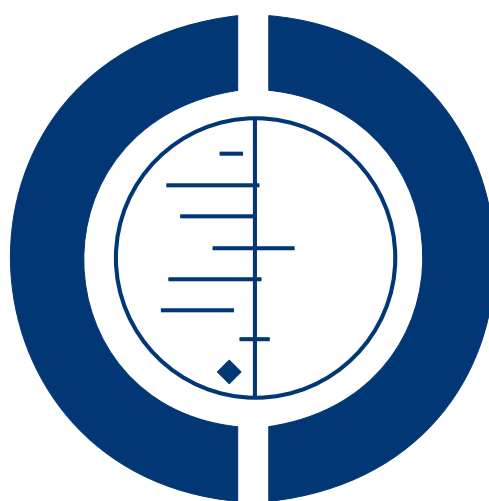


Combination fluticasone and salmeterol versus fixed dose combination budesonide and formoterol for chronic asthma in adults and children (Review)

Lasserson TJ, Cates CJ, Ferrara G, Casali L



**THE COCHRANE
COLLABORATION®**

This is a reprint of a Cochrane review, prepared and maintained by The Cochrane Collaboration and published in *The Cochrane Library* 2010, Issue 3

<http://www.thecochranelibrary.com>



Combination fluticasone and salmeterol versus fixed dose combination budesonide and formoterol for chronic asthma in adults and children (Review)
Copyright © 2010 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

TABLE OF CONTENTS

HEADER	1
ABSTRACT	1
PLAIN LANGUAGE SUMMARY	2
SUMMARY OF FINDINGS FOR THE MAIN COMPARISON	2
BACKGROUND	5
OBJECTIVES	5
METHODS	5
RESULTS	7
Figure 1.	8
Figure 2.	10
Figure 3.	11
Figure 4.	12
Figure 5.	12
Figure 6.	13
DISCUSSION	13
AUTHORS' CONCLUSIONS	14
ACKNOWLEDGEMENTS	14
REFERENCES	15
CHARACTERISTICS OF STUDIES	19
DATA AND ANALYSES	29
Analysis 1.1. Comparison 1 Combination fluticasone/salmeterol versus budesonide/formoterol, Outcome 1 Participants experiencing exacerbations requiring oral steroid treatment.	30
Analysis 1.2. Comparison 1 Combination fluticasone/salmeterol versus budesonide/formoterol, Outcome 2 Participants experiencing exacerbations requiring admission to hospital.	30
Analysis 1.3. Comparison 1 Combination fluticasone/salmeterol versus budesonide/formoterol, Outcome 3 Asthma-related serious adverse event.	31
Analysis 1.4. Comparison 1 Combination fluticasone/salmeterol versus budesonide/formoterol, Outcome 4 Participants experiencing exacerbations requiring ED visit/hospitalisation.	32
Analysis 1.5. Comparison 1 Combination fluticasone/salmeterol versus budesonide/formoterol, Outcome 5 Change in FEV1.	32
Analysis 1.6. Comparison 1 Combination fluticasone/salmeterol versus budesonide/formoterol, Outcome 6 Change in FEV1 predicted (%).	33
Analysis 1.7. Comparison 1 Combination fluticasone/salmeterol versus budesonide/formoterol, Outcome 7 Change in am PEF.	33
Analysis 1.8. Comparison 1 Combination fluticasone/salmeterol versus budesonide/formoterol, Outcome 8 Change in pm PEF.	34
Analysis 1.9. Comparison 1 Combination fluticasone/salmeterol versus budesonide/formoterol, Outcome 9 Change in daytime symptoms.	34
Analysis 1.10. Comparison 1 Combination fluticasone/salmeterol versus budesonide/formoterol, Outcome 10 Change in symptom-free days.	35
Analysis 1.11. Comparison 1 Combination fluticasone/salmeterol versus budesonide/formoterol, Outcome 11 Change in nocturnal awakenings.	35
Analysis 1.12. Comparison 1 Combination fluticasone/salmeterol versus budesonide/formoterol, Outcome 12 Change in rescue medication use.	36
Analysis 1.13. Comparison 1 Combination fluticasone/salmeterol versus budesonide/formoterol, Outcome 13 Withdrawals.	36
Analysis 1.14. Comparison 1 Combination fluticasone/salmeterol versus budesonide/formoterol, Outcome 14 Withdrawals (adverse events).	37
Analysis 1.15. Comparison 1 Combination fluticasone/salmeterol versus budesonide/formoterol, Outcome 15 Withdrawals (lack of efficacy).	37

Analysis 1.16. Comparison 1 Combination fluticasone/salmeterol versus budesonide/formoterol, Outcome 16 Adverse events.	38
Analysis 1.17. Comparison 1 Combination fluticasone/salmeterol versus budesonide/formoterol, Outcome 17 Headache.	38
Analysis 1.18. Comparison 1 Combination fluticasone/salmeterol versus budesonide/formoterol, Outcome 18 Candidiasis.	39
Analysis 1.19. Comparison 1 Combination fluticasone/salmeterol versus budesonide/formoterol, Outcome 19 Dysphonia.	39
Analysis 1.20. Comparison 1 Combination fluticasone/salmeterol versus budesonide/formoterol, Outcome 20 Upper respiratory tract infection.	40
Analysis 1.21. Comparison 1 Combination fluticasone/salmeterol versus budesonide/formoterol, Outcome 21 Rhinitis.	40
Analysis 1.22. Comparison 1 Combination fluticasone/salmeterol versus budesonide/formoterol, Outcome 22 Throat irritation.	41
Analysis 1.23. Comparison 1 Combination fluticasone/salmeterol versus budesonide/formoterol, Outcome 23 Cough.	41
Analysis 1.24. Comparison 1 Combination fluticasone/salmeterol versus budesonide/formoterol, Outcome 24 Tremor.	42
WHAT'S NEW	42
HISTORY	42
CONTRIBUTIONS OF AUTHORS	42
DECLARATIONS OF INTEREST	42
SOURCES OF SUPPORT	43
DIFFERENCES BETWEEN PROTOCOL AND REVIEW	43
NOTES	43
INDEX TERMS	43

[Intervention Review]

Combination fluticasone and salmeterol versus fixed dose combination budesonide and formoterol for chronic asthma in adults and children

Toby J Lasserson¹, Christopher J Cates¹, Giovanni Ferrara², Lucio Casali³

¹Community Health Sciences, St George's, University of London, London, UK. ²Section of Respiratory Diseases, Department of Internal Medicine, University of Perugia, Terni, Italy. ³Internal Medicine, University of Perugia, Terni, Italy

Contact address: Toby J Lasserson, Community Health Sciences, St George's, University of London, Cranmer Terrace, London, SW17 0RE, UK. tlassers@sgul.ac.uk. tlasserson@cochrane.org.

Editorial group: Cochrane Airways Group.

Publication status and date: New search for studies and content updated (no change to conclusions), published in Issue 3, 2010.

Review content assessed as up-to-date: 20 January 2010.

Citation: 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.

Copyright © 2010 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

ABSTRACT

Background

Combination therapies are frequently recommended as maintenance therapy for people with asthma, whose disease is not adequately controlled with inhaled steroids. Fluticasone/salmeterol (FP/SAL) and budesonide/formoterol (BUD/F) have been assessed against their respective monocomponents, but there is a need to compare these two therapies on a head-to-head basis.

Objectives

To estimate the relative effects of fluticasone/salmeterol and budesonide/formoterol in terms of asthma control, safety and lung function.

Search strategy

We searched the Cochrane Airways Group register of trials with prespecified terms. We performed additional hand searching of manufacturers' web sites and online trial registries. Searches are current to May 2009.

Selection criteria

Randomised studies comparing fixed dose FP/SAL and BUD/F were eligible, for a minimum of 12 weeks. Crossover studies were excluded. Our primary outcomes were: i) exacerbations requiring oral steroid bursts, ii) hospital admission and iii) serious adverse events.

Data collection and analysis

Two authors independently assessed studies for inclusion in the review. We combined continuous data outcomes with a mean difference (MD), and dichotomous data outcomes with an odds ratio (OR).

Combination fluticasone and salmeterol versus fixed dose combination budesonide and formoterol for chronic asthma in adults and children (Review)

Copyright © 2010 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

Main results

Five studies met the review entry criteria (5537 adults). **Primary outcomes:** The odds of an exacerbation requiring oral steroids did not differ significantly between treatments (OR 0.89; 95% CI 0.74 to 1.07, four studies, 4949 adults). The odds of an exacerbation leading hospital admission were also not significantly different (OR 1.29; 95% CI 0.68 to 2.47, four studies, 4879 participants). The odds of serious adverse events did not differ significantly between treatments (OR 1.47; 95% CI 0.75, 2.86, three studies, 4054 participants). **Secondary outcomes:** Lung function outcomes, symptoms, rescue medication, exacerbations leading ED visit/hospital admission and adverse events did not differ statistically between treatments.

Authors' conclusions

The evidence in this review indicates that differences in the requirement for oral steroids and hospital admission between BUD/F and FP/SAL do not reach statistical significance. However, the confidence intervals do not exclude clinically important differences between treatments in reducing exacerbations or causing adverse events. The width of the confidence intervals for the primary outcomes justify further trials in order to better determine the relative effects of these drug combinations. Although this review sought to assess the effects of these drugs in both adults and children, no trials were identified in the under-12s and research in this area is of a high priority.

PLAIN LANGUAGE SUMMARY

The effects of different combinations of inhaled steroids and long-acting beta-agonists for chronic asthma

Persistent asthma often requires the combination of inhaled corticosteroids (ICS) and long-acting beta2-agonists (LABA). This systematic review examined randomised controlled trials comparing two commonly available combinations administered at fixed dose with a single inhaler, fluticasone/salmeterol (FP/SAL) and budesonide/formoterol (BUD/F). We found that the number of adults who required treatment with oral steroids or admission to hospital was similar between the treatments, but that additional trials would improve the precision of our estimates. No statistical differences were found for pulmonary function, rescue medication use and adverse events. Well-designed studies on these questions on different types of patients are needed to confirm and to better explain these findings. In particular studies which assess the effects of these therapies in children are of a high priority.

SUMMARY OF FINDINGS FOR THE MAIN COMPARISON *[Explanation]*

Combination fluticasone/salmeterol or budesonide/formoterol for chronic asthma in adults						
Patient or population: patients with chronic asthma in adults ¹						
Settings: community						
Intervention: combination fluticasone/salmeterol or budesonide/formoterol						
Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
Control	Combination budesonide/formoterol in one inhaler device	Combination fluticasone/salmeterol in one inhaler device				
Participants experiencing exacerbations requiring oral steroid treatment Follow-up: mean 6 months	106 per 1000 ²	95 per 1000 (81 to 113)	OR 0.89 (0.74 to 1.07)	4949 (4 studies)	⊕⊕⊕○ moderate ³	
Participants experiencing exacerbations requiring admission to hospital Follow-up: mean 6 months	7 per 1000 ²	9 per 1000 (5 to 17)	OR 1.29 (0.68 to 2.47)	4879 (4 studies)	⊕⊕⊕○ moderate ³	
Asthma-related serious adverse event Follow-up: mean 6 months	7 per 1000 ²	10 per 1000 (5 to 20)	OR 1.47 (0.75 to 2.86)	4054 (3 studies)	⊕⊕⊕○ moderate ³	

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

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

GRADE Working Group grades of evidence

High quality: Further research is very unlikely to change our confidence in the estimate of effect.

Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.

Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.

Very low quality: We are very uncertain about the estimate.

1. No studies have been found in children. The findings of this review are only applicable to adults.
2. The mean event rate in the BDF arms of the trials was used to calculate the assumed risk.
3. The confidence interval is wide and could change with the addition of new evidence.

BACKGROUND

Asthma is a chronic inflammatory disease of the airways, and anti-inflammatory treatment is a cornerstone of asthma therapy. Treatment with inhaled corticosteroids (ICS) improves lung function and reduces asthma symptoms in mild persistent asthmatic patients (Adams 2008). Many patients remain symptomatic despite using optimal doses of ICS. However, patients do benefit by the addition of an inhaled long-acting beta2-agonist (LABA). This approach further improves lung function and quality of life in patients with moderate to severe persistent asthma (Ni Chroinin 2005).

The principal advantage of combining ICS and LABA in one inhaler is the simultaneous delivery of two effective inhaled therapies. This may lead users to better adhere to dosing regimens, especially given concerns over the use of LABA therapy without a regular background steroid (Walters 2007). Clinicians and people with asthma are faced with a choice between two treatments as maintenance treatment of asthma: the ICS fluticasone and LABA salmeterol preparation marketed as 'Seretide', 'Advair' or 'Viani', and the ICS budesonide and LABA formoterol preparation marketed as 'Symbicort'.

There is some uncertainty as to which particular combination may be suitable. Previous assessments have considered the addition of any LABA to any ICS when the dose of ICS is increased or when the study drugs are titrated according to symptoms (Greenstone 2005; Gibson 2005). Although the LABAs commonly used in combination preparations have a similar duration of effect of around 12 hours or more, salmeterol and formoterol also have differing pharmacological properties. The onset of action of formoterol is faster than that of salmeterol (Palmqvist 1997; van Noord 1996) and has as rapid an onset of action as salbutamol in asthma (Cazzola 2002). Some differences exist also between fluticasone and budesonide despite the shared anti-inflammatory effect (Adams 2007), and so a systematic exploration of the relative efficacy of these different drug combinations is justified.

OBJECTIVES

To compare the combinations of salmeterol/fluticasone and budesonide/formoterol in single inhaler devices in chronic asthma in terms of asthma control, safety and lung function.

METHODS

Criteria for considering studies for this review

Types of studies

Randomised, clinical trials comparing single inhaler devices containing combination fluticasone and salmeterol versus budesonide and formoterol. Only studies with a parallel design were eligible as the minimum washout period of inhaled steroids has not been adequately established.

Types of participants

Adults and children with a diagnosis of chronic asthma. We accepted trialist-defined asthma. Any severity of asthma and patients on any co-intervention were eligible (as long as the co-interventions were not part of the randomised treatment) but studies on acute asthma carried out in emergency departments were excluded.

Types of interventions

The preparations considered by this review were the combination of the inhaled steroid fluticasone and long-acting beta-agonist salmeterol (FP/SAL) against the inhaled steroid budesonide and long-acting beta-agonist formoterol (BUD/F) in one inhaler device. We included studies which assessed the combination of drugs in either metered dose inhalers (MDI) or dry powder inhaler (DPI). We considered fixed dose comparisons between these preparations and we have excluded studies assessing the efficacy and safety of different dosing strategies of budesonide/formoterol ('single inhaler therapy' or 'adjustable maintenance dosing') with fixed dose fluticasone/salmeterol. Studies had a minimum duration of 12 weeks in order to meet the entry criteria of this review.

Types of outcome measures

Primary outcomes

1. Exacerbations of asthma requiring oral steroids
2. Exacerbations of asthma requiring hospital admission
3. Serious adverse events (including asthma-related death and intubation)

Secondary outcomes

1. Exacerbations leading to ED visit/admission to hospital
2. Diary card morning and evening peak expiratory flow (PEF)
3. Clinic spirometry (FEV1, clinic PEF, FVC)
4. Rescue medication use
5. Symptoms
6. Quality of life
7. Adverse events
8. Study withdrawal

Search methods for identification of studies

Trials were identified using the Cochrane Airways Group Specialised Register of trials, which is derived from systematic searches of bibliographic databases including the Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE, EMBASE, CINAHL, AMED and PsycINFO, and hand searching of respiratory journals and meeting abstracts. All records in the Specialised Register coded as 'asthma' were searched using the following terms:

("single inhaler" or symbicort or seretide or advair or viani) or ((steroid* or corticosteroid* or ICS or fluticasone or FP or Flixotide or budesonide or BUD or Pulmicort) and ("long acting beta agonist*" or "*beta-agonist*" or LABA* or salmeterol or serevent or formoterol or eformoterol or oxis or foradil))

Reference lists of all primary studies and review articles were reviewed for additional references. Authors of identified randomised trials were asked about knowledge of other published and unpublished studies. Manufacturers of combination single inhaler devices were contacted regarding other published and unpublished studies.

