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Addition of long-acting beta2-agonists to inhaled corticosteroids versus same dose inhaled corticosteroids for chronic asthma in adults and children

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Abstract

Background—Long-acting inhaled β_2 -adrenergic agonists (LABAs) are recommended as 'addon' medication to inhaled corticosteroids (ICS) in the maintenance therapy of asthmatic adults and children aged two years and above.

Objectives—To quantify in asthmatic patients the safety and efficacy of the addition of LABAs to ICS in patients insufficiently controlled on ICS alone.

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CONTRIBUTIONS OF AUTHORS Francine Ducharme revised the protocol, supervised the literature search, created the methodology and data extraction forms, reviewed full-text publications for relevance, participated in the selection of trials, methodology assessment and data extraction, corresponded with authors and/or the pharmaceutical companies to identify other possibly relevant trials, verify methodology and data extraction and request additional information, supervised the analysis, interpretation, and wrote the 2010 version of the review.

Muireann Ni Chroinin reviewed the literature searches from 2002 to 2004, identified and reviewed the full-text publication of all citations of potential or potentially eligible RCTs, extracted the methodology and data, entered the description of studies and data entry in RevMan and analysed the data. Muireann interpreted results of the meta-analysis and wrote the 2005 review.

Toby Lasserson assessed titles and abstracts for the update in 2010, assessed studies for inclusion, corresponded with trialists and study sponsors, extracted data, entered data and wrote up results.

Dr Ilana Greenstone conceived the protocol, requested the literature search, identified and reviewed the full-text publication of all citations of potential or potentially eligible RCTs from 1999 to 2001, drafted the correspondence to authors and/or the pharmaceutical companies to solicit their collaboration in this review and to identify other possibly relevant trials, participated in extraction of the methodology and data, entering the description of studies and data entry in RevMan, interpreted results of the meta-analysis and approved the review.

Four research assistants participated in some aspects of the review. Helen Magdalinos (May to July 2001), Alya Danish (November 2001 to March 2002), Vincent Masse (June to August 2004) participated in the entry of data, references, characteristics of included and excluded studies, and revision of the table of comparisons. Under the guidance of Nils Chaillet, Marilyse Julien (2009) performed and assisted in the interpretation of the meta-regression in 2009.

Although not listed as an author, the data for the primary outcome were verified by Chris Cates.

DECLARATIONS OF INTEREST In the past five years, Francine Ducharme received some research funding from GSK and Merck & Co, USA and gave CME conferences supported by Merck Frosst. M Ni Chroinin, IR Greenstone, A Danish, H Magalinos, V Masse, M Julien and T Lasserson report no conflict of interest.

Search methods—We identified randomised controlled trials (RCTs) through electronic database searches (the Cochrane Airways Group Specialised Register, MEDLINE, EMBASE and CINAHL), bibliographies of RCTs and correspondence with manufacturers until May 2008.

Selection criteria—We included RCTs if they compared the addition of inhaled LABAs versus placebo to the same dose of ICS in children aged two years and above and in adults.

Data collection and analysis—Two review authors independently assessed studies for methodological quality and extracted data. We obtained confirmation from the trialists when possible. The primary endpoint was the relative risk (RR) of asthma exacerbations requiring rescue oral corticosteroids. Secondary endpoints included pulmonary function tests (PFTs), rescue beta2-agonist use, symptoms, withdrawals and adverse events.

Main results—Seventy-seven studies met the entry criteria and randomised 21,248 participants (4625 children and 16,623 adults). Participants were generally symptomatic at baseline with moderate airway obstruction despite their current ICS regimen. Formoterol or salmeterol were most frequently added to low-dose ICS (200 to 400 µg/day of beclomethasone (BDP) or equivalent) in 49% of the studies. The addition of a daily LABA to ICS reduced the risk of exacerbations requiring oral steroids by 23% from 15% to 11% (RR 0.77, 95% CI 0.68 to 0.87, 28 studies, 6808 participants). The number needed to treat with the addition of LABA to prevent one use of rescue oral corticosteroids is 41 (29, 72), although the event rates in the ICS groups varied between 0% and 38%. Studies recruiting adults dominated the analysis (6203 adult participants versus 605 children). The subgroup estimate for paediatric studies was not statistically significant (RR 0.89, 95% CI 0.58 to 1.39) and includes the possibility of the superiority of ICS alone in children.

Higher than usual dose of LABA was associated with significantly less benefit. The difference in the relative risk of serious adverse events with LABA was not statistically significant from that of ICS alone (RR 1.06, 95% CI 0.87 to 1.30). The addition of LABA led to a significantly greater improvement in FEV₁ (0.11 litres, 95% 0.09 to 0.13) and in the proportion of symptom-free days (11.88%, 95% CI 8.25 to 15.50) compared to ICS monotherapy. It was also associated with a reduction in the use of rescue short-acting β_2 -agonists (-0.58 puffs/day, 95% CI -0.80 to -0.35), fewer withdrawals due to poor asthma control (RR 0.50, 95% CI 0.41 to 0.61), and fewer withdrawals due to any reason (RR 0.80, 95% CI 0.75 to 0.87). There was no statistically significant group difference in the risk of overall adverse effects (RR 1.00, 95% 0.97 to 1.04), withdrawals due to adverse health events (RR 1.04, 95% CI 0.86 to 1.26) or any of the specific adverse health events.

Authors' conclusions—In adults who are symptomatic on low to high doses of ICS monotherapy, the addition of a LABA at licensed doses reduces the rate of exacerbations requiring oral steroids, improves lung function and symptoms and modestly decreases use of rescue short-acting β_2 -agonists. In children, the effects of this treatment option are much more uncertain. The absence of group difference in serious adverse health events and withdrawal rates in both groups provides some indirect evidence of the safety of LABAs at usual doses as add-on therapy to ICS in adults, although the width of the confidence interval precludes total reassurance.

Medical Subject Headings (MeSH)

Administration, Inhalation; Adrenal Cortex Hormones [*administration & dosage]; Adrenergic beta-Agonists [*administration & dosage]; Albuterol [administration & dosage; analogs & derivatives]; Anti-Asthmatic Agents [*administration & dosage]; Asthma [*drug therapy]; Beclomethasone [administration & dosage]; Chronic Disease; Drug Therapy, Combination [methods]; Ethanolamines [administration & dosage]; Randomized Controlled Trials as Topic

MeSH check words

Adolescent; Adult; Child; Child, Preschool; Humans

BACKGROUND

With the recognition of asthma as an inflammatory disease, the cornerstone of asthma management is the use of inhaled corticosteroids (Adams 2008; GINA 2007). Inhaled β_2 -agonists are powerful agents used to relieve the bronchoconstriction associated with asthma. They act by stimulating the β_2 -receptors located in airway smooth muscle resulting in smooth muscle relaxation (Nelson 1995). Inhaled β_2 -agonists can be differentiated by their onset and duration of action. Short-acting β_2 -agonists, such as salbutamol and terbutaline, are hydrophilic and interact directly with β_2 -receptors, leading to a fast onset of action with a duration of effect of six hours or less (D'Alonzo 1997). Long-acting β_2 -agonists (LABAs) provide longer symptom control, which is a particularly useful feature for preventing night-time symptoms. There are two main LABAs, namely salmeterol and formoterol. Salmeterol is highly lipophilic and diffuses through the lipid bi-layer in muscle cell membranes to reach the β_2 -receptors, explaining the slower onset and long duration of action (Nelson 1995). Formoterol, being less lipophilic, has a fast onset of action, similar to short-acting β_2 -agonists, and is believed to be incorporated into the lipid bilayer to serve as a reservoir, accounting for its prolonged action (Nelson 1995).

Frequent use of short- or long-acting β_2 -agonists generally indicates a significant inflammatory process that should be controlled with anti-inflammatory drugs such as inhaled corticosteroids. The role of long-acting β_2 -agonists in the management of asthma has previously been debated (Ernst 2006; Salpeter 2006). At present, the use of long-acting β_2 agonists as monotherapy clearly appears to be less effective than inhaled corticosteroids alone (Warner 1998), and has been associated with increased asthma deaths; these data resulted in an early trial termination (SMART). A recent systematic review, combining data from studies where patients received long-acting β_2 -agonists as monotherapy or adjunctive therapy to ICS, raised concerns regarding the safety of LABAs (Salpeter 2006). However, a subsequent commentary based on Cochrane Reviews strongly suggested that only the use of LABA as monotherapy was associated with the serious adverse health events, while the use of LABAs in combination with inhaled corticosteroids was protective (Ernst 2006).

A previous Cochrane systematic review suggested that an increased risk of exacerbations may be limited to patients receiving long-acting B2-agonists as monotherapy (Walters 2007). Although all national and international asthma consensus statements recommend the use of

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long-acting β2-agonists only in combination with inhaled corticosteroids (BTS 2007; Canadian Paediatic Asthma Guideline 2005; GINA 2007; NAC 2006; NAEPP 2007), some uncertainty remains regarding the safety of combination therapy (Cates 2009a; Cates 2009b).

In adults with unsatisfactory asthma control on inhaled corticosteroids, international guidelines clearly favour the addition of LABAs to low or moderate doses of inhaled steroids over other options such as increasing the dose of steroids or adding other agents. Variations across guidelines highlight ongoing uncertainties regarding the optimal use of LABAs as add-on treatment to inhaled steroids. First, the lowest dose of inhaled steroids to which LABAs could be considered as add-on therapy varies across guidelines. In adults, LABAs can be added to chlorofluorocarbon-propelled beclomethasone dipropionate (BDP) at a dose equivalent to or greater than 200 µg/day according to the American (NAEPP 2007), British (BTS 2007) and GINA guidelines (GINA 2007); 400 µg/day or more according to the Canadian consensus statement (Canadian Paediatic Asthma Guideline 2005); and 800 μ g/day or more according to the Australian recommendations (NAC 2006). Recommendations also vary by age group. In children aged five years and over, the addition of a LABA is recommended if inadequate control is achieved with 200 µg/day of BDP according to the British (BTS 2007) and American guidelines (NAEPP 2007); 400 µg/day according to the GINA recommendations (GINA 2007); and 800 µg/day according to the Australian (NAC 2006) and Canadian (Canadian Paediatic Asthma Guideline 2005) statements. Secondly, the preference of adding LABA to inhaled steroids as 'step three' option over other alternative strategies varies by age. Indeed, the Canadian (Canadian Paediatic Asthma Guideline 2005) and Australian (NAC 2006) guidelines clearly favour increasing the dose of inhaled corticosteroid to 800 µg/day BDP-equivalent before adding LABAs, as favoured by the British (BTS 2007) and American (NAEPP 2007) guidelines. In infants and preschool-aged children, a LABA is not recommended as add-on therapy, except by the American guidelines which suggest LABAs as add-on to 100 to 400 µg/day of BDP or equivalent (NAEPP 2007). Finally, the criteria for considering the addition of LABA are vaguely described as inadequate control with no clear instruction as to whether the severity of baseline obstruction, duration of use, type and dose of LABA, dose difference between ICS as monotherapy and combination therapy, number of devices to deliver combination therapy or atopy may be important factors. We sought to update our systematic review of randomised controlled trials in order to clarify ongoing uncertainties about the optimal use of LABAs as add-on therapy to inhaled steroids and the subgroups of patients that may benefit most from the intervention (Ni Chroinin 2005).

OBJECTIVES

The objective of this review was to assess the safety and clinical efficacy in asthma control resulting from the addition of long-acting β_2 -agonists to inhaled corticosteroids in asthmatic patients.

We also wished to examine whether the efficacy of long-acting β_2 -agonists was influenced by age, severity of airway obstruction, dose of inhaled corticosteroids to which long-acting β_2 -agonists were added, number of devices to deliver combination therapy, the dose and

type of long-acting β_2 -agonist and the duration of intervention. Additionally we wished to assess carefully the safety profile (and its possible determinants) of long-acting β_2 -agonists administered as add-on therapy to inhaled corticosteroids.

METHODS

Criteria for considering studies for this review

Types of studies—Only randomised controlled trials conducted in adults, children or both, in whom long-acting β 2-agonists were added to inhaled corticosteroids.

Types of participants—Children aged two years and above or adults with chronic asthma and having received daily inhaled corticosteroids for at least four weeks prior to study entry.

Types of interventions—Long-acting β_2 -agonist (salmeterol or formoterol) or placebo administered daily at a fixed dose for at least 28 days. The dose of inhaled corticosteroids had to be similar between the intervention (LABA + ICS) and the control (ICS monotherapy) groups. Other co-interventions such as xanthines, anticholinergics and other anti-asthmatic medications were accepted, provided that the dose remained unchanged throughout the study. Rescue inhaled short-acting β_2 -agonists and short courses of oral steroids were permitted.

Types of outcome measures

<u>Primary outcomes:</u> The primary outcome was the number of patients with asthma exacerbations of moderate intensity; that is requiring a short course of oral corticosteroids.

Secondary outcomes

- **1.** Other measures reflecting the severity of acute exacerbations, such as hospital admissions.
- 2. Measures reflecting chronic asthma control, including changes in pulmonary function tests, symptoms, days and nights without symptoms, functional status, quality of life and use of rescue short-acting β₂-agonists.
- **3.** Changes in measures of inflammation, such as serum eosinophils, serum eosinophil cationic protein and sputum eosinophils.
- 4. Withdrawals.
- 5. Rates of serious adverse events, clinical and biochemical adverse effects.

Search methods for identification of studies

We carried out the most recent searches in May 2008.

Electronic searches—We carried out a search in the Cochrane Airways Group Specialised Register of asthma trials, which is derived from systematic searches of bibliographic databases including the Cochrane Central Register of Controlled Trials

(CENTRAL), MEDLINE, EMBASE and CINAHL and handsearching of respiratory journals and meeting abstracts. This Register also contains a variety of studies published in foreign languages. We did not exclude trials on the basis of language.

The Register was searched using the following terms: (((beta* and agonist*) and long-acting or "long acting") or ((beta* and adrenergic*) and long-acting or "long acting") or (bronchodilat* and long-acting or "long acting") or (salmeterol or formoterol or advair or symbicort)) and (((steroid* or glucocorticoid* or corticosteroid*) and inhal*) or (budesonide or beclomethasone or fluticasone or triamcinolone or flunisolide).

Searching other resources—We searched the clinical trial websites of manufacturers of long-acting beta-agonists: GSK (GlaxoSmithKline (GSK) Clinical Trials Register), AstraZeneca (AstraZeneca Clinical Trials Register) and Novartis (Novartis Clinical Trials Database). We consulted an additional website listing results of published and unpublished clinical trials (Clinical Study Results).

We checked reference lists of all included studies and reviews to identify potentially relevant citations.

We also made enquiries regarding other published or unpublished studies known to the authors of the included studies or to pharmaceutical companies, namely GlaxoSmithKline and AstraZeneca who manufacture the agents.

Data collection and analysis

Selection of studies—From the title, abstract or descriptors, one of the review authors (IRG or MNC and FMD or TL) independently reviewed the literature searches. We excluded all studies that were clearly not randomised controlled trials or that clearly did not fit the inclusion criteria. Two review authors reviewed all other citations independently in full text, assessing for inclusion based on study design, population, intervention and outcome.

Data extraction and management—Two review authors (IRG or MNC and FMD or TL) independently extracted data from the trials and entered these into a designated Excel workbook for double-checking. Data were transferred by TL to the Review Manager software (RevMan 2008). Where necessary, we performed expansions of graphic reproductions and estimations from other data presented in the paper.

We reported the mean daily dose of inhaled corticosteroids in both the intervention and control groups, in chlorofluorocarbon (CFC)-propelled beclomethasone-equivalents, where 1 μ g of beclomethasone dipropionate equates to 1 μ g of budesonide and 0.5 μ g of fluticasone propionate (NAEPP 2007). All doses of inhaled medications were reported based on exvalve rather than ex-inhaler values.

Assessment of risk of bias in included studies—For the 2008 update of this review we undertook an assessment of the risk of bias for eligible studies, based on the recommendations described in the *Cochrane Handbook for Systematic Reviews of*

Interventions (Cochrane Handbook). This entailed describing potential sources of bias in eligible trials (allocation, blinding, missing data and the availability of our primary outcome), and providing our judgement of how the design of each study protects against each potential source of bias. We have collated our judgements in a graphical overview. The methodology applied in the previous version of this review is given in Appendix 1.

Measures of treatment effect—The analysis focused on long-acting ß2-agonist (LABA) and inhaled corticosteroids (ICS) (LABA + ICS) versus a similar dose of inhaled corticosteroids (ICS monotherapy) as second-line treatment, that is in patients already on inhaled corticosteroids.

Unit of analysis issues—We included data from cross-over studies in this review provided that we could obtain estimates of within-patient differences, and their associated standard errors from either back-calculating 95% confidence intervals or from P values from appropriate statistical tests.

When a trial had more than one intervention or control group, additional intervention-control comparisons were considered, if appropriate for this review. If two intervention-control comparisons used the same group twice as comparator (for example a three-arm study had two LABA + ICS arms and one ICS monotherapy arm) the number of participants in the group used twice (in this instance, the ICS monotherapy group) was halved to avoid over-representation (Buhl 2003a; Buhl 2003b; Zetterstrom2001a;Zetterstrom 2001b; Zimmerman 2004a; Zimmerman 2004b). For event rates, the numerator was also halved in the control group.

Dealing with missing data—We asked primary authors or sponsors to confirm the methodology and data extraction and to provide additional information and clarification for the trial, as needed. We contacted study authors/sponsors to obtain data on our primary outcome of exacerbations requiring oral steroids, and if possible hospital admissions and serious adverse events where they were not available in the primary study reports.

Assessment of heterogeneity—We tested homogeneity of effect sizes between studies being pooled with the I² statistic, with a value greater than 25% as the cut-off for heterogeneity (Higgins 2003). In the absence of heterogeneity we used the fixed-effect model (Greenland 1985). If heterogeneity was suggested by the I², we applied the Dersimonian and Laird random-effects model (DerSimonian 1986) to the summary estimates. Unless otherwise specified the fixed-effect model is reported. Equivalence was assumed if the relative risk estimate and its confidence interval were between 0.9 and 1.1.

Data synthesis—We calculated treatment effects for dichotomous variables using a relative risk (RR) with 95% confidence intervals (CI). For continuous outcomes, such as pulmonary function tests, we pooled data with weighted mean differences (WMD) for outcomes on the same scale or standardised mean differences (SMD) if the same construct was measured but done so with different scales. For both WMDs and SMDs we reported the mean difference with 95% confidence intervals.

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We derived numbers needed to treat (NNT) from the pooled risk ratios using Visual Rx (an online calculator at http://www.nntonline.net) (Cates 2002). In order to reflect the variation in control group event rates, we also calculated NNTs for an average risk across the lower, middle and upper quartiles of the events rates, weighting the control event rates (CERs) by sample size. We undertook a fail-safe N test to determine how many negative studies would be required to overturn the results (Gleser 1996).

Subgroup analysis and investigation of heterogeneity—We planned subgroup analyses to explore possible reasons for heterogeneity of the primary outcome and in the absence of heterogeneity, to identify potential effect modifiers for which the magnitude of effect may change according to the value of the characteristic (for example, severity of airway obstruction). We examined the following *a priori* defined subgroups to explore their influence on the magnitude of effect (effect modification).

- 1. Magnitude of airway obstruction at baseline as determined by the mean percent predicted forced expiratory volume in one second (FEV₁): classified as mild (FEV₁ 80% or more), moderate (FEV₁ 61% to 79%) or severe (FEV₁ 60% or less) (GINA 2007).
- 2. Children (less than 18 years of age) versus adults.
- **3.** Mean dose (ex-valve) of inhaled corticosteroids in both groups, reported in CFCpropelled beclomethasone-equivalent doses (μg/day), portrayed as the user-defined number.
- **4.** Usual versus higher than usual dose (reported as ex-valve in μg) of the long-acting β2-agonist (salmeterol or formoterol).
- 5. Type of long-acting ß2-agonist (salmeterol versus formoterol).
- 6. Use of one or two devices to deliver the combination of ICS plus LABA.
- 7. Trial duration (16 and > 16 weeks).

Since the publication of the original protocol in 1999 and prior to data analysis, we have added the last three subgroup analyses. Subgroup six was added because of recent data (Nelson 2003) suggesting a differential effect when using one or two devices to deliver the combination of LABA plus ICS. We added subgroup seven to investigate the risk of tachyphylaxis.

We examined differences in the magnitude of effect attributable to these subgroups with the residual Chi² test from the Peto odds ratios or with the t-test for weighted mean differences (Deeks 2001). We conducted a multivariate meta-regression to examine the simultaneous impact of, and interaction between, the above-named variables on the variance in the risk of patients with exacerbations requiring oral steroids. Backward and forward models were built using these subgroups as well as using FEV₁ (litres) and dose of inhaled corticosteroids (μ g/ day) as continuous variables (Small Stata for Windows, Version 11 2009, Stata Corporation, Texas, USA).

Sensitivity analysis—We used funnel plots to examine the possibility of publication bias (Egger 1997). We undertook a sensitivity analysis by source of data, by removing the study data which were made available from unpublished sources. We did this since a considerable number of unpublished studies were identified from pharmaceutical company trial registers, or data from published studies were made available through correspondence with pharmaceutical companies.

RESULTS

Description of studies

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

Results of the search—Electronic and handsearches yielded a total of 376 citations between April 2004 and May 2008 (see Table 1 for previous all-year search results). A flow diagram depicting the inclusion and exclusion of studies for this update is given in Figure 1.

Included studies—We have included 77 randomised treatment-control comparisons (referred to hereafter as studies) represented by 179 citations. This represents the addition of 44 studies to the original review, adding data from 14,043 participants to the 7205 patients recruited in studies included in the previous version (Ni Chroinin 2005). A full description of each study is given in the Characteristics of included studies table.

Fourteen trials contributed two treatment-control comparisons, as they assessed more than one mode of delivering combination therapy, or assessed more than one dose of inhaled steroids as a control intervention (Aubier 1999a; Aubier 1999b; Buhl 2003a; Buhl 2003b; D5896C0001a; D5896C0001b; Jenkins 2006a; Jenkins 2006b; Morice 2008a; Morice 2008b; Noonan 2006a; Noonan 2006b; O'Byrne 2001a; O'Byrne 2001b; Pauwels 1997a; Pauwels 1997b; Pohunek 2006a; Pohunek 2006b; SD 037 0344a; SD 037 0344b; SD 039 0725a; SD 039 0725b; SD 039 0726a; SD 039 0726b; Zetterstrom 2001a; Zetterstrom 2001b; Zimmerman 2004a; Zimmerman 2004b). Each comparison, hereafter counting as a separate study with the adjustment, is described in the methods to avoid overrepresentation of subjects.

Of the included studies 17 have not been published as full-text journal articles (Hultquist 2000; SAM40008; SAM40012; SAS40024; SAS40036; SAS40037; SD 037 0344a; SD 037 0344b; SD 039 0714; SD 039 0718; SD 039 0719; SD 039 0725a; SD 039 0725b; SD 039 0728; SFA100316; SFCF4026; SMS40012).

Participants: There were 21,248 participants (16,623 adults; 4625 children) randomised to the included studies. Study size varied from 16 (Simons 1997) to 2252 (GOAL). Twenty-eight (36%) studies recruited adults exclusively (> 18 years); 24 (31%) recruited children and 21 (27% of trials) studies permitted the enrolment of an unspecified number of adolescents aged 12 years or more. In two trials the lower age cut-off was 15 years (SAS40036; SAS40037). In Houghton 2007 and SD 039 0349 the mean age suggested that the participants were predominantly adults with an unspecified age limit for enrolment.

In adult trials, the mean age of participants was relatively homogeneous, varying from 35 years (Li 1999) to 48 years (Zetterstrom 2001a). In paediatric studies it ranged from eight years (Malone2005) to 14 years (Langton Hewer 1995). The gender distribution varied widely from 30% males in Norhaya 1999 to 71% in Langton Hewer 1995.

In all but three trials, participants clearly had inadequate asthma control (that is, ongoing symptoms and use of rescue short-acting β_2 -agonists in addition to maintenance inhaled steroids) at the time of enrolment. In the remaining three trials (Meijer 1995; Shapiro 2000; Simons 1997) participants appeared asymptomatic and well-controlled according to the Canadian consensus guidelines (Canadian Paediatic Asthma Guideline 2005).

In over half of the studies (N = 45, 58%) the mean severity of baseline airway obstruction was moderate (that is, FEV_1 or PEF predicted of 61% to 79%); while it was mild (80% or more of predicted) in 23 (30%) studies, and unavailable in the nine (12%) remaining studies (D'Urzo 2001; SAM40008; SAM40012; SAS40037; SD 037 0344a; SD 037 0344b; SFA100314; SFA100316; SFCF4026).

The presence of atopic disease at baseline was reported in only 13 studies, all of which reported atopy in 58% to 100% of participants (Akpinarli 1999; GOAL; Koopmans 2006; Langton Hewer 1995; Li 1999; Meijer 1995; Russell 1995; Simons 1997; Stelmach 2007; Tal 2002; van der Molen 1997; Verberne 1998; Wallin 2003).

Type, dose and delivery of inhaled therapy: The long-acting β_2 -agonist was formoterol in 42 (54%) studies and salmeterol xinafoate in 35 (46%). The overwhelming majority (N = 73) of studies tested recommended doses of the long-acting β_2 -agonist (that is, salmeterol 50 µg twice daily, formoterol 6 or 12 µg twice daily). In four studies a higher than usual dose of salmeterol (100 µg twice daily in Boyd 1995 and Langton Hewer 1995) or formoterol (24 µg twice daily in SD 039 0728; van der Molen 1997) was used.

All but five studies examined the combination of LABA plus ICS versus ICS monotherapy in a twice-daily regimen: Buhl 2003a; D5896C0001b; Kuna 2006 and SD 039 0725a; SD 039 0725b examined the two options as a once-daily administration regimen. Within each study the dose of inhaled corticosteroid to which LABA was added was similar to ICS monotherapy in the control groups and fixed for all patients. It was a uniform dose in 57 (73%) studies and a range or unspecified dose for the remaining 20 studies. Of the studies assessing LABA in conjunction with fixed-dose ICS, 36 (49%) tested the addition of LABA to low-dose inhaled corticosteroids (200 to 400 µg/day of beclomethasone, or equivalent), five (7%) added LABA to a medium dose of ICS (401 to 799 µg/day of beclomethasone, or equivalent) and 16 (21%) studies used a high dose of ICS (800 µg/day or more of beclomethasone, or equivalent). LABA was added to budesonide (31 studies), beclomethasone (four studies) budesonide or beclomethasone (one study) or fluticasone propionate (22 studies). The remaining trials only indicated that the ICS used was usual ICS therapy.

Thirty-four (44%) studies used two inhaler devices to deliver ICS and LABA, while 27 (42%) studies used one device. Five trials (represented by ten studies) tested both one and

two delivery devices against inhaled steroids (Aubier 1999a; Aubier 1999b; Jenkins 2006a; Jenkins 2006b; Noonan 2006a; Noonan 2006b; Pohunek 2006a; Pohunek 2006b; Zetterstrom 2001a; Zetterstrom 2001b).Wallin 2003 failed to report the number of devices used. Compliance was assessed or monitored in 13 studies.

Study duration: The duration of the intervention in 43 studies (56%) studies was between 12 and 16 weeks. Sixteen (21%) studies lasted between four and eight weeks while the remaining 18 studies (23%) lasted from 24 to 54 weeks. Of note, only available data from the initial 12 weeks of the GOAL study were included to isolate the portion of this 52-week trial that corresponded to the specific criteria of this review, and thus ensure homogeneity of included trial protocols. Indeed, GOAL used three 'step up' phases, each of 12 weeks duration in the initial phase of the study, during which the dose of inhaled corticosteroids was increased until either total asthma control was achieved or a pre-specified maximal dose was achieved. Upon achieving pre-defined asthma control by the end of the 'step', participants entered the second phase during which the background fluticasone dose was maintained for the remainder of the trial. Since the dose of ICS varied upward after the initial 12 weeks, we extracted data for the first 12 weeks while on a fixed dose.

Permitted co-treatment: Co-intervention with other prophylactic medications was explicitly permitted in six studies provided that doses remained unchanged throughout the trial. These included oral steroids, anti-cholinergics and xanthines (Langton Hewer 1995), cromoglycate and xanthines (Norhaya 1999) and immunotherapy (Zimmerman 2004a; Zimmerman 2004b). Two studies (Ind 2003; Russell 1995) permitted co-intervention with other agents but did not mention specifically which drugs. Patients taking prophylactic medications were excluded in 16 other trials and this factor was unreported in the remaining trials. Rescue medications such as inhaled short-acting β2-agonists and oral steroids were permitted in all the trials.

Outcomes: Data for the main outcome measure, the number of participants with one or more exacerbations requiring oral steroids, were reported or were made available to the authors on request for 30 studies.

Most studies reported changes in lung function, use of rescue β_2 -agonists, withdrawals due to any reason, withdrawals due to poor asthma control and overall adverse health events. There was a large variation in the way improvement in symptoms (symptom score, percent symptom-free days, percent days with symptoms, percentnight awakenings) and use of rescue fast-acting β_2 -agonist were reported, both using various parameters (average value, final value at endpoint, percent change and change in percent values). Wide variations in reporting prevented the aggregation of some of the available data.

Funding: The overwhelming majority (86%) of the studies were sponsored by producers of both LABA and ICS: 33 studies were supported by GSK; 32 by AstraZeneca; three by Astra Draco (Pauwels 1997a; Pauwels 1997b; van der Molen 1997); one by Allen & Hanburys, a subsidiary of GSK in the United Kingdom (Boyd 1995); and one by Novartis (Fitzgerald 1999). Only one trial was independently supported by a charity organisation (Langton Hewer 1995) and a further study was supported by a University grant (Stelmach 2007). One

study acknowledged AstraZeneca in the provision of active and placebo inhalers, but did not indicate that a grant had been awarded for the trial from the company (Green 2006). Four studies failed to declare a source of funding (Gardiner 1994; Teper 2005; Zimmerman 2004a; Zimmerman 2004b).

Excluded studies—A total of 315 studies did not meet the eligibility criteria of the review. They are listed in the section: Characteristics of excluded studies.

Risk of bias in included studies

Correspondence with GSK established the procedures used to allocate participants to treatment groups in studies sponsored by GSK (see Appendix 2). We have collated our judgements on the risk of bias for each study and present them in Figure 2.

Allocation—Information regarding the allocation of participants to treatment groups was sufficient to grade 45 (58%) studies as being of low risk of selection bias. Information regarding the remaining studies did not allow us to make judgements.

Blinding—Only one study had an open label design (Molimard 2001), the remainder being double-blind with an appropriate means of masking treatment (identical inhaler device, or double dummy design), except for D'Urzo 2001, Reddel 2007 and Teper 2005 where we could not establish how blinding was maintained.

Incomplete outcome data—The handling of withdrawals and drop-outs from analyses were not adequately described in many of the studies since the definition of 'intention-to-treat' population varied or was not adequately defined. Methods such as last observation carried forward and imputation were applied in only a few studies, with the majority of trials not defining what the intention-to-treat population was.

Selective reporting—We could not find definitive evidence of selective reporting in the studies, which we considered only in relation to our primary outcome of oral steroid-treated exacerbations. Although a number of studies did collect data on exacerbations, we were unable to obtain further information on which of these were managed in accordance with our stated primary endpoint. Some data specific to exacerbations requiring oral steroid were made available to us for a number of studies (see risk of bias tables in the Characteristics of included studies).

Other potential sources of bias—One study stated how many patients were screened for eligibility (Green 2006). Thirty-four studies reported the percent of run-in participants that were successfully randomised, ranging from 43% to 95% of recruited patients.

Effects of interventions

Primary outcome: exacerbations of asthma requiring oral steroids—Thirty studies (39% eligible studies) reported data for this outcome (two studies reported no events occurring in either group). The addition of a LABA to ICS therapy led to a 23% reduction (from 15% to 11%) in the relative risk of patients experiencing one or more exacerbations

requiring oral corticosteroids (RR 0.77, 95% CI 0.68 to 0.87, P < 0.0001, N = 6808) (Figure 3). We did not observe any more statistical heterogeneity than would be expected due to the play of chance ($I^2 = 0\%$). The result of the overall fail-safe N test was that 222 studies with negative findings would be needed to bring the estimate back to null (Gleser 1996).

The overall number needed to treat to prevent one rescue oral corticosteroids was 41 (29, 72) based on studies of between four and 54 weeks duration, and a pooled control group event rate of 15%. However, the baseline risk (i.e. the control group event rate) of exacerbations requiring treatment with oral corticosteroids varied between the studies, with quartiles of low (0% to 2%), low/medium (3% to 6%), medium/high (7% to 23%) and high (23% to 38%) risk (Table 2). Applying the pooled risk ratio to middle values across these quartiles, the NNTs were between 17 and 435:

Risk status	Median control group event rate (% (range))	Median study duration (weeks (range))	Mean FEV ₁ (% predicted (range))	NNT benefit
Low	1 (0 to 2)	4 (4 to 12)	70 (64 to 78)	435
Low/medium	4 (3 to 6)	12 (4 to 16)	77 (68 to 93.4)	109
Medium/high	14 (7 to 23)	26 (4 to 54)	76 (73 to 87)	32
High	26 (23 to 38)	24 (8 to 52)	75 (66 to 86)	17

Sensitivity analyses by risk of bias (allocation sequence generation, allocation concealment, blinding and completeness of follow up) did not alter the direction of the results and made little impact on the upper limit of the confidence interval (Analysis 2.9; Analysis 2.10; Analysis 2.11; Analysis 2.12).

Despite the absence of heterogeneity, we conducted *a priori* subgroup analyses to examine the impact of the following variables on the variance of the magnitude of effect observed (effect modification). There was no significant difference in the relative risks between subgroups based on airway obstruction (P = 0.20), age group (P = 0.53), dose of inhaled steroids (P = 0.34), type of LABA (P = 0.16), treatment duration (P = 0.13), number of devices (P = 0.45) or funding sources (P = 0.63). The effect in paediatric trials was not statistically significant (RR 0.89, 95% CI 0.58 to 1.39) and the confidence interval not only encompasses the limits of the estimate from the adult studies, it includes possibility of signifi-cant benefit of ICS alone over LABA in this age group. There were differences between usual and higher than licensed doses which reached statistical significance in favour of usual LABA doses (usual dose: RR 0.74 (95% CI 0.65 to 0.84) versus higher than usual dose: RR 1.10(95% CI 0.79 to 1.52, P = 0.03) (Analysis 2.5). The meta-regression suggested the independent effect-modifying effects of the LABA dose, baseline FEV1 and treatment duration, where higher than usual dose, higher baseline FEV_1 or longer duration was associated with less benefit of combination therapy; all three variables were correlated (0.29 to -0.63).

There was no evidence of systematic bias identified by the test for funnel plot asymmetry (intercept 0.264, 95% CI –0.233 to 0.761). Since data for our primary outcome were not available in a number of full-text articles and had to be requested through correspondence,

we undertook a sensitivity analysis to assess the robustness of the result to data source. We removed studies which were only available as short reports from manufacturer trials registers, or for which we had to correspond to obtain relevant data, leaving only those studies for which data were available in a full-text article. The resultant analysis restricted to published data gave a near identical result to the primary analysis (RR 0.77, 95% CI 0.67 to 0.88) (Analysis 2.13), although a funnel plot for this outcome did suggest some asymmetry without the unpublished data included (Figure 4). Since all but one trial contributing to the primary outcome was funded by manufacturers of LABA, we could not assess the impact of study sponsorship on the pooled effect size reliably.

Secondary outcomes

Exacerbations requiring hospitalisation, serious adverse events and withdrawal: There was no significant group difference in the risk of exacerbations requiring admission to hospital (RR 1.13, 95% CI 0.70 to 1.82, 24 studies (of which 15 contribute numerical data)) (Figure 5).

The risk of all-cause serious adverse events (events requiring or prolonging hospital admission or causing death) was similar in the two treatment groups (RR 1.06, 95% CI 0.87 to 1.3, 53 studies (of which 48 contribute numerical data)) (Figure 6).

The use of LABA significantly reduced the risk of overall withdrawals by 20% (all reasons included): RR 0.80 (95% CI 0.75 to 0.87, 53 studies) (Analysis 1.4) and reduced the risk of withdrawals due to poor asthma control by 50% (RR 0.50, 95% CI 0.41 to 0.61, 38 studies) (Analysis 1.5).

Lung function: The addition of LABA to ICS provided significantly greater improvement in lung function over using the same dose of ICS as monotherapy (outcomes Analysis 1.8 to Analysis 1.17), irrespective of whether the group differences were reported as endpoint or change from baseline: change from baseline in FEV₁ in litres (0.11 L/sec, 95% CI 0.09 to 0.13, random-effects model, 32 studies) (Analysis 1.9), change in percent predicted (3.73% predicted, 95% CI 2.66 to 4.8, random-effects model, eight studies) (Analysis 1.10), FEV₁ at endpoint in litres (0.12 L/sec, 95% CI 0.07 to 0.17, 10 studies) (Analysis 1.8), FEV₁ percent predicted at endpoint (5.34% predicted, 95% CI 3.29 to 7.38, four studies)(Analysis 1.11), change from baseline in morning peak expiratory flow (PEF) (19.24 litres/min, 17.08 to 22.20, random-effects model, 51 studies) (Analysis 1.14); or in evening PEF (17.89 litres/ min, 95% CI 14.82 to 20.95, random-effects model, 33 studies) (Analysis 1.16) and morning PEF at endpoint (26.21 litres/min, 95% CI 13.31 to 39.1, random-effects model, eight studies) (Analysis 1.13). There were insufficient data (fewer than two trials) to aggregate the change in PEF variability or evening PEF at endpoint.

While subgroup analysis of the change in FEV₁ with respect to duration of study (P = 0.67) (Analysis 1.12) did not identify statistically significant differences, the change in FEV₁ was significantly influenced by baseline % predicted FEV₁ with greater effect of LABA in patients with lowest baseline values (>= 80% predicted: 0.09 L (95% CI 0.03 to 0.14) versus 61% to 79% predicted: 0.12 L (95% CI 0.09 to 0.14, P = 0.03) (Analysis 1.9).

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Symptoms and rescue medication use: Use of LABA significantly reduced daytime symptoms (SMD -0.33, 95% CI -0.42 to -0.23, eight studies) (Analysis 1.19); nighttime symptoms (SMD -0.22, 95% CI -0.33 to -0.11, five studies) (Analysis 1.20) and overall 24-hour symptoms (SMD -0.23, 95% CI -0.34 to -0.12, six studies) (Analysis 1.18). The superiority of LABA and ICS over ICS monotherapy was also observed in the percent of symptom-free days during the observation period (WMD 7.31, 95% CI 0.50 to 14.12, random-effects model, six studies) (Analysis 1.21); the change from baseline in symptom-free days (11.88%, 95% CI 8.25 to 15.50, random-effects model, 16 studies) (Analysis 1.22) and in symptom-free nights (SMD 0.51, 95% CI 0.28 to 0.74, random-effects model, four studies) (Analysis 1.25). The favourable effect of LABA was observed in the change in "asthma-control" days (15.81%, 95% CI 10.85 to 20.77, four studies) (Analysis 1.26). There were no significant group differences for the change in percent nights with no awakening (1.01%, 95% CI -1.06 to 3.08, five studies) (Analysis 1.35) and in night-time awakening (SMD -0.10, 95% CI -0.21 to 0.01, five studies) (Analysis 1.37).

The addition of LABA to ICS also reduced the need for rescue short-acting B_2 -agonists whether reported as daytime use at endpoint (-0.73 puffs/day, 95% CI -1.24 to -0.22, random-effects model, two studies) (Analysis 1.29); night-time use at endpoint (-0.44 puffs/ night, 95% CI -0.81 to -0.07, random-effects model, two studies) (Analysis 1.30); change in overall 24-hour use (-0.58 puffs/24 hours, 95% CI -0.80 to -0.35, random-effects model, 14 studies) (Analysis 1.27); change in night-time use (-0.3 puffs/night, 95% CI -0.48 to -0.11, random-effects model, seven studies, Analysis 1.31); change in rescue-free days (6.43%, 95% CI -1.2 to 11.66, two studies) (Analysis 1.34) or change in daytime use (-0.68 puffs/day, 95% CI -0.94 to -0.42, random-effects model, 13 studies) (Analysis 1.28). The change in mean rescue-free days (17.05%, 95% CI 13.75 to 20.35, six studies) (Analysis 1.32) and in quality of life (as measured by the AQLQ) also favoured LABA (0.26, 95% CI 0.04 to 0.47, random-effects model, three studies) (Analysis 1.38). There was no group difference in the percent of nights with awakening (WMD -1.37, 95% CI -2.75 to 0.02, fixed-effect model, two studies) (Analysis 1.36).

Non-serious adverse events: There was no apparent group difference in the risk of overall adverse effects (RR 1.00, 95% CI 0.97 to 1.04, 41 studies) (Analysis 1.39), meeting our *a priori* defined limits of equivalence. There was also no group difference in the risk of specific side effects including headache (RR 0.99, 95% CI 0.87 to 1.13, 37 studies) (Analysis 1.40); hoarseness (RR 1.17, 95% CI 0.44 to 3.1, random-effects model, six studies) (Analysis 1.41); oral thrush (RR 1.65, 95% CI 0.71 to 3.86, nine studies) (Analysis 1.42); tachycardia or palpitations (RR 2.11, 95% CI 0.83 to 5.37, 12 studies) (Analysis 1.44); cardiovascular adverse effects such as chest pain (RR 0.90, 95% CI 0.32 to 2.54, four studies) (Analysis 1.46) or tremor (RR 1.74, 95% CI 0.72 to 4.20, random-effects model, 16 studies) (Analysis 1.43). There was no statistically significant difference from three studies reporting death (RR 2.46, 95% CI 0.48 to 12.65) (Analysis 1.45). However, the wide confidence interval (including the upper limit) for some adverse events was high for tachycardia, palpitations, tremor and death, indicating uncertainty. More dramatic was the scarce documentation of the impact on growth (in children), adrenal function and bone mineral density, preventing any aggregation due to the paucity (0 to 2) of trials measuring or

reporting these outcomes. Withdrawal due to adverse events showed no significant difference between treatment options (RR 1.04, 95% 0.86 to 1.26, 52 studies) (Analysis 1.6).

DISCUSSION

The strength of the evidence allows us to confirm the efficacy of adding a long-acting β_2 agonist (LABA) to inhaled corticosteroids (ICS) in reducing the risk of exacerbations requiring rescue oral corticosteroids in adults. In children the evidence in favour of LABAs is far less certain, with wide confidence intervals including both superiority and inferiority of LABA to ICS alone. The studies have largely recruited adults and older children with suboptimal asthma control on monotherapy with inhaled corticosteroids. The addition of a LABA to ICS reduced the relative risk of patients requiring oral steroids for an asthma exacerbation by 23% (from 15% to 11%) in studies of four to 54 weeks duration. The efficacy of adding a LABA to inhaled steroids was also supported by several secondary outcomes, namely the significantly greater improvement in FEV₁ (by 110 ml) and morning PEF (20 litres/min), in symptom-free days (12%), in rescue-free days (6%) and a reduction by half in the risk of withdrawal due to poor asthma control compared to ICS monotherapy. The addition of a LABA was not associated with an increase in serious adverse events (SAEs), although the width of the confidence interval was large and could not exclude as much as a 30% increase in risk or a 13% reduction in risk of SAEs. There was no group difference in any documented specific adverse events with the wide confidence intervals around the estimates of risk for tachycardia or palpitation and death, indicating remaining uncertainty. However, the overall relative risk of adverse events between groups reached our *a priori* definition of equivalence, and there was no group difference in the rate of withdrawals due to side effects.

There was no evidence of statistical heterogeneity between trials in the primary outcome, despite the inclusion of populations of different ages, baseline severity of airway obstruction, use of different ICS doses and different LABAs. The overall number needed to treat (NNT) was 41 patients. We do acknowledge variation of baseline risk of rescue oral steroids between the control groups. When baseline risk is broken down further by quartile (see Results), the highest NNT of 435 was estimated for studies with the lowest baseline risk (between 0% and 2%). These studies had a short duration (four weeks was the median), although mean baseline FEV₁ was the lowest for all of the risk quartiles at 70%.

As event rates in the control group increased across the medium and high-risk quartiles, the NNTs fell to 109, 32 and 17 respectively. Although the median study durations for studies in these risk quartiles were longer at 12, 26 and 24 weeks respectively, and the mean FEV_1 was higher (77%, 76% and 75% predicted respectively), these two factors probably do not well identify the risk groups defined by the baseline rate of exacerbations. In view of the wide confidence interval from the paediatric studies the similarity of the subgroup estimates for the primary outcome could reflect lower statistical power for the studies in this subgroup than for the adult studies, with children representing less than 10% of the overall number of study participants (605 children versus 6203 adults).

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While the results seem to apply to particularly to adults, irrespective of baseline characteristics and variation of intervention, the meta-regression and subgroup analyses both suggested that higher than usual dose of LABA significantly reduced the beneficial effect of LABA. Perhaps other factors such as baseline FEV_1 and treatment duration modify the magnitude of effect but until further confirmation it is safe to assume that the addition of LABA to ICS probably yields similar benefit irrespective of the baseline FEV_1 , starting dose of ICS, type of LABA, number of devices to deliver the combination therapy or treatment duration. Whether the addition of LABA to ICS is superior to increasing the dose of ICS is addressed in another review (Ducharme 2010).

The improvement in lung function with the use of LABAs might be anticipated from their physiologic action, although most studies obtained these measurements at the trough of the dosage interval (12 hours or more after the last LABA inhalation). Improvements were seen in all lung function tests (FEV₁ and PEF) whether measured in the respiratory laboratory or at home, in the morning or evening. While the addition of LABA reduced the need for rescue short-acting β 2-agonists slightly more than ICS, the effect was small: an average reduction of 0.58 puffs per 24 hours, -0.3 puffs/night and -0.68 puffs/day and a 6% increase in the percentage of rescue-free days. Similarly, a difference in the improvement of symptoms with LABAs was present but modest (SMD of between -0.2 to -0.3 for changes in symptom scores measured over 24 hours, day only or night only). Perhaps study eligibility criteria, which cited a requirement for frequent but not daily symptoms and short-acting β 2-agonist use during the run-in periods, explain this phenomenon. An alternative explanation may lie in the effectiveness of inhaled steroids alone for reducing symptoms and short-acting β 2-agonist use (Adams 2008; Manning 2008), perhaps magnified by enhanced compliance to inhaled corticosteroids in the context of these studies.

When used without ICS, salmeterol and formoterol increase the risk of serious adverse events (Cates 2008a; Cates 2008b). In this review, the outcomes relating to hospital admission and all cause serious adverse events did not provide evidence that the combination of use of LABAs and ICS increased the risk of these serious events. Our findings lend qualified support to the commentary by Ernst and colleagues (Ernst 2006), which attributed the adverse effect of LABA reported by Salpeter 2006 to its use without concomitant ICS. Due to the rarity of these events in the included studies, our pooled estimates were imprecise and the confidence intervals are not narrow enough to exclude either protection or harm confidently. This finding is concordant with separate analysis of salmeterol and formoterol as an additive treatment to ICS (Cates 2009a; Cates 2009b). Although the large confidence intervals around some other specific adverse effects highlight remaining uncertainties, the equivalence between groups in overall adverse effects is reassuring. Moreover, the absence of group difference in withdrawal due to adverse effects provides some support to the safety of adding LABA to ICS, when used up to 52 weeks.

The absence of data on airway inflammation that could be aggregated was disappointing. The concern that use of a LABA masks symptoms of poor asthma control and lead to deterioration of the airways is not supported by the evidence in our review. However, such a concern pertains to using a LABA as a steroid-sparing strategy, when used in combination with a lower dose of inhaled steroids than in the comparison group; in other words, when the

dose of inhaled corticosteroids is not equivalent to both treatment options. With similar improvement in FEV_1 irrespective of study duration, there was no evidence of tachyphylaxis associated with prolonged use of LABA.

Our review provides complementary information to other reviews examining the overall efficacy of LABA in paediatrics (Bisgaard 2003) and in adults (Walters 2007) when used as monotherapy and/or inconsistent co-treatment with ICS. There is enough power in our primary outcome to conclude firmly the efficacy of LABA as add-on to ICS when compared to a similar dose of ICS as monotherapy in adults: 222 studies with negative findings would be needed to reverse this finding. The efficacy of adding LABA to ICS applies to adults who are symptomatic on a ICS, as low as 200 μ g/day of beclomethasone or equivalent. In view of the subgroup result for paediatric studies we cannot currently be sure how the overall effect applies to children, and the priority remains for researchers to generate a more definitive evidence base for the effects of this strategy in children.

The generalisability of the findings to a clinic population must be considered with care. One of the main eligibility criteria of the studies was the presence of significant (12% to 15% or more) reversibility in FEV1 with a B2-agonist. However, such reversibility is demonstrated in less than 10% of patients at a given point in time (Storms 2003). Major exclusion criteria included smoking, pregnancy or lactation, as well as childbearing age without appropriate contraception. This may have excluded up to a half of our usual clinic patients. Finally, patients with severe airway obstruction, recent exacerbations, or both, were generally excluded. To how many of our patients would the results of these aggregated trials apply? Unfortunately only a limited amount of data were presented in the trials on the proportion of participants randomised to those screened for enrolment in the run-in period. Only 34% of studies reported the proportion of patients enrolled in the run-in period that were successfully randomised (varying between 43% and 95%). There was little reporting of adherence to treatment during the intervention period, mentioned in only 13 studies, with no adjustment or stratification in the analyses. Whether treatment with LABA plus ICS leads to improved compliance and thus better asthma control than ICS monotherapy could not be assessed in this review. The results of this review may not be generalised to the majority of our patients and in particular those with symptoms but poor reversibility in FEV₁.

Whether the addition of a LABA is more effective and safer than increasing the dose of inhaled corticosteroids (Ducharme 2010), adding anti-leukotrienes (Ducharme 2006) or whether it exerts a steroid-sparing effect (Gibson 2005) are addressed in other Cochrane Reviews.

AUTHORS' CONCLUSIONS

Implications for practice

In symptomatic adults with mild to moderate airway obstruction, who remain symptomatic despite a low, moderate or high dose of inhaled corticosteroids, the addition of a long-acting beta2-agonist at licensed doses is superior for reducing the rate of exacerbations requiring oral steroids, and for improving lung function, symptoms and quality of life, than remaining on similar doses of inhaled corticosteroids as monotherapy. There is little evidence to

support this treatment option in children as a means of reducing requirement for oral steroids, precluding firm recommendations regarding the use of LABA for children. The available evidence indicates that the risk of serious adverse events between treatments is not statistically significant, although imprecision of the estimate includes the possibility of both an increase and a decrease in the risk of serious adverse events with the addition of a LABA in all age groups.

Implications for research

Given the nature of the evidence, preschool-aged children and school-aged children warrant further investigation. Similarly, patients who are symptomatic on inhaled steroids, despite good compliance, but with little airway reversibility to short-acting β_2 -agonists should be targeted for inclusion in future studies. Stratified subgroup analyses on baseline FEV₁ and reporting effect size at different points in time would be useful to explore the potential modifying effect of these factors on response to therapy.

Future trials should be designed to take account of the following:

- **1.** double-blinding, adequate randomisation and complete reporting of withdrawals and drop-outs with intention-to-treat analysis;
- **2.** an intervention period of 12 weeks or more to assess properly the impact on exacerbations requiring oral corticosteroids;
- **3.** clear reporting of the percent (and reasons) of non-eligibility of approached patients and of those enrolled in the run-in period;
- **4.** complete reporting of continuous (denominators, mean change and mean standard deviation of change) and dichotomous (denominators and rate) data.

Outcomes of particular importance to assess include:

- 1. exacerbations requiring oral corticosteroids, to examine the effect of different patient characteristics, such as baseline lung function and baseline dose of ICS on this outcome;
- careful monitoring and reporting of compliance to ICS prior to randomisation and to ICS and LABA post-randomisation. The impact of compliance to combination therapy versus ICS monotherapy on the magnitude of the effect size should be examined;
- **3.** reporting of the cost-effectiveness of use of combination inhalers as compared to inhaled corticosteroids monotherapy;
- **4.** long-term side effects of long-acting β_2 -agonists.

