% CI 0.80 to 1.47; 6633 participants, 8 studies).

We carried out sensitivity analysis while excluding the two unblinded studies in the formoterol/budesonide versus salmeterol/fluticasone comparison (Aalbers 2004; Busse 2008). Restricting the analysis to blinded studies had no impact on mortality (as no deaths were reported in either of the open studies). All-cause SAEs in the blinded studies showed no important change (OR 1.05, 95% CI 0.72 to 1.53; I^2 = 20%; see Figure 10), and similarly, asthma-related events were not much altered (OR 0.74, 95% CI 0.39 to 1.40; I^2 = 0%; see Figure 11).

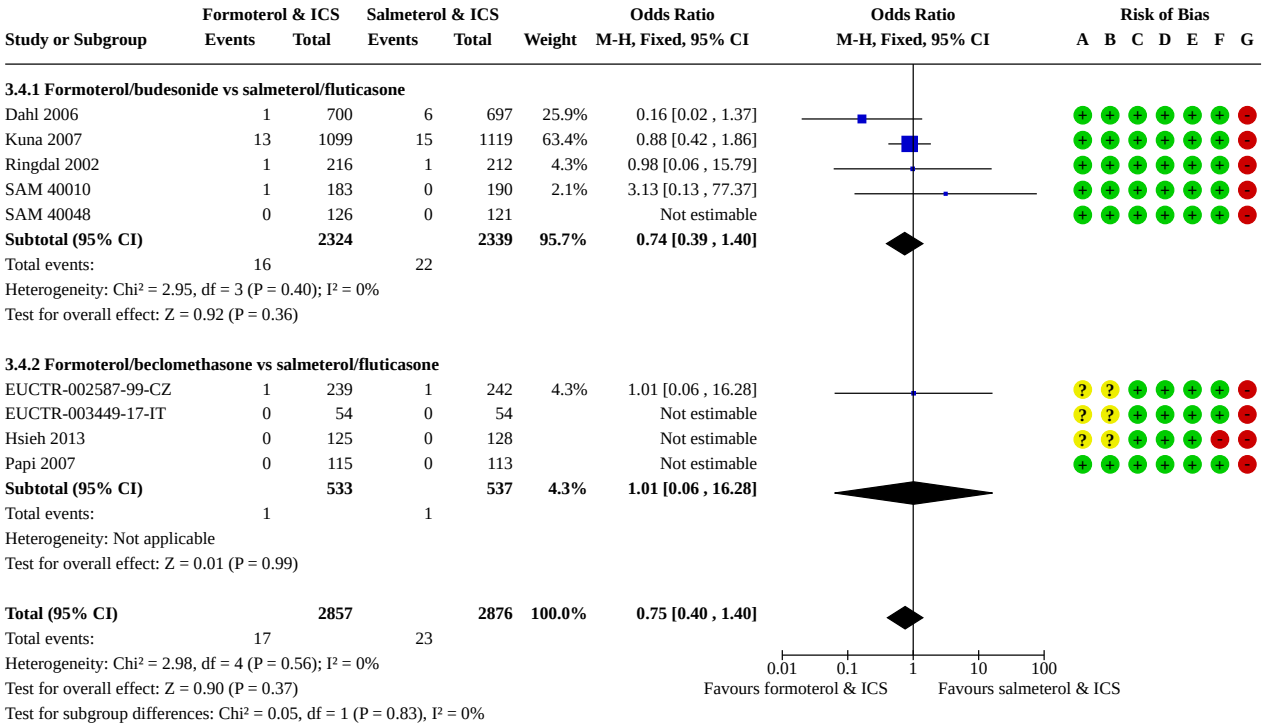
Figure 10. Forest plot of comparison: 3 Sensitivity analysis, outcome: 3.3 All-cause non-fatal SAE blinding.



Risk of bias legend

(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)

Figure 11. Forest plot of comparison: 3 Sensitivity analysis, outcome: 3.4 Asthma-related non-fatal SAE blinding.



Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Independent Outcome Assessment (Asthma events only): Asthma-related serious adverse events

We conducted a sensitivity analysis while excluding one unblinded study in the formoterol/beclomethasone versus salmeterol/fluticasone comparison (Papi 2012). This analysis was restricted to all SAEs and asthma-related SAEs (as there were no deaths in this study). All-cause SAEs in the blinded studies showed little change from the analysis of all studies (OR 1.11, 95% CI 0.48 to 2.59; I^2 = 0%; see Figure 8), and similarly, asthma-related events were not much changed (OR 1.01, 95% CI 0.06 to 16.28; I^2 = 0%; Figure 11).

We conducted another sensitivity analysis while excluding one unblinded study from the formoterol/mometasone versus salmeterol/fluticasone comparison (Maspero 2010). This analysis was restricted to all-cause SAEs, as this study did not report any asthma-related SAEs, and no deaths were reported in the remaining study in the subgroup (Bernstein 2011). These analyses showed little change (OR 0.95, 95% CI 0.27 to 3.29; I^2 = 0%; Figure 5).

Subgroup analysis

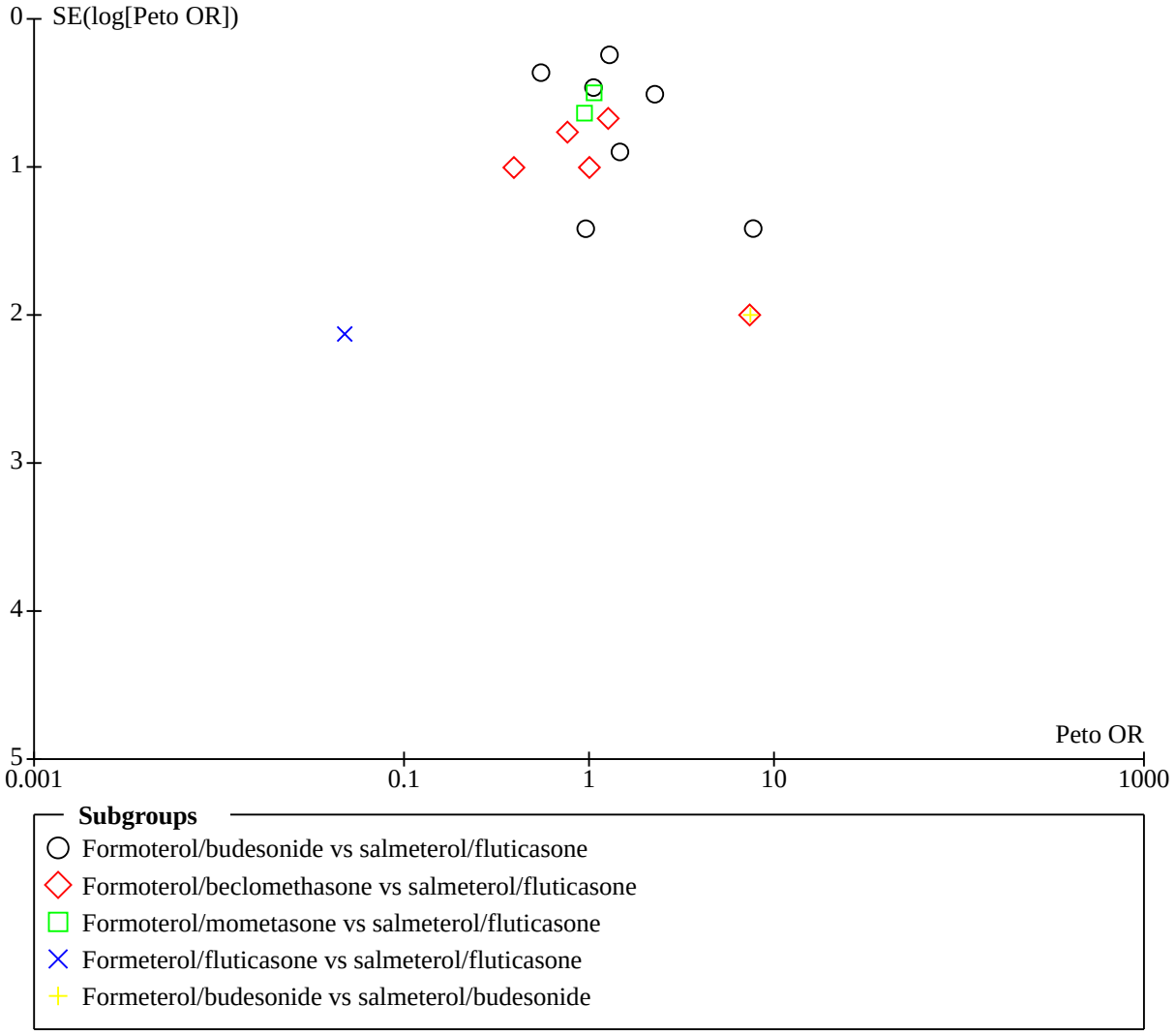
We conducted subgroup analysis to compare the studies in adults and children for all-cause non-fatal SAEs with formoterol/fluticasone versus salmeterol/fluticasone. The test for subgroup difference was negative (Chi^2 = 2.95; df = 1 (P = 0.09); I^2 = 66.1%; see Analysis 2.4).

We did not attempt to conduct subgroup analysis on the basis of dose equivalence of ICS or long-acting $beta_2$-agonists, as the data were too sparse.

Publication bias

A funnel plot is shown for all-cause SAEs in Figure 12, suggesting no small-study effects nor publication bias.

Figure 12. Funnel plot of comparison: 1 Adults formoterol/ICS versus salmeterol/ICS, outcome: 1.2 All-cause non-fatal serious adverse events.



DISCUSSION

Summary of main results

We identified 13 new studies in the updated search; in total, we included 23 studies in this review. Two studies were not included in the analysis, as results were not available. Nineteen studies contributing to the analysis involved adults and adolescents. Seven of these (N = 5935) compared formoterol and budesonide to salmeterol and fluticasone. Four studies (N = 1239) compared formoterol and beclomethasone to salmeterol and fluticasone; two (N = 1126) compared formoterol and mometasone to salmeterol and fluticasone; three (N = 1015) compared formoterol and fluticasone with salmeterol and fluticasone; and one (N = 229) compared formoterol and budesonide to salmeterol and budesonide. We identified two studies in children (N = 723), both of which compared formoterol and fluticasone to salmeterol and fluticasone. These studies recruited participants who were previously treated with moderate to high doses of inhaled steroids (with or without salmeterol or formoterol). All studies except Ringdal 2002 used combination inhalers.

We did not identify any certain differences between combination treatment on formoterol with inhaled corticosteroids (ICS) and salmeterol with fluticasone or budesonide for all-cause mortality, non-fatal adverse events of any cause, or events related to asthma. However the confidence intervals are wide, so we cannot rule out differences between formoterol and salmeterol combination inhalers.

Overall completeness and applicability of evidence

Although the included studies were sufficiently powered for equivalence in terms of the primary efficacy outcomes (e.g. Papi 2007), they remain underpowered to detect possible important differences in serious adverse events (SAEs) (Cates 2008). Therefore, although no certain differences have been found

between combination inhalers, the confidence intervals are too wide to indicate equivalence of safety.

Quality of the evidence

The included studies were generally well protected against bias (see Figure 3). Allocation concealment and sequence generation did not present undue risk of bias in the included studies, and results on SAEs have been obtained from all studies except Akamatsu 2014 and Scichilone 2010 (total of 96 participants). Aalbers 2004, Busse 2008, Bodzenta-Lukaszyk 2011, and Maspero 2010 were open studies, and Aalbers 2004 had a withdrawal rate of over 20%. We carried out sensitivity analysis using only blinded studies and found little change in the results. Consideration of asthma-related adverse events was at higher risk of bias, as none of the trials used independent outcome assessment for causation of adverse events.

Potential biases in the review process

Given that the included studies were designed to assess efficacy, it seems unlikely that publication bias would take the form of whole studies remaining unreported. However, it is apparent that reporting of SAEs in medical journals is sub-optimal (Cates 2008). For this review, it has been possible to obtain SAE data from all but two studies, following correspondence with trial sponsors. We therefore believe there is low risk of publication bias for this review, and the funnel plot was unremarkable (Figure 12).

Agreements and disagreements with other studies or reviews

Previous reviews have identified increased risk of SAEs with regular salmeterol (Cates 2008), and with regular formoterol (Cates 2008a), when compared to placebo. In contrast, in studies that used randomised inhaled corticosteroids, no significant increase in SAEs has been shown with regular combination salmeterol (Cates 2018), nor with regular combination formoterol (Janjua 2019). However, the confidence intervals in the latter reviews are too wide to conclude that adding an ICS renders regular combination formoterol or salmeterol completely safe, even with with the recent inclusion of four very large trials (Peters 2016; Stempel 2016; Stempel 2016a; Weinstein 2019). It is in keeping with these latter reviews that we have found no certain differences between regular combination formoterol and salmeterol. The results of this review are similar to those of Cates 2012, which found no significant differences between formoterol and salmeterol when all participants used background (rather than randomised) ICS.

The negative findings may be due in part to statistical power, as very large numbers of patients would need to be randomised to identify small differences between combination formoterol and salmeterol. We do not have enough information to make meaningful safety comparisons between the different formoterol/salmeterol and ICS combinations.

AUTHORS' CONCLUSIONS

Implications for practice

Overall, for both adults and children, evidence is insufficient to show whether regular formoterol in combination with budesonide, beclomethasone, fluticasone, or mometasone has a different safety profile from salmeterol in combination with fluticasone or budesonide. Five deaths of any cause were reported across all studies, and no deaths from asthma; this information is insufficient to permit any firm conclusions about the relative risks of mortality with combination formoterol in comparison to combination salmeterol inhalers. Evidence on all-cause non-fatal SAEs indicates there is probably little to no difference between formoterol/budesonide and salmeterol/fluticasone inhalers. However, the number of events for the other formoterol combination inhalers was too small to allow conclusions. Only 46 non-fatal SAEs were thought to be asthma-related; this small number in addition to absence of independent outcome assessment means that we have very low confidence for this outcome.

We found no evidence of safety issues that would affect the choice between salmeterol and formoterol combination inhalers used for regular maintenance therapy for adults and children with asthma.

Implications for research

The original review included a publication with more than 3000 participants, and a further two studies with more than 1000 participants. The median number of participants in the studies included in the updated review is 229 (ranging from 30 to 722). Furthermore, five different combinations are now compared in this review. To truly assess the safety of combination formoterol versus combination salmeterol, very large-scale randomised controlled trials would be needed. In view of the lack of any safety concerns from the large trials recently mandated by the FDA (Peters 2016; Stempel 2016; Stempel 2016a; Weinstein 2019|), head-to-head randomised comparisons of combination formoterol and salmeterol of sufficient size may involve prohibitive costs. Post-marketing surveillance may provide a viable way of collecting these data.

ACKNOWLEDGEMENTS

We acknowledge the assistance of Matthew Cates with the protocol and with appendices on the pharmacology and mechanisms of beta$_2$-agonists. We thank Gabriele Nicolini, Eleonora Ingrassia, and Eva Topoloe from Chiesi, for clarification of methods and confirmation of results from Papi 2007 and Papi 2012 Joe Gray for confirmation of results from data on record at AstraZeneca for Busse 2008 and Kuna 2007 and Richard Follows from GlaxoSmithKline for clarification of methods and results from Dahl 2006, Ringdal 2002, SAM 40010, and SAM 40048. We also acknowledge that Toby Lasserson extracted the data and co-wrote the original protocol and review (Cates 2009 Cates 2010).

The review authors and the Airways Editorial Team are grateful to the following peer and consumer reviewers for their time and comments.

Yohanes Aditya Adhi Satria (Indonesia), Luigino Calzetta (Italy), Ankita Mukherjee (India), and Paola Rogliani (Italy).

The Background and Methods sections of this review are based on a standard template used by Cochrane Airways.

This project was funded by the National Institute for Health Research Systematic Reviews Programme (project number 16/114/21). This project was also supported by the National Institute for Health Research (NIHR), via Cochrane Infrastructure funding to the Cochrane Airways Group. The views and opinions expressed therein are those of the authors and do not

necessarily reflect those of the Health Research Systematic Reviews Programme, NIHR, NHS, or the Department of Health.

REFERENCES

References to studies included in this review

Aalbers 2004 *{published data only}*

Aalbers R, Backer V, Kava TT, Welte T, Omenaas ER, Bergqvist PBF, et al. Adjustable dosing with budesonide/formoterol reduces the rate of asthma exacerbations compared with fixed dosing salmeterol/fluticasone. *European Respiratory Journal* 2003;**41**:2-20.

* Aalbers R, Backer V, Kava TTK, Omenaas ER, Sandstrom T, Jorup C, et al. Adjustable maintenance dosing with budesonide/formoterol compared with fixed-dose salmeterol/fluticasone in moderate to severe asthma. *Current Medical Research and Opinion* 2004;**20**(2):225-40.

Aalbers R, Harris A, Naya I. Adjustable dosing with budesonide/formoterol achieves sustained guideline 'well-controlled asthma' following step down in treatment. *European Respiratory Journal* 2005;**26**(Suppl 49):50s.

Aalbers R, Welte T, Jorup C. Adjustable maintenance dosing (AMD) with budesonide /formoterol (B/F) meets guideline-defined management goals more effectively than fixed dosing (FD) with B/F or salmeterol/fluticasone (S/FL). European Respiratory Journal 2004;**24**(Suppl 48):311s.

Aalbers R. Fixed or adjustable maintenance-dose budesonide/formoterol compared with fixed maintenance-dose salmeterol fluticasone propionate in asthma patients aged [greater-than or equal to]16 years: post hoc analysis of a randomised, double-blind open-label extension, parallel-group study. Clinical Drug Investigation 2010;**30**(7):439-51.

AstraZeneca SD-039-0686. A randomized, double-dummy, double-blind/open, parallel-group, phase-III, multicentre, 7-month study to assess the efficacy and safety of Symbicort® Turbuhaler® (budesonide/formoterol; 160/4.5 mcg delivered dose) given either as standard therapy (2 inhalations bid) or with an adjustable dosing regimen (1, 2 or 4 inhalations bid) versus Seretide™ Diskus™ (salmeterol/fluticasone; 50/250 mcg metered dose) given as standard therapy (1 inhalation bid) in adult and adolescent asthmatic patients. astrazenecagrouptrials.pharmacm.com/ST/Submission/View?id=1004 (first received 1 October 2001).

Welte T, Aalbers R, Naya I. Budesonide/formoterol adjustable maintenance dosing (B/F AMD) reduces the burden of asthma more effectively than fixed dosing (FD) with B/F or salmeterol/fluticasone (S/FL) [Abstract]. European Respiratory Journal 2004;**24**(Suppl 48):508s.

Akamatsu 2014 *{published data only}*

Akamatsu T, Shirai T, Kato M, Yasui H, Hashimoto D, Fujisawa T, et al. Switching from salmeterol/fluticasone to formoterol/budesonide combinations improves peripheral airway/alveolar inflammation in asthma. Pulmonary Pharmacology and Therapeutics 2014;**27**(1):52-6.

UMIN000009619. Treatment effect of switching from salmeterol/fluticasone to formoterol/budesonide combinations in patients with asthma. upload.umin.ac.jp/cgi-open-bin/ctr_e/ctr_view.cgi?recptno=R000011286 (first received 25 December 2012).

Bernstein 2011 *{published data only}*

Bernstein D, Murphy K, Nolte H. Efficacy comparison of mometasone furoate/formoterol versus fluticasone propionate/salmeterol combination therapies in subjects with persistent asthma: noninferiority and onset-of-action findings. *Breast* 2019;**44**:S62.

Bernstein D, Murphy K, Nolte H. Efficacy comparison of mometasone furoate/formoterol versus fluticasone propionate/salmeterol combination therapies in subjects with persistent asthma: noninferiority and onset-of-action findings. *World Allergy Organization Journal* 2012;**5**:S79.

Bernstein DI, Hebert J, Cheema A, Murphy KR, Cherrez-Ojeda I, Matiz-Bueno CE, et al. Efficacy and onset of action of mometasone furoate/formoterol and fluticasone propionate/salmeterol combination treatment in subjects with persistent asthma. Allergy, Asthma, and Clinical Immunology 2011;**7**(1):21.

Bernstein DI, Murphy KR, Nolte H. Non-inferiority efficacy comparison of mometasone furoate/formoterol versus fluticasone propionate/salmeterol combination therapies in subjects with persistent asthma. *Allergy, Asthma, and Clinical Immunology* 2010;**6**:33.

EUCTR-004169-33-SK. A 52-week efficacy and safety non-inferiority study of fluticasone propionate/salmeterol 250/50 mcg bid delivered by dry powder inhaler (DISKUS®) versus mometasone furoate/formoterol fumarate 200/10 mcg bid delivered by pressurized metered-dose inhaler in persistent asthmatics previously treated with medium doses of inhaled glucocorticosteroids. www.who.int/trialsearch/Trial2.aspx?TrialID=EUCTR2006-004169-33-SK (first received 10 April 2008).

NCT00424008. Study of inhaled glucocorticosteroids/long-acting bronchodilator drugs in subjects with asthma that have been taking inhaled glucocorticosteroids (study P04705AM1) [A 52-week efficacy and safety non-inferiority study of fluticasone propionate/salmeterol 250/50mcg bid delivered by dry powder inhaler (Diskus) versus mometasone furoate/formoterol fumarate 200/10mcg bid delivered by pressurized metered-dose inhaler in persistent asthmatics previously treated with medium doses of inhaled glucocorticosteroids]. clinicaltrials.gov/show/NCT00424008 (first received 18 January 2007).

Bodzenta-Lukaszyk 2011 *{published data only}*

Aalbers R, Brusselle G, McIver T, Grothe B, Bodzenta-Lukaszyk A. Fluticasone/formoterol provides a more rapid bronchodilation than fluticasone/salmeterol over 12 weeks of treatment in patients with asthma. In: 6th IPCRG World Conference; 2012 April 25-28; Edinburgh. 2012:Abstract 269.

Aalbers R, Brusselle G, McIver T, Grothe B, Bodzenta-Lukaszyk A. Onset of bronchodilation with fluticasone/formoterol combination versus fluticasone/salmeterol in an open-label, randomized study. *Advances in Therapy* 2012;**29**(11):958-69.

Bodzenta-Lukaszyk A, Dymek A, Mansikka H. Fluticasone propionate/formoterol fumarate combination therapy has a more rapid onset of action than fluticasone propionate/salmeterol xinafoate in the treatment of asthma: a randomised controlled trial. *Thorax* 2010;**65**(Suppl 4):P24.

Bodzenta-Lukaszyk A, Dymek A, Mansikka H. Fluticasone propionate/formoterol fumarate combination therapy is as effective as fluticasone propionate/salmeterol xinafoate, but has a more rapid onset of action in the treatment of asthma. In: European Respiratory Society Annual Congress; 2010 September 18-22; Barcelona. 2010:[P1205].

Bodzenta-Lukaszyk A, Dymek A, Mansikka H. Fluticasone propionate/formoterol fumarate combination therapy is as effective as fluticasone propionate/salmeterol xinafoate in the treatment of asthma: a randomised controlled trial [Abstract]. *Thorax* 2010;**65**(Suppl 4):P177.

Bodzenta-Lukaszyk A, Dymek A, McAulay K, Mansikka H. Fluticasone/formoterol combination therapy is as effective as fluticasone/salmeterol in the treatment of asthma, but has a more rapid onset of action: an open-label, randomized study. *BMC Pulmonary Medicine* 2011;**11**:28.

Brusselle G, Aalbers R, McIver T, Grothe B, Bodzenta-Lukaszyk A. Onset of bronchodilation with fluticasone/formoterol versus fluticasone/salmeterol. *European Respiratory Journal* 2012;**40**:P2082.

Busse 2008 *{published data only}*

Ambrose H, Lawrance R, Goldman M. Beta-adrenergic receptor gly16arg variation: effect on response to budesonide/formoterol or fluticasone propionate/salmeterol in asthma patients. *Chest* 2007;**132**(4):478a.