We contacted trialists and manufacturers in order to obtain unreported data and to establish whether other unpublished or ongoing studies are available for assessment. We undertook additional hand searching of clinical trial web sites (www.clinicalstudyresults.org; www.clinicaltrials.gov; www.fda.gov) and the clinical trial web sites of manufacturers (www.ctr.gsk.co.uk; www.astrazenecaclinicaltrials.com).

Searches are current to May 2009.

Data collection and analysis

Selection of studies

Following electronic literature searches, two review authors independently selected articles on the basis of title and/or abstract for full text scrutiny. The authors agreed a list of articles which were retrieved, and they subsequently assessed each reference to determine whether it met the review eligibility criteria.

Data extraction and management

One author (TJL) extracted information from each study for the following characteristics:

Design (description of randomisation, blinding, number of study centres and location, number of study withdrawals).

Participants (N, mean age, age range of the study, gender ratio, baseline lung function, % on maintenance ICS or ICS/LABA combination & average daily dose of steroid (BDP equivalent), entry criteria).

Intervention (type and dose of component ICS and LABA, dosing schedule, inhaler device, study duration & run-in)

Outcomes (type of outcome analysis, outcomes analysed, numerical data)

This information was double-checked by a second author (GF & CJC).

Assessment of risk of bias in included studies

We assessed study quality according to whether studies met the following pre-specified quality criteria (as yes, no or unclear, [Handbook 2005](#)):

1. Allocation generation - was sequence generation unpredictable?

2. Allocation concealment - were steps taken to prevent foreknowledge of treatment group assignment?

3. Blinding - were the treatments known to the patients, investigators and those assessing outcomes?

4. Withdrawal - were all participants who entered the study accounted for, and was the analysis likely to be biased by the handling of dropouts? This was considered in relation to the outcomes of oral steroid requirement and hospital admission.

5. Selective reporting - was there evidence of unreported outcome data in the trial report(s)?

6. Other bias - was the study free of other types of bias?

Additional information were sought on outcomes that were partially reported from the study sponsors.

Dealing with missing data

We contacted study sponsors for additional data which we required for our primary outcomes of oral steroid-treated exacerbations, and exacerbations leading to hospital admission.

Assessment of heterogeneity

We measured statistical variation between studies by the I square statistic ([Higgins 2003](#)). Where this exceeded 20% we also applied random effects modelling to assess whether assuming a distribution of related true effects (rather than a fixed true effect) altered the pooled effect estimate.

Data synthesis

Data were combined with RevMan 5, using a fixed effect odds ratio for dichotomous variables, and a fixed effect mean difference (calculated as either a weighted mean difference or a mean difference weighted by generic inverse variance) for continuous data variables. For the primary outcome of exacerbations we calculated NNT(benefit) for the different levels of risk as represented by control group event rates (www.nntonline.net), in order to express the number of patients needed to be treated with intervention to prevent one event from occurring.

We generated a summary of findings table for the primary outcomes in the review (exacerbations requiring oral steroids, exacerbations leading to hospital admission, and serious adverse events). We generated the table with [GRADEpro](#) software.

Subgroup analysis and investigation of heterogeneity

We intended to subgroup data from adults, adolescents and children in subgroups. Adult studies were considered as those which recruited participants from 18 upwards. Adult and adolescent studies were considered as those which recruited participants from 12 upwards. We considered participants in studies where the upper age limit was 12 years as children, and in studies where the upper age limit was 18 years as children and adolescents. Despite this categorisation we did not identify any studies performed in children less than 12 years of age.

Subgroup analyses was performed based on the severity of asthma as assessed according to international guidelines (GINA: controlled, partly controlled, uncontrolled), and trials on patients using oral steroid treatment were considered separately. We restricted subgroup analysis to our primary outcomes.

Sensitivity analysis

Sensitivity analysis was conducted on the risk of bias, where the predefined quality criteria of randomisation, blinding and withdrawal are met. We also considered the impact of dosing and in-

haler devices for both interventions. Funnel plots were inspected to assess the presence of publication bias.

R E S U L T S

Description of studies

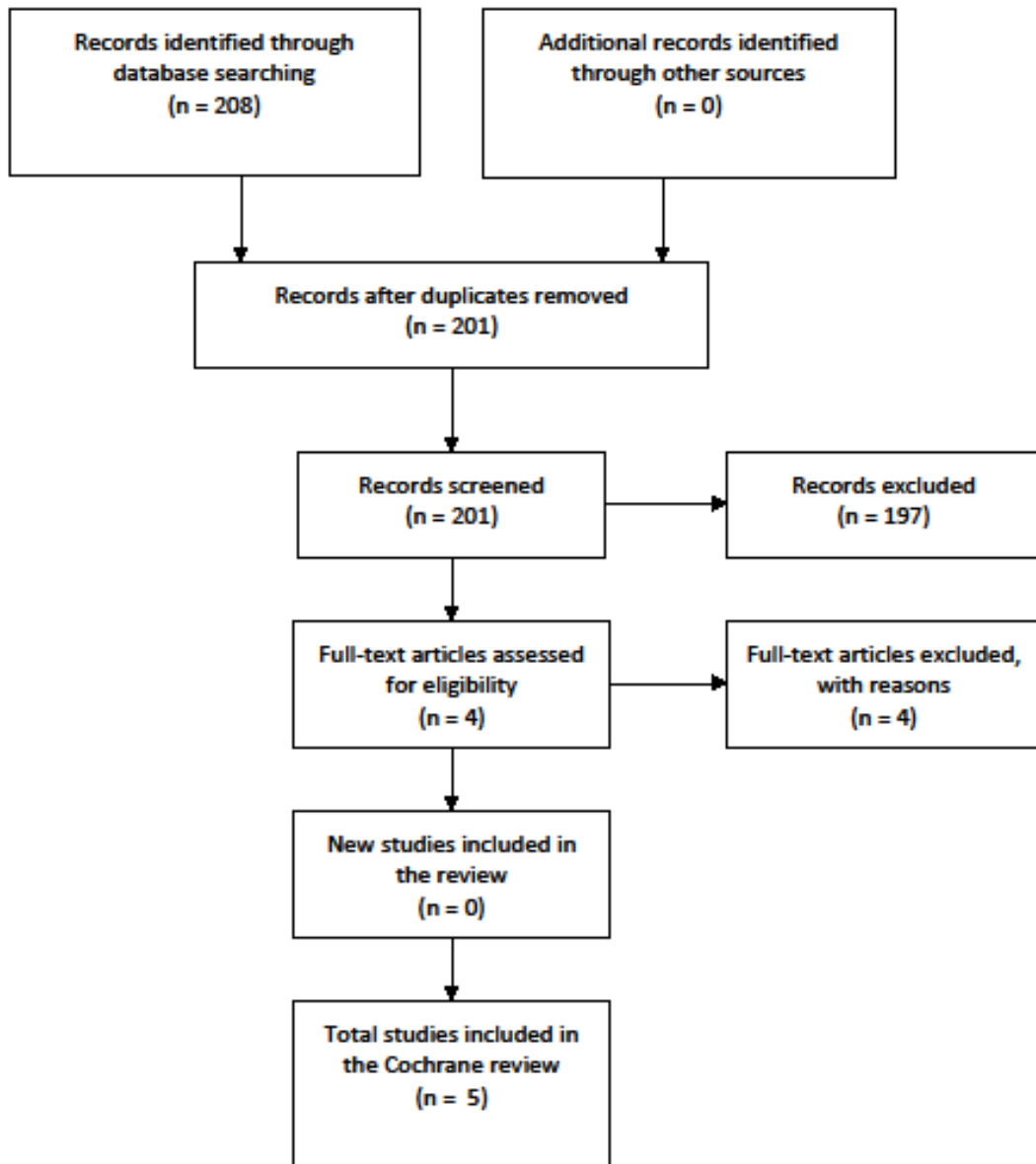
See: [Characteristics of included studies](#); [Characteristics of excluded studies](#).

Results of the search

From 747 references identified by literature searches up to May 2009, five studies (26 citations) met the entry criteria of the review. Of these, four are full-text publications, and one is available as a download from a manufacturer's web site ([SAM40048](#)).

Details of the literature search and study assessment processes for the 2009 literature search are provided in [Figure 1](#). Four studies (reported in five separate references) considered for this update failed to meet the eligibility criteria ([Adachi 2008](#); [Ambrose 2007](#); [Bleecker 2007](#); [Hampel 2007](#), see [Characteristics of excluded studies](#)). A further six references from this search were identified as additional publications from two included studies ([COMPASS](#); [Busse 2008](#)), and one excluded study ([AHEAD](#)).

Figure 1. Literature flow diagram for the review.



Included studies

Population

5537 adult and adolescent participants were recruited to the studies. The studies required participants to have a history of chronic asthma, treated with maintenance inhaled corticosteroids at moderate to high doses prior to study entry. In the five studies, participants had to be stable for one month before the run-in period. Once in the run-in phase, participants were further required to demonstrate the need for frequent reliever inhaler use. On the basis of these characteristics we adjudged the trial populations to be partly controlled, since the requirement for relief medication was in addition to chronically applied inhaled steroids (GINA). The severity of airway obstruction varied between the trials, with the participants with the lowest percentage predicted of FEV1 recruited to [SAM40048](#) (65%), [Busse 2008](#); [EXCEL](#) and [COMPASS](#) recruiting participants with moderate airway obstruction (79%, 79% and 73% respectively), and participants with milder obstruction represented in [Aalbers 2004](#) (84%).

Interventions & comparisons

Converting the inhaled steroid load to BDP equivalent indicated that the trials assessed high doses of inhaled steroids in both FP/SAL and BUD/F groups, although FP/SAL was higher in BDP equivalence terms than BUD/F (1000 versus 400-800 mcg/day). All doses were given twice daily via different inhalers (Diskus and Turbohaler for FP/SAL and BUD/F respectively). Two studies were open label ([Aalbers 2004](#); [Busse 2008](#)). In all studies the dose

of FP/SAL was 500/100 mcg/day, and that of BUD/F was 400-800/12-24 mcg/day.

Concomitant use of reliever medication was permitted in all four studies; terbutaline in [COMPASS](#), salbutamol in [Busse 2008](#) and [EXCEL](#), and terbutaline or salbutamol as preferred in [Aalbers 2004](#). In [SAM40048](#) the reliever medication was not reported.

Outcomes

Four trials measured exacerbations as oral steroid and hospitalisations ([Aalbers 2004](#); [Busse 2008](#); [EXCEL](#); [COMPASS](#)), and also gave numerical data for serious adverse events. All studies reported lung function measurements. Data on admission to hospital were made available to the review authors on request from GSK and AZ for [Aalbers 2004](#); [COMPASS](#); [EXCEL](#). We were informed verbally that exacerbations were not collected in a way that was suitable for us to use in our review in [SAM40048](#).

Excluded studies

A total of 19 studies failed to meet the review eligibility criteria. The reasons for their exclusion are listed in [Characteristics of excluded studies](#).

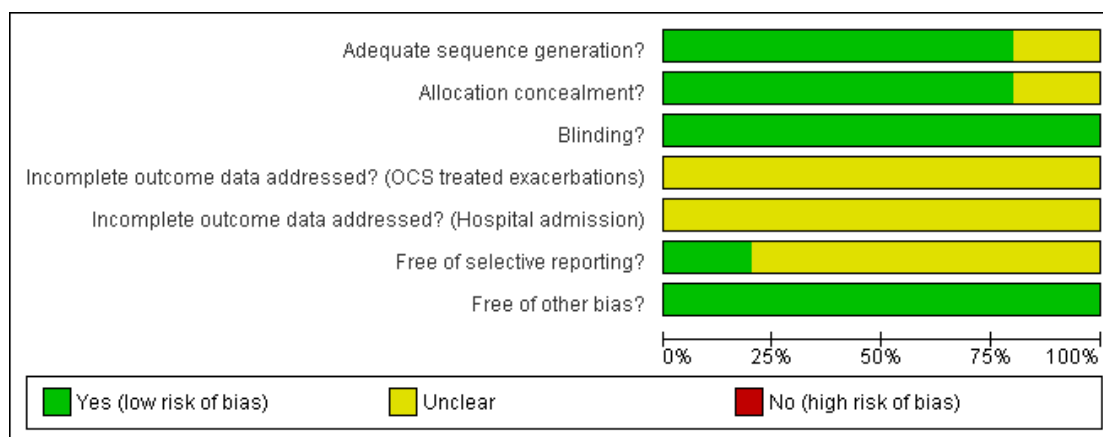
Risk of bias in included studies

See [Figure 2](#) and [Figure 3](#) for summaries of risk of bias. Additional details on items are provided in [Characteristics of included studies](#). Generally the studies were well designed although reliable assessment of selective reporting could not be ascertained. Primary outcome data were either reported in the studies or made available to the authors on request.

Figure 2. Risk of bias summary: review authors' judgments about each risk of bias item for each included study.

	Adequate sequence generation?	Allocation concealment?	Blinding?	Incomplete outcome data addressed? (OCS treated exacerbations)	Incomplete outcome data addressed? (Hospital admission)	Free of selective reporting?	Free of other bias?
Aalbers 2004	+	+	+	?	?	?	+
Busse 2008	+	+	+	?	?	?	+
COMPASS	+	+	+	?	?	+	+
EXCEL	+	+	+	?	?	?	+
SAM40048	?	?	+	?	?	?	+

Figure 3. Risk of bias graph: review authors' judgments about each risk of bias item presented as percentages across all included studies.



Allocation

The four studies available as full-text articles reported computer-generated randomisation sequences, with adequate concealment of treatment group allocation. Demographic characteristics of all four of the studies indicated that treatment groups were well balanced. Details on [SAM40048](#) were not adequately reported for us to establish the appropriateness of the concealment of allocation.

Blinding

We used outcome data from an open label phase in two studies ([Aalbers 2004](#); [Busse 2008](#)). The remaining studies used a double-dummy design to control for awareness of treatment group allocation. Blinding of outcome assessment was not reported in the studies.

Incomplete outcome data

Intention to treat analyses were used in all of the studies based on the population randomised, but explicit description of follow-up and handling of missing data were not provided.

Selective reporting

We needed to contact the study sponsors of [Aalbers 2004](#); [COMPASS](#) for data pertaining to our primary outcomes of exacerbations (AstraZeneca). The sponsors of [EXCEL](#) confirmed data

on the primary outcomes, and made available data for exacerbations leading to ED visits and admission to hospital (see [Published notes](#)).

Effects of interventions

See: [Summary of findings for the main comparison Combination fluticasone/salmeterol or budesonide/formoterol for chronic asthma in adults](#)

Using published data and unpublished data obtained through correspondence with manufacturers, we included four of the five eligible trials in the three co-primary outcomes representing 88% of randomised participants.

FP/SAL 500/100 mcg/d versus BUD/F 400-800/12-24 mcg/d

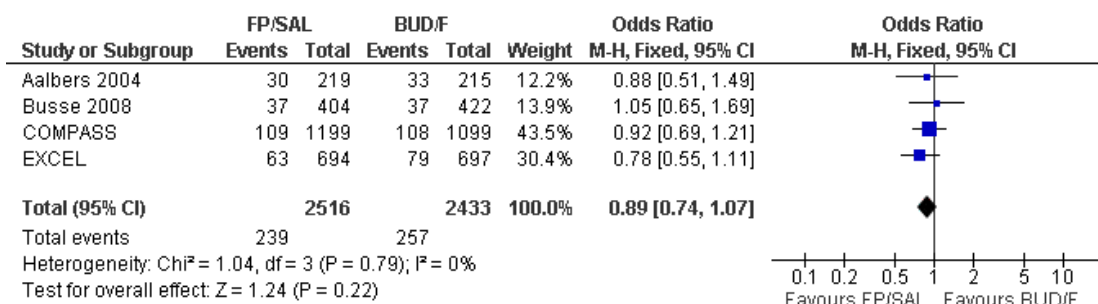
The comparisons are presented such that a reduction in the mean difference greater than 0, or an odds ratio of less than one represent a lowering for the FP/SAL group compared to the BUD/F group (the associated confidence intervals and P value indicate the statistical significance of this). In view of the absence of studies in children, the evidence we have relates to adults.