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Internal sources

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Appendix 1. Archive of methodological approach to study quality assessment (1999 to 2004)

Studies to be included underwent quality assessment, performed independently by two review authors, using two methods. First, using the Cochrane approach to assess allocation of concealment, trials were scored using the following principles.

Grade A: adequate concealment.

Grade B: unclear concealment.

Grade C: clearly inadequate concealment.

In addition, each study was assessed using a 0 to 5 scale described by Jadad (1995) and summarised as follows.

1. Was the study described as randomised (yes = 1; no = 0)?

- 2. Was the study described as double-blind (yes = 1; no = 0)?
- 3. Was there a description of withdrawals and drop-outs (yes = 1; no = 0)?
- 4. Was the method of randomisation well-described and appropriate (yes = 1; no = 0)?
- 5. Was the method of double-blinding well-described and appropriate (yes = 1; no = 0)?

6. Deduct one point if methods for randomisation or blinding were inappropriate.

Appendix 2. Randomisation procedures for GSK studies

The procedures for randomising GSK sponsored studies have been detailed in correspondence between Richard Follows and TL, the details of which are given below:

The randomisation software is a computer-generated, centralised programme (RandAll). After verification that the randomisation sequence is suitable for the study design (crossover, block or stratification), Clinical Supplies then package the treatments according the randomisation list generated. Concealment of allocation is maintained by a third party, since the sites phone in and are allocated treatments on that basis. Alternatively a third party may dispense the drug at the sites. Unblinding of data for interim analyses can only be done

through RandAll, and are restricted so that only those reviewing the data are unblinded to treatment group allocation.

CHARACTERISTICS OF STUDIES

Characteristics of included studies [ordered by study ID]

Akpinarli 1999

Methods	Parallel-group multicentre study	7
Participants	Symptomatic asthmatic children % ELIGIBLE OF SCREENED POPULATION: Not reported % RUN-IN PARTICIPANTS RANDOMISED: Not reported RANDOMISED: 32 (ICS + F12 (bid): 16; ICS: 16) WITHDRAWALS: Not described AGE mean (range) or mean (SD): 6 to 14 years GENDER (% male): 47% SEVERITY: Not reported BASELINE % PREDICTED FEV ₁ : Not reported (study categorised as 61% to 79 predicted) BASELINE DOSE OF ICS: 400 to 800 mcg ASTHMA DURATION: Not described ATOPY (%): 68 ELIGIBILITY CRITERIA: Met ATS criteria for asthma; >= 15% increase in FEV within the previous year EXCLUSION CRITERIA: Asthma exacerbation or respiratory infection in < mon ELIGIBILITY CRITERIA DURING RUN-IN: Only patients requiring salbutamo more than once a week were randomised	
Interventions	LABA + ICS vs SAME dose of ICS OUTCOMES reported at 6 weeks RUN-IN PERIOD: 2 weeks with ICS 400 to 800 mcg/day to document symptoms and beta2 use DOSE OPTIMISATION PERIOD: NONE INTERVENTION PERIOD: 6 weeks TEST GROUP: (ICS + F12) ICS 400 to 800 mcg/day + formoterol 12 mcg bid CONTROL GROUP: (ICS) ICS (400 to 800 mcg/day) + placebo bid DEVICE: MDI + large volume spacer (Volumatic) NUMBER OF DEVICES: 2 COMPLIANCE: assessed by weighing canisters CO-TREATMENT: Not described	
Outcomes	INTENTION-TO-TREAT ANALYSIS: Not described PULMONARY FUNCTION TEST: % of predicted FEV1; morning PEFR (L/min); evening PEFR (L/min); PEF variability (%); PC 20 (mg/ml) SYMPTOM SCORES: score of 0 to 3 (max 9); night-time symptom score; symptom-free days or nights FUNCTIONAL STATUS: rescue B2-agonist use per week (each use consisted of 2 puffs); exacerbation requiring oral steroids; exacerbations requiring admission INFLAMMATORY MARKERS: Not described ADVERSE EFFECTS: described WITHDRAWALS: Not described Primary outcome measure not reported	
Notes	Full-text publication Funded by AstraZeneca Author contacted and unable to confirm methodology or data User-defined number: 600 (mean ICS dose in LAB2 group in mcg/day of BDP- equivalent: 400 to 800)	
Risk of bias		
Item	Authors' judgement	Description
Adequate sequence generation?	Unclear	Described as randomised; no other information presented

Blinding? All outcomes	Yes	Double-blind; identical placebo used
Incomplete outcome data addressed? All outcomes	Unclear	No information available on the statistical handling of missing data
Free of selective reporting?	Yes	Data on OCS-treated exacerbations available

Aubier 1999a

Methods	Parallel-group, 55 centres in Germany, Netherlands & France. Three treatment arms: combination FP/SAL, concurrent FP/SAL, FP alone		
Participants	Moderately severe asthmatic adults % ELIGIBLE OF SCREENED POPULATION: Not reported % RUN-IN PARTICIPANTS RANDOMISED: Not reported RANDOMISED: 503 (Combination FP/SAL: 167; concurrent FP/SAL: 171; FP alone: 165) WITHDRAWALS: Combination FP/SAL: 31; concurrent FP/SAL: 28; FP: 48 AGE: mean (range) or mean (SD): 48 years GENDER: (% male): 54% SEVERITY: Moderate BASELINE % PREDICTED FEV1 (mean): 73 BASELINE % PREDICTED FEV1 (mean): 73 BASELINE DOSE OF ICS: 1500 to 2000 mcg BDP equivalent ASTHMA DURATION: < 1 year: 3%; 1 to 5 years: 23%; 5 to 10 years: 20%; > 10 years: 54% ATOPY (%): 52 ELIGIBILITY CRITERIA: > 12 years; documented history of reversible airways disease; ICS treatment for 12 weeks prior to run-in; BDP or BUD 1500 to 2000 mcg/d or FP 750 to 1000 mcg/d EXCLUSION CRITERIA: Not reported ELIGIBILITY CRITERIA: Not reported ELIGIBILITY CRITERIA: Not reported ELIGIBILITY CRITERIA DURING RUN-IN: At end of 2-week run-in eligible candidates were symptomatic (symptom score >/= 2 on 4 of last 7 consecutive days), mean am PEF > 50% and < 85% of maximum PEF 15 min post SABA, and (FEV1) between 50% and 100% predicted		
Interventions	PROTOCOL: Concurrent ICS and LABA versus ICS alone OUTCOMES: 1, 2, 3, 4, 5 to 8, 9 to 12 weeks for PEF; 28 weeks for FEV1 RUN- IN: 2 weeks DOSE OF ICS DURING RUN-IN: Pre-study dose of ICS INTERVENTION PERIOD: 28 weeks TEST GROUP: Fluticasone and salmeterol 500/50 mcg bid given via separate inhalers CONTROL GROUP: Fluticasone 500 mcg bid DEVICE: Diskus NUMBER OF DEVICES: 2 COMPLIANCE: Not assessed CO-TREATMENT: prn SABA		
Outcomes	PULMONARY FUNCTION TEST: am PEF*; am PEF predicted; pm PEF SYMPTOM SCORES: Daytime scores FUNCTIONAL STATUS: Not reported INFLAMMATORY MARKERS: Not reported ADVERSE EFFECTS: Stated by treatment group WITHDRAWALS: Stated by treatment group Primary outcome measure*		
Notes	Full-text publication, additional data from http://www.ctr.gsk.co.uk Source of funding GSK Confirmation of methodology and data: Not obtained User defined number: 1000		
Risk of bias			
	Authous' independent Description		
Item	Authors' judgement Description		

Allocation concealment?	Yes	See Appendix 2
Blinding? All outcomes	Yes	Double-blind, double-dummy design
Incomplete outcome data addressed? All outcomes	Unclear	Intention-to-treat analysis; no description of how population defined for analysis
Free of selective reporting?	Unclear	Not clear whether the study collected information on exacerbations treated with OCS

Aubier 1999b

Methods	See above	
Participants	See above	
Interventions		S and LABA versus ICS via one inhaler erventions identical to Aubier 1999a
Outcomes	See above	
Notes	See above	
Risk of bias		
Item	Authors' judgement	Description
Adequate sequence generation?	Yes	See Appendix 2
Allocation concealment?	Yes	See Appendix 2
Blinding? All outcomes	Yes	See above
Incomplete outcome data addressed? All outcomes	Unclear	See above
Free of selective reporting?	Unclear	See above

Bailey 2008

Methods	Parallel-group, multicentre study in USA
Participants	% ELIGIBLE OF SCREENED POPULATION: 60
L L	% RUN-IN PARTICIPANTS RANDOMISED: 90
	RANDOMISED: 475 (FP/SAL 239; FP 236)
	WITHDRAWALS: FP/SAL 67; FP 85
	AGE mean (range) or mean (SD): 32
	SEVERITY: Not reported
	BASELINE % PREDICTED FEV1: 78
	BASELINE DOSE OF ICS: 400 mcg BDP equivalent
	ASTHMA DURATION: 19 years
	ATOPY (%): Not reported
	ELIGIBILITY CRITERIA: African American by self-report; 12 to 65 years of age
	persistent asthma for at least 6 months; FEV1 60% to 90% predicted; FEV1
	reversibility of > 12% post-SABA; symptomatic while being treated with FP 200
	mcg daily or equivalent for at least 1 month prior to screening
	EXCLUSION CRITERIA: Asthma exacerbation during screening period
	(worsening of asthma that required treatment with asthma medications other than
	their ICS and albuterol)
	ELIGIBILITY CRITERIA DURING RUN-IN: FEV1 > 60% predicted normal; plu albuterol use on 4 or more days during the 7-day period prior to the clinical visit;
	and/or an asthma symptom score > 2 on 4 or more days during the 7-day period prior to the clinic visit

Interventions	PROTOCOL: LABA and ICS versus SAME DOSE ICS OUTCOMES: 52 weeks RUN-IN PERIOD: 4 weeks (FP250 mcg bid) INTERVENTION PERIOD: 52 weeks (plus 4-week run-out) TEST GROUP: Combination fluticasone and salmeterol 100/50 mcg bid CONTROL GROUP: Fluticasone 100 mcg bid NUMBER OF DEVICES: 1 COMPLIANCE: Not assessed CO-TREATMENT: prn SABA	
Outcomes	PULMONARY FUNCTION TEST: FEV1; am PEF; pm PEF SYMPTOM SCORES: Total symptoms FUNCTIONAL STATUS: Exacerbations (undefined)*; rescue medication use INFLAMMATORY MARKERS: Not reported ADVERSE EFFECTS: Reported WITHDRAWALS: Reported Primary outcome measure*	
Notes	Full-text publication, additional data from http://www.ctr.gsk.co.uk Source of funding GSK Confirmation of methodology and data: Not obtained User defined number: 400	
Risk of bias		
Item	Authors' judgement	Description
Adequate sequence generation?	Yes	See Appendix 2
Allocation concealment?	Yes	See Appendix 2
Blinding? All outcomes	Yes	Identical inhaler devices
Incomplete outcome data addressed? All outcomes	Unclear	"The primary analysis population was the intent to- treat (ITT) population, comprised of all subjects randomized to double-blind study medication. All data collected prior to early withdrawal was considered evaluable."
Free of selective reporting?	Yes	Exacerbations described in study report; these included OCS-treated exacerbations, but separate data could not be identified. Request for data submitted

Boyd 1995

Methods	Parallel-group, multicentre study (15 centres in the United Kingdom)
Participants	Symptomatic asthmatic adults % ELIGIBLE OF SCREENED POPULATION: Not reported % RUN-IN PARTICIPANTS RANDOMISED: 66% RANDOMISED: 119 (Salm100 + ICS: 55; placebo + ICS: 64) WITHDRAWALS: Salm100 + ICS: 8; placebo + ICS: 14 AGE: mean (range): 47 (18 to 79) GENDER: (% male): 43% BASELINE % PREDICTED FEV1 mean: 66 BASELINE % PREDICTED FEV1 mean: 66 BASELINE DOSE OF ICS: 1000 to 4000 mcg/day ASTHMA DURATION (years): 15 years ATOPY (%): Not described ELIGIBILITY CRITERIA: >= 15% improvement from baseline in lung function following inhaled salbutamol; at least 2 acute asthma exacerbations in the precedin 18 months EXCLUSION CRITERIA: Concurrent uncontrolled oral disease; having received treatment for an acute respiratory infection in the last 2 weeks or had a FEV1 < 40% predicted
Interventions	LABA + ICS vs SAME dose of ICS OUTCOMES: reported at 4, 8 and 12 weeks RUN-IN: 2 weeks DOSE OF ICS DURING RUN-IN: Usual ICS

	Intervention period: 12 weeks TEST GROUP: (Salm100 + ICS) Salmeterol 100 mcg bid + ICS CONTROL GROUP: Placebo + ICS DEVICE: Diskhaler NUMBER OF DEVICES: 2 COMPLIANCE: Assessed at each clinic visit CO-TREATMENT: Salbutamol metered dose inhaler	
Outcomes	PULMONARY FUNCTION TEST: FEV1; PEF(morning and evening)* SYMPTOMSCORE: Score of 0 to 4 (change); changes in daytime and night-time score FUNCTIONAL STATUS: Rescue B2-agonist (number of puffs per 24 hours); nocturnal awakening (change in symptom-free nights); symptom-free days change; severe exacerbation (requiring oral steroids) INFLAMMATORY MARKERS: None studied ADVERSE EFFECTS: Reported WITHDRAWALS: Reported Primary outcome measure*	
Notes	Full-text publication Funded by Allen & Hanburys Confirmation of methodology and data obtained User-defined number: 1681 (mean ICS dose in LAB2 group in mcg/day of BDP- equivalent)	
Risk of bias		
Item	Authors' judgement	Description
Adequate sequence generation?	Yes	Computer-generated random numbers
Allocation concealment?	Yes	Numbered coded inhalers supplied by pharmacy
Allocation concealment? Blinding? All outcomes	Yes Yes	Numbered coded inhalers supplied by pharmacy Identical placebo
Blinding?		** * * * *

Buhl 2003a

Methods	Parallel-group, multicentre study (56 centres in 9 countries)	
Participants	Symptomatic asthmatic adults % ELIGIBLE OF SCREENED POPULATION: Not reported % RUN-IN PATIENTS RANDOMISED: 95% (26 patients were recruited but were not randomised as they deteriorated during run-in) RANDOMISED 523 (Form 6 mcg + ICS bid: 176; Form 9 mcg + ICS: 176; placebo + ICS: 171) WITHDRAWALS: Form 6 bid + ICS: 14; Form 9 bid + ICS: 14; placebo + ICS: 14 AGE mean (range): 45 (18 to 78) GENDER (% male): 49% BASELINE % PREDICTED FEV1 mean: 77 BASELINE % PREDICTED FEV1 means: 13 (0 to 63) ATOPY (%): Not described ELIGIBILITY CRITERIA: Baseline FEV1 of 60% to 90% normal; >= 12% improvement from baseline in lung function following inhaled salbutamol; at least 2 acute asthma exacerbations in the preceding 18 months EXCLUSION CRITERIA: oral corticosteroids in 4 weeks before run-in; concurrent respiratory infection in the 4 weeks before run-in; severe cardiovascular disorder; use of beta blocker; heavy smoking	
Interventions	LABA + ICS TWICE A DAY versus SAME dose of ICS ONCE A DAY OUTCOMES: reported at 4, 8 and 12 weeks RUN-IN: 4 weeks DOSE OF ICS DURING RUN-IN: BUD 200 bid	

	INTERVENTION PERIOD: 12 weeks TEST GROUP: (Form 6 + ICS) formoterol 6 mcg bid + ICS bid CONTROL GROUP: Placebo + ICS od DEVICE: Turbuhaler NUMBER OF DEVICES: 2 COMPLIANCE: Not reported CO-TREATMENT: Salbutamol metered dose inhaler		
Outcomes	PULMONARY FUNCTION TEST: FEV1; change in morning PEF*; change in evening PEF SYMPTOMSCORE: Score of 0 to 3 grading daytime and night-time symptoms; Total daily asthma score = sum of daytime and night-time scores FUNCTIONAL STATUS: Exacerbations; rescue B2-agonists use; nocturnal awakening (% nights with awakening; % reliever use-free days -% symptom-free days; % asthma control days; % asthma control weeks INFLAMMATORY MARKERS: None studied ADVERSE EFFECTS: Reported WITHDRAWALS: Reported Primary outcome measure*		
Notes	Full-text publication Funded by AstraZeneca Confirmation of methodology and data obtained User-defined number: 400		
Risk of bias			
Item	Authors' judgement	Description	
Adequate sequence generation?	Unclear	Described as randomised; no other information presented	
Allocation concealment?	Yes	Numbered coded inhalers supplied by pharmacy	
Blinding? All outcomes	Yes	Double-dummy design	
Incomplete outcome data addressed? All outcomes	Unclear	Not enough information presented to determine how ITT population was defined: "All efficacy variables were analysed on an intent-to-treat basis and all randomized patients with data were included in the analysis."	
Free of selective reporting?	Yes	Exacerbations described in study report; these included OCS-treated exacerbations, but separate data could not be extracted	

Buhl 2003b

Methods	See Buhl 2003a	
Participants	See Buhl 2003a	
Interventions	LABA + ICS ONCE A DAY vs SAME dose of ICS ONCE A DAY TEST GROUP: (Form 12 + ICS) formoterol 12 mcg bid + ICS CONTROL GROUP: Placebo + ICS Other characteristics the same as above	
Outcomes	See Buhl 2003a	
Notes	See Buhl 2003a	
Risk of bias		
Item	Authors' judgement	Description
Adequate sequence generation?	Unclear	See above
Allocation concealment?	Yes	See above
Blinding? All outcomes	Yes	See above

Incomplete outcome data addressed? All outcomes	Unclear	See above
Free of selective reporting?	Yes	See above

D'Urzo 2001

Methods	Parallel-group, multicentre study (253	3 centres predominantly general practices)
Participants	Adults and adolescents with asthma % ELIGIBLE OF SCREENED POPULATION: Not reported % RUN-IN PARTICIPANTS RANDOMISED: Not reported RANDOMISED: 911 (Salm50 bid + ICS: 455; placebo + ICS: 456) WITHDRAWALS: Salm50 bid + ICS: 19%; placebo + ICS: 24% AGE mean (range): 46 (17 to 86) GENDER (% male): 46% SEVERITY: Moderate BASELINE FEV1 MEAN (SD): Not reported BASELINE DOSE OF ICS/day: BDP up to 500 mcg: 18% BDP 500 to 1000: 59% BDP > 1000 = 23% ASTHMA DURATION: Not reported ATOPY(%): Not reported ELIGIBILITY CRITERIA: History of asthma (ATS criteria); required regular ICS but still required rescue bronchodilator more than twice daily EXCLUSION CRITERIA: Uncontrolled pulmonary or oral disease or psychological condition that in then opinion of investigator precluded their entry into study; concurrent beta blocker therapy	
Interventions	LABA + ICS vs SAME dose of ICS OUTCOMES: measured at 4-weekly RUN-IN PERIOD: None DOSE OF ICS DURING RUN-IN: N DOSE OPTIMISATION PERIOD: N INTERVENTION PERIOD: 24 week TEST GROUP (LABA + SINGLE DO CONTROL GROUP: Placebo + usual DEVICE: MDI NUMBER OF DEVICES: 2 COMPLIANCE: Not reported CO-TREATMENT: Not reported	ot applicable one :s OSE ICS): Usual ICS + salmeterol 50 mcg bid
Outcomes	PULMONARY FUNCTION TEST: Change in clinic PEF SYMPTOM SCORES: Not reported FUNCTIONAL STATUS: Rescue medication use day and night; daytime and nighttime symptoms; nocturnal awakenings; serious asthma exacerbation* defined as days in hospital, days of prednisone treatment or ER visit; days requiring increased asthma medication; work or school days lost because of asthma limitation of activities because of asthma INFLAMMATORY MARKERS: Blood eosinophil count measured in subgroup with asthma exacerbation ADVERSE EFFECTS: Heart rate higher in salmeterol group; no other adverse effects reported WITHDRAWALS: Reported Primary outcome measure*	
Notes	Full-text publication Supported by GSK Confirmation of methodology and data extraction not obtained User defined number: Not reported (mean ICS dose in LAB2 group in mcg/day of BDP-equivalent: Not reported	
Risk of bias		
Item	Authors' judgement	Description
Adequate sequence generation?	Unclear	Described as randomised; no other information presented
Allocation concealment?	Unclear	Information not available

Blinding? All outcomes	Unclear	Described as double-blind. Information on masking of treatments not presented
Incomplete outcome data addressed? All outcomes	Unclear	Described as ITT; composition of ITT population not explicit: "The Intent-to- Treat (ITT) population consisted of all randomised subjects except those where verified proof existed that no study medication was taken. The ITT population was used for all analyses and tabulations."
Free of selective reporting?	Yes	Exacerbations described in study report; these included OCS-treated exacerbations; separate data could not be extracted

D5896C0001a

Methods	Parallel-group, multice	ntre 4-arm trial
Participants	% ELIGIBLE OF SCREENED POPULATION: 44 % RUN-IN PARTICIPANTS RANDOMISED: 63 RANDOMISED: 618 (BUD/F bid 155; BUD/F high qd 153; BUD/F low qd 153; BUD 153) WITHDRAWALS: Not stated AGE mean (range) or mean (SD): 35 (15) SEVERITY: Not stated BASELINE % PREDICTED FEV1: 76% BASELINE DOSE OF ICS: 375 mcg ASTHMA DURATION: Not stated ATOPY (%): Not stated ELIGIBILITY CRITERIA: > 12 years; documented clinical diagnosis of asthma for 6 months prior to screening; stable; maintenance asthma treatment with inhaled corticosteroids (ICS) for at least 4 weeks; FEV1 60% to 90% predicted EXCLUSION CRITERIA: Not stated ELIGIBILITY CRITERIA: Not stated	
Interventions	PROTOCOL: LABA and ICS versus SAME DOSE ICS OUTCOMES 12 weeks RUN-IN PERIOD: 4 to 5 weeks (combination therapy) INTERVENTION PERIOD: 12 weeks TEST GROUP: Combination budesonide and formoterol 200/12 mcg bid (400/24 mcg total) CONTROL GROUP: Budesonide 400 mcg qd NUMBER OF DEVICES: Two (double-dummy) COMPLIANCE: Not reported CO-TREATMENT: prn SABA	
Outcomes	PULMONARY FUNCTION TEST: FEV1; am PEF; pm PEF SYMPTOM SCORES: Total symptoms FUNCTIONAL STATUS: Rescue medication use INFLAMMATORY MARKERS: Not reported ADVERSE EFFECTS: Reported WITHDRAWALS: Stated for adverse events only	
Notes	Trial report available as download from AZ clinical trials website Funded by AZ Confirmation of methodology and data extraction not obtained User defined: 400	
Risk of bias		
Item	Authors' judgement	Description
Adequate sequence generation?	Unclear	Described as randomised; no other information presented
Allocation concealment?	Unclear	Information not available

Blinding? All outcomes	Yes	"To maintain blinding with the twice-daily dosing regimen, all subjects randomized to receive once-daily dosing were to take the active treatment in the evening and a matched placebo device (Batch numbers P6492 and P6856) in the morning."
Incomplete outcome data addressed? All outcomes	Unclear	"The efficacy analysis set (EAS), defined as all randomized subjects who took at least 1 dose of double- blind treatment and for whom the primary efficacy endpoint could be calculated, was used in the primary analysis of efficacy. Sensitivity analyses were performed using the per protocol (PP) analysis set, which excluded subjects with major violations of inclusion or exclusion criteria."
Free of selective reporting?	Unclear	Not clear whether the study collected information on exacerbations treated with OCS

D5896C0001b

Methods	See above	
Participants	See above	
Interventions	See above; except for: TEST GROUP: Combination budesonide and fo	ormoterol 400/12 mcg qd (evening)
Outcomes	See above	
Notes	See above	
Risk of bias		
Item	Authors' judgement	Description
Adequate sequence generation?	Unclear	See above
Allocation concealment?	Unclear	See above
Blinding? All outcomes	Yes	See above
Incomplete outcome data addressed? All outcomes	Unclear	See above
Free of selective reporting?	Unclear	See above

Fitzgerald 1999

Methods	Parallel-group, multicentre study (15 centres in Canada). Three groups of which 2 considered for this review (group which evaluated regular albuterol use not considered)
Participants	Symptomatic asthmatic adults % ELIGIBLE OF SCREENED POPULATION: Not reported % RUN-IN PARTICIPANTS RANDOMISED: 72 RANDOMISED: 271 (F 12 bid + usual dose ICS: 89; usual dose ICS and on demand albuterol: 91; usual dose ICS + regular albuterol: 91) WITHDRAWALS: F 12 bid + usual dose ICS: 17; usual dose ICS and on demand albuterol: 18 Mean AGE years (SD): 36 (13) GENDER (% male): 44 SEVERITY: Moderate BASELINE FEV1 PREDICTED: 79 BASELINE DOSE OF ICS mean (SD): 732 (280) mcg

	criteria; treated with ICS 400 to screening; >= 15% reversibility in, had used albuterol on at leass symptoms; use of beta agonist > turbuhaler; compliance with dai EXCLUSION: Respiratory infe exacerbation requiring an ER vi CRITERIA FOR RANDOMIS/ albuterol on at least 5 of the last randomisation if asthma was po	n-smoking adults with asthma as defined by ATS 1200 mcg/day for at least 1 month prior to after bronchodilator; during the last 7 days of run- t 5 days awakening on >= 1 night due to asthma >= 10 puffs as weekly mean; competence with ry cards and assessments ction within 2 months of screening; acute asthma
Interventions	LABA + ICS versus SAME dose of ICS OUTCOMES: after initial dose, 3, 6 months and 2 days after end of last dose RUN-IN PERIOD: 2 weeks DOSE OF ICS DURING RUN-IN: 400 to 1200 mcg BDP, BUD usual dose of patient DOSE OPTIMISATION PERIOD: None INTERVENTION PERIOD: 24 weeks TEST GROUP (LABA + SINGLE DOSE ICS): Formoterol 12 mcg bid + beclomethasone, budesonide 400 to 1200 mcg/day CONTROL GROUP: Beclomethasone, budesonide 400 to 1200 mcg bid DEVICE: Formoterol - dry powder inhalation capsules; albuterol MDI NUMBER OF DEVICES: 2 COMPLIANCE: Not reported CO-TREATMENT: Not reported	
Outcomes	PULMONARY FUNCTION TEST: Change in morning PEF*; Change in FEV1 SYMPTOM SCORES: Change in daytime and night-time scores FUNCTIONAL STATUS: Change in rescue medication use day and night (puffs per day or night) INFLAMMATORY MARKERS: Not described ADVERSE EFFECTS: Reported WITHDRAWALS: Reported Primary outcome measure*	
Notes	Full-text publication Supported by Novartis Confirmation of methodology and data extraction not obtained User defined number: (mean ICS dose in LAB2 group in mcg/day of BDP- equivalent: 730	
Risk of bias		
Item	Authors' judgement	Description
Adequate sequence generation?	Unclear	Described as randomised; no other information presented
Allocation concealment?	Unclear	Information not available
Blinding? All outcomes	Yes Double-dummy design	
Incomplete outcome data addressed? All outcomes	Unclear No information provided	
Free of selective reporting?	Yes OCS-treated exacerbations available in trial publication	

Gardiner 1994

Methods	Cross-over, single-centre study
Participants	Stable asthmatic adults % ELIGIBLE OF SCREENED POPULATION: Not reported % RUN-IN PARTICIPANTS RANDOMISED: Not reported RANDOMISED: 10

	ASTHMA DURATION: Not rep ATOPY (%): 70 ELIGIBILITY CRITERIA: Non reversibility following bronchod	V1: Not reported ore start of run-in): 400 to 1000 BDP equivalent ported -smoking; asthma diagnosed by ATS criteria; 15%
Interventions	LABA + ICS vs SAME dose of ICS OUTCOMES: 2 and 4 months RUN-IN PERIOD: 2 weeks DOSE OF ICS DURING RUN-IN: Usual ICS (400 to 1000) DOSE OPTIMISATION PERIOD: None INTERVENTION PERIOD: 8 weeks TEST GROUP (LABA + SINGLE DOSE ICS): salmeterol 50 mcg bid CONTROL GROUP: Usual ICS DEVICE: Not stated NUMBER OF DEVICES: 2 COMPLIANCE: Not stated CO-TREATMENT: Inhaled albuterol as rescue medication but no oral beta agonists, inhaled anticholinergic medication or theophylline	
Outcomes	PULMONARY FUNCTION TEST: PEF SYMPTOM SCORES: Not reported FUNCTIONAL STATUS: Not assessed INFLAMMATORY MARKERS: BAL differential cell count; BAL mast cell tryptase & al; serum ECP; respiratory burst; release of PAF before and after allergen inhalation challenge ADVERSE EFFECTS: Not reported WITHDRAWALS: Not reported	
Notes	Full-text publication Source of funding not reported Confirmation of methodology and data extraction not obtained User defined number: (mean ICS dose in LAB2 group in mcg/day of BDP- equivalent: Not reported range 400 to 1000	
Risk of bias		
Item	Authors' judgement	Description
Adequate sequence generation?	Unclear	Described as randomised; no other information presented
Allocation concealment?	Unclear	Information not available
Blinding? All outcomes	Yes	Identical placebo
Incomplete outcome data addressed? All outcomes	Unclear	Not enough information available to determine population analysed
Free of selective reporting?	Unclear	Not clear whether the study collected information on exacerbations treated with

GOAL

Methods	Parallel-group, multicentre study (326 centres in Europe, North America, Latin America and Asia Pacific)
Participants	Uncontrolled asthmatic adults % ELIGIBLE OF SCREENED POPULATION: 67 % RUN-IN PARTICIPANTS RANDOMISED: Not clear RANDOMISED: 3416 (FP/SAL: 1707; FP: 1709). NB - data in this review are taken from the strata of patients randomised who were on ICS prior to study entry (N = FP/SAL: 1133; FP: 1119)

Cochrane Database Syst Rev. Author manuscript; available in PMC 2014 September 21.

	AGE: mean (range) or me GENDER: (% male) 42 SEVERITY: Moderate BASELINE % PREDICT BASELINE DOSE OF IC 500 and 1000 mcg/d ASTHMA DURATION: 649; FP: 647 -> 10 years: ATOPY (%): 58 ELIGIBILITY CRITERI.	EDFEV1: 77 CS: Divided into 3 strata: 0; 500 mcg/d or less; between 0 to 1 year: FP/SAL: 56; FP: 97- 1 to 10 years: FP/SAL: FP/SAL: 1004; FP: 992 A: 12 to 80 years of age; 6-month history of asthma; FEV king history of less than 10 pack-years; no use of LABA evious 2 weeks
Interventions	LABA + ICS versus SAME DOSE ICS OUTCOMES: End of phase RUN-IN: 4 weeks DOSE OF ICS DURING RUN-IN: Usual maintenance dose of ICS (including 0 for participants not treated with ICS) INTERVENTION PERIOD: Two different phases: I = dose step-up until total asthma control achieved, or until maximum dose of study drug given for 12 weeks; II = constant dose of final dose of study drug until 52 weeks since randomisation had elapsed TEST GROUP: Combination fluticasone and salmeterol 50/100; 50/250 or 50/500 mcg bid CONTROL GROUP: Fluticasone 100, 250 or 500 mcg bid DEVICE: Diskus NUMBER OF DEVICES: 1 COMPLIANCE: Not assessed CO-TREATMENT: prn SABAa	
Outcomes	PULMONARY FUNCTION TEST: FEV1 SYMPTOM SCORES: Not reported FUNCTIONAL STATUS: N achieving total asthma control*; exacerbations (defined as OCS course, ED visit/hospitalisation) INFLAMMATORY MARKERS: Not reported ADVERSE EFFECTS: Reported by treatment group, but not collected since they refer to all phase, all strata participants WITHDRAWALS: Reported by treatment group Primary outcome measure*	
Notes	Full-text publication Source of funding: GSK Confirmation of methodology and data: Not obtained User defined number: 1000	
Risk of bias		
Item	Authors' judgement	Description
Adequate sequence generation?	Yes	See Appendix 2
Allocation concealment?	Yes	See Appendix 2
Blinding? All outcomes	Yes	Identical inhaler devices
Incomplete outcome data addressed? All outcomes	Unclear	"The Intent-To-Treat Population (ITT) consisting of all subjects who were randomised to treatment and received at least one single dose of study medication was the primary population for analysis of efficacy and safety."
Free of selective reporting?	Yes	Exacerbations requiring OCS treatment described as composite in a rate; data could not be extracted and used in metaanalysis

Cross-over, single-centre study in UK

Participants	treatment with 400 mcg/day beck increase in FEV1 post-SABA; 2/ twice daily over a 2-week period causing a 20% fall in FEV1 (PC/ BUD, participants were eligible symptoms on their diary cards on EXCLUSION: Current smokers comorbidity, treated with oral co	75 years, diagnosed with asthma; receiving omethasone dipropionate; one or more of 1) > 159) > 20% within-day variability in PEF assessed ; 3) provocative concentration of methacholine 20) < 8 mg/mL-1; following run-in on 200 mcg day if they had recorded day- or night-time asthma 1 at least 4 days in the third or fourth baseline weel or smoking history of > 10 pack-years, significant rticosteroids, long-acting B2-agonists, leukotriene ma exacerbation or lower respiratory tract infection
Interventions	LABA + ICS versus SAME DOS OUTCOMES: End of phase TREATMENT PERIOD: 6 week RUN-IN PERIOD: 4 weeks TEST GROUP: Budesonide 100 CONTROL: Budesonide 100 mg NUMBER OF DEVICES: 2 COMPLIANCE: Not assessed CO-TREATMENT: prn SABA	SE ICS ss mg bid + formoterol 12 mg bid
Outcomes	PULMONARY FUNCTION TESTS: am PEF; FEV1 SYMPTOM SCORES: *VAS; daytime symptoms; nocturnal symptoms FUNCTIONAL STATUS: Quality of life (AQLQ); exacerbations (deterioration in PEF or requirement for OCS. Patients who experienced 2 or more exacerbations were withdrawn from the study) INFLAMMATORY MARKERS: *sputum eosinophils; exhaled nitric oxide; *PC20 ADVERSE EFFECTS: Not reported WITHDRAWALS: Reported (not by treatment group) Primary outcome measure*	
Notes	Full-text publication Funding source: Not declared (A Confirmation of methodology an User defined number: 200	Z provided active and placebo inhalers) d data: Obtained
Risk of bias		
Item	Authors' judgement	Description
Adequate sequence generation?	Yes	Randomisation from correspondence with investigator: "I believe that this was generated using a computer statistical package generating random sequence. I don't know the package that was used and unfortunately the individual has left our organisation but had extensive clinical trials expertise None of the study investigators were aware of the randomisation schedule until the last patient had completed the cross-over study"
	Yes	Correspondence with investigator: "
Allocation concealment?		this was indeed generated by a third party, namely the pharmacist responsibl for dispensing the double blind medication."
Allocation concealment? Blinding? All outcomes	Yes	party, namely the pharmacist responsible for dispensing the double blind

Free of selective reporting? Yes

OCS-treated exacerbations described; could not extract data as proportion of participants with one or more events

Houghton 2007

Methods	Parallel-group, single-centre	study
Participants	% ELIGIBLE OF SCREENED POPULATION: Not reported % RUN-IN PARTICIPANTS RANDOMISED: 70 RANDOMISED: 39 WITHDRAWALS: FP/SAL: 1; FP: 1 AGE mean (range) or mean (SD): 40 SEVERITY: Mild BASELINE % PREDICTED FEV1: 94 BASELINE % PREDICTED FEV1: 94 BASELINE DOSE OF ICS: FP 200 mcg/day ASTHMA DURATION: Not specified ATOPY (%): Not reported ELIGIBILITY CRITERIA: Physician diagnosed asthma for >/= 6 months; receiving stable total daily dose of ICS (equivalent to 200 to 500 mcg BDP) for at least 4 weeks prior to the study; FEV1 > 80% predicted and demonstration of a > 30% decrease in sRaw in response to 400 mcg of inhaled salbutamol at screening EXCLUSION CRITERIA: Use of parenteral, oral and nebulised steroids 4 weeks prior to study (12 weeks for depot corticosteroids); positive pregnancy test; current smokers or ex-smokers for < 12 months ELIGIBILITY CRITERIA DURING RUN-IN: Not symptomatic on every day of run-in period	
Interventions	PROTOCOL: LABA + ICS versus SAME dose ICS OUTCOMES: 4 weeks RUN-IN PERIOD: 2 weeks DOSE OPTIMISATION PERIOD: Not reported INTERVENTION PERIOD: 4 weeks TEST GROUP: Combination fluticasone and salmeterol (100/50 mcg bid) CONTROL GROUP: Fluticasone 100 mcg bid NUMBER OF DEVICES: 1 COMPLIANCE: Not assessed CO-TREATMENT: prn SABA	
Outcomes	PULMONARY FUNCTION TEST: FEV1; PEF; airway resistance* SYMPTOM SCORES: Not reported FUNCTIONAL STATUS: Not reported INFLAMMATORY MARKERS: Not reported ADVERSE EFFECTS: Not reported WITHDRAWALS: Reported	
Notes	Funding source: GSK Confirmation of methodology and data: Not obtained User defined: 400	
Risk of bias		
Item	Authors' judgement	Description
Adequate sequence generation?	Unclear	"Randomised"
Allocation concealment?	Unclear	Information not available
Blinding? All outcomes	Yes	"identical Accuhaler devices"
Incomplete outcome data addressed? All outcomes	Unclear	"Statistical analysis was performed on an Intention To Treat basis with all subjects randomised to treatment being included."
Free of selective reporting?	Unclear	We could not determine whether information on oral steroid-treated exacerbations was collected

Hultquist 2000

Method	Parallel-group, multicentre in 49 clinical are considered for this review	centres in 6 countries; 3 groups of which
Participants	Symptomatic asthmatic patients aged 12 to 70 years % ELIGIBLE OF SCREENED POPULATION: Not reported % RUN-IN PARTICIPANTS RANDOMISED: 74% (126 enrolled patients not randomised for reasons as follows: eligibility criteria not fulfilled (110); adverse events (6); lost to follow up (1); other reasons (9)) RANDOMISED: 352 (F 9 bid + BUD 200 bid: 118; BUD 200 bid: 116 BUD + montelukast: 118) WITHDRAWALS: F 9 bid + BUD 200 bid: 10%; BUD 200 bid: 7% Mean AGE years: 38.1 GENDER (% male): 51 SEVERITY: Moderate BASELINE MOSE OF ICS: 400 to 1000 mcg per day ASTHMA DURATION (years): 11 years ATOPY (%): Not reported ELIGIBILITY CRITERIA: Aged 12 to 70 years; treated with ICS 400 to 1000 mcg/day for at least 3 months prior to visit 1; FEV1 between 50% to 80 % of pred normal; >= 12% reversibility after bronchodilator; smoking history <= 10 years EXCLUSION CRITERIA: Patients who had other diseases that may interfere with assessments; respiratory infection, COPD or pulmonary dysfunction other than asthma; pregnant or lactating women; use of LABA within 1 month prior to visit 1 previous use of leukotriene antagonist; known intolerance to study drugs or inhale lactose CRITERIA FOR RANDOMISATION DURING RUN-IN: During the last 7 days of run-in, having an asthma score >= 1 on 4 days or awakening on >= 1 night due asthma symptoms; use of beta agonist >= 10 puffs as weekly mean; competence with turbuhaler; compliance with dairy cards and assessments	
Interventions	with turbuhaler; compliance with dairy cards and assessments LABA + ICS versus SAME dose of ICS OUTCOMES: Not reported RUN-IN PERIOD: 2 weeks DOSE OF ICS DURING RUN-IN: Not stated DOSE OPTIMISATION PERIOD: None INTERVENTION PERIOD: 8 weeks TEST GROUP (LABA + SINGLE DOSE ICS): Budesonide 200 mcg bid + formoterol 9 mcg bid CONTROL GROUP: Budesonide 200 mcg bid DEVICE: Turbuhaler NUMBER OF DEVICES: 2 COMPLIANCE: Not reported CO-TREATMENT: prn SABA	
Outcomes	PULMONARY FUNCTION TEST: am PEF*; FEV1 SYMPTOM SCORES: Daytime and night-time score FUNCTIONAL STATUS: Rescue medication use per day; % night-time awakenings INFLAMMATORY MARKERS: Not described ADVERSE EFFECTS: Not described WITHDRAWALS: Reported Primary outcome measure*	
Notes	Abstract and full study report from sponsoring drug company Supported by AstraZeneca Confirmation of methodology and data extraction obtained User defined number: (mean ICS dose in LAB2 group in mcg/day of BDP- equivalent: 800	
Risk of bias		
Item	Authors' judgement	Description
Adequate sequence generation?	Unclear	Described as randomised; no other information presented
Allocation concealment?	Yes	Opaque consecutive numbered envelopes containing assignment
Blinding? All outcomes	Yes	Use of identical placebo (double- dummy)
Incomplete outcome data addressed?	Unclear	Analysis described as modified

Free of selective reporting?	Unclear	Not clear whether the study collected information on exacerbations treated
		with OCS

Ind 2003

Methods	Parallel-group, multicentre study in 100 hospitals and general practices in 6 countries (3 groups of which 2 are considered for this review)
Participants	Symptomatic asthmatic adults % ELIGIBLE OF SCREENED POPULATION: Not reported % RUN-IN PARTICIPANTS RANDOMISED: 58 RANDOMISED: 502 (496 with completed case report forms included in intent-to- treat population); FP/SAL: 171; FP250: 160 (additional treatment arm: FP500: 165) WITHDRAWALS: FP/SAL: 27; FP250: 15 AGE mean years (SD): 45 (15.4) GENDER: (% male): 45 SEVERITY: Moderate to severe BASELINE PREDICTED FEV1: 2.3 L/sec % PREDICTED PEF am: 75 BASELINE DOSE OF ICS (median): 1000 ASTHMA DURATION (range in years): 0.2 to 65 ATOPY (%): Information unavailable ELIGIBILITY CRITERIA: Aged 15 to 75; symptomatic on BDP 500 to 800 mcg bid or equivalent via MDI with good technique; 2 documented exacerbations needing hospitalisation or change in treatment with one occurring in last 6 months; PEF less than 85% of post bronchodilator PEF at first clinic visit INCLUSION CRITERIA FOR RANDOMISATION DURING RUN-IN: Period variation in PEF over 10 days of >= 15% (highest evening PEF minus lowest morning PEF as a percentage of highest value); PEF not exceeding 90% of the post- bronchodilator PEF at first clinic visit EXCLUSION CRITERIA: Patients receiving regular oral corticosteroid; patients who had serious uncontrolled oral disease; participation was deemed unsuitable by their physician from the study
Interventions	LABA + ICS vs SAME dose of ICS OUTCOMES: 6, 12 18 and 24 weeks RUN-IN PERIOD: 4 weeks DOSE OF ICS DURING RUN-IN: FP 250 mcg bid DOSE OPTIMISATION PERIOD: None INTERVENTION PERIOD: 24 weeks TEST GROUP (LABA + SAME DOSE ICS): Fluticasone propionate 250 mcg and salmeterol 50 mcg bid CONTROL GROUP: FP 250 mcg bid DEVICE: MDI NUMBER OF DEVICES: 2 COMPLIANCE: Not reported CO-TREATMENT: Rescue short-acting beta2-agonists (salbutamol MDI) as needed, other asthma drugs as needed except LABA
Outcomes	PULMONARY FUNCTION TEST: am PEF*; pm PEF SYMPTOM SCORES: Night-time scores 0 to 4; daytime score 0 to 5 FUNCTIONAL STATUS: % symptom-free days and nights; rescue medication use exacerbations (defined as: mild (requiring increase in relief medication); moderate (requiring the use of additional corticosteroid); severe (requiring emergency hospita treatment) INFLAMMATORY MARKERS: Not described ADVERSE EFFECTS: Reported WITHDRAWALS: Reported Primary outcome measure*
Notes	Full-text publication Supported by GSK Confirmation of methodology and data extraction not obtained User defined number: 1000
Risk of bias	
Item	Authors' judgement Description

Adequate sequence generation?	Yes	See Appendix 2
Allocation concealment?	Yes	See Appendix 2
Blinding? All outcomes	Yes	Identical placebo (double-dummy)
Incomplete outcome data addressed? All outcomes	Unclear	"intent-to-treat population () included all patients randomised to treatment with completed case report forms and verifiable data."
Free of selective reporting?	Yes	Moderate exacerbations extracted as proxy for OCS-treated exacerbations (moderate exacerbations)

Jenkins 2006a

Methods	Parallel-group, multicentre study	(54 centres in 6 countries)
Participants	Symptomatic asthmatic adults and adolescents % ELIGIBLE OF SCREENED POPULATION: Not reported % RUN-IN PARTICIPANTS RANDOMISED: 93% RANDOMISED: 341 (combination BUD/F: 226; BUD: 115) WITHDRAWALS: Not reported for 12 weeks data AGE: mean (range): (12 to 79) GENDER (% male): 40 SEVERITY: Moderate to severe persistent asthma BASELINE % PREDICTED FEV1(mean): 66 BASELINE DOSE OF ICS: 1040 mcg/d ASTHMA DURATION: 8 years ATOPY (%): Not reported ELIGIBILITY CRITERIA: >/= 12 years; diagnosis of asthma (for at least 6 months); FEV1 40% to 85% predicted; >/= 15% reversibility to SABA; use of >/= 750 mcg ICS for 4 months; symptomatic during run-in EXCLUSION CRITERIA: Deterioration in asthma leading to change in therapy	
Interventions	LABA + ICS versus SAME dose of ICS OUTCOMES: 12 weeks RUN-IN: 2 weeks DOSE OF ICS DURING RUN-IN: Regular ICS use from pre-study INTERVENTION PERIOD: 24 weeks in total (participants in budesonide group switched to combination therapy or separate administration of ICS and LABA af 12 weeks) TEST GROUP: Combination budesonide 320 mcg bid + formoterol 9 mcg bid (+placebo inhaler) CONTROL GROUP: Budesonide 400 mcg bid + placebo inhaler DEVICE: Turbuhaler NUMBER OF DEVICES: 1 COMPLIANCE: Self-report (98%) CO-TREATMENT: prn SABA	
Outcomes	PULMONARY FUNCTION TEST: am PEF*; pm PEF; FEV1 SYMPTOM SCORES: Total symptoms (0 to 6); symptom-free days % FUNCTIONAL STATUS: Asthma control days (%); rescue medication free days (%); puffs/day INFLAMMATORY MARKERS: Not reported ADVERSE EFFECTS: Reported WITHDRAWALS: Not reported by treatment group Primary outcome measure*	
Notes	Full-text publication Source of funding AstraZeneca Confirmation of methodology and data not obtained User defined number: 400	
Risk of bias		
Item	Authors' judgement	Description

Allocation concealment?	Yes	Codes "assigned to patients and kept in sealed envelopes until data analysis."
Blinding? All outcomes	Yes	Double-dummy
Incomplete outcome data addressed? All outcomes	Unclear	"Efficacy analysis was performed on all randomized patients (intention to treat population) over 12 weeks."
Free of selective reporting?	Unclear	Data presented in trial report for mild exacerbations; unclear with OCS- treated exacerbations collected and reported in the trial

Jenkins 2006b

Methods	See Jenkins 2006a	
Participants	See Jenkins 2006a; except for: RANDOMISED: 230 (BUD + F: 115; BUD: 115)	
Interventions	See Jenkins 2006a except for: TEST GROUP: Budesonide 400 mcg bid + formoterol 9 mcg bid via separate inhalers	
Outcomes	See Jenkins 2006a	
Notes	See Jenkins 2006a	
Risk of bias		
Item	Authors' judgement	Description
Adequate sequence generation?	Yes	See Jenkins 2006a
Allocation concealment?	Yes	See Jenkins 2006a
Blinding? All outcomes	Yes	See Jenkins 2006a
Incomplete outcome data addressed? All outcomes	Unclear	See Jenkins 2006a
Free of selective reporting?	Unclear	See Jenkins 2006a

Kavaru 2000

Methods	Parallel-group, multicentre (42 centres); 4 treatment arms of which 2 considered in this review
Participants	Asthmatic patients over 12 years % ELIGIBLE OF SCREENED POPULATION: Not reported % RUN-IN PARTICIPANTS RANDOMISED: 68 RANDOMISED: 182 randomised to treatment groups in this review: FP/SAL: 92; FP: 90 WITHDRAWALS: FP/SAL: 15; FP: 22 AGE mean: 39 years GENDER (% male): 56 SEVERITY: Moderate BASELINE FEV1 MEAN %: 64 BASELINE FOSE OF ICS (RANGE): BDP 300 to 500 mcg/day; triamcinolone acetate 600 to 1000 mcg/day; fluinsolide 1000 mcg/day; FP 200 mcg/day ASTHMA DURATION: Not reported ATOPY(%): Not reported

	ELIGIBILITY CRITERIA: Asthma (ATS criteria) of at least 6 months duration; required pharmacotherapy for at least 6 months before study; inhaled corticosteroids for at least 1 month without change before study; 15% improvement in FEV1 post- bronchodilator; female patients negative pregnancy test, surgically sterile, postmenopausal or using birth control EXCLUSION CRITERIA: History of life threatening asthma; hypersensitivity rxn to sympathomimetic drugs or corticosteroids; smoking in year before study or smoking history of > 10 pack-years; received a course of oral corticosteroids in 6 months before study of use of any other prescription or OTC medication that could affect asthma or interact with other medications; abnormal CXR or EKG; history of diabetes glaucoma, hypertension EXCLUSION CRITERIA FOR RANDOMISATION DURING RUN-IN: Unstable asthma during run-in periods, i.e. more than 3 nights with awakenings, during 7 days before randomisation, more than 12 puffs of rescue medication/day for more than 3 days; FEV1 not within 15% of value obtained at beginning of screening	
Interventions	LABA + ICS vs SAME dose of ICS OUTCOMES: Reported weekly weeks 1 to 4 and thereafter 2-weekly RUN-IN PERIOD: 2 weeks DOSE OF ICS DURING RUN-IN: Placebo in addition to usual medication DOSE OPTIMISATION PERIOD: None INTERVENTION PERIOD: 12 weeks TEST GROUP: Combination fluticasone and salmeterol 100/50 mcg bid CONTROL GROUP: Fluticasone 100 mcg bid DEVICE: Diskhaler NUMBER OF DEVICES: 1 COMPLIANCE: Measured using dose counter on DISKUS device CO-TREATMENT: Albuterol as needed; no other prophylactic asthma medication permitted	
Outcomes	PULMONARY FUNCTION TEST: am PEF; pm PEF; FEV1* SYMPTOM SCORES: Symptom score (rated daily on 6-point scale) FUNCTIONAL STATUS: Rescue B2-agonists (puffs per day); nocturnal awakenings (% of nights with no awakenings); % of days with no asthma symptoms OTHER: Probability of remaining in study over time* INFLAMMATORY MARKERS: Not described ADVERSE EFFECTS: Described WITHDRAWALS: Reported Primary outcome measure*	
Notes	Full-text publication Funded by Glaxo Wellcome Confirmation of methodology and data not obtained User-defined number: 400 (mean ICS dose in LAB2 group in mcg/day of BDP- equivalent: FP 200 × 2)	
Risk of bias		
Item	Authors' judgement	Description
Adequate sequence generation?	Yes	See Appendix 2
Allocation concealment?	Yes	See Appendix 2
Blinding? All outcomes	Yes	Identical inhaler devices
Incomplete outcome data addressed? All outcomes	No	"To compensate for differential withdrawal rates among the treatment groups, end-point analyses were used. End-point analyses included data from the final visit during treatment for patients completing the study and the last available data for patients who were withdrawn early."
Free of selective reporting?	Yes	OCS-treated exacerbations available on request from GSK