AstraZeneca D5896C00005. A two-stage randomized, open-label, parallel group, phase III, multicenter, 7 month study to assess the efficacy and safety of Symbicort pMDI administered either as fixed or as an adjustable regimen versus a fixed regimen of Advair in subjects 12 years of age and older with asthma. astrazenecagrouptrials.pharmacm.com/ST/Submission/View?id=1583 (first received 1 November 2003).

Busse WW, Shah SR, Somerville L, Martin P, Goldman M. Comparison of asthma exacerbations and lung function with adjustable-dose budesonide/formoterol pressurized metered-dose inhaler (BUD/FM pMDI), fixed-dose BUD/FM pMDI, and fixed-dose fluticasone/salmeterol dry powder inhaler (FP/SM DPI). www.abstracts2view.com/ats07 (accessed prior to 11 October 2020):A191.

* Busse WW, Shah SR, Somerville L, Parasuraman B, Martin P, Goldman M. Comparison of adjustable- and fixed-dose budesonide/formoterol pressurized metered-dose inhaler and fixed-dose fluticasone propionate/salmeterol dry powder inhaler in asthma patients. *Journal of Allergy and Clinical Immunology* 2008;**121**(6):1407-14.

NCT00646594. Atlantis Symbicort [A two stage randomized, open-label, parallel group, phase III, multicenter, 7 month study to assess the efficacy & safety of SYMBICORT pMDI adminstered either as fixed or as an adjustable regimen versus a fixed regimen of Advair in subjects 12 yrs of age and older with asthma]. clinicaltrials.gov/show/NCT00646594 (first received 28 March 2008).

Shah SR, Busse WW, McElhattan J, O'Brien CD, Goldman M. Efficacy and tolerability of fixed-dose (FD) and adjustable-dose (AD) budesonide/formoterol pressurized metered-dose inhaler (BUD/FM pMDI) and FD fluticasone propionate/salmeterol dry powder inhaler (FP/SAL DPI) within racial groups. *Journal of Allergy and Clinical Immunology* 2009;**123**(2 Suppl 1):S80.

Shah SR, Busse WW, Somerville L, Martin P, Goldman M. Asthma control with adjustable-and fixed-dose budesonide/formoterol pressurized metered-dose inhaler (BUD/FM pMDI) and fixed-dose fluticasone/salmeterol dry powder inhaler (FP/SM DPI). In: American Thoracic Society International Conference; 2007 May 18-23; San Francisco. 2007:Poster #K4.

Somerville L, Busse WW, Shah SR, Martin P, Goldman M. Safety of adjustable-dose budesonide (BUD)/formoterol (FM) pressurized metered-dose inhaler (pMDI), fixed-dose (BUD/FM pMDI and fixed-dose fluticasone (FP)/salmeterol (SM) dry powder inhaler (DPI) in asthma patients. In: American Thoracic Society International Conference; 2007 May 18-23; San Francisco. 2007:Poster #K3.

Dahl 2006 *{published data only}*

* Dahl R, Chuchalin A, Gor D, Yoxall S, Sharma R. EXCEL: a randomised trial comparing salmeterol/fluticasone propionate and formoterol/budesonide combinations in adults with persistent asthma. *Respiratory Medicine* 2006;**100**(7):1152-62.

Dahl R, Chuchalin A, Lindberg A, Jones M, Aggarwal K, Gor D. EXCEL regular maintenance therapy with salmeterol/fluticasone propionate combination (SFC) reduces exacerbations more effectively than the formoterol/budesonide combination (FBC). *European Respiratory Journal* 2004;**24**(Suppl 48):309s.

Dahl R, Chuchalin A, Ringdal N, Gor D, Jones M. Salmeterol/fluticasone (SFC) reduces moderate/severe exacerbations more effectively than formoterol/budesonide (FBC) with sustained maintenance therapy EXCEL. In: American Thoracic Society 2005 International Conference; 2005 May 20-25; San Diego. 2005:[C33] [Poster: F68].

GlaxoSmithKline SAM40040. A twenty-four week, randomised, double-dummy, double-blind, parallel group study to compare the rate of asthma exacerbations between SERETIDE DISKUS 50/250ìg 1 inhalation bd and formoterol/budesonide Breath-Actuated Dry Powder Inhaler (BADPI) 4.5/160ìg 2 inhalations bd in subjects with moderate to severe asthma. www.gsk-studyregister.com/en/trial-details/?id=SAM40040 (first received 1 November 2001).

Emeryk 2016 *{published data only}*

Emeryk A, Klink R, McIver T, Dalvi P. A 12-week open-label, randomized, controlled trial and 24-week extension to assess the efficacy and safety of fluticasone propionate/formoterol in children with asthma. *Therapeutic Advances in Respiratory Disease* 2016;**10**(4):324-37.

EUCTR-005928-16-FR. An open, randomised, parallel group, multicentre study to compare the efficacy and safety of

FlutiForm pMDI vs Seretide pMDI in paediatric subjects with mild to moderate persistent, reversible asthma. apps.who.int/trialsearch/Trial2.aspx?TrialID=EUCTR2006-005928-16-FR (first received 26 March 2007).

McIver T, Emeryk A, Klink R, Schwab B. Fluticasone propionate/formoterol fumarate (FLUT/FORM) combination therapy has comparable efficacy to fluticasone propionate/salmeterol xinafoate (FLUT/SAL) in paediatric patients with asthma. In: European Respiratory Society Annual Congress; 2011 Sep 24-28; Amsterdam,. 2011:882s [P4822].

EUCTR-002587-99-CZ *{published data only}*

EUCTR-002587-99-CZ. A 24-week, multicenter, multinational, randomized, double-blind, triple-dummy, 3-arm parallel group study comparing the efficacy and safety of CHF 1535 200/6 (beclomethasone dipropionate 200 µg plus formoterol 6 µg/actuation), 2 puffs b.i.d., versus beclomethasone dipropionate HFA (250 µg/actuation), 4 puffs b.i.d., versus Seretide® 500/50 (fluticasone 500 µg plus salmeterol 50 µg/actuation), 1 inhalation b.i.d., in patients with severe asthma. www.who.int/trialsearch/Trial2.aspx?TrialID=EUCTR2007-002587-99-CZ (first received 13 September 2007).

EUCTR-003449-17-IT *{published data only}*

EUCTR-003449-17-IT. A study, 12 weeks, conducted in more centers, treatment with randomly assigned, double-blind, ''double-dummy'', in two parallel groups to compare the efficacy and safety of the combination of Foster NEXThaler, 2 inhalations bid, compared to Seretide Accuhaler, 1 inhalation, the derived parameters of small airways in patients with asthma. www.who.int/trialsearch/Trial2.aspx?TrialID=EUCTR2011-003449-17-IT (first received 31 May 2012).

NCT01570478. A study in patients with asthma (NELSON) [A 12-week, multicenter, randomized, double-blind, double-dummy, 2-arm parallel group study comparing the efficacy and safety of Foster® NEXThaler® (beclomethasone dipropionate 100 µg plus formoterol 6 µg/actuation), 2 inhalations b.i.d., versus Seretide® Accuhaler® (fluticasone 250 µg plus salmeterol 50 µg/actuation), 1 inhalation b.i.d., on small airway derived parameters in patients with asthma]. clinicaltrials.gov/show/NCT01570478 (first received 4 April 2012).

EUCTR-004833-70-BG *{published data only}*

EUCTR-004833-70-BG. A phase III, randomized, parallel group, open study to compare the therapeutic efficacy and safety of SMB budesonide-salmeterol DPI capsule 150/25µg BID delivered by the Axahaler® versus Symbicort® Turbuhaler® 200/12µg BID over 12 weeks in moderate to severe persistent asthmatic patients. http://www.who.int/trialsearch/Trial2.aspx?TrialID=EUCTR2008-004833-70-BG (first received 19 January 2009).

Hsieh 2013 *{published data only}*

Hsieh M-J, Lai R-S, Wu C-L, Lai C-L, Wang C-C, Peng D-W, et al. A double-blind, double-dummy, randomized study of beclomethasone/formoterol versus fluticasone/salmeterol in treatment of moderate to severe asthma in Taiwan. *European Respiratory Journal* 2013;**42**:873s [P4120].

Hsieh MJ, Lin YC, Lai RS, Wu CL, Lai CL, Wang CC, et al. Comparative efficacy and tolerability of beclomethasone/formoterol and fluticasone/salmeterol fixed combination in Taiwanese asthmatic patients. *Journal of the Formosan Medical Association* 2017;**12**:1078-85.

Kuna 2007 *{published data only}*

Ambrose H, Lawrance R, Goldman M. Beta-adrenergic receptor gly16arg variation: effect on response to budesonide/formoterol or fluticasone propionate/salmeterol in asthma patients. *Chest* 2007;**132**(4):478a.

Ambrose HJ, Lawrance RM, Cresswell CJ, Goldman M, Meyers DA, Bleecker ER. Effect of β2-adrenergic receptor gene (ADRB2) 3' untranslated region polymorphisms on inhaled corticosteroid/long-acting β2-adrenergic agonist response. *Respiratory Research* 2012;**13**:37.

AstraZeneca (SD-0390735). Comparison of the efficacy and safety of one inhalation of Symbicort®Turbuhaler® 160/4.5 µg bid plus as-needed with two inhalations of SeretideTM EvohalerTM 25/125 µg bid plus Terbutaline Turbuhaler® 0.4 mg as-needed, and one inhalation of Symbicort® Turbuhaler® 320/9 µg bid plus Terbutaline Turbuhaler® 0.4 mg as-needed. A 6-month, randomised, double-blind, double-dummy, parallel-group, active-controlled,multicentre, phase IIIB study in adult and adolescent asthmatic patients. www.astrazenecaclinicaltrials.com/_mshost2715844/content/content/resources/media/2958892/sd-039-0735.pdf (first recevied 30 April 2009).

Bleecker ER, Postma DS, Lawrance R, Meyers DA, Ambrose H, Goldman M. Effect of polymorphisms in the beta2-adrenergic receptor gene (ADRB2) on response to long-acting beta2-agonist (LABA) therapy. *Journal Allergy and Clinical Immunology* 2007;**119**(2):523.

Boonsawat W. Cost-effectiveness of budesonide/formoterol maintenance and rescue therapy in Thailand. *Asian Biomedicine* 2010;**4**(4):571-8.

Buhl R, Kuna P. Does the choice of ICS/LABA regimen influence exacerbation rates in asthma patients with high as needed use? *European Respiratory Journal* 2007;**30**(Suppl 51):617s [P3620].

Goldman M, Lawrance RM, Bleecker ER, Meyers DA, Ambrose HJ. Effect of polymorphisms in the ADRB2 3' Untranslated Region (3'UTR) on response to inhaled corticosteroid and long-acting beta2-adrenergic agonist (ICS/LABA) combination therapy. Journal of Allergy and Clinical Immunology 2009;**123**(2):S137.

Kuna P, Peters J, Buhl R. Budesonide/formoterol as maintenance and reliever therapy reduces asthma exacerbations versus higher maintenance dose of budesonide/formoterol or salmeterol/fluticasone. *European Respiratory Journal* 2006;**28**(Suppl 50):205s [P1228].

* Kuna P, Peters MJ, Manjra AI, Jorup C, Naya IP, Martinez-Jimenez NE, et al. Effect of budesonide/formoterol maintenance and reliever therapy on asthma exacerbations. International Journal of Clinical Practice 2007;**61**(5):725-36.

Kuna P. Treatment comparison of budesonide formoterol with salmeterol fluticasone propionate in adults aged >= 16 years

with asthma: post hoc analysis of a randomized, double-blind study. Clinical Drug Investigation 2010;**30**(9):565-79.

Miller E, FitzGerald JM. Budesonide/formoterol as maintenance and reliever treatment compared to fixed dose combination strategies - a Canadian economic evaluation. *Canadian Journal of Clinical Pharmacology/Journal Canadien de Pharmacologie Clinique* 2008;**15**(2):e165-76.

O'Connor RD, Patrick DL, Parasuraman B, Martin P, Goldman M. Comparison of patient-reported outcomes during treatment with adjustable- and fixed-dose budesonide/formoterol pressurized metered-dose inhaler versus fixed-dose fluticasone propionate/salmeterol dry powder inhaler in patients with asthma. *Journal of Asthma* 2010;**47**(2):217-23.

Price D, Wiren A, Kuna P. Cost-effectiveness of budesonide/formoterol for maintenance and reliever asthma therapy. *European Journal of Allergy and Clinical Immunology* 2007;**62**(10):1189-98.

Tamminen K, Laine J, Soini E, Martikainen J, Kankaanranta H. Cost-effectiveness analysis of budesonide/formoterol maintenance and reliever therapy versus fixed combination treatments for asthma in Finland. *Current Medical Research and Opinion* 2008;**24**(12):3453-61.

Maspero 2010 *{published data only}*

FDA. Clinical review of Dulera (NDA 22-518). www.fda.gov/media/100092/download (accessed before 18 November 2020).

Maspero J, Cherrez I, Nolte H. Long-term safety and tolerability of two doses of mometasone furoate/formoterol (MF/F) combination, administered via a metered-dose inhaler, for the treatment of moderate-to-severe persistent asthma [Abstract]. *Journal of Allergy and Clinical Immunology* 2009;**123**(2 Suppl 1):S159.

Maspero J, Cherrez I, Nolte H. Mometasone furoate/formoterol (mf/f) combination treatment in patients with moderate-to-severe asthma: findings from a 1-yr safety trial [Abstract]. In: European Respiratory Society Annual Congress; 2009 Sep 12-16; Vienna. 2009:[E274].

Maspero J, Nolte H, Cherrez I. Long-term safety of medium- and high-dose mometasone furoate/formoterol combination in persistent asthmatics: analysis of adverse event incidence, plasma cortisol, and ocular changes [Abstract]. In: European Respiratory Society Annual Congress; 2010 Sep 18-22; Barcelona. 2010:[P1211].

Maspero J, Nolte H, Ojeda IC. Long-term safety of medium- and high-doses mometasone furoate/formoterol combination in persistent asthmatics: analysis of adverse events incidence, plasma cortisol, and ocular changes [Abstract]. *Journal of Allergy and Clinical Immunology* 2010;**125**(2 Suppl 1):AB197.

Maspero JF, Cherrez I, Nolte H. Mometasone furoate and formoterol (MF/F) combination administered via a metered-dose inhaler (MDI) for the treatment of asthma: results from a 1-yr safety study. In: American Thoracic Society International Conference; 2009 May 15-20; San Diego. 2009:A2768 [Poster #J37].

* Maspero JF, Nolte H, Cherrez-Ojeda I. Long-term safety of mometasone furoate formoterol combination for treatment of patients with persistent asthma. *Journal of Asthma* 2010;**47**(10):1106-15.

NCT00379288. Study of mometasone furoate/formoterol combination and fluticasone/salmeterol in persistent asthmatics previously treated with inhaled glucocorticosteroids (P04139) [A 1-Year safety study of medium and high doses of mometasone furoate/formoterol combination formulation and medium and high doses of fluticasone/salmeterol in persistent asthmatics previously treated with medium to high doses of inhaled glucocorticosteroids]. clinicaltrials.gov/show/nct00379288 (first received 21 September 2006).

NCT00901368 *{published data only}*

Barnes N, Van Noord JA, Brindicci C, Lindemann L, Varoli G, Perpina M, et al. Maintenance of lung function and asthma control with extrafine beclomethasone/formoterol. European Respiratory Journal 2011;**38**(55):140s [P833].

Barnes N, van Noord JA, Brindicci C, Lindemann L, Varoli G, Perpina M, et al. Stepping-across controlled asthmatic patients to extrafine beclometasone/formoterol combination. Pulmonary Pharmacology and Therapeutics 2013;**26**(5):555-61.

EUCTR-003740-11-ES. A phase 4, multinational, multicentre, double blind, double dummy, randomized, parallel group, controlled clinical study of fixed combination beclomethasone dipropionate 100 µg plus formoterol fumarate 6 µg pmdi with hfa-134a propellant (chf1535, Foster®) versus fluticasone 250 µg plus salmeterol 50 µg dpi (Seretide® Diskus®) as maintenance treatment in controlled asthmatic patients. - facto study [Estudio fase iv, multinacional, multicentrico, doble ciego, doble simulacion, randomizado, de grupos paralelos, controlado, sobre la combinacion de dosis fijas de dipropionato de beclometasona 100 µg mas fumarato de formoterol 6 µg pmdi con propelente hfa-134a (chf1535, foster®) versus fluticasona 250 µg mas salmeterol 50 µg ips (seretide® diskus®) como tratamiento de mantenimiento de pacientes asmaticos controlados]. www.who.int/trialsearch/Trial2.aspx?TrialID=EUCTR2008-003740-11-ES (first received 23 January 2009).

EUCTR-003740-11-NL. A phase 4, multinational, multicentre, double blind, double dummy, randomized, parallel group, controlled clinical study of fixed combination beclomethasone dipropionate 100 µg plus formoterol fumarate 6 µg pmdi with hfa-134a propellant (chf1535, Foster®) versus fluticasone 250 µg plus salmeterol 50 µg dpi (Seretide® Diskus®) as maintenance treatment in controlled asthmatic patients. - facto study. www.clinicaltrialsregister.eu/ctr-search/trial/2008-003740-11/results (first received 6 January 2017).

NCT00901368. FACTO study (Foster® As Complete Treatment Option) [A phase 4, multinational, multicentre, double blind, double dummy, randomized, parallel group, controlled clinical study of fixed combination beclomethasone dipropionate 100 µg plus formoterol fumarate 6 µg pmdi with hfa-134a propellant (chf1535, foster®) versus fluticasone 250 µg plus salmeterol 50 µg dpi (seretide® diskus®) as maintenance treatment in controlled asthmatic patients]. clinicaltrials.gov/show/NCT00901368 (first received 13 May 2009).

Papi 2007 *{published data only}*

NCT00394368. Efficacy and tolerability of beclomethasone dipropionate 100 µg + formoterol 6 µg pMDI VIA HFA-134a vs. fluticasone 125 µg + salmeterol 25 µg pMDI [DOUBLE BLIND, MULTINATIONAL, MULTICENTRE, PARALLEL-GROUP DESIGN CLINICAL TRIAL OF THE EFFICACY AND TOLERABILITY OF CHF 1535 (BECLOMETHASONE DIPROPIONATE 100 µg + FORMOTEROL 6 µg) pMDI VIA HFA-134a vs. FLUTICASONE 125 µg + SALMETEROL 25 µg pMDI (SERETIDE®) IN THE 12-WEEK TREATMENT OF ADULT PATIENTS WITH MODERATE TO SEVERE PERSISTENT ASTHMA]. clinicaltrials.gov/show/NCT00394368 (first received 1 November 2006).

Paggiaro P, Papi A, Feschenko YI, Nicolini G, Fabbri LM. Efficacy and safety of the new beclomethasone dipropionate/formoterol combination vs fluticasone propionate/salmeterol pMDIs in moderate to severe persistent asthma. *European Respiratory Journal* 2006;**28**(Suppl 50):205s [P1227].

* Papi A, Paggiaro P, Nicolini G, Vignola AM, Fabbri LM. Beclomethasone/formoterol vs fluticasone/salmeterol inhaled combination in moderate to severe asthma. *European Journal of Allergy and Clinical Immunology* 2007;**62**(10):1182-8.

Papi 2012 *{published data only}*

NCT00497237. Clinical trial of the efficacy and safety of beclomethasone dipropionate plus formoterol vs fluticasone propionate plus salmeterol in the 6 months step down treatment of asthma [Prospective, randomised, open-label, multicentre, active drug controlled, parallel group design clinical trial of the efficacy and safety of beclomethasone dipropionate 400 mcg + formoterol 24 mcg pMDI Via HFA-134a (Foster™) vs. fluticasone propionate 500 mcg + salmeterol xinafoate 100 mcg DPI (Seretide Diskus®) in the 6 months stepdown treatment of adult patients with controlled asthma]. clinicaltrials.gov/show/NCT00497237 (first received 6 July 2007).

Paggiaro P, Nicolini G, Crimi N, Fabbri LM, Olivieri D, Rossi A, et al. Asthma control and lung function after step down from high dose ICS/LABA combination therapy. *European Respiratory Journal* 2011;**38**(55):722s [P3967].

Papi A, Nicolini G, Crimi N, Fabbri L, Olivieri D, Rossi A, et al. Step-down from high dose fixed combination therapy in asthma patients: a randomized controlled trial. *Respiratory Research* 2012;**13**:54.

Ploszczuk 2014 *{published data only}*

CTRI//05/002704. Comparison of Flutiform, fluticasone and Seretide in treatment of moderate to severe asthma in paediatric patients aged 5 to less than 12 years. www.who.int/trialsearch/Trial2.aspx?TrialID=CTRI/2012/05/002704 (first received 28 May 2012).

Ploszczuk A, Bosheva M, Spooner K, McIver T, Dissanayake S. Efficacy and safety of fluticasone propionate/formoterol fumarate in pediatric asthma patients: a randomized controlled trial. *Therapeutic Advances in Respiratory Disease* 2018;**12**:1753466618777924.

Ploszczuk A, Bosheva M, Spooner K, McIver T, Dissanayake S. Efficacy and safety of fluticasone propionate/formoterol in paediatric patients with asthma. *European Respiratory Journal* 2014;**44**:P1167.

Ringdal 2002 *{published data only}*

Jenkins C, Wilson J, Rutherford C, Perry AS, Whitehead PJ. Asthma management costs are lower with combination fluticasone/salmeterol (25/50 mcg BD) in a single inhaler than with budesonide (800 mcg BD) plus eformoterol (12 mcg BD) via separate inhalers. *Respirology* 2002;**7**(Suppl):A20 Abstract number (P23).

Martin AA, Whitehead PJ, McCarthy TP. Asthma costs with salmeterol/fluticasone combination 50/250mcg bd compared to budesonide 800mcg bd plus formoterol 12mcg bd [abstract]. In: American Thoracic Society 99th International Conference; 2003 May 16-21; Seattle. 2003:D034 Poster C43.

Ringdal N, Chovan L, Chuchalin AG, Whitehead PJ. Advair™/Seretide™ (250µg/50µg bid) shows exacerbation benefit over budesonide 800µg + formoterol 12µg in moderate-severe asthma [abstract]. *American Journal of Respiratory and Critical Care Medicine* 2001;**163**(Suppl 5):A866.

* Ringdal N, Chuchalin A, Chovan L, Tudoric N, Maggi E, Whitehead PJ, et al. Evaluation of different inhaled combination therapies (EDICT): a randomised, double-blind comparison of Seretide (50/250 mug bd Diskus vs. formoterol (12 mug bd) and budesonide (800 mug bd) given concurrently (both via Turbuhaler) in patients with moderate-to-severe asthma. *Respiratory Medicine* 2002;**96**(11):851-61.

Ringdal N, Chuchalin AG, Chovan L, Whitehead PJ. A comparison of Advair™/Seretide™ (salmeterol 50 µg/fluticasone propionate 250 µg bid) with formoterol 12 µg + budesonide 800 µg bid in moderate-severe asthma. *American Journal of Respiratory and Critical Care Medicine* 2000;**161**(Suppl 3):A196.

Rodriguez JM, Sondhi Sl. Economic evaluation of salmeterol/fluticasone propionate combination vs budesonide/formoterol in Spain. *European Respiratory Journal* 2003;**22 (Suppl 45)**:Abstract No: [2255].

Sondhi S, Martin A. Economic evaluation of salmeterol/fluticasone propionate combination versus budesonide/formoterol in the UK. In: American Thoracic Society 99th International Conference; 2003 May 16-21; Seattle. 2003:[B106] Poster E5.

SAM 40010 *{published data only}*

SAM40010. A randomised, double blind, double-dummy, parallel-group, twelve week comparison of salmeterol/fluticasone propionate (FP) DISKUS/ACCUHALER 50/100mcg bd. with budesonide 200mcg bd. plus formoterol 4.5mcg bd. (both by breath-activated dry powder inhaler [BADPI]) in adult and adolescent asthmatics. www.gsk-studyregister.com/en/trial-details/?id=SAM40010 (first received 26 January 2000).