Primary outcomes

Exacerbations & asthma related serious adverse events

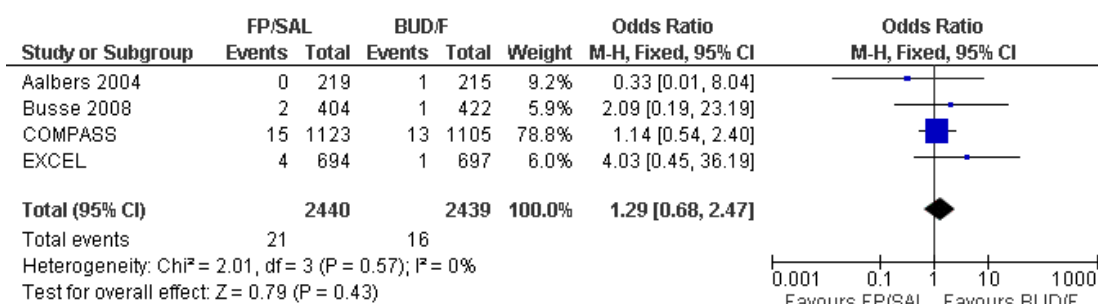
There was no significant difference in the risk of experiencing an exacerbation requiring oral-steroid treatment (four studies, OR 0.89; 95% CI 0.74 to 1.07, N = 4515 [Figure 4](#)).

Figure 4. Forest plot of comparison: I Combination fluticasone/salmeterol versus budesonide/formoterol, outcome: I.1 Participants experiencing exacerbations requiring oral steroid treatment.



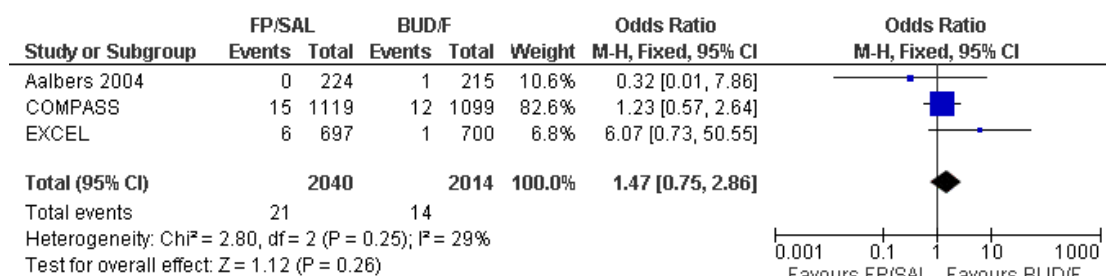
Exacerbations resulting in admission to hospital were not significantly different between FP/SAL and BUD/F (four studies, OR 1.29; 95% CI 0.68 to 2.47, N = 4053 [Figure 5](#)).

Figure 5. Forest plot of comparison: I Combination fluticasone/salmeterol versus budesonide/formoterol, outcome: I.2 Participants experiencing exacerbations requiring admission to hospital.



The risk of an asthma-related serious adverse event did not differ significantly between treatments (three studies, OR 1.47; 95% CI 0.75 to 2.86, N = 4879 [Figure 6](#)).

Figure 6. Forest plot of comparison: I Combination fluticasone/salmeterol versus budesonide/formoterol, outcome: I.3 Asthma-related serious adverse event.



The Summary of Findings table conveys the results of these outcomes as absolute effects and our assessment of the strength of the evidence ([Summary of findings for the main comparison](#)).

Secondary outcomes

Exacerbations requiring ED visit/hospital admission (composite)

There was no statistically significant difference in the odds of ED visit/admission to hospital between the treatments (four studies, OR 1.3; 95% CI 0.94 to 1.8, N = 4861, [Analysis 1.4](#)).

Diary card peak flow

There was no significant difference between treatments in mean change in morning (five studies, 2.24 L/min, 95% CI -0.24 to 4.73, N = 5101) or evening peak flow (four studies, 0.25 L/min; 95% CI -0.80 to 1.30, N = 4299).

FEV1

There was no significant difference in the change from baseline between treatments (three studies, 0 Litres; 95% CI -0.02 to 0.02, N = 4845).

Symptoms & rescue medication use

There was no significant difference between treatments in the mean change in symptom scores (three studies, -0.02; 95% CI -0.6 to 0.03, N = 3464). There was also no significant difference in change in rescue medication (three studies -0.06 puffs per day; 95% CI -0.13 to 0.02, N = 3469).

Withdrawals and tolerability

Study withdrawals were not significantly more frequent with either treatment in terms of overall discontinuations ([Analysis 1.13](#)), or when withdrawal due to adverse events or lack of efficacy were considered ([Analysis 1.14](#); [Analysis 1.15](#)). Headache, upper respiratory tract infection, dysphonia and throat irritation did not differ significantly between treatments ([Analysis 1.17](#); [Analysis 1.20](#); [Analysis 1.19](#); [Analysis 1.22](#)).

A summary of findings table has been incorporated to this version of the review. This outlines our assessment of the overall quality of the evidence based on the risk of bias assessments, availability of data, imprecision of our analyses, and size and direction of the results ([Summary of findings for the main comparison](#)). In view of the absence of studies in children, the findings of the review are directly relevant to adults with asthma.

DISCUSSION

This review has collected data from five well-designed studies randomising over 5000 patients. No studies recruited children under the age of 12 years. The dose comparisons across the studies were similar, except for [SAM40048](#) where the dose of budesonide was half of that in the other studies. Based on UK recommendations, the BUD/F dose was the maximum licensed dosing for asthma in the UK, and the FP/SAL dose is the medium dose recommended in the UK for asthma ([BNF 2007](#)). We identified three co-primary outcomes, two pertaining to different severities of asthma exacerbation (those requiring oral steroid treatment, and those leading to hospitalisation), and one relating to asthma-related serious adverse events. None of the results were statistically significant. Our assessment of the quality of the evidence for these outcomes was moderate. Findings from these three endpoints will be considered first.

Requirement for a course of oral steroid treatment is a treatment-driven rather than symptom-driven definition, but gives some in-

dication as to whether maintenance therapy reduces inflammation sufficiently to prevent requirement for additional steroid. The ratio of such events was close to 1 in the three studies, and the BUD/F event rate was similar between the trials (Aalbers 2004: 15%; Busse 2008: 9%; EXCEL: 11%; COMPASS: 10%). The lack of a statistically significant difference may reflect the effectiveness of combination therapy in reducing exacerbations when added to monotherapy ICS (Greenstone 2005).

The risk of hospitalisation did not differ significantly between therapies, although the confidence interval was wide and further evidence is necessary before a conclusion of no difference could be drawn definitively. The morbidity associated with hospital admission is considerable, and may indicate severe uncontrolled disease as well as predict future hospitalisation and mortality (Suisa 2001). Superiority of FP over BUD in dose ratio comparisons of 1:1 and 1:2 has been demonstrated for lung function endpoints, but not exacerbation rate data (Adams 2007). Our composite analysis of ED visit/hospitalisation did not show a significant difference between the treatments in contrast to a previous meta-analysis (Edwards 2007). The data for that analysis were in part based upon hospitalisation data from EXCEL and not additional ED visits from that study. Given that the data we obtained from GSK suggested parity between these event rates, we consider our data to represent a more complete assessment of the evidence available.

Based on evidence of harm, the use of LABAs as monotherapy is not recommended with serious adverse event data from previous studies implicating the bronchodilatory effects of LABAs as a possible mask for under-treated deterioration in underlying airway inflammation (Walters 2007; Cates 2008a; Cates 2008b). Serious adverse events did not occur with sufficient frequency in the studies to give precision to the results of our meta-analysis. The relative effects of either treatment in terms of serious harms remain to be fully elucidated. Based on evidence drawn from other comparisons involving adding LABA to ICS preparations, these therapies are well-tolerated (Greenstone 2005; Ni Chroinin 2005).

Neither lung function parameters, symptom scores nor rescue medication use identified statistically significant differences between treatments. Adverse event data indicated that the drugs were equally well-tolerated.

There are several limitations of the review. We limited our analyses to parallel studies on the assumption that optimum washout in steroid trials is uncertain, and that our primary outcome of exacerbations was best measured in long-term studies with a between-

patient design. We have assumed that requirement for oral steroids and admission to hospital are independent, although it is reasonable to expect that poor asthma control associated with lack of adherence to maintenance inhaled steroids is likely to predict both (Williams 2004). Assessment of patient severity was confined to GINA defined control status, and this may not be sensitive enough to discern between severities of asthma. The major limitation of the studies themselves is the absence of data in children under the age of 12 years.

AUTHORS' CONCLUSIONS

Implications for practice

The confidence intervals for our estimates in our primary outcomes include no statistically significant difference. However, the width of the confidence intervals for these endpoints also include possibly meaningful differences between the treatments in either direction and as such more evidence would help to improve their precision. Serious adverse events were too infrequent to generate findings which could be easily interpreted. Our analyses could not detect significant differences between these drugs in terms of lung function and symptoms. These observations pertain to adults and adolescents whose asthma is not adequately controlled with high doses of inhaled steroids.

Implications for research

The findings of our review would be strengthened by more data on exacerbations from further trials, in particular trials that include visits to emergency departments and hospitalisation. Evidence is required to establish the ratio of serious adverse events between these two drugs. Evidence for the effects of these drugs in children is also required.

ACKNOWLEDGEMENTS

We thank Susan Hansen for assistance in designing a search strategy and for electronic literature searching, and Veronica Stewart for assistance in retrieving the papers. We are grateful to René Aalbers, Jeff Fletcher and Steve Edwards from AZ in our efforts to obtain data for the Aalbers 2004 and COMPASS. We are grateful to Pim Kon and Richard Fellows from GSK for assisting us in obtaining ED visit data for EXCEL.

REFERENCES

References to studies included in this review

Aalbers 2004 {published and unpublished data}

* Aalbers R, Backer V, Kava TT, 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 & Opinion* 2004;**20**(2):225–40.

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 Society*. 2003. [: p–2–20]

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.

Astrazenca (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. AstraZeneca Clinical Trials Register issue <http://www.astrazenecaclinicaltrials.com/Article/512577.aspx> [Accessed 19/10/2007].

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). *European Respiratory Journal* 2004;**24**(Suppl 48):508s.

Busse 2008 {published and unpublished data}

Ambrose H, Lawrance R, Goldman M. Beta-adrenergic receptor for Gly16Arg variation: Effect on response to Budesonide/Formoterol or Fluticasone/Salmeterol in asthma patients. *Chest* 2007;**478**s.

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. AstraZeneca Clinical Trials Register (<http://www.astrazenecaclinicaltrials.com>) 2006 (accessed 13th March 2008).

Bleecker E, Postma DS, Lawrance RM, Meyers DA, Ambrose HJ, Goldman M. Effect of ADRB2 polymorphisms on response to long-acting β_2 -agonist therapy: a pharmacogenetic analysis of two randomised studies. *Lancet* 2008;**370**(9605):2118–25.

Bleecker ER, Lawrance R, Ambrose H, Goldman M. Beta2-adrenergic receptor Gly16Arg variation: effect on response to

budesonide/formoterol (BUD/FM) or budesonide (BUD; post-formoterol) in children and adolescents with asthma [Abstract]. American Thoracic Society International Conference, May 16-21. 2008.

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). <http://www.abstracts2view.com/ats07> (accessed 13th March 2008) 2007: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; Vol. 121, issue 6:1407–14.

O'Connor RD, Patrick DL, Parasuraman MB, Martin P, Goldman M. Patient satisfaction during treatment 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) [Abstract]. American Thoracic Society International Conference, May 16-21, 2008, Toronto. 2008:A609.

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). <http://www.abstracts2view.com/ats07> (accessed 13th March 2008) 2007: A192.

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. <http://www.abstracts2view.com/ats07> (accessed 13th March 2008) 2007:A191.

COMPASS {published and unpublished data}

AstraZeneca. SD-039-0735. Comparison of the efficacy and safety of one inhalation of Symbicort® Turbuhaler® 160/4.5 μ g bid plus as-needed with two inhalations of Seretide™ Evohaler™ 25/125 μ g bid plus Terbutaline Turbuhaler® 0.4 mg as-needed, and one inhalation of Symbicort® Turbuhaler® 320/9 μ g 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.. AstraZeneca Clinical Trials 2009.

AstraZeneca. SYM/050/DEC2007. Data on File.

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.

Buhl R, Kuna P. Does the choice of ICS/LABA regimen influence exacerbation rates in asthma patients with high as needed use?

[Abstract]. *European Respiratory Journal* 2007;**30**(Suppl 51):617s.

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

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

EXCEL {published and unpublished data}

Dahl OR, 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, 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, Ringdal N, Gor D, Jones M. Salmeterol/fluticasone (SFC) reduces moderate/severe exacerbations more effectively than formoterol/budesonide 9FBC with sustained maintenance therapy EXCEL. American Thoracic Society International Conference; May 20–25; San Diego, California. 2005: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 50/250ig 1 inhalation bd and formoterol/budesonide Breath-Actuated Dry Powder Inhaler (BADPI) 4.5/160ig 2 inhalations bd in subjects with moderate to severe asthma. GlaxoSmithKline Clinical Trials Register issue http://ctr.gsk.co.uk/Summary/fluticasone_salmeterol/IV_SAM40040.pdf [Accessed 19/10/2007].

SAM40048 {unpublished data only}

GlaxoSmithKline (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 turbuhaler administered twice daily in patients with moderate bronchial asthma. GlaxoSmithKline Clinical Trial Register 2005, issue http://ctr.gsk.co.uk/Summary/fluticasone_salmeterol/IV_SAM40048.pdf [Accessed 19/10/2007].

References to studies excluded from this review

Adachi 2008 {published data only}

Adachi M, Aizawa H, Ishihara K, Ohta K, Sano Y, Taniguchi H, et al. Comparison of salmeterol/fluticasone propionate (FP) combination with FP+sustained release theophylline in moderate asthma patients. *Respiratory Medicine* 2008;**102**(7):1055–64.

AHEAD {published data only}

AstraZeneca. Efficacy and safety of Symbicort® Turbuhaler® 160/4.5 µg/inhalation, two inhalations twice daily plus as-needed compared with Seretide™ Diskus™ 50/500 µg/inhalation, one inhalation twice daily plus terbutaline Turbuhaler 0.4 mg/inhalation as-needed - a 6-month, randomised, double-blind, parallel-group, active controlled, multinational phase IIIB study in

adult and adolescent patients with persistent asthma (AHEAD). www.clinicaltrials.gov 2005.

AstraZeneca (D5890C00002). Efficacy and safety of Symbicort® Turbuhaler® 160/4.5 mcg/inhalation, two inhalations twice daily plus as-needed compared with Seretide Diskus 50/500 mcg/inhalation, one inhalation twice daily plus terbutaline Turbuhaler 0.4 mg/inhalation as-needed - a 6-month, randomised, double-blind, parallel-group, active controlled, multinational phase IIIB study in adult and adolescent patients with persistent asthma. <http://www.astrazenecaclinicaltrials.com> (accessed 12th May 2008) 2007.

Bousquet J, Boulet L-P. Budesonide/formoterol as maintenance and reliever therapy in uncontrolled asthma compared with high dose salmeterol/fluticasone: the AHEAD double blind study [Abstract]. *European Respiratory Journal* 2007;**30**(Suppl 51):358s.

* Bousquet J, Boulet L-P, Peters MJ, Magnussen H, Quirarte J, Martínez-Aguilar NE, Carlshamer A. Budesonide/formoterol for maintenance and relief in uncontrolled asthma versus high-dose salmeterol/fluticasone. *Respiratory Medicine* 2007;**101**(12):2437–46.

Bousquet J, Miravittles M, Wren A. Budesonide/formoterol provides better efficacy at a lower or similar cost as compared to high dose salmeterol fluticasone treatment [Abstract]. *European Respiratory Journal* 2007;**30**(Suppl 51):193s.

ALLIANCE {published data only}

* Molimard M, Le Gros V, Bourdeix I. Efficacy of formoterol and beclomethasone dry powder capsules in asthmatic patients sub-optimally controlled with fixed combination formoterol-budesonide ALLIANCE study. *European Respiratory Journal* 2004;**24**(Suppl 48):261s.

Ambrose 2007 {published data only}

Ambrose H, Lawrance R, Goldman M. Beta-adrenergic receptor gly16arg variation: effect on response to budesonide/formoterol or budesonide (post-formoterol) in asthma patient. *Chest* 2007;**132**(4):436a.