Kemp 1998

Methods	Parallel-group, multicentre (44 cen	tres in USA)
Participants	Symptomatic asthmatic adolescents and adults % ELIGIBLE OF SCREENED POPULATION: Not reported % RUN-IN PARTICIPANTS RANDOMISED: 87 RANDOMISED: 506 (Salm 50 + ICS: 252; ICS: 254) WITHDRAWALS: Salm 50 + ICS: 25; ICS: 47 AGE: mean (range): 42 (12 to 85) GENDER (% male): 47 SEVERITY: Moderate BASELINE % PREDICTED FEV1: 63 BASELINE ODSE OF ICS: See below ASTHMA DURATION: Not described ATOPY(%): Not described ELIGIBILITY CRITERIA: Average daytime symptom score of 1 on a 0 to 3 point scale over a 2-week screening period; use of a short-acting bronchodilator on a daily basis; FEV1 of 40% to 80% predicted; >= 15% improvement from baseline in FEV1 following inhaled albuterol; use of one of the following inhaled corticosteroids on a daily basis at a fixed dose that is within package insert guidelines for a minimum of 6 weeks prior to the screening visit: beclomethasone (300 to 900 mcg/day), flunisolide (1000 to 2000 mcg/day), triamcinolone (600 to 1600 mcg/day) EXCLUSION CRITERIA: Concurrent tobacco use; oral corticosteroid therapy immunotherapy requiring dosage change; inability to withdraw asthma/allergy medication before PFTs at screening or clinic visits throughout the study; cystic fibrosis, COPD, any significant uncontrolled disease state other than asthma; any other significant illness; pregnancy or lactation; contraindication to study medications; unstable asthma requiring albuterol >= 12 puffs/day or 12 puffs for > 3 days/ week; hospitalisation for asthma within 3 months; mechanical ventilation during an asthma exacerbation within 2 years or > 2 albuterol (or equivalent) inhalers/month within 3 months of screening	
Interventions	LABA + ICS vs SAME dose of ICS OUTCOMES: Reported on day 1 and after 4, 8 and 12 weeks RUN-IN PERIOD: 2 weeks DOSE OPTIMISATION PERIOD: None INTERVENTION PERIOD: 12 weeks TEST GROUP: Salmeterol xinafoate 50 ug bid + usual but unspecified doses of ICS CONTROL GROUP: Placebo 2 puffs bid + usual but unspecified doses of ICS DEVICE: Metered dose inhaler NUMBER OF DEVICES: 2 COMPLIANCE: Not reported CO-TREATMENT: Rescue short-acting beta2-agonist (albuterol aerosol) as needed	
Outcomes	PULMONARY FUNCTION TEST: am PEF; pm PEF; FEV1 SYMPTOM SCORES: Overall score FUNCTIONAL STATUS: Asthma Quality of Life Questionnaire scores; rescue medication use; awakenings; exacerbations (undefined); symptoms INFLAMMATORY MARKERS: Not described ADVERSE EFFECTS: Described WITHDRAWALS: Reported Primary outcome measure not reported	
Notes	Full-text publication Funded by GSK Methodology and data extraction confirmed. User-defined number: 600 (mean ICS dose in LAB2 group in mcg/day of BDP- equivalent: between 300 to 900)	
Risk of bias		
Item	Authors' judgement	Description
Adequate sequence generation?	Yes	Computer-generated
Allocation concealment?	Yes	Assignment by opaque consecutive numbered envelopes
Blinding? All outcomes	Yes	Identical placebo
Incomplete outcome data addressed? All outcomes	Unclear	"intent-to-treat population (i.e., all patients exposed to the study drug), and efficacy analyses (including AQLQ

analyses) were done on the basis of data from the intent-to-treat population minus patients excluded because of significant protocol violations."

		protocol violations.
Free of selective reporting?	Yes	OCS-treated exacerbations available for meta-analysis

Koopmans 2006

Methods Parallel-group trial, single-centre trial		
Participants	Mild to moderately asthmatic adults % ELIGIBLE OF SCREENED POPULATION: 93 % RUN-IN PARTICIPANTS RANDOMISED: 90 RANDOMISED: 54 (FP/SAL: 27; FP: 27) WITHDRAWALS: FP/SAL: 0; FP: 4 AGE: mean (range): 32 (19 to 59) GENDER: (% male) 33 SEVERITY: Mild to moderate (GINA stage 2 & 3) BASELINE % PREDICTED FEV1 (mean): 92.9 BASELINE MOSE OF ICS: 500 mcg/d ASTHMA DURATION: Not reported ATOPY (%): 100 ELIGIBILITY CRITERIA: Documented, mild to moderate persistent, allergic asthma (GINA II and III); sensitisation to house dust mite and/or cat dander and/or grass pollen, as determined by Radio-Allergo-Sorbent-Test (RAST) and skin prick test; 18 to 60 years; FEV1 > 70 % predicted post-SABA bronchial hyper- responsiveness to histamine (PC20 histamine > 8.0 mg/ml at the end of the run-in period); exacerbation-free for 3 months prior to inclusion (defined as no requirement for oral steroids and/or antibiotics); no changes to regular asthma medication for 4 weeks before study entry; ability to use Diskus inhaler;reproducible lung function tests EXCLUSION CRITERIA: Comorbidity likely to interfere with the study; lower respiratory tract infection during 4 weeks before entry; use of theophyline, sodium cromoglycate, nedocromil sodium or anti-leukotrienes during the study or antibiotics 4 weeks prior to the study; current smoking, regularly smoking within 6 months before entry or a smoking history of more than 10 pack-years; pregnant or lactating females; inability to follow the therapy instructions; participation in another clinical trial within 4 weeks prior to the study	
Interventions	LABA + ICS versus SAME DOSE ICS OUTCOMES: 52 weeks RUN-IN: 4 weeks DOSE OF ICS DURING RUN-IN: 500 mcg/d INTERVENTION PERIOD: 52 weeks TEST GROUP: Combination fluticasone and salmeterol 250/50 mcg bid CONTROL GROUP: Fluticasone 250 mcg bid DEVICE: Diskus NUMBER OF DEVICES: 1 COMPLIANCE: Not assessed CO-TREATMENT: As needed SABA	
Outcomes	PULMONARY FUNCTION TEST: FEV1; am PEF; pm PEF SYMPTOM SCORES: Morning scores; evening scores FUNCTIONAL STATUS: Rescue medication use INFLAMMATORY MARKERS: PC20; sputum eosinophils*; eosinophil cationi- protein concentrations* ADVERSE EFFECTS: Not stated WITHDRAWALS: Stated Primary outcome measure*	
Notes	Full-text publication Source of funding: GSK Confirmation of methodology and data: Not obtained User defined number: 1000	
Risk of bias		
U U		

Adequate sequence generation?	Yes	See Appendix 2
Allocation concealment?	Yes	See Appendix 2
Blinding? All outcomes	Yes	Identical inhaler devices
Incomplete outcome data addressed? All outcomes	Unclear	"Intention to treat population was all subjects who received treatment"
Free of selective reporting?	Unclear	Not clear whether the study collected information on exacerbations treated with OCS

Kuna 2006

Methods	Parallel-group study conducted in 61 centres in Europe, Central America and New Zealand. Three treatment arms (BDF once daily; BDF twice daily; BUD once daily	
Participants	Moderately severe asthmatic adults % ELIGIBLE OF SCREENED POPULATION: Not stated % RUN-IN PARTICIPANTS RANDOMISED 94 RANDOMISED: 617 (ITT population: 616 - once daily BDF: 202; once daily BUD: 207, additional treatment arm not considered by this review: twice daily BDF: 207) WITHDRAWALS BDF: 21; BUD: 23 AGE: mean (range): 45.4 (18 to 80) GENDER (% male): 42 SEVERITY: Moderate BASELINE % PREDICTED FEV1 (mean): 78.8 BASELINE DOSE OF ICS: 365 mcg/d ASTHMA DURATION: 11 years ATOPY (%): Not reported ELIGIBILITY CRITERIA: Diagnosis of asthma (at least 6 months); not optimally controlled despite daily ICS dose of 200 to 500 mg for 1 month before study entry; baseline FEV1 60% to 90% predicted normal; reversibility of FEV1 at least 12% post-SABA EXCLUSION CRITERIA: Oral corticosteroids within one month; seasonal asthma (asthma exacerbated by seasonal increases in aeroallergens); respiratory infection i 4 weeks before study entry; severe cardiovascular disorder/any other significant disease; beta-blocker therapy (including eye drops); history of heavy smoking (10 pack-years)	
Interventions	LABA + ICS versus SAME DOSE ICS alone OUTCOMES: 12 weeks RUN-IN: 2 weeks DOSE OF ICS DURING RUN-IN: BUD 200 mcg/d INTERVENTION PERIOD: 12 weeks TEST GROUP: Combination budesonide and formoterol 160/9 mcg/d CONTROL GROUP: Budesonide 200 mcg/d DEVICE: Turbuhaler NUMBER OF DEVICES: 1 (double-dummy design: use of additional inhaler to control for third treatment group in the study, combination BUD/F 320/18 mcg/d) COMPLIANCE: Self-reported > 97% CO-TREATMENT: As needed SABA (terbutaline or preferred SABA)	
Outcomes	PULMONARY FUNCTION TEST: am PEF; pm PEF; FEV1 SYMPTOM SCORES: % symptom-free days FUNCTIONAL STATUS: Asthma control days; night-time awakenings due to asthma; % rescue-free days INFLAMMATORY MARKERS: Not stated ADVERSE EFFECTS: Stated WITHDRAWALS: Stated by treatment group Primary outcome measure*	
Notes	Full-text publication Source of funding: AstraZeneca Confirmation of methodology and data: Not obtained User defined number: 200	

Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	Unclear	Described as randomised; no other information presented
Allocation concealment?	Unclear	Information not available
Blinding? All outcomes	Yes	Double-dummy
Incomplete outcome data addressed? All outcomes	Unclear	Stated as intention-to-treat analysis for diary cards FEV1 analysed as last observation carried forward: "treatment value was that obtained at the last clinic visit."
Free of selective reporting?	Unclear	Not clear whether the study collected information on exacerbations treated with OCS

Langton Hewer 1995

Methods	Parallel-group, single-centre study
Participants	Symptomatic children % ELIGIBLE OF SCREENED POPULATION: Not reported % RUN-IN PARTICIPANTS RANDOMISED: Not reported NUMBER RECRUITED NOT RANDOMISED: Not stated RANDOMISED: 23 (usual ICS + Sal 100 bid: 11; usual ICS: 12) WITHDRAWALS: Usual ICS + S: 0; usual ICS: 2 AGE median (range) years: 15 (12 to 17) GENDER (% male): 70 SEVERITY: Severe BASELINE % PREDICTED FEV1: 82 BASELINE DOSE OF ICS (start of run-in): 400 ASTHMA DURATION: 13 years ATOPY (%): 100% ELIGIBILITY CRITERIA: Severe asthma (not defined but severe enough to be attending residential school for asthma and persistent symptoms) EXCLUSION CRITERIA: Already on LABA CRITERIA FOR RANDOMISATION DURING RUN-IN: None specified
Interventions	LABA + ICS versus SAME DOSE (usual dose) of ICS OUTCOMES reported at 8 and 10 weeks RUN-IN PERIOD: 2 weeks DOSE OF ICS DURING RUN-IN: Same as during study DOSE OPTIMISATION PERIOD: None INTERVENTION PERIOD: 8 weeks TEST GROUP: (Usual ICS + S): Salmeterol 100 mcg bid CONTROL GROUP: Usual ICS and placebo bid DEVICE: Diskhaler NUMBER OF DEVICES: 2 COMPLIANCE: Supervised in school taking medication by investigators CO-TREATMENT oral steroids, methylxanthines and anticholinergics taken by 20% participants Outcomes PULMONARY FUNCTION TEST: FEV1; am PEF; pm PEF SYMPTOM SCORES: Morning and evening symptom scores FUNCTIONAL STATUS: Rescue B2-agonist; symptom-free days/nights; exacerbation (requiring oral steroids); quality of life score INFLAMMATORY MARKERS: none ADVERSE EFFECTS: Described WITHDRAWALS: Described Primary outcome measure not reported
Notes	Full-text publication Funded by charity Confirmation of methodology and data pending User-defined number: Not reported

Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	Unclear	Described as randomised; no other information presented
Allocation concealment?	Unclear	Information not available
Blinding? All outcomes	Yes	Identical placebo
Incomplete outcome data addressed? All outcomes	Unclear	Not stated
Free of selective reporting?	Yes	Data on OCS-treated exacerbations available for meta-analysis

Leblanc 1996

Methods	Cross-over, multicentre study. 4 treatment arms, of which 2 considered for this review
Participants	Symptomatic asthmatic adults % ELIGIBLE OF SCREENED POPULATION: Not reported % RUN-IN PARTICIPANTS RANDOMISED: Not reported RANDOMISED: 367 WITHDRAWALS: 66 (18%) AGE: mean (range) or mean (SD): 40 GENDER; (% male): 45 SEVERITY: Moderate BASELINE % PREDICTED FEV1: 77.1 BASELINE DOSE OF ICS: Not reported ASTHMA DURATION: <1 years = 10; 1 to 5 years = 89; 6 to 10 years = 71; > 10 years = 197 ATOPY (%): Not reported ELIGIBILITY CRITERIA: >= 18 to 70 years old; demonstrated both FEV1 of at least 60% of their predicted value and an increase in FEV1 of at least 15% after inhalation of 200 ug salbutamol; on 4 of the last 7 days of the pre-randomisation period, patients had to be either symptomatic or demonstrate a greater than 20% diurnal variation in PEF EXCLUSION CRITERIA: FEV1 < 60% of predicted having withheld inhaler bronchodilators for at least 4 hours previously; have lab or clinical evidence in the opinion of the investigator to suggest a serious or uncontrolled systemic disease; clinically significant abnormalities at Visit 1 lab test; have had a lower respiratory tract infection within previous 1 month; abnormal 12-lead ECG measurement; experienced an acute asthma exacerbation requiring emergency room treatment within the past 3 months; required a booster course of oral prednisolone in access of 10 mg prednisolone or equivalent per day within the previous month; a history of acute sudden deterioration of their asthma symptoms; are pregnant or lactating. Females of childbearing potential may be included in the study providing that in the opinion of the investigator is that they are taking adequate contraceptive precautions; hypersensitive to beta-receptor agonists; treatment with beta-receptor antagonists; known to abuse alcohol or drugs; unable to use the peak flow meter properly; unlikely to take their medication in the prescribed manner, complete daily record card properly or attend the clinic on the required occasions; unwilling to sign consent form; in the opinion of the investigator are unsuitable for th
Interventions	Assumed to be single-dose ICS and LABA versus same dose of ICS OUTCOMES: Reported from 14 daily observations from each 1 month treatment period RUN-IN PERIOD: 2 weeks DOSE OF ICS DURING RUN-IN: Usual ICS DOSE OPTIMISATION PERIOD: None INTERVENTION PERIOD: 12 weeks TEST GROUP: (Salm 50 bid) Salmeterol 50 ug bid

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	CONTROL GROUP: Placebo DEVICE: Not reported NUMBER OF DEVICES: 2 COMPLIANCE: Medications taken recorded by patients in diary card CO-TREATMENT: Salbutamol as rescue medication; other medication which could be taken concurrently provided they had been initiated at least one month prior to visit 1 and that the dose remain constant throughout the study: inhaled and intranasala corticosteroids, inhaled sodium cromoglycate, antihistamines and immunotherapy (e.g. Pollinex anti-hay fever injection)	
Outcomes	PULMONARY FUNCTION TEST: am PEF*; pm PEF; diurnal variation in PEF SYMPTOM SCORES: 0 to 10 FUNCTIONAL STATUS: Rescue medication use; symptom-free days/nights; sleep disturbance INFLAMMATORY MARKERS: Not described ADVERSE EFFECTS: Not described WITHDRAWALS: Described Primary outcome measure*	
Notes	Full-text publication Funded by GSK Methodology confirmed but data extraction not confirmed User-defined number: Not reported	
Risk of bias		
Item	Authors' judgement	Description
Adequate sequence generation?	Yes	Computer-generated random numbers
Allocation concealment?	Yes	Numbered coded randomisation envelopes supplied by pharmacy
Blinding? All outcomes	Yes	Use of identical placebo
Incomplete outcome data addressed? All outcomes	No	Completers used as population analysed
Free of selective reporting?	Unclear	Not clear whether data on OCS-treated exacerbations collected during study

Li 1999

Methods

Parallel-group; 3 groups of which 2 are considered for this review

Participants	Symptomatic asthmatic adults % ELIGIBLE OF SCREENED POPULATION: Not reported % RUN-IN PARTICIPANTS RANDOMISED: 70 RANDOMISED: 34 (Sal 50 mcg bid + usual ICS: 16; placebo + usual ICS: 18) WITHDRAWALS: Sal 50 mcg bid + usual ICS: 3; placebo + usual ICS: 2 AGE: mean (range) 35 (20 to 70) GENDER (% male): 53 SEVERITY: Mild BASELINE % PREDICTED FEV1: 84 BASELINE DOSE OF ICS (median): 400 ASTHMA DURATION: Not reported ATOPY (%): 87 ELIGIBILITY CRITERIA: > 20 to 70 years old; non-smokers; diagnosed asthma treated for at least 12 months with ICS in a dose up to 500 mg of beclomethasone dipropionate or budesonide per day; FEV1 at baseline) >= 60% of its predicted value EXCLUSION CRITERIA: Having suffered from acute respiratory tract infection during the previous 4 weeks; change in asthma medication in < 4 weeks; admission to hospital with airway disease in the < 4 weeks; patients unable to discontinue use of methylxanthines, inhaled anticholinergics and oral steroids CRITERIA FOR RANDOMISATION DURING RUN-IN: Symptom score of more than 2 on 7 of the last 14 days; required the use of rescue inhaled albuterol on more than 7 of the last 14 days; and some degree of symptoms and rescue medication use during that time	
Interventions	LABA + ICS vs SAME dose of ICS OUTCOMES: measured at 12 weeks RUN-IN PERIOD: 2 to 6 weeks DOSE OF ICS DURING RUN-IN: Same as baseline dose of ICS DOSE OPTIMISATION PERIOD: None INTERVENTION PERIOD: 12 weeks TEST GROUP: Salmeterol 50 mcg bid + usual ICS CONTROL GROUP: Placebo + usual ICS DEVICE: Dry powder Diskhaler NUMBER OF DEVICES: 2 COMPLIANCE: Not reported CO-TREATMENT: Not described	
Outcomes	PULMONARY FUNCTION TEST: am PEF; FEV1 SYMPTOM SCORES: score of 0 to 4 (mean/day) FUNCTIONAL STATUS: Rescue medication use; night awakenings OTHER: Methacholine challenge - PD 20 methacholine before and after treatment INFLAMMATORY MARKERS: On BAL and bronchial biopsy; mast cells in BAL; eosinophils in BAL; lymphocytes in BAL; macrophages in BAL and bronchial biopsies ADVERSE EFFECTS: Not reported WITHDRAWALS: Reported Primary outcome not specified	
Notes	Full-text publication Funded by GSK, Alfred Foundati Confirmation of methodology and User-defined number: 400	ion and the NH & MRC of Australia d data obtained
Risk of bias		
Item	Authors' judgement	Description
Adequate sequence generation?	Yes	Computer-generated numbers in balanced blocks
Allocation concealment?	Yes	Opaque consecutive numbered envelopes containing assignment
Blinding? All outcomes	Yes	Identical inhaler devices
T 1 1.	No	Completers analysed
Incomplete outcome data addressed? All outcomes		

Malone 2005

Methods	Parallel-group, multicentre (66 centres in North America)	
Participants	Steroid-using asthmatic children % ELIGIBLE OF SCREENED POPULATION: Not reported % RUN-IN PARTICIPANTS RANDOMISED: 48 RANDOMISED: 203 (FP/SAL: 101; FP: 102) WITHDRAWAL: FP/SAL: 19; FP: 16 AGE mean: 8 years GENDER (% male): 64 ASTHMA SEVERITY: Mild-moderate BASELINE % PREDICTED FEV1 mean: 80 BASELINE % PREDICTED FEV1 mean: 90 BASELINE % PREDICTED % TO 10 years; ATS defined asthma for at least 2 months; ICS therapy (BDP equivalent 252 to 336 mcg /d) for 1 month prior to beta-agonist at screening visit or within one year of screening visit EXCLUSION CRITERIA: History of life-threatening asthma; hospitalisation with asthma twice or more in previous year; significant concurrent disease; oral or parenteral use of steroids in month prior to study entry CRITERIA FOR RANDOMISATION DURING RUN-IN: am FEV1 50% to 95% pred	
Interventions	LABA + ICS versus SAME dose of ICS OUTCOMES: 12 weeks RUN-IN PERIOD: 2 weeks DOSE OF ICS DURING RUN-IN: Usual maintenance dose INTERVENTION PERIOD: 12 weeks TEST GROUP: Combination salmeterol 50/fluticasone 100 mcg bid CONTROL GROUP: Fluticasone 100 mcg bid DEVICE: Diskus NUMBER OF DEVICES: 1 COMPLIANCE: Not reported CO-TREATMENT: prn SABA	
Outcomes	PULMONARY FUNCTION TEST: FEV1; clinic PEF; am PEF; pm PEF SYMPTOM SCORES: Symptom scores; symptom-free days FUNCTIONAL STATUS: OCS-treated exacerbations; hospitalisations; use of reliever medication; SABA-free days INFLAMMATORY MARKERS: Not reported ADVERSE EFFECTS: Reported WITHDRAWAL: Stated *Primary outcome: Not identified (safety study)	
Notes	Full-text publication Funded by GSK User-defined number: 400 Confirmation of data and methodology obtained	
Risk of bias		
Item	Authors' judgement	Description
Adequate sequence generation?	Yes	See Appendix 2
Allocation concealment?	Yes	See Appendix 2
Blinding? All outcomes	Yes	Identical placebo used
Incomplete outcome data addressed? All outcomes	No	Last observation carried forward: "al available data up to the time of discontinuation were included in the intent to treat population."
Free of selective reporting?	Yes	OCS-treated exacerbations available on request from GSK

Meijer 1995

Methods	Parallel-group, single-centre stu	dy
Participants	Asymptomatic asthmatic children % ELIGIBLE OF SCREENED POPULATION: Not reported % RUN-IN PARTICIPANTS RANDOMISED: Not reported RANDOMISED: 40 (Sal 50 mcg bid + ICS: 20; ICS + placebo: 20) WITHDRAWALS: Sal50 mcg bid + ICS: 0; ICS + placebo: 1 (5%) AGE: mean (SD): 11.4 (2.6) GENDER (% male): 58 SEVERITY: Mild BASELINE % PREDICTED FEV1: 94 BASELINE MORE OF ICS: Twice daily 200 or 400 mcg beclomethasone dipropionate Rotadisk ASTHMA DURATION: 8.4 years ATOPY (%): 100 ELIGIBILITY CRITERIA: None reported EXCLUSION CRITERIA: None reported CRITERIA FOR RANDOMISATION DURING RUN-IN: N/A	
Interventions	LABA + ICS versus SAME dose of ICS OUTCOMES: reported at 1, 8, 16 weeks RUN-IN PERIOD: None DOSE OPTIMISATION PERIOD: None INTERVENTION PERIOD: 16 weeks TEST GROUP: Salmeterol 50 mcg bid + BDP 250 mcg bid CONTROL GROUP: BDP 250 mcg bid + placebo DEVICE: Dry powder inhaler (Diskhaler) NUMBER OF DEVICES: 2 COMPLIANCE: Returned powder disks counted CO-TREATMENT: prn SABA	
Outcomes	PULMONARY FUNCTION TEST: FEV1 predicted; PC20 doubling doses (DD); circadian variation (day-night differences in FEV1) SYMPTOM SCORES: Only individual symptoms reported (yes/no) FUNCTIONAL STATUS: Rescue medication use INFLAMMATORY MARKERS: Not reported ADVERSE EFFECTS: Not reported WITHDRAWALS: Reported Primary outcome not specified	
Notes	Full-text publication Funded by GSK User-defined number: 500 Confirmation of data and methodology not obtained	
Risk of bias		
Item	Authors' judgement	Description
Adequate sequence generation?	Unclear	Described as randomised; no other information presented
Allocation concealment?	Unclear	Information not available
Blinding? All outcomes	Yes	Use of identical placebo
Incomplete outcome data addressed? All outcomes	Unclear	Not enough information presented to determine this
Free of selective reporting?	Unclear	Not clear whether data on OCS-treated exacerbations collected during study

Molimard 2001

Methods	Parallel-group, multicentre study	
Participants	Symptomatic asthmatic adults % ELIGIBLE OF SCREENED POPULATION: Not reported	

Interventions	before randomisation 3 failed to fui consent and 2 were lost to follow u RANDOMISED: 259 (Form 12 mc WITHDRAWALS: 30 (Form 12 m AGE: mean: Form 12 mcg bid: 39 GENDER: (% male): 57 SEVERITY: Moderate BASELINE % PREDICTED FEV: BASELINE DOSE OF ICS (start o mcg BDP equivalent ASTHMA DURATION: 15 years ATOPY (%): Not reported ELIGIBILITY CRITERIA: 18 year daily treatment with an ICS, same of daily treatment with an ICS, same of daily treatment with inhaled bronof ATS; FEV1 >= 60% of predicted n (increase in FEV1 >= 10% of predi within 3 months prior to visit; refra spirometry EXCLUSION CRITERIA: Known lactose; pregnancy or breast-feedin use a reliable contraceptive method medication; asthma exacerbation of the first visit; incapacity to use a m patient diary; concomitant treatmer bronchodilators and inhaled or oral were not allowed CRITERIA FOR RANDOMISATT reported LABA + ICS versus SAME dose o OUTCOMES: measured at 12 wee RUN-IN PERIOD: 2 to 6 weeks DOSE OF TIMISATION PERIOD: INTERVENTION PERIOD: 12 we TEST GROUP: (Form 12 + ICS) ff CONTROL GROUP: (ODS) On-dd beclomethasone or 800 mcg budess DEVICE: Dry powder Diskhaler NUMBER OF DEVICES: 2 (test g COMPLIANCE: Not reported CO-TREATMENT: Salbutamol pr	g bid: 130; on-demand salbutamol (ODS): 129) cg bid: 12; ODS: 18) years 1: 73 f run-in): Not reported; maximum dose 1000 rs or over; moderate persistent asthma; taking one for at least 1 month prior to first visit; require todilators; asthma defined according to criteria of ormal value for patient; reversibility test cted value) had to be documented at first visit in from taking salbutamol 6 hours before each hypersensitivity to sympathetic amines or to g; women of childbearing potential who did not t; significant change in the regular asthma r respiratory tract infection in the month prior to etered-dose inhaler correctly or to complete tts with theophylline, anticholinergic B2 agonists other than the trial medications ON DURING RUN-IN: No additional criteria f ICS ks Same as usual None texts proterol 12 mcg bid + ICS emand salbutamol + usual ICS (up to 1000 ucg onide or 500 mcg fluticasone per day) roup)
Outcomes	CO-TREATMENT: Salbutamol prn PULMONARY FUNCTION TEST: am PEF* (average of 2 weeks); FEV1; bronchial responsiveness to methacholine (PD20) SYMPTOM SCORES: Score of 0 to 4 (mean/day) FUNCTIONAL STATUS: Rescue medication use; nocturnal awakenings INFLAMMATORY MARKERS: BAL and bronchial biopsy; mast cells in BAL; eosinophils in BAL; lymphocytes in BAL; macrophages in BAL and bronchial biopsies ADVERSE EFFECTS: Not reported WITHDRAWALS: Reported Primary outcome measure*	
Notes	Full-text publication Funded by GSK, Alfred Foundation Confirmation of methodology and User-defined number: Not reported	data not obtained
Risk of bias		
Item	Authors' judgement	Description
Adequate sequence generation?	Unclear	Described as randomised; no other information presented
Allocation concealment?	Yes	Telephone notification of assignment by co-ordinating centre
Blinding? All outcomes	No	Open label
Incomplete outcome data addressed?	Unclear "The analyses were carried out in the intent-to-treat population, i.e. in all	

All outcomes		randomized patients with a post- baseline efficacy measurement."
Free of selective reporting?	Unclear	Not clear whether data on OCS- treated exacerbations collected during study

Morice 2008a

Methods	Parallel-group, multicentre study (53 centres in South America, Europe, Hong Kong and Taiwan)	
Participants	% ELIGIBLE OF SCREENED POPULATION: Not reported % RUN-IN PARTICIPANTS RANDOMISED: 77 RANDOMISED: 622 (BUD: 207; BUD/F (DPI): 203; BUD/F (MDI): 212) WITHDRAWALS: BUD: 14 BUD/F (DPI): 11; BUD/F (MDI): 14 AGE: mean (range): 9 (6 to 11 years) GENDER (% male): 66 SEVERITY: Not specified BASELINE % PREDICTED FEV1: 89 BASELINE MORE OF ICS: (Start of run-in): 470 mcg ASTHMA DURATION: Not reported ATOPY (%): Not reported ELIGIBILITY CRITERIA: Age 6 to 11 years; diagnosis of asthma for at least 6 months; PEF > 50% of predicted normal; history daily ICS use (stable dose of 375 to 1000 mcg 30 days prior to enrolment); clinically important exercise-induced bronchoconstriction for 3 months before enrolment; ability to use DPI, pMDI and peak flow meter EXCLUSION CRITERIA: Not reported CRITERIA FOR RANDOMISATION DURING RUN-IN: Symptom score 1 to 4; mean morning PEF 50% to 85% post-SABA	
Interventions	OUTCOMES: 12 weeks RUN-IN PERIOD: 2 weeks DOSE OF ICS DURING RUN-IN: 470 DOSE OPTIMISATION PERIOD: Not reported INTERVENTION PERIOD: 12 weeks TEST GROUP: Combination formoterol and budesonide (160/9 mcg) bid via dry powder inhaler + placebo metered dose inhaler CONTROL GROUP: Budesonide 100 mcg bid DEVICE: BUD/F MDI and budesonide: MDI; BUD/F DPI: DPI NUMBER OF DEVICES: 2 COMPLIANCE: Not reported CO-TREATMENT: Terbutaline	
Outcomes	PULMONARY FUNCTION TEST: am PEF*; pm PEF; FEV1 SYMPTOM SCORES: Day/night scores FUNCTIONAL STATUS: Paediatric AQLQ INFLAMMATORY MARKERS: NA ADVERSE EFFECTS: Stated WITHDRAWALS: Stated Primary outcome measure*	
Notes	Full-text publication AZ funded User defined: 200 Confirmation of data and methodology not obtained	
Risk of bias		
Item	Authors' judgement	Description
Adequate sequence generation?	Yes	Computer-generated schedule (blocks of 6
Allocation concealment?	Unclear	Information not available
Blinding? All outcomes	Yes	Double-dummy
Incomplete outcome data addressed? All outcomes	Unclear	"The intent-to-treat (ITT) population (i. e. all randomised patients with post-

randomisation data) was used for the main efficacy analyses."

Free of selective reporting? Unclear	Not clear whether data on OCS-treated exacerbations collected during study
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Morice 2008b

Methods	As above	
Participants	As above	
Interventions	As above except for: TEST GROUP: Combination formoterol and budesonide (160/9 mcg) bid via metered dose inhaler + placebo dry powder inhaler	
Outcomes	As above	
Notes	As above	
Risk of bias		
Item	Authors' judgement	Description
Adequate sequence generation?	Yes	See above
Allocation concealment?	Unclear	See above
Blinding? All outcomes	Yes	See above
Incomplete outcome data addressed? All outcomes	Unclear	See above
Free of selective reporting?	Unclear	See above

Nathan 2006

Methods	Parallel-group, multicentre study (45 centres in USA)	
Participants	Moderately severe asthmatic adults on ICS % ELIGIBLE OF SCREENED POPULATION: Not reported % RUN-IN PARTICIPANTS RANDOMISED: 48 RANDOMISED: 365 (185 to study groups of interest to the review: FP/SAL: 94 FP: 91) WITHDRAWALS: FP/SAL: 13; FP: 20 AGE: mean (range): 39 (12 to 82) GENDER (% male): 38 SEVERITY: Moderate BASELINE % PREDICTED FEV1 (mean): 69 BASELINE DOSE OF ICS: 470 mcg FP ASTHMA DURATION: Not reported ATOPY (%): Not reported ELIGIBILITY CRITERIA: > 12 years; ATS defined asthma for at least 6 months; FEV1 40% to 85% predicted; >/= 15% reversibility post-SABA; 440 to 660 mcg/c FP or equivalent for at least 1 month prior to visit 1 with no change in regimen EXCLUSION CRITERIA: Not reported CRITERIA FOR RANDOMISATION DURING RUN-IN: >/= 3 nights with awakenings requiring SABA over last 7 days of run-in; >/= 3 days where SABA was used 12 times or more over last 7 days of run-in	
Interventions	LABA + ICS versus SAME DOSE ICS OUTCOMES: 12 weeks RUN-IN: 2 weeks DOSE OF ICS DURING RUN-IN: Usual dose of ICS INTERVENTION PERIOD: 12 weeks	

	TEST GROUP: Combination fluticasone and salmeterol 220/42 mcg bid CONTROL GROUP: Fluticasone 220 mcg bid DEVICE: MDI NUMBER OF DEVICES: 1 COMPLIANCE: Not assessed CO-TREATMENT: prn SABA	
Outcomes	PULMONARY FUNCTION TEST: am PEF; pm PEF; FEV1* SYMPTOM SCORES: Daily symptom score; % days with no symptoms FUNCTIONAL STATUS: Night-time awakenings; % nights with no awakenings; rescue medication use; % days with no rescue medication use INFLAMMATORY MARKERS: Not reported ADVERSE EFFECTS: Reported WITHDRAWALS: Due to worsening asthma* Primary outcome measure*	
Notes	Full-text publication and unpublished data available from http://www.ctr.gsk.co.uk Source of funding: GSK Confirmation of methodology and data: Not obtained User defined number: 880	
Risk of bias		
Item	Authors' judgement Description	
Adequate sequence generation?	Yes	See Appendix 2
Allocation concealment?	Yes	See Appendix 2
Blinding? All outcomes	Yes	Identical inhaler devices used
Incomplete outcome data addressed? All outcomes	Unclear	"The intent-to-treat (ITT) population included all patients who were randomized to treatment and received > 1 dose of study medication."
Free of selective reporting?	Yes	OCS-treated exacerbations available on request from GSK

Noonan 2006a

Methods	Parallel-group, multicentre study (84 centres in USA). Five treatment groups (formoterol and placebo not considered in this review)
Participants	Moderately severe asthmatic adults % ELIGIBLE OF SCREENED POPULATION: 43 RUN-IN PARTICIPANTS RANDOMISED: Not reported RANDOMISED: 233 (BUD/F: 124; BUD: 109) WITHDRAWALS: BUD/F: 27; BUD: 39 AGE: mean (range): 40.7 (12 to 87) GENDER (% male): 35 SEVERITY: Moderate BASELINE % PRED FEV1 (mean): 68 BASELINE DOSE OF ICS: 580 mcg/d ASTHMA DURATION: 22 years ATOPY (%): Not stated ELIGIBILITY CRITERIA: >/= 12 years; documented history of asthma for >/= 6 months according to ATS; moderate to high doses of ICS for more than 4 weeks; FEV1 45% to 85% predicted; FEV1 reversibility of > 12% and > 200 mL EXCLUSION CRITERIA: Hospitalisation within previous 6 months; requirement for oral CS within previous 4 weeks; > 10 pack-year smoking habit
Interventions	LABA + ICS versus SAME DOSE ICS OUTCOMES: 12 weeks RUN-IN: 2 weeks DOSE OF ICS DURING RUN-IN: BUD 160 mcg bid INTERVENTION PERIOD: 12 weeks TEST GROUP: Combination budesonide and formoterol 320/9 mcg bid + placebo DPI CONTROL GROUP: Budesonide 320 mcg bid DEVICE: Combination BUD/F and BUD: Metered dose inhaler

	NUMBER OF DEVICES: 2 COMPLIANCE: Not assessed CO-TREATMENT: prn SABA	
Outcomes	PULMONARY FUNCTION TEST: am PEF; pm PEF; FEV1* SYMPTOM SCORES: Daytime symptoms; night-time symptoms; % symptom-free days FUNCTIONAL STATUS: % awakening-free nights; rescue medication use (puffs/d) INFLAMMATORY MARKERS: Not reported ADVERSE EFFECTS: Stated WITHDRAWALS: Stated Primary outcome measure*	
Notes	Full-text publication Source of funding: AstraZeneca Confirmation of methodology and data. OCS and hospitalisation obtained from AZ User defined number: 640	
Risk of bias		
Item	Authors' judgement Description	
Adequate sequence generation?	Yes	Computer-generated randomisation schedule, stratified by baseline ICS dose
Allocation concealment?	Unclear	Information not available
Blinding? All outcomes	Yes	Double-dummy design
Incomplete outcome data addressed? All outcomes	Unclear	Population used for analysis comprised participants who received more than one dose of study medication
Free of selective reporting?	Yes	OCS-treated exacerbations available from AZ

Noonan 2006b

Methods	As above	
Participants	Moderately severe asthmatic adults % ELIGIBLE OF SCREENED POPULATION: 43 RUN-IN PARTICIPANTS RANDOMISED: Not reported RANDOMISED: 224 (BUD + F: 115; BUD: 109) WITHDRAWALS: BUD + F: 29; BUD: 39 AGE: mean (range): 40.7 (12 to 87) GENDER (% male): 35 SEVERITY: Moderate BASELINE % PREDICTED FEV1(mean): 68 BASELINE % PREDICTED FEV1(mean): 68 BASELINE DOSE OF ICS: 580 mcg/d ASTHMA DURATION: 22 years ATOPY (%): Not stated As for Noonan 2006a	
Interventions	LABA + ICS versus SAME DOSE ICS OUTCOMES: 12 weeks RUN-IN: 2 weeks DOSE OF ICS DURING RUN-IN: BUD 160 mcg bid INTERVENTION PERIOD: 12 weeks TEST GROUP: Budesonide 320 mcg bid + formoterol 9 mcg bi CONTROL GROUP: Budesonide 320 mcg bid DEVICE: BUD: Metered dose inhaler; formoterol DPI NUMBER OF DEVICES: 2 COMPLIANCE: Not assessed CO-TREATMENT: prn SABA	
Outcomes		

Risk of bias		
Item	Authors' judgement	Description
Adequate sequence generation?	Yes	As for Noonan 2006a
Allocation concealment?	Unclear	As for Noonan 2006a
Blinding? All outcomes	Yes	As for Noonan 2006a
Incomplete outcome data addressed? All outcomes	Unclear	As for Noonan 2006a
Free of selective reporting?	Yes	As for Noonan 2006a

Norhaya 1999

Methods	Cross-over study; single-centre in Malaysia	
Participants	Symptomatic asthmatic adults % ELIGIBLE OF SCREENED POPULATION: Not reported % RUN-IN PARTICIPANTS RANDOMISED: 83 (5 patients were withdrawn as they did not meet the selection criteria, 3 were unable to record their symptoms satisfactorily, 1 had no nocturnal symptoms or significant PEF variability and 1 had taken prednisolone in excess of 10 mg per day) RANDOMISED: 25 (20 completed) WITHDRAWALS: 5 AGE: mean (SD): 41.8 years (9.5) GENDER (% male): 30 SEVERITY: Moderate BASELINE % PREDICTED FEV1: 68 BASELINE MORE OF ICS (range): 885 (200 to 1600) ASTHMA DURATION: Not reported ATOPY (%): Not reported ELIGIBILITY CRITERIA: 15% improvement from baseline in FEV1 following salbutamol via Diskhaler EXCLUSION CRITERIA: Lower respiratory tract infection within previous 28 days; need for maintenance oral prednisolone > 10 mg/day within previous 28 days pregnant or lactating women CRITERIA FOR RANDOMISATION DURING RUN-IN: Night-time symptom score >= 2/5 or diurnal variation in peak flow >= 20% on at least 3 nights in the 1 week run-in	
Interventions	LABA + ICS vs SAME dose ICS OUTCOMES: 4 weeks RUN-IN PERIOD: 1 week DOSE OF ICS DURING RUN-IN: Usual dose of ICS INTERVENTION PERIOD: 4 weeks per group with 2 week wash-out in between DOSE OPTIMISATION PERIOD: None TEST GROUP: (Salm 50) salmeterol 50 ug bid + usual, but unspecified dose of IC CONTROL GROUP: Placebo + usual, but unspecified, dose of ICS DEVICE: Diskhaler NUMBER OF DEVICES: 2 COMPLIANCE: Not reported CO-TREATMENT: sodium cromoglycate, theophylline and short-acting b2-agonis (salbutamol) as needed	
Outcomes	PULMONARY FUNCTION TEST: am PEF*; pm PEF; FEV1; FVC SYMPTOM SCORES: Score of 0 to 5 daytime; score of 0 to 4 night-time FUNCTIONAL STATUS: Daytime dose of rescue bronchodilator; night-time dc of rescue bronchodilator; episode-free days; exacerbations requiring oral steroids INFLAMMATORY MARKERS: Not reported ADVERSE EFFECTS: Not reported WITHDRAWALS: Described *Primary outcome measure	
Notes	Full-text publication Funded by GSK Confirmation of methodology and data not obtained; GSK unable to provide confirmation	

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Risk of bias			
Item	Authors' judgement	Description	
Adequate sequence generation?	Unclear	Described as randomised; no other information presented	
Allocation concealment?	Unclear	Information not available	
Blinding? All outcomes	Yes	Identical placebo used	
Incomplete outcome data addressed? All outcomes	No	Completers used for analysis	
Free of selective reporting?	Yes	Data available for OCS-treated exacerbations	

User-defined number: Not reported

O'Byrne 2001a

Methods	Parallel-group multicentre study (7 groups of which 2 considered here)
Participants	Symptomatic asthmatic teenagers and adults % ELIGIBLE OF SCREENED POPULATION: Not reported % RUN-IN PARTICIPANTS RANDOMISED: Not reported RANDOMISED: 645 (BUD200: 322; BUD200 + F: 323) WITHDRAWALS: Not reported AGE: mean: 37 years GENDER (% male): 44 SEVERITY: Mild BASELINE % PREDICTED FEV1: 86.4 BASELINE DOSE OF ICS: Not reported (= 400 mcg/d BUD)<br ASTHMA DURATION: Not reported ATOPY(%): Not reported ELIGIBILITY CRITERIA: >= 12 years of age with mild asthma; taking <= 400 mcg/daily of inhaled budesonide or its equivalent for >= 3 months; FEV1 >= 70% predicted normal after terbutaline CRITERIA FOR RANDOMISATION DURING RUN-IN: Randomised patients demonstrated a need for 2 or more inhalations per week of rescue medication during the last 2 weeks of run-in, a >= 15% variability in peak expiratory flows, or a >= 12% increase in FEV1 after terbutaline EXCLUSION CRITERIA: Experience 3 severe exacerbations during the initial 6 months or 5 exacerbations in total; 2 poorly controlled asthma days, defined as days with morning PEF values >= 2 above baseline, or with asthma awakening
Interventions	LABA + ICS vs SAME dose ICS OUTCOMES: Reported at 52 weeks RUN-IN PERIOD: 4 weeks DOSE OF ICS DURING RUN-IN: BDP 100 bid DOSE OPTIMISATION PERIOD: None INTERVENTION PERIOD: 52 weeks TEST GROUP: Budesonide 200 mcg + formoterol 9 mcg via separate inhalers CONTROL GROUP: Budesonide 200 mcg DEVICE: Turbuhaler NUMBER OF DEVICES: 2 COMPLIANCE: Not reported CO-TREATMENT: prn SABA

Outcomes	PULMONARY FUNCTION TEST: am PEF; FEV1 SYMPTOM SCORES: Not reported FUNCTIONAL STATUS: Percentage of days with symptoms; percentage of asthma awakenings; number of rescue inhalations; rate per patient per year of severe asthma exacerbations INFLAMMATORY MARKERS: Not reported ADVERSE EFFECTS: Reported WITHDRAWAL: Reported *Primary outcome: time to the first severe asthma exacerbation defined as need for treatment with oral corticosteroids or hospital admission or emergency treatment for worsening asthma or a decrease in morning PEF > 25% from baseline	
Notes	Full-text publication Funded by AstraZeneca Confirmation of methodology and data not obtained User-defined order: 400 (BUD 200 bid)	
Risk of bias		
Item	Authors' judgement	Description
Adequate sequence generation?	Yes	Computer-generated random numbers
Allocation concealment?	Yes	Opaque consecutive numbered envelopes containing assignment
Blinding? All outcomes	Yes	Identical placebo
Incomplete outcome data addressed? All outcomes	Unclear	"The study was analyzed using intention-to-treat principles."
Free of selective reporting?	Yes	OCS-treated exacerbations available from study report

O'Byrne 2001b

Methods	Parallel-group multicentre study (7 groups of which 2 considered here)
Participants	Symptomatic asthmatic teenagers and adults % ELIGIBLE OF SCREENED POPULATION: Not reported % RUN-IN PARTICIPANTS RANDOMISED: Not reported RANDOMISED: 627 (BUD400: 312; BUD400 + F: 315) WITHDRAWALS: Not reported by subgroup AGE mean: 37 years GENDER (% male): 42 SEVERITY: Mild BASELINE % PREDICTED FEV1: 87 BASELINE DOSE OF ICS : = 400 mcg/d BUD<br ASTHMA DURATION: Not reported ATOPY(%): Not reported ELIGIBILITY CRITERIA: >= 12 years of age with mild asthma; taking <= 400 mcg/daily of inhaled budesonide or its equivalent for >= 3 months; FEV1 >= 70% predicted normal after terbutaline EXCLUSION CRITERIA: Experience 3 severe exacerbations during the initial 6 months or five exacerbations in total; 2 poorly controlled asthma days, defined as days with morning PEF values >= 2 above baseline, or with asthma awakening CRITERIA FOR RANDOMISATION FOLLOWING RUN-IN: Randomised patients demonstrated a need for two or more inhalations per week of rescue medication during the last 2 weeks of run-in, a >= 15% variability in peak expiratory flows, or a >= 12% increase in FEV1 after terbutaline
Interventions	LABA + ICS vs SAME dose ICS OUTCOMES: Reported at 52 weeks RUN-IN PERIOD: 4 weeks DOSE OF ICS DURING RUN-IN: BUD 100 bid DOSE OPTIMISATION PERIOD: None INTERVENTION PERIOD: 52 weeks TEST GROUP: Budesonide 800 mcg + formoterol 9 mcg via separate inhalers CONTROL GROUP: Budesonide 800 mcg

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	DEVICE: Turbuhaler NUMBER OF DEVICES: 2 COMPLIANCE: Not reported CO-TREATMENT: prn SABA	
Outcomes	PULMONARY FUNCTION TEST: am PEF; FEV1 SYMPTOM SCORES: Not reported FUNCTIONAL STATUS: Percentage of days with symptoms; percentage of asthma awakening; rescue medication use; exacerbations (defined as need for treatment with oral corticosteroids or hospital admission or emergency treatment for worsening asthma or a decrease in morning PEF > 25% from baseline); rate per patient per year of severe asthma exacerbations* INFLAMMATORY MARKERS: Not reported ADVERSE EFFECTS: Reported WITHDRAWAL: Reported Primary outcome measure*	
Notes	Full-text publication Funded by AstraZeneca Confirmation of methodology and data not obtained User-defined number: 800 (BUD 400 bid)	
Risk of bias		
Item	Authors' judgement	Description
Adequate sequence generation?	Yes	See O'Byrne 2001a
Allocation concealment?	Yes	See O'Byrne 2001a
Blinding? All outcomes	Yes	See O'Byrne 2001a
Incomplete outcome data addressed? All outcomes	Unclear	See O'Byrne 2001a
Free of selective reporting?	Yes	See O'Byrne 2001a

Pauwels 1997a

Methods	Parallel-group, multicentre study (71 centres in North America, Europe, and Middle East); 4 treatment arms
Participants	Symptomatic asthmatic adults % ELIGIBLE OF SCREENED POPULATION: Not reported % RUN-IN PARTICIPANTS RANDOMISED: 77 RANDOMISED: 423 (F12 + BUD 100 bid: 210; BUD 100 bid: 213) WITHDRAWAL: F12 + BUD 100 mcg bid: 62; BUD 100 mcg bid: 82 AGE: mean (range): 42 years (18 to 70) GENDER (% male): 51% SEVERITY: Moderate BASELINE % PREDICTED FEV1 mean: 76 BASELINE DOSE OF ICS mean (range): 822 (100 to 2000) ASTHMA DURATION: Not reported ATOPY(%): Not reported ELIGIBILITY CRITERIA: Asthma for at least 6 months; treated with an inhaled corticosteroid for at least 3 months; baseline FEV1 >= 50% predicted; >= 15% improvement following inhalation of 1 mg of terbutaline EXCLUSION CRITERIA: Use of beclomethasone > 2000 ug/day or budesonide by MDI > 1600 ug/day or budesonide by turbuhaler > 800 ug/day or fluticasone > 800 ug/day; >= 3 courses of oral steroids in past 6 months; hospitalisation for asthma in past 6 months CRITERIA FOR RANDOMISATION DURING RUN-IN: Compliance with 75% to 125% of the recommended dose of budesonide; stable asthma over the preceding 10 days as defined by the absence of the following criteria: diurnal variation of more than 20% in PEF on 2 consecutive days; waskening due to asthma on 2 consecutive nights or the need to use oral glucocorticoids
Interventions	LABA + ICS vs SAME dose ICS OUTCOMES: 1, 2, 3, 6, 9 and 12 months of treatment

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	CONTROL GROUP: Bud DEVICE: Turbuhaler NUMBER OF DEVICES:	RUN-IN: BUD 800 bid ERIOD: None D: 52 weeks le 100 mcg bid + formoterol 12 mcg bid esonide 100 mcg bid + placebo 2 den mechanical counter built into inhaler which could ors
Outcomes	PULMONARY FUNCTIC SYMPTOM SCORES: Me study (4-point scale: avera FUNCTIONAL STATUS: exacerbation (requiring ora INFLAMMATORY MAR ADVERSE EFFECTS: Re WITHDRAWAL: Reporte	Rescue medication use; nocturnal awakening; *severe al steroids); episode-free days (mean % of year) KERS: Not reported ported
Notes	Full-text publication Funded by Astra Draco, Lund, Sweden Confirmation of methodology and data obtained User-defined order: 200 (BUD 100 bid)	
Risk of bias		
Item	Authors' judgement	Description
Adequate sequence generation?	Yes	Computer-generated randomisation sequence
Allocation concealment?	Unclear	Information not available
Blinding? All outcomes	Yes	Identical placebo
Incomplete outcome data addressed? All outcomes	Unclear	"The analysis included all randomized patients (intention-to-treat approach). Data for patients who withdrew or discontinued therapy were included up to the time of their withdrawal."
Free of selective reporting?	Yes	OCS-treated exacerbations available for meta- analysis

Pauwels 1997b

Methods	Parallel-group, multicentre study (71 centres in North America, Europe, and Middl East); 4 treatment arms
Participants	Symptomatic asthmatic adults % ELIGIBLE OF SCREENED POPULATION: Not reported % RUN-IN PARTICIPANTS RANDOMISED: 77 RANDOMISED: 429 (F12 bid + BUD 400 bid: 215; BUD 400 mcg bid: 214) WITHDRAWAL: F12 bid + BUD 400 bid: 41; BUD 400 mcg bid: 60 AGE: mean (range): 42 years (17 to 70) GENDER (% male): 48 SEVERITY: Moderate BASELINE % PREDICTED FEV1: 76 BASELINE DOSE OF ICS (start of run-in): 835 (100 to 2000) ASTHMA DURATION: Not reported ATOPY(%): Not reported ELIGIBILITY CRITERIA: Asthma for at least 6 months; treated with an inhaled corticosteroid for at least 3 months; baseline FEV1 >= 50% predicted; >= 15% improvement following inhalation of 1 mg of terbutaline EXCLUSION CRITERIA: Use of beclomethasone > 2000 ug/day or budesonide b MDI > 1600 ug/day or budesonide by turbuhaler > 800 ug/day or fluticasone > 800 ug/day; >= 3 courses of oral steroids in past 6 months; hospitalisation for asthma ir past 6 months