SAM 40048 *{published data only}*

SAM40048. Randomised, double-blind, parallel group study on the efficacy and tolerability of the salmeterol 50 mcg/fluticasone 250 mcg combination Diskus compared to the formoterol 6mcg / budesonide 200mcg combination Turbohaler administered twice daily in patients with moderate bronchial

asthma. GlaxoSmithKline Clinical Trial Register (first received 16 August 2001).

Scichilone 2010 *{published data only}*

EUCTR-000512-25-IT. Double blind, double dummy, randomised, parallel group, monocentric clinical trial on the effects of chf 1535 mdi or seretide dpi on biological and functional markers of small airways in patients with asthma: a pilot study - nd. www.who.int/trialsearch/Trial2.aspx?TrialID=EUCTR2006-000512-25-IT (first received 20 April 2006).

Scichilone N, Battaglia S, Sorino C, Paglino G, Martino L, Paterno A, et al. Effects of extra-fine inhaled beclomethasone/formoterol on both large and small airways in asthma. *Allergy* 2010;**65**(7):897-902.

Usmani 2017 *{published data only}*

Kemppinen A, Gardener E, Thomas V, Raju P, Callan C, McLoughlin A, et al. Pragmatic trial stepping down Flutiform in patients maintained on high dose ICS. *Journal of Thoracic Disease* 2016;**8**(Suppl 5):AB039.

Usmani OS, Kemppinen A, Gardener E, Thomas V, Konduru PR, Callan C, et al. A randomized pragmatic trial of changing to and stepping down fluticasone/formoterol in asthma. *Journal of Allergy and Clinical Immunology* 2017;**5**(5):1378-87.e5.

Woo 2020 *{published data only}*

Woo SD, Ye YM, Lee Y, Lee SH, Shin YS, Park JH, et al. Efficacy and safety of a pressurized metered-dose inhaler in older asthmatics: comparison to a dry powder inhaler in a 12-week randomized trial. *Allergy, Asthma and Immunology Research* 2020;**12**(3):454-66.

References to studies excluded from this review

Bleecker 2008 *{published data only}*

Bleecker ER, Postma DS, Lawrance RM, Meyers DA, Ambrose HJ, Goldman M. Effect of ADRB2 polymorphisms on response to long acting beta2-agonist therapy: a pharmacogenetic analysis of two randomised studies. *Lancet* 2008;**370**(9605):2118-25.

Dhillon 2006 *{published data only}*

Dhillon S, Keating GM. Beclometasone dipropionate/formoterol in an HFA-propelled pressurised metered-dose inhaler. *Drugs* 2006;**66**(11):1475-83.

Hampel 2008 *{published data only}*

Hampel FC, Martin P, Mezzanotte WS. Early bronchodilatory effects of budesonide/formoterol pMDI compared with fluticasone/salmeterol DPI and albuterol pMDI: 2 randomized controlled trials in adults with persistent asthma previously treated with inhaled corticosteroids. *Journal of Asthma* 2008;**45**(4):265-72.

Jung 2008 *{published data only}*

Jung KS, Uh ST, Lee YC, Shim JJ, Park SK, Williams AE, et al. Comparison of the clinical efficacy and safety of salmeterol/fluticasone propionate versus current care in the management of persistent asthma in Korea. *Current Medical Research and Opinion* 2008;**24**(12):3571-82.

Lee 2003 *{published data only}*

Lee DKC, Currie GP, Cockburtn WJ, Lipworth BJ. Comparison of budesonide/formoterol versus fluticasone/salmeterol combination inhalers in moderate persistent asthma. In: American Thoracic Society 99th International Conference; 2003 May 16-21; Seattle. 2003:D094 Poster 613.

Lyseng-Williamson 2003 *{published data only}*

Lyseng-Williamson KA, Plosker GL. Inhaled salmeterol/fluticasone propionate combination: a pharmacoeconomic review of its use in the management of asthma. *Pharmacoeconomics* 2003;**21**(13):951-89.

NCT02491970 *{published data only}*

NCT02491970. Small airway function of fluticasone/formoterol (Flutiform®) and fluticasone/salmeterol (RECONFFIRM) [A single-blind, randomized, active-controlled, multi-center and phase IV study to evaluate the small airway parameters of fluticasone/formoterol (Flutiform®) compared to fluticasone/salmeterol in asthma patients]. clinicaltrials.gov/show/NCT02491970 (first received 8 July 2015).

Rani 2016 *{published data only}*

Rani S, Rawal M, Kumar S, Lamba S. To compare efficacy and safety of fixed drug combination of salmeterol / fluticasone and budesonide / formoterol on the lung functions in childhood patients with moderate persistent asthma. *Indian Journal of Public Health Research and Development* 2016;**7**(4):203-7.

UMIN000006572 *{published data only}*

JPRN-UMIN000006572. Study on the effects of the budesonide/formoterol combination formulation in improving airway inflammation and airway resistance in patients with bronchial asthma. www.who.int/trialsearch/Trial2.aspx?TrialID=JPRN-UMIN000006572 (first received 18 October 2011).

References to ongoing studies

NCT03387241 *{published data only}*

NCT03387241. Efficacy of FLUTIFORM ® vs Seretide® in moderate to severe persistent asthma in subjects aged ≥12 years [A double blind, double dummy, randomised, multicentre, two arm parallel group study to assess the efficacy and safety of FLUTIFORM® pMDI (2 puffs bid) vs Seretide® pMDI (2 puffs bid) in subjects aged ≥12 years with moderate to severe persistent, reversible asthma]. ClinicalTrials.gov/show/NCT03387241 (first received 2 January 2018).

Additional references

Altman 2003

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

Anderson 2006

Anderson GP. Current issues with beta(2)-adrenoceptor agonists - pharmacology and molecular and cellular mechanisms. *Clinical Reviews in Allergy and Immunology* 2006;**31**(2-3):119-30.

Arnold 1985

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

Barnes 1993

Barnes PJ. Beta-adrenoceptors on smooth-muscle, nerves and inflammatory cells. *Life Sciences* 1993;**52**(26):2101-9.

Barnes 1995

Barnes PJ. Beta-adrenergic receptors and their regulation. *American Journal of Respiratory and Critical Care Medicine* 1995;**152**(3):838-60.

Barnes 2002

Barnes PJ. Scientific rationale for inhaled combination therapy with long-acting beta2-agonists and corticosteroids. *European Respiratory Journal* 2002;**19**:182-91.

Bennett 1994

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

Bijl-Hofland 2001

Bijl-Hofland ID, Cloosterman SG, Folgering HT, Van den Elshout FJ, Van Weel C, Van Schayck CP. Inhaled corticosteroids, combined with long-acting beta(2)-agonists, improve the perception of bronchoconstriction in asthma. *American Journal of Respiratory and Critical Care Medicine* 2001;**164**(5):764-9.

Brown 1983

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

Burgess 1991

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

Burggraaf 2001

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

Cates 2008

Cates CJ, Cates MJ. Regular treatment with salmeterol for chronic asthma: serious adverse events. *Cochrane Database of Systematic Reviews* 2008, Issue 3. Art. No: CD006363. [DOI: 10.1002/14651858.CD006363.pub2]

Cates 2008a

Cates CJ, Cates MJ, Lasserson TJ. Regular treatment with formoterol for chronic asthma: serious adverse events. *Cochrane Database of Systematic Reviews* 2008, Issue 4. Art. No: CD006923. [DOI: 10.1002/14651858.CD006923.pub2]

Cates 2012

Cates CJ, Lasserson TJ. Regular treatment with formoterol versus regular treatment with salmeterol for chronic asthma: serious adverse events. *Cochrane Database of Systematic Reviews* 2012, Issue 3. Art. No: CD007695. [DOI: 10.1002/14651858.CD007695.pub3]

Cates 2018

Cates CJ, Schmidt S, Ferrer M, Sayer B, Waterson S. Inhaled steroids with and without regular salmeterol for asthma: serious adverse events. *Cochrane Database of Systematic Reviews* 2018, Issue 12. Art. No: CD006922. [DOI: 10.1002/14651858.CD006922.pub4]

Cochrane Airways 2019

Cochrane Airways Trials Register. airways.cochrane.org/trials-register (accessed 7 May 2019).

Cockcroft 1993

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

Collins 1969

Collins JM, McDevitt DG, Shanks RG, Swanton JG. Cardiotoxicity of isoprenaline during hypoxia. *British Journal of Pharmacology* 1969;**36**(1):35-45.

Crane 1989

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

Ducharme 2010

Ducharme FM, Ni Chroinin M, Greenstone I, Lasserson TJ. Addition of long-acting beta2-agonists to inhaled steroids versus higher dose inhaled steroids in adults and children with persistent asthma. *Cochrane Database of Systematic Reviews* 2010, Issue 4. Art. No: CD005533. [DOI: 10.1002/14651858.CD005533.pub2]

Ducharme 2011

Ducharme FM, Lasserson TJ, Cates CJ. Addition to inhaled corticosteroids of long-acting beta2-agonists versus anti-leukotrienes for chronic asthma. *Cochrane Database of Systematic Reviews* 2011, Issue 5. Art. No: CD003137. [DOI: 10.1002/14651858.CD003137.pub4]

Giembycz 2006

Giembycz MA, Newton R. Beyond the dogma: novel ß2-adrenoceptor signalling in the airways. *European Respiratory Journal* 2006;**27**(6):1286-306.

Grainger 1991

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

Guhan 2000

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

Hall 1989

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

Hanania 2002

Hanania NA, Sharfkhaneh A, Barber R, Dickey BF. Beta-agonist intrinsic efficacy - measurement and clinical significance. *American Journal of Respiratory and Critical Care Medicine* 2002;**165**(10):1353-8.

Hanania 2007

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

Hancox 1999

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

Hancox 2006

Hancox RJ. Interactions between corticosteroids and beta2-agonists. *Clinical Reviews in Allergy and Immunology* 2006;**31**(2-3):231-46.

Haney 2006

Haney S, Hancox RJ. Recovery from bronchoconstriction and bronchodilator tolerance. *Clinical Reviews in Allergy and Immunology* 2006;**31**(2-3):181-96.

Harvey 1982

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

Higgins 2011

Higgins JPT, Green S (editors). Cochrane Handbook for Systematic Reviews of Interventions Version 5.1. [updated March 2011]. The Cochrane Collaboration, 2011. Available from www.cochrane-handbook.org 2011.

Higgins 2019

Higgins JPT, Li T, Deeks JJ. Choosing effect measures and computing estimates of effect. In: Higgins JP, Thomas J, Chandler J, Cumpston M, Li T, Page MJ, et al, editors(s). Cochrane Handbook for Systematic Reviews of Interventions, 2nd edition. 2019:143-76.

Higgins 2020

Higgins JP, Thomas J, Chandler J, Cumpston M, Li T, Page MJ, editor(s). Cochrane Handbook for Systematic Reviews of Interventions Version 6.1 [updated September 2020]. Cochrane, 2020. Available from training.cochrane.org/handbook.

ICHE2A

Clinical safety data management: definitions and standards for expedited reporting. www.ema.europa.eu/en/ich-e2a-clinical-safety-data-management-definitions-standards-expedited-reporting (accessed before 19 November 2020).

Janjua 2019

Janjua S, Schmidt S, Ferrer M, Cates CJ. Inhaled steroids with and without regular formoterol for asthma: serious adverse events. *Cochrane Database of Systematic Reviews* 2019, Issue 9. Art. No: CD006924. [DOI: 10.1002/14651858.CD006924.pub4]

Jones 2001

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

Lasserson 2008

Lasserson TJ, Cates CJ, Ferrara G, Casali L. Combination fluticasone and salmeterol versus fixed dose combination budesonide and formoterol for chronic asthma in adults and children. *Cochrane Database of Systematic Reviews* 2008, Issue 1. Art. No: CD004106. [DOI: 10.1002/14651858.CD004106.pub3]

Lee 2003a

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

Lefebvre 2020

Lefebvre C, Glanville J, Briscoe S, Littlewood A, Marshall C, Metzendorf M-I, et al. Chapter 4. Searching for studies. In: Cochrane Handbook for Systematic Reviews of Interventions version 6.1 [updated September 2020]. Cochrane, 2020.

Lipworth 1989

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

Lipworth 1992

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

Lipworth 1997

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

Lipworth 2000

Lipworth BJ, Aziz I. Bronchodilator response to albuterol after regular formoterol and effects of acute corticosteroid administration. *Chest* 2000;**117**(1):156-62.

Lotvall 2001

Lötvall J. Pharmacological similarities and differences between beta2-agonists. *Respiratory Medicine* 2001;**95**(Suppl B):S7-11. [DOI: 10.1053/rmed.2001.1139]

Marshall 2018

Marshall IJ, Noel-Storr AH, Kuiper J, Thomas J, Wallace BC. Machine learning for identifying randomized controlled trials: an evaluation and practitioner's guide. *Research Synthesis Methods* 2018;**9**(4):602-14.

McDevitt 1974

McDevitt DG, Shanks RG, Swanton JG. Further observations on cardiotoxicity of isoprenaline during hypoxia. *British Journal of Pharmacology* 1974;**50**(3):335-44.

McDonald 2017

McDonald S, Noel-Storr AH, Thomas J. Harnessing the efficiencies of machine learning and Cochrane Crowd to identify randomised trials for individual Cochrane reviews. In: Global Evidence Summit; 2017 September 13-16; Cape Town, South Africa. 2017.

McIvor 1998

McIvor RA, Pizzichini E, Turner MO, Hussack P, Hargreave FE, Sears MR. Potential masking effects of salmeterol on airway inflammation in asthma. *American Journal of Respiratory and Critical Care Medicine* 1998;**158**(3):924-30.

Morrison 1993

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

Nelson 1977

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

Ni Chroinin 2009

Ni Chroinin M, Greenstone I, Lasserson TJ, Ducharme FM. Addition of inhaled long-acting beta2-agonists to inhaled steroids as first line therapy for persistent asthma in steroid-naive adults. *Cochrane Database of Systematic Reviews* 2009, Issue 4. Art. No: CD005307. [DOI: 10.1002/14651858.CD005307]

Ni Chroinin 2010

Ducharme FM, Ni Chroinin M, Greenstone I, Lasserson TJ. Addition of long-acting beta2-agonists to inhaled corticosteroids versus same dose inhaled corticosteroids for chronic asthma in adults and children. *Cochrane Database of Systematic Reviews* 2010, Issue 5. Art. No: CD005535. [DOI: 10.1002/14651858.CD005535.pub2]

Noel-Storr 2018

Noel-Storr AH, Project Transform Team. Cochrane Crowd: new ways of working together to produce health evidence. In: Evidence Live; 2018 June 18-20; Oxford, UK.

Ouzzani 2016

Ouzzani M, Hammady H, Fedorowicz Z, Elmagarmid A. Rayyan - a web and mobile app for systematic reviews. *Systematic Reviews* 2016;**5**:210. [DOI: 10.1186/s13643-016-0384-4.]

Palmqvist 1999

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

Pearce 1990

Pearce N, Grainger J, Atkinson M, Crane J, Burgess C, Culling C, et al. Case-control study of prescribed fenoterol and death from asthma in New Zealand, 1977-81. *Thorax* 1990;**45**(3):170-5.

Pearce 2007

Pearce N. Adverse Reactions: The Fenoterol Story. 1st edition. Auckland: Auckland University Press, 2007. [9781869403744]

Peters 2016

Peters SP, Bleecker ER, Canonica GW, Park YB, Ramirez R, Hollis S, et al. Serious asthma events with budesonide plus formoterol vs. budesonide alone. *New England Journal of Medicine* 2016;**375**(9):850-60.

RevMan 5 [Computer program]

The Nordic Cochrane Centre: The Cochrane Collaboration Review Manager (RevMan) Version 5.1. Copenhagen: The Nordic Cochrane Centre: The Cochrane Collaboration, 2008.

Salpeter 2006

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

Sears 1990

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

SMART 2006

Nelson HS, Weiss ST, Bleecker ER, Yancey SW, Dorinsky PM, the SMART Study Group. The Salmeterol Multicenter Asthma Research Trial: a comparison of usual pharmacotherapy for asthma or usual pharmacotherapy plus salmeterol. *Chest* 2006;**129**:15-26.

Speizer 1968

Speizer FE, Doll R, Heaf P. Observations on recent increase in mortality from asthma. *British Medical Journal* 1968;**1**(5588):335-9.

Stempel 2016

Stempel DA, Raphiou IH, Kral KM, Yeakey AM, Emmett MS, Prazma CM, et al. Serious asthma events with fluticasone plus salmeterol versus fluticasone alone. *New England Journal of Medicine* 2016;**374**(19):1822-30. [DOI: 10.1056/NEJMoa1511049]

Stempel 2016a

Stempel DA, Szefler SJ, Pedersen S, et al. Safety of adding salmeterol to fluticasone propionate in children with asthma. *New England Journal of Medicine* 2016;**375**(9):840-9. [DOI: 10.1056/NEJMoa1606356]

Thomas 2017

Thomas J, Noel-Storr AH, Marshall I, Wallace B, McDonald S, Mavergames C, et al. Living systematic review network. Living systematic reviews: 2. Combining human and machine effort. *Journal of Clinical Epidemiology* 2017;**91**:31-7.

van der Woude 2001

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

vanNoord 1996

vanNoord JA, Smeets JJ, Raaijmakers JAM, Bommer AM, Maesen FPV. Salmeterol versus formoterol in patients with moderately severe asthma: onset and duration of action. *European Respiratory Journal* 1996;**9**(8):1684-8.

Walters 2002

Walters EH, Walters JAE, Gibson PW. Regular treatment with long acting beta agonists versus daily regular treatment with short acting beta agonists in adults and children with stable asthma. *Cochrane Database of Systematic Reviews* 2002, Issue 3. Art. No: CD003901. [DOI: 10.1002/14651858.CD003901]

Walters 2007

Walters EH, Gibson PG, Lasserson TJ, Walters JAE. Long-acting beta2-agonists for stable chronic asthma. *Cochrane Database of Systematic Reviews* 2007, Issue 1. Art. No: CD001385. [DOI: 10.1002/14651858.CD001385.pub2]

Weber 1982

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

Weinstein 2019

Weinstein CLJ, Ryan N, Shekar T, Gates D, Lane SJ, Agache I, et al. Serious asthma events with mometasone furoate plus formoterol compared with mometasone furoate. *Journal of Allergy and Clinical Immunology* 2019;**143**(4):1395-402. [DOI: 10.1016/j.jaci.2018.10.065]

Wilson 1981

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

Wong 1990

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

Yates 1996

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

References to other published versions of this review

Cates 2009

Cates CJ, Lasserson T. Regular fixed-dose treatment with formoterol and inhaled corticosteroids versus regular treatment with salmeterol and inhaled corticosteroids for chronic asthma: serious adverse events. *Cochrane Database of Systematic Reviews* 2009, Issue 2. Art. No: CD007694. [DOI: 10.1002/14651858.CD007694]

Cates 2010

Cates CJ, Lasserson TJ. Regular treatment with formoterol and an inhaled corticosteroid versus regular treatment with salmeterol and an inhaled corticosteroid for chronic asthma: serious adverse events. *Cochrane Database of Systematic Reviews* 2010, Issue 1. Art. No: CD007694. [DOI: 10.1002/14651858.CD007694.pub2]

* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

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

Aalbers 2004

Study characteristics	
Methods	A randomised, double-blind/open-extension, double-dummy, multi-centre, parallel-group study over 4 weeks from October 2001 to December 2002 at outpatient clinics in 93 centres in 6 countries (Denmark (9), Finland (10), Germany (11), The Netherlands (12), Norway (41), and Sweden (10)). Open run-in 10 to 14 days Open-extension period was 6 months, in which 2 arms of the study continued on fixed-dose BDF and FPS

Aalbers 2004 *(Continued)*

Participants	658 adolescents and adults (12 to 85 years) with perennial asthma **Baseline characteristics:** mean age 46 years. FEV_1 84% predicted. Concomitant ICS used by 100% of participants, mean dose 735 µg/d. Run-in on previous dose of ICS alone (LABA discontinued in the 28% of participants taking it previously) **Inclusion criteria:** aged 12 years or over with diagnosis of perennial asthma and using 500 to 1200 µg daily of inhaled GCS. FEV_1 % predicted 50% or greater. Must have had a total asthma symptom score ≥ 1 on at least 4 of the last 7 days of the run-in period and a mean morning PEF during the last 7 days of the run-in period of between 50% and 85% of post-bronchodilatory PEF measured at Visit 1 or 2. Run-in on previous ICS alone **Exclusion criteria:** respiratory infection affecting asthma within 1 month of study entry, smoking history of > 10 pack-years, use of systemic corticosteroids within 1 month of study entry, and any significant disorder that, in the opinion of the investigator, may have put the patient at risk or influenced the study
Interventions	• Salmeterol/fluticasone 50/250 µg twice daily × 1 DPI • Budesonide/formoterol 160/4.5 µg twice daily × 2 DPI • Third arm was on adjustable maintenance dose and not included in this review
Outcomes	Primary efficacy endpoint was the odds of having a well-controlled asthma week during the randomised treatment period. SAEs reported in the paper for each group. No deaths occurred in the study (Web report)
Notes	Sponsored by AstraZeneca

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomisation schedule was generated via a computer programme by a statistician independent of the study team
Allocation concealment (selection bias)	Low risk	Patients were consecutively allocated to the lowest available patient number and were randomised strictly sequentially in blocks
Blinding of participants and personnel (performance bias) All outcomes	High risk	No blinding in the 6-month open-extension period
Blinding of outcome assessment (detection bias) All outcomes	Low risk	No impact on all-cause outcomes
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	575/658 (76%) completed the study, with similar loss in all groups
Selective reporting (reporting bias)	Low risk	SAEs reported in paper for each group
Independent Outcome Assessment (Asthma events only) Asthma-related serious adverse events	High risk	No independent outcome assessment reported

Akamatsu 2014

Study characteristics	
Methods	A prospective, multi-centre, randomised, open-label study. Patients with asthma who attended out-patient clinics at Hamamatsu University School of Medicine and Shizuoka General Hospital for routine check-ups between January and August 2011 were enrolled in this study There was an 8-week run-in period, after which eligible subjects were randomised to the 2 treatment groups for 12 weeks
Participants	**Population:** 66 adult patients (18+ years) with asthma (as per GINA definition) **Baseline characteristics:** N = 31 were randomised to the FBC group; mean age 61.6 (SD 12.1) years, 14:17 (M:F), FEV_1 1.97 (SD 0.60) L; N = 30 to the SFC group; mean age 57.1 (SD 14.6), 17:13 (M:F), FEV_1 2.25 (SD 0.72) L. Duration of treatment with SFC (months): FBC group mean 10.3 (SD 7.9), SFC group mean 12.9 (SD 8.4) **Inclusion criteria:** age over 18 years; ability to perform an adequate forced expiratory manoeuvre; asthma duration longer than 6 months; receiving SFC 50/250 mg 1 inhalation bid with or without other medications for asthma, including leukotriene receptor antagonists, or sustained-release theophylline for at least 8 weeks **Exclusion criteria:** any acute viral infection within at least 1 month before the study; chronic obstructive pulmonary disease; cardiovascular disease; pregnant
Interventions	• Salmeterol/fluticasone combination (SFC) 50/250 µg twice daily × 1 DPI • Formoterol/budesonide combination (FBC) 4.5/160 µg twice daily × 2 DPI
Outcomes	ACQ5 score, PEF, spirometry, FeNO, alveolar NO concentration (CANO), maximal NO flux in the conductive airways (J'awNO) measured
Notes	Funding details not included

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	No details
Allocation concealment (selection bias)	Unclear risk	No details
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open-label
Blinding of outcome assessment (detection bias) All outcomes	Low risk	No impact on all-cause outcomes
Incomplete outcome data (attrition bias) All outcomes	Low risk	8.9% (n = 3/34) in the FBC group and 6.3% (n = 2/32) in the SFC group

Akamatsu 2014 *(Continued)*

Selective reporting (reporting bias)	High risk	No safety data reported
Independent Outcome Assessment (Asthma events only) Asthma-related serious adverse events	High risk	No independent outcome assessment reported