Bleecker 2007 {published data only}

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

Brambilla 2003 {published data only}

Brambilla C, Le Gros V, Bourdeix I. Efficacy of Foradil in Asthma (EFORA) French Study Group. Formoterol 12 microg BID administered via single-dose dry powder inhaler in adults with asthma suboptimally controlled with salmeterol or on-demand salbutamol: a multicenter, randomized, open-label, parallel-group study. *Clinical Therapeutics* 2003;**25**(7):2022–36.

CONCEPT {published data only}

Fitzgerald JM, Boulet LP, Follows R. Improved control of symptoms, exacerbations and quality of life with stable dose treatment with salmeterol/fluticasone (SFC) compared with adjustable maintenance dosing with formoterol/budesonide. XIX World Allergy Organization Congress, June 26–July 1, Munich, Germany. 2005:Abstract 289.

* FitzGerald JM, Boulet LP, Follows RMA. The CONCEPT trial: A 1-year, multicenter, randomized, double-blind, double-dummy comparison of a stable dosing regimen of salmeterol/fluticasone

propionate with an adjustable maintenance dosing regimen of formoterol/ budesonide in adults with persistent asthma. *Clinical Therapeutics* 2005;**27**(4):393–406.

Fitzgerald M, Boulet LP, Pieters WR. Improved control of symptoms and exacerbations with stable dose treatment with salmeterol/fluticasone propionate (SFC) compared with adjustable maintenance dosing with formoterol/budesonide (FBC). *European Respiratory Journal* 2005; Vol. 26, issue Suppl 49:Abstract No. 2765.

GlaxoSmithKline (SAM40056). A randomised, double-blind, double-dummy, 52 week, parallel group study of a standard dosing regimen with salmeterol/fluticasone combination 50/250mcg bid (via the DISKUS/ACCUHALER inhaler) versus a symptom-driven, variable dosing regimen with formoterol/budesonide combination 6/200mcg (via a breath-actuated dry powder reservoir inhaler) in adult asthmatics. GlaxoSmithKline Clinical Trial Register 2005, issue http://ctr.gsk.co.uk/Summary/fluticasone_salmeterol/IV_SAM40056.pdf [Accessed 19/10/2007].

Price DB, Williams AE, Yoxall S. Salmeterol/fluticasone stable-dose treatment compared with formoterol/budesonide adjustable maintenance dosing: impact on health-related quality of life. *Respiratory Research* 2007;**8**:46.

Creemers 2002 *{published data only}*

Creemers JP, Bantje T, Eliraz A, Ekstrom T, Buhl R. Budesonide/formoterol in a single inhaler once or twice daily provides better control than inhaled fluticasone or budesonide alone in patients with moderate persistent asthma. *European Respiratory Journal* 2002;**20**(Suppl 38):387s.

EDICT *{published data only}*

Alonso JF, Badiola C, Kielhorn A. Economic evaluation of salmeterol/fluticasone combination versus budesonide plus formoterol in Spain. *European Respiratory Journal* 2001;**18**(Suppl 33):49s.

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

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.

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]. American Thoracic Society 99th International Conference. 2003: D034 Poster C43.

Price MJ, Karia N, Whitehead P. Comparison of asthma treatment costs of salmeterol/fluticasone combination product 50/250mcg bid with budesonide 800mcg plus formoterol 12mcg bid. *European Respiratory Journal* 2000;**16**(Suppl 31):353s.

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. *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.

SAS40002 (SERL05). A randomised, double-blind, double-dummy, parallel-group comparison of Seretide (Diskus/Accuhaler) 250/50 µg bid with Budesonide 800 µg bid plus Formoterol 12.0 µg bid (both via breath-actuated dry powder inhaler) in adolescent and adult moderate-severe asthmatics. GlaxoSmithKline Clinical Trials Register issue http://ctr.gsk.co.uk/Summary/fluticasone_salmeterol/III_SAS40002.pdf [Accessed 19/10/2007].

Hampel 2007 *{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.

Hampel Jr FC, Martin P, Mezzanotte WS. Early bronchodilatory effects of budesonide formoterol pressurized metered dose inhaler (pMDI) compared with fluticasone propionate salmeterol dry powder inhaler (DPI) and albuterol pMDI in adults with asthma [Abstract]. *Journal of Allergy and Clinical Immunology* 2008;**121**(2 Suppl 1):S220.

Jenkins 2000 *{published and unpublished data}*

Becker I, Kielborn A, Price MJ, Volmer T, Lloyd AC. Cost-effectiveness of salmeterol/fluticasone combination product and budesonide in asthma patients in Germany. *European Respiratory Society*; 1999 Oct 9-13; Madrid, Spain. 1999:854.

* Jenkins C, Woolcock AJ, Saarelainen P, Lundbaack B James MH. Salmeterol /fluticasone propionate combination therapy 50/250mcgs twice daily is more effective than budesonide 800 twice daily in treating moderate to severe asthma.. *Respiratory Medicine* 2000;**94**:715–23.

Jenkins C, Woolcock A James M. Superior overall control of moderate to severe asthma with salmeterol/fluticasone propionate (FP) combination (50/250 mcg bd) compared with three-fold-higher dose of budesonide (800mcg bd). *European Respiratory Journal*. 2000; Vol. 16, issue Suppl 31:456s.

Lundback B, Jenkins C, Price MJ, Thwaites RM. Cost-effectiveness of salmeterol/fluticasone propionate combination product 50/250 microg twice daily and budesonide 800 microg twice daily in the treatment of adults and adolescents with asthma. *Respiratory Medicine* 2000;**94**(7):724–32.

Lundback B, Ronmark E, Jonsson AC, et al. Treatment effectiveness and exacerbations during one year with Seretide compared to fluticasone propionate and salmeterol in mild to moderate asthma. *European Respiratory Journal* 2001; Vol. 18, issue Suppl 33:176s.

SAS40006. A randomised, double-blind, double-dummy, parallel group comparison of Seretide Diskus/Accuhaler (50/250µg strength) b.i.d. with Budesonide 800µg b.i.d. in adolescents and adults with reversible airways obstruction. <http://www.clinicalstudyresults.org> issue http://ctr.gsk.co.uk/Summary/fluticasone_salmeterol/IV_SAS40006.pdf [Accessed 19/10/2007].

Kaik 2002 *{published data only}*

Kaik G, Kottakis I, Anagnostopoulou O, Sichletidis L, Bachlitzanakis N, D'Amato M, et al. Sequential flexible therapy with formoterol (Foradil®) plus budesonide (Miflonide®) versus a fixed combination of salmeterol and fluticasone (Seretide®) in asthma self-management. European Respiratory Society Annual Congress. 2002:abstract nr: P2407.

Lee 2003 *{published data only}*

* Lee DK, Jackson CM, Currie GP, Cockburn WJ, Lipworth B J. Comparison of combination inhalers versus inhaled corticosteroids alone in moderate persistent asthma. *British Journal of Clinical Pharmacology* 2003;**56**(5):494–500.

Lee DKC, Currie GP, Cockburn WJ, Lipworth BJ. Budesonide/formoterol and fluticasone/salmeterol combination inhalers delay immediate albuterol recovery following acute bronchoconstriction. *Journal of Allergy and Clinical Immunology* 2003;**111**(Suppl 2):202s. Lee DKC, Currie GP, Cockburn WJ, Lipworth BJ. Comparison of budesonide/formoterol versus fluticasone/salmeterol combination inhalers in moderate persistent asthma. American Thoracic Society 99th International Conference. 2003:D094 Poster 613.

Lotvall 2002 *{published data only}*

Lötvall J, van der Woude HJ, Palmqvist M, Arvidsson P, Beckman O, Boersma M, et al. More rapid onset of action of budesonide/formoterol (Symbicort®) than salmeterol/fluticasone (seretide™). *American Journal of Respiratory and Critical Care Medicine* 2002;**165**(Suppl 8):A567.

Palmqvist 2001 *{published data only}*

AstraZeneca (SD-039-0617). Onset of Action of Symbicort Turbuhaler® compared with Seretide Diskus™ in asthmatic patients. <http://www.astrazenecaclinicaltrials.com/article/512581.aspx> [Accessed 19/10/2007].

* Palmqvist M, Arvidsson P, Beckman O, Peterson S, Lotvall J. Onset of bronchodilation of budesonide/formoterol versus salmeterol/fluticasone in single inhalers. *Pulmonary Pharmacology & Therapeutics* 2001;**14**(1):29–34.

SAM40042 *{unpublished data only}*

GlaxoSmithKline (SAM40042). A double-blind, double-dummy, randomised, cross-over study to compare the bronchodilator effect of SERETID ACCUHALER 50/100mcg and formoterol/budesonide combination breath-actuated dry powder inhaler 6/200mcg in subjects with asthma following a single dose and after 4 weeks of regular treatment. GlaxoSmithKline Clinical Trial Register issue http://ctr.gsk.co.uk/Summary/fluticasone_salmeterol/IV_SAM40042.pdf [Accessed 19/10/2007].

SAM40047 *{unpublished data only}*

GlaxoSmithKline (SAM40047). Duration of action of single inhalations of the salmeterol/fluticasone combination product (50/250µg) in comparison with the formoterol/budesonide combination product (4.5/160µg) in patients with moderate asthma - a randomised, double-blind, double-dummy, crossover study. GlaxoSmithKline Clinical Trial Register issue http://ctr.gsk.co.uk/Summary/fluticasone_salmeterol/IV_SAM40047.pdf [Accessed 19/10/2007].

SAM40062 *{published data only}*

GlaxoSmithKline (SAM40062). A single-centre, single-dose, double-blind, double-dummy, placebo-controlled, randomised,

three-way crossover study to compare the duration of action of SERETIDE DISKUS 50/100mcg versus formoterol/budesonide combination 4.5/160mcg breath-actuated dry powder inhaler (BADPI) in subjects with asthma. GlaxoSmithKline Clinical Trial Register 2005, issue http://ctr.gsk.co.uk/Summary/fluticasone_salmeterol/IV_SAM40062.pdf [Accessed 19/10/2007].

Vogelmeier 2005 *{published data only}*

D'Urzo A, Vogeimeier C, Jaspal M, Merino JM, Boulet S. Symbicort (budesonide/formoterol) for both maintenance and relief reduces the exacerbation burden compared with titration of seretide (salmeterol/fluticasone) in patients with asthma, a real life study. American Thoracic Society International Conference; May 20–25; San Diego, California. 2005:Poster G24. Johansson G, Andreasson EB, Larsson PE, Vogelmeier CF. Cost effectiveness of budesonide/formoterol for maintenance and reliever therapy versus salmeterol/fluticasone plus salbutamol in the treatment of asthma. *Pharmacoeconomics* 2006;**24**(7):695–708. Miller E, Sears MR, McIvor A, Liovas A. Canadian economic evaluation of budesonide-formoterol as maintenance and reliever treatment in patients with moderate to severe asthma. *Canadian Respiratory Journal* 2007;**14**(5):269–75. Vogelmeier C, D'Urzo A. Maintenance plus as-needed budesonide/formoterol vs salmeterol/fluticasone in a real-life setting. *European Respiratory Journal* 2006; Vol. 26, issue Suppl 49:Ab no: 2770. * Vogelmeier C, D'Urzo A, Pauwels R, Merino JM, Jaspal M, Boutet S, et al. Budesonide/formoterol maintenance and reliever therapy: An effective asthma treatment option?. *European Respiratory Journal* 2005;**26**(5):819–28.

Additional references**Adams 2007**

Adams N, Bestall JM, Lasserson TJ, Jones PW. Fluticasone versus beclomethasone or budesonide for chronic asthma in adults and children. *Cochrane Database of Systematic Reviews* 2007, Issue 4. [Art. No.: CD002310. DOI: 10.1002/14651858.CD002310.pub4]

Adams 2008

Adams NP, Bestall JC, Lasserson TJ, Jones PW, Cates CJ. Fluticasone versus placebo for chronic asthma in adults and children. *Cochrane Database of Systematic Reviews* 2008, Issue 4. [Art. No.: CD003135. DOI: 10.1002/14651858.CD003135.pub4]

BNF 2007

British National Formulary. www.bnf.org 2007, issue 53.

Cates 2008a

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

Cates 2008b

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

Cazzola 2002

Cazzola M, Grella E, Matera MG, Mazzarella G, Marsico SA. Onset of action following formoterol Turbuhaler and salbutamol pMDI in reversible chronic airway obstruction. *Pulmonary Pharmacology and Therapeutics* 2002;**15**(2):97–102.

Edwards 2007

Edwards SJ, Gruffydd-Jones K, Ryan DP. Systematic review and meta-analysis of budesonide/formoterol in a single inhaler. *Current Medical Research and Opinion* 2007;**23**(8):1809–20.

Gibson 2005

Gibson PG, Powell H, Ducharme F. Long-acting beta2-agonists as an inhaled corticosteroid-sparing agent for chronic asthma in adults and children. *Cochrane Database of Systematic Reviews* 2005, Issue 4. [Art. No.: CD005076. DOI: 10.1002/14651858.CD005076.pub2]

GINA

From the Global Strategy for Asthma Management and Prevention, Global Initiative for Asthma (GINA). <http://www.ginasthma.org> 2006.

Greenstone 2005

Greenstone IR, Ni Chroinin MN, Masse V, Danish A, Magdalinos H, Zhang X, et al. Combination of inhaled long-acting beta2-agonists and inhaled steroids versus higher dose of inhaled steroids in children and adults with persistent asthma. *Cochrane Database of Systematic Reviews* 2005, Issue 4. [Art. No.: CD005533. DOI: 10.1002/14651858.CD005533]

Handbook 2005

Higgins JPT, Green S, editors. Assessment of study quality. *Cochrane Handbook for Systematic Reviews of Interventions* 4.2.5 [updated May 2005] <http://www.cochrane.org/resources/handbook/hbook.htm> (accessed 25th January 2007). Chichester: John Wiley & Sons Ltd, 2005.

Higgins 2003

Higgins JPT, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. *British Medical Journal* 2003;**327**: 557–60.

Ni Chroinin 2005

Ni Chroinin M, Greenstone IR, Danish A, Magdolinos H, Masse V, Zhang X, et al. Long-acting beta2-agonists versus placebo in addition to inhaled corticosteroids in children and adults with chronic asthma. *Cochrane Database of Systematic Reviews* 2005, Issue 4. [Art. No.: CD005535. DOI: 10.1002/14651858.CD005535]

Palmqvist 1997

Palmqvist M, Persson G, Lazer L, Rosenborg J, Larsson P, Lotvall J. Inhaled dry-powder formoterol and salmeterol in asthmatic patients: onset of action, duration of effect and potency. *European Respiratory Journal* 1997;**10**(11):2484–9.

Suissa 2001

Suissa S, Ernst P. Inhaled corticosteroids: impact on asthma morbidity and mortality. *Journal of Allergy and Clinical Immunology* 2001;**107**(6):937–44.

van Noord 1996

van Noord J, Smeets JJ, Raaijmakers JA, Bommer AM, Maesen FP. Salmeterol versus formoterol in patients with moderately severe asthma: onset and duration of action. *European Respiratory Journal* 1996;**9**:1684–8.

Walters 2007

Walters EH, Gibson PG, Lasserson TJ, Walters JA. Long-acting beta2-agonists for chronic asthma in adults and children where background therapy contains varied or no inhaled corticosteroid. *Cochrane Database of Systematic Reviews* 2007, Issue 1. [Art. No.: CD001385. DOI: 10.1002/14651858.CD001385.pub2]

Williams 2004

Williams LK, Pladevall M, Xi H, Peterson EL, Joseph C, Lafata JE, et al. Relationship between adherence to inhaled corticosteroids and poor outcomes among adults with asthma. *Journal of Allergy and Clinical Immunology* 2004;**114**(6):1288–93.

www.nntonline.net

Cates C. Visual Rx. www.nntonline.net 2001.

* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

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

Aalbers 2004

Methods	Randomised, parallel group trial. Open label design with adjustable dosing criteria. 93 centres in Denmark, Finland, Germany, Norway, Sweden, Netherlands. Description of withdrawals: Stated.
Participants	N SCREENED: Not reported (1044 enrolled in run-in period) N RANDOMISED: 658: FPS fixed dose: 224; BDF fixed dose: 215; BDF adjustable maintenance dose: 219 (not included in this review) N COMPLETED: 383 M= 205 F= 234 MEAN AGE: 46 BASELINE CHARACTERISTICS: FEV1 % predicted: 84; PEF L/min: 468; % combination LABA/ICS treatment at entry: 45; asthma duration: 12; Average ICS dose (BDP equivalent): 735 GINA status: mild persistent INCLUSION CRITERIA: >12 years; minimum 6 months asthma duration (ATS definition); FEV1 predicted >50%; ICS use >3 months; stable dose +/- LABA; Post-run-in entry criteria: symptom score >1 on at least 4 of last 7 days of run-in period; mean PEF of 50-85% predicted; use of PEF meter to record DC data EXCLUSION CRITERIA: Respiratory infection <4 weeks prior to study entry; smoking history >10 pack years; use of systemic steroids within 4 weeks of study entry; significant co-morbidities.
Interventions	1. Combination fluticasone and salmeterol 250/50 mcg bid (double-blind phase); 250/50 bid fixed (open label phase). BDP equivalent 1000 mcg. 2. Combination budesonide and formoterol 400/12mcg bid (double-blind phase); 400/12 bid fixed (open label phase). BDP equivalent 800 mcg. 3. Combination budesonide and formoterol 320/9 mcg bid (double-blind phase); 320/9 bid or 160/4.5 bid plus temporary increase if needed (open label period). BDP equivalent 800 mcg. DELIVERY DEVICE: BUD/F: Turbuhaler; FP/SAL: Diskus TREATMENT PERIOD: Double-blind fixed dose period: 4 weeks; open label period: 24 weeks RUN-IN: 10-14 days on ICS only RESCUE: Terbutaline or salbutamol as preferred
Outcomes	Primary outcome: Well controlled asthma week Secondary outcomes: Am PEF; pm PEF; FEV1; rescue medication use; symptoms; exacerbations (requiring OCS treatment on >3 days; hospitalisation or ER treatment)

Aalbers 2004 (Continued)

Notes	DOSE ADJUSTMENT CRITERIA: Step down to one inhalation bid if symptoms controlled for last week of double-blind period; increase to up to four inhalations bid (for 7-14 days) of symptomatic over last week of double-blind period. Study sponsors: AstraZeneca	
Risk of bias		
Item	Authors' judgement	Description
Adequate sequence generation?	Yes	'The randomisation schedule was generated using a computer programme by a statistician (...) Patients were consecutively allocated to the lowest available patient number and were randomised strictly sequentially in blocks.'
Allocation concealment?	Yes	Third party not involved with primary study.
Blinding? OCS treated exacerbations & hospitalisation	Yes	Open label study design not a threat to primary outcomes in this review.
Incomplete outcome data addressed? OCS treated exacerbations	Unclear	ITT analysis described; no explicit details on how withdrawals were handled
Incomplete outcome data addressed? Hospital admission	Unclear	ITT analysis described; no explicit details on how withdrawals were handled
Free of selective reporting?	Unclear	Unable to ascertain this reliably
Free of other bias?	Yes	

Busse 2008

Methods	Randomised, parallel group open label design with adjustable dosing criteria (from month 2 onwards). Participants randomised 2:1 to receive fixed dose BUD/F or FP/SAL. Subsequently BUD/F treated participants were re-randomised to continue with fixed dose regimen or adjustable maintenance dosing. 145 centres in USA Description of withdrawals: stated
Participants	N SCREENED: 2080 N RANDOMISED: 1225 N COMPLETED: 1052 M= 490 F= 735 MEAN AGE: 39

	<p>BASELINE CHARACTERISTICS: FEV1 79% predicted INCLUSION CRITERIA: >12 years; ATS defined asthma for 6 months; stable condition; pre-bronchodilator FEV1 \geq50% predicted; maintained on a daily medium-dose ICS or ICS/LABA combination for 12 weeks or longer before screening. EXCLUSION CRITERIA: Systemic corticosteroid use within 30 days; 20 pack-year or longer smoking history; significant disease, respiratory tract infection, or illness that might interfere with lung function/study participation.</p>	
Interventions	<p>1. Combination fluticasone and salmeterol 250/50mcg BID 2. Combination budesonide and formoterol 400/12mcg BID DELIVERY DEVICE: BUD/F: MDI; FP/SAL: DPI TREATMENT PERIOD: 7 months RUN-IN: 10-14 days RESCUE: prn SABA</p>	
Outcomes	<p>Primary outcome: Time to first exacerbation Secondary outcomes: Exacerbations requiring OCS; hospitalisation; ED visits; FEV1; am PEF; symptoms; rescue medication use; adverse events; withdrawals</p>	
Notes	<p>Study sponsors: AstraZeneca</p>	
Risk of bias		
Item	Authors' judgement	Description
Adequate sequence generation?	Yes	Computer generated randomisation sequence.
Allocation concealment?	Yes	Third party not involved with primary study
Blinding? OCS treated exacerbations & hospitalisation	Yes	Open label study design not a threat to primary outcomes in this review
Incomplete outcome data addressed? OCS treated exacerbations	Unclear	Intention to treat population described as: 'Efficacy analyses included randomized patients who received 1 or more doses of randomized study medication and contributed data sufficient to calculate 1 or more primary or secondary efficacy end points.'
Incomplete outcome data addressed? Hospital admission	Unclear	Intention to treat population described as: 'Efficacy analyses included randomized patients who received 1 or more doses of randomized study medication and contributed data sufficient to calculate 1 or more primary or secondary efficacy end points.'

Busse 2008 (Continued)

Free of selective reporting?	Unclear	Unable to ascertain this reliably.
Free of other bias?	Yes	

COMPASS

Methods	Randomised, parallel group trial. Double-blind, treble-dummy design. 235 centres in 16 countries. Description of withdrawals: Stated
Participants	N SCREENED: Not reported (4399 enrolled) N RANDOMISED: 2228 (two treatment groups: FPS: 1123; BDF: 1105; one treatment group not considered by this review: BDF (plus BDF as needed): 1107). N COMPLETED: 2120 M= 932 F= 1296 MEAN AGE: 38 (N 12-17 years: 424; >18 years: 1696) BASELINE CHARACTERISTICS: FEV1 predicted: 73%; mean ICS consumption at baseline: 747mcg/d; INCLUSION CRITERIA: >12 years; ATS defined asthma for >6 months; use of ICS >3 months (500mcg/d FP or equivalent); >50% predicted FEV1; >1 exacerbation in previous 12 months; use of reliever medication >5 days of previous 7 during run-in. EXCLUSION CRITERIA: >puffs/d rescue medication on any day of run-in; asthma exacerbation during run-in; use of systemic corticosteroids/respiratory infection affecting asthma control within 30 days of study entry.
Interventions	1. Combination fluticasone and salmeterol 250/50 mcg bid. BDP equivalent 1000 mcg 2. Combination budesonide and formoterol 400/12 mcg bid. BDP equivalent 800 mcg 3. Combination budesonide/formoterol 200/6mcg bid (plus additional puffs as required) DELIVERY DEVICE: FPS: MDI; BDF: DPI TREATMENT PERIOD: 24 weeks RUN-IN: 2 weeks - regular ICS therapy plus terbutaline prn RESCUE: Terbutaline
Outcomes	Primary outcome: Time to first severe exacerbation Secondary outcomes: Exacerbations; lung function (FEV1; diary card PEF); rescue medication use; symptom scores”
Notes	Dose adjustment criteria: Symptoms and rescue medication use determined whether treatment should be increased. If absence of symptoms & rescue medication use (>/= 6 puffs/d or nocturnal symptoms) then maintenance treatment was stepped down Study sponsors: AstraZeneca

Risk of bias

Item	Authors' judgement	Description
------	--------------------	-------------

COMPASS (Continued)

Adequate sequence generation?	Yes	'The randomisation schedule was computer-generated at AstraZeneca Research and Development, Charnwood, UK. Within each centre, patients were randomised strictly sequentially as they became eligible.'
Allocation concealment?	Yes	Third party not involved in the primary study. 'Individual treatment codes and code envelopes (indicating the treatment allocation for each randomised patient) were provided, but code envelopes were to be opened only in case of medical emergencies.'
Blinding? OCS treated exacerbations & hospitalisation	Yes	Participants and investigators blinded to treatment group assignment. Blinding achieved with treble-dummy design; participants given three devices (two matched for maintenance administration of drug and one as reliever).
Incomplete outcome data addressed? OCS treated exacerbations	Unclear	ITT analysis described. Explicit details of how withdrawals handled were not described
Incomplete outcome data addressed? Hospital admission	Unclear	ITT analysis described. Explicit details of how withdrawals handled were not described
Free of selective reporting?	Yes	Unable to ascertain this reliably.
Free of other bias?	Yes	

EXCEL

Methods	Randomised, parallel group trial. Double-blind, double-dummy design. 178 centres in 18 countries. Description of withdrawals: Stated
Participants	N SCREENED: 1769 N RANDOMISED: 1397 (FPS: 694; BDF: 697) N COMPLETED: 1258 M= 595 F= 796

EXCEL (Continued)

	<p>MEAN AGE: 46 BASELINE CHARACTERISTICS: FEV1 predicted: 79%; 353 L/min am PEF INCLUSION CRITERIA: >18 years; clinical history of asthma (>6 months); 1000-2000mcg/d BDP equivalent; reversibility of 12% & 200mL or more post SABA; 2 or more episodes of asthma during day/night on 4 of last 7 days of run-in. EXCLUSION: Upper/lower RTI; hospitalisation with asthma in 4 weeks prior to baseline visit; oral steroids within 4 weeks/depot steroids within 12 weeks of baseline visit; FEV1 <50% predicted; smoking history of >10 pack years</p>
Interventions	<p>1. Combination fluticasone and salmeterol 250/50 mcg bid (+ placebo turbuhaler). BDP equivalent 1000 mcg. 2. Combination budesonide and formoterol 400/12 mcg bid (+ placebo Diskus). BDP equivalent 800 mcg. DELIVERY: FPS: Diskus; BDF: Turbuhaler TREATMENT PERIOD: 24 weeks RUN-IN: ICS + salbutamol prn (2 weeks) RESCUE: Salbutamol</p>
Outcomes	<p>Primary outcome: rate of exacerbations Secondary outcomes: Exacerbations (use of oral steroids; hospitalisations); asthma symptoms; rescue medication use; am PEF; pm PEF; FEV1; withdrawals; adverse events</p>
Notes	<p>Study sponsors: GSK</p>

Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	Yes	'Patients 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?	Yes	Third party not involved with primary study
Blinding? OCS treated exacerbations & hospitalisation	Yes	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.

EXCEL (Continued)

Incomplete outcome data addressed? OCS treated exacerbations	Unclear	ITT analysis described. Explicit details of how withdrawals handled were not described
Incomplete outcome data addressed? Hospital admission	Unclear	ITT analysis described. Explicit details of how withdrawals handled were not described
Free of selective reporting?	Unclear	Unable to ascertain this reliably
Free of other bias?	Yes	

SAM40048

Methods	Randomised, parallel group trial. Double-blind, double dummy design. 27 centres in Germany. Description of withdrawals: Stated
Participants	N SCREENED: Not reported N RANDOMISED: 248 (ITT population: 241) N COMPLETED: 235 M= 102 (based on ITT) F= 139 (based on ITT) MEAN AGE: 48 BASELINE CHARACTERISTICS: FEV1 predicted: 65%; am PEF 310 L/min INCLUSION CRITERIA: 'Moderate' asthma; >18 years; FEV1 50-80% predicted; >15% reversibility; ICS dose 1000 mcg/d (BDP equivalent); symptomatic (symptom score of 1 on 7 days of the run-in period). EXCLUSION CRITERIA: Exacerbations/emergency visits during 4-week pre-study period; smoking (>20 cigarettes/d).
Interventions	1. Combination fluticasone and salmeterol 250/50 mcg bid + placebo Turbohaler. BDP equivalent 1000 mcg. 2. Combination budesonide and formoterol 200/6mcg bid + placebo Diskus inhaler. BDP equivalent 400 mcg. DELIVERY DEVICE: FPS: Diskus; BDF: Turbohaler TREATMENT PERIOD: 12 weeks RUN-IN: 2 weeks (treatment not clear) RESCUE: Not reported
Outcomes	Primary outcome: FEV1 predicted Secondary outcomes: Morning PEF; evening PEF; daytime and evening asthma symptoms; symptom-free days; rescue medication-free days; safety
Notes	Study sponsors: GSK

<i>Risk of bias</i>		
Item	Authors' judgement	Description
Adequate sequence generation?	Unclear	Information not available.
Allocation concealment?	Unclear	Not reported
Blinding? OCS treated exacerbations & hospitalisation	Yes	Participants and investigators blinded to treatment group allocation with double-dummy design
Incomplete outcome data addressed? OCS treated exacerbations	Unclear	ITT analysis described. Explicit details of how withdrawals handled were not described
Incomplete outcome data addressed? Hospital admission	Unclear	ITT analysis described. Explicit details of how withdrawals handled were not described
Free of selective reporting?	Unclear	Unable to ascertain this reliably
Free of other bias?	Yes	

ATS: American Thoracic Society; BDF: budesonide/formoterol; BDP: Beclomethasone; BID: twice daily; DPI: Dry powder inhaler; FEV1: Forced expiratory volume in 1 second; FPS: Fluticasone/salmeterol combination; ICS: inhaled corticosteroid; MDI: metered dose inhaler; PEF: peak expiratory flow; RTI: Respiratory tract infection; SABA: Short-acting beta-agonist.

Characteristics of excluded studies [ordered by study ID]

Adachi 2008	Study compared combination FP/SAL with FP and theophylline.
AHEAD	Study comparing FP/SAL with BUD/F as an adjustable dosing strategy
ALLIANCE	Combinations assessed not relevant to this review.
Ambrose 2007	Study compared different doses of BUD/F. No comparison with FP/SAL.
Bleecker 2007	Study randomised participants to FP/SAL or SAL. No comparison with BUD/F
Brambilla 2003	Separate inhalers: Formoterol versus Salmeterol as add on to ICS.
CONCEPT	Assessment of combination FP/SAL against BUD/F given as an adjustable dosing strategy.

(Continued)

Creemers 2002	Study summarised data from two studies comparing BDF with ICS alone.
EDICT	Combination FPS versus BUD/F given via separate inhalers.
Hampel 2007	Report of two crossover studies: ineligible design.
Jenkins 2000	Study assessed FPS with ICS alone.
Kaik 2002	Separate F and BUD preparations versus combination FPS.
Lee 2003	Crossover design.
Lotväll 2002	Summary of two crossover studies.
Palmqvist 2001	Crossover design.
SAM40042	Crossover design.
SAM40047	Crossover design.
SAM40062	Crossover design.
Vogelmeier 2005	Comparison of FP/SAL with BUD/F as maintenance and relief.