	CRITERIA FOR RANDOMISATION DURING RUN-IN: Compliance with 75 to 125 % of the recommended dose of budesonide; stable asthma over the preceding 10 days as defined by the absence of the following criteria: diurnal variation of more than 20% in PEF on 2 consecutive days; use of 4 or more inhalations of rescue medication per day on 2 consecutive days; awakening due to asthma on 2 consecutive nights or the need to use oral glucocorticoids	
Interventions	LABA + ICS vs SAME dose ICS OUTCOMES: Reported at 1, 2, 3, 6, 9 and 12 months RUN-IN PERIOD: 4 weeks DOSE OF ICS DURING RUN-IN: BUD 800 bid DOSE OPTIMISATION PERIOD: None INTERVENTION PERIOD: 52 weeks TEST GROUP: Formoterol 12 mcg bid + budesonide 400 mcg bid CONTROL GROUP: Budesonide 400 mcg bid + placebo DEVICE: Turbuhaler NUMBER OF DEVICES: 2 COMPLIANCE: Yes; hidden mechanical counter built into inhaler which could only be seen by investigators CO-TREATMENT: prn SABA	
Outcomes	OUTCOMES: Reported at 1, 2, 3, 6, 9 and 12 months PULMONARY FUNCTION TEST: FEV1 predicted; am PEF; pm PEF SYMPTOM SCORES: Mean daytime and night-time symptom scores at end of study (4-point scale: averaged over 10 days) FUNCTIONAL STATUS: Rescue medication use; nocturnal awakening; *severe exacerbation (requiring oral steroids); episode-free days (mean % of year) INFLAMMATORY MARKERS: Not reported ADVERSE EFFECTS: Reported WITHDRAWAL: Reported *Primary outcome measures: rates of severe and mild exacerbations of asthma per patient per year	
Notes	Full-text publication Funded by Astra Draco, Lund, Sweden Confirmation of methodology and data obtained User-defined order: 200 (BUD 100 bid)	
Risk of bias		
Item	Authors' judgement	Description
Adequate sequence generation?	Yes	See Pauwels 1997a
Allocation concealment?	Unclear	See Pauwels 1997a
Blinding? All outcomes	Yes	See Pauwels 1997a
Incomplete outcome data addressed? All outcomes	Unclear	See Pauwels 1997a

Pohunek 2006a

Methods	Parallel-group, multicentre study (80 centres in Europe); 3 treatment groups
Participants	Steroid-using asthmatic children % ELIGIBLE OF SCREENED POPULATION: Not reported % RUN-IN PARTICIPANTS RANDOMISED: 77 RANDOMISED: 429 (BUD/F: 216; BUD: 213) WITHDRAWAL: BUD/F: 14 BUD: 13 AGE mean (range) 8 (4 to 11) GENDER (% male): 67 ASTHMA SEVERITY: Mild-moderate BASELINE % PREDICTED FEV1 mean: 92% BASELINE MS POSE OF ICS (start of run-in): 454 mcg/d ASTHMA DURATION: 3 ATOPY(%): Not reported

	at least 12 weeks before entry in mcg/d during the 30 days prior t important exercise induced bron months leading up to the study; meter EXCLUSION CRITERIA: Oral respiratory infection affecting as coexisting disease/disorder; kno or inhaled lactose; inhaled anticl xanthines and other anti-asthma POST-RUN-IN: Total asthma-sy	re-SABA PEF >/= 50% predicted; ICS treatment for to the study, at a constant dose of 375 to 1000 o enrolment; history an average of >/= 1 clinically choconstriction per week during the 12 weeks ability to use Turbuhaler device and peak flow , parenteral or rectal corticosteroids within 30 days; sthma control within 30 days; any significant wn/suspected hypersensitivity to study medication holinergics, B-blockers (including eye drops), agents not permitted during the study ymptom score of at least one on a minimum of 4 of during last 7 days of the run-in, patients had to have 85% of the post-SABA PEF
Interventions	LABA + ICS versus SAME dos OUTCOMES: 12 weeks RUN-IN PERIOD: 10 to 14 day DOSE OF ICS DURING RUN- INTERVENTION PERIOD: 12 TEST GROUP: Combination bu CONTROL GROUP: Budesonid DEVICE: Turbuhaler	e ICS s IN: Usual dose of ICS weeks idesonide/formoterol 200/6 mcg bid
Outcomes	PULMONARY FUNCTION TEST: am PEF*; pm PEF; FEV1 SYMPTOM SCORES: 24-hour symptom scores; symptom-free days FUNCTIONAL STATUS: Rescue SABA use; reliever-free days; night-time awakenings; paediatric AQLQ INFLAMMATORY MARKERS: Not reported ADVERSE EFFECTS: Reported WITHDRAWAL: Reported by treatment group Primary outcome measure	
Notes	Full-text publication Funded by AstraZeneca Confirmation of methodology and data: Obtained User-defined order: 400	
Risk of bias		
Item	Authors' judgement	Description
Adequate sequence generation?	Unclear	Described as randomised; no other information presented
Allocation concealment?	Unclear	Information not available
Blinding? All outcomes	Yes	Identical inhaler devices
Incomplete outcome data addressed? All outcomes	Unclear	"Intent to treat analysis was performed using data from all randomized patients."
Free of selective reporting?	Unclear	Not clear whether data on OCS-treated exacerbations collected during study

Pohunek 2006b

Methods

As for Pohunek 2006a

Participants	Steroid-using asthmatic children % ELIGIBLE OF SCREENED POPULATION: Not reported % RUN-IN PARTICIPANTS RANDOMISED: 77 RANDOMISED: 414 (BUD + F: 201; BUD: 213) WITHDRAWAL: BUD: 13; BUD + F: 11 Baseline characteristics and eligibility criteria as for Pohunek 2006a	
Interventions	LABA + ICS versus SAME dose ICS OUTCOMES: 12 weeks RUN-IN PERIOD: 10 to 14 days DOSE OF ICS DURING RUN-IN: Usual dose of ICS INTERVENTION PERIOD: 12 weeks TEST GROUP: Formoterol 4.5 mcg + budesonide 80 mcg bid (separate inhaler devices) CONTROL GROUP: Budesonide 200 mcg bid DEVICE: Turbuhaler NUMBER OF DEVICES: 2 COMPLIANCE: Not reported CO-TREATMENT: prn SABA	
Outcomes	As for Pohunek 2006a	
Notes	As for Pohunek 2006a	
Risk of bias		
Item	Authors' judgement	Description
Adequate sequence generation?	Unclear	See Pohunek 2006a
Allocation concealment?	Unclear	See Pohunek 2006a
Blinding? All outcomes	Yes	See Pohunek 2006a
Incomplete outcome data addressed? All outcomes	Unclear	See Pohunek 2006a
Free of selective reporting?	Unclear	See Pohunek 2006a

Price 2002

Methods	Parallel-group, multicentre (72 centres in 14 countries). Three treatment groups (of which 2 are considered here)
Participants	Symptomatic asthmatic patients aged > 12 years % ELIGIBLE OF SCREENED POPULATION: Not reported % RUN-IN PARTICIPANTS RANDOMISED: 88 (of a total of 750 patients 87 were discontinued before randomisation; 15 due to adverse event, 51 failed eligibility criteria and 21 discontinued for other reasons) RANDOMISED: 663 (F12 bid + BUD 400 bid: 332; BUD 400 bid: 331) WITHDRAWALS: F12 bid + BUD 400 bid: 32; BUD 400 bid: 331) WITHDRAWALS: F12 bid + BUD 400 bid: 19; BUD 400 bid: 18 AGE mean years: 38.5 GENDER (% male): 42 SEVERITY: Mild to moderate BASELINE PEF % PREDICTED (SD): 74 (13) BASELINE DOSE OF ICS Mean: 358 ASTHMA DURATION : (%): < 1 year 8; 1 to 5 years: 25; > 5 years: 67 ATOPY (%): Not reported ELIGIBILITY CRITERIA: > 12 years; asthma diagnosed > 3 months; treated with ICS < 400 mcg/day at constant dose for at least 1 month prior to entry; asthma symptoms on at least 3 days per week EXCLUSION CRITERIA: Severe or recent unstable asthma; PEF < 50% predicted; oral corticosteroids, nebulised therapy, leukotriene antagonist or LABA within 4 weeks of study entry; upper respiratory infection, COPD CRITERIA FOR RANDOMISATION DURING RUN-IN: To randomise into part 1: asthma symptoms on 3 of previous 7 days; >= reversibility after bronchodilator of > 12% or (% of predicted normal); diurnal variation of > 20% on at least one day during run-in period
Interventions	LABA + ICS vs SAME dose of ICS

	formoterol 9 mcg bid CONTROL GROUP: Budese DEVICE: Turbuhaler NUMBER OF DEVICES: 2	RIOD: None 4 weeks NGLE DOSE ICS): Budesonide 400 mcg bid + onide 400 mcg bid es recorded by patients in diary
Outcomes	PULMONARY FUNCTION TEST: Change in morning PEF; change in FEV1 SYMPTOM SCORES: Change in day and night-time score FUNCTIONAL STATUS: Time to asthma control i.e. 3 consecutive nights with a symptom score of 0*; rescue medication use day and night (inhalations per day or night); daytime and night-time symptoms; nights per week with sleep disturbance INFLAMMATORY MARKERS: Not described ADVERSE EFFECTS: Not described Primary outcome measure*	
Notes	Full-text publication Supported by AstraZeneca Confirmation of methodology obtained User defined number (mean ICS dose in LAB2 group in mcg/day of BDP- equivalent): 800	
Risk of bias		
Item	Authors' judgement	Description
Adequate sequence generation?	Yes	Computer-generated random numbers
Allocation concealment?	Yes	Numbered coded solutions supplied by pharmacy
Blinding? All outcomes	Yes	Identical inhaler devices
Incomplete outcome data addressed? All outcomes	Unclear	"Efficacy was analysed using an intent-to-treat approach using all available data."
Free of selective reporting?	Yes	Exacerbations reported in full-text article; OCS- treated exacerbations could not be extracted

Reddel 2007

Methods Parallel-group study. Dose of ICS titrated after 8 weeks.	
Participants	% ELIGIBLE OF SCREENED POPULATION: Not reported % RUN-IN PARTICIPANTS RANDOMISED: Not reported RANDOMISED: 82 (FP/SAL: 41; FP: 41) WITHDRAWALS: Not described AGE mean: 47 years SEVERITY: Not reported BASELINE % PREDICTED FEV1: 86 BASELINE DOSE OF ICS: 1000 mcg bid BDP equivalent ASTHMA DURATION: Not reported ATOPY (%): Not reported ELIGIBILITY CRITERIA: 18 to 80 years; using combination therapy (FPSAL 500/50 bid) for 4 weeks or more prior to study entry EXCLUSION CRITERIA: Not reported ELIGIBILITY CRITERIA: Not reported ELIGIBILITY CRITERIA DURING RUN-IN: Not reported
Interventions	LABA plus ICS versus SAME DOSE ICS OUTCOMES 8 weeks RUN-IN PERIOD: Not stated DOSE OPTIMISATION PERIOD: Not stated INTERVENTION PERIOD: 8 weeks TEST GROUP: Combination fluticasone and salmeterol 500/50 mcg bid CONTROL GROUP: Fluticasone 500 mcg bid

	NUMBER OF DEVICES: 1 COMPLIANCE: Not reported CO-TREATMENT: prn SABA	
Outcomes	PULMONARY FUNCTION TEST: am PEF; pm PEF; FEV1 SYMPTOM SCORES: Asthma-free days FUNCTIONAL STATUS: Exacerbations; asthma quality of life questionnaire INFLAMMATORY MARKERS: Not reported ADVERSE EFFECTS: Not stated WITHDRAWALS: Not stated	
Notes	Conference abstract Funding source: GSK Confirmation of methodology and data: pending User defined: 2000	
Risk of bias		
Item	Authors' judgement	Description
Adequate sequence generation?	Unclear	Described as randomised, no other information reported
Allocation concealment?	Unclear	Information not available
Blinding? All outcomes	Unclear	Information not available
Incomplete outcome data addressed? All outcomes	Unclear	Information not available
Free of selective reporting?	Unclear	Information not available

Russell 1995

Methods	Parallel-group, multicentre study (78 centres) Symptomatic asthmatic children % ELIGIBLE OF SCREENED POPULATION: Not reported % RUN-IN PARTICIPANTS RANDOMISED: Not reported RANDOMISED: 208 (Salm50 + ICS: 99; placebo + ICS: 109) WITHDRAWALS: Salm50 + ICS: 22%; placebo + ICS: 16.8% AGE: mean (SD): 10.2 (2.7) GENDER: (% male): 60 SEVERITY: Moderate BASELINE MEAN % PREDICTED FEV1: 78 BASELINE DOSE OF ICS: 750 mcg ASTHMA DURATION (%): < 1 year: 3; 1 to 5 years: 20; > 5 years: 77 ATOPY (%): 77 ELIGIBILITY CRITERIA DURING RUN-IN: Morning PEF-PP (percent predicted) <= 90 on 4 or more days of the last 10 days of the baseline period; either recorded symptoms on at least 7 of 14 days of the baseline period for which they used at least on at least 7 occasions during baseline period EXCLUSION CRITERIA: Received a course of oral corticosteroids; change in prophylactic therapy during the previous 2 weeks	
Participants		
Interventions	LABA + ICS vs SAME dose of ICS OUTCOMES: Reported at 4, 8 and 12 weeks RUN-IN PERIOD: 2 weeks DOSE OF ICS DURING RUN-IN: Continued on usual ICS of at least 400 mcg/day BDP DOSE OPTIMISATION PERIOD: None INTERVENTION PERIOD: 12 weeks TEST GROUP: (Salm 50 + ICS) salmeterol 50 mg bid + ICS 400 to 2400 mg/day (average: 750 mcg/day) CONTROL GROUP: (Placebo + ICS) placebo + ICS 400 to 2400 mg/day (average 750 mcg/day) DEVICE: Diskhaler NUMBER OF DEVICES: 2 COMPLIANCE: Evaluated using patient kept record booklets	

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	CO-TREATMENT: Salbutamol as needed and any other prophylactic asthma medication via Diskhaler	
Outcomes	PULMONARY FUNCTION TEST: am PEF percent predicted*; pm PEF percent predicted SYMPTOMSCORES: Symptoms were recorded daily as either being present or absent, wheeze or cough during day or night FUNCTIONAL STATUS: Proportion symptom-free days; proportion symptom-free nights; rescue medication use INFLAMMATORY MARKERS: Not described ADVERSE EFFECTS: Described WITHDRAWALS: Described Primary outcome measure*	
Notes	Full-text publication Funded by Allen & Hanburys Confirmation of methodology and data obtained. User-defined number: 750 (750 mcg/day)	
Risk of bias		
Item	Authors' judgement	Description
Adequate sequence generation?	Yes	Computer-generated random numbers
Allocation concealment?	Yes	Numbered coded envelopes supplied by pharmacy
Blinding? All outcomes	Yes	Identical placebo
Incomplete outcome data addressed? All outcomes	No	"Total population used, this comprised of all subjects who received at least one puff of medication and recorded at least one day of valid diary or clinic data during the treatment period. Where a subject withdrew before completion of the study, data recorded after this withdrawal data was excluded."
		data was excluded.

SAM40008

Methods	Parallel-group, multicentre study (34 centres in Europe and New Zealand). Dose o ICS tapered at 6 weeks intervals from 500 to 250 to 100 mcg bid. Endpoint data reported at 6 weeks (stable 500 mcg bid dosing regimen)
Participants	Moderately severe asthmatic adults maintained on high dose ICS % ELIGIBLE OF SCREENED POPULATION: Not reported % RUN-IN PARTICIPANTS RANDOMISED: Not reported RANDOMISED: 186 (FP/SAL: 93; FP: 93) WITHDRAWALS: Not reported for initial dosing phase AGE: mean (range) or mean (SD): 49 (15.5) GENDER: (% male): 47 SEVERITY: Moderate to severe BASELINE % PREDICTED FEV1 (mean): Not reported BASELINE % PREDICTED FEV1 (mean): Not reported BASELINE NOSE OF ICS: Usual dose of ICS ASTHMA DURATION: Not reported ATOPY (%): Not reported ELIGIBILITY CRITERIA: >/= 18 years; documented history of asthma; 1500 to 2000 mcg/d BUD or equivalent (not FP) for 3 months prior to baseline EXCLUSION CRITERIA: Not reported
Interventions	LABA and ICS versus SAME DOSE ICS OUTCOMES: TIMING 6, 12, 18 and 26 weeks (outcome data taken from end of first stable dose phase 6 weeks) RUN-IN: Not reported DOSE OF ICS DURING RUN-IN: Not clear INTERVENTION PERIOD: 26 weeks (data taken at 6 weeks) TEST GROUP: Combination fluticasone and salmeterol 500/50 mcg bid CONTROL GROUP: Fluticasone 500 mcg bid

	DEVICE: Diskus NUMBER OF DEVIC COMPLIANCE: Not a CO-TREATMENT: pr	ssessed
Outcomes	PULMONARY FUNCTION TEST: am PEF; pm PEF; FEV1 SYMPTOM SCORES: Proportion of symptom-free days FUNCTIONAL STATUS: Rescue medication use; exacerbations (hospital admission data available from Bateman 2008; minimum acceptable dose of ICS* INFLAMMATORY MARKERS: Not assessed ADVERSE EFFECTS: Reported (but not collected) WITHDRAWALS: Reported (but not collected) Primary outcome measure*	
Notes	Full unpublished data set available from http://www.ctr.gsk.co.uk Source of funding GSK Confirmation of methodology and data: Not obtained User defined number: 1000	
Risk of bias		
Item	Authors' judgement	Description
Adequate sequence generation?	Yes	See Appendix 2
Allocation concealment?	Yes	See Appendix 2
Allocation concealment? Blinding? All outcomes	Yes Yes	See Appendix 2 Identical inhaler devices
Blinding?		· · ·

SAM40012

Methods	Parallel-group, multicentre study in Europe and Middle East
Participants	Steroid-using asthmatic children % ELIGIBLE OF SCREENED POPULATION: Not reported % RUN-IN PARTICIPANTS RANDOMISED: Not reported RANDOMISED: 362 (FP/SAL: 181; FP: 181) WITHDRAWAL: FP/SAL: 3; FP: 10 AGE mean: 8 years GENDER (% male): 68 ASTHMA SEVERITY: Moderate BASELINE % PREDICTED FEV1 mean: Not reported BASELINE 0OSE OF ICS (start of run-in): Not reported ASTHMA DURATION: Not reported ATOPY(%): Not reported ELIGIBILITY CRITERIA: 400 to 500 mcg BDP equivalent; documented history of asthma EXCLUSION CRITERIA: Not reported ELIGIBILITY CRITERIA: Not reported ELIGIBILITY CRITERIA DURING RUN-IN: Symptom score >/= 2 on 3 of las 7 days of run-in
Interventions	LABA + ICS versus SAME dose of ICS OUTCOMES: Reported at 6 months RUN-IN PERIOD: 2 weeks DOSE OF ICS DURING RUN-IN: Not clear DOSE OPTIMISATION PERIOD: None reported INTERVENTION PERIOD: 24 weeks TEST GROUP: Combination salmeterol 50/fluticasone 100 mcg bid CONTROL GROUP: Fluticasone 100 mcg bid DEVICE: Diskus NUMBER OF DEVICES: 1

	COMPLIANCE: Not r CO-TREATMENT: pr	
Outcomes	OUTCOMES: Reported at 6 months PULMONARY FUNCTION TEST: am PEF; pm PEF; FEV1 SYMPTOM SCORES: Symptom-free days FUNCTIONAL STATUS: Use of reliever medication; exacerbations (undefined) INFLAMMATORY MARKERS: Not reported ADVERSE EFFECTS: Reported WITHDRAWAL: Reported Primary outcome measure*	
Notes	Full unpublished data set available from http://www.ctr.gsk.co.uk Source of funding: GSK Confirmation of methodology and data: Not obtained User defined number: 400	
Risk of bias		
Item	Authors' independent	
	Authors' judgement	Description
Adequate sequence generation?	Yes	See Appendix 2
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Adequate sequence generation?	Yes	See Appendix 2
Adequate sequence generation? Allocation concealment? Blinding?	Yes Yes	See Appendix 2 See Appendix 2

SAS40024

Methods	Parallel-group, 53 centres in USA Moderately asthmatic adults % ELIGIBLE OF SCREENED POPULATION: Not reported % RUN-IN PARTICIPANTS RANDOMISED: Not reported RANDOMISED: 192 (FP/SAL: 102; FP: 90) WITHDRAWALS: FP/SAL: 4; FP: 3 AGE: mean (range) or mean (SD): 29.3 (11.2) GENDER (% male): 39 SEVERITY: Moderate BASELINE % PREDICTED FEV1 (mean): Not reported BASELINE % PREDICTED FEV1 (mean): Not reported BASELINE 00SE OF ICS: FP 500 mcg/d or equivalent ASTHMA DURATION: Not reported ATOPY (%): Not reported ELIGIBILITY CRITERIA: 12 to 50 years; diagnosis of asthma for at least 6 months; treatment with FP500 mcg/d equivalent; use of SABA in 6 weeks prior to screening; 65% to 90% predicted; ability to perform stepped treadmill exercises; fall in FEV1 by 20% post-exercise at screening and 2 to 4 weeks post open label treatment with FP250 EXCLUSION CRITERIA: Not reported	
Participants		
Interventions	PROTOCOL: Combination FP/SAL versus SAME DOSE FP OUTCOMES: TIMING 4 weeks RUN-IN: 2 to 4 weeks DOSE OF ICS DURING RUN-IN: FP 250 mcg bid INTERVENTION PERIOD: 4 weeks TEST GROUP: Combination fluticasone and salmeterol 250/50 mcg bid CONTROL GROUP: Fluticasone 250 mcg bid DEVICE: MDI NUMBER OF DEVICES: 1 COMPLIANCE: Not assessed CO-TREATMENT: prn SABA	

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Outcomes	PULMONARY FUNCTION TEST: FEV1 post-exercise*; FEV1; am PEF SYMPTOM SCORES: % symptom-free days FUNCTIONAL STATUS: Not reported INFLAMMATORY MARKERS: Not reported ADVERSE EFFECTS: Reported by treatment group WITHDRAWALS: Reported by treatment group Primary outcome measure*	
Notes	Unpublished data set available from http://www.ctr.gsk.co.uk Source of funding: GSK Confirmation of methodology and data: Obtained User defined number: 1000	
Risk of bias		
Item	Authors' judgement	Description
Adequate sequence generation?	Yes	See Appendix 2
Allocation concealment?	Yes	See Appendix 2
Blinding? All outcomes	Yes	Identical inhalers
Incomplete outcome data addressed? All outcomes	Yes	"The ITT population consisted of all subjects who were randomized to study drug. All data collected on these subjects, including subjects who discontinued the study, was included."
Free of selective reporting?	Yes	OCS-treated exacerbation data available on request from GSK

SAS40036

Methods	Parallel-group, multicentre study (85 centres in USA). Four treatment groups: FF SAL; SAL; FP; MON (SAL & MON not considered in this review)	
Participants	Moderately severe asthmatic adults % ELIGIBLE OF SCREENED POPULATION: Not reported % RUN-IN PARTICIPANTS RANDOMISED: Not reported RANDOMISED: 331 (FP/SAL: 172; FP: 159) WITHDRAWALS: FP/SAL: 29; FP: 59 AGE mean (SD): 41 (14) GENDER: (% male): 41 SEVERITY: Moderate BASELINE % PREDICTED FEV1 (mean): 69% to 70% BASELINE DOSE OF ICS: Participants had 2-week run-in on current ICS therap followed by combination treatment for 4 weeks ASTHMA DURATION: Not reported ATOPY (%): Not reported ELIGIBILITY CRITERIA: > 15 years; ATS defined asthma; treatment with a fixed dose of ICS for at least 4 weeks prior to screening visit; FEV1 40% to 85% predicted; FEV1 > 12% post-SABA EXCLUSION CRITERIA: Not reported	
Interventions	LABA + ICS versus SAME dose ICS OUTCOMES: 16 weeks RUN-IN: 2 weeks (plus 4 weeks open label treatment with FP/SAL 100/50 mcg bid) DOSE OF ICS DURING RUN-IN: Usual ICS INTERVENTION PERIOD: 16 weeks TEST GROUP: Combination fluticasone and salmeterol 100/50 mcg bid CONTROL GROUP: Fluticasone 100 mcg bid DEVICE: Diskus NUMBER OF DEVICES: 1 COMPLIANCE: Not assessed CO-TREATMENT: prn SABA	
Outcomes PULMONARY FUNCTION TEST: am PEF*; FEV1 SYMPTOM SCORES: % symptom-free days FUNCTIONAL STATUS: % rescue-free days		

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	INFLAMMATORY MARKERS: Not reported ADVERSE EFFECTS: Reported by treatment group WITHDRAWALS: Reported by treatment group Primary outcome measure*	
Notes	Unpublished data set from http://www.ctr.gsk.co.uk Source of funding GSK Confirmation of methodology and data: obtained User defined number: 400	
Risk of bias		
Item	Authors' judgement	Description
Adequate sequence generation?	Yes	See Appendix 2
Allocation concealment?	Yes	See Appendix 2
Blinding? All outcomes	Yes	Double-dummy
Incomplete outcome data addressed? All outcomes	Unclear	"The Intent-to-Treat (ITT) population consisted of all subjects who were randomized to treatment and formed the basis for all safety and efficacy measures."
Free of selective reporting?	Yes	OCS-treated exacerbations available on request from GSK

SAS40037

Methods	Parallel-group, multicentre study (87 centres in USA). Four treatment groups: FP/ SAL; SAL; FP; MON (SAL and MON not considered in this review) Moderately severe asthmatic adults % ELIGIBLE OF SCREENED POPULATION: Not reported % RUN-IN PARTICIPANTS RANDOMISED: Not reported RANDOMISED: 322 (FP/SAL: 161; FP: 161) WITHDRAWALS: FP/SAL: 38; FP: 54 AGE mean (SD): 41 (14.5) GENDER (% male): 39 SEVERITY: Moderate BASELINE W PREDICTED FEV1 (mean): Not reported BASELINE MORE OF ICS: Not reported ASTHMA DURATION: Not reported ASTHMA DURATION: Not reported ASTHMA DURATION: Not reported ASELINE USE OF ICS: Not reported ASTHMA DURATION: Not reported ASELINE USE OF ICS SABA EXCLUSION CRITERIA: > 15 years of age; ATS defined asthma; treatment with a fixed dose of ICS for at least 4 weeks prior to screening visit; FEV1 40% to 85% predicted; FEV1 > 12% post-SABA EXCLUSION CRITERIA: Life-threatening asthma; hospitalised with asthma in previous 6 months; concurrent respiratory disease, intermittent or seasonal asthma only-RTI, or use of antibiotics within 14 days of visit 1 LABA + ICS versus SAME dose IC	
Participants		
Interventions		
Outcomes PULMONARY FUNCTION TEST: am PEF; FEV1 SYMPTOM SCORES: % symptom-free days FUNCTIONAL STATUS: % rescue-free days INFLAMMATORY MARKERS: Not reported ADVERSE EFFECTS: Reported by treatment group WITHDRAWALS: Reported by treatment group		

Primary outcome measure*		
Notes	Unpublished data set from http://www.ctr.gsk.co.uk Source of funding: GSK Confirmation of methodology and data: Obtained User defined number: 400	
Risk of bias		
Item	Authors' judgement	Description
Adequate sequence generation?	Yes	See Appendix 2
Allocation concealment?	Yes	See Appendix 2
Blinding? All outcomes	Yes	Double-dummy
Incomplete outcome data addressed? All outcomes	Unclear	"The Intent-to-Treat (ITT) population consisted of all subjects who were randomized to treatment and formed the basis for all safety and efficacy measures."
Free of selective reporting?	Yes	OCS-treated exacerbations available on request from GSK

SD 037 0344a

Methods	Parallel-group, multicentre study in Central and South America, Southern Europe, Eastern Europe, South Africa and Asia). Three treatment groups % ELIGIBLE OF SCREENED POPULATION: Not reported % RUN-IN PARTICIPANTS RANDOMISED: Not reported RANDOMISED: 639 (formoterol HFA: 216; formoterol DPI: 213; placebo: 210) WITHDRAWALS: Not stated AGE mean (range) or mean (SD): 35 (17) SEVERITY: Not reported BASELINE % PREDICTED FEV1: Not reported BASELINE MOSE OF ICS: Not reported ASTHMA DURATION: 14 years ATOPY (%): Not reported ELIGIBILITY CRITERIA: 12 years and older; treatment with 200 to 1000 mg/day of inhaled steroids for previous 3 months and stable dose for 30 days prior to run- in period EXCLUSION CRITERIA: Not reported ELIGIBILITY CRITERIA DURING RUN-IN: Total asthma symptom score (night-time plus daytime) of > 1 on at least 4 of the last 7 days of the run-in period LABA + ICS versus SAME dose ICS OUTCOMES: 12 weeks RUN-IN PERIOD: 2 weeks DOSE OPTIMISATION PERIOD: Not stipulated INTERVENTION PERIOD: 12 weeks TEST GROUP: Formoterol 9 mcg via HFA pMDI plus usual ICS therapy CONTROL GROUP: Placebo in addition to usual ICS therapy NUMBER OF DEVICES: 2 CO	
Participants		
Interventions		
Outcomes	PULMONARY FUNCTION TEST: am PEF; pm PEF; FEV1 SYMPTOM SCORES: Day and night-time symptoms FUNCTIONAL STATUS: Use of relief medication; exacerbations (undefined) INFLAMMATORY MARKERS: Not reported ADVERSE EFFECTS: Reported WITHDRAWALS: Not reported	
Notes	Unpublished data downloaded from AZ website (http:// www.astrazenecaclinicaltrials.com) Funded by AstraZeneca Confirmation of data and methodology: Not obtained User defined order: NA	

Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	Unclear	Described as randomised; no other information presented
Allocation concealment?	Unclear	Information not available
Blinding? All outcomes	Yes	Double-dummy
Incomplete outcome data addressed? All outcomes	Unclear	"All efficacy analyses were performed on both the Per Protocol (PP) and Intention to Treat (ITT) populations, but the primary presentation of efficacy was based on the PP population" ITT and PP populations similar
Free of selective reporting?	Yes	Exacerbations described in trial report; OCS-treated exacerbations not available for meta-analysis

SD 037 0344b

Methods	As for SD 037 0344a	
Participants	As for SD 037 0344a	
Interventions	As for SD 037 0344a except for: TEST GROUP: Formoterol 9 mcg via Turbuhaler plus usual ICS therapy	
Outcomes	As for SD 037 0344a	
Notes	As for SD 037 0344a	
Risk of bias		
Item	Authors' judgement	Description
Adequate sequence generation?	Unclear	As for SD 037 0344a
Allocation concealment?	Unclear	As for SD 037 0344a
Blinding? All outcomes	Yes	As for SD 037 0344a
Incomplete outcome data addressed? All outcomes	Unclear	As for SD 037 0344a
Free of selective reporting?	Yes	As for SD 037 0344a

SD 039 0349

Methods	Parallel-group, multicentre study in Western and Northern Europe	
Participants	% ELIGIBLE OF SCREENED POPULATION: Not reported % RUN-IN PARTICIPANTS RANDOMISED: Not reported RANDOMISED: 239 (BUD + F: 115; BUD: 124) WITHDRAWALS: BUD + F: 17; BUD: 16 AGE mean (range) or mean (SD): 46.7 SEVERITY: Not reported BASELINE % PREDICTED FEV1: 73.8 BASELINE DOSE OF ICS: 960 ASTHMA DURATION: Not reported ATOPY (%): Not reported ELIGIBILITY CRITERIA: Diagnosis of asthma; FEV1 predicted 50% to 90%; reversibility in FEV1 > 15 % of basal value; fixed-dose ICS for 30 days prior to visit 1; daily inhaled dose had to be > 800 mcg inhaled budesonide Turbuhaler, > 500 mcg FP, > 1000 mcg BDP any formulation, or budesonide pMDI	

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	EXCLUSION CRITERIA: Use of oral, parenteral or rectal GCS within 30 days prior to visit 1; seasonal asthma; females who were pregnant or planning a pregnancy during the study; tobacco smokers or previous smokers, if they had a history of smoking > 10 pack-years; use of any blocker therapy (including eye- drops) ELIGIBILITY CRITERIA DURING RUN-IN: Ability to use a peak flow meter; complete a daily diary card; morning PEF data recorded on at least 7 of the last 10 days of the run-in period	
Interventions	LABA and ICS versus SAME dose ICS OUTCOMES 12 weeks RUN-IN PERIOD: 2 weeks DOSE OPTIMISATION PERIOD: NA INTERVENTION PERIOD: 12 weeks TEST GROUP: Budesonide 200 mcg bid and formoterol 9 mcg bid CONTROL GROUP: Budesonide 200 mcg bid NUMBER OF DEVICES: 2 COMPLIANCE: Not assessed CO-TREATMENT prn SABA	
Outcomes	PULMONARY FUNCTION TEST: am PEF; FEV1; pm PEF SYMPTOM SCORES: Awakenings FUNCTIONAL STATUS: Rescue medication use; participants withdrawn if required oral steroids INFLAMMATORY MARKERS: Not reported ADVERSE EFFECTS: Not reported WITHDRAWALS: Reported	
Notes	Unpublished data downloaded from AZ website (http:// www.astrazenecaclinicaltrials.com) Funded by AstraZeneca Confirmation of data and methodology: Not obtained User defined order: 400	
Risk of bias		
Item	Authors' judgement	Description
Adequate sequence generation?	Unclear	Described as randomised; no other information presented
Allocation concealment?	Unclear	Information not available
Blinding? All outcomes	Yes	Double-dummy
Incomplete outcome data addressed? All outcomes	Unclear	"The primary analysis was an intention-to- treat analysis, including all randomised patients who had received at least one dose of study medication."
Free of selective reporting?	No	Exacerbation data not reported (OCS requirement criterion for study withdrawal

SD 039 0714

Methods	Parallel-group, multicentre study
Participants	Steroid-using symptomatic asthmatic adolescents % ELIGIBLE OF SCREENED POPULATION: Not reported % RUN-IN PARTICIPANTS RANDOMISED: 60% RANDOMISED: 271 (F6/BUD 200 mcg bid: 136; BUD 200 mcg bid: 135; WITHDRAWAL: F6/BUD 200 mcg bid: 25; BUD 200 mcg bid: 27 AGE: mean (range): 14 (11 to 17) GENDER (% male): 42 ASTHMA SEVERITY: Moderate BASELINE % PREDICTED FEV1 mean: 75 BASELINE MODES OF ICS (start of run-in): Not reported
	ASTHMA DURATION: Not reported ATOPY (%): Not reported

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Interventions	LABA + ICS versus SAME dose of ICS OUTCOMES: Reported at 1, 2 and 3 months RUN-IN PERIOD: 2 weeks to document stability DOSE OF ICS DURING RUN-IN: Not clear DOSE OF ICS DURING RUN-IN: Not clear DOSE OPTIMISATION PERIOD: None reported INTERVENTION PERIOD: 12 weeks TEST GROUP: Combination budesonide and formoterol 200/6 mcg bid CONTROL GROUP: Budesonide 200 mcg bid DEVICE: Turbuhaler NUMBER OF DEVICES: 1 COMPLIANCE: Not reported CO-TREATMENT: pm SABA		
Outcomes	PULMONARY FUNCTION TEST: FEV1; am PEF*; pm PEF SYMPTOM SCORES: Recorded but not reported FUNCTIONAL STATUS: Rescue medication use (recorded but not reported); nocturnal awakening (recorded but not reported); episode-free days (recorded but not reported) INFLAMMATORY MARKERS: Not reported ADVERSE EFFECTS: Reported WITHDRAWAL: Reported Primary outcome measure*		
Notes	Unpublished data downloaded from AZ website (http:// www.astrazenecaclinicaltrials.com) Funded by AstraZeneca Confirmation of data and methodology: Obtained User defined: 400		
Risk of bias			
Item	Authors' judgement	Description	
Adequate sequence generation?	Unclear	Described as randomised; no other information presented	
Allocation concealment?	Unclear	Information not available	
Blinding? All outcomes	Yes	Identical placebo	
Incomplete outcome data addressed? All outcomes	Unclear	"The statistical analysis was based on the intention to treat (ITT) population."	
Free of selective reporting?	Unclear	Not clear whether the study collected information on exacerbations treated with OCS	

SD 039 0718

Methods	Parallel-group; multicentre study (52 centres in USA)
Participants	% ELIGIBLE OF SCREENED POPULATION: Not reported % RUN-IN PARTICIPANTS RANDOMISED: 60 RANDOMISED: 273 (BUD/F: 128; BUD: 145) WITHDRAWALS: BUD/F: 36; BUD: 51 AGE mean (range) or mean (SD): 10.4 (2.6) SEVERITY: Not stated BASELINE % PREDICTED FEV1: 82 BASELINE % PREDICTED FEV1: 82 BASELINE DOSE OF ICS: 235 mcg/d ASTHMA DURATION: 7 years ATOPY (%): Not stated ELIGIBILITY CRITERIA: 6 to 15 years; low to medium dose of ICS; FEV1 predicted > 50%; reversibility criteria age dependent: > 12 years 14% and 0.2L; < 12 years: 12%

	EXCLUSION CRITERIA: Not reported ELIGIBILITY CRITERIA DURING RUN-IN: Symptoms and lung function not otherwise described	
Interventions	LABA + ICS versus SAME DOSE ICS OUTCOMES: 12 weeks RUN-IN PERIOD: 1 to 2 weeks DOSE OPTIMISATION PERIOD: Not applicable INTERVENTION PERIOD: 12 weeks TEST GROUP: Combination budesonide/formoterol (100/9 mcg) bid via metered dose inhaler CONTROL GROUP: Budesonide 100 mcg bid via metered dose inhaler NUMBER OF DEVICES: 1 COMPLIANCE: Not assessed CO-TREATMENT: prn SABA	
Outcomes	PULMONARY FUNCTION TEST: am PEF; pm PEF; FEV1 SYMPTOM SCORES: NA FUNCTIONAL STATUS: NA INFLAMMATORY MARKERS: NA ADVERSE EFFECTS: Stated WITHDRAWALS: Stated	
Notes	Unpublished data from AZ clinical trials website Funded by AstraZeneca Confirmation of data and methodology: Obtained User defined: 200	
Risk of bias		
Item	Authors' judgement	Description
Adequate sequence generation?	Unclear	Described as randomised; no other information presented
Allocation concealment?	Unclear	Information not available
Blinding? All outcomes	Yes	Double-dummy
Incomplete outcome data addressed? All outcomes	Unclear	"The efficacy analysis set (EAS) was defined as all randomized subjects who took at least 1 dose of study medication and contributed at least 1 PEF value to the primary end-point." No information given on whether EAS population included last observation
Free of selective reporting?	Unclear	OCS-treated exacerbations were not reported in the study publication. Data request has been made to study sponsors for this information

SD 039 0719

	OUTCOMES: 26 weeks RUN-IN PERIOD: 1 week DOSE OPTIMISATION PERIOD: NA INTERVENTION PERIOD: 26 weeks TEST GROUP: Combination budesonide and formoterol 160/4.5 mcg per actuation, 2 puffs bid via MDI CONTROL GROUP: Budesonide 160 mcg per actuation, 2 puffs bid via MDI NUMBER OF DEVICES: 1 COMPLIANCE: Not assessed CO-TREATMENT: prn SABA	
Outcomes	PULMONARY FUNCTION TEST: FEV1; am PEF SYMPTOM SCORES: NA FUNCTIONAL STATUS: Paediatric AQLQ INFLAMMATORY MARKERS: NA ADVERSE EFFECTS: Adverse events* WITHDRAWALS: Stated per treatment group Primary outcome measure* Downloaded from AZ clinical trials website (accessed 4 January 2008) Funded by AstraZeneca Confirmation of data: Provided by AZ in April 2008 User-defined number: 640	
Risk of bias		
Item	Authors' judgement	Description
Adequate sequence generation?	Unclear	Described as randomised; no other information presented
Allocation concealment?	Unclear	Information not available
Blinding? All outcomes	No	Open label
Incomplete outcome data addressed? All outcomes	Unclear	"The safety analysis set was defined as all randomized subjects who took at least 1 dose of study medication. The safety analysis set was used for the analyses of efficacy, health economic, and safety variables."
Free of selective reporting?	Unclear	Not clear whether the study collected information on exacerbations treated with

SD 039 0725a

Methods	Parallel-group; multicentre study	
Participants	% ELIGIBLE OF SCREENED POPULATION: 35 % RUN-IN PARTICIPANTS RANDOMISED: 79 RANDOMISED: 521 (BUD/F bid: 184; BUD/F qd: 168; BUD: 169) WITHDRAWALS: BUD/F bid: 21; BUD/F qd: 37; BUD: 33 AGE mean (range) or mean (SD): 10.3 (2.5) SEVERITY: Not stated BASELINE % PREDICTED FEV1: 78.3 (8.56) BASELINE 00SE OF ICS: 245.3 ASTHMA DURATION: 6.8 ATOPY (%): Not reported ELIGIBILITY CRITERIA: 6 to 15 years; diagnosis of asthma for at least 6 months: maintenance inhaled corticosteroids treatment for at least 4 weeks prior to screening; FEV1 predicted 60% to 90% predicted; reversibility of FEV1 of 12% or more and > 0.20 L from baseline; children > 11 years were required to demonstrate reversibility of > 12% only EXCLUSION CRITERIA: Not stated ELIGIBILITY CRITERIA DURING RUN-IN: Stable asthma symptoms	
Interventions	Combination ICS and LABA versus SAME DOSE ICS OUTCOMES: 12 weeks RUN-IN PERIOD: 4 to 5 weeks DOSE OPTIMISATION PERIOD: Not reported	

	INTERVENTION PERIOD: 12 weeks TEST GROUP: Combination budesonide and formoterol 80/9 mcg bid via MDI CONTROL GROUP: Budesonide 160 mcg qd via MDI NUMBER OF DEVICES: 1 COMPLIANCE: Not assessed CO-TREATMENT: prn SABA	
Outcomes	PULMONARY FUNCTION TEST: FEV1; am PEF; pm PEF* SYMPTOM SCORES: Day and nocturnal symptoms FUNCTIONAL STATUS: AQLQ INFLAMMATORY MARKERS: Not reported ADVERSE EFFECTS: Reported WITHDRAWALS: Reported by treatment group	
Notes	Funding source: AZ Confirmation of methodology and data obtained from AZ in April 2008 Unpublished data downloaded from: http://www.astrazenecaclinicaltrials.com User defined: 160	
Risk of bias		
Item	Authors' judgement	Description
Adequate sequence generation?	Unclear	Described as randomised; no other information presented
Allocation concealment?	Unclear	Information not available
Blinding? All outcomes	Yes	Double-dummy
Incomplete outcome data addressed? All outcomes	Unclear	"The efficacy analysis set (EAS), defined as all randomized subjects who took at least 1 dose of double-blind treatment and who contributed at least 1 evening PEF diary entry after receiving double-blind medication, was used in the primary analysis."
Free of selective reporting?	Unclear	Not clear whether the study collected information on exacerbations treated with

SD 039 0725b

Methods	As for SD 039 0725a	
Participants	As for SD 039 0725a	
Interventions	As for SD 039 0725a except for test group: Combination budesonide and formoterol 160/9 mcg qd via MDI	
Outcomes	As for SD 039 0725a	
Notes	As for SD 039 0725a	
Risk of bias		
Item	Authors' judgement	Description
Adequate sequence generation?	Unclear	As for SD 039 0725a
Allocation concealment?	Unclear As for SD 039 0725a	
Blinding? All outcomes	Yes As for SD 039 0725a	
Incomplete outcome data addressed? All outcomes	Unclear As for SD 039 0725a	
Free of selective reporting?	Unclear As for SD 039 0725a	

SD 039 0726a

Methods	Parallel-group, multice	Parallel-group, multicentre trial (151 centres in USA)		
Participants	 % ELIGIBLE OF SCREENED POPULATION: 28 % RUN-IN PARTICIPANTS RANDOMISED: 63 RANDOMISED: 446 (BUD/F 400 qd: 147; BUD/F 200 bid: 154; BUD 400 qd: 145) WITHDRAWALS: BUD/F 200 bid: 14.3%; BUD/F 400 qd: 17%; BUD/F 200 qd: 12.4%; BUD 400 qd: 19.3% AGE mean: 38 SEVERITY: Not reported BASELINE % PREDICTED FEV1: 75.3% BASELINE MORATION: 19.7 ATOPY (%): Not reported ELIGIBILITY CRITERIA: > 16 years; documented clinical diagnosis of asthma for at least 6 months prior to screening; stable condition; maintenance asthma treatment with a low to medium dose ICS for at least 4 weeks prior to the screening; FEV1 60% to 90% predicted EXCLUSION CRITERIA: Not reported ELIGIBILITY CRITERIA: Not reported 			
Interventions	LABA + ICS versus SAME dose ICS OUTCOMES: 12 weeks RUN-IN PERIOD: 4 to 5 weeks DOSE OPTIMISATION PERIOD: None INTERVENTION PERIOD: 12 weeks TEST GROUP: Combination budesonide and formoterol (400/12 mcg) qd CONTROL GROUP: Budesonide 400 mcg qd NUMBER OF DEVICES: 2 (double-dummy design; LABA co-delivered with ICS in one inhaler) COMPLIANCE: Not assessed CO-TREATMENT prn SABA			
Outcomes	PULMONARY FUNCTION TEST: am PEF; pm PEF; FEV1 SYMPTOM SCORES: Day symptoms; night symptoms FUNCTIONAL STATUS: Quality of life (AQLQ) INFLAMMATORY MARKERS: Not reported ADVERSE EFFECTS: Reported WITHDRAWALS: Reported			
Notes	Unpublished trial data from http://www.astrazenecaclinicaltrials.com Funding source: AZ Confirmation of data and methodology: Not obtained User defined number: 400			
Risk of bias				
Item	Authors' judgement	Description		
Adequate sequence generation?	Unclear	Described as randomised; other information not available		
Allocation concealment?	Unclear	Information not available		
Blinding? All outcomes	Yes	Double-dummy		
Incomplete outcome data addressed? All outcomes	Unclear	"The efficacy analysis set (EAS), defined as all randomized subjects who took at least 1 dose of double- blind treatment and who contributed at least 1 evening PEF diary entry after receiving randomized study medication, was used in the primary analysis. Sensitivity analyses of evening PEF were performed using the per protocol (PP) analysis set."		
Free of selective reporting?	Unclear Not clear whether OCS-treated exacerbations collected in the study			

SD 039 0726b

Methods	See SD 039 0726a	
Participants	See SD 039 0726a	
Interventions	As for SD 039 0726a except for: TEST GROUP: Combination budesonide and formoterol (200/6 mcg) bid	
Outcomes	See SD 039 0726a	
Notes	See SD 039 0726a	
Risk of bias		
Item	Authors' judgement	Description
Adequate sequence generation?	Unclear	See SD 039 0726a
Allocation concealment?	Unclear See SD 039 0726a	
Blinding? All outcomes	Yes See SD 039 0726a	
Incomplete outcome data addressed? All outcomes	Unclear See SD 039 0726a	
Free of selective reporting?	Unclear See SD 039 0726a	

SD 039 0728

Methods	Parallel-group, multicentre study (77 centres in USA). Three treatment arms, of which 2 are considered here	
Participants	% ELIGIBLE OF SCREENED POPULATION: 62 % RUN-IN PARTICIPANTS RANDOMISED: 88 RANDOMISED: 576 (BUD/F 640/18 bid: 443; BUD: 133) WITHDRAWALS: Not reported AGE mean (SD): 40 (16.5) SEVERITY: Moderate to severe asthma BASELINE % PREDICTED FEV1: 73 BASELINE DOSE OF ICS: 500 mcg/d ASTHMA DURATION: 22.7 years ATOPY (%) Not reported ELIGIBILITY CRITERIA: > 12 years of age; documented clinical diagnosis of moderate-to-severe asthma for at least 6 months prior to screening; stable condition; maintenance asthma treatment with a stable dose of inhaled corticosteroids (ICS) for at least 4 weeks; FEV1 > 45% of predicted normal EXCLUSION CRITERIA: Not reported ELIGIBILITY CRITERIA DURING RUN-IN: Not reported	
Interventions	LABA + ICS versus SAME dose ICS OUTCOMES: 52 weeks RUN-IN PERIOD: 2 weeks DOSE OPTIMISATION PERIOD: None INTERVENTION PERIOD: 52 weeks TEST GROUP: Combination budesonide and formoterol 800/24 mcg bid CONTROL GROUP: Budesonide 800 mcg bid NUMBER OF DEVICES: 1 COMPLIANCE: Not assessed CO-TREATMENT: prn SABA	
Outcomes	PULMONARY FUNCTION TEST: am PEF; pm PEF; FEV1 SYMPTOM SCORES: Not measured FUNCTIONAL STATUS: Days without symptoms; exacerbations (defined as requirement for OCS, ED visit and hospitalisation); rescue medication use INFLAMMATORY MARKERS: Not reported ADVERSE EFFECTS: Reported WITHDRAWALS: Reported due to adverse events	
Notes	Unpublished data set available from http://www.astrazenecaclinicaltrials.com Funding source: AZ	

Risk of bias		
Item	Authors' judgement	Description
Adequate sequence generation?	Unclear	Described as randomised; other information not available
Allocation concealment?	Unclear	Information not available
Blinding? All outcomes	Yes	Double-dummy design
Incomplete outcome data addressed? All outcomes	Unclear	"all randomized subjects who received at least 1 dose of randomized study drug, the post-dose analysis set, consisting of all subjects who had clinic visit safety assessments measured 1-2 hours after randomized treatment at all visits, was also used in the analysis of some safety data."
Free of selective reporting?	Yes	Exacerbations including OCS treated events reported as composite endpoint. Separate data could not be extracted

Data and methodology: Not obtained User defined: 1600

SFA100314

Methods	Parallel-group, multicentr	e study (51 centres in USA)
Participants	% ELIGIBLE OF SCREENED POPULATION: Not reported % RUN-IN PARTICIPANTS RANDOMISED: Not reported RANDOMISED: 248 (FP/SAL: 124; FP: 124) WITHDRAWALS: FP/SAL: 13/124; FP: 22/124 AGE mean (range) or mean (SD): 11 SEVERITY: Not reported BASELINE % PREDICTED FEV1: Not reported BASELINE DOSE OF ICS: 400 mcg/day (BDP equivalent) ASTHMA DURATION: Not reported ATOPY (%): Not reported ELIGIBILITY CRITERIA: Age 4 to 17 years; diagnosed with persistent asthn experienced activity-induced bronchospasm EXCLUSION CRITERIA: Not reported ELIGIBILITY CRITERIA: Not reported ELIGIBILITY CRITERIA DURING RUN-IN : Not reported	
Interventions	PROTOCOL: LABA + ICS versus SAME dose ICS OUTCOMES: 4 weeks RUN-IN PERIOD: 7 to 14 days DOSE OPTIMISATION PERIOD: Not reported INTERVENTION PERIOD: 4 weeks TEST GROUP: Combination fluticasone and salmeterol 100/50 mcg bid CONTROL GROUP: Fluticasone 100 mcg bid DEVICE: Diskus NUMBER OF DEVICES: 1 COMPLIANCE: Not assessed CO-TREATMENT: prn SABA	
Outcomes	PULMONARY FUNCTION TEST: FEV1 AUC SYMPTOM SCORES: Not reported FUNCTIONAL STATUS: Oral-steroid treated exacerbations INFLAMMATORY MARKERS: Not reported ADVERSE EFFECTS: Reported WITHDRAWALS: Reported	
Notes		logy and data obtained from GSK in August 2008 aded from: http://www.ctr.gsk.co.uk
Risk of bias		
Item	Authors' judgement	Description
Adequate sequence generation?	Yes	See Appendix 2

Allocation concealment?	Yes	See Appendix 2
Blinding? All outcomes	Yes	Identical inhaler devices
Incomplete outcome data addressed? All outcomes	Unclear	"The ITT population consisted of all subjects who were randomized to study drug."
Free of selective reporting?	Yes	OCS-treated exacerbation data available from GSK on request