Bernstein 2011

Study characteristics	
Methods	A multi-centre, 12-week, open-label, evaluator-blinded, active-controlled, non-inferiority efficacy and safety trial in subjects (aged ≥ 12 years) with uncontrolled persistent asthma previously treated with medium-dose ICS with or without a LABA
Participants	**Population:** A total of 722 subjects were randomised to receive formoterol/mometasone MDI 200/10 µg twice daily (n = 371) or salmeterol/fluticasone DPI 250/50 µg twice daily (n = 351) **Baseline characteristics:** mean age 44.8 (12 to 82) years on formoterol/mometasone and 45.1 (12 to 80) years on salmeterol/fluticasone propionate. Baseline FEV_1 73.8% and 74.1% predicted; 44% and 51% of participants were previously on LABA/ICS (respectively). Subjects had moderate persistent asthma that was uncontrolled after the MF 200 µg twice daily run-in period, based on FEV_1 (i.e. 60% to 80% predicted) and ACQ (i.e. score ≥ 1.5) findings as related to definitions from the NAEPP **Inclusion criteria:** ≥ 12 years of age; asthma diagnosis for ≥ 12 months; previous treatment with medium-dose ICS, alone or with a LABA, for ≥ 12 weeks before screening; stable asthma treatment regimen (daily dose unchanged) for ≥ 2 weeks before screening; history of ≥ 2 unscheduled asthma-related visits to a physician or emergency department within the past year or ≥ 3 unscheduled asthma-related visits within the past 2 years; forced expiratory volume in 1 second (FEV_1) 60% to 90% predicted at screening and at baseline; increase in absolute FEV_1 ≥ 12% and ≥ 200 mL within 15 to 20 minutes after administration of short-acting β_2-agonist (SABA) rescue medication or peak expiratory flow (PEF) variability > 20%; use of ≥ 12 inhalations of rescue medication in the final 10 days of the run-in period **Exclusion criteria:** > 20% change in absolute FEV_1 between screening and baseline; use of > 8 inhalations per day of a SABA-MDI or ≥ 2 nebulised treatments per day of 2.5 mg SABA on any 2 consecutive days between screening and baseline; 2 consecutive days before randomisation with decrease in PEF below the run-in stability limit, calculated over the preceding 7 days; clinical deterioration of asthma between screening and baseline that resulted in emergency treatment or hospitalisation, or treatment with asthma medications other than a SABA; asthma-related emergency department visit or hospital admission in the past 3 months; current smoker or ex-smoker (i.e. smoked in the previous year or had a cumulative smoking history > 10 pack-years)
Interventions	• Formoterol/mometasone furoate 5/100 µg twice daily × 2 pMDI • Salmeterol/fluticasone propionate 50/250 µg twice daily × 1 DPI
Outcomes	Primary outcome was lung function as measured by change from baseline in AUC in FEV_1 measured serially over 0 to 12 hours post dose
Notes	This study was funded by Merck Sharp & Dohme Corp
Risk of bias	
Bias	**Authors' judgement** **Support for judgement**

Bernstein 2011 *(Continued)*

Random sequence generation (selection bias)	Low risk	Eligible subjects were randomised in a 1:1 ratio according to a computer-generated randomisation schedule
Allocation concealment (selection bias)	Unclear risk	No details
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open-label
Blinding of outcome assessment (detection bias) All outcomes	Low risk	No impact on all-cause outcomes
Incomplete outcome data (attrition bias) All outcomes	High risk	Percentages of participants who discontinued the trial through Week 12 were 42% and 41% in the MF/F-MDI 200/10 µg BID and FP/S-DPI 250/50 µg BID treatment groups, respectively
Selective reporting (reporting bias)	Low risk	SAE data from NCT site
Independent Outcome Assessment (Asthma events only) Asthma-related serious adverse events	High risk	No independent outcome assessment reported

Bodzenta-Lukaszyk 2011

Study characteristics	
Methods	A 12-week, open-label, randomised, active-controlled, parallel-group, phase 3 study, conducted at 25 centres across 5 European countries (Germany, Hungary, Poland, Romania, and the UK; clinicaltrials.gov identifier: NCT00476073)
Participants	**Population:** 202 adults (18+ years) with mild to moderate to severe persistent asthma **Baseline characteristics:** mean age 47 years; FEV_1 67% predicted; concomitant ICS used by 93% of participants **Inclusion criteria:** required to demonstrate FEV_1 ≥ 40% and ≤ 85% of predicted normal values (17) during the screening phase following appropriate withholding of asthma medications (if applicable); also required to show reversibility of ≥ 15% in FEV_1 after salbutamol inhalation (2 actuations, 100 µg per actuation) to be eligible for randomisation. Only patients who could demonstrate correct inhaler technique were entered into the study **Exclusion criteria:** life-threatening asthma within the past year; hospitalisation or emergency department visit for asthma in the 4 weeks before screening; systemic corticosteroid use in the month before screening; omalizumab use in the past 6 months; use of a leukotriene receptor antagonist in the week before screening; a smoking history that was recent (in the 12 months before screening) or equivalent to ≥ 10 pack-years (e.g. ≥ 20 cigarettes/d for 10 years); significant non-reversible active pulmonary disease; clinically significant respiratory tract infection in the 4 weeks before screening. Also prohibited was recent use (in the past week) of β-blocking agents, tricyclic antidepressants, monoamine oxidase inhibitors, astemizole, quinidine-type antiarrhythmics or potent CYP3A4 inhibitors. Current use of medications that would have an effect on bronchospasm and/or lung function was also a criterion for exclusion

Bodzenta-Lukaszyk 2011 *(Continued)*

Interventions	Patients randomised to receive fluticasone/formoterol were to take 2 actuations of 50/5 µg or 125/5 µg every 12 hours (i.e. 100/10 µg or 250/10 µg twice daily) Patients randomised to receive fluticasone/salmeterol were to take 2 actuations of 50/25 µg or 125/25 µg every 12 hours (i.e. 100/50 µg or 250/50 µg twice daily) Both study treatments were administered via a hydrofluoroalkane pressurised metered-dose inhaler with an AeroChamber Plus spacer device Patients receiving the low dose of study medication were permitted to switch to the high dose during the treatment period if their asthma was not controlled, at the investigator's discretion
Outcomes	**Primary outcome:** FEV_1 SAE results reported in the paper: "serious AEs (SAEs) were also reported for one patient in each treatment group. The SAEs experienced by the patient in the fluticasone/formoterol group (haemorrhagic stroke and cardiac arrest, approximately 2 months after randomisation) led to withdrawal from the study, and had a fatal outcome. The SAE reported in the fluticasone/ salmeterol group was pneumococcal pneumonia"
Notes	Sponsored by Mundipharma Research Limited

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Random permuted block design
Allocation concealment (selection bias)	Low risk	Eligible patients were assigned a unique randomisation number selected sequentially from a randomisation list via an interactive voice randomisation system
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open-label
Blinding of outcome assessment (detection bias) All outcomes	Low risk	No impact on all-cause outcomes
Incomplete outcome data (attrition bias) All outcomes	Low risk	7% and 6% withdrawn from each arm
Selective reporting (reporting bias)	Low risk	SAE events reported in the paper for each group
Independent Outcome Assessment (Asthma events only) Asthma-related serious adverse events	High risk	No independent outcome assessment reported

Busse 2008

Study characteristics

Busse 2008 *(Continued)*

Methods	A randomised, open-label, multi-centre, parallel-group, phase 3 study over 7 months at 145 centres in the United States. Run-in 10 to 14 days The study comprised 3 phases: run-in (10 to 14 days), treatment period 1 (1 month, fixed-dose regimens), treatment period 2 (6 months, adjustable-dose or fixed-dose regimen)
Participants	**Population:** 1225 adolescents and adults (12 to 87 years) with moderate to severe persistent asthma **Baseline characteristics:** mean age 39 years; FEV_1 78.7% predicted; concomitant ICS used by 100% of participants; mean dose 550 µg/d; run-in on previous asthma therapy (ICS or LABA/ICS) **Inclusion criteria:** 12 years and older with a documented diagnosis of asthma, as defined by the American Thoracic Society, for 6 months or longer before screening and in stable condition; had to be maintained on a daily medium-dose ICS or ICS/LABA combination for 12 weeks or longer before screening; FEV_1 % predicted ≥ 50% 6 or more hours after short-acting $beta_2$-adrenergic agonist use and 24 or more hours after LABA use; had received ≥ 8 inhalations of albuterol during the last 10 days of the run-in period and demonstrated a mean morning peak expiratory flow (PEF) between 50% and 85% of the PEF value obtained 15 minutes after albuterol pMDI (2 to 4 inhalations (90 µg per inhalation)) during the last 7 days of the run-in period **Exclusion criteria:** systemic corticosteroid use within 30 days before screening; ≥ 20 pack-year smoking history at screening, or significant disease, respiratory tract infection, or illness that might interfere with lung function or participation in the study
Interventions	• Fluticasone/salmeterol 250/50 µg twice daily DPI • Budesonide/formoterol 320/9 µg twice daily pMDI The AMD treatment arm was not included in this review
Outcomes	Primary efficacy variable was asthma control, as assessed by asthma exacerbations SAE results reported on the sponsor's website. Uncertainty over the 2 participants mentioned in the footnotes to Table S4 in the report from the trial register was resolved after correspondence with the sponsors. The participant who suffered an SAE after finishing treatment had already been counted in the formoterol/budesonide arm due to another SAE while on treatment, but the patient who was admitted to hospital for an episode that was judged to have started during run-in had not been included in the 9 participants on formoterol/budesonide. After discussion, we therefore used 10 for this arm in our primary analysis
Notes	Sponsored by AstraZeneca

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomisation schedule was computer-generated
Allocation concealment (selection bias)	Low risk	The site called in to an IVRS, which assigned participants the next lowest available randomisation number
Blinding of participants and personnel (performance bias) All outcomes	High risk	No blinding in 6-month study extension
Blinding of outcome assessment (detection bias) All outcomes	Low risk	No impact on all-cause outcomes

Busse 2008 *(Continued)*

Incomplete outcome data (attrition bias) All outcomes	Low risk	1052/1225 (86%) completed the study
Selective reporting (reporting bias)	Low risk	SAE data found on website
Independent Outcome Assessment (Asthma events only) Asthma-related serious adverse events	High risk	No independent outcome assessment reported

Dahl 2006

Study characteristics	
Methods	A randomised, double-blind, double-dummy, multi-centre, parallel-group study over 24 weeks from November 2001 to January 2003 at 178 centres in 18 European countries. Run-in 2 weeks
Participants	**Population:** 1397 adults (18 to 91 years) with moderate to severe asthma **Baseline characteristics:** mean age 46 years; FEV_1 78.6% predicted; concomitant ICS used by 100% of participants; run-in on previous dose of ICS alone; LABA (if previously used) was withdrawn during the run-in period **Inclusion criteria:** aged 18 years or over, with documented clinical history of asthma of at least 6 months and receiving 1000 to 2000 µg/d of beclomethasone dipropionate or equivalent. Combination therapy, if used, was discontinued and was replaced by ICS alone, at least 4 weeks before the study start (screening visit). Bronchodilator reversibility by an increase of ≥ 12% in FEV_1 15 minutes after inhaling salbutamol 200 to 400 µg For the randomised treatment period (baseline), bronchodilator reversibility by an increase of ≥ 12% in FEV_1 (and ≥ 200 mL) 15 minutes after inhaling salbutamol 200 to 400 µg, and an asthma symptom score (day and night combined) of ≥ 2 (≥ 2 episodes of symptoms during the day/night) on at least 4 of the last 7 evaluable days of the run-in period **Exclusion criteria:** suffered an upper or lower respiratory tract infection or an acute asthma exacerbation (requiring emergency treatment or hospitalisation) within 4 weeks of Visit 1; used oral corticosteroids within 4 weeks or depot steroids within 12 weeks of Visit 1; pre-bronchodilator FEV_1 % predicted of < 50%, smoking history of ≥ 10 pack-years
Interventions	• Salmeterol/fluticasone 50/250 µg 1 inhalation twice daily DPI • Formoterol/budesonide 6/200 µg 2 inhalations twice daily DPI
Outcomes	Primary efficacy measure was the number of exacerbations, expressed as a rate over the 24-week treatment period SAE data described in paper only as "no deaths in the study and only a small proportion of patients reported serious AEs" SAE data obtained from sponsors' website
Notes	Sponsored by GSK
Risk of bias	

Dahl 2006 *(Continued)*

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Participants were assigned to study treatment in accordance with the randomisation schedule from the Interactive Voice Recognition System, which was part of the GSK System for the Central Allocation of Medication
Allocation concealment (selection bias)	Low risk	Blinded study medication was packed and supplied by GSK. All treatment packs contained both Diskus/Accuhaler and Turbuhaler devices (either active Diskus/Accuhaler + placebo Turbuhaler, or active Turbuhaler + placebo Diskus/Accuhaler) and looked identical
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind, double-dummy
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Double-blind, double-dummy
Incomplete outcome data (attrition bias) All outcomes	Low risk	1258/1397 (90%) completed the study
Selective reporting (reporting bias)	Low risk	SAE data found on website
Independent Outcome Assessment (Asthma events only) Asthma-related serious adverse events	High risk	No independent outcome assessment reported

Emeryk 2016

Study characteristics	
Methods	An open-label, randomised, controlled, 12-week phase 3 trial and extension (24-week extension). The study consisted of a 4– to 10-day screening phase, after which patients discontinued their pre-study asthma medication Patients were recruited across 6 sites in Europe: Prague, Czech Republic; Laon, France; Wiesal, Germay; Budapest, Hungary; Lublin, W. Chodzki, Poland; Bucharest, Hungary
Participants	**Population:** 211 children with asthma, aged 4 to 12 years, were recruited **Baseline characteristics:** median age 9 years (range 4 to 12). FEV_1 82% predicted (SD 9.5). ICS used by 90% of children, median dose 200 µg/d; ICS/LABA used by 59% of children **Inclusion criteria:** had to have had asthma for at least 6 months before screening. At screening, had an FEV_1 between at least 60% and up to and including 100% of predicted normal levels following appropriate withholding of asthma medication, and documented FEV_1 reversibility of ≥ 15%. Required to demonstrate satisfactory use of both inhaler and spacer devices and had to be able to substitute study medication for their pre-study prescribed asthma treatment **Exclusion criteria:** had experienced near-fatal or life-threatening asthma (including intubation) within the past year, required hospitalisation or an emergency visit due to asthma in the previous 4 weeks,

Emeryk 2016 *(Continued)*

	had a history of systemic (injectable) corticosteroid use within 1 month before, or LTRA use (e.g. montelukast) within 1 week before screening. Any clinically significant disease or abnormality, a clinically relevant upper or lower respiratory infection within 4 weeks before screening, or significant non-reversible pulmonary disease
Interventions	• Formoterol/fluticasone propionate 5/50 µg twice daily × 2 pMDI • Salmeterol/fluticasone propionate 25/50 µg twice daily × 2 pMDI
Outcomes	Primary endpoint was change in pre-dose FEV_1 over the 12-week treatment period. SAEs reported in the paper and in the EU-CTR report
Notes	This study was sponsored by Mundipharma Research Limited ClinicalTrials.gov identifier: NCT00475813; EudraCT number: 2006-005928-16

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomisation was stratified by age groups (4 to 6 years and 7 to 12 years of age) to ensure balance across treatment groups
Allocation concealment (selection bias)	Unclear risk	No details
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open-label
Blinding of outcome assessment (detection bias) All outcomes	Low risk	No impact on all-cause outcomes
Incomplete outcome data (attrition bias) All outcomes	Low risk	Only 1 participant dropped out during the core trial
Selective reporting (reporting bias)	Low risk	SAE data in Eu-CTR report and paper
Independent Outcome Assessment (Asthma events only) Asthma-related serious adverse events	High risk	No independent assessment of SAE causation described

EUCTR-002587-99-CZ

Study characteristics

Methods	A 24-week, multi-centre, multi-national, randomised, double-blind, triple-dummy, 3-arm, parallel-group study

EUCTR-002587-99-CZ *(Continued)*

Participants	FEV_1 < 80% predicted normal value and symptomatic on high doses of ICS as monotherapy or medium doses of ICS + LABA, to demonstrate superiority of CHF 1535 200/6 (2 puffs twice daily) vs high dose of BDP (beclomethasone dipropionate 2000 µg/d) given as monotherapy, in terms of: • pulmonary function (change from baseline in pre-dose morning FEV_1 measured at clinic); • asthma control (change from baseline in percentage of complete days without asthma symptoms); and • non-inferiority vs Seretide 500/50 (1 inhalation twice daily) in terms of pulmonary function (change from baseline in pre-dose morning FEV_1 measured at clinic) during a 24-week treatment period 721 participants were randomised (237 in the CHF 1535 group, 242 in the BDP monotherapy group, and 242 in the Seretide® group) and received at least 1 dose of randomised study drug **Baseline characteristics:** reporting group values CHF 1535 ITT and Seretide ITT Number of subjects: 234 and 241 Adolescents (12 to 17 years): 2 and 5 Adults (18 to 64 years): 213 and 217 From 65 to 84 years: 19 and 19 **Inclusion criteria:** severe asthma patients with FEV_1 < 80% predicted normal value and symptomatic on high doses of ICS as monotherapy or medium doses of ICS + LABA **Exclusion criteria:** no details
Interventions	• CHF 1535 HFA-134a pMDI inhaler (fixed combination of beclomethasone dipropionate 200 µg + formoterol 6 µg/unit dose), 2 inhalations of CHF 1535 HFA pMDI twice daily • Beclomethasone dipropionate HFA pMDI 250 µg/unit dose (Clenil 250) (daily dose of BDP "non extra-fine" 2000 µg BDP), 4 inhalations twice daily. We did not use this arm in our analysis • Seretide Accuhaler 500/50 µg/actuation (daily dose of fluticasone 1000 µg + salmeterol 100 µg), 1 inhalation twice daily
Outcomes	Change from baseline in pre-dose morning FEV_1 measured at clinic
Notes	Sponsored by Chiesi

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	No details
Allocation concealment (selection bias)	Unclear risk	No details
Blinding of participants and personnel (performance bias) All outcomes	Low risk	A 24-week, multi-centre, multi-national, randomised, double-blind, triple-dummy, 3-arm, parallel-group study
Blinding of outcome assessment (detection bias) All outcomes	Low risk	A 24-week, multi-centre, multi-national, randomised, double-blind, triple-dummy, 3-arm, parallel-group study

EUCTR-002587-99-CZ *(Continued)*

Incomplete outcome data (attrition bias) All outcomes	Low risk	197/237 and 202/242 participants from each group completed the study
Selective reporting (reporting bias)	Low risk	SAE data in Eu-CTR report
Independent Outcome Assessment (Asthma events only) Asthma-related serious adverse events	High risk	No independent outcome assessment reported

EUCTR-003449-17-IT

Study characteristics	
Methods	A 12-week, multi-centre, randomised, double-blind, double-dummy, 2-arm, parallel-group study
Participants	A study comparing the efficacy and safety of Foster NEXThaler (beclomethasone dipropionate 100 µg + formoterol 6 µg/actuation), 2 inhalations twice daily, vs Seretide Accuhaler (fluticasone 250 µg + salmeterol 50 µg/actuation), 1 inhalation twice daily, on small airway–derived parameters in patients with asthma A total of 149 patients were screened, and 41 of them were not randomised, mainly for ineligibility. Therefore, 108 patients in total were randomised to receive the assigned treatment: 54 were assigned to the Foster NEXThaler group (Foster) and 54 to the Seretide Accuhaler group (Seretide) **Baseline characteristics:** mean age 50 years (SD 15.7) and 51 years (SD 16.1), respectively **Inclusion criteria:** no details **Exclusion criteria:** no details
Interventions	• Foster NEXThaler DPI (beclomethasone dipropionate 100 µg + formoterol 6 µg per actuation), 2 inhalations twice daily (daily dose of BDP 400 µg + FF 24 µg) + Seretide Accuhaler placebo, 1 inhalation twice daily • Seretide Accuhaler DPI: fixed combination of fluticasone propionate 250 µg + salmeterol xinafoate 50 µg per actuation (daily dose of FP 500 µg + SX 100 µg) + Foster NEXThaler placebo, 2 inhalations twice daily
Outcomes	Primary: change from baseline to end of treatment in post-dose peripheral airway resistance [R(5Hz) - R(20Hz)]
Notes	Sponsored by Chiesi

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	No details
Allocation concealment (selection bias)	Unclear risk	No details

EUCTR-003449-17-IT *(Continued)*

Blinding of participants and personnel (performance bias) All outcomes	Low risk	Realisation of the double-blind design was made possible by the use of a Foster NEXThaler and Seretide Accuhaler placebo, which was totally indistinguishable from the respective active item in terms of size, shape, colour, and mode of inhalation. Each placebo was administered together with the alternate active ingredient
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Subject, Investigator, Monitor, Data analyst, Carer, Assessor - all blinded
Incomplete outcome data (attrition bias) All outcomes	Low risk	49/54 and 46/54 participants in each group completed the study
Selective reporting (reporting bias)	Low risk	SAE data in Eu-CTR report
Independent Outcome Assessment (Asthma events only) Asthma-related serious adverse events	High risk	No independent outcome assessment reported

EUCTR-004833-70-BG

Study characteristics	
Methods	A randomised, parallel-group, non-inferiority, open-label, multi-centre study
Participants	**Population:** patients were recruited from 26 centres across Bulgaria, Romania, Macedonia, and Serbia **Baseline characteristics:** 229 patients were recruited **Inclusion criteria:** men and women, 18 to 65 years old, with diagnosis of moderate to severe persistent asthma for minimum of 6 months' duration, with FEV_1 range of 50% to 80% predicted at screening and at baseline, ≥ 12% in FEV_1 and 200 mL reversibility to 4 puffs of salbutamol 100 µg, with asthma symptoms partly controlled or uncontrolled according to GINA guidelines **Exclusion criteria:** received oral or parental corticosteroids in the past 8 weeks, were hospitalised for an asthma exacerbation or a related disorder in the 3 months before screening visit
Interventions	Group 1: SMB budesonide-salmeterol 150/25 µg twice daily 12 weeks Group 2: Symbicort Turbuhaler 200/12 µg twice daily 12 weeks
Outcomes	Mean change in morning pre-dose PEF over weeks from baseline to Week 12
Notes	2008-004833-70

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	No details

EUCTR-004833-70-BG *(Continued)*

Allocation concealment (selection bias)	Unclear risk	No details
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open-label
Blinding of outcome assessment (detection bias) All outcomes	Low risk	No impact on all-cause outcomes
Incomplete outcome data (attrition bias) All outcomes	Low risk	Everyone who was randomised was included in the safety analysis
Selective reporting (reporting bias)	Low risk	SAE data in Eu-CTR report
Independent Outcome Assessment (Asthma events only) Asthma-related serious adverse events	High risk	No independent outcome assessment described

Hsieh 2013

Study characteristics	
Methods	A double-blind, double-dummy, phase 3, multi-centre, randomised, 2-arm, parallel-group, controlled study. After a 2-week run-in period, participants were randomised to a 12-week treatment period
Participants	**Population:** 253 Taiwanese patients with moderate to severe asthma (20 to 65 years of age) were recruited between June 2010 and May 2012 at 15 hospitals in Taiwan **Baseline characteristics:** N = 125 to the BDP/F group and N = 128 to the FP/S group. Mean (SD) age in years per group was 46.2 (14.3) and 44 (14.7) in the BDP/F group and in the FP/S group, respectively **Inclusion criteria:** aged 20 to 65 years with clinical diagnosis of moderate to severe asthma (according to GINA guidelines 2008); symptoms partly controlled or uncontrolled with ICS alone (daily dose ICS 1000 mg of BDP-equivalent) during run-in period; confirmed evidence of asthma through a positive response to the reversibility test (defined as a an increase in FEV_1 of 12% and 200 mL over baseline), within 30 minutes after administration of 400 mg of salbutamol pMDI, or through a positive response to methacholine challenge test (historically documented FEV_1 reversibility or response to methacholine challenge test within previous 6 months was acceptable) **Exclusion criteria:** if any of the following was present: diagnosis of COPD; current/ex-smokers; increase in PEF > 15% during run-in period; respiratory tract infection of the airways or severe asthma exacerbation within 8 weeks before the screening visit; treatment with LABAs or anticholinergics in the week preceding the screening visit; treatment with LTRA or change in ICS dosage in the 4 weeks preceding the screening visit; use of antihistamines during the run-in period; pregnant or lactating women
Interventions	• Beclomethasone/formoterol 100/6 mg twice daily × 2 pMDI • Fluticasone/salmeterol 125/25 mg twice daily × 2 pMDI
Outcomes	The difference in the mean change in FEV_1 from pre-dose baseline at Week 0