DATA AND ANALYSES

Comparison 1. Combination fluticasone/salmeterol versus budesonide/formoterol

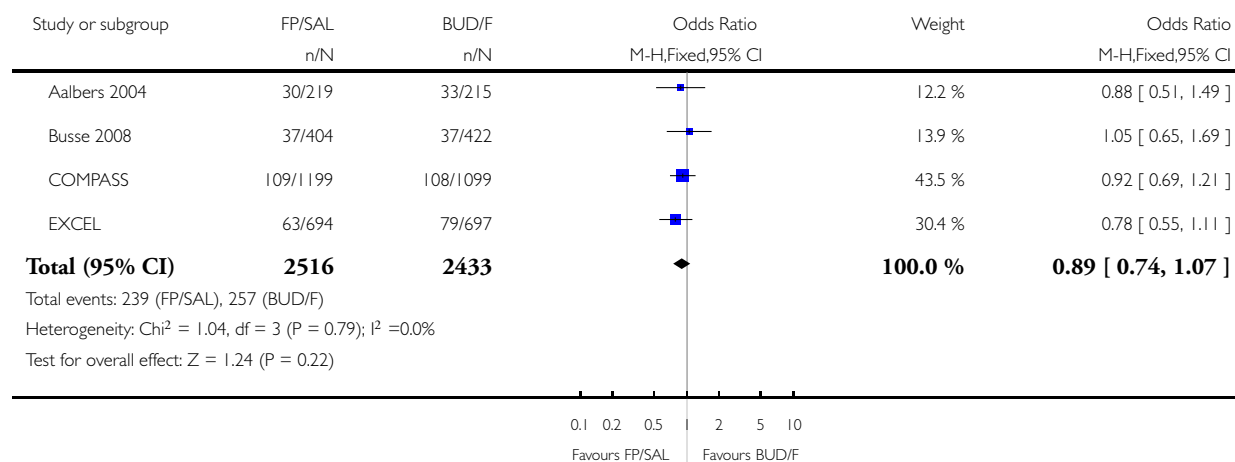
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Participants experiencing exacerbations requiring oral steroid treatment	4	4949	Odds Ratio (M-H, Fixed, 95% CI)	0.89 [0.74, 1.07]
2 Participants experiencing exacerbations requiring admission to hospital	4	4879	Odds Ratio (M-H, Fixed, 95% CI)	1.29 [0.68, 2.47]
3 Asthma-related serious adverse event	3	4054	Odds Ratio (M-H, Fixed, 95% CI)	1.47 [0.75, 2.86]
4 Participants experiencing exacerbations requiring ED visit/hospitalisation	4	4861	Odds Ratio (M-H, Fixed, 95% CI)	1.30 [0.94, 1.80]
5 Change in FEV1	4	4845	L (Fixed, 95% CI)	Not estimable
6 Change in FEV1 predicted (%)	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
7 Change in am PEF	5	5101	L/min (Fixed, 95% CI)	2.24 [-0.24, 4.73]
8 Change in pm PEF	4	4299	L/min (Fixed, 95% CI)	0.25 [-0.80, 1.30]
9 Change in daytime symptoms	3	3464	Symptoms (Fixed, 95% CI)	-0.02 [-0.06, 0.03]
10 Change in symptom-free days	2	3027	Symptoms (Fixed, 95% CI)	1.25 [-1.18, 3.67]
11 Change in nocturnal awakenings	1		Symptoms (Fixed, 95% CI)	Totals not selected
12 Change in rescue medication use	3	3469	Puffs/d (Fixed, 95% CI)	-0.06 [-0.13, 0.02]
13 Withdrawals	5	5082	Odds Ratio (M-H, Fixed, 95% CI)	0.97 [0.78, 1.20]
14 Withdrawals (adverse events)	5	5082	Odds Ratio (M-H, Fixed, 95% CI)	0.94 [0.60, 1.46]
15 Withdrawals (lack of efficacy)	1		Odds Ratio (M-H, Fixed, 95% CI)	Totals not selected
16 Adverse events	2	1644	Odds Ratio (M-H, Fixed, 95% CI)	1.08 [0.89, 1.31]
17 Headache	4	2916	Odds Ratio (M-H, Fixed, 95% CI)	1.08 [0.82, 1.43]
18 Candidiasis	2	1272	Odds Ratio (M-H, Fixed, 95% CI)	1.64 [0.68, 4.00]
19 Dysphonia	3	2669	Odds Ratio (M-H, Fixed, 95% CI)	1.45 [0.87, 2.43]
20 Upper respiratory tract infection	2	1644	Odds Ratio (M-H, Fixed, 95% CI)	1.09 [0.81, 1.47]
21 Rhinitis	1		Odds Ratio (M-H, Fixed, 95% CI)	Totals not selected
22 Throat irritation	2	1644	Odds Ratio (M-H, Fixed, 95% CI)	1.39 [0.82, 2.35]
23 Cough	1		Odds Ratio (M-H, Fixed, 95% CI)	Totals not selected
24 Tremor	1		Odds Ratio (M-H, Fixed, 95% CI)	Totals not selected

Analysis 1.1. Comparison 1 Combination fluticasone/salmeterol versus budesonide/formoterol, Outcome 1 Participants experiencing exacerbations requiring oral steroid treatment.

Review: Combination fluticasone and salmeterol versus fixed dose combination budesonide and formoterol for chronic asthma in adults and children

Comparison: 1 Combination fluticasone/salmeterol versus budesonide/formoterol

Outcome: 1 Participants experiencing exacerbations requiring oral steroid treatment

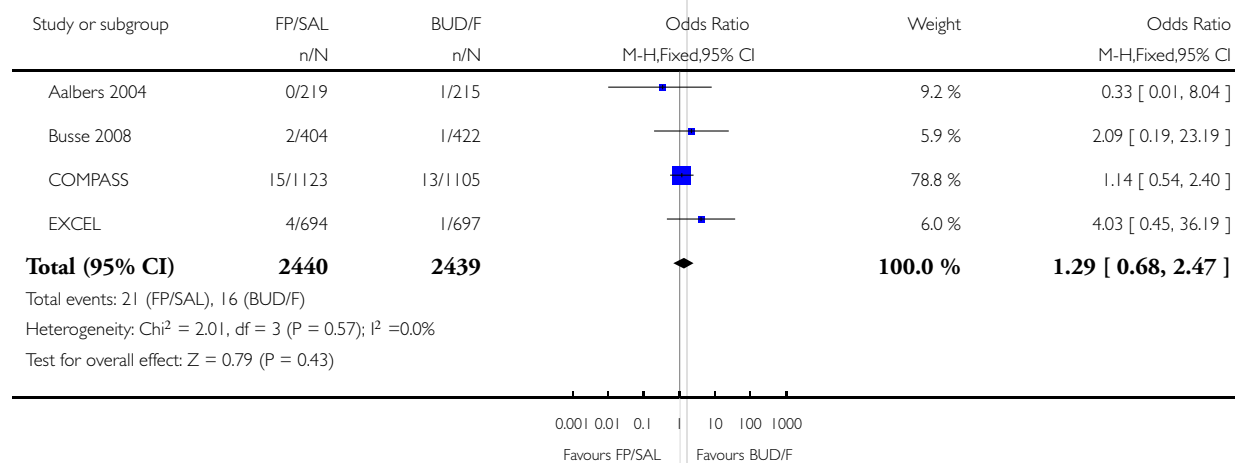


Analysis 1.2. Comparison 1 Combination fluticasone/salmeterol versus budesonide/formoterol, Outcome 2 Participants experiencing exacerbations requiring admission to hospital.

Review: Combination fluticasone and salmeterol versus fixed dose combination budesonide and formoterol for chronic asthma in adults and children

Comparison: 1 Combination fluticasone/salmeterol versus budesonide/formoterol

Outcome: 2 Participants experiencing exacerbations requiring admission to hospital

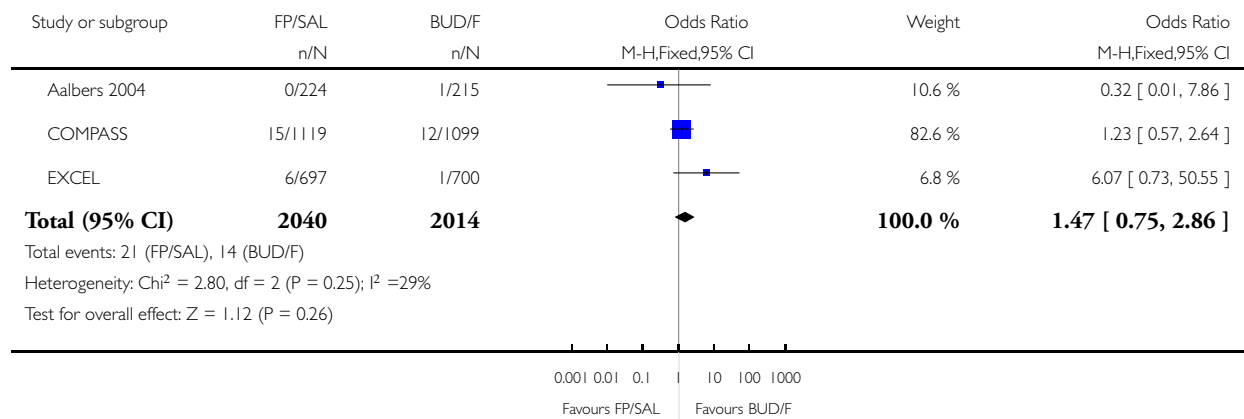


Analysis 1.3. Comparison 1 Combination fluticasone/salmeterol versus budesonide/formoterol, Outcome 3 Asthma-related serious adverse event.

Review: Combination fluticasone and salmeterol versus fixed dose combination budesonide and formoterol for chronic asthma in adults and children

Comparison: 1 Combination fluticasone/salmeterol versus budesonide/formoterol

Outcome: 3 Asthma-related serious adverse event

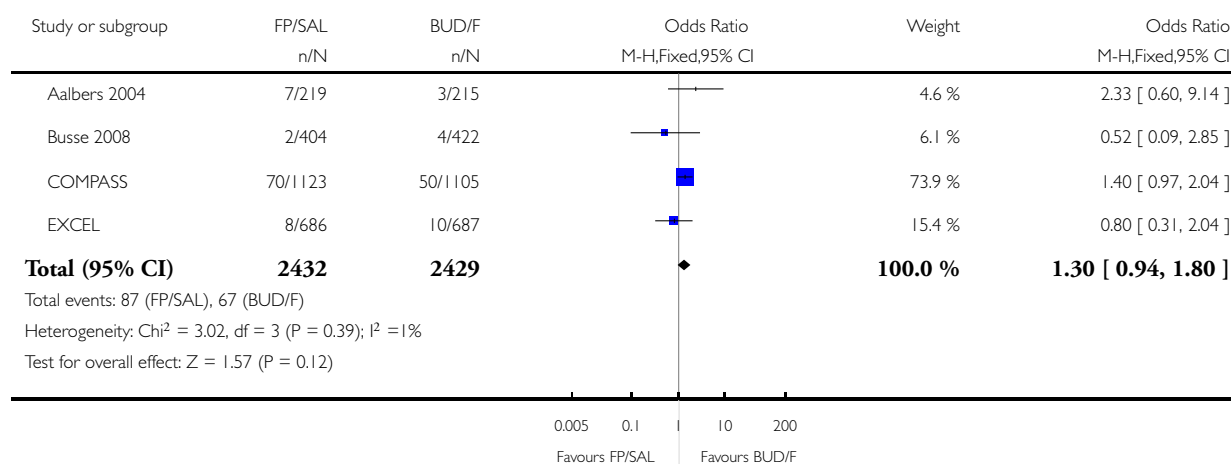


Analysis 1.4. Comparison 1 Combination fluticasone/salmeterol versus budesonide/formoterol, Outcome 4 Participants experiencing exacerbations requiring ED visit/hospitalisation.

Review: Combination fluticasone and salmeterol versus fixed dose combination budesonide and formoterol for chronic asthma in adults and children

Comparison: 1 Combination fluticasone/salmeterol versus budesonide/formoterol

Outcome: 4 Participants experiencing exacerbations requiring ED visit/hospitalisation

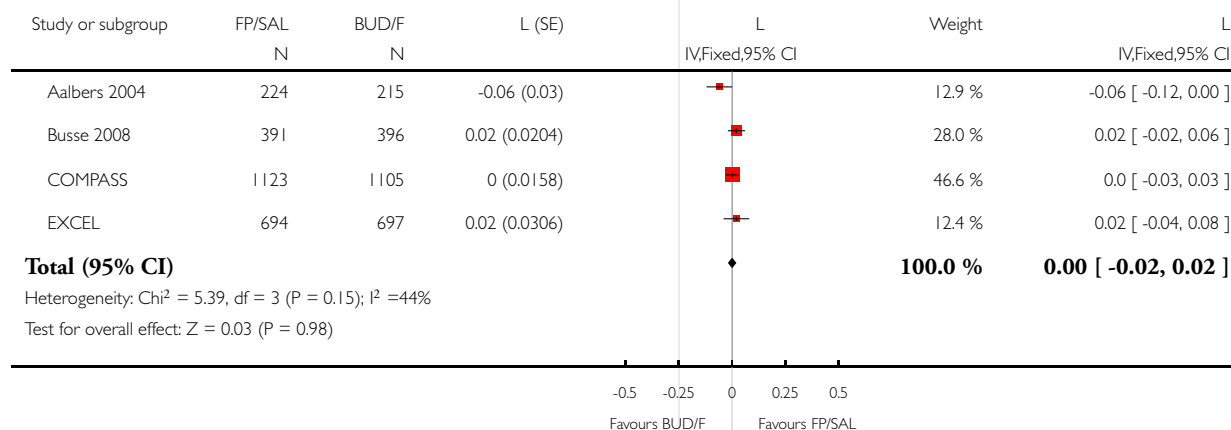


Analysis 1.5. Comparison 1 Combination fluticasone/salmeterol versus budesonide/formoterol, Outcome 5 Change in FEV1.

Review: Combination fluticasone and salmeterol versus fixed dose combination budesonide and formoterol for chronic asthma in adults and children

Comparison: 1 Combination fluticasone/salmeterol versus budesonide/formoterol

Outcome: 5 Change in FEV1

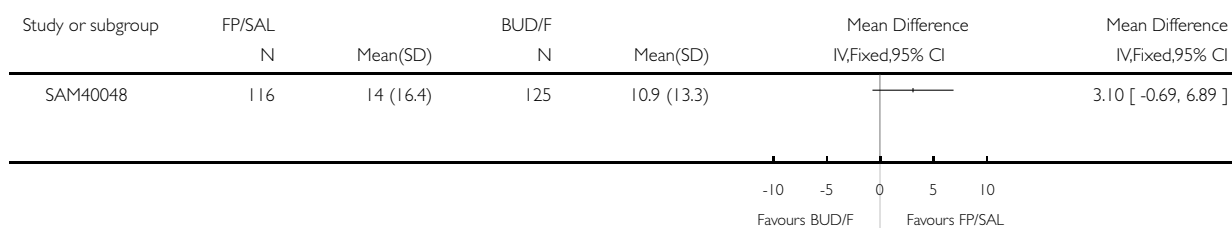


Analysis 1.6. Comparison 1 Combination fluticasone/salmeterol versus budesonide/formoterol, Outcome 6 Change in FEV1 predicted (%).

Review: Combination fluticasone and salmeterol versus fixed dose combination budesonide and formoterol for chronic asthma in adults and children

Comparison: 1 Combination fluticasone/salmeterol versus budesonide/formoterol

Outcome: 6 Change in FEV1 predicted (%)

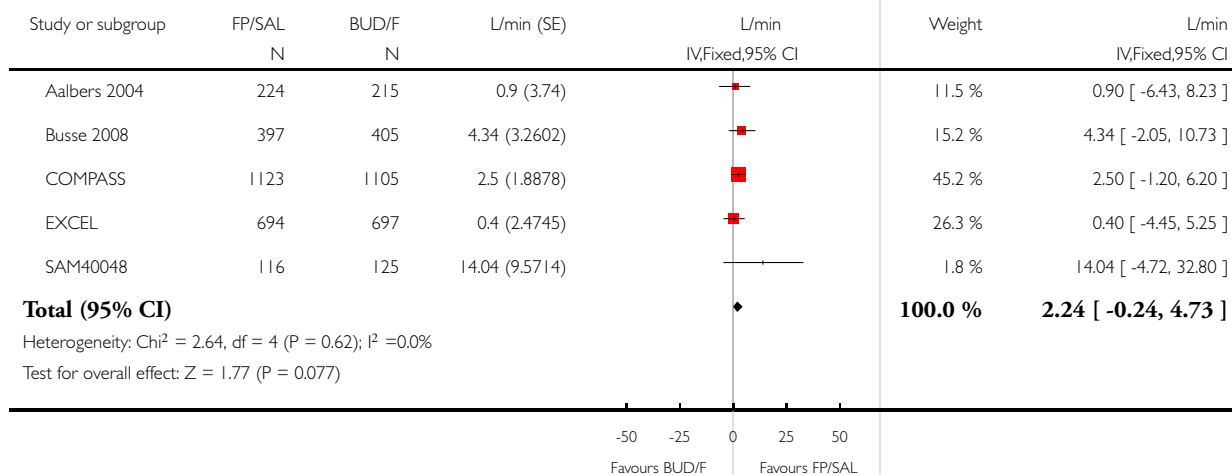


Analysis 1.7. Comparison 1 Combination fluticasone/salmeterol versus budesonide/formoterol, Outcome 7 Change in am PEF.