SFA100316

Methods	Parallel-group, multicentre study (49 centres in USA)	
Participants	% ELIGIBLE OF SCREENED POPULATION: Not reported % RUN-IN PARTICIPANTS RANDOMISED: Not reported RANDOMISED: 231 (FP/SAL: 113; FP: 118) WITHDRAWALS: FP/SAL: 7/113; FP 10/118 AGE mean (range) or mean (SD): 11.6 SEVERITY: Not reported BASELINE % PREDICTED FEV1: Not reported BASELINE DOSE OF ICS: FP 100 mcg ASTHMA DURATION: Not reported ATOPY (%): Not reported ELIGIBILITY CRITERIA: Diagnosed with persistent asthma for 3 months or longer; experience worsened asthma symptoms during physical activity; using or used an inhaled steroid for the last 4 weeks or longer (such as Aerobid, Azmacort, Flovent, Pulmicort, QVAR, or Vanceril) EXCLUSION CRITERIA: Use of oral steroids as either liquids, pills or injections to treat asthma within the last 3 months; intermittent, seasonal, or exercise-induced asthma, and not persistent asthma; admitted to a hospital within the last 6 months due to asthma symptoms; poorly controlled medical conditions that may make study participation unsafe or inappropriate in the opinion of the study physician (such as cystic fibrosis, congenital heart disease, insulin dependent diabetes, glaucoma, drug allergies, etc.) ELIGIBILITY CRITERIA DURING RUN-IN: Not reported	
Interventions	PROTOCOL: LABA + ICS versus SAME dose ICS OUTCOMES: 4 weeks RUN-IN PERIOD: 7 to 14 days DOSE OPTIMISATION PERIOD: Not reported INTERVENTION PERIOD: 4 weeks TEST GROUP: Combination fluticasone and salmeterol 100/50 mcg bid CONTROL GROUP: Fluticasone 100 mcg bid DEVICE: Diskus NUMBER OF DEVICES: 1 COMPLIANCE: Not assessed CO-TREATMENT: prn SABA	
Outcomes	PULMONARY FUNCTION TEST: FEV1 AUC SYMPTOM SCORES: Not reported FUNCTIONAL STATUS: Oral-steroid treated exacerbations INFLAMMATORY MARKERS: Not reported ADVERSE EFFECTS: Reported WITHDRAWALS: Reported	
Notes	Funding source: GSK Confirmation of methodology and data obtained from GSK in August 2008 Unpublished data downloaded from: http://www.ctr.gsk.co.uk User defined: 400	
Risk of bias		
Item	Authors' judgement	Description
Adequate sequence generation?	Yes	See Appendix 2
Allocation concealment?	Yes	See Appendix 2

Blinding? All outcomes	Yes	Identical inhaler devices
Incomplete outcome data addressed? All outcomes	Unclear	"The ITT population consisted of all subjects who were randomized to study drug."
Free of selective reporting?	Yes	OCS-treated exacerbation data available from GSK on request

SFCF4026

Methods	Parallel-group, multicentre study (124 centres in France). Three treatment groups (FP/SAL 250/50; FP/SAL 100/50; FP250)	
Participants	Moderately severe well-controlled asthmatic adults % ELIGIBLE OF SCREENED POPULATION: Not reported % RUN-IN PARTICIPANTS RANDOMISED: Not reported RANDOMISED: 318 (FP/SAL: 159; FP: 159) WITHDRAWALS: FP/SAL: 18; FP: 30 AGE: mean (range) or mean (SD): 45 (16) GENDER (% male): 50 SEVERITY: Moderately severe BASELINE % PREDICTED FEV1 (mean): Not reported BASELINE MOSE OF ICS: 1000 mcg/d BDP ASTHMA DURATION: Not reported ATOPY (%): Not reported ATOPY (%): Not reported ELIGIBILITY CRITERIA: >/= 18 years of age; documented history of asthma for at least 6 months; treatment with high dose BDP and LABA for 4 weeks; symptoms < 2 days per week; use of rescue medication < 2 days and < 4 occasions per week; PEF > 80% every day during run-in EXCLUSION CRITERIA: Significant smoking history; RTI in 4 weeks prior to randomisation; exacerbation in 4 weeks prior to baseline; use of depot steroid in 12 weeks prior to visit 1; change in asthma medication	
Interventions	LABA + ICS versus SAME dose ICS OUTCOMES: 24 weeks RUN-IN: 8 weeks DOSE OF ICS DURING RUN-IN: 500 mcg/d (combination FP/SAL 250/50 mcg bid) INTERVENTION PERIOD: 12 weeks TEST GROUP: Combination fluticasone and salmeterol 250/50 mcg bid CONTROL GROUP: Fluticasone 250 mcg bid DEVICE: Diskus NUMBER OF DEVICES: 1 COMPLIANCE: Not assessed CO-TREATMENT: pm SABA	
Outcomes	PULMONARY FUNCTION TEST: am PEF*; pm PEF; FEV1 SYMPTOM SCORES: Not reported FUNCTIONAL STATUS: Exacerbations (not defined) INFLAMMATORY MARKERS: Not reported ADVERSE EFFECTS: Reported WITHDRAWALS: Reported Primary outcome measure*	
Notes	Full unpublished data set available from http://www.ctr.gsk.co.uk Source of funding GSK Confirmation of methodology and data: Not obtained User defined number: 1000	
Risk of bias		
Item	Authors' judgement	Description
Adequate sequence generation?	Yes	See Appendix 2
Allocation concealment?	Yes	See Appendix 2
Blinding? All outcomes	Yes	Identical devices

Incomplete outcome data addressed? All outcomes	Unclear	"Full Analysis Set (FAS) population consisted of all subjects who received at least one dose of study medication and for whom the assessment data for at least one assessment criterion was available."
Free of selective reporting?	Yes	Exacerbations reported as rates; severity of exacerbations not adequately defined for this review

Shapiro 2000

Methods	Parallel-group, multicentre study (42 centres). Four treatment arms, of which 2 are considered for this review	
Participants	% ELIGIBLE OF SCREENED POPULATION: Not reported % RUN-IN PARTICIPANTS RANDOMISED: 72% (of 484 patients screened 135 not eligible) RANDOMISED: 168 (Salm50 + ICS: 84; placebo + ICS: 84) WITHDRAWALS: Salm50 + ICS: 13; placebo + ICS: 22 AGE mean (range): 39 (12 to 69) GENDER: (% male): 51 SEVERITY: Moderate BASELINE FEV1 MEAN (SD): 67 BASELINE DOSE OF ICS mcg/day: BDP 462 to 672 mcg/day; triamcinolone acetate 1100 to 1600 mcg/day; flunisolide 1250 to 2000 mcg/day; FP 440 mcg/day ASTHMA DURATION: Not reported ATOPY(%): Not reported ELIGIBILITY CRITERIA: Asthma (ATS criteria) of at least 6 months duration; required pharmacotherapy for at least 6 months before study and inhaled corticosteroids for at least 12 weeks before study; 15% improvement in FEV1 post bronchodilator; female patients negative pregnancy test, surgically sterile, postmenopausal or using birth control EXCLUSION CRITERIA: History of life threatening asthma; hypersensitivity rxn to sympathomimetic drugs or corticosteroids; smoking in year before study or smoking history of > 10 pack-years; received a course of oral corticosteroids in 6 months before study of use of any other prescription or OTC medication that could affect asthma or interact with other medications; abnormal CXR or EKG; history of diabetes glaucoma, hypertension CRITERIA FOR RANDOMISATION DURING RUN-IN: Unstable asthma during run-in periods, i.e. more than 3 nights with awakenings during 7 days before randomisation, more than 12 puffs of rescue medication/day for more than 3 days, FEV1 not within 15% of value obtained at beginning of screening	
Interventions	LABA + ICS vs SAME dose of ICS OUTCOMES: Reported weekly weeks 1 to 4 and thereafter 2-weekly RUN-IN PERIOD: 2 weeks DOSE OF ICS DURING RUN-IN: Not reported DOSE OPTIMISATION PERIOD: None INTERVENTION PERIOD: 12 weeks TEST GROUP: Combination fluticasone and salmeterol 250/50 mcg bid CONTROL GROUP: Fluticasone 250 mcg bid DEVICE: Diskhaler NUMBER OF DEVICES: 1 COMPLIANCE: Measured with dose counter CO-TREATMENT: prn SABA	
Outcomes	PULMONARY FUNCTION TEST: am PEF; pm PEF; FEV1* SYMPTOM SCORES: Asthma symptom score FUNCTIONAL STATUS: Rescue medication use; % nights with no awakenings; days with no asthma symptoms INFLAMMATORY MARKERS: Not described ADVERSE EFFECTS: Described WITHDRAWALS: Described Primary outcome measure*	

Notes	Full-text publication Funded by GSK Confirmation of methodology not obtained User-defined number: 1000	
Risk of bias		
Item	Authors' judgement	Description
Adequate sequence generation?	Yes	See Appendix 2
Allocation concealment?	Yes	See Appendix 2
Blinding? All outcomes	Yes	Identical inhaler devices used
Incomplete outcome data addressed? All outcomes	Unclear	"The population used for all efficacy analyses was the intent-to-treat population minus 13 patients at one site who were excluded because their data did not meet study standards."
Free of selective reporting?	Yes	OCS-treated exacerbations available on request from GSK

Simons 1997

Methods	Cross-over, single-centre study	
Participants	Asymptomatic children % ELIGIBLE OF SCREENED POPULATION: Not reported % RUN-IN PARTICIPANTS RANDOMISED: Not reported RANDOMISED: 16 WITHDRAWALS: 2 (13%) AGE mean (range): 13.1 (12 to 16 years) GENDER (% male): 44 SEVERITY: Not described BASELINE % PREDICTED FEV1: 93.4 BASELINE DOSE OF ICS: 100 to 200 mcg BDP bid ASTHMA DURATION: 5.9 +/- 3.4 years ATOPY (%): 100 ELIGIBILITY CRITERIA: 12 to 18 years old; well-controlled chronic asthma; diagnosed according to American Thoracic Society criteria; able to perform treadmill running tests; do pulmonary function tests satisfactorily; use a Nebulizer Chronolog correctly EXCLUSION CRITERIA: Any significant medical conditions other than mild asthma, allergic rhinitis, or eczema; respiratory tract infection, or an acute asthma exacerbation within the previous month; prednisone treatment, and emergency department visit or hospitalisation within 3 months; life-threatening asthma episod or an adverse reaction to any B2-adrenergic agonist, or used salmeterol previously CRITERIA FOR RANDOMISATION DURING RUN-IN: NA	
Interventions	LABA + ICS vs SAME dose of ICS OUTCOMES measured at: day 1 and 28 RUN-IN PERIOD: Not specified DOSE OF ICS DURING RUN-IN: Not reported DOSE OPTIMISATION PERIOD: None INTERVENTION PERIOD: 4 weeks WASH OUT PERIOD: 14 days TEST GROUP: Salmeterol 50 mcg once daily + BDP 100 to 200 mcg bid CONTROL GROUP: BDP 100 to 200 mcg bid + placebo DEVICE: Metered-dose inhaler and Nebulizer Chronolog device NUMBER OF DEVICES: 2 COMPLIANCE: Medication usage recorded in patient diary. A device inserted int MDI recorded date, hour and minute of each inhalation CO-TREATMENT: prn SABA (200 ug up to 3 times daily) except that albuterol was not permitted 8 hours before each exercise test. If subjects had allergic rhinitis they were permitted to use pseudoephedrine (Sudafed) 1 to 3 times daily as needed except on the days when exercise tests were scheduled	

Outcomes	PULMONARY FUNCTION TEST: Exercise challenge (max % fall in FEV1 from preexercise baseline) SYMPTOM SCORES: Symptoms FUNCTIONAL STATUS: Rescue medication use; exacerbations requiring oral steroids INFLAMMATORY MARKERS: Not reported ADVERSE EFFECTS: Reported WITHDRAWALS: Described Primary outcome: Not specified	
Notes	Full-text publication Funded by GSK Confirmation of data and methodology obtained User defined number: 300 (1/2 with BDP 100 bid; 1/2 with BDP 200 bid)	
Risk of bias		
Item	Authors' judgement	Description
Adequate sequence generation?	Yes	Computer-generated random numbers
Allocation concealment?	Unclear	Information not available
Blinding? All outcomes	Yes	Use of identical placebo
Incomplete outcome data addressed? All outcomes	Unclear	No indication how withdrawals handled in the analysis
Free of selective reporting?	Yes	OCS-treated exacerbations available for meta- analysis

SMS40012

Methods	Parallel-group, multicentre study (56 centres in France)
Participants	Asthmatic adults with mild airway obstruction % ELIGIBLE OF SCREENED POPULATION: Not reported % RUN-IN PARTICIPANTS RANDOMISED: Not reported RANDOMISED: 188 (SAL: 93; PLA: 95) WITHDRAWALS: SAL: 15; PLA: 16 AGE: mean (range) or mean (SD): 40 GENDER (% male): 37 SEVERITY: Mild BASELINE MPREDICTED FEV1 (mean): 91 BASELINE DOSE OF ICS: 800 to 1200 mcg/day BDP equivalent ASTHMA DURATION: Not reported ATOPY (%): Not reported ELIGIBILITY CRITERIA: > 18 years; requirement for 800 to 1200 mcg/d BDP equivalent; SABA treatment in previous 3 months EXCLUSION CRITERIA: More than 1 day with PEF variation > 20%; hospitalisation with asthma in previous year; respiratory tract infection in previous month; oral steroid treatment in previous 3 months; treatment with anti-leukotrient agent, theophylline, anticholinergic, LABA, fixed-dose SABA CRITERIA FOR RANDOMISATION DURING RUN-IN: am PEF > 80% predicted; SABA requirement < 3 × daily
Interventions	LABA + ICS versus SAME dose ICS OUTCOMES: 24 weeks RUN-IN: 2 weeks DOSE OF ICS DURING RUN-IN: Not clear INTERVENTION PERIOD: 24 weeks TEST GROUP: Salmeterol 50 mcg bid in addition to usual maintenance steroid dose CONTROL GROUP: Placebo in addition to usual maintenance steroid dose DEVICE: Not reported NUMBER OF DEVICES: 2 COMPLIANCE: Not assessed CO-TREATMENT: prn SABA

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Outcomes	PULMONARY FUNCTION TEST: am PEF*; pm PEF; FEV1; FVC SYMPTOM SCORES: Not reported FUNCTIONAL STATUS: Rescue medication use; time to treatment failure INFLAMMATORY MARKERS: ECP ADVERSE EFFECTS: Reported by treatment group WITHDRAWALS: Reported by treatment group Primary outcome measure*	
Notes	Unpublished data set available from http://www.ctr.gsk.co.uk Source of funding GSK Confirmation of methodology and data: Not obtained User defined number: Unclear	
Risk of bias		
Item	Authors' judgement Description	
Adequate sequence generation?	Yes	See Appendix 2
Allocation concealment?	Yes	See Appendix 2
Blinding? All outcomes	Yes	Identical devices
Incomplete outcome data addressed? All outcomes	Unclear	"ITT population was defined as all randomised subjects who had received at least one dose of study medication and who had at least one efficacy criterion."
Free of selective reporting?	Unclear	Not clear whether the study collected information on exacerbations treated with OCS

Stelmach 2007

Methods	Parallel-group single-centre study in Poland % ELIGIBLE OF SCREENED POPULATION: Not reported % RUN-IN PARTICIPANTS RANDOMISED: Not reported RANDOMISED: 58 (BUD/F: 29; BUD: 29) WITHDRAWALS: BUD/F: 0; BUD: 0 AGE mean (range) or mean (SD): 10 years SEVERITY: Moderate BASELINE % PREDICTED FEV1: 94% BASELINE DOSE OF ICS: < 400 mcg/d BDP equivalent ASTHMA DURATION: 4 years ATOPY (%): 100 ELIGIBILITY CRITERIA: 6 to 18 years; history of asthma requiring up to 400 mcg mcg daily BDP equivalent EXCLUSION CRITERIA: Upper RTI in previous 3 weeks; sinus disease requiring antibiotics within 4 weeks; oral steroids within 4 weeks of study entry; immunotherapy ELIGIBILITY CRITERIA DURING RUN-IN: Not reported	
Participants		
Interventions	ICS and LABA versus SAME DOSE ICS OUTCOMES: 8 weeks RUN-IN PERIOD: 4 weeks DOSE OPTIMISATION PERIOD: NA INTERVENTION PERIOD: 8 weeks TEST GROUP: Budesonide 200 mcg + formoterol 9 mcg via Turbuhaler CONTROL GROUP: Budesonide 200 mcg daily via Turbuhaler NUMBER OF DEVICES: 2 COMPLIANCE: Not assessed CO-TREATMENT: prn SABA	

Outcomes	PULMONARY FUNCTION TEST: FEV1 predicted; FEF25-75; SRaw SYMPTOM SCORES: Not reported FUNCTIONAL STATUS: Not reported INFLAMMATORY MARKERS: Not reported ADVERSE EFFECTS: Not reported WITHDRAWALS: Reported	
Notes	Full-text article Funded by grant from Lodz University, Poland Confirmation of data and methodology: Not obtained User defined: 200	
Risk of bias		
Item	Authors' judgement	Description
Adequate sequence generation?	Yes	Computer-generated randomisation list
Allocation concealment?	Unclear	Information not available
Blinding? All outcomes	Yes	Double-dummy design
Incomplete outcome data addressed? All outcomes	Yes	All completed
Free of selective reporting?	Unclear	Not clear whether the study collected information on exacerbations treated with OCS

Tal 2002

Methods	Parallel-group, multicentre study (48 centres in 7 countries)	
Participants	Asymptomatic children % ELIGIBLE OF SCREENED POPULATION: Not reported % RUN-IN PARTICIPANTS RANDOMISED: Not reported RANDOMISED: 286 (F + BDP: 148; BDP: 138) WITHDRAWALS: F/BDP: 9; BDP: 9 AGE: mean (range): 11 (4 to 17) GENDER (% male): 62 SEVERITY: Mild BASELINE % PREDICTED FEV1: 75 BASELINE % PREDICTED FEV1: 75 BASELINE bOSE OF ICS: 548 ASTHMA DURATION: 6.8 years ATOPY (%): Not reported ELIGIBILITY CRITERIA: 4 to 17 years old; asthma diagnosed minimum 6 months; FEV1 40% to 90% predicted and > 15% reversibility in FEV1 within 15 minutes of bronchodilator; constant dose ICS for prior 6 weeks (> 400 mcg budesonide turbuhaler, > 600 mcg budesonide via MDI, > 375 mcg fluticasone propionate or > 600 mcg CFC beclomethasone dipropionate) EXCLUSION CRITERIA: Unstable asthma (defined as use of oral, parenteral or rectal corticosteroids within 30 days of study commencement); respiratory tract infection within previous 4 weeks; if they had known hypersensitivity to study medications or inhaled lactose; use of inhaled ICS other than study medication not allowed CRITERIA FOR RANDOMISATION DURING RUN-IN: No other additional criteria	
Interventions	LABA + ICS vs SAME dose of ICS OUTCOMES measured at: 4,8 and 12 weeks RUN-IN PERIOD: 2 to 4 weeks DOSE OF ICS DURING RUN-IN: BUD 200 bid DOSE OPTIMISATION PERIOD: None INTERVENTION PERIOD: 12 weeks TEST GROUP: Formoterol 12 mcg bid + BDP 200 mcg bid CONTROL GROUP: BDP 200 mcg bid and placebo DEVICE: Turbuhaler NUMBER OF DEVICES: 2 COMPLIANCE: Not reported	

	CO-TREATMENT: prn SABA. If subjects had allergic rhinitis, they were permitted to use nasal corticosteroids; treatment with other asthma medication not permitted	
Outcomes	PULMONARY FUNCTION TEST: am PEF*; pm PEF; FEV1 predicted SYMPTOM SCORES: Daily and nocturnal on 4-point scale FUNCTIONAL STATUS: Rescue medication use; night-time awakening; symptom- free days INFLAMMATORY MARKERS: Not reported ADVERSE EFFECTS: Reported WITHDRAWALS: Described Primary outcome measure*	
Notes	Full-text publication Source of funding: AstraZeneca Confirmation of data and methodology obtained User defined number: 400	
Risk of bias		
Item	Authors' judgement	Description
Adequate sequence generation?	Yes	Computer-generated random numbers
Allocation concealment?	Yes	"Individual treatment code envelopes were provided for each subject."
Blinding? All outcomes	Yes	Double-dummy design
Incomplete outcome data addressed? All outcomes	Unclear	"An intention-to-treat analysis was used with all available data."
Free of selective reporting?	Unclear	Not clear whether the study collected information on exacerbations treated with OCS

Teper 2005

Methods	Parallel-group, single-centre study	
Participants	Mild-moderate asthmatic children % ELIGIBLE OF SCREENED POPULATION: Not reported % RUN-IN PARTICIPANTS RANDOMISED: Not reported RANDOMISED: 82 (FP/SAL: 43; FP: 39) WITHDRAWAL: Not reported AGE mean: 10 years GENDER (male%): 59 ASTHMA SEVERITY: Mild to moderate BASELINE % PREDICTED FEV1: 95 BASELINE DOSE OF ICS (start of run-in): Not reported ASTHMA DURATION: Not reported ATOPY(%): Not reported ELIGIBILITY CRITERIA: ATS diagnosed mild or moderate asthma; age 6 to 14 years participants; FEV1 > 70 % predicted; methacholine PC20 < 2 mcg/ml EXCLUSION CRITERIA: Not reported CRITERIA FOR RANDOMISATION DURING RUN-IN: Not reported	
Interventions	LABA + ICS versus SAME dose ICS OUTCOMES: 12 months RUN-IN PERIOD: Unclear DOSE OF ICS DURING RUN-IN: Not reported DOSE OPTIMISATION PERIOD: None reported INTERVENTION PERIOD: 52 weeks TEST GROUP: Combination fluticasone and salmeterol 125/25 bid CONTROL GROUP: Fluticasone 125 mcg bid DEVICE: MDI (+ aerochamber) NUMBER OF DEVICES: 1 COMPLIANCE: Not reported CO-TREATMENT: prn SABA	
Outcomes	PULMONARY FUNCTION TEST: FEV1 % predicted SYMPTOM SCORES: % symptom-free days; % symptom-free nights	

	FUNCTIONAL STATUS: % SAI INFLAMMATORY MARKERS: ADVERSE EFFECTS: Reported WITHDRAWAL: Not reported Primary outcome: Not clear	
Notes	Unpublished conference abstract Source of funding: Not reported Confirmation of data and methodology: Not obtained User defined number: 500	
Risk of bias		
Item	Authors' judgement	Description
Adequate sequence generation?	Unclear	Described as randomised; no other information available
Allocation concealment?	Unclear	Information not available
Blinding? All outcomes	Unclear	Described as double-blind; no other information available
Incomplete outcome data addressed? All outcomes	Unclear	Information not available
Free of selective reporting?	Unclear	Not clear whether the study collected information on exacerbations treated with OCS

van der Molen 1997

Methods	Parallel-group, multicentre trial (6 centres in the Netherlands; 10 centres in Canada)	
Participants	Asthmatic adults % ELIGIBLE OF SCREENED POPULATION: Not reported % RUN-IN PARTICIPANTS RANDOMISED: Not reported RANDOMISED: 239 (ICS + F 48: 125; ICS: 114) WITHDRAWALS: ICS + F 48: 125; ICS: 114) WITHDRAWALS: ICS + F 48: 18; ICS: 13 AGE: mean: 42.8 GENDER (% male): 49 SEVERITY: Moderate BASELINE FEV1 MEAN (SD): 67.1 BASELINE DOSE OF ICS (mcg/d: n) <= 400 mcg: 45 401 to 800: 47 801 to 1600: 99 ASTHMA DURATION: 20.6 years ATOPY (%): 68 ELIGIBILITY CRITERIA: Asthma according to the definition of the ATS; regular use of any dose of inhaled corticosteroids; use of >= 5 inhalations of short-acting beta2 agonist/week before entry visit; > 15% reversibility in baseline FEV1 after 2 inhalations of terbutaline or equivalent EXCLUSION CRITERIA: Use of oral steroids at any time in the last month; smoking history of > 20 pack-years; FEV1 < 40% predicted; exacerbation of asthma symptoms in the last month; use of cromoglycate, theophylline or anticholinergics CRITERIA FOR RANDOMISATION DURING RUN-IN: No additional criteria	
Interventions	LABA + ICS versus SAME dose of ICS OUTCOMES: Reported at 4, 12 and 24 weeks RUN-IN PERIOD: 4 weeks DOSE OF ICS DURING RUN-IN: Usual dose of ICS WASH-OUT PERIOD: 4 weeks DOSE OPTIMISATION PERIOD: None INTERVENTION PERIOD: 24 weeks TEST GROUP: Formoterol 24 mcg bid + usual dose of ICS 400 to 1600/d (mean: 980/day) CONTROL GROUP: Placebo + usual dose of ICS (400 to 1600/d) (mean: 1030/day DEVICE: Turbohaler NUMBER OF DEVICES: 2 COMPLIANCE: Not reported	

	CO-TREATMENT: prn SABA. Cromoglycate, theophylline and anticholinergic drugs were not permitted. The dose of inhaled corticosteroids remained constant throughout	
Outcomes	PULMONARY FUNCTION TEST: FEV1; am PEF*; pm PEF SYMPTOM SCORES: Symptom score (score 0 to 3)* FUNCTIONAL STATUS: Blood pressure and pulse rate; rescue medication use; asthma exacerbations (number of courses of oral prednisolone) INFLAMMATORY MARKERS: Not reported ADVERSE EFFECTS: Reported WITHDRAWALS: Described Primary outcome measure*	
Notes	Full-text publication Funded by Astra Draco Confirmation of methodology and data extraction: Obtained User-defined number: 980	
Risk of bias		
Item	Authors' judgement	Description
Adequate sequence generation?	Yes	Computer-generated random numbers
Allocation concealment?	Unclear	Information not available
Blinding? All outcomes	Yes	Identical inhaler devices
Incomplete outcome data addressed? All outcomes	No	"missing data were substituted according to the last value extended principle, were used to illustrate the lung function and asthma symptoms during the entire study."
Free of selective reporting?	Yes	OCS-treated exacerbations reported in full-text article

Verberne 1998

Methods	Parallel-group, multicentre study (9 centres). Three groups of which 2 are considered in this review
Participants	Asthmatic children % ELIGIBLE OF SCREENED POPULATION: Not reported % RUN-IN PARTICIPANTS RANDOMISED: Not reported RANDOMISED: 117 (BDP400 + Salm: 60; BDP400: 57) WITHDRAWALS: BDP400 + Salm: 5; BDP400: 4 AGE: mean (SD): 11 (2.6) years GENDER (% male): 65 SEVERITY: Mild BASELINE % PREDICTED FEV1: 88 BASELINE MOSE OF ICS (SD): 489 (153) ASTHMA DURATION mean (SD): 8.1 (3.2) ATOPY(%): 88 ELIGIBILITY CRITERIA: FEV1 between 55% and 90% predicted or a FEV1/FVC ratio of 50% to 75%; >= 10% improvement in FEV1 after inhalation of salbutamol; airway hyper-responsiveness to methacholine (PD20); ability to reproduce lung function test; history of stable asthma for >= 1 month without exacerbation or respiratory tract infection; use of inhaled steroids between 200 and 800 mg/day for at least 3 months prior to the beginning of the study; EXCLUSION CRITERIA: Operations for congenital heart disease, oesophageal atresia, congenital or acquired anatomical malformation of the lungs or airways, dyskinetic cilia syndrome; bronchiectasis; bronchopulmonary dysplasia; diabetes; renal disease; other serious conditions which may influence the possibility of continuation of the study; were using oral corticosteroids continuously or inhaled corticosteroids at a dose of more than 800 mcg daily; were using B-blocking agents or had used cromoglycate or nedocromil sodium within the previous 2 weeks; were allergic to B-agonists; were pregnant or lactating, or females of childbearing age who in the opinion of the supervising physician were not taking adequate contraceptive precautions; an ongoing hyposensitising programme; inability to follow therapy instructions, inability to inhale medications adequately or inability to follow therapy instructions; inability to inhale medications adequately or inability to follow therapy instructions; inability to inhale medications adequately or inability to follow therapy instructions; an ongoing hyposensitising programme; inability to follow therapy instructions; non-compliance

	investigators discretion; tota allowed in study	diary cards, clinic visits; withdrawal at own or al number of course of oral corticosteroids more than MISATION DURING RUN-IN: No additional criteria
Interventions	LABA + ICS vs SAME dose ICS OUTCOMES: Reported at 6, 12, 18, 24, 30, 36, 42, 48 and 54 weeks RUN-IN PERIOD: 6 weeks DOSE OF ICS DURING RUN-IN: BDP 200 bid INTERVENTION PERIOD: 54 weeks DOSE OPTIMISATION PERIOD: None TEST GROUP: (Salm50 + BDP200) salmeterol 50 mcg bid and beclomethasone 200 mcg bid CONTROL GROUP: (BDP 200 + placebo) beclomethasone 200 mcg bid + placebo DEVICE: Rotadisks in combination with a Diskhaler NUMBER OF DEVICES: 2 COMPLIANCE: Not reported CO-TREATMENT: prn SABA	
Outcomes	PULMONARY FUNCTION TEST: FEV1; am PEF; pm PEF; FVC SYMPTOM SCORES: Asthma symptoms like wheezing, dyspnoea, exercise induced asthma and cough were scored in the morning and evening using a scale from 1 to 3 FUNCTIONAL STATUS: Rescue medication use; exacerbation (requiring oral steroids); height, body weight, heart rate, systolic and diastolic blood pressure were measured INFLAMMATORY MARKERS: Total IgE ADVERSE EFFECTS: Reported WITHDRAWALS: Reported *Primary outcome: airway calibre measured as FEV1 and airway responsiveness to methacholine	
Notes	Full-text publication Funded by GSK Confirmation of methodology and data obtained User-defined number: 400	
Risk of bias		
Item	Authors' judgement	Description
Adequate sequence generation?	Yes	Computer-generated random numbers
Allocation concealment?	Yes	Telephone notification of assignment by co- ordinating centre
Blinding? All outcomes	Yes	Identical placebo
Incomplete outcome data addressed? All outcomes	Unclear	"Where patients failed to complete their daily record cards for more than 7 d in any 14-d perio such assessments were not included in the analysis. Otherwise, when there were missing days in the record, pro rata adjustment was made to give a 2-week assessment."
	Yes	OCS-treated exacerbations available for meta-

Wallin 2003

Methods	Parallel-group, multicentre study. Three treatment arms of which 2 are considered for this review
Participants	Asthmatic adults % ELIGIBLE OF SCREENED POPULATION: Not reported % RUN-IN PARTICIPANTS RANDOMISED: Not reported RANDOMISED: 37 (FP 200 bid + Sal 50 bid: 18; FP 200 bid: 19) WITHDRAWALS: FP 200 bid + Sal 50 bid: 4; FP 200 bid: 3 AGE mean: 43 GENDER: (% male): 50 SEVERITY: Not stated

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	 BASELINE FEV1 % PRED: 85 BASELINE DOSE OF ICS BDP equivalent (range): 600 to 1200 mcg/d ASTHMA DURATION years: 17 ATOPY (%): 62 ELIGIBILITY CRITERIA: Free of respiratory tract infection for 4 weeks before study CRITERIA FOR RANDOMISATION DURING RUN-IN: Despite use of BUD/BDP 800 to 1200 mcg/day or FP 400 to 500 mcg/day patients were included if they had one or more of the following symptoms: symptoms on 6 or more days, symptoms on 4 or more nights; need for rescue bronchodilator on 6 or more nights, greater than 20% variation between AM and PM PEF on 4 or more days. One or more of the following pulmonary function criteria: at least 15% improvement in FEV1 after bronchodilator, 15% increase in PEF post bronchodilator compared to mean PEF on previous week; more than 20% variation between am and pm PEF on at least 4 consecutive days, PC20 methacholine < 4 mg/ml EXCLUSION CRITERIA: None specified 	
Interventions	LABA + ICS vs SAME dose of ICS OUTCOMES: Before and after 12 weeks treatment RUN-IN PERIOD: 2 to 4 weeks DOSE OF ICS DURING RUN-IN (mean): 876 DOSE OF ICS DURING RUN-IN (mean): 876 DOSE OPTIMISATION PERIOD: None INTERVENTION PERIOD: 12 weeks TEST GROUP: (FP200 + Sal 50 bid) fluticasone propionate 200 mcg bid + salmeterol 50 mcg bid CONTROL GROUP: (FP200 bid) fluticasone propionate 200 mcg bid DEVICE: Diskhaler (dry powder inhaler) NUMBER OF DEVICES: Not reported COMPLIANCE: Not reported CO-TREATMENT: prn SABA	
Outcomes	PULMONARY FUNCTION TEST: am PEF predicted; pm PEF predicted; FEV1 SYMPTOM SCORES: None reported FUNCTIONAL STATUS: Exacerbations (requiring OCS treatment) INFLAMMATORY MARKERS: Submucosal mast cells; submucosal eosinophils; adhesion molecules and cytokines ADVERSE EFFECTS: Not reported by group WITHDRAWALS: Reported	
Notes	Full-text publication Funded by GSK Confirmation of methodology and data not obtained User-defined number: 800	
Risk of bias		
Item	Authors' judgement	Description
Adequate sequence generation?	Yes	See Appendix 2
Allocation concealment?	Yes	See Appendix 2
Blinding? All outcomes	Yes	Identical inhaler devices
Incomplete outcome data addressed? All outcomes	Unclear	Information not available
Free of selective reporting?	Yes	OCS-treated exacerbations available for meta-analysis

Weiler 2005

Methods	Parallel-group, multicentre study (53 centres in USA)
Participants	Moderately asthmatic adults % ELIGIBLE OF SCREENED POPULATION: Not reported % RUN-IN PARTICIPANTS RANDOMISED: Not reported RANDOMISED: 192 (FP/SAL: 102; FP: 90) WITHDRAWALS: FP/SAL: 4; FP: 3 AGE: mean (SD): 29.3 (11.2)

	months; treatment with FP 500 mcg/c screening 65% to 90% predicted; abit	mcg/day ears years; diagnosis of asthma for at least 6 d equivalent; use of SABA in 6 weeks prior to lity to perform stepped treadmill exercises; fall eening and 2 to 4 weeks post open label
Interventions	PROTOCOL: LABA + ICS versus S. OUTCOMES: 4 weeks RUN-IN: 2 to 4 weeks DOSE OF ICS DURING RUN-IN: F INTERVENTION PERIOD: 4 weeks TEST GROUP: Combination fluticas CONTROL GROUP: Fluticasone 250 DEVICE: MDI NUMBER OF DEVICES: 1 COMPLIANCE: Not assessed CO-TREATMENT: prn SABA	P 250 mcg bid s sone and salmeterol 250/50 mcg bid
Outcomes	PULMONARY FUNCTION TEST: FEV1 post exercise*; FEV1; am PEF SYMPTOM SCORES: % symptom-free days FUNCTIONAL STATUS: OCS-treated exacerbations INFLAMMATORY MARKERS: Not reported ADVERSE EFFECTS: Reported by treatment group WITHDRAWALS: Reported by treatment group Primary outcome measure*	
Notes	Unpublished data available from http://www.ctr.gsk.co.uk Source of funding: GSK Confirmation of methodology and data: Obtained User defined number: 1000	
Risk of bias		
Item	Authors' judgement	Description
Adequate sequence generation?	Yes	See Appendix 2
Allocation concealment?	Yes	See Appendix 2
Blinding? All outcomes	Yes	Identical inhaler devices used
Incomplete outcome data addressed? All outcomes	Yes	"The ITT population consisted of all subjects who were randomized to study drug. All data collected on these subjects, including subjects who discontinued the study, was included."
Free of selective reporting?	Yes	OCS-treated exacerbations available on request from GSK

Zetterstrom 2001a

Methods	Parallel-group, multicentre study (59 clinical centres in 6 countries). Three treatment arms. Two groups will be considered here and since the same control group is being used for both comparisons half the control group will be applied to each
Participants	Symptomatic asthmatic adults % ELIGIBLE OF SCREENED POPULATION: Not reported % RUN-IN PARTICIPANTS RANDOMISED: 89 RANDOMISED: 247 (F + Bud: 123; Bud: 124) WITHDRAWALS: F + Bud: 20; Bud: 16 Mean AGE years (range): 47.5 (18 to 78) GENDER (% male): 52 SEVERITY: Moderate

	BASELINE % PREDICTED FEV1: 73.4 BASELINE DOSE OF ICS: 954 ASTHMA DURATION (years): 18 ATOPY (%): Not reported ELIGIBILITY CRITERIA: Aged >= 18; treated with ICS >= 500 mcg/day for at least 1 month prior to entry; FEV1 between 50% to 90% of predicted normal; >= 15% reversibility after bronchodilator EXCLUSION CRITERIA: Oral corticosteroids within 30 days of study entry; smoking history <= 10 years; respiratory infection, seasonal asthma, severe cardiovascular disorder beta blocker therapy; pregnant or failure to use acceptable contraceptives in women of childbearing potential	
Interventions	LABA + ICS versus SAME dose of ICS OUTCOMES: Measured at 4-weekly intervals RUN-IN PERIOD: 2 weeks DOSE OF ICS DURING RUN-IN: Usual ICS DOSE OPTIMISATION PERIOD None INTERVENTION PERIOD: 12 weeks TEST GROUP (LABA + SINGLE DOSE ICS COMBINATION INHALER): Combination budesonide 200 mcg bid + formoterol 6 mcg bid CONTROL GROUP: Budesonide 200 mcg bid DEVICE: Turbuhaler NUMBER OF DEVICES: 1 (study had double-dummy design as BUD/F compared as combination and concomitant delivery) COMPLIANCE: Not reported CO-TREATMENT: Not reported	
Outcomes	PULMONARY FUNCTION TEST: am PEF*; pm PEF; FEV1 SYMPTOM SCORES: Change from baseline in total asthma symptom score (daytime and night-time score graded 1 to 3 (1 mild; 2 moderate; 3 severe)) FUNCTIONAL STATUS: Rescue medication use; night-time awakenings; symptom-free days; asthma control days INFLAMMATORY MARKERS: Not described ADVERSE EFFECTS: No medication related side effect WITHDRAWALS: Described Primary outcome measure*	
Notes	Full-text publication Supported by AstraZeneca Confirmation of methodology and data extraction not obtained User defined number: 400	
Risk of bias		
Item	Authors' judgement	Description
Adequate sequence generation?	Yes	Computer-generated random numbers
Allocation concealment?	Yes	Opaque consecutive numbered envelopes containing assignment
Blinding? All outcomes	Yes	Use of identical placebo (double-dummy)
Incomplete outcome data addressed? All outcomes	Unclear	"All efficacy variables were analysed on an intention-to-treat basis, using data from all patients who had taken more than 1 dose of study medication."
Free of selective reporting?	Yes	Exacerbations reported including events requiring OCS-treatment; could not be extracted for meta- analysis

Zetterstrom 2001b

Methods	See Zetterstrom 2001a
Participants	As for Zetterstrom 2001a, except for RANDOMISED: 247 (F + BUD: 123; BUD: 124) WITHDRAWALS: F + BUD: 17; BUD: 16

Interventions	As for Zetterstrom 2001a, except for TEST GROUP (LABA + SINGLE DOSE ICS SEPARATE INHALERS): budesonide 200 mcg bid + formoterol 6 mcg bid NUMBER OF DEVICES: 2	
Outcomes	See Zetterstrom 2001a	
Notes	Full-text publication Supported by AstraZeneca Confirmation of methodology and data extraction not obtained User defined number: 400	
Risk of bias		
Item	Authors' judgement	Description
Adequate sequence generation?	Yes	See Zetterstrom 2001a
Allocation concealment?	Yes	See Zetterstrom 2001a
Blinding? All outcomes	Yes	See Zetterstrom 2001a
Incomplete outcome data addressed? All outcomes	Unclear	See Zetterstrom 2001a
Free of selective reporting?	Yes	See Zetterstrom 2001a

Zimmerman 2004a

Methods	Parallel-group, multicentre study (27 centres in Canada). Three treatment arms comparing LABA/ICS with 2 doses of LABA and ICS alone. Two groups will be considered here and since the same control group is being used for both comparisons half the control group will be applied to each
Participants	Children aged >= 6 to 11 years % ELIGIBLE OF SCREENED POPULATION: Not reported % RUN-IN PARTICIPANTS RANDOMISED: 68 RANDOMISED: 196 (F + usual ICS bid: 95; usual ICS: 101) WITHDRAWALS: F + usual ICS: 7; usual ICS: 16 Mean AGE years (range): 9 (6 to 11) GENDER (% male): 63 SEVERITY: Moderate BASELINE DOSE OF ICS: 445 ASTHMA DURATION (years): 5.7 ATOPY (%): Not reported ELIGIBILITY CRITERIA: Aged >= 12 years; clinical diagnosis of asthma according to ATS criteria for at least 12 months; treated with ICS for at least 3 month prior to entry; FEV1 between 50% to 90% predicted normal; >= 15% reversibility after bronchodilator; asthma symptoms suggestive that additional therapy might be needed; able to use peak flow meter and turbuhaler, answer questions form the Pediatric Asthma Quality of Life Questionnaire and parent or guardian had to complete a daily diary card EXCLUSION CRITERIA: Oral corticosteroids or anti-leukotrienes within 30 days of study entry, astemizole within 120 days, sodium cromoglycate or ketotifen within 7 days, salmeterol or formoterol within 72 hours or xanthines or antihistamines within 48 hours; nasal corticosteroids and immunotherapy permitted provided dose had been constant for at least 30 days and 90 days respectively prior to study entry; smoking history RANDOMISATION CRITERIA FOLLOWING RUN-IN: Post-bronchodilator reversibility of at least 12% of the pre-bronchodilator value or at least 9% of predicted normal or diurnal variability or at least 15% on any 5 of the last 10 days o run-in; 75% to 124% compliance with prescribed dose as assessed by diary card; symptoms during the last 10 days of run-in (defined as having one or more of the following: 4 or more inhalations of rescue medication; daytime symptoms on 4 or more days, or night-time awakening on 1 or more nights)
Interventions	LABA + Usual ICS versus usual dose of ICS OUTCOMES: Measured at trial entry and after 4, 8 AND 12 week intervals RUN-IN PERIOD: 2 weeks

	DOSE OF ICS DURING RUN-IN: DOSE OPTIMISATION PERIOD: INTERVENTION PERIOD: 12 wea TEST GROUP: Usual dose ICS + fc CONTROL GROUP: Usual dose IC DEVICE: Turbuhaler NUMBER OF DEVICES: 2 COMPLIANCE: Measured during r CO-TREATMENT: prn SABA	None eks prmoterol 12 mcg bid SS + placebo bid
Outcomes	during treatment for 12 weeks repor SYMPTOM SCORES: Total asthmatic	a symptom score nedication use; paediatric asthma quality of life
Notes	Full-text publication Supported by: Not stated Confirmation of methodology and data extraction not obtained User defined number (mean ICS dose in LABA group in mcg/day of BDP- equivalent): 444	
Risk of bias		
Item	Authors' judgement	Description
Adequate sequence generation?	Unclear	Described as randomised; no other information presented
Allocation concealment?	Unclear	Information not available
Blinding? All outcomes	Yes	Identical inhaler devices used
Incomplete outcome data addressed? All outcomes	Unclear	Information not available
Free of selective reporting?	Yes	Exacerbations described as those requiring OCS-treatment and those requiring increased inhaled steroid. Separate OCS treated exacerbation data could not be extracted

Zimmerman 2004b

Methods	See Zimmerman 2004a	
Participants	As for Zimmerman 2004a, except for: RANDOMISED: 207 (F + usual ICS: 106; usual ICS: 101) WITHDRAWALS: F + usual ICS: 7; usual ICS: 16	
Interventions	As for Zimmerman 2004a, except for: TEST GROUP: Usual dose ICS + formoterol 6 mcg bid	
Outcomes	See Zimmerman 2004a	
Notes		and data extraction not obtained CS dose in LABA group in mcg/day of BDP-
Risk of bias		
Item	Authors' judgement	Description
Adequate sequence generation?	Unclear	See Zimmerman 2004a

Allocation concealment?	Unclear	See Zimmerman 2004a
Blinding? All outcomes	Yes	See Zimmerman 2004a
Incomplete outcome data addressed? All outcomes	Unclear	See Zimmerman 2004a
Free of selective reporting?	Yes	See Zimmerman 2004a
AQLQ = Asthma quality of life qu	estionnaire	
ATS = American Thoracic Society	,	
AZ = AstraZeneca		
BDP = beclomethasone		
bid = twice a day		
BUD = budesonide		
COPD = chronic obstructive pulm	onary disease	
CS = corticosteroids		
d = day		
DPI = Dry powder inhaler		
ED = emergency department		
F = formoterol		
FEV1 = forced expiratory volume	in one second	
Form = formoterol		
FP = fluticasone		
GSK = GlaxoSmithKline		
ICS = inhaled corticosteroids		
LAB2 = long-acting B2 agonist		
mcg = microgram		
MDI = metered dose inhaler		
NA = not applicable		
OCS = Oral corticosteroids		
PEFR = peak expiratory flow rate		
PP = per protocol		
PRN = as needed		
qd = four times a day		
RTI = respiratory tract infection		
SABA = short-acting ß2 agonist		
SAL = salmeterol		
Salm = salmeterol		
SD = standard deviation		
SL = salmeterol		
URTI = upper respiratory tract info	ection	
VAS = visual analogue scale		
vs = versus		

Characteristics of excluded studies [ordered by study ID]

Study	Reason for exclusion	
Aalbers 2004	No group with inhaled corticosteroids alone	
Adinoff 1998	No consistent use of inhaled corticosteroids in either the intervention or control groups. C intervention with other non-steroidal anti-asthmatic drugs not stable during the interventio period	
Ankerst 2003	No group with inhaled corticosteroids alone	
Anonymous 2003	No group with inhaled corticosteroids alone	
Arvidsson 1991	No group with inhaled corticosteroids alone.	
Aziz 1998	Duration of intervention < 30 days	
Aziz 1999a	Intervention duration < 30 days	
Aziz 1999b	Outcome measure did not reflect asthma control	
Aziz 2000	Duration of intervention < 30 days	
Bacci 2002	No consistent co-intervention with ICS	
Baker 1998	Duplicate references	
Baki 1998	No consistent intervention with ICS	
Baraniuk 1999	Compared LABA and ICS to increased dose of ICS	
Bateman 1998	The treatment and intervention groups compared the same classes of medications either in combination or with different delivery devices	
Bateman 2003a	Increased dose of ICS in control group	
Bateman 2003b	Control not ICS alone	
Behling 1999	Duration < 30 days	
Bensch 2002	Not a RCT	
Berger 2001	Duplicate references	
Berggren 2001	Intervention not regular but prn inhaled long-acting beta2-agonists. PM LABA versus PM SABA. Duplicate references	
Bergmann	2004 Compared LABA and ICS to increase dose of ICS	
Bernstein 2002	Not a RCT	
Bessmertny 2002	Intervention not LAB2 agonists	
Bijl-Hofland 2001	No consistent co-treatment with ICS	
Bjermer 2000	Control not inhaled glucocorticoids alone but montelukast LABA not compared to ICS alone	
Bjermer 2002	Duplicate references	
Bjermer 2003	No group with ICS alone	
Bloom 2003	Compared LABA and ICS to increased dose ICS	
Boonsawat 2003	Outcome measures not asthma control	
Booth 1993	No consistent co-intervention with ICS	
Boskovska 2001	Not a RCT	
Bouchard 2000	Comparison of LABA + ICS with higher dose ICS	
Boulet 2003	Increased dose of ICS in control group	
Bouros 1999	Increased dose of ICS in control group	
Brambilla 1994	Control intervention not ICS but rather slow-release oral bela2-agonists	

Study	Reason for exclusion				
Braniuk 1999	Not a RCT				
Brenner 1988	Intervention not regular inhaled long-acting beta2-agonists. Control intervention not ICS alone				
Britton 1992	No group with inhaled corticosteroids alone (control is regular SAB2). No consistent intervention with inhaled glucocorticoids in all subjects				
Britton 1998	The treatment and intervention groups compared the same classes of medications either in combination or with different delivery devices. Duplicate references				
Brogden 1991	Not a RCT				
Buchvald 2003	No group with inhaled corticosteroids alone				
Busse 1999	No group with inhaled corticosteroids alone (control is LTRA). No consistent intervention with inhaled glucocorticoids in all subjects				
Busse 2003a	Increased dose of ICS in control group				
Busse 2003b	Increased dose of ICS in control group				
Byrnes 2000	No group with inhaled corticosteroids alone (control is LAB2 at a different dose and SAB2 as maintenance Tx)				
Calhoun 2001	No group with inhaled corticosteroids alone. (Control intervention is anti-leukotrienes). Duplicate references				
Calverley 2002	Pat ients not asthmatics				
Castle 1993	Not a RCT				
Cazzola 2000	Patients not asthmatics				
Chan 2001	Intervention not regular inhaled long-acting beta2-agonists. Control intervention not ICS alone (but oral prednisolone). Setting acute asthma ED. Duplicate references				
Chapman 1999	Tx and i ntervention compared LAB2 and ICS but in combined versus concurrent devices				
Cheer 2003	Duplicate references				
Cloosterman 2001	No consistent co-intervention with ICS. No group with inhaled corticosteroids alone. (Control is regular short-acting beta2-antagonist)				
Condemi 1999	Increased dose of ICS in control group				
Condemi 2001	No group with inhaled corticosteroids alone. (Control is another LAB2). Duplicate references				
Cook 2001	Duplicate references				
Corren 2007	Study participants interrupted ICS therapy during run-in				
Crompton 1999	No group with inhaled corticosteroids alone. (Control is oral bambuterol)				
Currie 2002	Control is increased dose of ICS				
Currie 2003a	Duration of intervention < 30 days. Co-intervention with non permitted Rx				
Currie 2003b	Co -intervention with non- permitted treatment. Duration of intervention < 30 days				
Currie 2003c	Duration < 1 month				
D'Alonzo 1994	No consistent co-intervention with ICS - approximately 1/4 of participants were taking regular inhaled corticosteroids at baseline. Control intervention was a short-acting beta2 agonist				
Dahl 1989	Intervention not inhaled LAB2				
Dahl 1991	No consistent co-treatment with ICS				
Dal Negro 2001a	Not a RCT				
Dal Negro 2001b	The treatment and intervention groups compared the same medications either in combination or with different delivery devices				
Dal Negro 2002a	Not a RCT				

Study	Reason for exclusion				
Dal Negro 2002b	Control not ICS alone				
Davis 2001	Not a RCT				
Del Rio-Navarro 2001a	Outcome measures do not reflect asthma control (but rather serum potassium, CPK-MB an ECG)				
Del-Rio-Navarro 2001b	Outcome measures do not reflect asthma control (but rather saliva flow and IgA)				
Dempsey 2000a	Control intervention not inhaled glucocorticoids alone. No consistent intervention with inhaled glucocorticoids in all subjects				
Dempsey 2000b	Not a RCT				
Dente 2001a	Duplicate references				
Dente 2001b	Not a RCT				
Dicpinigaitis 2002	Intervention not regular inhaled long-acting beta2 agonist				
Didier 1997	Control intervention is not ICS: this is a randomised, open, parallel-group, multicentre study comparing salmeterol with an oral bronchodilator, terbutaline				
Djordjevic 1999	Not a RCT				
Dorinsky 2001a	Not a RCT				
Dorinsky 2001b	Duplicate references				
Eliraz 2001	Both the treatment and control group compared ICS with LAB2 with different inhaler devices				
Eliraz 2002a	Not a RCT				
Eliraz 2002b	Not a RCT				
Ericsson 2001a	Duplicate references				
Ericsson2001b	Not a RCT				
Everden 2002	The treatment and intervention groups compared the same medications either in combination or with different delivery devices				
Faurschou 1994	Duration of intervention < 30 days. Intervention not regular inhaled long-acting beta2- agonists				
Faurschou 1996	Control intervention not ICS alone (but regular SAB2)				
Fish 2000	Duplicate references				
Fish 2001	Control intervention not ICS (but rather anti-leukotrienes)				
Fitzpatrick 1990	Duration of intervention < 30 days: the treatment period was only 2 weeks. No consistent intervention with ICS in all patients: 19/20 participants were taking regular ICS and 6 were taking oral steroids at baseline. Both treatment groups received different doses of long-acting beta2-agonists				
Fowler 2002	Increased dose of ICS in control group				
Fuglsang 1995	Duration < 30 days				
Gabrijelcic 2004	Outcomes not related to asthma control				
Giannini 1996	Duration < 30 days				
Giannini 1998a	Duration < 30 days. Duplicate references.				
Giannini 1998b	Duration < 30 days				
Giannini 1999	Duration < 30 days				
Giannini 2000	Duration < 30 days. Intervention is not LAB2 but 1 dose of salbutamol. Control intervention is not ICS alone (but placebo)				
Giannini 2001	Duration of intervention < 30 days				
Giannini 2002a	No consistent intervention with inhaled glucocorticoids in all subjects				