Hsieh 2013 *(Continued)*

	5 minutes after drug intake at Week 12 between the 2 treatment groups
Notes	The study was sponsored by Orient EuroPharma Co., Ltd, Taiwan

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	No details
Allocation concealment (selection bias)	Unclear risk	No details
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind, double-dummy
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Double-blind, double-dummy
Incomplete outcome data (attrition bias) All outcomes	Low risk	8.8% (n = 11) and 10.2% (n = 13) dropouts in BDP/F and FP/S groups, respectively
Selective reporting (reporting bias)	High risk	No useable SAE data; no response from study authors
Independent Outcome Assessment (Asthma events only) Asthma-related serious adverse events	High risk	No independent outcome assessment described

Kuna 2007

Study characteristics

Methods	A randomised, double-blind, double-dummy, multi-centre, parallel-group study over 24 weeks from December 2003 to March 2005 at 235 centres in 16 countries: Argentina (15), Australia (22), Bulgaria (9), Czech Republic (12), Great Britain (25), Hungary (27), India (7), Malaysia (4), Mexico (15), The Netherlands (24), the Philippines (8), Poland (29), South Korea (7), South Africa (26), Thailand (4), Vietnam (1). Run-in 2 weeks
Participants	**Population:** 3335 adolescents and adults (12 to 83 years) with persistent asthma **Baseline characteristics:** mean age 38 years; FEV_1 73% predicted; concomitant ICS used by 100% of participants; run-in on previous dose of ICS alone (LABA discontinued in the 47% of participants taking it previously) **Inclusion criteria**: outpatients 12 years of age or over with diagnosis of asthma for at least 6 months and using ICS for at least 3 months; FEV_1 % predicted ≥ 50%; bronchodilator reversibility by an increase of ≥ 12% in FEV_1 following terbutaline 1 mg and ≥ 1 asthma exacerbation in the previous 1 to 12 months; using reliever medication on at least 5 of the last 7 days of the 2-week run-in

Kuna 2007 *(Continued)*

	Combination therapy, if used, was discontinued and was replaced with ICS alone, at least 4 weeks before study start (screening visit) **Exclusion criteria:** using systemic corticosteroids or with respiratory infection affecting asthma control within 30 days of study entry
Interventions	• Salmeterol/fluticasone 25/125 µg 2 inhalations twice daily pMDI • Formoterol/budesonide 12/400 µg 1 inhalation twice daily DPI (reported in the paper as 9/320 delivered dose) • Single-inhaler therapy arm not included in this review
Outcomes	Primary outcome variable was time to first severe asthma exacerbation, defined as deterioration in asthma leading to at least 1 of the following: hospitalisation or emergency room treatment due to asthma, or oral corticosteroid treatment due to asthma for at least 3 days, as judged by the investigator SAE data were reported in the paper and asthma-related SAE data were obtained from AstraZeneca (data on file). One death in the salmeterol/fluticasone group due to cardiac failure was reported, as was 1 death in the single-inhaler therapy group due to respiratory failure (arm is not included in this review)
Notes	Sponsored by AstraZeneca

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomisation schedule was computer-generated at AstraZeneca Research and Development, Charnwood, UK. Within each centre, participants were randomised strictly sequentially as they became eligible
Allocation concealment (selection bias)	Low risk	Individual treatment codes and code envelopes (indicating treatment allocation for each randomised patient) were provided, but code envelopes were to be opened only in case of medical emergency
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind, double-dummy
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Double-blind, double-dummy
Incomplete outcome data (attrition bias) All outcomes	Low risk	3172/3335 (95%) completed the study
Selective reporting (reporting bias)	Low risk	SAE data were obtained from the paper and from sponsors
Independent Outcome Assessment (Asthma events only) Asthma-related serious adverse events	High risk	No independent outcome assessment described

Maspero 2010

Study characteristics	
Methods	A 52-week, randomised, multi-centre, parallel-group, open-label, evaluator-blinded study conducted at 27 clinical sites in South America
Participants	**Population:** 404 adults (> 12 years of age) with persistent asthma **Baseline characteristics:** mean age 36 years, FEV_1 77% predicted; all had received ICS (with or without LABA) for at least 12 weeks **Inclusion criteria:** 12 years of age or older with diagnosis of persistent asthma ≥ 12 months; FEV_1 ≥ 50% predicted values; received medium- or high-dose ICS with or without LABA for ≥ 12 weeks before screening; on a stable regimen for ≥ 2 weeks before screening. Additional inclusion criteria were evidence of β_2 reversibility (increase in FEV_1 of ≥ 12% and ≥ 200 mL within 10 to 15 minutes of SABA use); normal electrocardiogram (ECG), clinical laboratory tests, and chest radiograph; adequate contraceptive precautions for women of childbearing age **Exclusion criteria:** demonstrated change > 20% in FEV_1; required use of > 12 inhalations of SABA or 2 nebulised treatments with 2.5 mg salbutamol on 2 consecutive days at any time between screening and baseline visits; experienced clinically judged deterioration (deterioration resulting in emergency treatment, hospitalisation, or treatment with additional asthma medication other than SABA); with intraocular pressure ≥ 22 mmHg in either eye, glaucoma, or evidence of cataract(s) at screening; current smoker (had smoked within the previous year) or ex-smoker (> 10 pack-years); received emergency treatment for airway obstruction in the past 3 months; suffered a respiratory infection within 2 weeks before screening
Interventions	• Mometasone/formoterol 100/5 (n = 141) or 200/5 (n = 130) µg 2 puffs twice daily • Fluticasone/salmeterol 125/25 (n = 68) or 250/25 (n = 65) µg 2 puffs twice daily Delivered by MDI; spacers were not permitted. Dose allocated according to previous ICS use of the participant
Outcomes	**Primary outcome:** adverse events
Notes	Sponsored by Merck and Co. Two deaths occurred (electrocution and gastric cancer), both in mometasone/formoterol 200/10 group (see FDA report at www.fda.gov/downloads/Drugs/.../UCM224593.pdf

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	No details
Allocation concealment (selection bias)	Unclear risk	No details
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open-label
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Evaluator blinded; no impact on all-cause outcomes
Incomplete outcome data (attrition bias)	Low risk	Over 80% in each arm completed the study

Maspero 2010 *(Continued)*

All outcomes		
Selective reporting (reporting bias)	Low risk	Mortality details obtained from FDA report
Independent Outcome Assessment (Asthma events only) Asthma-related serious adverse events	High risk	No independent outcome assessment reported

NCT00901368

Study characteristics	
Methods	A multi-national, multi-centre, double-blind, double-dummy, randomised, parallel-group, controlled clinical study carried out at 41 centres in France, Germany, The Netherlands, and Spain
Participants	**Population:** a total of 416 asthmatic patients already controlled with FP/S 500/100 µg/d (Diskus, pMDI or separate inhalers) **Baseline characteristics:** mean age 44 (SD 14.4) years on formoterol/BDP and 44 (SD 13.8) on salmeterol/FP. Baseline FEV_1 97.0% and 97.4% predicted (respectively) **Inclusion criteria:** adult patients 18 to 65 years of age, with controlled asthma in the previous week before study entry; all patients were treated with fluticasone propionate 500 mg/ salmeterol 100 mg daily delivered via DPI or pMDI, or by separate inhalers for 4 weeks before screening visit; had features of controlled asthma according to GINA guidelines, defined as: FEV_1 > 80% predicted normal values or personal best; no nocturnal symptoms or awakenings; no exacerbations; no limitations of activities; daytime symptoms and use of rescue medication 2 days per week in the last 4 weeks. These findings were to be confirmed at the end of the 4-week run-in period **Exclusion criteria:** diagnosis of COPD as defined by GOLD guidelines; history of near-fatal asthma; evidence of severe asthma exacerbation or symptomatic infection of the lower airways in the previous 6 months; ≥ 3 courses of CS or hospitalisation due to asthma during previous 6 months; treated with LTRA during previous 4 weeks; current smokers or recent (less than 1 year) ex-smokers defined as smoking at least 15 packs/y; asthma exacerbations during the run-in period
Interventions	• Formoterol/beclomethasone dipropionate extra-fine 6/100 µg 2 inhalations twice daily pMDI • Salmeterol/fluticasone propionate 50/250 µg 1 inhalation twice daily DPI
Outcomes	Primary efficacy variable was pre-dose morning FEV_1 (L) at end of 12-week treatment period
Notes	This study was funded by Chiesi Farmaceutici S.p.A.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	No details
Allocation concealment (selection bias)	Unclear risk	No details

NCT00901368 *(Continued)*

Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind, double-dummy
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Double-blind, double-dummy
Incomplete outcome data (attrition bias) All outcomes	Low risk	17 patients (7.9%) in the BDP/F group and 21 patients (9.7%) in the FP/S group were withdrawn from the study; 198 patients in the BDP/F group and 195 in the FP/S group completed the 12-week treatment period. Overall, 393 patients (91.2%) completed the study
Selective reporting (reporting bias)	High risk	No safety data reported and not made available by Chiesi, apart from all-cause non-fatal SAEs
Independent Outcome Assessment (Asthma events only) Asthma-related serious adverse events	High risk	No independent outcome assessment reported

Papi 2007

Study characteristics	
Methods	A randomised, double-blind, multi-centre, parallel-group study over 12 weeks from November 2004 to June 2005 at 12 outpatient respiratory clinics in Europe (Poland (6) Ukraine (6)). Run-in 2 weeks
Participants	**Population:** 228 adults (18 to 65 years of age) with moderate to severe persistent asthma **Baseline characteristics:** mean age 48 years; FEV_1 67% predicted; concomitant ICS used by 100% of participants; average ICS dose 731 µg/d (BDP equivalent); run-in on ICS alone (no other anti-asthma medication permitted) **Inclusion criteria:** clinical diagnosis of moderate to severe persistent asthma for ≥ 6 months; FEV_1 % predicted between 50% and 80%; bronchodilator reversibility by an increase of ≥ 12% in FEV_1 (or, alternatively, of 200 mL) over baseline measured 30 minutes after 2 puffs (2 × 100 µg) of inhaled salbutamol administered via pMDI. Treated with ICS at a daily dose < 1000 µg of BDP-equivalent with asthma symptoms not adequately controlled as defined by presence of daily symptoms at least once a week, nighttime symptoms at least twice a month, and daily use of short-acting β_2-agonists **Exclusion criteria:** COPD; current or ex-smokers (> 10 pack-years); severe asthma exacerbation or symptomatic infection of the airways in the previous 8 weeks; > 3 courses of oral corticosteroids or hospitalisation due to asthma in the previous 6 months; treatment with LABAs, anticholinergics, or antihistamines in the previous 2 weeks; topical or intranasal corticosteroids and leukotriene antagonists in the previous 4 weeks; change in ICS dose in the previous 4 weeks
Interventions	• Beclomethasone/formoterol 100/6 µg × 2 twice daily • Fluticasone/salmeterol 125/25 µg × 2 twice daily Delivery was via pMDI
Outcomes	Primary outcome variable was morning pre-dose PEF measured by patients in the last 2 weeks of the treatment period (Weeks 11 and 12). No serious adverse events were reported in either arm of the trial,

Papi 2007 *(Continued)*

	and absence of deaths and hospitalisations has been confirmed by Chiesi; no details on 1 patient who was withdrawn due to "development of an exclusion criteria"
Notes	Sponsored by Chiesi

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomisation was in balanced-block design stratified by centres
Allocation concealment (selection bias)	Low risk	"Each patient was identified with a randomisation number, from 001 to 260 (in blocks of four); each investigator assigned the lowest available randomisation number at each site"
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Described as double-blind but not double-dummy; inhalers were of different shape and size, but this was "masked" by a non-removable external covering for the inhalers
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Described as double-blind but not double-dummy; inhalers were of different shape and size, but this was "masked" by a non-removable external covering for the inhalers
Incomplete outcome data (attrition bias) All outcomes	Low risk	225/228 (99%) completed the study
Selective reporting (reporting bias)	Low risk	"During the study no deaths or hospitalizations occurred" (data on file at Chiesi)
Independent Outcome Assessment (Asthma events only) Asthma-related serious adverse events	High risk	No independent outcome assessment described

Papi 2012

Study characteristics

Methods	A prospective, randomised, controlled, multi-national, multi-centre, open, 2-arm, parallel-group study. This study was carried out at 67 Respiratory Clinics across Europe in Italy, Spain, Bulgaria, and Ukraine
Participants	**Population:** 422 patients (18 to 65 years old) were recruited to this study. PEF values remained above 95% of predicted values throughout the study **Baseline characteristics:** mean (standard deviation) age was 44 (13) years; 146 were male and 267 were female; FEV_1 (L) by group was fluticasone/salmeterol (FP/S) Diskus DPI: 3.0 (0.8) L, and beclomethasone/formoterol (BDP/FP) pMDI: 2.9 (0.9) L **Inclusion criteria:** outpatients who were 18 to 65 years old with diagnosis of asthma for ≥ 6 months if they had been treated with 1000 mcg fluticasone propionate + 100 mcg salmeterol daily for ≥ 4 weeks before screening visit and had features of controlled asthma, which was defined in the following manner: FEV_1 or PEF > 80% of predicted normal values; no nocturnal symptoms or awakenings; no exacer-

Papi 2012 *(Continued)*

	bations; no limitations of activities; daytime symptoms and use of rescue medication ≤ 2 days per week in the 4 weeks previous to screening visit **Exclusion criteria:** satisfying any of the following criteria: diagnosis of COPD, as defined by the GOLD guidelines; current or ex-smokers (≥ 10 packs/y); history of near-fatal asthma; symptomatic infection of the airways in the previous 8 weeks; ≥ 3 courses of OCS or hospitalisation due to asthma in the previous 6 months; treatment with anticholinergics and antihistamines during the previous 2 weeks; treatment with topical or intranasal corticosteroids and LTRA during the previous 4 weeks
Interventions	• Formoterol/beclomethasone dipropionate extra-fine 6/12 µg twice daily × 2 pMDI • Salmeterol/fluticasone propionate 25/125 µg twice daily × 2 DPI
Outcomes	Primary outcome was change in morning PEF values between baseline and end of treatment
Notes	This study was funded by Chiesi Farmaceutici SpA, Parma, Italy; clinicaltrials.gov NCT00497237

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Participants were randomised according to pre-determined balanced-block randomisation list that was computer-generated for each centre
Allocation concealment (selection bias)	Low risk	Concealed random allocation was done via fully automated functionality built into the electronic Case Report Form (e-CRF)
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open-label
Blinding of outcome assessment (detection bias) All outcomes	Low risk	No impact on all-cause outcomes
Incomplete outcome data (attrition bias) All outcomes	Low risk	Equal percentage of dropouts across the 2 groups: 14% and 14.6%, respectively
Selective reporting (reporting bias)	Low risk	SAE data obtained from Chiesi
Independent Outcome Assessment (Asthma events only) Asthma-related serious adverse events	High risk	No independent outcome assessment reported

Ploszczuk 2014

Study characteristics

Methods	A double-blind, double-dummy, parallel-group, multi-centre, 12-week study, at 59 centres in 8 countries (Bulgaria, Czech Republic, Hungary, India, Poland, Romania, Russia, and Ukraine). Eligible patients entered a 14-day run-in period before being randomised to either of the 2 treatment groups

Ploszczuk 2014 *(Continued)*

Participants	**Population:** A total of 713 patients 5 to 12 years of age were screened, and 512 randomised **Baseline characteristics:** mean age 8.5 years (SD 1.82); FEV_1 73% predicted (SD 7.2); ICS used by 75% of children at median dose of 200 µg/d; ICS/LABA used by 25% of children. Run-in on fluticasone pMDI 100 µg twice daily (LABA discontinued in the 28% of participants taking it previously) **Inclusion criteria:** male and female patients, 5 to < 12 years of age; persistent asthma for ≥ 6 months; on a stable ICS dose for ≥ 4 weeks, with pre-dose FEV_1 ≥ 60% to ≤ 90% predicted; ≥ 15% FEV_1 reversibility and inadequate asthma control on ICS alone at a dose ≤ 500 µg/d fluticasone (or equivalent), or controlled asthma on ICS/LABA combination at an ICS dose ≤ 200 µg/d fluticasone (or equivalent) At the end of the 14-day run-in period, only patients fulfilling the following criteria were eligible for randomisation: FEV_1 ≤ 90% predicted (following appropriate withholding of study medication) and, during the last 7 days of the run-in period, rescue medication use for ≥ 3 days and ≥ 1 night with sleep disturbance (i.e. sleep disturbance score ≥ 1) and/or ≥ 3 days with asthma symptoms (i.e. symptom score ≥ 1). Note that the run-in period could be extended to 28 days if a patient failed to meet randomisation criteria after the initial 14-day period **Exclusion criteria:** potentially brittle asthma evidenced by life-threatening asthma within the past year, hospitalisation, or an emergency room visit for asthma within the past 6 months; systemic (injectable or oral) corticosteroid medication within 1 month; current or prior non-response or partial response only to an ICS/LABA combination; Exclusion criteria were also specified to ensure disease stability at study entry, for example, by excluding patients with a clinically significant upper or lower respiratory infection within 4 weeks before study entry. Patients with coexistent pulmonary disease (e.g. cystic fibrosis, bronchiectasis, tuberculosis) were also excluded
Interventions	• Formoterol/fluticasone propionate 10/100 µg daily pMDI (Flutiform) • Salmeterol/fluticasone propionate 50/100 µg twice daily pMDI (Seretide Evohaler) The third arm was receiving fluticasone alone and was not used in this review
Outcomes	Study objectives were to demonstrate superiority of fluticasone/formoterol to fluticasone and non-inferiority to fluticasone/salmeterol Primary endpoint was change from pre-dose FEV_1 at baseline (Day 1) to 2 hours post dose FEV_1 over the 12-week treatment period. SAEs reported in the EU-CTR report
Notes	Sponsored by Mundipharma

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomisation was performed by the study sponsor using a validated system that automates random assignment of treatment groups to randomisation numbers; stratified to ensure balanced allocation within age groups 5 to < 8 years and 8 to < 12 years
Allocation concealment (selection bias)	Unclear risk	Not reported.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open-label
Blinding of outcome assessment (detection bias) All outcomes	Low risk	No impact on all-cause outcomes

Ploszczuk 2014 *(Continued)*

Incomplete outcome data (attrition bias) All outcomes	Low risk	Analysis of safety data was based on the safety population, that is, all randomised participants who received ≥ 1 dose of study medication; 161/169 and 159/170 completed in formoterol/ICS and salmeterol/ICS groups
Selective reporting (reporting bias)	Low risk	SAE data in Eu-CTR report
Independent Outcome Assessment (Asthma events only) Asthma-related serious adverse events	High risk	No independent outcome assessment reported

Ringdal 2002

Study characteristics	
Methods	A randomised, double-blind, double-dummy, multi-centre, parallel-group study over 12 weeks from May 1998 to June 1999 at 52 primary care practices and hospital respiratory units in 11 countries (Austria (4), Belgium(4), Croatia (2), Denmark (4), Finland (2), Germany (7), Italy (3), Norway (5), Russia (2), Slovakia (3), United Kingdom (16)). Run-in 2 weeks
Participants	**Population:** 428 adolescents and adults (16 to 75 years of age) with moderate to severe asthma uncontrolled on existing corticosteroid therapy **Baseline characteristics:** mean age 47 years; FEV_1 69% predicted; concomitant ICS used by 100% of participants; run-in on previous dose of ICS (no LABA allowed in previous 2 weeks before recruitment) **Inclusion criteria:** aged 16 to 75 years with documented clinical history of asthma; currently receiving 1000 to 1600 µg/d of budesonide, beclomethasone dipropionate, or flunisolide, or 500 to 800 µg/d fluticasone propionate, for at least 4 weeks before Visit 1; at the end of run-in, FEV_1 % predicted 50% to 85% at Visit 1 or 2/2A (bronchodilators withheld for 6 hours); bronchodilator reversibility by an increase of ≥ 15% in FEV_1 over baseline 15 minutes after inhaling 400 µg of salbutamol at Visit 1 or 2/2A; symptom score (day and night combined) ≥ 2 or relief bronchodilator use on ≥ 2 separate occasions (any dose) per day on ≥ 4 of the last 7 days of the run-in period **Exclusion criteria:** smoking history of ≥ 10 pack-years; asthma exacerbation or upper or lower respiratory tract infection within the previous month; systemic or nasal steroids or anti-leukotrienes within previous 4 weeks; long-acting/oral/slow-release $beta_2$-agonists in the previous 2 weeks before Visit 1
Interventions	• Salmeterol/fluticasone 50/250 µg twice daily via Diskus • Formoterol (12 µg twice daily) + budesonide (800 µg twice daily) via separate turbuhaler
Outcomes	Primary efficacy measure was mean PEF_{am} over the week before the end of treatment (Week 12) SAE data obtained from sponsor's website and reported in the paper publication
Notes	Sponsored by GSK

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	A randomisation code was generated via the GlaxoWellcome computer programme "Patient Allocation for Clinical Trials" (block size of 4), and non-overlapping sets of treatment numbers were allocated to each centre. Treatment

Ringdal 2002 *(Continued)*

		numbers were allocated at Visit 2 in consecutive order, starting with the lowest number available at that centre
Allocation concealment (selection bias)	Low risk	Numbered treatment packs of study drugs were labelled to ensure that both patients and investigators were blinded to treatment allocation; randomisation codes were not revealed to investigators or other study participants until after recruitment, treatment, data collection, and analyses were complete
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind, double-dummy
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Double-blind, double-dummy
Incomplete outcome data (attrition bias) All outcomes	Low risk	379/428 (89%) completed the study
Selective reporting (reporting bias)	Low risk	SAEs reported in the paper and in the sponsor's trial report
Independent Outcome Assessment (Asthma events only) Asthma-related serious adverse events	High risk	No independent outcome assessment described

SAM 40010

Study characteristics	
Methods	A randomised, double-blind, double-dummy, multi-centre, parallel-group study over 12 weeks from January 2000 to July 2000 at 50 centres in Europe (Belgium, Denmark, Germany, Ireland, Poland, and The Netherlands). Run-in 2 to 4 weeks
Participants	**Population:** 373 adolescents and adults with asthma that is poorly controlled by low doses of ICS **Baseline characteristics:** mean age 42 years; concomitant ICS used by 100% of participants; no details of treatment given during run-in **Inclusion criteria:** aged 12 years o**r** older with reversible airways obstruction; remained symptomatic with ICS treatment (400 to 500 µg/d budesonide or equivalent) for ≥ 4 weeks before Visit 1 (start of the run-in period); clinical history of asthma with symptoms including cough, wheeze, and shortness of breath requiring treatment with short-acting beta$_2$-agonist for ≥ 6 months; mean morning PEF during the last 7 consecutive days of the run-in period between 50% and 85% of PEF measured 15 minutes after administration of 400 µg of salbutamol at Visit 1; had recorded a cumulative total symptom score (daytime plus night-time) ≥ 8 for the last 7 consecutive days of the run-in period **Exclusion criteria:** not reported
Interventions	• Salmeterol/fluticasone 50/100 µg twice daily via Diskus • Budesonide 200 µg twice daily + formoterol 6 µg twice daily via DPI

SAM 40010 *(Continued)*

Outcomes	Primary study endpoint was morning peak expiratory flow, assessed as the mean of morning PEF values recorded during the 12-week treatment period. SAE data available from Web report. One death in formoterol/budesonide group due to gastrointestinal obstruction, cardiac failure, and septic shock
Notes	Sponsored by GSK