Review: Combination fluticasone and salmeterol versus fixed dose combination budesonide and formoterol for chronic asthma in adults and children

Comparison: 1 Combination fluticasone/salmeterol versus budesonide/formoterol

Outcome: 7 Change in am PEF

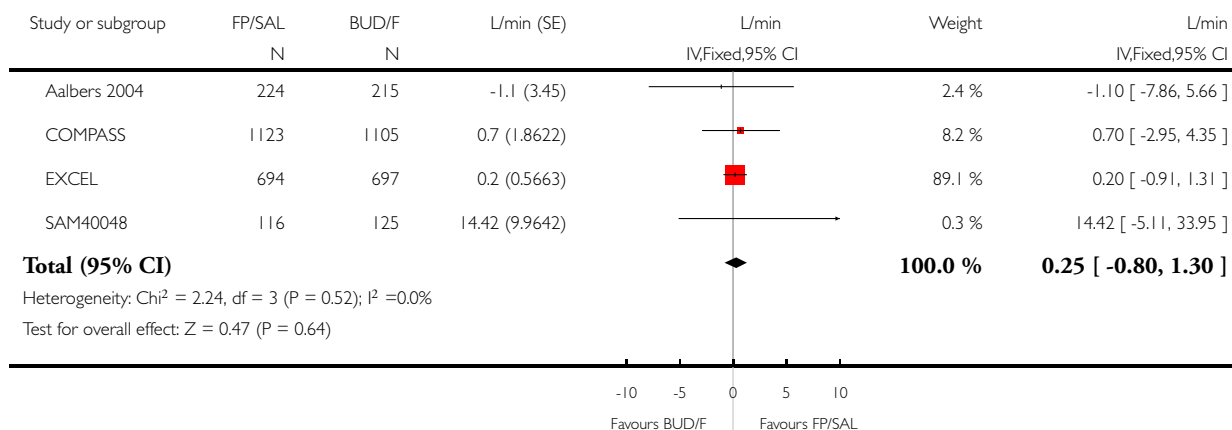


Analysis 1.8. Comparison 1 Combination fluticasone/salmeterol versus budesonide/formoterol, Outcome 8 Change in pm PEF.

Review: Combination fluticasone and salmeterol versus fixed dose combination budesonide and formoterol for chronic asthma in adults and children

Comparison: 1 Combination fluticasone/salmeterol versus budesonide/formoterol

Outcome: 8 Change in pm PEF

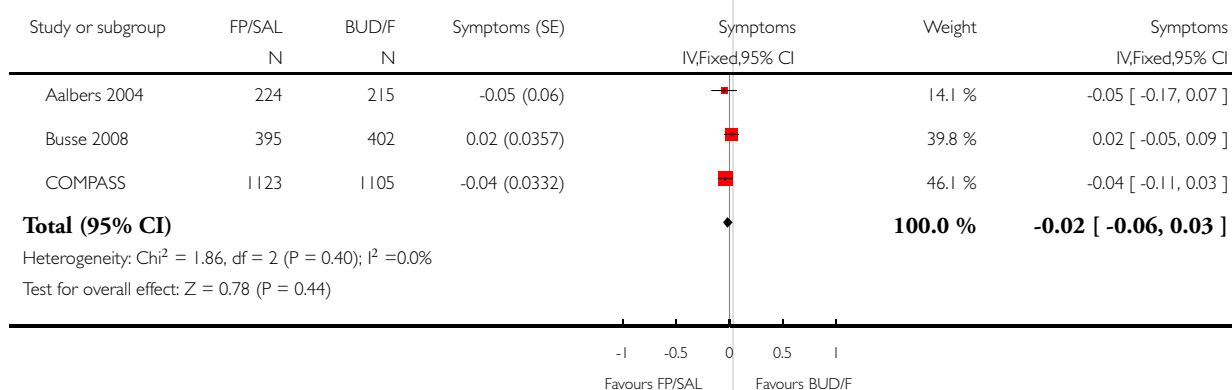


Analysis 1.9. Comparison 1 Combination fluticasone/salmeterol versus budesonide/formoterol, Outcome 9 Change in daytime symptoms.

Review: Combination fluticasone and salmeterol versus fixed dose combination budesonide and formoterol for chronic asthma in adults and children

Comparison: 1 Combination fluticasone/salmeterol versus budesonide/formoterol

Outcome: 9 Change in daytime symptoms

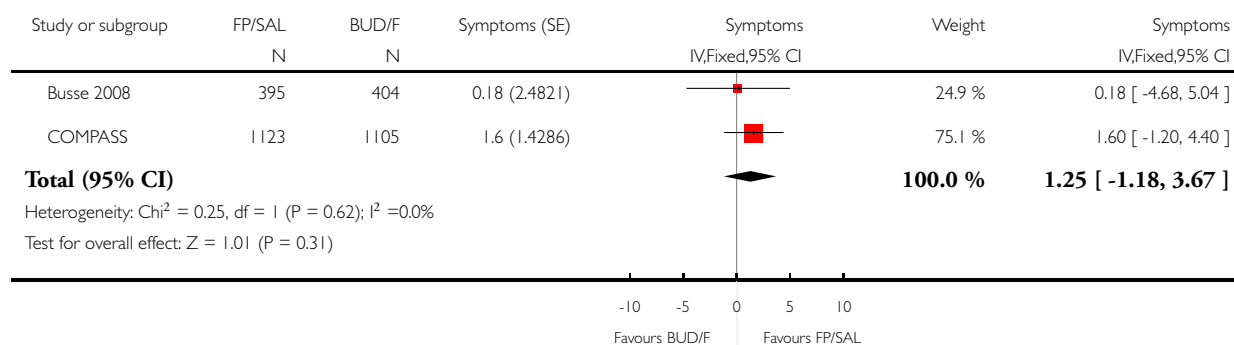


Analysis 1.10. Comparison 1 Combination fluticasone/salmeterol versus budesonide/formoterol, Outcome 10 Change in symptom-free days.

Review: Combination fluticasone and salmeterol versus fixed dose combination budesonide and formoterol for chronic asthma in adults and children

Comparison: 1 Combination fluticasone/salmeterol versus budesonide/formoterol

Outcome: 10 Change in symptom-free days

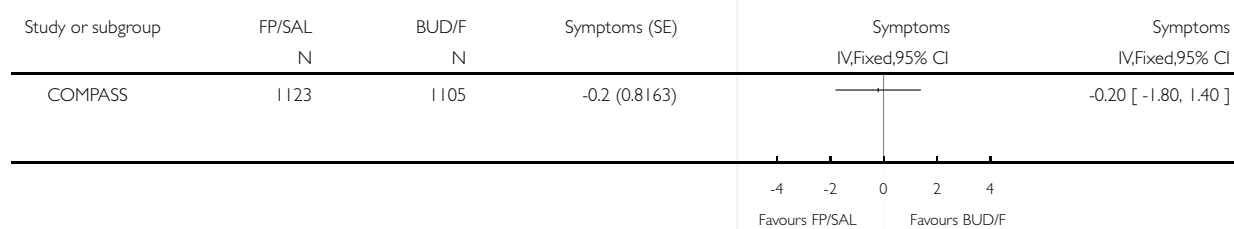


Analysis 1.11. Comparison 1 Combination fluticasone/salmeterol versus budesonide/formoterol, Outcome 11 Change in nocturnal awakenings.

Review: Combination fluticasone and salmeterol versus fixed dose combination budesonide and formoterol for chronic asthma in adults and children

Comparison: 1 Combination fluticasone/salmeterol versus budesonide/formoterol

Outcome: 11 Change in nocturnal awakenings

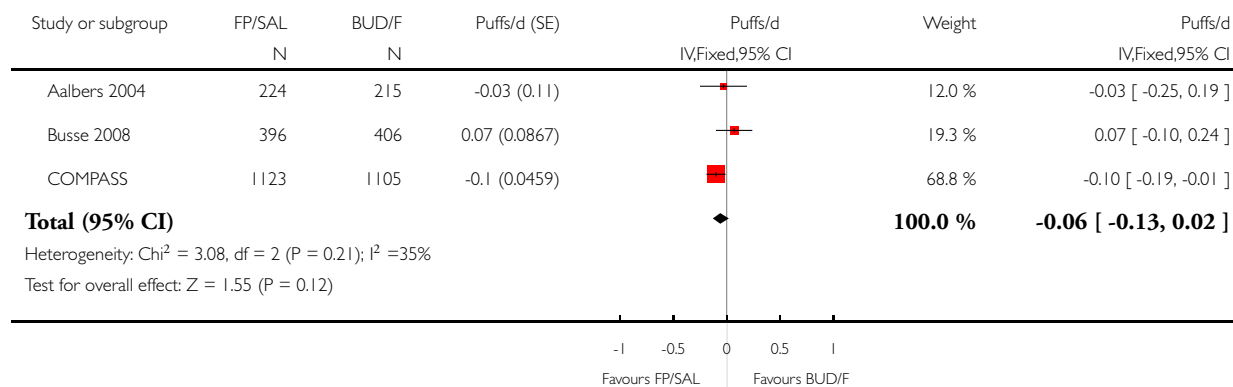


Analysis 1.12. Comparison 1 Combination fluticasone/salmeterol versus budesonide/formoterol, Outcome 12 Change in rescue medication use.

Review: Combination fluticasone and salmeterol versus fixed dose combination budesonide and formoterol for chronic asthma in adults and children

Comparison: 1 Combination fluticasone/salmeterol versus budesonide/formoterol

Outcome: 12 Change in rescue medication use

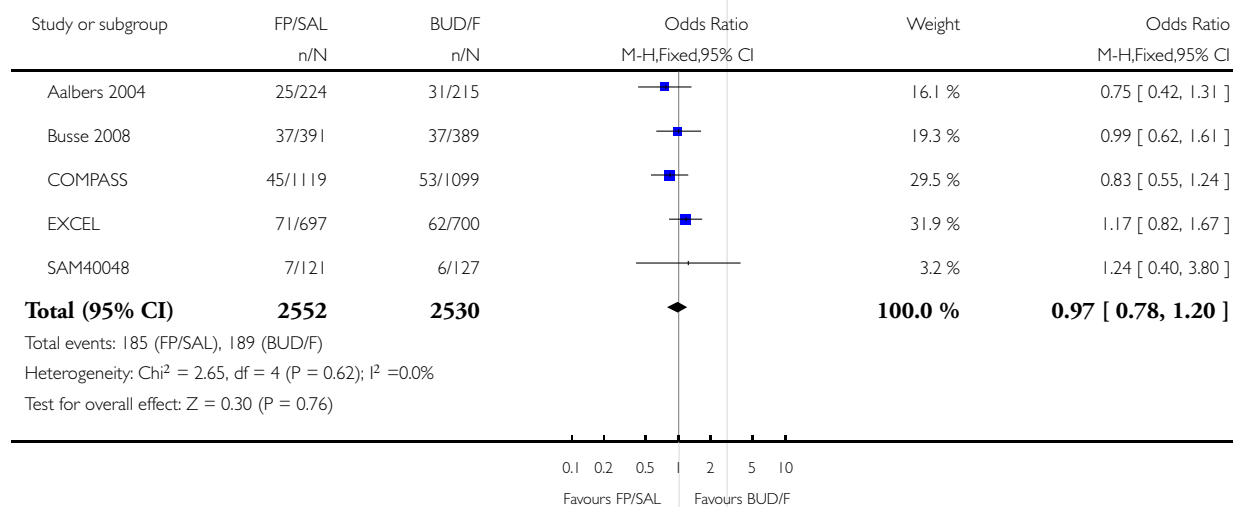


Analysis 1.13. Comparison 1 Combination fluticasone/salmeterol versus budesonide/formoterol, Outcome 13 Withdrawals.

Review: Combination fluticasone and salmeterol versus fixed dose combination budesonide and formoterol for chronic asthma in adults and children

Comparison: 1 Combination fluticasone/salmeterol versus budesonide/formoterol

Outcome: 13 Withdrawals

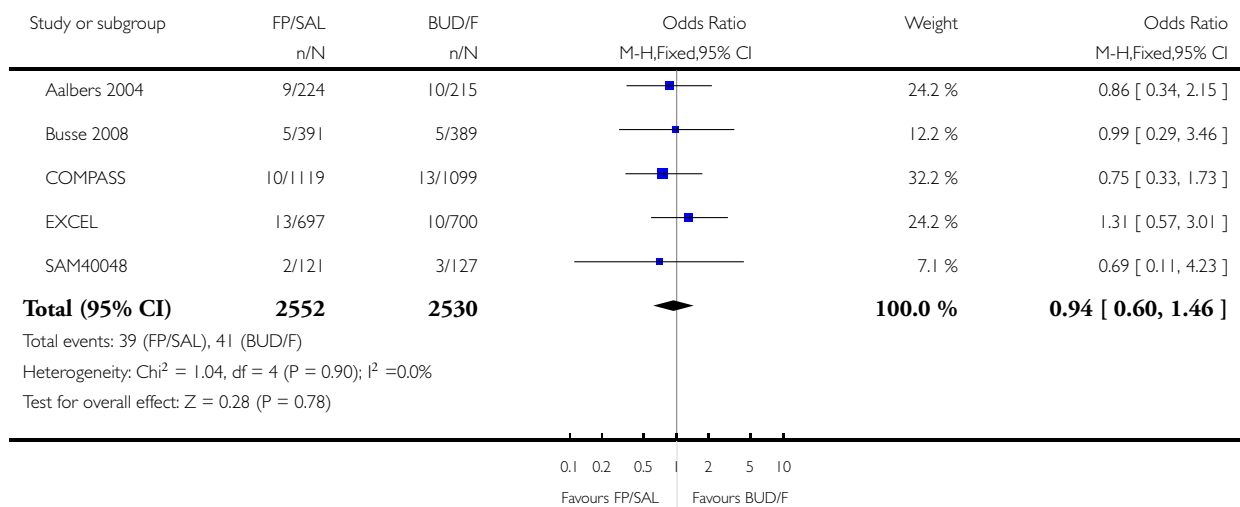


Analysis 1.14. Comparison 1 Combination fluticasone/salmeterol versus budesonide/formoterol, Outcome 14 Withdrawals (adverse events).

Review: Combination fluticasone and salmeterol versus fixed dose combination budesonide and formoterol for chronic asthma in adults and children

Comparison: 1 Combination fluticasone/salmeterol versus budesonide/formoterol

Outcome: 14 Withdrawals (adverse events)

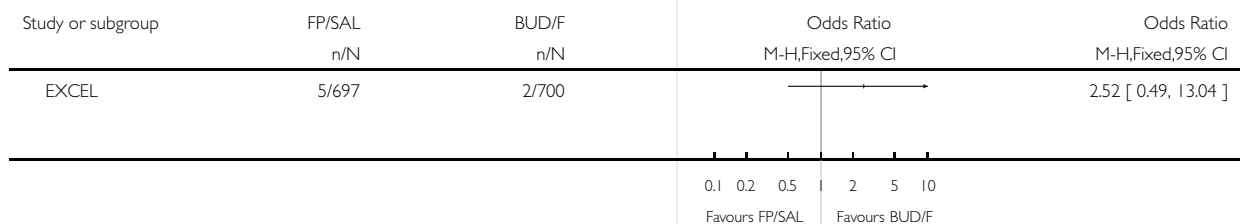


Analysis 1.15. Comparison 1 Combination fluticasone/salmeterol versus budesonide/formoterol, Outcome 15 Withdrawals (lack of efficacy).

Review: Combination fluticasone and salmeterol versus fixed dose combination budesonide and formoterol for chronic asthma in adults and children

Comparison: 1 Combination fluticasone/salmeterol versus budesonide/formoterol

Outcome: 15 Withdrawals (lack of efficacy)

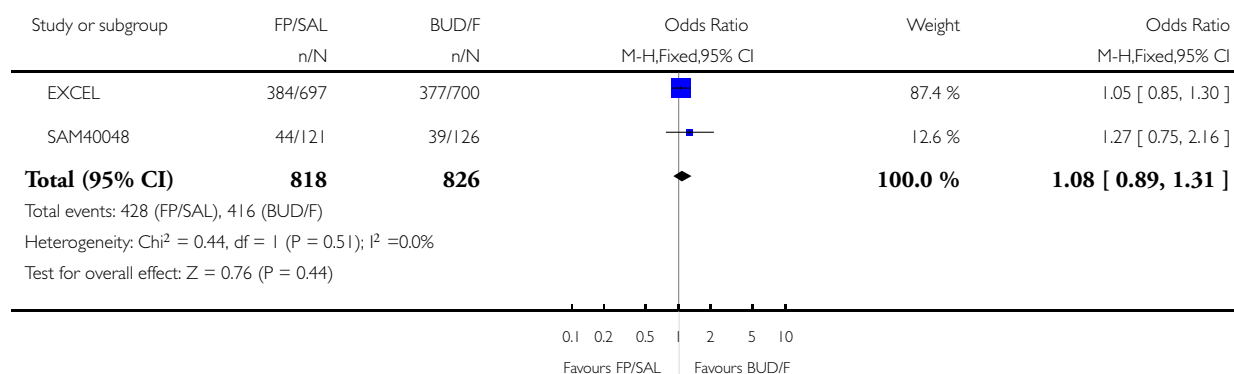


Analysis 1.16. Comparison 1 Combination fluticasone/salmeterol versus budesonide/formoterol, Outcome 16 Adverse events.