Study	Reason for exclusion				
Giannini 2002b	Not a RCT				
Gizycki 2000	No consistent intervention with inhaled glucocorticoids in all subjects. Duplicate references				
Gold 2001	Control intervention not inhaled glucocorticoids alone				
Green 2002	No consistent intervention with inhaled glucocorticoids in all subjects				
Greening 1994	Increased dose of ICS in control group				
Grosclaude 2003	No group with inhaled corticosteroids alone				
Grzelewska-Rzymowska 2003	No treatment with LABA				
Gustafsson 1994	$Tx\ and\ intervention\ compared\ ICS+LAB2\ combination\ therapy\ using\ 2\ different\ devices$				
Hasani 2003	No consistent intervention with inhaled glucocorticoids in all subjects				
Haughney 2002	Not a RCT				
Heuck 1999	Not a RCT				
Heuck 2000	Increased dose of ICS in control group				
Hyland 1995	Not a RCT				
Ind 2002a	No ICS alone				
Ind 2002b	No ICS alone				
Ind 2003a	Increased dose of ICS in control group				
Isabelle 2001	Not a RCT				
Jeffery 2002	No group with inhaled corticosteroids alone. Intervention not regular inhaled long-acting beta2-agonists				
Jenkins 1995	No group with inhaled corticosteroids alone. (LAB2 delivered with new propellant HFA134a)				
Jenkins 2000	Increased dose of ICS in control group				
Jenkins 2002	The treatment and intervention groups compared the same medications either in combination or with different delivery devices				
Johansson 2001	Increased dose of ICS in control group				
Jones 1994	No consistent intervention with ICS - $< 1/3$ of participants were taking regular ICS at entry				
Juniper 1995	No consistent co-intervention with ICS - 80% were taking regular ICS at entry. No subgroup analyses available				
Juniper 1999	Duplicate of Pauwel's study (NEJM 1997;337:1405-11)				
Kaik 2002	No ICS alone				
Kalberg 1998	Increased dose of ICS in control group				
Kalra 1996	Duration < 30 days				
Karaman 2007	No prior ICS exposure				
Kardos 2001	Tx and intervention compared ICS + LAB2 in a fixed versus flexible schedule				
Keith 2001	Allocation to treatment group determined by pre-study asthma therapy				
Kelsen 1999	Increased dose of ICS in control group				
Kerwin 2001	Duplicate references				
Ketchell 2002	Duration < 30 days				
Kidney 1995	No consistent intervention with inhaled glucocorticoids in all subject				
Kips 2000	Increased dose of ICS in control group				
Kirby 2000	Subjects not asthmatics				

Study	Reason for exclusion			
Knobil 2000	Control intervention not inhaled glucocorticoids alone			
Knorr 2001	Intervention is not LAB2 (but rather an anti-leukotriene agent: montelukast)			
Kraft 2003	No consistent co-treatment with ICS			
LaForce 1994	Not a RCT			
Lai 1995	Control intervention was not ICS alone but regular short-acting beta2-agonists instead of placebo. Duration < 30 days (2 weeks). Co-intervention with non-permitted drugs: oral steroids			
Lalloo 2000	Duplicate references			
Lalloo 2001a	Duplicate references			
Lalloo 2001b	Duplicate references			
Lalloo 2001c	Not a RCT			
Lalloo 2003	Increased dose of ICS in control group			
Lange 2001	Inadequate duration			
Lazarus 2001	No consistent co-intervention with ICS - intervention is monotherapy with LAB2			
Lee 2003	Duration of control period less than 4 weeks			
Lemanske 2001	Complicated protocol. No data provided for comparison groups of interest. No consistent intervention with inhaled glucocorticoids in all subjects			
Lenney 1995	Not a RCT			
Leuppi 2003	No consistent co-treatment with ICS			
LHSRG 2000	Subjects not asthmatics (but rather have COPD)			
Lindqvist 2001	No consistent co-treatment with ICS			
Lindqvist 2003	No consistent co-treatment with ICS			
Lipworth	Not a RCT			
Lipworth 1996	Not a RCT			
Lipworth 1998	Duration < 30 days			
Lipworth 1999a	Duration < 30 days			
Lipworth 1999b	Duration < 30 days			
Lipworth 2000a	Duration < 30 days			
Lipworth 2000b	Duration < 30 days			
Lockey 1999	No consistent co-treatment with ICS			
Lowhagen 2002	Intervention not regular inhaled long-acting beta2-agonists			
Lundback 2002	No group with ICS alone			
Lyseng-Williamson 2003	Outcomes not related to asthma control - pharmacoeconomic review			
Lötvall 2002	The treatment and intervention groups compared the same medications either in combination or with different delivery devices			
Magadle 2001	Duration < 30 days. Duplicate references.			
Malmqvist-Granlund 2000) Not a RCT			
Malolepszy 2001	Outcome of LABA in acute asthma rather than asthma control			
Malolepszy 2002	Control intervention not ICS (but oral theophylline). Duplicate references			
Martinat 2003	No group with inhaled corticosteroids alone			
Matz 2001	Duplicate publication of 2 RCT s, namely that of Condemi JJ (Ann Allergy Asthma Immunol 1999;82:383-9) and of Kalberg CJ (J Allergy Clin Immunol 1998;101 (Suppl):S6			

Study	Reason for exclusion				
McCarthy 2000	Control intervention not inhaled glucocorticoids alone				
McCarthy 2001a	Not a RCT				
McCarthy 2001b	Not a RCT				
McCarthy 2002	Not a RCT				
McCarthy 2003	No ICS alone group				
Mcivor 1998	No consistent co-treatment with a stable dose of ICS (tapering)				
Michel 2000	Compared LABA with increased doses of ICS rather than the same dose. Intervention duration < 30 days				
Midgren 1992	No group with inhaled corticosteroids alone				
Miraglia del Giudice 2007	No prior ICS exposure				
Mitchell 2000	Duration < 30 days. Duplicate references.				
Mitchell 2003	Control group had increased dose of ICS				
Murray 1998	No consistent intervention with inhaled glucocorticoids in all subjects. Duplicate references				
Murray 1999	Increased dose of ICS in control group				
Nathan 1995	No consistent co-intervention with ICS in all patients: only 1/4 of participants were taking regular ICS at entry. The usual dose of inhaled corticosteroids taken by participants was no stated in the manuscript. The control intervention was not ICS but a short-acting beta2-agonist				
Nathan 1999a	Not a RCT				
Nathan 1999b	Not a RCT				
Nathan 2001	Not a RCT				
Nelson 1999	Not a RCT				
Nelson 2000a	Not a RCT				
Nelson 2000b	Duplicate references				
Nelson 2001	Control intervention not ICS alone (but LTRA - zafirlukast)				
Newnham 1995	No consistent co-treatment with ICS				
Nielsen 1999	Not a RCT				
Nightingale 2002	Treatment and intervention groups compared the same medications either in combination or with different delivery devices				
Nsouli 2001	No group with inhaled corticosteroids alone. Duplicate references				
O'Brian 2001	Duration < 30 days				
Odeback 1998	Duplicate references				
Olsson 2002	Comparison of adjustable maintenance treatment with LABA + ICS rather than ICS alone				
Ortega-Cisnero 1998	Increased dose of ICS in control group				
Overbeck 2003	Patients were steroid naive				
Ozkaya 1999	Not a RCT				
Palmer 1992	No group with inhaled corticosteroids alone (treatment groups received different doses of long-acting beta2-antagonists)				
Palmqvist 2001	Both the treatment and control groups compared ICS and LAB2 with different drugs and inhaler devices (concurrent versus combined therapy)				
Paterson 1999	Treatment and intervention groups compared the same medications either in combination or with different delivery devices				

Study	Reason for exclusion				
Pauwels 1998	Intervention not LAB2 but another ICS				
Pearlman 1992	No consistent co-intervention with ICS - < 1/2 the participants were taking regular inhaled corticosteroids at entry. No group with inhaled corticosteroids alone. (Control was short-acting beta2-agonists)				
Pearlman 1994	No consistent co-treatment with ICS 26%				
Pearlman 1999a	Not a RCT				
Pearlman 1999b	Not a RCT				
Pearlman 2001	Not a RCT				
Pearlman 2002	No group with inhaled corticosteroids alone. (Control is anti-leukotriene montelukast as maintenance). Duplicate references				
Peters 2000	No group with inhaled corticosteroids alone. (Control is oral steroids, SAB2 and anticholinergics). In hospital setting				
Pieters 1999b	Duplicate references				
Pieters 2001	Duplicate references				
Pinnas 1998	No consistent intervention with inhaled glucocorticoids in all subjects. Duplicate references				
Pizzichini 1996	Duration < 30 days. Outcomes measures did not reflect asthma control				
Pljaskic-Kamenov 2000	Cannot determine prior ICS exposure				
Price 2003	No ICS alone				
Pujet 1995	Intervention is not LAB2 (but theophylline)				
Pyke 2001	Comparison of LABA and ICS in separate versus combination devices. No ICS alone. Duplicate references				
Rance 2002	Abstract				
Rickard 1999	Outcomes measures did not reflect asthma control				
Rickard 2001	Control intervention not inhaled glucocorticoids alone				
Rijssenbeek-Nouwens 2002	Intervention is not LAB2 (but anti-allergic casing)				
Ringbaek 1996	No group with inhaled corticosteroids alone. (Control is oral SAB2 as maintenance)				
Ringdal 1997	Not a RCT				
Ringdal 2002	Abstract				
Ringdal 2003	Control intervention no inhaled glucocorticoids alone. Outcomes measures did not reflect asthma control				
Rocca-Serra 2002	Intervention not regular long acting beta2 agonists. Duration < 30 days				
Rooklin 2001	Not a RCT				
Rosenhall 2001a	Duplicate references				
Rosenhall 2001b	Duplicate references				
Rosenhall 2001c	Duplicate references				
Rosenhall 2002	Treatment and intervention groups compared the same medications either in combination o with different delivery devices. Abstract				
Rosenhall 2003	Treatment and intervention groups compared the same medications either in combination or with different delivery devices				
Rosenhall 56	Not a RCT				
Rosenthal 1999	No consistent co-intervention with ICS. Control intervention not ICS alone but SAB2 on demand				

Study	Reason for exclusion			
Rumbak 1998	Study of step-down ICS treatment			
Sahn 2002	Duplicate references			
SAM30007	Dose of ICS stepped down after 6 weeks, but if participants were unstable their medication was also changed			
SAM40004	Mixed population at baseline			
Schreurs 1996	No consistent co-intervention with ICS. 90% used regular ICS at entry. Control intervention not inhaled glucocorticoids alone (but a different dose of LAB2)			
Sears 2003	Not a RCT			
Serrier 2003	Treatment and intervention groups compared the same medications either in combination or with different delivery devices. Abstract. Duplicate references			
Shapiro 2001	Intervention is not LAB2			
Sheth 2002	Outcomes measures did not reflect asthma control			
Shrewsbury 2002	Duplicate references			
Sienra-Monge 2001	The treatment and intervention groups compared the same medications either in combination or with different delivery devices			
Simons 1997b	No consistent co-intervention with inhaled corticosteroids. Treatment groups compared ICS to long-acting beta2-agonist alone			
Sims 2003	Duration < 30 days			
Staehr 1995	Control intervention not ICS (but SAB2 maintenance)			
Stahl 2003	No regular LABA rather prn LABA versus SABA			
Stallberg 2003	No group with inhaled glucocorticoids alone			
Stanford 2002	Outcomes measures did not reflect asthma control			
Stankovic 2000	Not a RCT			
Stelmach 2001	Duplicate references. No consistent intervention with inhaled glucocorticoids in all subjects			
Stelmach 2002a	No co-intervention with ICS. Duplicate references.			
Stelmach 2002b	No co-intervention with ICS			
Stelmach 2008	No prior ICS exposure			
Stojkovic-Andjelkovi 20	01Not a RCT			
Stoloff 2002	Not a RCT			
Tan 1997	Outcomes measures did not reflect asthma control			
Tattersfield 1999	Intervention is not daily LAB2 (but rather on-demand LAB2)			
Tattersfield 2001	Not a RCT			
Tolley 2002	Not a RCT			
Tonelli 2001	No consistent intervention with inhaled glucocorticoids in all subjects			
Trautmann 2001	Not a RCT			
Turner 1998	No consistent co-intervention with ICS alone. Intervention duration < 30 days			
Ullman 1990	Duration < 30 days			
Van den Berg 2000	No consistent co-intervention with LAB2-both groups received LAB2 but compared deliver devices. Duplicate references			
van der Woude 2001	Duplicate references. The treatment and intervention groups compared the same medications either in combination or with different delivery devices			
Van Der Woude 2004	No ICS alone			
Van Der Woude 2004	No consistent intervention with ICS alone			

Study	Reason for exclusion				
Van Noord 1999	Increased dose of ICS in control group				
van Noord 2001	Tx and intervention compared ICS + LAB2 in 2 different combination devices				
Van Schayck 2002	Duplicate references				
Vastagh 2003	No LABA				
Verberne 1997	No consistent co-intervention with ICS - approximately 20% were taking regular ICS at entry				
Vermetten 1999	Not a RCT				
Vestbo 2000	Patients are not asthmatics (but rather have COPD)				
Vickers 2000	The intervention is not LAB2 but placebo. No consistent co-intervention with ICS. Ongoing study - protocol only published				
Vilsvik 2001	Intervention duration < 30 days				
Virchow 2002	Duplicate references				
Von Berg 1989	Duration < 30 days				
Von Berg 2003	No concurrent ICS				
Wallaert 1999	No group with inhaled corticosteroids alone. (Control is another LAB2)				
Wallin 1990	No group with inhaled corticosteroids alone. (Control is regular SAB2). No consistent intervention with inhaled glucocorticoids in all subjects. Outcomes measures did not reflect asthma control				
Wallin 1998	Not a RCT				
Wallin 1999	No consistent co-treatment with ICS				
Weinberger 2004	No LABA				
Weinstein 1998	No consistent co-intervention with ICS - only 57% were on ICS				
Weinstein 2001	Not a RCT				
Wempe 1992	No consistent co-treatment with ICS				
White 2001	Duplicate references				
Wilcke 1998	Duration < 30 days				
Wilding 1997	Not a RCT				
Wilson 1999	Duplicate references.				
Wilson 2000	Duplicate references				
Wilson 2001a	Control intervention is not ICS alone (but rather ICS with an anti-leukotriene agent - montelukast)				
Wilson 2001b	Not a RCT				
Wong 1992	Duration < 30 days				
Woolcock 1995	Not a RCT				
Woolcock 1996	Increased dose of ICS in control group				
Yates 1995	No consistent co-treatment with ICS. Duration < 30 days.				
Yates 1996	Duration < 30 days. Outcomes measures did not reflect asthma control				
Youngchaiyud 1995	Intervention not LAB2 (but theophylline)				
Yurdakul 2002	Control not regular long-acting beta2-agonists alone. Outcomes measures did not reflect asthma control				
Zarkovic 1998	No consistent co-intervention with ICS. No group with inhaled corticosteroids alone. (Control is placebo)				

COPD = chronic obstructive pulmonary disease

ED = emergency department

 $ICS = inhaled \ corticosteroids$

 $LABA/LAB2 = long-acting \ \beta 2 \ agonist$

LTRA = leukotriene receptor antagonist

NEJM = New England Journal of Medicine

RCT = randomised controlled trial

 $\mathbf{R}\mathbf{x} = prescription$

SABA/SAB2 = short-acting ß2 agonist

Tx = treatment

Characteristics of studies awaiting assessment [ordered by study ID]

Bateman 2001

Methods	Parallel-group, multicentre study
Participants	% ELIGIBLE OF SCREENED POPULATION: Not reported % RUN-IN PARTICIPANTS RANDOMISED: 69 RANDOMISED: 497 (FP/SAL MDI: 165; FP/SAL DPI: 167; FP: 165) WITHDRAWALS: FP/SAL MDI: 20; FP/SAL DPI: 22; FP: 25) AGE mean (range): 40 (11 to 79) SEVERITY: Mild to moderate BASELINE % PREDICTED FEV1: 75 BASELINE 00SE OF ICS: BDP equivalent 4 to 500 mcg/d ASTHMA DURATION: 0 to 1 years: 7% 1 to 5 years: 23% 5 to 10 years: 20 > 10 years: 50 SMOKING STATUS: Current: 11%; ex-smoker: 21% ATOPY (%): Not reported ELIGIBILITY CRITERIA: aged ?12; documented clinical history of reversible airways obstruction; treatment with BDP equivalent 400 to 500 mcg/day or FP at a dose of 200 to 250 mcg/day for > 4 weeks prior to Visit 1 EXCLUSION CRITERIA: Long-acting or oral ?2-agonists within 2 weeks of run-in; change in asthma medication, taken oral, depot or parenteral corticosteroids or taken a combination therapy (including ? 2-agonist or inhaled corticosteroid); lower respiratory tract infection within 4 weeks of the study. Participants were withdrawn at randomisation visit if they required more salbutamol than maximum in prescribing information sheet during run-in, failed to withhold short-acting ?2-agonists in 6 hours prior to visit or had an FEV1 ? 50% or ? 100% of the predicted normal ELIGIBILITY CRITERIA DURING RUN-IN: Mean morning PEFR during the last 7 consecutive days of the run-in period of > 50% and < 85% of PEFR measured 15 minutes after administration of 400 mcg of salbutamol at randomisation visit; cumulative total symptom score (daytime plus night-time) in diary of ? 8 for the last 7 consecutive days of the run-in period
Interventions	PROTOCOL: LABA + ICS versus SAME DOSE ICS OUTCOMES: 12 weeks RUN-IN PERIOD: 2 weeks DOSE OPTIMISATION PERIOD: NA INTERVENTION PERIOD: 12 weeks TEST GROUP: i) Combination fluticasone and salmeterol 100/50 mcg bid via HFA metered dose inhaler (+ placebo Diskus) ii) Combination fluticasone and salmeterol 100/50 mcg bid via Diskus (+ placebo metered dose inhaler, CONTROL GROUP: Fluticasone 100 mcg bid via CFC metered dose inhaler (+ placebo Diskus) NUMBER OF DEVICES: 1 (additional inhaler given as dummy device) COMPLIANCE: Not reported CO-TREATMENT: prn SABA
Outcomes	PULMONARY FUNCTION TEST: am PEF*; pm PEF; pm PEF predicted; FEV1 SYMPTOM SCORES: Symptom-free days FUNCTIONAL STATUS: Rescue medication use INFLAMMATORY MARKERS: Not reported ADVERSE EFFECTS: Reported WITHDRAWALS: Reported

Notes

Yancey 1997

Methods	
Participants	
Interventions	
Outcomes	
Notes	
BDP = beclomethas	one
FEV1 = forced expi	ratory volume in one second
FP = fluticasone	
ICS = inhaled cortic	osteroids
mcg = microgram	
PEFR = peak expira	tory flow rate
SAL = salmeterol	

DATA AND ANALYSES

Comparison 1

Long-acting beta2 versus placebo: both groups receiving similar dose ICS

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 # patients with exacerbations requiring oral steroids	30	6808	Risk Ratio (M-H, Fixed, 95% CI)	0.77 [0.68, 0.87]
1.1 Mean baseline FEV1 >/= 80% of predicted	8	1713	Risk Ratio (M-H, Fixed, 95% CI)	0.70 [0.56, 0.86]
1.2 Mean baseline FEV1 61% to 79% of predicted	18	4095	Risk Ratio (M-H, Fixed, 95% CI)	0.81 [0.70, 0.94]
1.3 Mean baseline FEV1 not reported	4	1000	Risk Ratio (M-H, Fixed, 95% CI)	0.63 [0.24, 1.65]
2 # patients with exacerbations requiring hospitalisation	24	7297	Risk Ratio (M-H, Fixed, 95% CI)	1.13 [0.70, 1.82]
2.1 Mean baseline FEV1 >/= 80% of predicted	3	193	Risk Ratio (M-H, Fixed, 95% CI)	0.99 [0.18, 5.39]
2.2 Mean baseline FEV1 61% to 79% of predicted	18	5685	Risk Ratio (M-H, Fixed, 95% CI)	1.11 [0.67, 1.84]
2.3 Mean baseline FEV1 not reported	3	1419	Risk Ratio (M-H, Fixed, 95% CI)	3.0 [0.12, 72.71]
3 Serious adverse event including respiratory	57	16213	Risk Ratio (M-H, Fixed, 95% CI)	1.06 [0.87, 1.30]

3.1 Mean baseline FEV1 >/= 80% of predicted 3.2 Mean baseline	14	4219	Risk Ratio (M-H, Fixed,	
3.2 Mean baseline			85% CI)	0.88 [0.64, 1.21]
FEV1 61% to 79% of predicted	32	8397	Risk Ratio (M-H, Fixed, 95% CI)	1.20 [0.89, 1.62]
3.3 Mean baseline FEV1 not reported	11	3597	Risk Ratio (M-H, Fixed, 95% CI)	1.18 [0.74, 1.87]
4 Total # withdrawals	58	14718	Risk Ratio (M-H, Fixed, 95% CI)	0.80 [0.75, 0.87]
4.1 Mean baseline FEV1 >/= 80% of predicted	16	2501	Risk Ratio (M-H, Fixed, 95% CI)	0.84 [0.67, 1.04]
4.2 Mean baseline FEV1 61% to 79% of predicted	35	9644	Risk Ratio (M-H, Fixed, 95% CI)	0.83 [0.75, 0.90]
4.3 Mean baseline FEV1 not reported	7	2573	Risk Ratio (M-H, Fixed, 95% CI)	0.71 [0.60, 0.85]
5 # withdrawals due to poor asthma control or exacerbation	38	9505	Risk Ratio (M-H, Fixed, 95% CI)	0.50 [0.41, 0.61]
5.1 Mean baseline FEV1 >/= 80% of predicted	6	596	Risk Ratio (M-H, Fixed, 95% CI)	0.49 [0.20, 1.17]
5.2 Mean baseline FEV1 61% to 79% of predicted	27	6879	Risk Ratio (M-H, Fixed, 95% CI)	0.52 [0.42, 0.66]
5.3 Mean baseline FEV1 not reported	5	2030	Risk Ratio (M-H, Fixed, 95% CI)	0.40 [0.24, 0.66]
6 # withdrawals due to adverse events	52	14038	Risk Ratio (M-H, Fixed, 95% CI)	1.04 [0.86, 1.26]
6.1 Mean baseline FEV1 >/= 80% of predicted	9	1647	Risk Ratio (M-H, Fixed, 95% CI)	0.74 [0.41, 1.34]
6.2 Mean baseline FEV1 61% to 79% of predicted	35	9199	Risk Ratio (M-H, Fixed, 95% CI)	1.14 [0.90, 1.45]
6.3 Mean baseline FEV1 not reported	9	3192	Risk Ratio (M-H, Fixed, 95% CI)	0.92 [0.62, 1.36]
7 # withdrawals due to serious non-respiratory event	2		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
7.1 Mean baseline FEV1 61% to 79% of predicted	2		Risk Ratio (M-H, Random, 95% CI)	Not estimable
8 FEV1 (L) at endpoint	10	2045	Mean Difference (IV, Fixed, 95% CI)	0.12 [0.07, 0.17]
8.1 Mean baseline FEV1 >/- 80% of predicted	2	615	Mean Difference (IV, Fixed, 95% CI)	0.10 [0.03, 0.17]
8.2 Mean baseline FEV1 61% to 79% of predicted	6	914	Mean Difference (IV, Fixed, 95% CI)	0.15 [0.07, 0.22]
8.3 Mean baseline FEV1 not reported	2	516	Mean Difference (IV, Fixed, 95% CI)	0.12 [-0.02, 0.26]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
9 Change in FEV1 at endpoint stratifying on baseline FEV1	32	9784	L (Random, 95% CI)	0.11 [0.09, 0.13]
9.1 Mean baseline FEV1 >= 80% of predicted	5	1036	L (Random, 95% CI)	0.09 [0.03, 0.14]
9.2 Mean baseline FEV1 61% to 79% of predicted	24	7917	L (Random, 95% CI)	0.12 [0.09, 0.14]
9.3 Mean baseline FEV1 predicted not reported	3	831	L (Random, 95% CI)	0.13 [0.05, 0.21]
10 Change in FEV1 predicted endpoint stratifying on baseline FEV1	8		% (Random, 95% CI)	3.73 [2.66, 4.80]
10.1 Mean baseline FEV1 >= 80% of predicted	6		% (Random, 95% CI)	4.06 [2.96, 5.16]
10.2 Mean baseline FEV1 61% to 79% of predicted	1		% (Random, 95% CI)	3.46 [1.40, 5.52]
10.3 Mean baseline FEV1 predicted not reported	1		% (Random, 95% CI)	-0.40 [-5.03, 4.23]
11 FEV1 % predicted at endpoint	4	939	Mean Difference (IV, Fixed, 95% CI)	5.34 [3.29, 7.38]
11.1 Mean baseline FEV1 >- 80% of predicted	2	87	Mean Difference (IV, Fixed, 95% CI)	2.67 [-2.21, 7.55]
11.2 Mean baseline FEV1 61% to 79% of predicted	2	852	Mean Difference (IV, Fixed, 95% CI)	5.90 [3.65, 8.16]
12 Change in FEV1 (L or % predicted) stratifying on trial duration	14	4008	Std. Mean Difference (IV, Random, 95% CI)	0.34 [0.26, 0.42]
12.1 Change in FEV1 (L) or (% predicted) at 6 +/- 2 weeks of treatment	2	299	Std. Mean Difference (IV, Random, 95% CI)	0.41 [0.18, 0.64]
12.2 Change in FEV1 (L) or (% predicted) at 12 +/- 4 weeks of treatment	11	2003	Std. Mean Difference (IV, Random, 95% CI)	0.36 [0.24, 0.49]
12.3 Change in FEV1 (L) or (% predicted) at 24 +/- 4 weeks of treatment	2	352	Std. Mean Difference (IV, Random, 95% CI)	0.30 [0.09, 0.51]
12.4 Change in FEV1 (L) or (% predicted) at 52 +/- 4 weeks of treatment	3	1354	Std. Mean Difference (IV, Random, 95% CI)	0.28 [0.12, 0.44]
13 Morning PEF (L/min) at endpoint	8	1787	Mean Difference (IV, Random, 95% CI)	26.21 [13.31, 39.10
13.1 Mean baseline FEV1 >/= 80%	1	29	Mean Difference (IV, Random, 95% CI)	86.0 [17.11, 154.89
13.2 Mean baseline FEV1 61% to 79% of predicted	5	1127	Mean Difference (IV, Random, 95% CI)	19.14 [2.93, 35.34]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
13.3 Mean baseline FEV1 not reported	2	631	Mean Difference (IV, Random, 95% CI)	34.26 [17.83, 50.70]
14 Change in morning PEF (L/min) at endpoint stratifying on baseline FEV1	53	14365	L/min (Random, 95% CI)	19.64 [17.08, 22.20]
14.1 Mean baseline FEV1 >/= 80% of predicted	12	3364	L/min (Random, 95% CI)	11.96 [8.68, 15.24]
14.2 Mean baseline FEV1 61% to 79% of predicted	32	8348	L/min (Random, 95% CI)	23.41 [19.84, 26.98]
14.3 Mean baseline FEV1 not reported	9	2653	L/min (Random, 95% CI)	17.09 [12.99, 21.18]
15 Evening PEF (L/min) at endpoint	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
15.1 Mean baseline FEV1 61% to 79% of predicted	1		Mean Difference (IV, Fixed, 95% CI)	Not estimable
16 Change in evening PEF at endpoint	33	8248	L/min (Random, 95% CI)	17.89 [14.82, 20.95]
16.1 Mean baseline FEV1 > /= 80% of predicted	7	1345	L/min (Random, 95% CI)	13.37 [5.98, 20.76]
16.2 Mean baseline FEV1 61% to 79% of predicted	23	6058	L/min (Random, 95% CI)	19.70 [16.36, 23.03]
16.3 Mean baseline FEV1 not reported	3	845	L/min (Random, 95% CI)	13.85 [5.05, 22.64]
17 Change in PEF variability at endpoint	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
17.1 Mean baseline FEV1 61% to 79% of predicted	1		Mean Difference (IV, Fixed, 95% CI)	Not estimable
18 Change in 24-hour symptom score at endpoint	6	1473	Std. Mean Difference (IV, Fixed, 95% CI)	-0.23 [-0.34, -0.12]
18.1 Mean baseline FEV1 61% to 79% of predicted	6	1473	Std. Mean Difference (IV, Fixed, 95% CI)	-0.23 [-0.34, -0.12]
19 Change in daytime symptom score at endpoint	8	1767	Std. Mean Difference (IV, Fixed, 95% CI)	-0.33 [-0.42, -0.23]
19.1 Mean baseline FEV1 >/= 80%	1	54	Std. Mean Difference (IV, Fixed, 95% CI)	-0.27 [-0.80, 0.27]
19.2 Mean baseline FEV1 61% to 79% of predicted	7	1713	Std. Mean Difference (IV, Fixed, 95% CI)	-0.33 [-0.43, -0.23]
20 Change in night-time symptom score at endpoint	5	1319	Std. Mean Difference (IV, Fixed, 95% CI)	-0.22 [-0.33, -0.11]
20.1 Mean baseline FEV1 >/= 80%	1	54	Std. Mean Difference (IV, Fixed, 95% CI)	-0.53 [-1.08, 0.01]
20.2 Mean baseline FEV 1 61-79% of predicted	4	1265	Std. Mean Difference (IV, Fixed, 95% CI)	-0.21 [-0.32, -0.10]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
21 % symptom-free days	6	2169	Mean Difference (IV, Random, 95% CI)	7.31 [0.50, 14.12]
21.1 Mean baseline FEV1 >/= 80% of predicted	1	627	Mean Difference (IV, Random, 95% CI)	4.60 [0.69, 8.51]
21.2 Mean baseline FEV1 61% to 79% of predicted	4	1460	Mean Difference (IV, Random, 95% CI)	10.35 [0.05, 20.65]
21.3 Mean baseline FEV1 not reported	1	82	Mean Difference (IV, Random, 95% CI)	-1.0 [-4.47, 2.47]
22 Change in % symptom-free days at endpoint	16	4186	Mean Difference (IV, Random, 95% CI)	11.88 [8.25, 15.50]
22.1 Mean baseline FEV1 >/= 80% of predicted	1	203	Mean Difference (IV, Random, 95% CI)	3.20 [-8.08, 14.48]
22.2 Mean baseline FEV1 61% to 79% of predicted	13	3344	Mean Difference (IV, Random, 95% CI)	13.37 [9.31, 17.44]
22.3 Mean baseline FEV1 not reported	2	639	Mean Difference (IV, Random, 95% CI)	6.57 [1.11, 12.03]
23 Change in # of symptom-free nights at endpoint	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
23.1 Mean baseline FEV1 61% to 79% of predicted	1		Mean Difference (IV, Fixed, 95% CI)	Not estimable
24 % symptom-free nights at 12 +/- 4 weeks	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
24.1 Mean baseline FEV1 61% to 79% of predicted	1		Mean Difference (IV, Fixed, 95% CI)	Not estimable
25 Change in % symptom-free nights at endpoint	4	1052	Std. Mean Difference (IV, Random, 95% CI)	0.51 [0.28, 0.74]
25.1 Mean baseline FEV1 61% to 79% of predicted	4	1052	Std. Mean Difference (IV, Random, 95% CI)	0.51 [0.28, 0.74]
26 Change in asthma control days %	4	813	Mean Difference (IV, Fixed, 95% CI)	15.81 [10.85, 20.7]
26.1 Mean baseline FEV1 61% to 79% of predicted	4	813	Mean Difference (IV, Fixed, 95% CI)	15.81 [10.85, 20.7]
27 Change in # overall daily rescue inhalations at endpoint	14	4654	Mean Difference (IV, Random, 95% CI)	-0.58 [-0.80, -0.3
27.1 Mean baseline FEV1 >/= 80% of predicted	2	1272	Mean Difference (IV, Random, 95% CI)	-0.17 [-0.29, -0.0
27.2 Mean baseline FEV1 61% to 79% of predicted	12	3382	Mean Difference (IV, Random, 95% CI)	-0.73 [-1.05, -0.4
28 Change in # daytime rescue inhalations at endpoint	13		puffs per day (Random, 95% CI)	-0.68 [-0.94, -0.4

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
28.1 Mean baseline FEV 1 >/= 80% of predicted	3		puffs per day (Random, 95% CI)	-0.27 [-0.62, 0.07]
28.2 Mean baseline FEV1 61% to 79% of predicted	10		puffs per day (Random, 95% CI)	-0.82 [-1.18, -0.46]
28.3 Mean baseline FEV1 not reported	0		puffs per day (Random, 95% CI)	Not estimable
29 # daytime rescue inhalations (puffs per day) at endpoint	2	277	Mean Difference (IV, Random, 95% CI)	-0.73 [-1.24, -0.22]
29.1 Mean baseline FEV1 61% to 79% of predicted	2	277	Mean Difference (IV, Random, 95% CI)	-0.73 [-1.24, -0.22]
30 # night-time rescue inhalations (puffs per night) at endpoint	2	546	Mean Difference (IV, Random, 95% CI)	-0.44 [-0.81, -0.07]
30.1 Mean baseline FEV1 61% to 79% of predicted	2	546	Mean Difference (IV, Random, 95% CI)	-0.44 [-0.81, -0.07]
31 Change in # night- time rescue inhalations at endpoint	7	2219	Mean Difference (IV, Random, 95% CI)	-0.30 [-0.48, -0.11]
31.1 Mean baseline FEV1 >/= 80% of predicted	1	168	Mean Difference (IV, Random, 95% CI)	-0.11 [-0.20, -0.02]
31.2 Mean baseline FEV1 61% to 79% of predicted	6	2051	Mean Difference (IV, Random, 95% CI)	-0.33 [-0.57, -0.10]
32 Change in mean rescue-free days	6	1698	% (Fixed, 95% CI)	17.05 [13.75, 20.35]
32.1 Mean baseline FEV1 61% to 79% of predicted	5	1381	% (Fixed, 95% CI)	17.63 [14.03, 21.23]
32.2 Mean baseline FEV1 not reported	1	317	% (Fixed, 95% CI)	14.0 [5.77, 22.23]
33 Rescue medication- free days	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
33.1 Mean baseline FEV1 61% to 79% of predicted	1		Mean Difference (IV, Fixed, 95% CI)	Not estimable
34 Change in % rescue medication-free days	2	667	Mean Difference (IV, Random, 95% CI)	6.43 [1.20, 11.66]
34.1 Mean baseline FEV1 61% to 79% of predicted	1	475	Mean Difference (IV, Random, 95% CI)	5.20 [-1.78, 12.18]
34.2 Mean baseline FEV1 not reported	1	192	Mean Difference (IV, Random, 95% CI)	8.0 [0.10, 15.90]
35 Change in % nights with no awakening	5	1158	Mean Difference (IV, Fixed, 95% CI)	1.01 [-1.06, 3.08]
35.1 Mean baseline FEV1 61% to 79% of predicted	5	1158	Mean Difference (IV, Fixed, 95% CI)	1.01 [-1.06, 3.08]
36 % nights with awakening	2	913	Mean Difference (IV, Fixed, 95% CI)	-1.37 [-2.75, 0.02]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
36.1 Mean baseline FEV1 >/= 80% of predicted	1	627	Mean Difference (IV, Fixed, 95% CI)	-1.50 [-3.19, 0.19]
36.2 Mean baseline FEV1 61% to 79% of predicted	1	286	Mean Difference (IV, Fixed, 95% CI)	-1.10 [-3.51, 1.31]
37 Change in night-time awakening (number of nights) at endpoint	5	1308	Std. Mean Difference (IV, Fixed, 95% CI)	-0.10 [-0.21, 0.01]
37.1 Mean baseline FEV1 61% to 79% of predicted	5	1308	Std. Mean Difference (IV, Fixed, 95% CI)	-0.10 [-0.21, 0.01]
38 Change in quality of life (AQLQ score) at endpoint	3		Mean Difference (Random, 95% CI)	0.26 [0.04, 0.47]
38.1 Mean baseline FEV1 61% to 79% of predicted	3		Mean Difference (Random, 95% CI)	0.26 [0.04, 0.47]
39 Total # adverse events	41	10622	Risk Ratio (M-H, Fixed, 95% CI)	1.00 [0.97, 1.04]
39.1 Mean baseline FEV1 >/= 80% of predicted	7	1424	Risk Ratio (M-H, Fixed, 95% CI)	1.09 [1.01, 1.19]
39.2 Mean baseline FEV1 61% to 79% of predicted	25	6555	Risk Ratio (M-H, Fixed, 95% CI)	0.98 [0.94, 1.02]
39.3 Mean baseline FEV1 not reported	9	2643	Risk Ratio (M-H, Fixed, 95% CI)	1.01 [0.92, 1.10]
40 # patients with headache	37	10020	Risk Ratio (M-H, Fixed, 95% CI)	0.99 [0.87, 1.13]
40.1 Mean baseline FEV1 >/= 80% of predicted	4	779	Risk Ratio (M-H, Fixed, 95% CI)	1.02 [0.78, 1.33]
40.2 Mean baseline FEV1 61% to 79% of predicted	26	6644	Risk Ratio (M-H, Fixed, 95% CI)	0.96 [0.81, 1.13]
40.3 Mean baseline FEV1 not reported	7	2597	Risk Ratio (M-H, Fixed, 95% CI)	1.12 [0.74, 1.70]
41 # patients with hoarseness	6	1602	Risk Ratio (M-H, Random, 95% CI)	1.17 [0.44, 3.10]
41.1 Mean baseline FEV1 61% to 79% of predicted	5	1284	Risk Ratio (M-H, Random, 95% CI)	1.02 [0.36, 2.88]
41.2 Mean baseline FEV1 not reported	1	318	Risk Ratio (M-H, Random, 95% CI)	5.0 [0.24, 103.33]
42 # patients with oral thrush	9	1379	Risk Ratio (M-H, Fixed, 95% CI)	1.65 [0.71, 3.86]
42.1 FEV1 >/= 80% predicted	3	356	Risk Ratio (M-H, Fixed, 95% CI)	4.04 [0.46, 35.52]
42.2 Mean baseline FEV1 61% to 79% of predicted	6	1023	Risk Ratio (M-H, Fixed, 95% CI)	1.34 [0.52, 3.46]
43 # patients with tremor	16	3833	Risk Ratio (M-H, Random, 95% CI)	1.74 [0.72, 4.20]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
43.1 Mean baseline FEV1 >/= 80% of predicted	2	530	Risk Ratio (M-H, Random, 95% CI)	5.30 [0.26, 109.66]
43.2 Mean baseline FEV1 61% to 79% of predicted	14	3303	Risk Ratio (M-H, Random, 95% CI)	1.63 [0.64, 4.15]
44 # patients with tachycardia or palpitations	12	3491	Risk Ratio (M-H, Fixed, 95% CI)	2.11 [0.83, 5.37]
44.1 Mean baseline FEV1 >/= 80% of predicted	1	116	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
44.2 Mean baseline FEV1 61% to 79% of predicted	10	2464	Risk Ratio (M-H, Fixed, 95% CI)	2.13 [0.77, 5.88]
44.3 Mean baseline FEV1 not reported	1	911	Risk Ratio (M-H, Fixed, 95% CI)	2.00 [0.18, 22.03]
45 Deaths	3	1673	Risk Ratio (M-H, Fixed, 95% CI)	2.46 [0.48, 12.65]
45.1 Mean baseline FEV1 61% to 79% of predicted	1	336	Risk Ratio (M-H, Fixed, 95% CI)	2.90 [0.12, 70.57]
45.2 Mean baseline FEV1 not reported	2	1337	Risk Ratio (M-H, Fixed, 95% CI)	2.31 [0.34, 15.63]
46 # patients with adverse cardiovascular events	4	792	Risk Ratio (M-H, Fixed, 95% CI)	0.90 [0.32, 2.54]
46.1 Mean baseline FEV1 >/= 80% of predicted	1	116	Risk Ratio (M-H, Fixed, 95% CI)	0.31 [0.01, 7.49]
46.2 Mean baseline FEV1 61% to 79% of predicted	3	676	Risk Ratio (M-H, Fixed, 95% CI)	1.06 [0.35, 3.24]
47 # Worsening asthma	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
47.1 Mean baseline FEV1 61% to 79% of predicted	1		Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
48 Change in height (cm) as SD scores at 24 +/- 4 weeks	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
48.1 Mean baseline FEV1 >/= 80% of predicted	1		Mean Difference (IV, Fixed, 95% CI)	Not estimable
49 PC20 Methacholine- adjusted odds ratio increase from baseline	1		Mean Difference (IV, Random, 95% CI)	Totals not selected
49.1 Mean baseline FEV1 61% to 79% of predicted	1		Mean Difference (IV, Random, 95% CI)	Not estimable
50 ACTH induced cortisol < 18 microg/dl at endpoint	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
50.1 Mean baseline FEV1 61% to 79% of predicted	1		Risk Ratio (M-H, Fixed, 95% CI)	Not estimable

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Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
51 am cortisol < 5 microg/dl at endpoint	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
51.1 Mean baseline FEV1 61% to 79% of predicted	1		Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
52 Change in % PC20 at endpoint	1	39	Mean Difference (IV, Fixed, 95% CI)	0.30 [-0.68, 1.28]
52.1 Mean baseline FEV1 >/= 80% of predicted	1	39	Mean Difference (IV, Fixed, 95% CI)	0.30 [-0.68, 1.28]
53 PC20 histamine	1		Doub'g doses (Fixed, 95% CI)	Totals not selected
53.1 Mean baseline FEV1 >/= 80% of predicted	1		Doub'g doses (Fixed, 95% CI)	Not estimable

Comparison 2

Additional comparisons for same dose

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 # patients with exacerbations requiring oral steroids by baseline predicted FEV1	30		Risk Ratio (IV, Fixed, 95% CI)	Subtotals only
1.1 Mean baseline FEV1 >/= 80% of predicted	8	1713	Risk Ratio (IV, Fixed, 95% CI)	0.70 [0.57, 0.87]
1.2 Mean baseline FEV1 61% to 79% of predicted	17	3764	Risk Ratio (IV, Fixed, 95% CI)	0.83 [0.72, 0.96]
1.3 Mean baseline FEV1 not reported	5	1331	Risk Ratio (IV, Fixed, 95% CI)	0.49 [0.21, 1.16]
2 # patients with exacerbations requiring oral steroids children versus adults	30		Risk Ratio (IV, Fixed, 95% CI)	Subtotals only
2.1 Children	6	605	Risk Ratio (IV, Fixed, 95% CI)	0.89 [0.58, 1.39]
2.2 Adults	24	6203	Risk Ratio (IV, Fixed, 95% CI)	0.77 [0.68, 0.88]
3 # patients with exacerbations requiring oral steroids by dose of ICS in both groups	30	6808	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.72 [0.62, 0.83]
3.1 Low dose of ICS (<= 400 mcg/day of BDP-eq)	12	3398	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.63 [0.51, 0.78]
3.2 Moderate dose of ICS (401 to 800 mcg/day of BDP-eq)	6	1067	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.68 [0.48, 0.97]
3.3 High dose of ICS (>800 mcg/day of BDP-eq)	7	1366	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.94 [0.58, 1.54]
3.4 Unspecified dose of ICS or range of dose only mentioned	5	977	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.89 [0.65, 1.22]
4 # patients with exacerbations requiring oral steroids by combination inhaler or separate inhaler for LABA	30		Risk Ratio (IV, Fixed, 95% CI)	Subtotals only
4.1 Combination inhaler	13	2718	Risk Ratio (IV, Fixed, 95% CI)	0.81 [0.50, 1.32]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
4.2 Separate inhaler	16	4053	Risk Ratio (IV, Fixed, 95% CI)	0.78 [0.69, 0.89]
4.3 Not reported	1	37	Risk Ratio (IV, Fixed, 95% CI)	0.21 [0.03, 1.64]
5 # patients with exacerbations requiring oral steroids by whether LABA dose is usual or higher than usual	30		Risk Ratio (IV, Fixed, 95% CI)	Subtotals only
5.1 LABA at usual dose	27	6427	Risk Ratio (IV, Fixed, 95% CI)	0.74 [0.65, 0.84]
5.2 LABA at higher than usual dose	3	381	Risk Ratio (IV, Fixed, 95% CI)	1.10 [0.79, 1.52]
6 # patients with exacerbations requiring oral steroids by type of LABA	30		Risk Ratio (IV, Fixed, 95% CI)	Subtotals only
6.1 Formoterol	9	2923	Risk Ratio (IV, Fixed, 95% CI)	0.74 [0.64, 0.85]
6.2 Salmeterol	21	3885	Risk Ratio (IV, Fixed, 95% CI)	0.89 [0.72, 1.10]
7 # patients with exacerbations requiring oral steroids by trial duration	30		Risk Ratio (IV, Fixed, 95% CI)	Subtotals only
7.1 <= 16 weeks	21	3645	Risk Ratio (IV, Fixed, 95% CI)	0.91 [0.72, 1.14]
7.2 > 16 weeks	9	3163	Risk Ratio (IV, Fixed, 95% CI)	0.74 [0.64, 0.85]
8 # patients with exacerbations requiring oral steroids study unsupported by pharmaceutical industry excluded	30		Risk Ratio (IV, Fixed, 95% CI)	Subtotals only
8.1 Charity funded	1	23	Risk Ratio (IV, Fixed, 95% CI)	1.09 [0.28, 4.32]
8.2 Funded by pharmaceutical industry	29	6785	Risk Ratio (IV, Fixed, 95% CI)	0.78 [0.69, 0.88]
9 Sensitivity analysis: exacerbations requiring oral steroids: studies with low risk of bias of selection bias (adequate allocation sequence generation)	26	6513	Risk Ratio (M-H, Fixed, 95% CI)	0.77 [0.69, 0.87]
10 Sensitivity analysis: exacerbations requiring oral steroids: studies with low risk of bias of selection bias (adequate allocation concealment)	20	5042	Risk Ratio (M-H, Fixed, 95% CI)	0.77 [0.66, 0.91]
11 Sensitivity analysis: exacerbations requiring oral steroids: studies with low risk of detection bias (adequate blinding)	30	6808	Risk Ratio (M-H, Fixed, 95% CI)	0.77 [0.68, 0.87]
12 Sensitivity analysis: exacerbations requiring oral steroids: studies with low risk of bias of attrition bias (complete follow up of study participants)	2	391	Risk Ratio (M-H, Fixed, 95% CI)	0.63 [0.10, 3.89]
13 Sensitivity analysis: exacerbations requiring oral steroids by data publication status (data available from published source)	14	3161	Risk Ratio (IV, Fixed, 95% CI)	0.77 [0.67, 0.88]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
14 Change in FEV1 at endpoint stratifying on age (children versus adults)	32		L (Random, 95% CI)	Subtotals only
14.1 Children	9		L (Random, 95% CI)	0.08 [0.05, 0.11]
14.2 Adults	23		L (Random, 95% CI)	0.13 [0.10, 0.15]
15 Change in FEV1 at endpoint stratifying on LABA (formoterol versus salmeterol)	32	9784	L (Random, 95% CI)	0.11 [0.09, 0.13]
15.1 Formoterol	17	4057	L (Random, 95% CI)	0.09 [0.07, 0.12]
15.2 Salmeterol	15	5727	L (Random, 95% CI)	0.14 [0.10, 0.18]
16 Change in FEV1 at endpoint stratifying on baseline FEV1	32		L (Random, 95% CI)	Subtotals only
16.1 <= 16 weeks	25		L (Random, 95% CI)	0.12 [0.09, 0.14]
16.2 > 16 weeks	7		L (Random, 95% CI)	0.10 [0.06, 0.13]

Comparison 3

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Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Change in morning PEF (L/min) at endpoint stratifying on baseline FEV1	42		Mean Difference (IV, Random, 95% CI)	Totals not selected
2 Change in evening PEF (L/min) at endpoint	25		Mean Difference (IV, Random, 95% CI)	Totals not selected
3 Change in % symptom-free days at endpoint	13	2935	Mean Difference (IV, Random, 95% CI)	13.34 [9.43, 17.24]
3.1 Mean baseline FEV1 >/= 80% of predicted	0	0	Mean Difference (IV, Random, 95% CI)	Not estimable
3.2 Mean baseline FEV1 61% to 79% of predicted	11	2296	Mean Difference (IV, Random, 95% CI)	14.98 [11.03, 18.92]
3.3 Mean baseline FEV1 not reported	2	639	Mean Difference (IV, Random, 95% CI)	6.57 [1.11, 12.03]
4 Change in mean % rescue free days at 12 +/ - 4 weeks	6	1698	Mean Difference (IV, Fixed, 95% CI)	17.05 [13.75, 20.35]
4.1 Mean baseline FEV1 61% to 79% of predicted	5	1381	Mean Difference (IV, Fixed, 95% CI)	17.63 [14.03, 21.23]
4.2 Mean baseline FEV1 not reported	1	317	Mean Difference (IV, Fixed, 95% CI)	14.0 [5.77, 22.23]
5 Change in FEV1 at endpoint (L) stratifying on baseline FEV1	26		Mean Difference (IV, Random, 95% CI)	Totals not selected
6 Change in # daytime rescue inhalations (puffs per day) at endpoint	12		Mean Difference (IV, Random, 95% CI)	Totals not selected
7 Change in FEV1 at endpoint (% predicted)	7		Mean Difference (IV, Fixed, 95% CI)	Totals not selected

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
stratifying on baseline FEV1				
8 Change in # overall daily rescue inhalations at endpoint	10	3088	Mean Difference (IV, Random, 95% CI)	-0.74 [-1.07, -0.42]
8.1 Mean baseline FEV1 >/= 80% of predicted	2	1272	Mean Difference (IV, Random, 95% CI)	-0.17 [-0.29, -0.05]
8.2 Mean baseline FEV1 61% to 79% of predicted	8	1816	Mean Difference (IV, Random, 95% CI)	-1.06 [-1.76, -0.37]
9 Change in quality of life (AQLQ score) at endpoint	3	1354	Mean Difference (IV, Random, 95% CI)	0.33 [0.05, 0.60]

Analysis 1.1. Comparison 1 Long-acting beta2 versus placebo: both groups receiving similar dose ICS, Outcome 1 # patients with exacerbations requiring oral steroids

Review: Addition of long-acting beta2-agonists to inhaled corticosteroids versus same dose inhaled corticosteroids for chronic asthma in adults and children

Comparison: 1 Long-acting beta2 versus placebo: both groups receiving similar dose ICS

Outcome: 1 # patients with exacerbations requiring oral steroids

Study or subgroup	LABA + ICS	ICS alone	Risk Ratio	Weight	Risk Rati
	n/N	n/N	M-H,Fixed,95% CI		M-H,Fixed,95% (
I Mean baseline FEVI >/= 80	% of predicted				
Langton Hewer 1995	3/11	3/12		0.6 %	1.09 [0.28, 4.32
Li 1999	2/13	1/16		0.2 %	2.46 [0.25, 24.21
Malone 2005	2/101	3/102		0.6 %	0.67 [0.11, 3.94
O'Byrne 2001a	58/323	81/322	-	16.6 %	0.71 [0.53, 0.96
O'Byrne 2001b	39/315	61/312	•	12.6 %	0.63 [0.44, 0.92
Simons 1997	0/16	1/16		0.3 %	0.33 [0.01, 7.62
Verberne 1998	10/60	10/57	-	2.1 %	0.95 [0.43, 2.11
Wallin 2003	1/18	5/19		1.0 %	0.21 [0.03, 1.64
Subtotal (95% CI)	857	856	•	34.0 %	0.70 [0.56, 0.86
Total events: 115 (LABA + IC	S), 165 (ICS alone)				
Heterogeneity: Chi ² = 3.96, d	$f = 7 (P = 0.78); I^2 = 0.0$)%			
Test for overall effect: $Z = 3.3$	0 (P = 0.00095)				
2 Mean baseline FEV1 61% to	79% of predicted				
Akpinarli 1999	0/16	0/16			Not estimab
Aubier 1999a	5/171	7/83		1.9 %	0.35 [0.11, 1.06
Aubier 1999b	17/167	7/82		1.9 %	1.19 [0.52, 2.76