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomisation code was computer-generated via Patient Allocation for Clinical Trials developed by GlaxoSmithKline research and development
Allocation concealment (selection bias)	Low risk	Treatment numbers were assigned sequentially to all eligible participants, starting with the lowest number available to the investigator
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind, double-dummy
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Double-blind, double-dummy
Incomplete outcome data (attrition bias) All outcomes	Low risk	362/373 (97%) completed the study
Selective reporting (reporting bias)	Low risk	SAE data presented in Web report
Independent Outcome Assessment (Asthma events only) Asthma-related serious adverse events	High risk	No independent outcome assessment described;

SAM 40048

Study characteristics

Methods	A randomised, double-blind, double-dummy, multi-centre, parallel-group study over 12 weeks from August 2001 to September 2002 at 27 centres in Germany. Run-in 2 weeks
Participants	**Population:** 248 adults with moderate bronchial asthma **Baseline characteristics:** mean age 48 years; FEV_1 65% predicted (at Visit 2 (baseline)); concomitant ICS used by 100% of participants; no details of treatment given during run-in **Inclusion criteria:** aged 18 years and older with moderate asthma; FEV_1 % predicted between 50% and 80%; bronchodilator reversibility by an increase in $FEV_1 \geq 15\%$; ICS treatment 1000 µg beclomethasone dipropionate (BDP)/d or equivalent; symptomatic asthma **Exclusion criteria:** exacerbations or emergency visits during the 4-week pre-study period; smoking (> 20 cigarettes per day)

SAM 40048 *(Continued)*

Interventions	• Salmeterol/fluticasone 50/250 µg twice daily via Diskus • Formoterol/budesonide 6/200µg twice daily via DPI
Outcomes	Primary variable was the change in FEV_1 (% predicted) after 12 weeks of treatment compared to baseline SAE data in Web report
Notes	Sponsored by GSK

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"The allocation of patients to the two treatment groups was undertaken according to a predetermined randomisation schedule (in a ratio of 1 to 1)" (GSK data on file)
Allocation concealment (selection bias)	Low risk	"The allocation was undertaken as a block randomisation, with identical allocation ratios in each study centre. Every investigator had to allocate the patient to the lowest available number at visit 2. Adherence to this randomisation schedule was checked during the process of data management"
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind, double-dummy
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Double-blind, double-dummy
Incomplete outcome data (attrition bias) All outcomes	Low risk	235/248 (95%) completed the study
Selective reporting (reporting bias)	Low risk	SAE data in Web report
Independent Outcome Assessment (Asthma events only) Asthma-related serious adverse events	High risk	No independent outcome assessment described

Scichilone 2010

Study characteristics

Methods	A double-blind, double-dummy, randomised, parallel-group study. Participants were recruited prospectively from the outpatient population between August 2006 and January 2008 in the Department of Medicine and Respiratory Diseases at the University of Palermo
Participants	**Population:** 41 screened patients (18 to 50 years old); 30 were randomised and 27 completed the 12-week study period

Scichilone 2010 *(Continued)*

	Baseline characteristics: mean age 42 (SD 12) years on formoterol/BDP and 44 (SD 12) on salmeterol/FP; baseline FEV_1 69% and 73% predicted (respectively); moderate persistent asthma that was uncontrolled after the MF 200-µg twice daily run-in period, based on FEV_1 (i.e. 60% to 80% predicted) and ACQ (i.e. score ≥ 1.5) findings as related to definitions from the NAEPP **Inclusion criteria:** between 18 and 50 years of age; clinical diagnosis of moderate persistent asthma for ≥ 6 months and FEV_1 > 60% of predicted normal value **Exclusion criteria:** current smokers or recent (< 1 year) quitters; in case of diagnosis of COPD, history of near-fatal asthma or recent severe asthma exacerbation or hospitalisation. Patients who had changed their dose of ICS during the previous 4 weeks or who were under treatment with ICS at a daily dose > 1000 µg of BDP or equivalent were also excluded. All patients had to be in stable condition before study entry with no history of recent (4 weeks) upper or lower airway infection
Interventions	• Formoterol/beclomethasone dipropionate extra-fine 6/100 µg twice daily × 2 pMDI (formoterol/BDP 6/100 2 puffs twice daily) • Salmeterol/fluticasone propionate 10/125 µg twice daily × 2 DPI Study medication compliance was > 90% in both groups
Outcomes	The sbN_2 test used 100% oxygen supplementation and a nitrogen meter connected to the mouthpiece, to allow for continuous sampling of N_2 concentrations in the expired air. N_2 concentration measured during a single breath expiration was plotted against lung volume to obtain a nitrogen washout curve. The slope of the nitrogen curve (phase 3), the closing volume (CV), and closing capacity (CC) were derived by the operator and were included for analysis. Conventional Mch broncho provocation followed standardised ERS guidelines (18), using doubling doses of the spasmogen (Lofarma, Italy). Mch was delivered through an ampul-dosimeter (Mefar Elettromedicali; Bovezzo, Italy), which was activated by an inspiratory effort for 0.5 seconds at a time. The provocative dose of Mch that could induce a 20% fall in FEV_1 from baseline was measured by linear interpolation (PD_{20}Mch FEV_1)
Notes	This study was funded by Chiesi Farmaceutici S.p.A.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	No details
Allocation concealment (selection bias)	Unclear risk	No details
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind, double-dummy
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Double-blind, double-dummy
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	No CONSORT flow; 3 participants withdrew but not clear from which group(s)
Selective reporting (reporting bias)	High risk	SAE data not reported and could not be obtained from Chiesi

Scichilone 2010 *(Continued)*

Independent Outcome Assessment (Asthma events only) Asthma-related serious adverse events	High risk	No independent outcome assessment described

Usmani 2017

Study characteristics	
Methods	A 24-week, randomised, controlled, pragmatic, open-label trial
Participants	**Population:** 259 participants were enrolled in the study; there were n = 34 screening failures and n = 225 were randomised (2:1) **Baseline characteristics:** there were n = 151 participants in group 1 and n = 74 participants in group 2. Mean (SD) age for group 1 was 53 (13.4) and for group 2 65.03 (6.51). The FEV_1 (%) for group 1 was 87.1 (21.2) and for group 2, 55.1 (13.7) **Inclusion criteria:** 18 to 75 years of age; diagnosis of asthma; prescribed FP/SAL (1000) (as Seretide 250 Evohaler pMDI 2 puffs twice a day) for ≥ 6 months before enrolment; demonstrated satisfactory inhaler technique without serious inhaler technique errors, after device training if required, at screening **Exclusion criteria:** diagnosis of any chronic respiratory disease other than asthma; pregnancy; ≥ 1 severe asthma exacerbations in the 3 months before enrolment; ≥ 3 severe asthma exacerbations in the 12 months before enrolment; uncontrolled asthma assessed in accordance with 2012 GINA recommendations on the basis of symptoms in the last week. A severe exacerbation was defined as worsening of asthma requiring treatment with a course of oral corticosteroids, hospitalisation, or accident and emergency department attendance
Interventions	• Group 1: fluticasone propionate/formoterol fumarate (FP/FOR) treatment via pMDI • Group 2: fluticasone propionate/salmeterol xinafoate (FP/SAL) treatment via pMDI
Outcomes	Primary outcome in both phases was asthma control measured with the 7-question ACQ7 score. Secondary outcome measures included occurrence of asthma exacerbations (as defined in the previous section), asthma control assessed by the research healthcare professional at each site in accordance with 2012 GINA recommendations (i.e. uncontrolled, partially controlled, and controlled asthma), Mini-AQLQ score, VAS test score (to assess patients' perception of asthma symptoms on a scale from 0 (not at all bothersome) to 10 (extremely bothersome); lung function (as assessed by FVC, FEV_1, FVC% predicted, FEV_1 % predicted, and FEV_1/FVC ratio)
Notes	This was an investigator-initiated study sponsored by Research in Real Life Ltd, with partial funding and study inhalers provided by Napp Pharmaceuticals Ltd.

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Randomisation for both phases was performed via a centralized computer-based programme, stratified in blocks of 3 for phase 1 and in blocks of 4 for phase 2, on the basis of centre code and occurrence of exacerbations in the 12 months before enrolment into phase 1 (no exacerbation or 1 to 2 exacerbations)
Allocation concealment (selection bias)	Unclear risk	No details

Usmani 2017 *(Continued)*

Blinding of participants and personnel (performance bias) All outcomes	High risk	Open-label
Blinding of outcome assessment (detection bias) All outcomes	Low risk	No impact on all-cause outcomes
Incomplete outcome data (attrition bias) All outcomes	High risk	Total of 134 (88.7%) participants in the FP/FOR (1000) group and 73 (98.6%) in the FP/SAL (1000) group completed the 12-week outcome visit
Selective reporting (reporting bias)	Low risk	Provided in email communication
Independent Outcome Assessment (Asthma events only) Asthma-related serious adverse events	High risk	No independent outcome assessment described

Woo 2020

Study characteristics	
Methods	A 12-week, randomised, open-label, parallel-design trial. Conducted in March 2016 and February 2018 from Ajou University Hospital in Suwon, Korea. Patients completed a 4-week run-in period
Participants	**Population:** 72 patients (55+ years) were recruited and entered the run-in period. Of these, 4 could not be randomised because they did not fulfil the eligibility criteria and declined to participate. The 68 eligible patients were randomised into the 2 treatment groups **Baseline characteristics:** There were n = 35 participants in group 1 and n = 33 participants in group 2. Mean (SD) age for group 1 was 65.97 (7.66), and for group 2, 65.03 (6.51). FEV_1 (%) for group 1 was mean (SD) 87.1 (21.2), and for group 2, 88.2 (23.3). Before study entry, n = 7 participants in both groups were on a low-dose ICS LABA, and n = 28 and n = 26 were on a medium/high-dose ICS LABA in groups 1 and 2, respectively **Inclusion criteria:** over 55 years of age; diagnosis of asthma > 6 months before enrolment in the study; current treatment was combination therapy of inhaled ICS (budesonide 400 µg/d or equivalent) and LABA for over 30 days before study participation; required to have normal results on complete blood count, routine chemistry, urinalysis, and electrocardiogram at screening **Exclusion criteria:** well-controlled asthma after a 4-week run-in period; other acute disease within 30 days before administration of trial medications; smoking history > 30 pack-years; history of hypersensitivity to ICS; prescribed any medication influencing asthma control, such as immunomodulatory drugs (omalizumab, cyclosporine, *etc*.) or systemic steroids due to disease other than asthma
Interventions	• Fluticasone propionate/formoterol fumarate (FP/FOR) 250/10 mcg twice daily × 1 pMDI (pMDI group) • Fluticasone propionate/salmeterol xinafoate (FP/SAL) 125/25 mcg twice daily × 1 DPI (DPI group)
Outcomes	Primary endpoint was the proportion of participants reaching well-controlled asthma after the 12-week study period based on GINA guidelines. Primary endpoints were also assessed in pre-specified subgroups according to the duration of asthma (≥ 15 years or < 15 years) and the RV-to-TLC ratio (≥ 45% or < 45%)

Woo 2020 *(Continued)*

Notes	This study was supported in part by a grant from Investigator-initiated Studies Program of Mundipharma Korea and in part by a grant of the Korea Health Technology R&D Project through the Korea Health Industry Development Institute (KHIDI), funded by the Ministry of Health & Welfare, Republic of Korea (HI16C0992)

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Participants were stratified according to duration of asthma (longer (≥ 15 years) or shorter duration of asthma (< 15 years)) (Fig. 1). They were randomly assigned to receive either FP/FOR-pMDI or FP/SAL-DPI for a 12-week study period. Randomisation was performed according to a balanced-block design with a centrally generated randomisation code
Allocation concealment (selection bias)	Unclear risk	No details
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open-label
Blinding of outcome assessment (detection bias) All outcomes	Low risk	No impact on all-cause outcomes
Incomplete outcome data (attrition bias) All outcomes	Low risk	5 participants were withdrawn from the study: 3 from one arm and 2 from the other
Selective reporting (reporting bias)	Low risk	All outcomes reported
Independent Outcome Assessment (Asthma events only) Asthma-related serious adverse events	High risk	No independent outcome assessment reported

ACQ: Asthma Control Questionnaire; AMD: adjustable maintenance dosing; BDF: budesonide; DPI: dry powder inhaler; COPD: chronic obstructive pulmonary disease; CS: corticosteroids; FDA: Food and Drug Administration; FEV_1: forced expiratory volume in one second; FPS: fluticasone propionate and salmeterol inhaler; FBC: formoterol/budesonide combination; GINA: Global Initiative for Asthma; GCS: glucocorticosteroid; GSK: GlaxoSmithKline; ICS: inhaled corticosteroid; IVRS: Interactive voice recording system; LABA: long-acting $beta_2$-agonist; LTRA: leukotriene receptor antagonist; MF: mometasone furoate; Mini-AQLQ: Mini- Asthma Quality of Life Questionnaire; NAEPP: National Asthma Education and Prevention Programme; OCS: oral corticosteroid; PEF: peak expiratory flow; pMDI: pressurised metered-dose inhaler; SABA: short-acting $beta_2$-agonist; SAE: serious adverse event; SFC: salmeterol/fluticasone combination; VAS: visual analogue scale.

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

Study	Reason for exclusion
Bleecker 2008	Review of 2 other studies (Busse 2008; Kuna 2007)
Dhillon 2006	Review of studies on BDP/formoterol

Study	Reason for exclusion
Hampel 2008	Single-dose study
Jung 2008	Fluticasone/salmeterol vs current care
Lee 2003	4-week cross-over study
Lyseng-Williamson 2003	Pharmacoeconomic review of studies on fluticasone/salmeterol inhaler
NCT02491970	Study terminated due to poor recruitment
Rani 2016	Only a 6-week intervention
UMIN000006572	Single-arm study; not randomised

BDP: beclomethasone

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

NCT03387241

Study name	A Double Blind, Double Dummy, Randomised, Multicentre, Two Arm Parallel Group Study to Assess the Efficacy and Safety of FLUTIFORM pMDI (2 Puffs Twice Daily) vs Seretide® pMDI (2 Puffs Twice Daily) in Subjects Aged ≥ 12 Years With Moderate to Severe Persistent, Reversible Asthma
Methods	A 12-week, randomised, controlled, double-blind, double-dummy, parallel-group design
Participants	Inclusion criteria • Male or female subjects aged ≥ 12 years • Known history of moderate to severe persistent, reversible asthma for ≥ 6 months before the Screening Visit characterised by inadequate asthma control on treatment with an ICS alone OR controlled asthma on treatment with an ICS-LABA combination • Demonstrated pre-dose FEV_1 ≥ 40% to ≤ 80% for predicted normal values during the Screening Visit (Visit 1) following appropriate withholding of asthma medications (if applicable). No LABA use within 12 hours and/or no SABA use within 6 hours of the PFT. No SAMA (e.g. ipratropium) use within 8 hours and/or no LAMA (e.g. tiotropium) use within 72 hours of the PFT. No use of inhaled ICS-LABA combination asthma therapy within 12 hours of the PFT. ICS is allowed on the day of screening. Oral aminophylline should be withheld for at least 24 hours before the PFT • Documented FEV_1 reversibility ≥ 12% (+ ≥ 200 mL if the participant is older than 18 years of age) within the last 12 months, which could be accepted by the investigator, or during the screening phase or at Visit 2 • Demonstrated satisfactory technique in the use of study medication • Female of child-bearing potential or < 1 year post-menopausal must have a negative serum pregnancy test recorded at the Screening Visit and a negative urine pregnancy test result before the first dose of study medication, non-lactating, and willing to use adequate and highly effective methods of contraception throughout the study. A highly effective method of birth control is defined as one that results in a low failure rate (i.e. < 1% per year) when used consistently and correctly, such as sterilisation, implants, injectables, combined oral contraceptives, some IUDs (intrauterine devices, hormonal), sexual abstinence, or vasectomised partner • Willing and able to enter information into the diary and to attend all study visits • Willing and able to substitute study medication for pre-study prescribed asthma medication for the duration of the study • Written informed consent obtained; for < 18-year-old participants, both parental consent and participant assent are needed

NCT03387241 *(Continued)*

Besides inclusion/exclusion criteria checking, additional randomisation criteria required following run-in period

- Demonstrated pre-dose FEV_1 ≥ 40% to ≤ 80% for predicted normal values at Randomisation Visit (Visit 3) following appropriate withholding of asthma medications (if applicable)
- ACQ score at Visit 3 ≥ 1.0
- Good compliance with treatment or patient dairy. The definition of good compliance is that completeness of the diary during the last 14 days of the run-in period is ≥ 80%. Compliance on diary completeness will be assessed from the aspects below and agreed by the investigator, and study Medical Monitor:Diary info will be filled out on ≥ 80% of days during the last 14 days before randomisation (e.g. ≥ 11 days with diary filled completed out of the last 14 days before randomisation) .80% main items including study endpoint related ones were filled out within the last 14 days before randomisation. No other significant compliance as judged by the investigator that indicates the potential future in compliance for critical data collection during the study treatment period

Exclusion criteria

- Adolescent participants (age ≥ 12 years to < 18 years) who are on ICS alone at a dose > 250µg twice daily fluticasone or equivalent OR ICS-LABA combination at a dose of Seretide > 250/50 µg twice daily or equivalent
- Near-fatal or life-threatening (including intubation) asthma within the past year
- Chest X-ray at the Investigator's discretion from clinical perspective that reveals evidence of clinically significant abnormalities not believed to be due to asthma
- Hospitalisation or emergency visit for asthma within the 4 weeks before Screening Visit or during Screening Visit
- Use of systemic (injectable or oral) corticosteroid medication within 1 month of the Screening Visit
- Omalizumab use within the past 6 months before the Screening Visit
- Current evidence or known history of any clinically significant disease or abnormality including uncontrolled coronary artery disease, congestive heart failure, myocardial infarction, or cardiac dysrhythmia. "Clinically significant" is defined as any disease that, in the opinion of the Investigator, would put the patient at risk through study participation, or that would affect the outcome of the study
- In the investigator's opinion, a clinically significant upper or lower respiratory infection within 4 weeks before the Screening Visit
- Significant, non-reversible, active pulmonary disease (e.g. chronic obstructive pulmonary disease (COPD), cystic fibrosis, bronchiectasis, tuberculosis)
- Smoking history equivalent to ≥ 10 pack-years (i.e. ≥ 1 pack of 20 cigarettes/d for 10 years or 10 packs/d for 1 year, etc.) or significant history of exposure to biomass fuel combustion that may be considered a plausible contributory cause of obstructive lung disease
- Current smoking history within 12 months before the Screening Visit
- Current evidence or known history of alcohol and/or substance abuse within 12 months before the Screening Visit
- Has taken β-blocking agents, tricyclic antidepressants, monoamine oxidase inhibitors, astemizole (Hismanal), quinidine-type antiarrhythmics, or potent CYP 3A4 inhibitors, such as ketoconazole, within the past week
- Current use of medications other than those allowed in the protocol that will have an effect on bronchospasm and/or pulmonary function
- Current evidence or known history of hypersensitivity or contraindications to investigational products or components, including history of paradoxical bronchospasm after inhalation therapy such as immediate increase in wheezing and shortness of breath
- Has received an investigational drug within 30 days of the Screening Visit (12 weeks, if an oral or injectable steroid)
- Currently participating in another clinical study or has already been randomised in this study
- Mental incapacity, unwillingness, or language barrier precluding adequate understanding, co-operation, or any factor that might block patients from protocol-defined visits and may impact patient diary completion at the Investigator's discretion

NCT03387241 *(Continued)*

Interventions	• Group 1: FLUTIFORM (fluticasone/formoterol) pMDI (2 puffs twice daily) • Group 2: Seretide (fluticasone/salmeterol) pMDI (2 puffs twice daily)
Outcomes	Primary efficacy endpoint is the change in pre-dose forced expiratory volume in 1 second (FEV_1) from baseline to 2 hours post dose FEV_1 at Week 12
Starting date	2 June 2017
Contact information	Ling Li ling.li@mundipharma.com.cn
Notes	Responsible party: Mundipharma (China) Pharmaceutical Co., Ltd.

ACQ: Asthma Control Questionnaire.
FEV_1: forced expiratory volume in one second.
ICS: inhaled corticosteroid.
LABA: long-acting beta-agonist.
PFT: pulmonary function test.
pMDI: pressurised metered-dose inhaler.
SABA: short-acting beta-agonist.
SAMA: short-acting muscarinic agonist.