Review: Combination fluticasone and salmeterol versus fixed dose combination budesonide and formoterol for chronic asthma in adults and children

Comparison: 1 Combination fluticasone/salmeterol versus budesonide/formoterol

Outcome: 16 Adverse events

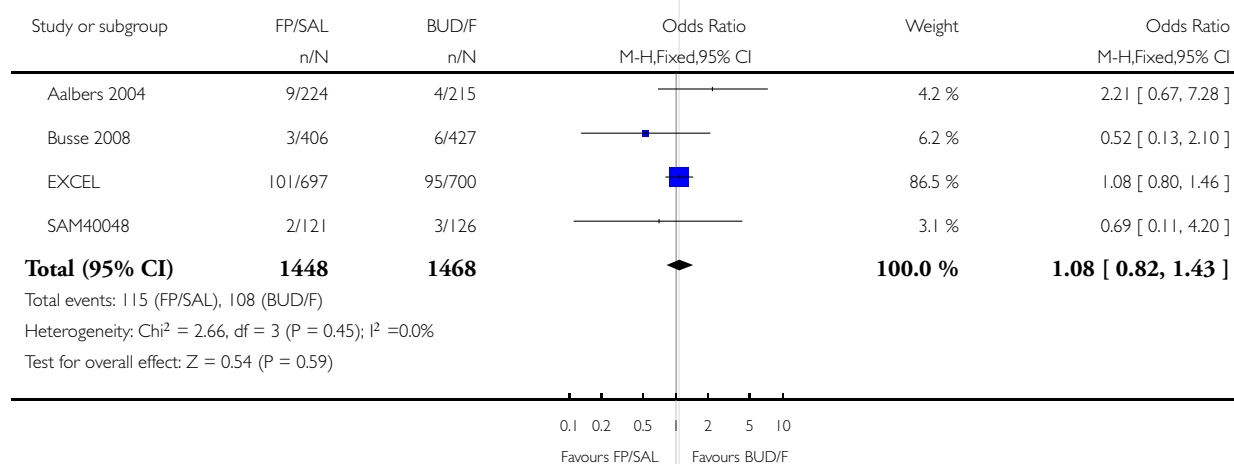


Analysis 1.17. Comparison 1 Combination fluticasone/salmeterol versus budesonide/formoterol, Outcome 17 Headache.

Review: Combination fluticasone and salmeterol versus fixed dose combination budesonide and formoterol for chronic asthma in adults and children

Comparison: 1 Combination fluticasone/salmeterol versus budesonide/formoterol

Outcome: 17 Headache

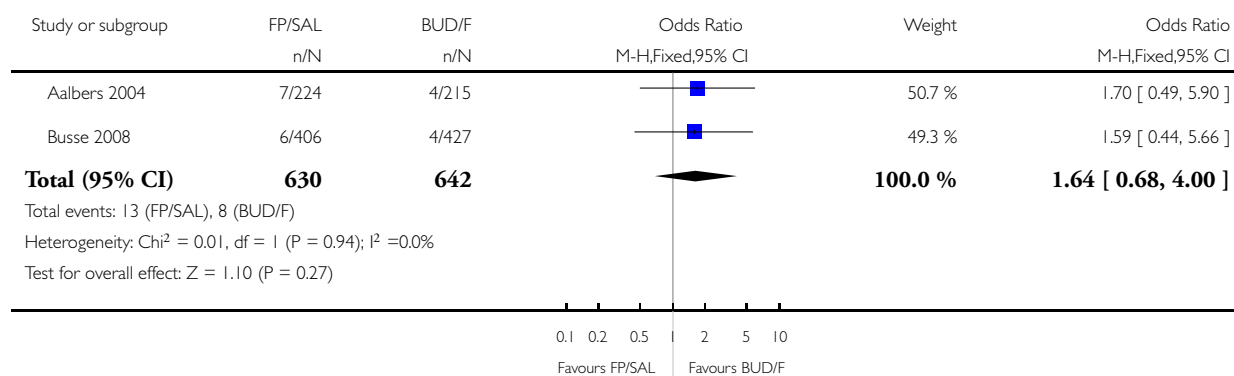


Analysis 1.18. Comparison 1 Combination fluticasone/salmeterol versus budesonide/formoterol, Outcome 18 Candidiasis.

Review: Combination fluticasone and salmeterol versus fixed dose combination budesonide and formoterol for chronic asthma in adults and children

Comparison: 1 Combination fluticasone/salmeterol versus budesonide/formoterol

Outcome: 18 Candidiasis

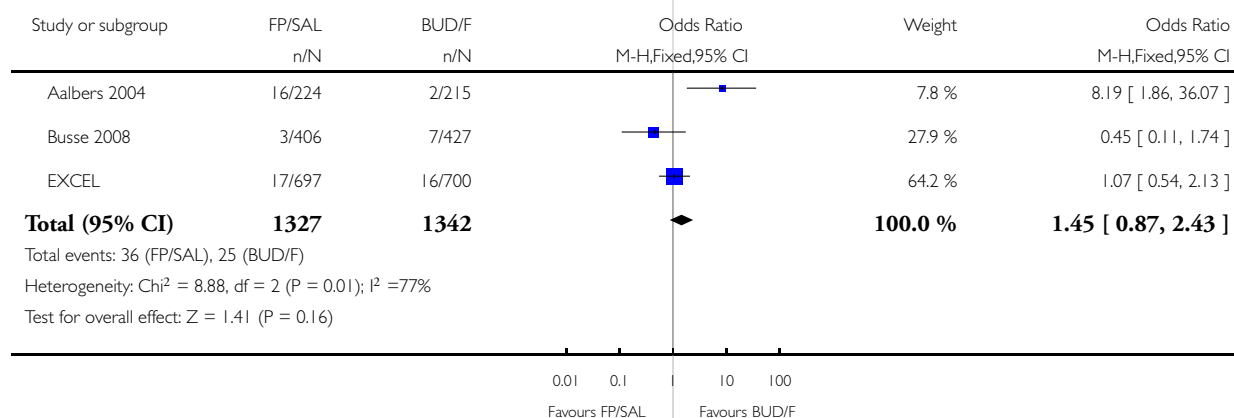


Analysis 1.19. Comparison 1 Combination fluticasone/salmeterol versus budesonide/formoterol, Outcome 19 Dysphonia.

Review: Combination fluticasone and salmeterol versus fixed dose combination budesonide and formoterol for chronic asthma in adults and children

Comparison: 1 Combination fluticasone/salmeterol versus budesonide/formoterol

Outcome: 19 Dysphonia

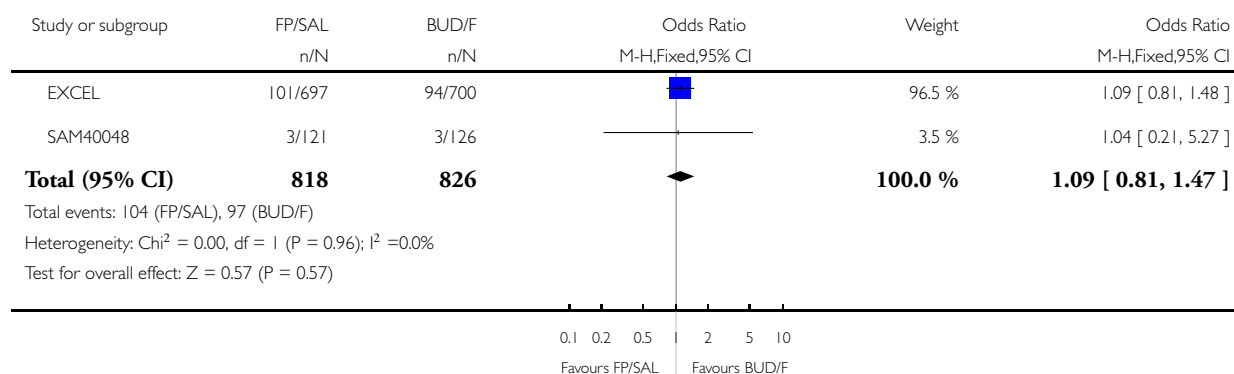


Analysis 1.20. Comparison 1 Combination fluticasone/salmeterol versus budesonide/formoterol, Outcome 20 Upper respiratory tract infection.

Review: Combination fluticasone and salmeterol versus fixed dose combination budesonide and formoterol for chronic asthma in adults and children

Comparison: 1 Combination fluticasone/salmeterol versus budesonide/formoterol

Outcome: 20 Upper respiratory tract infection

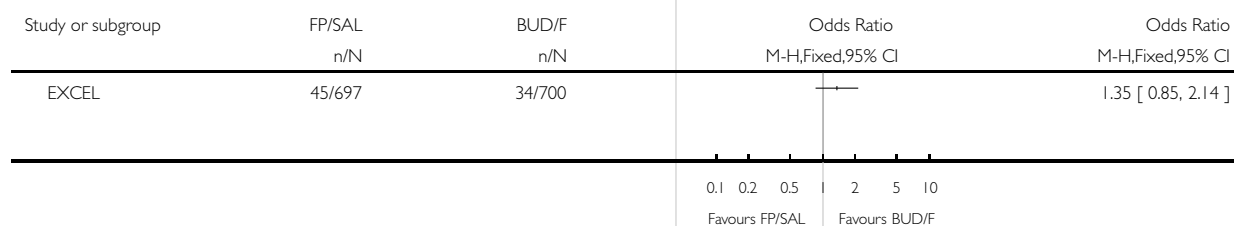


Analysis 1.21. Comparison 1 Combination fluticasone/salmeterol versus budesonide/formoterol, Outcome 21 Rhinitis.

Review: Combination fluticasone and salmeterol versus fixed dose combination budesonide and formoterol for chronic asthma in adults and children

Comparison: 1 Combination fluticasone/salmeterol versus budesonide/formoterol

Outcome: 21 Rhinitis

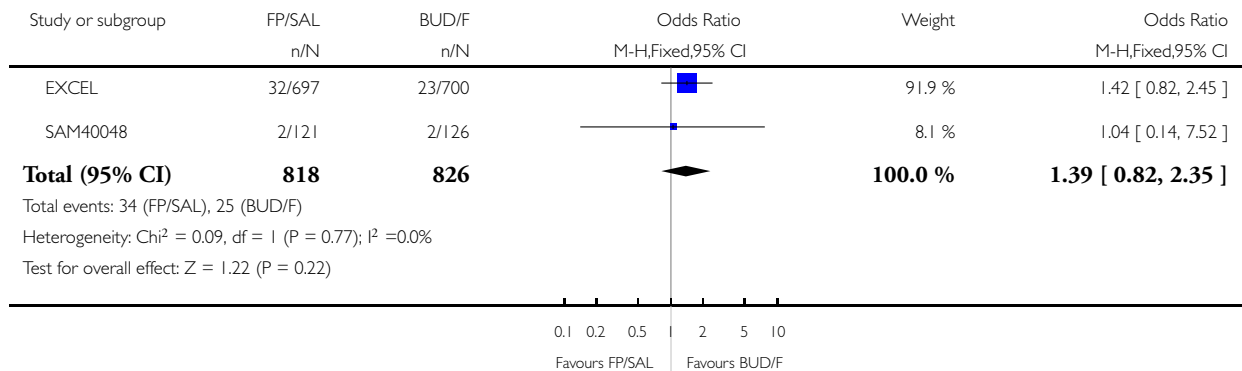


Analysis 1.22. Comparison 1 Combination fluticasone/salmeterol versus budesonide/formoterol, Outcome 22 Throat irritation.

Review: Combination fluticasone and salmeterol versus fixed dose combination budesonide and formoterol for chronic asthma in adults and children

Comparison: 1 Combination fluticasone/salmeterol versus budesonide/formoterol

Outcome: 22 Throat irritation

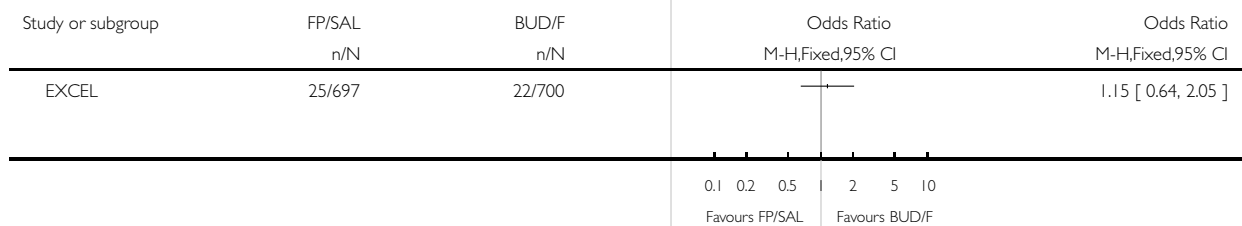


Analysis 1.23. Comparison 1 Combination fluticasone/salmeterol versus budesonide/formoterol, Outcome 23 Cough.

Review: Combination fluticasone and salmeterol versus fixed dose combination budesonide and formoterol for chronic asthma in adults and children

Comparison: 1 Combination fluticasone/salmeterol versus budesonide/formoterol

Outcome: 23 Cough



Analysis 1.24. Comparison 1 Combination fluticasone/salmeterol versus budesonide/formoterol, Outcome 24 Tremor.

Review: Combination fluticasone and salmeterol versus fixed dose combination budesonide and formoterol for chronic asthma in adults and children

Comparison: 1 Combination fluticasone/salmeterol versus budesonide/formoterol

Outcome: 24 Tremor

Study or subgroup	FP/SAL n/N	BUD/F n/N	Odds Ratio	
			M-H,Fixed,95% CI	Odds Ratio M-H,Fixed,95% CI
Busse 2008	1/406	8/427	0.13 [0.02, 1.04]	

WHAT'S NEW

Last assessed as up-to-date: 20 January 2010.

8 May 2009	New search has been performed	Literature search re-run: no new studies identified. Risk of bias table completed and Summary of Findings table added.
------------	-------------------------------	--

HISTORY

Protocol first published: Issue 1, 2003

Review first published: Issue 3, 2008

19 June 2008	Amended	Data from Aalbers 2004 added to the primary endpoint (OCS-treated exacerbations)
13 May 2008	Amended	Converted to new review format.

CONTRIBUTIONS OF AUTHORS

TJL devised the protocol with editorial support from CJC; Assessed studies, extracted data, contacted trialists and study sponsors for additional outcome data; analysis and write-up

GF developed the protocol; wrote up study characteristics, extracted data and assisted with development of discussion section.

LC developed discussion section.

CJC: helped with data extraction and checking, interpretation and guidance on conceptual issues.

DECLARATIONS OF INTEREST

There are no known conflicts of interest.

SOURCES OF SUPPORT

Internal sources

- No sources of support supplied

External sources

- NHS Cochrane Collaboration Programme Grant Scheme, UK.

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

Added items to the risk of bias tool (allocation generation, selective reporting bias & other bias domains).

NOTES

A previous version of this review was withdrawn prior to publication following the identification of incomplete data by GSK for the outcome ED visit/admission to hospital. The data included in the original version of the review indicated a significant increase in the odds of ED visit/hospitalisation with FP/SAL. However, this reflected data that were drawn from those participants who were admitted to hospital only. The pooled outcome data did not accurately represent the composite outcome of presentation at ED or hospital admission ([EXCEL](#)). We have now included data made available to us by GSK which are an accurate record of ED visit or admission to hospital.

INDEX TERMS

Medical Subject Headings (MeSH)

Albuterol [administration & dosage; analogs & derivatives]; Androstadienes [administration & dosage]; Anti-Asthmatic Agents [*administration & dosage]; Asthma [*drug therapy]; Budesonide [administration & dosage]; Drug Combinations; Ethanolamines [administration & dosage]; Randomized Controlled Trials as Topic

MeSH check words

Adult; Child; Humans