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Study or subgroup	LABA + ICS n/N	ICS alone n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% C
Boyd 1995	19/55	15/64		2.8 %	1.47 [0.83, 2.61
Fitzgerald 1999	3/89	6/91		1.2 %	0.51 [0.13, 1.98
Kavaru 2000	0/92	0/90			Not estimable
Kemp 1998	53/252	59/254	+	12.0 %	0.91 [0.65, 1.26
Nathan 2006	1/94	3/91		0.6 %	0.32 [0.03, 3.05
Noonan 2006a	5/124	2/55		0.6 %	1.11 [0.22, 5.54
Noonan 2006b	4/115	2/54		0.6 %	0.94 [0.18, 4.97
Norhaya 1999	1/30	3/30		0.6 %	0.33 [0.04, 3.03
Pauwels 1997a	62/210	82/213	-	16.7 %	0.77 [0.59, 1.00
Pauwels 1997b	41/215	60/214		12.3 %	0.68 [0.48, 0.96
Russell 1995	16/99	18/99	_	3.7 %	0.89 [0.48, 1.64
SAS40036	2/172	7/159		1.5 %	0.26 [0.06, 1.25
Shapiro 2000	1/84	2/84		0.4 %	0.50 [0.05, 5.41
van der Molen 1997	33/125	32/114	+	6.9 %	0.94 [0.62, 1.42
Weiler 2005	1/102	0/90		0.1 %	2.65 [0.11, 64.26
ubtotal (95% CI)	2212	1883		63.9 %	0.81 [0.70, 0.94
tal events 264 (JABA + IC) leterogeneity: Chi ² = 1391, st for overall effect: Z = 2.7 Mean baseline FEV1 not rep SA540024 SA5400316 sFA100316 ubtotal (95% CI) at events 6 (JABA + ICS).	df = 15 (P = 0.53); P = 8 (P = 0.0054) oorted 0/99 3/161 1/124 2/113 497	2/100 6/161 1/124 1/118 503	 	0.5 % 1.2 % 0.2 % 0.2 % 2.1 %	0.20 [0.01, 4:15 0.50 [0.13, 1:96 1:00 [0.06, 1581 2.09 [0.19, 22.71 0.63] (0.24, 1.65
	f = 3 (P = 0.63); I ² =0.1 5 (P = 0.34)	1%		100.0 %	0.77 [0.68, 0.87

Analysis 1.2. Comparison 1 Long-acting beta2 versus placebo: both groups receiving similar dose ICS, Outcome 2 # patients with exacerbations requiring hospitalisation

Review: Addition of long-acting beta2-agonists to inhaled corticosteroids versus same dose inhaled corticosteroids for chronic asthma in adults and children

Comparison: 1 Long-acting beta2 versus placebo: both groups receiving similar dose ICS

Outcome: 2 # patients with exacerbations requiring hospitalisation

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Study or subgroup	LABA + ICS n/N	ICS alone n/N	Risk Ratio M-H,Fixed,95% Cl	Weight	Risk Rati M-H.Fixed,95% (
I Mean baseline FEVI >/= 80	% of predicted				
Koopmans 2006	0/27	0/27			Not estimat
Langton Hewer 1995	1711	0/12		1.5 %	3.25 [0.15, 72.36
Verberne 1998	1/60	2/56		6.7 %	0.47 [0.04, 5.01
Subtotal (95% CI)	98	95	+	8.2 %	0.99 [0.18, 5.39
Total events: 2 (LABA + ICS). Heterogeneity: Chi ² = 0.95, c Test for overall effect: $Z = 0.0$	$f = 1 (P = 0.33); I^2 = 0.$	0%			
2 Mean baseline FEV1 61% to					
Aubier 1999a	1/171	0/82		2.2 %	1.45 [0.06, 35.16
Aubier 1999b	0/167	0/83			Not estimat
Bailey 2008	2/239	3/236	-	9.7 %	0.66 [0.11, 3.90
Ind 2003	1/173	2/160		6.7 %	0.46 [0.04, 5.0
Kavaru 2000	0/92	0/90			Not estimat
Kemp 1998	2/261	0/264		1.6 %	5.06 [0.24, 104.8
Nathan 2006	0/94	0/91			Not estimat
Noonan 2006a	2/124	0/109		1.7 %	4.40 [0.21, 90.66
Noonan 2006b	0/115	0/109			Not estimat
Pauwels 1997a	1/210	3/213		9.6 %	0.34 [0.04, 3.22
Pauwels 1997b	2/215	5/214		16.1 %	0.40 [0.08, 2.03
Price 2002	0/332	0/331			Not estimab
Russell 1995	9/99	9/107	+	27.8 %	1.08 [0.45, 2.61
SAS40036	0/172	0/159			Not estimat
SD 039 0714	4/136	1/134	+	3.2 %	3.94 [0.45, 34.80
Shapiro 2000	0/84	1/84		4.8 %	0.33 [0.01, 8.07
Tal 2002	5/158	0/138		1.7 %	9.62 [0.54, 172.36
van der Molen 1997	0/125	1/114		5.0 %	0.30 [0.01, 7.39

Favours LABA + ICS Favours ICS alone

Risk Rati	Weight	Risk Ratio	ICS alone	LABA + ICS	Study or subgroup
M-H,Fixed,95% (M-H,Fixed,95% CI	n/N	n/N	
1.11 [0.67, 1.84	90.2 %	•	2718	2967	Subtotal (95% CI)
				25 (ICS alone)	Total events: 29 (LABA + ICS),
				II (P = 0.54); I ² =0.0	Heterogeneity: Chi ² = 9.86, df :
				P = 0.68)	Test for overall effect: $Z = 0.42$
				ted	3 Mean baseline FEV1 not repo
Not estimab			0/456	0/455	D'Urzo 2001
3.00 [0.12, 72.71	1.6 %		0/93	1/93	SAM40008
Not estimab			0/161	0/161	SAS40037
3.00 [0.12, 72.71	1.6 %		710	709	Subtotal (95% CI)
				(ICS alone)	Total events: I (LABA + ICS), 0
					Heterogeneity: not applicable
				P = 0.50	Test for overall effect: $Z = 0.68$
1.13 [0.70, 1.82	100.0 %	•	3523	3774	Total (95% CI)
				27 (ICS alone)	Total events: 32 (LABA + ICS),
				$= 14 (P = 0.67); I^2 = 0.67$	Heterogeneity: Chi ² = 11.25, df
				P = 0.61)	Test for overall effect: $Z = 0.51$
		0.01 0.1 1 10 100 1000	C		
		ABA + ICS Favours ICS alone	Favo		

Analysis 1.3. Comparison 1 Long-acting beta2 versus placebo: both groups receiving similar dose ICS, Outcome 3 Serious adverse event including respiratory

Review: Addition of long-acting beta2-agonists to inhaled corticosteroids versus same dose inhaled corticosteroids for chronic asthma in adults and children

Comparison: 1 Long-acting beta2 versus placebo: both groups receiving similar dose ICS

Outcome: 3 Serious adverse event including respiratory

Risk	Weight	Risk Ratio	ICS alone	LABA + ICS	Study or subgroup
M-H,Fixed,95		M-H,Fixed,95% CI	n/N	n/N	
				0% of predicted	I Mean baseline FEVI >/= 80
0.33 [0.01, 7	0.8 %		1/27	0/27	Koopmans 2006
3.25 [0.15, 72	0.3 %		0/12	1711	Langton Hewer 1995
Not estin			0/102	0/101	Malone 2005
0.49 [0.07, 3	1.5 %		2/104	2/212	Morice 2008a
0.17[0.01,4	1.1 %		1/103	0/203	Morice 2008b
1.13 [0.47, 2	4.9 %	+	9/213	10/210	O'Byrne 2001a
1.33 [0.64, 2	6.5 %	-	12/214	16/215	O'Byrne 2001b
0.63 [0.31, 1	10.4 %	-	19/322	12/323	Pauwels 1997a
0.78 [0.40,]	10.4 %	-	19/312	15/315	Pauwels 1997b
0.70 [0.12, 4	1.5 %		2/101	3/216	Pohunek 2006a
2.49 [0.29, 21	0.7 %		1/100	5/201	Pohunek 2006b
Not estin			0/145	0/128	SD 039 0718
1.02 [0.09, 11	0.7 %		1/63	2/123	SD 039 0719
0.70 [0.16, 2	2.3 %		4/56	3/60	Verberne 1998
0.88 [0.64, 1.2	40.9 %	+	1874	2345	Subtotal (95% CI)
			0.0%	# = 11 (P = 0.87); 1 ² =0 79 (P = 0.43)	Total events: 69 (LABA + ICS Heterogeneity: Chi ² = 6.02, c Test for overall effect: $Z = 0.7$ 2 Mean baseline FEV1 61% to
0.74 [0.13, 4	1.5 %		2/82	3/167	Aubier 1999a
1.29 [0.35, 4	2.2 %	_	3/83	8/171	Aubier 1999b
0.54 [0.20, 1	6.0 %		11/236	6/239	Bailey 2008
1.16 [0.44, 3	3.5 %		7/64	7/55	Boyd 1995
0.98 [0.09, 10	0.7 %		1/86	2/176	Buhl 2003a
0.49 [0.03, 7	0.7 %		1/86	1/176	Buhl 2003b
4.94 [0.24, 101	0.3 %		0/153	2/155	D5896C0001a

0.005 0.1 I IO 200 Favours LABA + ICS Favours ICS alone

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Risk Rat M-H/Fixed,95% (Weight	Risk Ratio M-H,Fixed,95% CI	ICS alone n/N	LABA + ICS n/N	Study or subgroup
0.34 [0.04, 3.22	1.6 %		3/91	1/89	Fitzgerald 1999
1.68 [0.58, 4.92	2.8 %		5/160	9/171	Ind 2003
1.26 [0.15, 10.58	0.9 %		1/57	5/226	Jenkins 2006a
0.17 [0.01, 4.10	1.1 %		1/58	0/115	lenkins 2006b
1.96 [0.18, 21.20	0.6 %		1/90	2/92	Kavaru 2000
3.02 [0.12, 73.87	0.3 %		0/254	1/252	Kemp 1998
0.51 [0.09, 2.77	2.1 %		4/207	2/202	Kuna 2006
Not estimat	21.10		0/129	0/130	Molimard 2001
Not estimat			0/91	0/94	Nathan 2006
	0.4%		0/55	4/124	Noonan 2006
4.03 [0.22, 73.62					
3.32 [0.17, 63.14	0.4 %		0/54	3/115	Noonan 2006b
0.83 [0.38, 1.8	6.8 %		13/107	10/99	Russell 1995
Not estimat			0/159	0/172	SAS40036
0.99 [0.06, 15.5	0.5 %		1/134	1/136	SD 039 0714
2.30 [0.11, 47.33	0.4 %		0/84	2/184	SD 039 0725a
1.52 [0.16, 14.33	0.7 %		1/85	3/168	SD 039 0725b
1.42 [0.15, 13.44	0.7 %		1/73	3/154	SD 039 0726a
1.48 [0.06, 35.88	0.4 %		0/72	1/147	SD 039 0726b
1.26 [0.48, 3.28	4.2 %		5/133	21/443	SD 039 0728
0.33 [0.01, 8.07	0.8 %		1/84	0/84	Shapiro 2000
13.99 [0.81, 242.7	0.3 %	· · · ·	0/138	7/148	Tal 2002
3.03 [0.12, 73.49	0.3 %		0/100	1/99	Weiler 2005
2.02 [0.23, 17.66	0.7 %		1/62	4/123	Zetterstrom 2001a
Not estimat			0/62	0/115	Zetterstrom 2001b
4.03 [0.46, 35.57	0.5 %		1/124	4/123	Zimmerman 2004a
1.20 [0.89, 1.62	41.4 %	•	3453	4944	ubtotal (95% CI)
				df = 27 (P = 0.95); l ² = 19 (P = 0.24)	tal events: 113 (LABA + IC leterogeneity: $Chi^2 = 16.14$, est for overall effect: $Z = 1.1$ Mean baseline FEV1 not res
1.09 [0.62, 1.92	12.0 %	+	22/456	24/455	D'Urzo 2001
7.00 [0.37, 133.66	0.3 %		0/93	3/93	SAM40008
	0.5 %		1/181	2/181	SAM40012

Risk Rati	Weight	Risk Ratio	ICS alone	LABA + ICS	Study or subgroup
M-H,Fixed,95% (M-H,Fixed,95% CI	n/N	n/N	
Not estimab			0/90	0/102	SAS40024
0.50 [0.05, 5.46	1.1 %		2/161	1/161	SAS40037
1.46 [0.15, 13.85	0.7 %		1/105	3/216	SD 037 0344a
2.48 [0.12, 51.13	0.4 %		0/105	2/213	SD 037 0344b
Not estimab			0/124	0/124	SFA100314
Not estimab			0/118	0/113	SFA100316
3.00 [0.32, 28.53	0.5 %		1/159	3/159	SFCF4026
0.26 [0.03, 2.24	2.2 %		4/95	1/93	SM540012
1.18 [0.74, 1.87	17.7 %	+	1687	1910	Subtotal (95% CI)
				31 (ICS alone)	Fotal events: 39 (LABA + ICS)
			6	= 7 (P = 0.66); I ² =0.09	Heterogeneity: Chi ² = 4.98, df
				(P = 0.49)	Test for overall effect: $Z = 0.65$
1.06 [0.87, 1.30	100.0 %	•	7014	9199	Total (95% CI)
), 166 (ICS alone)	fotal events: 221 (LABA + ICS
			0%	$f = 47 (P = 0.99); I^2 = 0.99$	-leterogeneity: Chi ² = 28.43, o
				(P = 0.54)	Test for overall effect: $Z = 0.62$
		.005 0.1 1 10 200			
		rs LABA + ICS Favours ICS alon			

Analysis 1.4. Comparison 1 Long-acting beta2 versus placebo: both groups receiving similar dose ICS, Outcome 4 Total # withdrawals

Review: Addition of long-acting beta2-agonists to inhaled corticosteroids versus same dose inhaled corticosteroids for chronic asthma in adults and children

Comparison: 1 Long-acting beta2 versus placebo: both groups receiving similar dose ICS

Outcome: 4 Total # withdrawals

Study or subgroup	LABA + ICS n/N	ICS alone n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% C
I Mean baseline FEVI >/= 80	% of predicted				
Houghton 2007	1/19	1/20		0.1 %	1.05 [0.07, 15.66
Koopmans 2006	0/27	4/27		0.4 %	0.11[0.01, 1.97]
Langton Hewer 1995	0/11	2/12		0.2 %	0.22 [0.01, 4.07
Malone 2005	19/101	16/102		1.3 %	1.20 [0.65, 2.20
Meijer 1995	0/20	1/20		0.1 %	0.33 [0.01, 7.72
Morice 2008a	11/212	7/104		0.8 %	0.77 [0.31, 1.93
Morice 2008b	14/203	7/103	-	0.8 %	1.01 [0.42, 2.44
Pohunek 2006a	14/216	6/106		0.7 %	1.15 [0.45, 2.90
Pohunek 2006b	11/201	7/107		0.8 %	0.84 [0.33, 2.10
SD 039 0718	36/128	51/145	-	4.0 %	0.80 [0.56, 1.14
SD 039 0719	13/123	10/63		1.1 %	0.67 [0.31, 1.43
Simons 1997	0/16	2/16		0.2 %	0.20 [0.01, 3.86
SMS40012	15/93	16/95	+	1.3 %	0.96 [0.50, 1.82
Stelmach 2007	0/29	0/29			Not estimable
Verberne 1998	5/60	4/56		0.3 %	1.17 [0.33, 4.13
Wallin 2003	0/18	2/19		0.2 %	0.21 [0.01, 4.11
Subtotal (95% CI) Total events: 139 (LABA + IC Heterogeneity: Chi ² = 7.64, c Test for overall effect: Z = 1.6	$f = 14 (P = 0.91); I^2 = 0$ 0 (P = 0.11)	1024	·	12.2 %	0.84 [0.67, 1.04]
2 Mean baseline FEVI 61% to Aubier 1999a	28/171	20/82		2.2 %	0.67 [0.40, 1.12
Aubier 1999b	31/167	21/83	4	2.3 %	0.73 [0.45, 1.19
Bailey 2008	70/239	85/236		7.1 %	0.81 [0.63, 1.05]
Boyd 1995	8/55	14/64		1.1 %	0.66 [0.30, 1.47
Buyu 1995 Buhl 2003a	15/176	7/85		0.8 %	1.03 [0.44, 2.44

0.01 0.1 1 10 100 Favours LABA + ICS Favours ICS alone

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Study or subgroup	LABA + ICS n/N	ICS alone n/N	Risk Ratio M-H.Fixed,95% Cl	Weight	Risk Ratic M-H,Fixed,95% C
Buhl 2003b	14/176	7/86		0.8 %	0.98 [0.41, 2.33
Fitzgerald 1999	17/89	18/91		1.5 %	0.97 [0.53, 1.75]
Hultguist 2000	12/118	9/116		0.8 %	1.31 [0.57, 2.99
Ind 2003	27/171	15/160		1.3 %	1.68 [0.93, 3.05
Kavaru 2000	20/92	27/90	-	2.3 %	0.72 (0.44, 1.19
Kemp 1998	25/252	47/254	+	3.9 %	0.54 [0.34, 0.84
Kuna 2006	21/202	24/207	_	2.0 %	0.90 [0.52, 1.56
Molimard 2001	12/130	18/129		1.5 %	0.66 [0.33, 1.32
Nathan 2006	13/94	20/91		1.7 %	0.63 [0.33, 1.19
Noonan 2006a	27/124	15/54		1.7 %	0.78 [0.45, 1.35
Noonan 2006b	29/115	16/55	-	1.8 %	0.87 [0.52, 1.46
Pauwels 1997a	47/210	53/213	-	4.4 %	0.90 [0.64, 1.27
Pauwels 1997b	39/215	41/214	-	3.4 %	0.95 [0.64, 1.41
Price 2002	19/332	18/331	_	1.5 %	1.05 [0.56, 1.97
Russell 1995	22/99	18/107		1.4 %	1.32 [0.75, 2.31
SAS40036	29/172	59/159		5.1 %	0.45 [0.31, 0.67
SD 039 0349	17/115	16/124		1.3 %	1.15 [0.61, 2.16
SD 039 0725a	21/184	16/84		1.8 %	0.60 [0.33, 1.09
SD 039 07256	37/168	17/85	+	1.9 %	1.10 { 0.66, 1.84
SD 039 0726a	22/154	14/73		1.6 %	0.74 [0.40, 1.37
SD 039 0726b	25/147	14/72	-	1.6 %	0.87 (0.48, 1.58
SD 039 0728	82/443	26/133	_	3.3 %	0.95 [0.64, 1.41
Shapiro 2000	13/84	22/84		1.8 %	0.59 [0.32, 1.09
Tal 2002	9/148	9/138		0.8 %	0.93 [0.38, 2.28
van der Molen 1997	18/125	13/114		1.1 %	1.26 [0.65, 2.46
Weiter 2005	2/99	9/100		0.7 %	0.22 [0.05, 1.01
Zetterstrom 2001a	20/123	8/62		0.9 %	1.26 [0.59, 2.70
Zetterstrom 2001b	17/115	8/62	+	0.9 %	1.15 [0.52, 2.50
Zimmerman 2004a	11/95	8/50		0.9 %	0.72 [0.31, 1.68
Zimmerman 2004b	7/106	8/51		0.9 %	0.42 [0.16, 1.10
ubtotal (95% CI)	5505	4139		67.9 %	0.83 [0.75, 0.90]
otal events: 826 (LABA + K					

rs LABA + ICS Favours ICS alone

Study or subgroup	LABA + ICS	ICS alone	Risk Ratio	Weight	Risk Ratic
	n/N	n/N	M-H,Fixed,95% CI		M-H,Fixed,95% C
Heterogeneity: $Chi^2 = 40.10$, d	$ff = 34 (P = 0.22); I^2 =$	15%			
Test for overall effect: $Z = 4.12$	(P = 0.000039)				
3 Mean baseline FEV1 not repo	orted				
D'Urzo 2001	88/455	111/456	•	9.2 %	0.79 [0.62, 1.02
SAM40012	3/176	10/175		0.8 %	0.30 [0.08, 1.07
SA540024	4/102	3/90		0.3 %	1.18 [0.27, 5.12
SAS40037	38/161	54/161	+	4.5 %	0.70 [0.49, 1.00
SFA100314	13/124	22/124		1.8 %	0.59 [0.31, 1.12
SFA100316	7/113	10/118		0.8 %	0.73 [0.29, 1.85
SFCF4026	18/159	30/159		2.5 %	0.60 [0.35, 1.03
Subtotal (95% CI)	1290	1283	•	19.9 %	0.71 [0.60, 0.85]
Total events: 171 (LABA + ICS), 240 (ICS alone)				
Heterogeneity: Chi ² = 3.71, df	= 6 (P = 0.72); I ² =0.	0%			
Test for overall effect: $Z = 3.78$	(P = 0.00016)				
Total (95% CI)	8272	6446	,	100.0 %	0.80 [0.75, 0.87]
Total events: 1136 (LABA + IC	S), 1116 (ICS alone)				
Heterogeneity: Chi ² = 53.51, d	$f = 56 (P = 0.57); I^2 =$	-0.0%			
Test for overall effect: $Z = 5.62$	(P < 0.00001)				
			0.01 0.1 1 10 100		
		Favo	urs LABA + ICS Favours ICS alc	one	

Analysis 1.5. Comparison 1 Long-acting beta2 versus placebo: both groups receiving similar dose ICS, Outcome 5 # withdrawals due to poor asthma control or exacerbation

Review: Addition of long-acting beta2-agonists to inhaled corticosteroids versus same dose inhaled corticosteroids for chronic asthma in adults and children

Comparison: 1 Long-acting beta2 versus placebo: both groups receiving similar dose ICS

Outcome: 5 # withdrawals due to poor asthma control or exacerbation

Study or subgroup	LABA + ICS	ICS alone	Risk Ratio	Weight	Risk
	n/N	n/N	M-H,Fixed,95% Cl		M-H,Fixed,95
I Mean baseline FEVI >/= 8					
Langton Hewer 1995	0/11	0/12			Not estin
Li 1999	2/13	1/16		0.3 %	2.46 [0.25, 24
Malone 2005	3/101	5/102		1.9 %	0.61 [0.15, 2
SM540012	1/93	6/95		2.3 %	0.17 [0.02, 1
Verberne 1998	0/60	1/56		0.6 %	0.31 [0.01, 7
Wallin 2003	0/18	1/19		0.6 %	0.35 [0.02, 8
Subtotal (95% CI)	296	300	•	5.7 %	0.49 [0.20, 1.]
Total events: 6 (LABA + ICS)	, 14 (ICS alone)				
Heterogeneity: Chi ² = 3.10, o	df = 4 (P = 0.54); $l^2 = 0.54$	0%			
Test for overall effect: $Z = 1.6$	()				
2 Mean baseline FEVI 61% to					
Aubier 1999a	1/171	2/82		1.0 %	0.24 [0.02, 2
Aubier 1999b	3/167	2/83		1.0 %	0.75 [0.13, 4
Bailey 2008	6/239	9/236	-+-	3.5 %	0.66 [0.24, 1
Boyd 1995	2/55	2/64		0.7 %	1.16 [0.17, 7
Buhl 2003a	4/176	2/86		1.0 %	0.98 [0.18, 5
Buhl 2003b	5/176	3/86		1.5 %	0.81 [0.20, 3
Hultquist 2000	3/118	2/116		0.8 %	1.47 [0.25, 8
Ind 2003	5/173	4/162	+	1.6 %	1.17 [0.32, 4
Kavaru 2000	3/92	9/90		3.5 %	0.33 [0.09, 1
Kemp 1998	2/252	9/254		3.4 %	0.22 [0.05, 1
Kuna 2006	10/202	11/207	+	4.2 %	0.93 [0.40, 2
Molimard 2001	0/130	3/129		1.3 %	0.14 [0.01, 2
Nathan 2006	7/94	11/91		4.3 %	0.62 [0.25, 1
Noonan 2006a	13/124	11/54	-	5.9 %	0.51 [0.25, 1
Noonan 2006b	13/115	11/55	-	5.7 %	0.57 [0.27,]

0.001 0.01 0.1 1 10 100 1000 Favours LABA + ICS Favours ICS alone

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	LABA + ICS n/N	ICS alone n/N	Risk Ratio M-H,Fixed,95% Cl	Weight	Risk Ratio M-H,Fixed,95% C
Norhaya 1999	1/30	3/30		1.1 %	0.33 [0.04, 3.03
Pauwels 1997a	7/210	10/213		3.8 %	0.71 [0.28, 1.83
Pauwels 1997b	0/215	4/214		1.7 %	0.11 [0.01, 2.04
Russell 1995	3/99	2/107		0.7 %	1.62 [0.28, 9.50]
SAS40036	10/172	34/159	-	13.5 %	0.27 [0.14, 0.53
Shapiro 2000	3/81	18/81		6.9 %	0.17 [0.05, 0.54
Tal 2002	5/148	6/138	-	2.4 %	0.78 [0.24, 2.49
van der Molen 1997	1/125	6/114		2.4 %	0.15 [0.02, 1.24]
Zetterstrom 2001 a	5/123	2/62	_	1.0 %	1.26 [0.25, 6.31]
Zetterstrom 2001b	8/115	2/62	<u> </u>	1.0 %	2.16 [0.47, 9.84
Zimmerman 2004a	1/95	1/50		0.5 %	0.53 [0.03, 8.24
Zimmerman 2004b	0/106	1/51		0.8 %	0.16 [0.01, 3.91]
Subtotal (95% CI)	3803	3076	•	75.2 %	0.52 [0.42, 0.66]
Test for overall effect: $Z = 5.5$	df = 26 (P = 0.42); l^2 = 6 (P < 0.00001)	370			
Test for overall effect: Z = 5.5 3 Mean baseline FEVL not rec	6 (P < 0.00001)	570			
Test for overall effect: Z = 5.5 3 Mean baseline FEV1 not rep D'Urzo 2001	6 (P < 0.00001)	11/456		4.2 %	0.27 [0.08, 0.97
3 Mean baseline FEV1 not rep	6 (P < 0.00001) iorted		-	4.2 % 9.9 %	0.27 [0.08, 0.97
3 Mean baseline FEVT not rep D'Urzo 2001	6 (P < 0.00001) Norted 3/455	11/456	•		0.42 [0.22, 0.83
3 Mean baseline FEVI not rep D'Urzo 2001 SAS40037	6 (P < 0.00001) iorted 3/455	11/456 26/161	•	9.9 %	
3 Mean baseline FEV1 not rep D'Urzo 2001 SAS40037 SFA100314	6 (P < 0.00001) ionted 3/455 11/161 2/124	11/456 26/161 2/124		9.9 % 0.8 %	0.42 [0.22, 0.83
3 Mean baseline FEV1 not rep D'Urzo 2001 SAS40037 SFA100314 SFA100316	6 (P < 0.00001) ionted 3/455 11/161 2/124 2/113 2/159 1012), 50 (ICS alone) f = 4 (P = 0.42); P = 0.4	11/456 26/161 2/124 1/118 10/159 1018	 •	9.9 % 0.8 % 0.4 %	0.42 [0.22, 0.83 1.00 [0.14, 6.99 2.09 [0.19, 22.71

Analysis 1.6. Comparison 1 Long-acting beta2 versus placebo: both groups receiving similar dose ICS, Outcome 6 # withdrawals due to adverse events

Review: Addition of long-acting beta2-agonists to inhaled corticosteroids versus same dose inhaled corticosteroids for chronic asthma in adults and children

Comparison: 1 Long-acting beta2 versus placebo: both groups receiving similar dose ICS

Outcome: 6 # withdrawals due to adverse events

Study or subgroup	LABA + ICS n/N	ICS alone n/N	Risk Ratio M-H.Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% C
I Mean baseline FEVI >/= 80			TTTT BOOK STOCK		1110000000
Langton Hewer 1995	0/11	0/11			Not estimable
Malone 2005	3/101	0/102		0.3 %	7.07 [0.37, 135.12]
Morice 2008a	1/212	4/104	•	2.7 %	0.12 [0.01, 1.08]
Morice 2008b	3/203	3/103		2.0 %	0.51 [0.10, 2.47]
SD 039 0718	4/128	10/145		4.7 %	0.45 [0.15, 1.41
SD 039 0719	2/123	2/63		1.3 %	0.51 [0.07, 3.55
SMS40012	3/93	1/95		0.5 %	3.06 [0.32, 28.93]
Verberne 1998	2/60	0/56		0.3 %	4.67 [0.23, 95.24]
Wallin 2003	0/18	0/19			Not estimable
Subtotal (95% CI)	949	698	+	11.8 %	0.74 [0.41, 1.34]
Test for overall effect: Z = 1.0 2 Mean baseline FEV1 61% to					
Aubier 1999a	16/171	11/82		7.5 %	0.70 [0.34, 1.43
Aubier 1999b	16/167	11/83		7.4 %	0.72 [0.35, 1.49]
Bailey 2008	5/239	6/236		3.1 %	0.82 [0.25, 2.66
Boyd 1995	4/55	2/64		0.9 %	2.33 [0.44, 12.22
D5896C0001a	2/155	1/77		0.7 %	0.99 [0.09, 10.79
D5896C0001b	2/153	1/76		0.7 %	0.99 [0.09, 10.78
Hultquist 2000	4/118	2/116		1.0 %	1.97 [0.37, 10.53
Kavaru 2000	0/92	1/90	·	0.8 %	0.33 [0.01, 7.90]
Kemp 1998	7/252	5/254		2.5 %	1.41 [0.45, 4.39]
Kuna 2006	5/202	2/207		1.0 %	2.56 [0.50, 13.05
Molimard 2001	2/130	3/129		1.5 %	0.66 [0.11, 3.89]

0.02 0.1 I IO 50 Favours LABA + ICS Favours ICS alone

Risk Ratio	Weight	Risk Ratio	ICS alone	LABA + ICS	Study or subgroup
M-H,Fixed,95% C		M-H,Fixed,95% CI	n/N	n/N	
1.74 [0.38, 7.93	1.4 %		2/54	8/124	Noonan 2006a
2.15 [0.48, 9.63	1.4 %		2/55	9/115	Noonan 2006b
0.33 [0.04, 3.03	1.5 %		3/30	1/30	Norhaya 1999
1.01 [0.33, 3.09	3.0 %		6/213	6/210	Pauwels 1997a
1.12 [0.44, 2.85	4.1 %		8/214	9/215	Pauwels 1997b
0.66 [0.19, 2.33	3.0 %		6/331	4/332	Price 2002
2.16 [0.40, 11.54	1.0 %		2/107	4/99	Russell 1995
1.54 [0.37, 6.34	1.6 %		3/159	5/172	SA540036
0.49 { 0.15, 1.60	4.1 %		8/134	4/136	SD 039 0714
3.22 [0.17, 61.57	0.3 %		0/84	3/184	SD 039 0725a
4.58 [0.25, 84.09	0.3 %		0/85	4/168	SD 039 0725b
1.42 [0.29, 6.88	1.4 %		2/73	6/154	SD 039 0726a
2.45 [0.29, 20.58	0.7 %		1/72	5/147	SD 039 0726b
1.65 [0.71, 3.86	4.7 %		6/133	33/443	SD 039 0728
Not estimable			0/84	0/84	Shapiro 2000
4.66 [0.23, 96.30	0.3 %		0/138	2/148	Tal 2002
4.56 [0.54, 38.45	0.5 %		1/114	5/125	van der Molen 1997
Not estimable			0/19	0/18	Wallin 2003
0.34 { 0.04, 3.18	1.5 %		3/100	1/99	Weiler 2005
1.34 [0.37, 4.89	2.0 %		3/62	8/123	Zetterstrom 2001a
0.90 [0.22, 3.64	2.0 %		3/62	5/115	Zetterstrom 2001b
1.59 [0.07, 38.42	0.3 %		0/50	1/95	Zimmerman 2004a
2.43 [0.12, 49.70	0.3 %		0/51	2/106	Zimmerman 2004b
1.14 [0.90, 1.45]	63.5 %	•	3929	5270	Subtotal (95% CI)
				df = 32 (P = 0.96); I ² = 0 (P = 0.27) ported	Fotal events: 189 (LABA + IC) -leterogeneity: Chi ² = 19.63, a fest for overall effect: Z = 1.11 8 Mean baseline FEV1 not rep
1.15 [0.65, 2.03	10.6 %	-	21/456	24/455	D'Urzo 2001
3.27 [0.69, 15.53	1.0 %		2/160	7/171	Ind 2003
1.76 [0.16, 19.14	0.5 %		1/90	2/102	SAS40024
1.00 [0.25, 3.93	2.0 %	_	4/161	4/161	SAS40037
0.32 [0.05, 1.91	2.0 %		3/105	2/216	SD 037 0344a

Study or subgroup	LABA + ICS	ICS alone	Risk Ratio	Weight	Risk Ratio
	n/N	n/N	M-H,Fixed,95% CI		M-H,Fixed,95% CI
SD 037 0344b	1/213	2/105		1.4 %	0.25 [0.02, 2.69]
SFA100314	2/124	7/124		3.5 %	0.29 [0.06, 1.35]
SFA100316	1/113	1/118		0.5 %	1.04 [0.07, 16.50]
SFCF4026	3/159	6/159		3.0 %	0.50 [0.13, 1.96]
Subtotal (95% CI)	1714	1478	+	24.7 %	0.92 [0.62, 1.36]
Total events: 46 (LABA + ICS),	47 (ICS alone)				
Heterogeneity: Chi ² = 8.87, df	= 8 (P = 0.35); I ² = 10	%			
Test for overall effect: Z = 0.44	(P = 0.66)				
Total (95% CI)	7933	6105	•	100.0 %	1.04 [0.86, 1.26]
Total events: 253 (LABA + ICS), 173 (ICS alone)				
Heterogeneity: Chi ² = 39.36, d	$f = 48 (P = 0.81); I^2 =$	0.0%			
Test for overall effect: Z = 0.38	(P = 0.70)				
			0.02 0.1 1 10 50		
		Fa	wours LABA + ICS Favours ICS alo	ne	

Analysis 1.7. Comparison 1 Long-acting beta2 versus placebo: both groups receiving similar dose ICS, Outcome 7 # withdrawals due to serious non-respiratory event

Review: Addition of long-acting beta2-agonists to inhaled corticosteroids versus same dose inhaled corticosteroids for chronic asthma in adults and children

Comparison: 1 Long-acting beta2 versus placebo: both groups receiving similar dose ICS

Outcome: 7 # withdrawals due to serious non-respiratory event

Study or subgroup	LABA + ICS	ICS alone	Risk Ratio M-	Risk Ratio M-
	n/N	n/N	H,Random,95% Cl	H,Random,959 Cl
I Mean baseline FEVI 61%	to 79% of predicted			
Tal 2002	2/148	0/138		4.66 [0.23, 96.30]
Akpinarli 1999	0/1	0/1		Not estimable
			0.01 0.1 1 10 100	
			0.01 0.1 I 10 100 Favours LABA + ICS Favours ICS alone	

Analysis 1.8. Comparison 1 Long-acting beta2 versus placebo: both groups receiving similar dose ICS, Outcome 8 FEV1 (L) at endpoint

Review: Addition of long-acting beta2-agonists to inhaled corticosteroids versus same dose inhaled corticosteroids for chronic asthma in adults and children

Comparison: 1 Long-acting beta2 versus placebo: both groups receiving similar dose ICS

Outcome: 8 FEV1 (L) at endpoint

Study or subgroup	LABA + ICS N	Mean(SD)	ICS alone N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mear Difference IV,Fixed,95% C
I Mean baseline FEVI >/-	80% of predicted						
Morice 2008a	209	1.82 (0.42)	103	1.72 (0.44)	-	22.8 %	0.10 [0.00, 0.20]
Morice 2008b	201	1.82 (0.43)	102	1.72 (0.44)		22.0 %	0.10 [0.00, 0.20]
Subtotal (95% CI)	410		205		•	44.8 %	0.10 [0.03, 0.17]
Heterogeneity: Chi ² = 0.0	, df = 1 (P = 1.00); l ² =0.0%					
Test for overall effect: Z =	2.69 (P = 0.0072)					
2 Mean baseline FEV1 619	% to 79% of predi	ted					
Boyd 1995	47	1.99 (0.78)	49	2.01 (0.68)		2.8 %	-0.02 [-0.31, 0.27]
Fitzgerald 1999	89	2.92 (0.8)	91	2.68 (0.78)		4.5 %	0.24 [0.01, 0.47
Norhaya 1999	20	1.74 (0.61)	20	1.67 (0.57)		1.8 %	0.07 [-0.30, 0.44]
van der Molen 1997	125	2.51 (0.85)	111	2.25 (0.84)		5.1 %	0.26 [0.04, 0.48
Zetterstrom 2001a	123	2.47 (0.42)	62	2.35 (0.42)		14.5 %	0.12 [-0.01, 0.25]
Zetterstrom 2001b	115	2.5 (0.41)	62	2.35 (0.42)		14.4 %	0.15 [0.02, 0.28
Subtotal (95% CI)	519		395		•	43.0 %	0.15 [0.07, 0.22]
Heterogeneity: Chi ² = 3.2	6, df = 5 (P = 0.6	6); I ² =0.0%					
Test for overall effect: Z =	3.90 (P = 0.0000	96)					
3 Mean baseline FEV1 not							
Ind 2003	171	2.4 (0.9)	160	2.3 (0.9)		6.3 %	0.10 [-0.09, 0.29]
SAS40024	98	2.99 (0.7)	87	2.85 (0.7)		5.8 %	0.14 [-0.06, 0.34
Subtotal (95% CI)	269		247		-	12.2 %	0.12 [-0.02, 0.26]
Heterogeneity: Chi ² = 0.0		8); I ² =0.0%					
Test for overall effect: Z = Total (95% CI)	1.67 (P = 0.095) 1198		847		•	100.0 %	0.12 [0.07, 0.17]
Heterogeneity: Chi ² = 4.1		0)-12 -0.0%	04/		•	100.0 %	0.12 [0.0/, 0.1/]
Test for overall effect: Z =							
Test for subgroup differen		/), ² =0.0%				
			,				
				-0.5	-0.25 0 0.25	0.5	

Analysis 1.9. Comparison 1 Long-acting beta2 versus placebo: both groups receiving similar dose ICS, Outcome 9 Change in FEV1 at endpoint stratifying on baseline FEV1

Review: Addition of long-acting beta2-agonists to inhaled corticosteroids versus same dose inhaled corticosteroids for chronic asthma in adults and children

Comparison: 1 Long-acting beta2 versus placebo: both groups receiving similar dose ICS

Outcome: 9 Change in FEV1 at endpoint stratifying on baseline FEV1

Study or subgroup	LABA + ICS	ICS	L (SE)	L	Weight	L
	N	N		IV,Random,95% CI		IV,Random,95% CI
I Mean baseline FEVI >= 8						
Langton Hewer 1995	II.	10	0.42 (0.1071)		0.9 %	0.42 [0.21, 0.63]
Malone 2005	101	102	0.06 (0.0357)		4.0 %	0.06 [-0.01, 0.13]
Pohunek 2006a	216	106	0.08 (0.0306)	-+-	4.5 %	0.08 [0.02, 0.14]
Pohunek 2006b	201	107	0.05 (0.0306)	+	4.5 %	0.05 [-0.01, 0.11]
SD 039 0719	119	63	0.08 (0.0306)	-	4.5 %	0.08 [0.02, 0.14
Subtotal (95% CI)	648	388		•	18.3 %	0.09 [0.03, 0.14]
Heterogeneity: Tau ² = 0.00	; Chi ² = 11.27, df =	4 (P = 0.02)	; I ² =65%			
Test for overall effect: $Z = 3$						
2 Mean baseline FEV1 61%			0.02 (0.05 ())		25.07	0.00 5 0.00 0.14
Aubier 1999a	171	165	0.03 (0.0561)		2.5 %	0.03 [-0.08, 0.14]
Aubier 1999b	167	82	0.04 (0.0561)		2.5 %	0.04 [-0.07, 0.15
Bailey 2008	239	236	0.11 (0.0332)	+	4.2 %	0.11 [0.04, 0.18]
Boyd 1995	47	49	0.04 (0.0816)		1.4 %	0.04 [-0.12, 0.20]
D5896C0001a	151	75	0.19 (0.0306)	+	4.5 %	0.19 [0.13, 0.25]
D5896C0001b	152	76	0.1 (0.0306)	+	4.5 %	0.10 [0.04, 0.16
GOAL	1133	1199	0.12 (0.0204)	•	5.5 %	0.12 [0.08, 0.16]
Green 2006	39	39	0.02 (0.047449)	+	3.0 %	0.02 [-0.07, 0.11]
Hultquist 2000	117	116	0.12 (0.0714)		1.8 %	0.12 [-0.02, 0.26]
Kavaru 2000	87	85	0.23 (0.0714)		1.8 %	0.23 [0.09, 0.37]
Kemp 1998	252	254	0.27 (0.0408)	+	3.5 %	0.27 [0.19, 0.35]
Molimard 2001	130	129	0.11 (0.0561)		2.5 %	0.11 [0.00, 0.22]
Nathan 2006	92	89	0.22 (0.0561)		2.5 %	0.22 [0.11, 0.33]
Noonan 2006a	117	54	0.09 (0.0663)	+-	2.0 %	0.09 [-0.04, 0.22]
Noonan 2006b	111	54	0.04 (0.0663)		2.0 %	0.04 [-0.09, 0.17
Russell 1995	76	87	0.09 (0.0612)	L	2.2 %	0.09 [-0.03, 0.21]

-1 -0.5 0 0.5 I Favours ICS alone Favours LABA+ICS

Study or subgroup	LABA + ICS	ICS	L (SE)	L	Weight	l
	N	N		IV,Random,95% CI		IV,Random,95% Cl
SD 039 0714	133	131	0.13 (0.05)	+	2.8 %	0.13 [0.03, 0.23]
SD 039 0725a	131	60	0.07 (0.0255)	•	5.0 %	0.07 [0.02, 0.12]
SD 039 0725b	124	60	0.08 (0.0255)	•	5.0 %	0.08 [0.03, 0.13]
SD 039 0726a	152	72	0.16 (0.051)		2.8 %	0.16 [0.06, 0.26]
SD 039 0726b	147	72	0.13 (0.051)		2.8 %	0.13 [0.03, 0.23]
SD 039 0728	436	132	0.1 (0.0255)	•	5.0 %	0.10 [0.05, 0.15]
Shapiro 2000	81	81	0.23 (0.0714)		1.8 %	0.23 [0.09, 0.37]
van der Molen 1997	124	111	0.12 (0.051)		2.8 %	0.12 [0.02, 0.22]
Subtotal (95% CI)	4409	3508		•	74.3 %	0.12 [0.09, 0.14]
leterogeneity: Tau ² = 0.00; C	∑hi² = 46.30, df =	23 (P = 0.003	3); I ² =50%			
est for overall effect: Z = 9.3	8 (P < 0.00001)					
Mean baseline FEV1 predict	ed not reported					
SAM40008	93	93	0.15 (0.099)		1.1 %	0.15 [-0.04, 0.34]
SAS40036	170	158	0.18 (0.0459)	+	3.1 %	0.18 [0.09, 0.27]
SAS40037	158	159	0.07 (0.0459)	+	3.1 %	0.07 [-0.02, 0.16]
Subtotal (95% CI)	421	410		•	7.3 %	0.13 [0.05, 0.21]
Heterogeneity: $Tau^2 = 0.00$; C	$Chi^2 = 2.93$, df = 2	(P = 0.23); P	1 =32%			
est for overall effect: Z = 3.2	5 (P = 0.0012)					
lotal (95% CI)	5478	4306		•	100.0 %	0.11 [0.09, 0.13]
Heterogeneity: $Tau^2 = 0.00$; C	Chi ² = 65.85, df =	31 (P = 0.000	026); I ² =53%			
	17 (P < 0.00001)					
est for overall effect: $Z = 10$,						

Analysis 1.10. Comparison 1 Long-acting beta2 versus placebo: both groups receiving similar dose ICS, Outcome 10 Change in FEV1 predicted endpoint stratifying on baseline FEV1

Review: Addition of long-acting beta2-agonists to inhaled corticosteroids versus same dose inhaled corticosteroids for chronic asthma in adults and children

Comparison: 1 Long-acting beta2 versus placebo: both groups receiving similar dose ICS

Outcome: 10 Change in FEV1 predicted endpoint stratifying on baseline FEV1

Study or subgroup	% (SE)	%	Weight	9
		IV,Random,95% CI		IV,Random,95% C
I Mean baseline FEVI >= 80%	6 of predicted			
O'Byrne 2001a	5.28 (0.6786)		26.1 %	5.28 [3.95, 6.61
O'Byrne 2001b	3.23 (0.6786)	-	26.1 %	3.23 [1.90, 4.56
Verberne 1998	3.08 (1.8214)		7.5 %	3.08 [-0.49, 6.65
Meijer 1995	3.6 (3.3367)		2.5 %	3.60 [-2.94, 10.14
SM540012	5.8 (2.051)		6.1 %	5.80 [1.78, 9.82
Koopmans 2006	2.7 (1.5)		10.2 %	2.70 [-0.24, 5.64
Subtotal (95% CI)		•	78.5 %	4.06 [2.96, 5.16]
2 Mean baseline FEV1 61% to Bailey 2008	79% of predicted 3.46 (1.05)	-•-	16.7 %	
Bailey 2008	3.46 (1.05)		16.7 %	3.46 [1.40, 5.52
Subtotal (95% CI) Heterogeneity: not applicable		-	16.7 %	3.46 [1.40, 5.52]
Test for overall effect: $Z = 3.3$) (P = 0.00098)			
3 Mean baseline FEV1 predicte	ed not reported			
Teper 2005	-0.4 (2.3622)		4.8 %	-0.40 [-5.03, 4.23
Subtotal (95% CI)			4.8 %	-0.40 [-5.03, 4.23
Heterogeneity: not applicable				
Test for overall effect: Z = 0.17 Total (95% CI)	(P = 0.87)	•	100.0 %	3.73 [2.66, 4.80
	hi ² = 10.31, df = 7 (P = 0.17); l ² = 3	32%	100.0 /0	5.75 [2.00, 4.00
Test for overall effect: $Z = 6.8^{4}$				
		-10 -5 0 5 10		

Analysis 1.11. Comparison 1 Long-acting beta2 versus placebo: both groups receiving similar dose ICS, Outcome 11 FEV1 % predicted at endpoint

Review: Addition of long-acting beta2-agonists to inhaled corticosteroids versus same dose inhaled corticosteroids for chronic asthma in adults and children

Comparison: 1 Long-acting beta2 versus placebo: both groups receiving similar dose ICS

Outcome: 11 FEV1 % predicted at endpoint

Study or subgroup	LABA + ICS	+ ICS ICS alone				Mean Difference		Mean Difference
	Ν	Mean(SD)	Ν	Mean(SD)	IV,Fixed	,95% CI		IV,Fixed,95% CI
I Mean baseline FEVI >- 8	0% of predicted							
Li 1999	13	88.75 (9)	16	82.5 (15)			5.4 %	6.25 [-2.58, 15.08]
Stelmach 2007	29	98.3 (12.4)	29	97.2 (10.23)			12.2 %	1.10 [-4.75, 6.95]
Subtotal (95% CI)	42		45				17.6 %	2.67 [-2.21, 7.55]
Heterogeneity: Chi ² = 0.91	df = 1 (P = 0.3)	14); I ² =0.0%						
Test for overall effect: $Z = 1$.07 (P = 0.28)							
2 Mean baseline FEV1 61%	to 79% of predi	cted						
Pauwels 1997a	210	85.38 (16.66)	213	79.62 (16.78)			41.2 %	5.76 [2.57, 8.95]
Pauwels 1997b	215	87.4 (16.86)	214	81.35 (16.82)			41.2 %	6.05 [2.86, 9.24]
Subtotal (95% CI)	425		427			+	82.4 %	5.90 [3.65, 8.16]
Heterogeneity: Chi ² = 0.02	df = 1 (P = 0.9	0); l ² =0.0%						
Test for overall effect: $Z = 5$	5.14 (P < 0.0000	01)						
Total (95% CI)	467		472			•	100.0 %	5.34 [3.29, 7.38]
Heterogeneity: Chi ² = 2.32	df = 3 (P = 0.5	i); l ² =0.0%						
Test for overall effect: $Z = 5$	5.II (P < 0.0000	01)						
Test for subgroup difference	es: Chi ² = 1.39,	df = 1 (P = 0.24),	12 =28%					

Analysis 1.12. Comparison 1 Long-acting beta2 versus placebo: both groups receiving similar dose ICS, Outcome 12 Change in FEV1 (L or % predicted) stratifying on trial duration

Review: Addition of long-acting beta2-agonists to inhaled corticosteroids versus same dose inhaled corticosteroids for chronic asthma in adults and children

Comparison: 1 Long-acting beta2 versus placebo: both groups receiving similar dose ICS

Outcome: 12 Change in FEV1 (L or % predicted) stratifying on trial duration

Change in FEV1 (L) or (% Meijer 1995	N		ICS alone		Difference	Weight	Mean Difference
		Mean(SD)	N	Mean(SD)	IV,Random,95% CI		IV,Random,95% CI
Meijer 1995	predicted) at 6	+/- 2 weeks of th	eatment				
	20	2.9 (8.9)	20	-0.3 (11.2)	Ť	1.4 %	0.31 [-0.31, 0.93]
Molimard 2001	130	0.15 (0.42)	129	-0.01 (0.33)		6.9 %	0.42 [0.18, 0.67]
ubtotal (95% CI)	150		149		•	8.4 %	0.41 [0.18, 0.64]
leterogeneity: $Tau^2 = 0.0$; (=0.0%				
est for overall effect: $Z = 3$,					
Change in FEV1 (L) or (% Verberne 1998	predicted) at 1 60		reatment 57	1.2.(0.(1))		3.7 %	0.38 [0.01, 0.75]
		4.64 (8.83)		1.3 (8.61)			
Hultquist 2000	117	0.22 (0.54)	116	0.1 (0.54)		6.5 %	0.22 [-0.04, 0.48]
Kavaru 2000	87	0.51 (0.47)	85	0.28 (0.46)	•	5.1 %	0.49 [0.19, 0.80]
Meijer 1995	20	5.8 (11.6)	19	2.2 (9.15)	+	1.4 %	0.34 [-0.30, 0.97]
Russell 1995	76	0.12 (0.41)	87	0.03 (0.37)	T	4.9 %	0.23 [-0.08, 0.54]
Boyd 1995	47	0.19 (0.38)	49	0.15 (0.44)	+	3.2 %	0.10 [-0.30, 0.50]
Kemp 1998	252	0.42 (0.48)	254	0.15 (0.48)	•	10.6 %	0.56 [0.38, 0.74]
Langton Hewer 1995	11	0.22 (0.32)	10	-0.2 (0.16)		0.6 %	1.57 [0.56, 2.57]
Molimard 2001	130	0.17 (0.5)	129	0.06 (0.42)	•	7.0 %	0.24 [-0.01, 0.48]
van der Molen 1997	124	0.13 (0.42)	111	0.03 (0.42)	•	6.5 %	0.24 [-0.02, 0.49]
Shapiro 2000	81	0.48 (0.45)	81	0.25 (0.45)	•	4.8 %	0.51 [0.20, 0.82]
ubtotal (95% CI)	1005		998		•	54.3 %	0.36 [0.24, 0.49]
leterogeneity: Tau ² = 0.02;	Chi ² = 17.34, d	ff = 10 (P = 0.07)	, I² =42%				
est for overall effect: $Z = 5$							
Change in FEV1 (L) or (%							
Verberne 1998	60	4.36 (10.53)	57	1.28 (9.13)	r i	3.7 %	0.31 [-0.05, 0.67]
van der Molen 1997	124	0.14 (0.44)	111	0.02 (0.37)		6.5 %	0.29 [0.04, 0.55]
ubtotal (95% CI)	184		168		•	10.2 %	0.30 [0.09, 0.51]
leterogeneity: $Tau^2 = 0.0$; C	$Chi^2 = 0.01, df$	= I (P = 0.94); I ²	=0.0%				