DATA AND ANALYSES

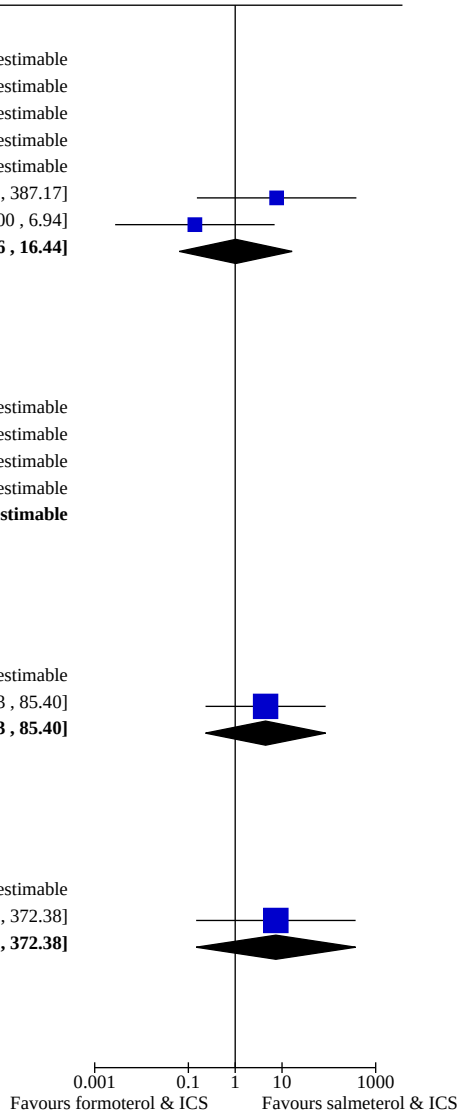
Comparison 1. Adults formoterol/ICS versus salmeterol/ICS

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.1 All-cause mortality	15		Peto Odds Ratio (Peto, Fixed, 95% CI)	Subtotals only
1.1.1 Formoterol/budesonide vs salmeterol/fluticasone	7	5935	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.03 [0.06, 16.44]
1.1.2 Formoterol/beclomethasone vs salmeterol/fluticasone	4	1257	Peto Odds Ratio (Peto, Fixed, 95% CI)	Not estimable
1.1.3 Formoterol/mometasone vs salmeterol/fluticasone	2	1126	Peto Odds Ratio (Peto, Fixed, 95% CI)	4.46 [0.23, 85.40]
1.1.4 Formoterol/fluticasone vs salmeterol/fluticasone	2	270	Peto Odds Ratio (Peto, Fixed, 95% CI)	7.39 [0.15, 372.38]
1.2 All-cause non-fatal serious adverse events	18		Peto Odds Ratio (Peto, Fixed, 95% CI)	Subtotals only
1.2.1 Formoterol/budesonide vs salmeterol/fluticasone	7	5935	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.14 [0.82, 1.59]
1.2.2 Formoterol/beclomethasone vs salmeterol/fluticasone	6	1941	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.94 [0.43, 2.08]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.2.3 Formoterol/mometasone vs salmeterol/fluticasone	2	1126	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.02 [0.47, 2.20]
1.2.4 Formeterol/fluticasone vs salmeterol/fluticasone	2	293	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.05 [0.00, 3.10]
1.2.5 Formeterol/budesonide vs salmeterol/budesonide	1	229	Peto Odds Ratio (Peto, Fixed, 95% CI)	7.45 [0.15, 375.68]
1.3 Asthma related non-fatal serious adverse events	16		Peto Odds Ratio (Peto, Fixed, 95% CI)	Subtotals only
1.3.1 Formoterol/budesonide vs salmeterol/fluticasone	7	5935	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.69 [0.37, 1.26]
1.3.2 Formoterol/beclomethasone vs salmeterol/fluticasone	5	1510	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.01 [0.06, 16.24]
1.3.3 Formoterol/mometasone v's salmeterol/fluticasone	1	722	Peto Odds Ratio (Peto, Fixed, 95% CI)	7.00 [0.14, 353.37]
1.3.4 Formoterol/fluticasone vs salmeterol/fluticasone	2	293	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.05 [0.00, 3.10]
1.3.5 Formeterol/budesonide vs salmeterol/budesonide	1	229	Peto Odds Ratio (Peto, Fixed, 95% CI)	Not estimable

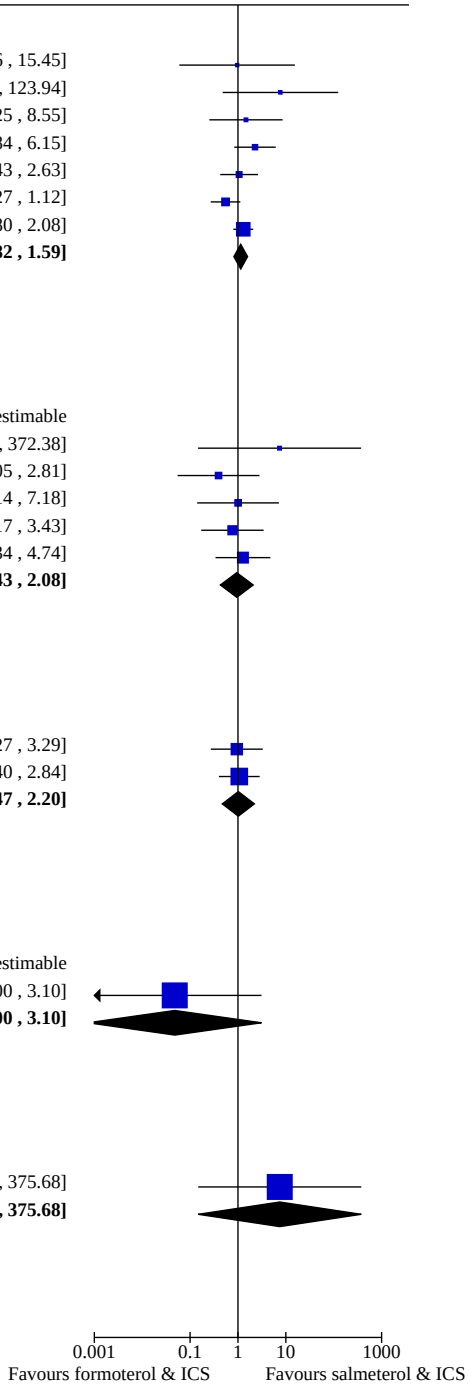
Analysis 1.1. Comparison 1: Adults formoterol/ICS versus salmeterol/ICS, Outcome 1: All-cause mortality

Study or Subgroup	Formoterol & ICS Events	Total	Salmeterol & ICS Events	Total	Weight	Peto Odds Ratio Peto, Fixed, 95% CI
1.1.1 Formoterol/budesonide vs salmeterol/fluticasone						
Aalbers 2004	0	215	0	224		Not estimable
Dahl 2006	0	700	0	697		Not estimable
Busse 2008	0	427	0	406		Not estimable
SAM 40048	0	126	0	121		Not estimable
Ringdal 2002	0	216	0	212		Not estimable
SAM 40010	1	183	0	190	50.0%	7.68 [0.15 , 387.17]
Kuna 2007	0	1099	1	1119	50.0%	0.14 [0.00 , 6.94]
Subtotal (95% CI)		**2966**		**2969**	**100.0%**	**1.03 [0.06 , 16.44]**
Total events:	1		1			
Heterogeneity: Chi² = 2.02, df = 1 (P = 0.16); I² = 50%						
Test for overall effect: Z = 0.02 (P = 0.98)						
1.1.2 Formoterol/beclomethasone vs salmeterol/fluticasone						
Papi 2007	0	115	0	113		Not estimable
EUCTR-003449-17-IT	0	54	0	54		Not estimable
Papi 2012	0	212	0	228		Not estimable
EUCTR-002587-99-CZ	0	239	0	242		Not estimable
Subtotal (95% CI)		**620**		**637**		**Not estimable**
Total events:	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						
1.1.3 Formoterol/mometasone vs salmeterol/fluticasone						
Bernstein 2011	0	371	0	351		Not estimable
Maspero 2010	2	271	0	133	100.0%	4.46 [0.23 , 85.40]
Subtotal (95% CI)		**642**		**484**	**100.0%**	**4.46 [0.23 , 85.40]**
Total events:	2		0			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.99 (P = 0.32)						
1.1.4 Formoterol/fluticasone vs salmeterol/fluticasone						
Woo 2020	0	35	0	33		Not estimable
Bodzenta-Lukaszyk 2011	1	101	0	101	100.0%	7.39 [0.15 , 372.38]
Subtotal (95% CI)		**136**		**134**	**100.0%**	**7.39 [0.15 , 372.38]**
Total events:	1		0			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.00 (P = 0.32)						
Test for subgroup differences: Chi² = 0.83, df = 2 (P = 0.66), I² = 0%						



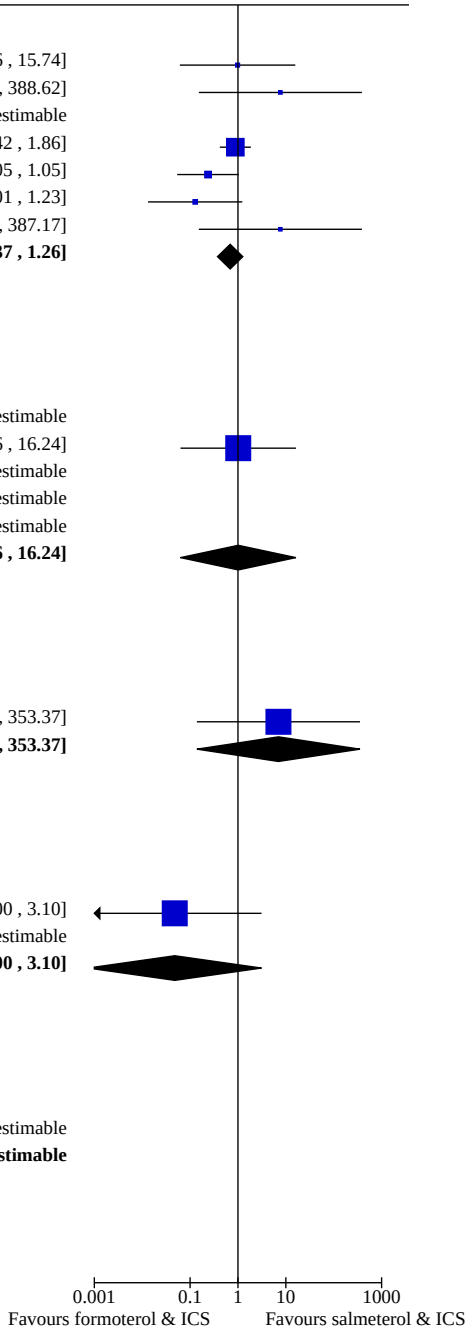
Analysis 1.2. Comparison 1: Adults formoterol/ICS versus salmeterol/ICS, Outcome 2: All-cause non-fatal serious adverse events

Study or Subgroup	Formoterol & ICS Events	Formoterol & ICS Total	Salmeterol & ICS Events	Salmeterol & ICS Total	Weight	Peto Odds Ratio Peto, Fixed, 95% CI
1.2.1 Formoterol/budesonide vs salmeterol/fluticasone						
SAM 40048	1	126	1	121	1.4%	0.96 [0.06 , 15.45]
SAM 40010	2	183	0	190	1.4%	7.72 [0.48 , 123.94]
Ringdal 2002	3	216	2	212	3.5%	1.47 [0.25 , 8.55]
Aalbers 2004	11	215	5	224	10.9%	2.27 [0.84 , 6.15]
Busse 2008	10	427	9	406	13.2%	1.06 [0.43 , 2.63]
Dahl 2006	11	700	20	697	21.5%	0.55 [0.27 , 1.12]
Kuna 2007	39	1099	31	1119	48.1%	1.29 [0.80 , 2.08]
Subtotal (95% CI)		**2966**		**2969**	**100.0%**	**1.14 [0.82 , 1.59]**
Total events:	77		68			
Heterogeneity: Chi² = 8.06, df = 6 (P = 0.23); I² = 26%						
Test for overall effect: Z = 0.79 (P = 0.43)						
1.2.2 Formoterol/beclomethasone vs salmeterol/fluticasone						
Papi 2007	0	115	0	113		Not estimable
EUCTR-003449-17-IT	1	54	0	54	4.1%	7.39 [0.15 , 372.38]
Papi 2012	1	212	3	228	16.1%	0.39 [0.05 , 2.81]
NCT00901368	2	215	2	216	16.1%	1.00 [0.14 , 7.18]
Hsieh 2013	3	125	4	128	27.7%	0.76 [0.17 , 3.43]
EUCTR-002587-99-CZ	5	239	4	242	35.9%	1.27 [0.34 , 4.74]
Subtotal (95% CI)		**960**		**981**	**100.0%**	**0.94 [0.43 , 2.08]**
Total events:	12		13			
Heterogeneity: Chi² = 2.10, df = 4 (P = 0.72); I² = 0%						
Test for overall effect: Z = 0.14 (P = 0.89)						
1.2.3 Formoterol/mometasone vs salmeterol/fluticasone						
Bernstein 2011	5	371	5	351	38.1%	0.95 [0.27 , 3.29]
Maspero 2010	13	271	6	133	61.9%	1.07 [0.40 , 2.84]
Subtotal (95% CI)		**642**		**484**	**100.0%**	**1.02 [0.47 , 2.20]**
Total events:	18		11			
Heterogeneity: Chi² = 0.02, df = 1 (P = 0.88); I² = 0%						
Test for overall effect: Z = 0.05 (P = 0.96)						
1.2.4 Formeterol/fluticasone vs salmeterol/fluticasone						
Woo 2020	0	35	0	33		Not estimable
Usmani 2017	0	151	1	74	100.0%	0.05 [0.00 , 3.10]
Subtotal (95% CI)		**186**		**107**	**100.0%**	**0.05 [0.00 , 3.10]**
Total events:	0		1			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.43 (P = 0.15)						
1.2.5 Formeterol/budesonide vs salmeterol/budesonide						
EUCTR-004833-70-BG	1	114	0	115	100.0%	7.45 [0.15 , 375.68]
Subtotal (95% CI)		**114**		**115**	**100.0%**	**7.45 [0.15 , 375.68]**
Total events:	1		0			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.00 (P = 0.32)						
Test for subgroup differences: Chi² = 3.32, df = 4 (P = 0.51), I² = 0%						



Analysis 1.3. Comparison 1: Adults formoterol/ICS versus salmeterol/ICS, Outcome 3: Asthma related non-fatal serious adverse events

Study or Subgroup	Formoterol & ICS Events	Total	Salmeterol & ICS Events	Total	Weight	Peto Odds Ratio Peto, Fixed, 95% CI
1.3.1 Formoterol/budesonide vs salmeterol/fluticasone						
Ringdal 2002	1	216	1	212	4.8%	0.98 [0.06 , 15.74]
Aalbers 2004	1	215	0	224	2.4%	7.70 [0.15 , 388.62]
SAM 40048	0	126	0	121		Not estimable
Kuna 2007	13	1099	15	1119	66.5%	0.88 [0.42 , 1.86]
Dahl 2006	1	700	6	697	16.7%	0.24 [0.05 , 1.05]
Busse 2008	0	427	3	406	7.2%	0.13 [0.01 , 1.23]
SAM 40010	1	183	0	190	2.4%	7.68 [0.15 , 387.17]
Subtotal (95% CI)		**2966**		**2969**	**100.0%**	**0.69 [0.37 , 1.26]**
Total events:	17		25			
Heterogeneity: Chi² = 7.49, df = 5 (P = 0.19); I² = 33%						
Test for overall effect: Z = 1.21 (P = 0.23)						
1.3.2 Formoterol/beclomethasone vs salmeterol/fluticasone						
Hsieh 2013	0	125	0	128		Not estimable
EUCTR-002587-99-CZ	1	239	1	242	100.0%	1.01 [0.06 , 16.24]
Papi 2012	0	212	0	228		Not estimable
EUCTR-003449-17-IT	0	54	0	54		Not estimable
Papi 2007	0	115	0	113		Not estimable
Subtotal (95% CI)		**745**		**765**	**100.0%**	**1.01 [0.06 , 16.24]**
Total events:	1		1			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.01 (P = 0.99)						
1.3.3 Formoterol/mometasone v's salmeterol/fluticasone						
Bernstein 2011	1	371	0	351	100.0%	7.00 [0.14 , 353.37]
Subtotal (95% CI)		**371**		**351**	**100.0%**	**7.00 [0.14 , 353.37]**
Total events:	1		0			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.97 (P = 0.33)						
1.3.4 Formoterol/fluticasone vs salmeterol/fluticasone						
Usmani 2017	0	151	1	74	100.0%	0.05 [0.00 , 3.10]
Woo 2020	0	35	0	33		Not estimable
Subtotal (95% CI)		**186**		**107**	**100.0%**	**0.05 [0.00 , 3.10]**
Total events:	0		1			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.43 (P = 0.15)						
1.3.5 Formeterol/budesonide vs salmeterol/budesonide						
EUCTR-004833-70-BG	0	114	0	115		Not estimable
Subtotal (95% CI)		**114**		**115**		**Not estimable**
Total events:	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						
Test for subgroup differences: Chi² = 2.99, df = 3 (P = 0.39), I² = 0%						



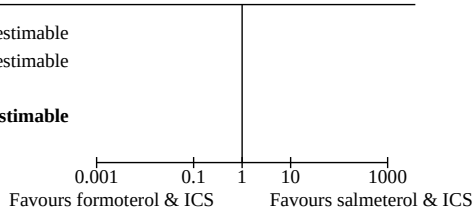
Comparison 2. Children formoterol/fluticasone versus salmeterol/fluticasone

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
2.1 All-cause mortality	2	548	Peto Odds Ratio (Peto, Fixed, 95% CI)	Not estimable
2.2 All-cause non-fatal serious adverse events	2	548	Peto Odds Ratio (Peto, Fixed, 95% CI)	2.72 [0.38, 19.46]
2.3 Asthma related non-fatal serious adverse events	2	548	Peto Odds Ratio (Peto, Fixed, 95% CI)	Not estimable
2.4 All-cause non-fatal serious adverse events	2	548	Peto Odds Ratio (Peto, Fixed, 95% CI)	2.72 [0.38, 19.46]
2.4.1 Children	2	548	Peto Odds Ratio (Peto, Fixed, 95% CI)	2.72 [0.38, 19.46]

Analysis 2.1. Comparison 2: Children formoterol/fluticasone versus salmeterol/fluticasone, Outcome 1: All-cause mortality

	Formoterol & ICS		Salmeterol & ICS			Peto Odds Ratio	Peto Odds Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	Peto, Fixed, 95% CI	Peto, Fixed, 95% CI
Ploszczuk 2014	0	168	0	169		Not estimable	
Emeryk 2016	0	106	0	105		Not estimable	
Total (95% CI)		**274**		**274**		**Not estimable**	
Total events:	0		0				

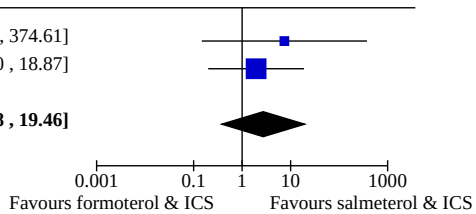
Heterogeneity: Not applicable
Test for overall effect: Not applicable
Test for subgroup differences: Not applicable



Analysis 2.2. Comparison 2: Children formoterol/fluticasone versus salmeterol/fluticasone, Outcome 2: All-cause non-fatal serious adverse events

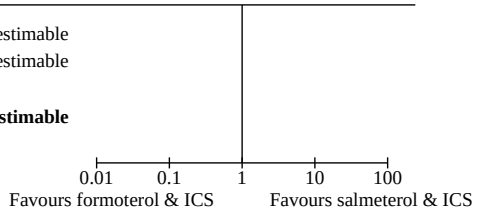
	Formoterol & ICS		Salmeterol & ICS			Peto Odds Ratio	Peto Odds Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	Peto, Fixed, 95% CI	Peto, Fixed, 95% CI
Ploszczuk 2014	1	168	0	169	25.2%	7.43 [0.15 , 374.61]	
Emeryk 2016	2	106	1	105	74.8%	1.94 [0.20 , 18.87]	
Total (95% CI)		**274**		**274**	**100.0%**	**2.72 [0.38 , 19.46]**	
Total events:	3		1				

Heterogeneity: Chi² = 0.34, df = 1 (P = 0.56); I² = 0%
Test for overall effect: Z = 1.00 (P = 0.32)
Test for subgroup differences: Not applicable



Analysis 2.3. Comparison 2: Children formoterol/fluticasone versus salmeterol/fluticasone, Outcome 3: Asthma related non-fatal serious adverse events

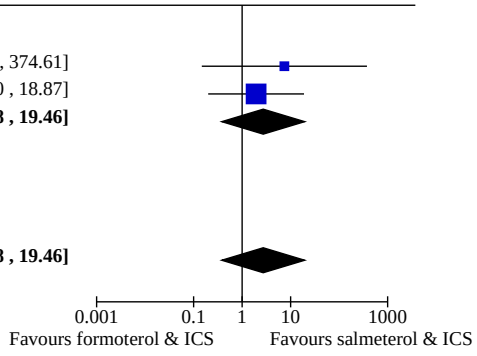
Study or Subgroup	Formoterol & ICS Events	Total	Salmeterol & ICS Events	Total	Weight	Peto Odds Ratio Peto, Fixed, 95% CI
Ploszczuk 2014 (1)	0	168	0	169		Not estimable
Emeryk 2016 (1)	0	106	0	105		Not estimable
Total (95% CI)		**274**		**274**		**Not estimable**
Total events:	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						
Test for subgroup differences: Not applicable						



Footnotes
(1) Children

Analysis 2.4. Comparison 2: Children formoterol/fluticasone versus salmeterol/fluticasone, Outcome 4: All-cause non-fatal serious adverse events

Study or Subgroup	Formoterol & ICS Events	Total	Salmeterol & ICS Events	Total	Weight	Peto Odds Ratio Peto, Fixed, 95% CI
2.4.1 Children						
Ploszczuk 2014	1	168	0	169	25.2%	7.43 [0.15 , 374.61]
Emeryk 2016	2	106	1	105	74.8%	1.94 [0.20 , 18.87]
Subtotal (95% CI)		**274**		**274**	**100.0%**	**2.72 [0.38 , 19.46]**
Total events:	3		1			
Heterogeneity: Chi² = 0.34, df = 1 (P = 0.56); I² = 0%						
Test for overall effect: Z = 1.00 (P = 0.32)						
Total (95% CI)		**274**		**274**	**100.0%**	**2.72 [0.38 , 19.46]**
Total events:	3		1			
Heterogeneity: Chi² = 0.34, df = 1 (P = 0.56); I² = 0%						
Test for overall effect: Z = 1.00 (P = 0.32)						
Test for subgroup differences: Not applicable						



Comparison 3. Sensitivity analysis

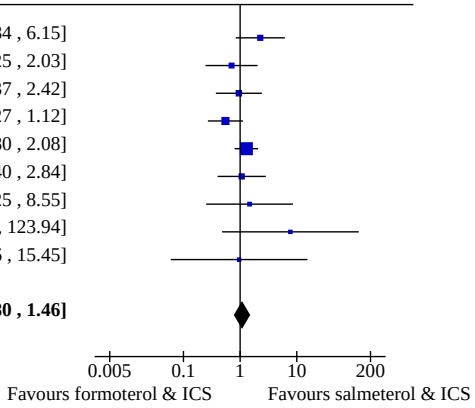
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
3.1 Busse SAE sensitivity analysis	9	7061	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.08 [0.80, 1.46]
3.2 Bernstein SAE sensitivity analysis	2	1126	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.88 [0.43, 1.81]
3.2.1 Formoterol/mometasone vs salmeterol/fluticasone	2	1126	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.88 [0.43, 1.81]
3.3 All-cause non-fatal SAE blinding	11	6886	Odds Ratio (M-H, Fixed, 95% CI)	1.05 [0.75, 1.46]
3.3.1 Formoterol/budesonide vs salmeterol/fluticasone	5	4663	Odds Ratio (M-H, Fixed, 95% CI)	1.05 [0.72, 1.53]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
3.3.2 Formoterol/beclomethasone vs salmeterol/fluticasone	5	1501	Odds Ratio (M-H, Fixed, 95% CI)	1.11 [0.48, 2.59]
3.3.3 Formoterol/mometasone vs salmeterol/fluticasone	1	722	Odds Ratio (M-H, Fixed, 95% CI)	0.95 [0.27, 3.29]
3.4 Asthma-related non-fatal SAE blinding	9	5733	Odds Ratio (M-H, Fixed, 95% CI)	0.75 [0.40, 1.40]
3.4.1 Formoterol/budesonide vs salmeterol/fluticasone	5	4663	Odds Ratio (M-H, Fixed, 95% CI)	0.74 [0.39, 1.40]
3.4.2 Formoterol/beclomethasone vs salmeterol/fluticasone	4	1070	Odds Ratio (M-H, Fixed, 95% CI)	1.01 [0.06, 16.28]
3.5 Single-inhaler SAE sensitivity analysis	8	6633	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.08 [0.80, 1.47]

Analysis 3.1. Comparison 3: Sensitivity analysis, Outcome 1: Busse SAE sensitivity analysis

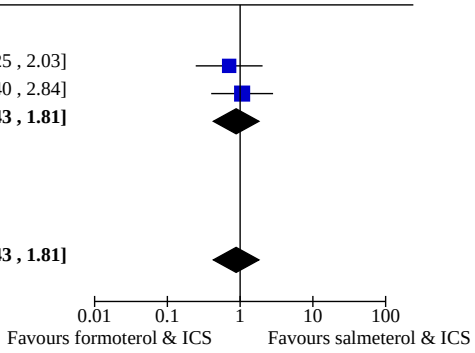
Study or Subgroup	Formoterol & ICS Events	Formoterol & ICS Total	Salmeterol & ICS Events	Salmeterol & ICS Total	Weight	Peto Odds Ratio Peto, Fixed, 95% CI
Aalbers 2004	11	215	5	224	9.1%	2.27 [0.84 , 6.15]
Bernstein 2011	6	371	8	351	8.1%	0.71 [0.25 , 2.03]
Busse 2008	9	427	9	406	10.4%	0.95 [0.37 , 2.42]
Dahl 2006	11	700	20	697	17.9%	0.55 [0.27 , 1.12]
Kuna 2007	39	1099	31	1119	39.9%	1.29 [0.80 , 2.08]
Maspero 2010	13	271	6	133	9.4%	1.07 [0.40 , 2.84]
Ringdal 2002	3	216	2	212	2.9%	1.47 [0.25 , 8.55]
SAM 40010	2	183	0	190	1.2%	7.72 [0.48 , 123.94]
SAM 40048	1	126	1	121	1.2%	0.96 [0.06 , 15.45]
Total (95% CI)		**3608**		**3453**	**100.0%**	**1.08 [0.80 , 1.46]**
Total events:	95		82			

Heterogeneity: Chi² = 8.86, df = 8 (P = 0.35); I² = 10%
Test for overall effect: Z = 0.50 (P = 0.62)
Test for subgroup differences: Not applicable



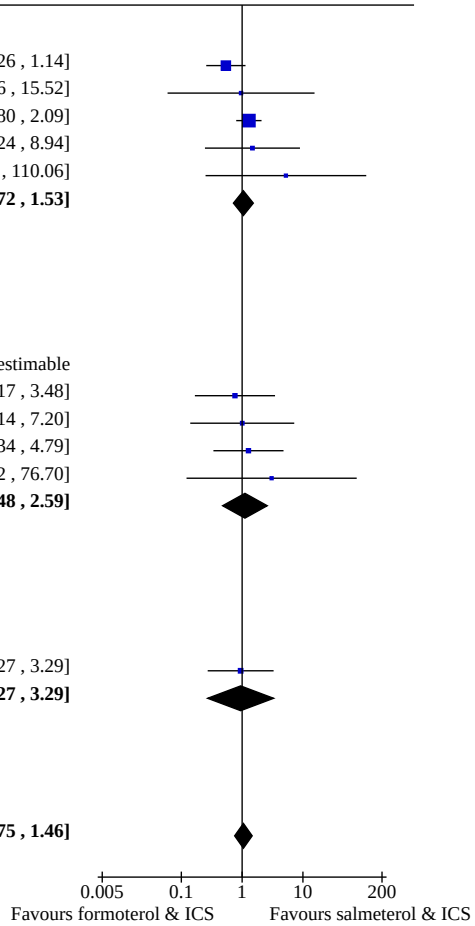
Analysis 3.2. Comparison 3: Sensitivity analysis, Outcome 2: Bernstein SAE sensitivity analysis

Study or Subgroup	Formoterol & ICS Events	Total	Salmeterol & ICS Events	Total	Weight	Peto Odds Ratio Peto, Fixed, 95% CI
3.2.1 Formoterol/mometasone vs salmeterol/fluticasone						
Bernstein 2011	6	371	8	351	46.1%	0.71 [0.25 , 2.03]
Maspero 2010	13	271	6	133	53.9%	1.07 [0.40 , 2.84]
Subtotal (95% CI)		**642**		**484**	**100.0%**	**0.88 [0.43 , 1.81]**
Total events:	19		14			
Heterogeneity: Chi² = 0.31, df = 1 (P = 0.58); I² = 0%						
Test for overall effect: Z = 0.34 (P = 0.73)						
Total (95% CI)		**642**		**484**	**100.0%**	**0.88 [0.43 , 1.81]**
Total events:	19		14			
Heterogeneity: Chi² = 0.31, df = 1 (P = 0.58); I² = 0%						
Test for overall effect: Z = 0.34 (P = 0.73)						
Test for subgroup differences: Not applicable						



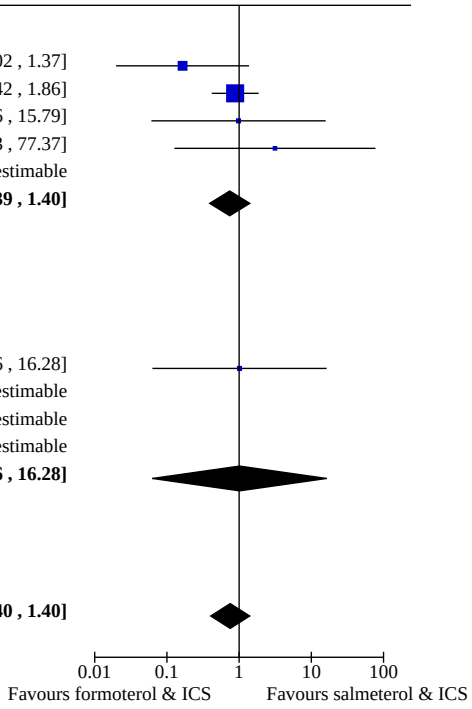
Analysis 3.3. Comparison 3: Sensitivity analysis, Outcome 3: All-cause non-fatal SAE blinding

Study or Subgroup	Formoterol & ICS Events	Total	Salmeterol & ICS Events	Total	Weight	Odds Ratio M-H, Fixed, 95% CI
3.3.1 Formoterol/budesonide vs salmeterol/fluticasone						
Dahl 2006	11	700	20	697	29.0%	0.54 [0.26 , 1.14]
SAM 40048	1	126	1	121	1.5%	0.96 [0.06 , 15.52]
Kuna 2007	39	1099	31	1119	43.5%	1.29 [0.80 , 2.09]
Ringdal 2002	3	216	2	212	2.9%	1.48 [0.24 , 8.94]
SAM 40010	2	183	0	190	0.7%	5.25 [0.25 , 110.06]
Subtotal (95% CI)		**2324**		**2339**	**77.6%**	**1.05 [0.72 , 1.53]**
Total events:	56		54			
Heterogeneity: Chi² = 5.00, df = 4 (P = 0.29); I² = 20%						
Test for overall effect: Z = 0.24 (P = 0.81)						
3.3.2 Formoterol/beclomethasone vs salmeterol/fluticasone						
Papi 2007	0	115	0	113		Not estimable
Hsieh 2013	3	125	4	128	5.7%	0.76 [0.17 , 3.48]
NCT00901368	2	215	2	216	2.9%	1.00 [0.14 , 7.20]
EUCTR-002587-99-CZ	5	239	4	242	5.7%	1.27 [0.34 , 4.79]
EUCTR-003449-17-IT	1	54	0	54	0.7%	3.06 [0.12 , 76.70]
Subtotal (95% CI)		**748**		**753**	**15.0%**	**1.11 [0.48 , 2.59]**
Total events:	11		10			
Heterogeneity: Chi² = 0.67, df = 3 (P = 0.88); I² = 0%						
Test for overall effect: Z = 0.25 (P = 0.80)						
3.3.3 Formoterol/mometasone vs salmeterol/fluticasone						
Bernstein 2011	5	371	5	351	7.4%	0.95 [0.27 , 3.29]
Subtotal (95% CI)		**371**		**351**	**7.4%**	**0.95 [0.27 , 3.29]**
Total events:	5		5			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.09 (P = 0.93)						
Total (95% CI)		**3443**		**3443**	**100.0%**	**1.05 [0.75 , 1.46]**
Total events:	72		69			
Heterogeneity: Chi² = 5.70, df = 9 (P = 0.77); I² = 0%						
Test for overall effect: Z = 0.29 (P = 0.77)						
Test for subgroup differences: Chi² = 0.05, df = 2 (P = 0.98), I² = 0%						



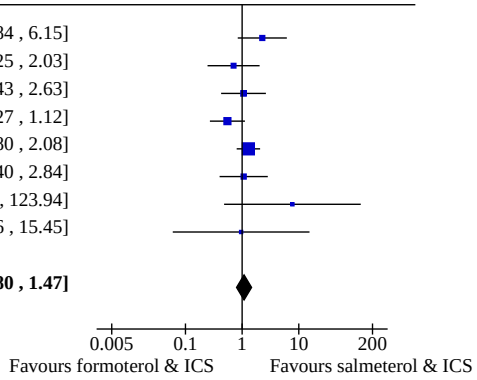
Analysis 3.4. Comparison 3: Sensitivity analysis, Outcome 4: Asthma-related non-fatal SAE blinding

Study or Subgroup	Formoterol & ICS Events	Total	Salmeterol & ICS Events	Total	Weight	Odds Ratio M-H, Fixed, 95% CI
3.4.1 Formoterol/budesonide vs salmeterol/fluticasone						
Dahl 2006	1	700	6	697	25.9%	0.16 [0.02 , 1.37]
Kuna 2007	13	1099	15	1119	63.4%	0.88 [0.42 , 1.86]
Ringdal 2002	1	216	1	212	4.3%	0.98 [0.06 , 15.79]
SAM 40010	1	183	0	190	2.1%	3.13 [0.13 , 77.37]
SAM 40048	0	126	0	121		Not estimable
Subtotal (95% CI)		**2324**		**2339**	**95.7%**	**0.74 [0.39 , 1.40]**
Total events:	16		22			
Heterogeneity: Chi² = 2.95, df = 3 (P = 0.40); I² = 0%						
Test for overall effect: Z = 0.92 (P = 0.36)						
3.4.2 Formoterol/beclomethasone vs salmeterol/fluticasone						
EUCTR-002587-99-CZ	1	239	1	242	4.3%	1.01 [0.06 , 16.28]
EUCTR-003449-17-IT	0	54	0	54		Not estimable
Hsieh 2013	0	125	0	128		Not estimable
Papi 2007	0	115	0	113		Not estimable
Subtotal (95% CI)		**533**		**537**	**4.3%**	**1.01 [0.06 , 16.28]**
Total events:	1		1			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.01 (P = 0.99)						
Total (95% CI)		**2857**		**2876**	**100.0%**	**0.75 [0.40 , 1.40]**
Total events:	17		23			
Heterogeneity: Chi² = 2.98, df = 4 (P = 0.56); I² = 0%						
Test for overall effect: Z = 0.90 (P = 0.37)						
Test for subgroup differences: Chi² = 0.05, df = 1 (P = 0.83), I² = 0%						



Analysis 3.5. Comparison 3: Sensitivity analysis, Outcome 5: Single-inhaler SAE sensitivity analysis

Study or Subgroup	Formoterol & ICS Events	Total	Salmeterol & ICS Events	Total	Weight	Peto Odds Ratio Peto, Fixed, 95% CI
Aalbers 2004	11	215	5	224	9.3%	2.27 [0.84 , 6.15]
Bernstein 2011	6	371	8	351	8.3%	0.71 [0.25 , 2.03]
Busse 2008	10	427	9	406	11.2%	1.06 [0.43 , 2.63]
Dahl 2006	11	700	20	697	18.3%	0.55 [0.27 , 1.12]
Kuna 2007	39	1099	31	1119	40.9%	1.29 [0.80 , 2.08]
Maspero 2010	13	271	6	133	9.7%	1.07 [0.40 , 2.84]
SAM 40010	2	183	0	190	1.2%	7.72 [0.48 , 123.94]
SAM 40048	1	126	1	121	1.2%	0.96 [0.06 , 15.45]
Total (95% CI)		**3392**		**3241**	**100.0%**	**1.08 [0.80 , 1.47]**
Total events:	93		80			
Heterogeneity: Chi² = 8.67, df = 7 (P = 0.28); I² = 19%						
Test for overall effect: Z = 0.51 (P = 0.61)						
Test for subgroup differences: Not applicable						



ADDITIONAL TABLES

Table 1. Details of the dose and type of medication used

Study ID	Formoterol device	Formoterol dose[a]	ICS type and dose[a]	Salmeterol device	Salmeterol dose[a]	ICS type and dose[a]
Aalbers 2004	DPI	12 µg	Budesonide 400 µg	DPI	50 µg	Fluticasone 250 µg
Akamatsu 2014	DPI	12 µg	Budesonide 400 µg	DPI	50 µg	Flucticasone 250 µg
NCT00901368	pMDI	12 µg	Beclomethasone extra-fine 200 µg	DPI	12 µg	Flucticasone 250
Bernstein 2011	pMDI	10 µg	Mometasone 200 µg	pMDI	50 µg	Fluticasone 250
Bodzenta-Lukaszyk 2011	HFA pMDI with AeroChamber	10 µg	Fluticasone 100 µg or 250 µg	HFA pMDI with AeroChamber	50 µg	Fluticasone 100 µg or 250 µg
	pMDI	12 µg	Budesonide 400 µg	DPI	50 µg	Fluticasone 250 µg
Dahl 2006	DPI	12 µg	Budesonide 400 µg	DPI	50 µg	Fluticasone 250 µg
Emeryk 2016	pMDI with AeroChamber	10 µg	Fluticasone 100 µg	pMDI with AeroChamber	50 µg	Fluticasone 100 µg
Hsieh 2013	pMDI (Foster)	12 µg	Beclomethasone extra-fine 200 µg	pMDI	50 µg	Fluticasone 250 µg
Kuna 2007	DPI	12 µg	Budesonide 400 µg	pMDI	50 µg	Fluticasone 250 µg
Maspero 2010	pMDI	10 µg	Mometasone 200 µg or 400 µg	pMDI	50 µg	Fluticasone 250 µg or 500 µg
Papi 2007	pMDI	12 µg	Beclomethasone extra-fine 200 µg	pMDI	50 µg	Fluticasone 250 µg
Papi 2012	pMDI (Foster)	12 µg	Beclomethasone extra-fine 200 µg	DPI	50 µg	Flucticasone 250 µg
Ploszczuk 2014	pMDI	10 µg	Fluticasone 100 µg	pMDI	50 µg	Fluticasone 100 µg
	DPI 2 separate inhalers	12 µg	Budesonide 800 µg	DPI	50 µg	Fluticasone 250 µg
	DPI	6 µg	Budesonide 200 µg	DPI	50 µg	Fluticasone 100 µg
SAM 40048	DPI	6 µg	Budesonide 200 µg	DPI	50 µg	Fluticasone 250 µg
Scichilone 2010	pMDI (Foster)	12 µg	Beclomethasone extra-fine 200 µg	DPI	50 µg	Fluticasone 250 µg
Usmani 2017	pMDI	20 µg	Fluticasone 500 µg	pMDI	50 µg	Fluticasone 500 µg

Table 1. Details of the dose and type of medication used *(Continued)*

Woo 2020	pMDI	10 µg	Fluticasone 250 µg	DPI	50 µg	Flucticasone 250 µg
EUC-TR-004833-70-BG	DPI	12 µg	Budesonide 200 µg	DPI	25 µg	Budesonide 150 µg
EUC-TR-003449-17-IT	pMDI	12 µg	Beclomethasone 200 µg	DPI	50 µg	Fluticasone 250 µg
EUC-TR-002587-99-CZ	pMDI	12 µg	Beclomethasone 400 µg	pMDI	50 µg	Fluticasone 500 µg

[a]All doses taken twice daily.
Doses shown are ex-actuator rather than delivered doses.
DPI: dry powder inhaler.
ICS: inhaled corticosteroid.
HFA: hydrofluoroalkane.
pMDI: pressurised metered-dose inhaler.

Table 2. Details of study participants, locations, and sponsors

Study ID	Number randomised	Duration (weeks)	Age (years)	Location	Sponsors
Aalbers 2004	658	26 (open-extension)	12+	Europe	AstraZeneca
Akamatsu 2014	66	12	18+	Japan	Unknown
NCT00901368	431	12	18 to 65	Europe	Chiesi Farmaceutici S.p.A.
Bernstein 2011	722	12	12+	No location details provided	Merck Sharp & Dohme Corp.
Bodzenta-Lukaszyk 2011	202	12	18+	Europe	Mundipharma
Busse 2008	1225	30	12+	USA	AstraZeneca
Dahl 2006	1397	24	18+	Europe	GlaxoSmithKline
Emeryk 2016	211	12	4 to 12	Europe	Mundipharma Research Limited
Hsieh 2013	253	12	20 to 65	Taiwan	Orient EuroPharma Co., Ltd., Taiwan.
Kuna 2007	3335	24	12+	Multi-national	AstraZeneca
Maspero 2010	404	52	12+	South America	Merck
Papi 2007	228	12	18+	Europe	Chiesi
Papi 2012	422	24	18 to 65	Europe	Chiesi Farmaceutici S.p.A.

Table 2. Details of study participants, locations, and sponsors *(Continued)*

Ploszczuk 2014	512	12	5 to 2	Euope and India	Mundipharma
Ringdal 2002	428	12	16+	Europe	GlaxoSmithKline
SAM 40010	373	12	12+	Europe	GlaxoSmithKline
SAM 40048	248	12	18+	Germany	GlaxoSmithKline
Scichilone 2010	30	12	18 to 50	Italy	Chiesi Farmaceutici S.p.A.
Usmani 2017	225	24	18 to 75	England	Research in Real Life & Napp
Woo 2020	68	12	55+	Korea	Mundipharma Korea
EUC-TR-004833-70-BG	229	12	18 to 65	Bulgaria, Serbia, Romania, Macedonia	Laboratoires SMB S.A.
EUC-TR-003449-17-IT	108	12	No details	Italy	Chiesi Farmaceutici S.p.A.
EUC-TR-002587-99-CZ	481[a]	24	12 to 84	Poland, Slovenia, Spain, Bulgaria, Czech Republic, Estonia, France, Germany, Hungary, Italy, Latvia, Lithuania, Belarus, Croatia, Romania, Russian Federation Ukraine	Chiesi Farmaceutici S.p.A.

[a]Third arm not included.

APPENDICES

Appendix 1. Pharmacology of beta$_2$-agonists

Beta$_2$-agonists are thought to cause bronchodilation primarily through binding of 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 in 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 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 related 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 it is probably best to concentrate on specific adverse 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 an abundance of well-coupled beta$_2$-adrenoceptors are 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). 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, good evidence suggests 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 causes 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 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). It is interesting to note that 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 2003a - 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 to 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 higher doses of either 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 in 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. Search strategies

Source and date of search	Search strategy	Results retrieved
Cochrane Airways Trials Register (Cochrane Register of Studies) Date of most recent search: 24 February 2021	1 AST:MISC1 AND INSEGMENT 2 MeSH DESCRIPTOR Asthma Explode All AND INSEGMENT 3 asthma*:ti,ab AND INSEGMENT 4 #1 or #2 or #3 AND INSEGMENT 5 MESH DESCRIPTOR Salmeterol Xinafoate EXPLODE ALL AND INSEGMENT 6 salmeterol* AND INSEGMENT 7 #5 OR #6 8 MESH DESCRIPTOR Formoterol Fumarate EXPLODE ALL AND INSEGMENT 9 formoterol* AND INSEGMENT 10 #8 OR #9 11 #4 AND #7 AND #10 12 INREGISTER 13 #11 AND #12	March 2020 = 259 February 2021 = 3
CENTRAL (Cochrane Register of Studies) Date of most recent search: 24 February 2021	1 AST:MISC1 AND CENTRAL:TARGET 2 MeSH DESCRIPTOR Asthma Explode All AND CENTRAL:TARGET 3 asthma*:ti,ab AND CENTRAL:TARGET 4 #1 or #2 or #3 AND CENTRAL:TARGET 5 MESH DESCRIPTOR Salmeterol Xinafoate EXPLODE ALL AND CENTRAL:TARGET 6 salmeterol* AND CENTRAL:TARGET 7 #5 OR #6 AND CENTRAL:TARGET 8 MESH DESCRIPTOR Formoterol Fumarate EXPLODE ALL AND CENTRAL:TARGET 9 formoterol* AND CENTRAL:TARGET 10 #8 OR #9 AND CENTRAL:TARGET 11 #4 AND #7 AND #10 AND CENTRAL:TARGET	March 2020 = 376 February 2021 = 4
MEDLINE (Ovid SP) ALL Date of most recent search: 24 February 2021	1 exp Asthma/ 2 asthma$.tw. 3 1 or 2 4 exp Salmeterol Xinafoate/ 5 salmeterol$.tw. 6 4 or 5 7 exp Formoterol Fumarate/ 8 formoterol$.tw. 9 7 or 8 10 3 and 6 and 9 11 (controlled clinical trial or randomised controlled trial).pt. 12 (randomised or randomised).ab,ti. 13 placebo.ab,ti. 14 dt.fs. 15 randomly.ab,ti. 16 trial.ab,ti. 17 groups.ab,ti. 18 or/11-17 19 Animals/ 20 Humans/ 21 19 not (19 and 20) 22 18 not 21 23 10 and 22	March 2020 = 397 February 2021 = 5
Embase (Ovid SP)	1 exp asthma/	March 2020 = 987

(Continued)

Date of most recent search: 24 February 2021	2 asthma$.tw. 3 1 or 2 4 fluticasone propionate plus salmeterol xinafoate/ or budesonide plus salmeterol/ or fluticasone propionate plus salmeterol/ or salmeterol xinafoate/ or salmeterol/ 5 salmeterol$.tw. 6 formoterol fumarate/ or formoterol fumarate plus mometasone furoate/ or beclometasone dipropionate plus formoterol fumarate/ or fluticasone propionate plus formoterol fumarate/ or budesonide plus formoterol/ or formoterol/ 7 formoterol$.tw. 8 4 or 5 9 6 or 7 10 3 and 8 and 9 11 Randomized Controlled Trial/ 12 randomisation/ 13 controlled clinical trial/ 14 Double Blind Procedure/ 15 Single Blind Procedure/ 16 Crossover Procedure/ 17 (clinica$ adj3 trial$).tw. 18 ((singl$ or doubl$ or trebl$ or tripl$) adj3 (mask$ or blind$ or method$)).tw. 19 exp Placebo/ 20 placebo$.ti,ab. 21 random$.ti,ab. 22 ((control$ or prospectiv$) adj3 (trial$ or method$ or stud$)).tw. 23 (crossover$ or cross-over$).ti,ab. 24 or/11-23 25 exp animals/ or exp invertebrate/ or animal experiment/ or animal model/ or animal tissue/ or animal cell/ or nonhuman/ 26 human/ or normal human/ or human cell/ 27 25 and 26 28 25 not 27 29 24 not 28 30 10 and 29	February 2021 = 22
ClincalTrials.gov Date of most recent search: 24 February 2021	Study type: Interventional Condition: asthma Intervention: formoterol AND salmeterol	March 2020 = 30 February 2021 = 0
WHO ICTRP Date of most recent search: 9 March 2020	Condition: asthma Intervention: formoterol AND salmeterol	March 2020 = 6 February 2021 = not searched

WHAT'S NEW

Date	Event	Description
15 April 2021	Amended	Plain language summary title added.

HISTORY

Protocol first published: Issue 2, 2009

Review first published: Issue 1, 2010

Date	Event	Description
24 February 2021	New search has been performed	New literature search run
24 February 2021	New citation required but conclusions have not changed	Thirteen studies added, including studies on children
11 April 2013	Amended	NIHR acknowledgement added
17 August 2011	New search has been performed	New search in August 2011 identified 1 new included study on 202 adults comparing formoterol and fluticasone with salmeterol and fluticasone (Bodzenta-Lukaszyk 2011), and 1 new study on 404 adults comparing formoterol and mometasone with salmeterol and fluticasone (Maspero 2010)
15 August 2011	Amended	Typological error in abstract corrected (dose of formoterol changed from 50 µg to 12 µg)

CONTRIBUTIONS OF AUTHORS

CJC: conception of the idea and co-writing of the protocol, inclusion of studies, risk of bias assessment, data extraction, analysis, writing of the review for the original version and all updates.

OOS: inclusion of studies, risk of bias assessment, data analysis, writing of updates of the review.

ES: writing of 'Search methods' and search results sections, design and conduct of the literature search.

Contributions of editorial team

Rebecca Fortescue (Coordinating Editor): edited the review update; advised on methods; approved the review update prior to publication.

Lucy Goldsmith (Statistician): checked data entry.

Katy Pike (Contact Editor): edited the review; advised on methods, interpretation, and content.

Emma Dennett (Managing Editor): co-ordinated the editorial process; advised on interpretation and content; edited the review.

Emma Jackson (Assistant Managing Editor): conducted peer review; edited the references and other sections of the protocol and of the review.

DECLARATIONS OF INTEREST

OOS: none known.

ES: none known.

CJC: none known.

SOURCES OF SUPPORT

Internal sources

- St George's, University of London, UK

  Chris Cates and Elizabeth Stovold are salaried employees of St George's, University of London

External sources

- National Institute for Health Research (NIHR), UK

  National Institute for Health Research Systematic Reviews Programme Grant (project number 16/114/21)

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

No subgroup analysis of the basis for dose-equivalence of inhaled corticosteroids was possible. No risk differences in meta-analyses were reported for the 2021 update, as this is not recommended by the new *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2019). Cardiovascular mortality was not investigated as a secondary outcome due to the small number of deaths, but a further sensitivity analysis was restricted to combination inhalers only. There was a change to the search terms, and a new author team was created.

INDEX TERMS

Medical Subject Headings (MeSH)

Administration, Inhalation; Albuterol [administration & dosage] [adverse effects] [*analogs & derivatives]; Androstadienes [administration & dosage] [adverse effects]; Anti-Asthmatic Agents [administration & dosage] [*adverse effects]; Asthma [*drug therapy] [mortality]; Budesonide [administration & dosage] [adverse effects]; Drug Therapy, Combination [adverse effects]; Ethanolamines [administration & dosage] [*adverse effects]; Fluticasone; Formoterol Fumarate; Glucocorticoids [administration & dosage] [*adverse effects]; Randomized Controlled Trials as Topic; Salmeterol Xinafoate

MeSH check words

Adolescent; Adult; Humans