-10 -5 0 5 10 Favours ICS alone Favours LABA + ICS

Study or subgroup	LABA + ICS		ICS alone		Std. Mean Difference	Weight	Std. Mean Difference
	N	Mean(SD)	N	Mean(SD)	IV,Random,95% CI		IV,Random,95% CI
4 Change in FEV1 (L) or (% predicted) at 5	2 +/- 4 weeks of	treatment				
O'Byrne 2001a	323	2.55 (8.63)	322	0.27 (8.61)		12.3 %	0.26 [0.11, 0.42]
O'Byrne 2001b	315	4.13 (8.52)	312	0.9 (8.48)	•	12.0 %	0.38 [0.22, 0.54]
Teper 2005	43	6.9 (13)	39	7.3 (8)	+	2.8 %	-0.04 [-0.47, 0.40]
Subtotal (95% CI)	681		673		•	27.1 %	0.28 [0.12, 0.44]
Heterogeneity: $Tau^2 = 0.0$	I; Chi ² = 3.49, df	= 2 (P = 0.17); I	2 =43%				
Test for overall effect: Z =	3.52 (P = 0.0004	4)					
Total (95% CI)	2020		1988)	100.0 %	0.34 [0.26, 0.42]
Heterogeneity: Tau ² = 0.0	I; Chi ² = 22.49, c	f = 17 (P = 0.17)); I ² =24%				
Test for overall effect: Z =	8.68 (P < 0.0000	1)					
				-10	0 -5 0 5	10	
				Favour	rs ICS alone Favours LAB	BA + ICS	

Analysis 1.13. Comparison 1 Long-acting beta2 versus placebo: both groups receiving similar dose ICS, Outcome 13 Morning PEF (L/min) at endpoint

Review: Addition of long-acting beta2-agonists to inhaled corticosteroids versus same dose inhaled corticosteroids for chronic asthma in adults and children

Comparison: 1 Long-acting beta2 versus placebo: both groups receiving similar dose ICS

Outcome: 13 Morning PEF (L/min) at endpoint

ABA + ICS		ICS alone		Mean Difference	Weight	Mea Differeno
N	Mean(SD)	N	Mean(SD)	IV,Random,95% CI	0	IV,Random,95% C
0%						
13	496 (89.8)	16	410 (99.2)		• 3.2 %	86.00 [17.11, 154.89
13		16			3.2 %	86.00 [17.11, 154.89
2						
45 (P = 0.014	ŧ)					
o 79% of pre	dicted					
205	412 (114)	206	385 (118)		16.9 %	27.00 [4.57, 49.43
75	260 (75)	88	260 (76)		16.3 %	0.0 [-23.24, 23.24
207	420 (118)	206	383 (106)		17.5 %	37.00 [15.37, 58.63
48	319.2 (97.5)	52	321.2 (121.1)		7.1 %	-2.00 [-44.94, 40.94
20	297 (70)	20	275 (77)		6.5 %	22.00 [-23.61, 67.61
555		572		+	64.3 %	19.14 [2.93, 35.34
2; Chi ² = 6.6	0, $df = 4$ (P = 0.1	6); I ² =399	6			
31 (P = 0.02	I)					
ported						
215	386.9 (101.9)	104	350.6 (99.4)		16.1 %	36.30 [12.84, 59.76
209	382.9 (93.8)	103	350.6 (99.4)		16.4 %	32.30 [9.27, 55.33
424		207		+	32.5 %	34.26 [17.83, 50.70
$hi^2 = 0.06, d$	f = 1 (P = 0.81); I	2 =0.0%				
09 (P = 0.000)044)					
992		795		+	100.0 %	26.21 [13.31, 39.10
9; Chi² = 11.	41, df = 7 (P = 0.	12); 12 =35	%			
98 (P = 0.000	0068)					
	N 13 15 (P = 0.01- 205 75 207 48 20 555 2: Chi ² = 6.6 31 (P = 0.02 ported 215 205 424 hi ² = 0.06, d 99 (P = 0.000 99 (P = 0.000) 99 (P = 0.000) 90 (P =	N Mean(SD) 7% 13 496 (89.8) 13 5 69 (00.4) 57% of prodicted 205 412 (114) 75 260 (75) 207 420 (118) 48 319.2 (97.5) 20 297 (70) 555 207 382.9 (01.9) 209 ported 215 386.9 (101.9) 209 902 382.9 (03.8) 424 ha ² = 0.06, df = 1 (P = 0.8) ; 1 1 9(P = 0.00004) 992 924 1	N Mean(SD) N 7% 13 496 (89.8) 16 13 496 (89.8) 16 15 CP 0014) 579% of predicted 205 412 (114) 206 75 260 (75) 88 207 420 (118) 206 48 319.2 (97.5) 52 20 297 (70) 20 555 572 20 3297 (70) 104 207 326 (910.9) 104 209 36.9 (101.9) 104 209 32.9 (30.8) 103 90 (P = 0.0004) 109 2005 90 (P = 0.0004) 9004 207 920 (D = 0.0004) 929 755	N Mean(SD) N Mean(SD) 78 496 (69.8) 16 410 (99.2) 13 16 5 5 205 412 (114) 206 385 (118) 75 260 (75) 88 260 (76) 207 420 (118) 206 383 (106) 48 319.2 (97.5) 52 321.2 (121.1) 20 297 (70) 20 275 (77) 55 572 2 2 16 (P = 0.016): P = 39% 35.06 (99.4) 209 209 382.9 (10.9) 104 35.06 (99.4) 209 382.9 (10.9) 104 35.06 (99.4) 209 382.9 (10.9) 104 35.06 (99.4) 209 382.9 (10.9) 104 35.06 (99.4) 209 382.9 (10.9) 104 35.06 (99.4) 209 382.9 (10.9) 104 35.06 (99.4) 200 382.9 (10.9) 104 35.06 (99.4) 201 109 109 35.06 (99.	N Mean(SD) N Mean(SD) N Mean(SD) N Mean(SD) N N Mean(SD) N N Mean(SD) Mean(SD) Mean(SD) <	N Mean(SD) N Mean(SD) INRandom.95% CI 7% 13 496 (89.8) 16 410 (99.2) 3.2% 13 16 3.2 % 3.2% 15 (P = 0.014) - - 16.9 % 75 260 (75) 88 260 (76) - 207 420 (118) 206 383 (106) - - 207 20118) 206 383 (106) - - 1.6 % 207 420 (118) 206 383 (106) - - 1.75 % 48 319.2 (97.5) 52 321.2 (121.1) 7.1 % 20 297 (70) 20 275 (77) 65.5 % 555 572 64.3 % 64.3 % 209 16.4 % 209 322.9 (93.8) 103 350.6 (99.4) - 16.4 % 424 207 32.5 % 92.5 % 92.5 % 90.00 % 92.5 % 100.0 % % 100.0 % % 100.0 % 100.0 % % 100.0 %<

Analysis 1.14. Comparison 1 Long-acting beta2 versus placebo: both groups receiving similar dose ICS, Outcome 14 Change in morning PEF (L/ min) at endpoint stratifying on baseline FEV1

Review: Addition of long-acting beta2-agonists to inhaled corticosteroids versus same dose inhaled corticosteroids for chronic asthma in adults and children

Comparison: 1 Long-acting beta2 versus placebo: both groups receiving similar dose ICS

Outcome: 14 Change in morning PEF (L/min) at endpoint stratifying on baseline FEV1

Study or subgroup	LABA+ICS N	ICS alone N	L/min (SE)	L/min IV,Random,95% CI	Weight	L/min IV,Random,95% CI
Mean baseline FEV >/=	80% of predicted					
Koopmans 2006	27	27	29 (9)		1.2 %	29.00 [11.36, 46.64]
Langton Hewer 1995	11	10	61 (24.801)		0.3 %	61.00 [12.39, 109.61]
Malone 2005	101	102	4.6 (4)		2.3 %	4.60 [-3.24, 12.44]
Morice 2008a	207	103	6.4 (3.376)		2.4 %	6.40 [-0.22, 13.02]
Morice 2008b	212	104	8.7 (3.376)		2.4 %	8.70 [2.08, 15.32]
O'Byrne 2001a	323	322	10.11 (3.4949)		2.4 %	10.11 [3.26, 16.96]
O'Byme 2001b	315	312	16.77 (3.5408)		2.4 %	16.77 [9.83, 23.71]
Pohunek 2006a	216	106	10 (3.7092)		2.4 %	10.00 [2.73, 17.27]
Pohunek 2006b	201	107	15 (3.7449)		2.4 %	15.00 [7.66, 22.34]
SD 039 0718	128	145	15.61 (3.6633)		2.4 %	15.61 [8.43, 22.79]
SMS40012	83	85	13 (6.5408)		1.7 %	13.00 [0.18, 25.82]
Verberne 1998	60	57	15.03 (7.1582)		1.6 %	15.03 [1.00, 29.06]
ubtotal (95% CI)	1884	1480		•	23.9 %	11.96 [8.68, 15.24]
leterogeneity: Tau ² = 12.7	75; Chi ² = 18.67, c	f = II (P = 0.	07); I ² =41%			
est for overall effect: $Z = $		·				
Mean baseline FEV1 61% Aubier 1999a	to 79% of predict	ted 82	18 (5.3776)		2.0 %	18.00 [7.46, 28.54]
Aubier 1999b	167	83	20 (5.3571)		2.0 %	20.00 [9.50, 30.50]
Bailey 2008	239	236	20 (5.3571)		2.0 %	20.00 [9.50, 30.50]
Bailey 2008 Boyd 1995	48	52	26 (9.1837)		1.2 %	
,			. ,			26.00 [8.00, 44.00]
Buhl 2003a	176	86	22.8 (10.1122)		1.1 %	22.80 [2.98, 42.62]
Buhl 2003b	176	85	27.4 (10.1122)		1.1 %	27.40 [7.58, 47.22]
Green 2006	39	39	17.2 (6.377551)		1.7 %	17.20 [4.70, 29.70]
Hultquist 2000	117	116	17.61 (8.3138)		1.3 %	17.61 [1.32, 33.90]
enkins 2006a	222	57	32.9 (6.1939)		1.8 %	32.90 [20.76, 45.04]

-50 -25 0 25 50 Favours ICS Favours LABA+ICS

L/mir IV,Random,95% C	Weight	L/min IV.Random,95% Cl	L/min (SE)	ICS alone N	LABA+ICS N	Study or subgroup
31.70 [18.58, 44.82	1.7 %		31.7 (6.6939)	58	114	Jenkins 2006b
35.20 [21.70, 48.70]	1.6 %		35.2 (6.8878)	85	87	Kavaru 2000
33.00 [23.28, 42.72]	2.1 %		33 (4.9592)	254	252	Kemp 1998
17.90 [10.54, 25.26]	2.4 %		17.9 (3.7551)	207	202	Kuna 2006
21.20 [12.76, 29.64]	2.2 %		21.2 (4.3061)	129	130	Molimard 2001
35.70 [22.10, 49.30]	1.6 %		35.7 (6.9388)	91	94	Nathan 2006
26.00 [12.37, 39.63]	1.6 %		26 (6.9541)	54	121	Noonan 2006a
19.00 [5.30, 32.70]	1.6 %		19 (6.9898)	55	113	Noonan 2006b
19.00 [9.58, 28.42	2.1 %		19 (4.8061)	331	332	Price 2002
8.50 [-3.63, 20.63]	1.8 %		8.5 (6.1888)	88	75	Russell 1995
32.00 [13.18, 50.82]	1.1 %		32 (9.602)	124	115	SD 039 0349
4.80 [-4.00, 13.60	2.2 %		4.8 (4.49)	131	133	SD 039 0714
12.25 [5.67, 18.83	2.5 %		12.25 (3.3571)	84	183	SD 039 0725a
8.95 [1.87, 16.03	2.4 %		8.95 (3.6122)	84	168	SD 039 0725b
33.00 [14.21, 51.79	1.1 %		33 (9.5867)	72	152	SD 039 0726a
28.00 [9.21, 46.79	1.1 %		28 (9.5867)	72	147	SD 039 0726b
34.69 [27.52, 41.86	2.4 %		34.69 (3.6582)	132	441	SD 039 0728
38.30 [24.10, 52.50	1.5 %		38.3 (7.2449)	81	81	Shapiro 2000
12.00 [5.39, 18.61	2.4 %		12 (3.3724)	138	148	Tal 2002
32.40 [23.17, 41.63	2.1 %		32.4 (4.7092)	113	125	van der Molen 1997
23.00 [13.20, 32.80	2.0 %		23 (5)	100	99	Weiler 2005
35.50 [22.80, 48.20	1.7 %		35.5 (6.4796)	62	123	Zetterstrom 2001a
31.80 [19.01, 44.59	1.7 %		31.8 (6.5255)	62	115	Zetterstrom 2001b
23.41 [19.84, 26.98	57.0 %	•	,	3443	4905	Subtotal (95% CI)
	,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,		0001); I ² =70%	df = 31 (P<0.0	3; Chi ² = 102.74, 12.85 (P < 0.0000	Heterogeneity: Tau ² = 68.1 Fest for overall effect: Z = 1 8 Mean baseline FEV1 not r
24.30 [15.04, 33.56	2.1 %		24.3 (4.7245)	160	171	Ind 2003
23.30 [12.44, 34.16	1.9 %		23.3 (5.54)	93	93	SAM40008
5.70 [-2.62, 14.02	2.2 %		5.7 (4.244)	175	176	SAM40012
12.90 [2.46, 23.34	2.0 %		12.9 (5.3265)	90	102	SAS40024
21.20 [11.77, 30.63	2.1 %		21.2 (4.8112)	158	169	SAS40036
21.20 [11.77, 30.03				159	158	SAS40037

Study or subgroup	LABA+ICS	ICS alone	L/min (SE)	Um	in V	Veight	L/min
	N	Ν		IV,Random,9	5% CI		IV,Random,95% CI
SD 037 0344a	215	104	14.6 (4.2755)	-	_	2.2 %	14.60 [6.22, 22.98]
SD 037 0344b	219	103	12.8 (4.2959)		-	2.2 %	12.80 [4.38, 21.22]
SFCF4026	154	154	20.1 (3.9235)	-		2.3 %	20.10 [12.41, 27.79]
Subtotal (95% CI)	1457	1196			• 19	.2 %	17.09 [12.99, 21.18]
Heterogeneity: Tau ² = 17.8	30; Chi ² = 14.72, d	f = 8 (P = 0.06)	i); I ² =46%				
Test for overall effect: Z =	8.18 (P < 0.00001)					
Total (95% CI)	8246	6119			 100 	0 %	19.64 [17.08, 22.20]
Heterogeneity: Tau ² = 58.3	35; Chi ² = 177.33,	df = 52 (P<0.0	0001); 12 =71%				
Test for overall effect: Z =	15.03 (P < 0.0000	1)					
			4	50 -25 0	25 50		
				Favours ICS F	avours LABA+ICS		

Analysis 1.15. Comparison 1 Long-acting beta2 versus placebo: both groups receiving similar dose ICS, Outcome 15 Evening PEF (L/min) at endpoint

Review: Addition of long-acting beta2-agonists to inhaled corticosteroids versus same dose inhaled corticosteroids for chronic asthma in adults and children

Comparison: 1 Long-acting beta2 versus placebo: both groups receiving similar dose ICS

Outcome: 15 Evening PEF (L/min) at endpoint

Study or subgroup	LABA + ICS N	Mean(SD)	ICS alone N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Mean Difference IV,Fixed,95% CI
I Mean baseline FEVI	61% to 79% of pred	licted				
Boyd 1995	47	330.3 (97.7)	52	343.7 (114.7)		-13.40 [-55.26, 28.46]
					-100 -50 0 50 10	00
					Favours ICS alone Favours LAB	A + ICS

Analysis 1.16. Comparison 1 Long-acting beta2 versus placebo: both groups receiving similar dose ICS, Outcome 16 Change in evening PEF at endpoint

Review: Addition of long-acting beta2-agonists to inhaled corticosteroids versus same dose inhaled corticosteroids for chronic asthma in adults and children

Comparison: 1 Long-acting beta2 versus placebo: both groups receiving similar dose ICS

Outcome: 16 Change in evening PEF at endpoint

Study or subgroup	LABA+ICS N	ICS alone N	L/min (SE)	L/min IV,Random,95% CI	Weight	L/mir IV,Random,95% C
1 Mean baseline FEV1 > /=						
Koopmans 2006	27	27	36 (9)		1.8 %	36.00 [18.36, 53.64
Langton Hewer 1995		10	90 (25.06)		0.4 %	90.00 [40.88, 139.12
Malone 2005	101	102	6.4 (3.69)		3.7 %	6.40 [-0.83, 13.63
Morice 2008a	212	104	8.7 (3.376)	+	3.8 %	8.70 [2.08, 15.32
Morice 2008b	207	103	6.4 (3.376)		3.8 %	6.40 [-0.22, 13.02
SD 039 0718	128	145	15.61 (4.6327)		3.3 %	15.61 [6.53, 24.69
SM540012	83	85	8.6 (6.4949)		2.6 %	8.60 [-4.13, 21.33
Subtotal (95% CI)	769	576		•	19.5 %	13.37 [5.98, 20.76
2 Mean baseline FEV1 61%	to 79% of predict	ted				
Test for overall effect: Z = 2						
Aubier 1999a	171	82	14 (5.3214)		3.0 %	14.00 [3.57, 24.43
Aubier 1999b	167	83	20 (5.3571)		3.0 %	20.00 [9.50, 30.50
Bailey 2008	239	236	13.6 (5.1684)		3.1 %	13.60 [3.47, 23.73
Buhl 2003a	176	86	23.6 (3.949)	+	3.6 %	23.60 [15.86, 31.34
Buhl 2003b	176	85	16.6 (3.949)	+	3.6 %	16.60 [8.86, 24.34
Hultquist 2000	117	116	12.63 (8.1684)		2.1 %	12.63 [-3.38, 28.64
Ind 2003	171	160	16.2 (5.3469)	-+-	3.0 %	16.20 [5.72, 26.68
Jenkins 2006a	222	57	30.9 (5.7908)		2.9 %	30.90 [19.55, 42.25
Jenkins 2006a Jenkins 2006b	222	57 58	30.9 (5.7908) 30.8 (6.2908)		2.9 % 2.7 %	-
,				+ + +		30.80 [18.47, 43.13
Jenkins 2006b	114	58	30.8 (6.2908)		2.7 %	30.90 [19.55, 42.25 30.80 [18.47, 43.13 17.00 [7.42, 26.58 11.30 [3.98, 18.62
Jenkins 2006b Kavaru 2000	87	58	30.8 (6.2908) 17 (4.8878)		2.7 % 3.2 %	30.80 [18.47, 43.13 17.00 [7.42, 26.58 11.30 [3.98, 18.62
Jenkins 2006b Kavaru 2000 Kuna 2006	114 87 202	58 85 207	30.8 (6.2908) 17 (4.8878) 11.3 (3.7347)		2.7 % 3.2 % 3.7 %	30.80 [18.47, 43.13 17.00 [7.42, 26.58

LABA+ICS	ICS alone	L/min (SE)	L/min	Weight	L/min
					IV,Random,95% CI
332	331	15.8 (4.5816)	-	3.3 %	15.80 [6.82, 24.78]
183	84	12.53 (4.1888)	+	3.5 %	12.53 [4.32, 20.74]
168	84	6.29 (4.2296)		3.5 %	6.29 [-2.00, 14.58]
152	72	33.02 (4.6684)	+	3.3 %	33.02 [23.87, 42.17]
147	72	17.6 (5.0153)		3.2 %	17.60 [7.77, 27.43]
81	81	37.5 (6.8776)		2.5 %	37.50 [24.02, 50.98]
148	138	11.7 (3.2755)	-+	3.9 %	11.70 [5.28, 18.12]
123	62	28.5 (5.8622)		2.8 %	28.50 [17.01, 39.99]
115	62	26 (5.898)		2.8 %	26.00 [14.44, 37.56]
3617	2441		•	70.3 %	19.70 [16.36, 23.03]
	· · ·	19.6 (5.64)	-	2.9 %	19.60 [8.55, 30.65]
176	175	5 (4.38)	+	3.4 %	5.00 [-3.58, 13.58]
154	154	17.43 (3.4286)	+	3.8 %	17.43 [10.71, 24.15]
	422 = 2 (P = 0.04)	; I ² =68%	•	10.2 %	13.85 [5.05, 22.64]
4809	3439		•	100.0 %	17.89 [14.82, 20.95]
	$\begin{tabular}{ c c c c } \hline N \\ \hline & 332 \\ \hline & 332 \\ \hline & 183 \\ \hline & 168 \\ \hline & 152 \\ \hline & 147 \\ \hline & 81 \\ \hline & 148 \\ \hline & 123 \\ \hline & 115 \\ \hline & 3617 $	N N 332 331 183 84 168 84 152 72 147 72 81 81 148 138 123 62 115 62 3617 2441 5h ² 55.88, df = 22 (P = 0.0 93 93 176 175 154 154 423 422 5h ² 6.21, df = 2 (P = 0.04) (P = 0.0020) 4809 3439	N N 332 331 15.8 (45816) 183 84 1253 (4.1888) 168 84 6.29 (42296) 152 72 3302 (46684) 147 72 17.6 (50153) 81 81 375 (6.8776) 148 138 11.7 (32755) 123 62 28.5 (5.8622) 115 62 26 (5.898) 3617 2441 2h ² 5.688, df = 22 (P = 0.00006); P = 61% 8 (P = 0.00001) 93 19.6 (5.64) 176 175 5 (438) 154 154 17.43 (3.4286) 423 422 2h ² 6.21, df = 2 (P = 0.04); P = 68% (P = 0.020)	N N IV/Random/95% CI 332 331 15.8 (4.5816) 183 84 12.3 (4.1886) 168 84 6.29 (4.2296) 152 72 33.02 (4.664) 147 72 17.6 (5.0153) 148 138 11.7 (3.2755) 148 138 11.7 (3.2755) 115 6.22 2.6 (5.898) 3617 2441 176 175 5 (4.38) 176 175 5 (4.38) 154 154 17.43 (3.4286) 154 154 17.43 (3.4286) 154 154 17.43 (3.4286) 154 154 17.49 (3.4286) 154 154 17.49 (3.4286) 154 154 17.49 (3.4286) 154 154 <td>N N IVRandom/95% CI 332 331 15.8 (4.5816) 33.3 % 183 84 12.53 (4.1888) 35.5 % 168 84 6.29 (4.2286) 35.5 % 152 7.2 33.02 (4.6684) 33.3 % 147 7.2 17.6 (5.0153) 32.2 % 81 81 37.5 (6.8776) 2.5 % 148 138 11.7 (3.2755) 3.9 % 123 62 2.85 (5.8622) 2.8 % 3617 2441 2.8 % - 115 6.2 2.6 (5.898) 2.8 % 3617 2441 2.9 % - 176 175 5 (4.38) 2.9 % 176 175 5 (4.38) 3.8 % 154 154 17.4 (3.4286) +- 3.8 % 154 154 17.4 (3.2 %</td>	N N IVRandom/95% CI 332 331 15.8 (4.5816) 33.3 % 183 84 12.53 (4.1888) 35.5 % 168 84 6.29 (4.2286) 35.5 % 152 7.2 33.02 (4.6684) 33.3 % 147 7.2 17.6 (5.0153) 32.2 % 81 81 37.5 (6.8776) 2.5 % 148 138 11.7 (3.2755) 3.9 % 123 62 2.85 (5.8622) 2.8 % 3617 2441 2.8 % - 115 6.2 2.6 (5.898) 2.8 % 3617 2441 2.9 % - 176 175 5 (4.38) 2.9 % 176 175 5 (4.38) 3.8 % 154 154 17.4 (3.4286) +- 3.8 % 154 154 17.4 (3.2 %

Analysis 1.17. Comparison 1 Long-acting beta2 versus placebo: both groups receiving similar dose ICS, Outcome 17 Change in PEF variability at endpoint

Review: Addition of long-acting beta2-agonists to inhaled corticosteroids versus same dose inhaled corticosteroids for chronic asthma in adults and children

Comparison: 1 Long-acting beta2 versus placebo: both groups receiving similar dose ICS

Outcome: 17 Change in PEF variability at endpoint

Study or subgroup	LABA + ICS		ICS alone		Mean Difference	Mea Differeno
	N	Mean(SD)	Ν	Mean(SD)	IV,Fixed,95% CI	IV,Fixed,95% C
I Mean baseline FEVI	61% to 79% of predi	cted				
Russell 1995	75	-4.64 (9.01)	88	-3.35 (7.15)	•	-1.29 [-3.82, 1.24
					-100 -50 0 50	100
					-100 -50 0 50 Favours ICS alone Favour	

Analysis 1.18. Comparison 1 Long-acting beta2 versus placebo: both groups receiving similar dose ICS, Outcome 18 Change in 24-hour symptom score at endpoint

Review: Addition of long-acting beta2-agonists to inhaled corticosteroids versus same dose inhaled corticosteroids for chronic asthma in adults and children

Comparison: 1 Long-acting beta2 versus placebo: both groups receiving similar dose ICS

Outcome: 18 Change in 24-hour symptom score at endpoint

Study or subgroup	LABA + ICS		ICS alone		Std. Mean Difference	Weight	Std. Mean Difference
	N	Mean(SD)	N	Mean(SD)	IV,Fixed,95% CI		IV,Fixed,95% CI
I Mean baseline FEVI 6	1% to 79% of pre	edicted					
Bailey 2008	239	-0.26(1)	236	-0.23 (0.9)	-	36.3 %	-0.03 [-0.21, 0.15]
Jenkins 2006a	222	-0.62 (0.8)	57	-0.36 (0.8)		13.7 %	-0.32 [-0.62, -0.03]
Jenkins 2006b	4	-0.66 (0.81)	58	-0.36 (0.81)		11.6 %	-0.37 [-0.69, -0.05]
Nathan 2006	94	-0.5 (1.07)	91	-0.2 (0.86)		13.9 %	-0.31 [-0.60, -0.02]
Zetterstrom 2001a	123	-0.52 (0.78)	62	-0.2 (0.78)		12.4 %	-0.41 [-0.72, -0.10]
Zetterstrom 2001b	115	-0.44 (0.75)	62	-0.2 (0.78)		12.2 %	-0.31 [-0.62, 0.00]
Total (95% CI)	907		566		+	100.0 %	-0.23 [-0.34, -0.12]
Heterogeneity: Chi ² = 7	7.65, df = 5 (P =	0.18); 12 =35%					
Test for overall effect: Z	= 4.16 (P = 0.00	00031)					
Test for subgroup differe	ences: Not applica	able					
					-0.5 0 0.5	í.	
				Favours	ICS + LABA Favours ICS	alone	

Analysis 1.19. Comparison 1 Long-acting beta2 versus placebo: both groups receiving similar dose ICS, Outcome 19 Change in daytime symptom score at endpoint

Review: Addition of long-acting beta2-agonists to inhaled corticosteroids versus same dose inhaled corticosteroids for chronic asthma in adults and children

Comparison: 1 Long-acting beta2 versus placebo: both groups receiving similar dose ICS

Outcome: 19 Change in daytime symptom score at endpoint

eterogeneity: not applicable st for overall effect. Z = 0.97 (P = 0.33) Mean baseline EEVI 61% to 79% of predicted Kavaru 2000 87 -0.7 (1.03) 85 -0.2 (0.83) → 9.8 % -0.53 [-0.84, -0.23 Noonan 2006b 112 -0.35 (0.48) 55 -0.19 (0.48) → 8.6 % -0.33 [-0.64, -0.01 Noonan 2006a 121 -0.32 (0.48) 54 -0.19 (0.48) → 8.7 % -0.27 [-0.59, 0.05 Price 2002 332 -0.5 (0.6) 331 -0.35 (0.61) → Boyd 1995 53 -0.21 (0.41) 62 -0.12 (0.32) → 6.7 % -0.25 [-0.40, -0.09 Boyd 1995 53 -0.21 (0.41) 62 -0.12 (0.32) → Molimard 2001 130 -0.3 (0.48) 129 -0.1 (0.43) → Shapiro 2000 81 -0.8 (1.08) 81 -0.4 (0.81) → 9.3 % -0.42 [-0.73, -0.11] ubtotal (05% CI) 91.6 797 → eterogeneity: Chi ² = 4.17, df = 6 (P = 0.65); h ² = 0.0% st for overall effect. Z = 6.7 (P < 0.00001)	Study or subgroup	LABA + ICS		ICS alone		Std. Mean Difference	Weight	Std Mear Difference
Koopmans 2006 27 $0.1 (0.37)$ 27 $0 (0.37)$ $32.\%$ $0.227 [-0.80, 0.27]$ ubtocal (95% CI) 27 27 27 $32.\%$ $0.27 [-0.80, 0.27]$ ubtocal (95% CI) 27 27 $32.\%$ $0.27 [-0.80, 0.27]$ dem baseline FV1 (% to 7% of predicted $32.\%$ $-0.27 [-0.80, 0.27]$ Kavaru 2000 87 $-0.7 (10.3)$ 85 $-0.2 (0.83)$ Noonan 2006b 112 $0.35 (0.48)$ 55 $-0.19 (0.48)$ $46.\%$ $-0.33 [-0.64, -0.01]$ Noonan 2006a 121 $0.32 (0.48)$ 54 $-0.19 (0.48)$ $46.\%$ $-0.33 [-0.64, -0.02]$ Boyd 1995 53 $0.21 (0.41)$ 62 $0.12 (0.32)$ $48.\%$ $-0.25 [-0.40, -0.09]$ Boyd 1995 53 $0.21 (0.41)$ 62 $0.12 (0.32)$ $67.\%$ $0.25 [-0.46, -0.01]$ Molmard 2001 130 $0.3 (0.48)$ 129 $-0.1 (0.43)$ 41.9% $0.33 [-0.44, -0.23]$ Shapico 2000 81 $0.8 (1.08)$ 81 $0.4 (0.81)$ $93.\%$ $-0.33 [-0.42, -0.23]$ 9		N	Mean(SD)	N	Mean(SD)	IV,Fixed,95% CI		IV,Fixed,95% C
ubtoral (95% CI) 27 27 3.2 % -0.27 [-0.80, 0.27] eterogeneity: not applicable st for overall effect: $Z = 0.97$ ($P = 0.33$)	Mean baseline FEVI >/= 8	0%						
$\begin{array}{c} \text{tetrogenety, not applicable} \\ \text{st for overall effect. } Z = 0.97 (P = 0.33) \\ \text{Mean baseline FEV1 61% to 79% of predicted} \\ \text{Kavaru 2000} & 87 & -0.7 (1.03) & 85 & -0.2 (0.83) \\ \text{Noonan 2006b} & 112 & -0.35 (0.48) & 55 & -0.19 (0.48) \\ \text{Noonan 2006a} & 121 & -0.32 (0.48) & 54 & -0.19 (0.48) \\ \text{Price 2002} & 332 & -0.5 (0.6) & 331 & -0.35 (0.61) \\ \text{Price 2002} & 332 & -0.5 (0.6) & 331 & -0.35 (0.61) \\ \text{Boyd 1995} & 53 & -0.21 (0.41) & 62 & -0.12 (0.32) \\ \text{Molimard 2001} & 130 & -0.3 (0.48) & 129 & -0.1 (0.43) \\ \text{Shapiro 2000} & 81 & -0.8 (1.08) & 81 & -0.4 (0.81) \\ \text{st for overall effect. } Z = 6.71 (P < 0.00001) \\ \text{Stafi (95% CI)} & 946 & -0.75; P = 0.00\% \\ \text{st for overall effect. } Z = 6.78 (P < 0.00001) \\ \end{array}$	Koopmans 2006	27	-0.1 (0.37)	27	0 (0.37)		3.2 %	-0.27 [-0.80, 0.27
st for overall effect Z = 097 (P = 0.3) Man baseline FEV1 61% to 79% of predicted Kavaru 2000 87 $-0.71(0.3)$ 85 -0.2 (0.83) → 9.8 % -0.53 [$-0.64, -0.02$ Noonan 2006b 112 -0.35 (0.48) 55 -0.19 (0.48) & 86 % -0.33 [$-0.66, -0.01$ Noonan 2006a 121 -0.32 (0.48) 54 -0.19 (0.48) & 86 % -0.227 [$-0.59, 0.05$ Price 2002 332 -0.52 (0.6) 331 -0.35 (0.61) \bullet Boyd 1995 53 -0.21 (0.41) 62 -0.12 (0.32) \bullet Molimard 2001 130 -0.3 (0.48) 129 -0.1 (0.43) \bullet Shapiro 2000 81 -0.38 (1.08) 81 -0.4 (0.81) \bullet Shapiro 2000 81 -0.38 (1.68) 81 -0.4 (0.81) \bullet Shapiro 2000 81 -0.35 ($F = -0.055$); $F = -0.05$ est for overall effect; Z = 6.71 (P < -0.055); $F = -0.05$ est for overall effect; Z = 6.78 (P < -0.055); $F = -0.05$ est for overall effect; Z = 6.78 (P < -0.055); $F = -0.05$	Subtotal (95% CI)	27		27			3.2 %	-0.27 [-0.80, 0.27]
Mean baseline FEV1 61% to 79% of predicted Kawaru 2000 87 $0.7 (1.03)$ 85 $-0.2 (0.83)$ 98.% $-0.53 [-0.84, 0.23]$ Noonan 2006b 112 $0.35 (0.48)$ 55 $0.19 (0.48)$ 86.% $-0.33 [-0.66, -0.01]$ Noonan 2006a 121 $0.32 (0.48)$ 54 $0.19 (0.48)$ 86.% $-0.33 [-0.66, -0.01]$ Noonan 2006a 121 $0.32 (0.48)$ 54 $0.19 (0.48)$ 87.% $-0.27 [-0.59, 0.05]$ Price 2002 332 $-0.5 (0.6)$ 331 $-0.35 (0.61)$ 4 88.8% $-0.25 [-0.40, -0.09]$ Boyd 1995 53 $0.21 (0.41)$ 62 $-0.12 (0.32)$ 6 67.% $-0.25 [-0.40, -0.19]$ Molmard 2001 130 $-0.3 (0.48)$ 129 $-0.1 (0.43)$ 4 9.3% $-0.42 [-0.73, -0.11]$ uboral (055% CI) 916 797 96.8.% 9.3.3 [-0.42, -0.23 eterogeneity: Chi ² = 41.7, df = 6 (P = 0.55); P = 0.0% 82.4 4 96.8.% -0.33 [-0.42, -0.23 st for overall effect: Z = 6.71 (P < 0.00001)	leterogeneity: not applicable	2						
Kavaru 2000 87 -0.7 (1.03) 85 -0.2 (0.83) \rightarrow 9.8% -0.53 [$-0.84, -0.23$ Noonan 2006b 112 -0.35 (0.48) 55 -0.19 (0.48) \rightarrow 8.6% -0.33 [$-0.64, -0.23$ Noonan 2006a 121 -0.32 (0.48) 54 -0.19 (0.48) \rightarrow 8.6% -0.33 [$-0.64, -0.01$ Noonan 2006a 121 -0.32 (0.48) 54 -0.19 (0.48) \rightarrow 8.7% -0.27 [$-0.59, 0.05$ Price 2002 332 -0.5 (0.6) 331 -0.35 (0.61) \rightarrow 8.7% -0.27 [$-0.59, 0.05$ Boyd 1995 53 0.21 (0.41) 62 -0.12 (0.32) \rightarrow 6.7% -0.25 [$-0.61, 0.12$ Molimard 2001 130 -0.3 (0.48) 129 -0.1 (0.43) \rightarrow 14.9% -0.44 [$-0.68, -0.19$ Shapiro 2000 81 -0.8 (1.08) 81 -0.4 (0.81) \rightarrow 9.3% -0.33 [$-0.42, -0.23$] eterogeneity. Chr ² = 4.17, df = 6 (P = 0.65); P = 0.00\% st for overall effect Z = 6.71 (P < 0.00001)	Test for overall effect: $Z = 0$.	97 (P = 0.33)						
Noonan 2006b 112 -0.35 (0.48) 55 -0.19 (0.48) -0.31 (-0.46, -0.01) Noonan 2006a 121 -0.32 (0.48) 54 -0.19 (0.48) -0.37 (-0.59, 0.05) Price 2002 332 -0.5 (0.6) 331 -0.35 (0.61) -0.88% -0.225 (-0.40, -0.09) Boyd 1995 53 -0.21 (0.41) 62 -0.12 (0.32) -67% -0.255 (-0.40, -0.09) Shapiro 2000 81 -0.81 (0.81) -9 -0.44 (-0.68, -0.19) Shapiro 2000 81 -0.40 (0.81) -9 -9.3% -0.42 (-0.73 , -0.11) ubtotal (95% C1) 916 797 -96.8% -0.33 (-0.43 , -0.23) est for overall effect: $Z = 671$ ($P < -0.05\%$): $P = -0.0\%$ $=42.47 - 7.23$ $=0.33$ (-0.42 , -0.23) est for overall effect: $Z = 6.78$ ($P < = 0.55\%$): $P = -0.0\%$ $=0.33$ (-0.42 , -0.23) $=0.33$ (-0.42 , -0.23) est for overall effect: $Z = 6.71$ ($P < = 0.05\%$): $P = 0.0\%$ $=0.33$ (-0.42 , -0.23) $=0.33$ (-0.42 , -0.23) est for overall effect: $Z = 6.78$ ($P < = 0.05\%$): $P = 0.0\%$ $=0.33$ (-0.42 , -0.23) $=0.33$ (-0.42 , -0.23)	Mean baseline FEVI 61% t	o 79% of pred	icted					
Noonan 2006a 121 0.32 (0.48) 54 -0.19 (0.48) $= 0.27$ $= 0.27$ [-0.59, 0.05] Price 2002 332 -0.5 (0.6) 331 -0.35 (0.61) $= 0.27$ [-0.59, 0.05] Boyd 1995 53 -0.21 (0.41) 62 -0.12 (0.32) $= 67\%$ -0.225 [-0.40, -0.09] Molmard 2001 130 -0.3 (0.48) 129 -0.1 (0.43) $= 14.9\%$ -0.44 [-0.68, 0.19] Shapiro 2000 81 -0.4 (0.81) $= 0.44$ (0.81) $= 93.\%$ $= 0.422$ [-0.73, -0.11] ubtotal (95% C1) 916 797 $= 96.8\%$ $= 0.33$ [-0.42, -0.23] et or overall effect: $Z = 6.71$ (P < 0.00001)	Kavaru 2000	87	-0.7 (1.03)	85	-0.2 (0.83)		9.8 %	-0.53 [-0.84, -0.23
Price 2002 332 -0.5 (0.6) 331 -0.35 (0.61) -0.25 [-0.40 , -0.09 Boyd 1995 53 -0.21 (0.41) 62 -0.12 (0.32) 67% -0.25 [-0.40 , -0.09 Molimard 2001 130 -0.3 (0.48) 129 -0.11 (0.43) -0.41 [-0.68 , -0.19 Shapiro 2000 81 -0.4 (0.81) -0.41 [-0.68 , -0.19 9.3% -0.42 [-0.73 , -0.11 ubtotal (95% CI) 916 797 -0.33 [-0.43 , -0.23] -0.33 [-0.43 , -0.23] etrogeneity: $Ch^2 = 4.17$, $df = 6$ ($P = 0.055$; $P = 0.00\%$ 824 -0.33 [-0.42 , -0.23] st for overall effect: $Z = 6.71$ ($P < 0.00001$) 824 -0.33 [-0.42 , -0.23] st for overall effect: $Z = 6.78$ ($P < = 0.57$; $P = 0.00\%$ -0.33 [-0.42 , -0.23] st for overall effect: $Z = 6.78$ ($P < = 0.57$; $P = 0.00\%$ -0.33 [-0.42 , -0.23]	Noonan 2006b	112	-0.35 (0.48)	55	-0.19 (0.48)		8.6 %	-0.33 [-0.66, -0.01
Boyd 1995 53 -0.21 (0.41) 62 -0.12 (0.32) 6.7 % -0.25 [-0.61, 0.12 Molimard 2001 130 -0.3 (0.48) 129 -0.1 (0.43) - 14.9 % -0.44 [-0.68, -0.19 Shapiro 2000 81 -0.4 (0.81) - 9.3 % -0.42 [-0.73, -0.11 ubtotal (95% CI) 916 797 + 96.8 % -0.33 [-0.43, -0.23 st for ownall effect: Z = 671 (P < 0.00001)	Noonan 2006a	121	-0.32 (0.48)	54	-0.19 (0.48)		8.7 %	-0.27 [-0.59, 0.05
$ \begin{array}{c c c c c c c c c c c c c c c c c c c $	Price 2002	332	-0.5 (0.6)	331	-0.35 (0.61)		38.8 %	-0.25 [-0.40, -0.09
Shapiro 2000 81 -0.6 (1.08) 81 -0.4 (0.81) 9.3 % -0.42 [-0.73, -0.11 ubtotal (95% CI) 916 797 96.8 % -0.33 [-0.43, -0.23] eterogeneity: Ch ² = 4.17, df = 6 (P = 0.65); P = 0.0% st for overall effect Z = 671 (P < 0.0001)	Boyd 1995	53	-0.21 (0.41)	62	-0.12 (0.32)		6.7 %	-0.25 [-0.61, 0.12
ubtotal (95% CI) 916 797 96.8 % -0.33 [-0.43, -0.23] eterogenety: Ch ² = 4.17, df = 6 (P = 0.65); P = 0.0% st for overall effect Z = 671 (P < 0.0001)	Molimard 2001	130	-0.3 (0.48)	129	-0.1 (0.43)		14.9 %	-0.44 [-0.68, -0.19
$\begin{array}{c} \text{detrogeneity: Ch}^2 = 4.17, \text{ df} = 6 \ (P = 0.65); \ P = 0.0\% \\ \text{st for overall effect: } Z = 6.71 \ (P < 0.00001) \\ \text{otal (95% CI)} & 943 \\ \text{eterogeneity: Ch}^2 = 4.22, \ \text{df} = 7 \ (P = 0.75); \ P = 0.0\% \\ \text{st for overall effect: } Z = 6.78 \ (P < 0.00001) \\ \text{st for overall effect: } Z = 6.78 \ (P < 0.00001) \\ \end{array}$	Shapiro 2000	81	-0.8 (1.08)	81	-0.4 (0.81)		9.3 %	-0.42 [-0.73, -0.11
st for overall effect: Z = 6/1 (P < 0.00001) tatl (95% CI) 943 824 ◆ teterogeneity: Ch ² = 4.22, df = 7 (P = 0.75); P = 0.0% st for overall effect: Z = 6.78 (P < 0.00001)	Subtotal (95% CI)	916		797		•	96.8 %	-0.33 [-0.43, -0.23]
Statil (95% CI) 943 824 100.0 % -0.33 [-0.42, -0.23] eterogeneity: Chi ² = 4.22, df = 7 (P = 0.75); P = 0.0% st for overall effect; Z = 6.78 (P < 0.00001)	Heterogeneity: Chi ² = 4.17,	df = 6 (P = 0.)	65); I ² =0.0%					
eterogeneity. Ch² = 4.22, df = 7 (P = 0.75); P =0.0% est for overall effect; Z = 6.78 (P < 0.00001)			01)					
est for overall effect: $Z = 6.78$ (P < 0.00001)	Total (95% CI)			824		•	100.0 %	-0.33 [-0.42, -0.23
	0 ,							
est for subgroup differences: $Chi^2 = 0.05$, $df = 1$ (P = 0.82), $l^2 = 0.0\%$,					
	fest for subgroup differences	:: Chi² = 0.05,	df = 1 (P = 0.82)	!), ⊮ =0.0%				
						-0.5 0 0.5	1	

Analysis 1.20. Comparison 1 Long-acting beta2 versus placebo: both groups receiving similar dose ICS, Outcome 20 Change in night-time symptom score at endpoint

Review: Addition of long-acting beta2-agonists to inhaled corticosteroids versus same dose inhaled corticosteroids for chronic asthma in adults and children

Comparison: 1 Long-acting beta2 versus placebo: both groups receiving similar dose ICS

Outcome: 20 Change in night-time symptom score at endpoint

ABA + ICS		ICS alone		Std. Mean Difference	Weight	Std Mear Difference
Ν	Mean(SD)	Ν	Mean(SD)	IV,Fixed,95% CI		IV,Fixed,95% C
%						
27	-0.2 (0.37)	27	0 (0.37) +		4.1 %	-0.53 [-1.08, 0.01
27		27	-		4.1 %	-0.53 [-1.08, 0.01]
121	-0.22 (0.48)	54	-0.1 (0.48)		11.7 %	-0.25 [-0.57, 0.07
113	-0.27 (0.48)	55	-0.1 (0.48)		11.5 %	-0.35 [-0.68, -0.03
332	-0.38 (0.66)	331	-0.28 (0.65)	-=-	52.3 %	-0.15 [-0.30, 0.00
130	-0.1 (0.43)	129	0 (0.35)		20.3 %	-0.25 [-0.50, -0.01
696		569		•	95.9 %	-0.21 [-0.32, -0.10
f = 3 (P = 0.	59); l ² =0.0%					
·	26)					
		596		•	100.0 %	-0.22 [-0.33, -0.11
	<i>,</i> .					
Chi ² = 1.30,	df = 1 (P = 0.25)	, I² =23%				
	N 27 27 27 2 (P = 0.055) % of predicte 121 113 332 130 696 f = 3 (P = 0.0 5 (P = 0.000) 723 f = 4 (P = 0.000) 723 f = 4 (P = 0.000)	N Mean(SD) % 27 -0.2 (0.37) 27 -202 (0.37) 27 27 -22 (0.48) 113 113 -0.27 (0.48) 332 332 -0.38 (0.66) 330 300 -0.1 (0.43) 6566 f = 3 (P = 0.69); P = 0.07% 5 (P = 0.00%; P = 0.07% 7 (P = 0.000; P = 0.00%; 7 (P = 0.00%; 7 (P = 0.00%); P = 0.00% 7 (P = 0.000072)	N Mean(SD) N % 27 -0.2 (0.37) 27 27 27 27 27 27 27 27 27 27 27 27 27 27 27 27 27 27 27 27 27 27 27 27 27 27 27 27 27 27 27 27 27 27 27 27 27 27 27 27 27 27 27 27 27 27 27 27 27 332 0.38 (0.64) 331 130 -0.1 (0.43) 129 696 569 569 5 72.3 596 f= 4 (P = 0.60); P = 0.00); 20.00;	N Mean(SD) N Mean(SD) % 27 -0.2 (0.37) 27 0 (0.37) - 27 27 27 0 (0.37) - - 27 27 27 - - - 2 (P = 0.055) 5 - 0.1 (0.48) - <td< td=""><td>ABA + ICS ICS alone Difference N Mean(SD) N Mean(SD) IV/Fixed.95% CD % 27 -0.2 (0.37) 27 0 (0.37) 27 27 27 27 27 27 27 27 27 27 27 27 27 27 27 27 0 (0.37) 4 -0.1 (0.48) 113 -0.27 (0.48) 55 -0.1 (0.48) 124 -0.28 (0.65) 5 -0.1 (0.43) 129 0 (0.35) 5 (P = 0.00026) 7 23 596 569 7 (P = 0.00027) 5 (P = 0.00027)</td><td>ABA + ICS ICS alone Difference Weight N Mean(SD) N Mean(SD) N/Fixed,95% CI % 27 -0.2 (0.37) 27 0 (0.37) 4.1 % 27 27 27 4.1 % 4.1 % 20 0.035) 4.1 % 4.1 % 21 -0.2 (0.48) 54 -0.1 (0.48) 4.1 % 113 -0.27 (0.48) 55 -0.1 (0.48) 4.1 % 332 -0.38 (0.66) 331 -0.28 (0.65) 52.3 % 332 -0.38 (0.66) 331 -0.28 (0.65) 52.3 % 50 ← 569 95.9 % 52.3 % 51 = 3 (P = 0.69); P = 0.00% 596 95.9 % 95.9 % 723 596 100.0 % 100.0 % 7 (P = 0.000; P = 0.00%; P = 0.00% 7 (P = 0.000; P = 0.00%); P = 0.00% 100.0 %</td></td<>	ABA + ICS ICS alone Difference N Mean(SD) N Mean(SD) IV/Fixed.95% CD % 27 -0.2 (0.37) 27 0 (0.37) 27 27 27 27 27 27 27 27 27 27 27 27 27 27 27 27 0 (0.37) 4 -0.1 (0.48) 113 -0.27 (0.48) 55 -0.1 (0.48) 124 -0.28 (0.65) 5 -0.1 (0.43) 129 0 (0.35) 5 (P = 0.00026) 7 23 596 569 7 (P = 0.00027) 5 (P = 0.00027)	ABA + ICS ICS alone Difference Weight N Mean(SD) N Mean(SD) N/Fixed,95% CI % 27 -0.2 (0.37) 27 0 (0.37) 4.1 % 27 27 27 4.1 % 4.1 % 20 0.035) 4.1 % 4.1 % 21 -0.2 (0.48) 54 -0.1 (0.48) 4.1 % 113 -0.27 (0.48) 55 -0.1 (0.48) 4.1 % 332 -0.38 (0.66) 331 -0.28 (0.65) 52.3 % 332 -0.38 (0.66) 331 -0.28 (0.65) 52.3 % 50 ← 569 95.9 % 52.3 % 51 = 3 (P = 0.69); P = 0.00% 596 95.9 % 95.9 % 723 596 100.0 % 100.0 % 7 (P = 0.000; P = 0.00%; P = 0.00% 7 (P = 0.000; P = 0.00%); P = 0.00% 100.0 %

Analysis 1.21. Comparison 1 Long-acting beta2 versus placebo: both groups receiving similar dose ICS, Outcome 21 % symptom-free days

Review: Addition of long-acting beta2-agonists to inhaled corticosteroids versus same dose inhaled corticosteroids for chronic asthma in adults and children

Comparison: 1 Long-acting beta2 versus placebo: both groups receiving similar dose ICS

Outcome: 21 % symptom-free days

Mea Difference	Weight	Mean Difference		ICS alone		LABA + ICS	Study or subgroup
IV,Random,95%		IV,Random,95% CI	Mean(SD)	Ν	Mean(SD)	N	
					d	80% of predicte	I Mean baseline FEVI >/=
4.60 [0.69, 8.51	17.6 %	-	70.3 (24.9)	312	74.9 (25)	315	O'Byme 2001b
4.60 [0.69, 8.51	17.6 %	•		312		315	Subtotal (95% CI)
						ble	Heterogeneity: not applical
						2.31 (P = 0.021)	Test for overall effect; Z =
					icted	to 79% of pred	2 Mean baseline FEVI 61%
6.60 [0.98, 12.22	16.6 %	-	43.4 (29)	207	50 (29)	202	Kuna 2006
2.40 [-2.24, 7.04	17.2 %	-	75.1 (20)	138	77.5 (20)	148	Tal 2002
24.50 [18.78, 30.22	16.5 %	-	13.6 (28.69)	254	38.1 (36.51)	252	Kemp 1998
7.90 [-0.75, 16.55	14.4 %	-	63.4 (36)	129	71.3 (35)	130	Molimard 2001
10.35 [0.05, 20.65	64.6 %	•		728		732	Subtotal (95% CI)
			!%	001); I ² =92	2, df = 3 (P<0.00	1.31; Chi ² = 36.5	Heterogeneity: Tau ² = 100
						1.97 (P = 0.049)	Test for overall effect: $Z =$
						reported	3 Mean baseline FEV1 not
-1.00 [-4.47, 2.47	17.8 %	•	93 (7)	39	92 (9)	43	Teper 2005
-1.00 [-4.47, 2.47	17.8 %	•		39		43	Subtotal (95% CI)
						ble	Heterogeneity: not applical
						0.56 (P = 0.57)	Test for overall effect: $Z =$
7.31 [0.50, 14.12	100.0 %	•		1079		1090	Total (95% CI)
			6	01); I ² =919	df = 5 (P<0.000	67; Chi ² = 58.01	Heterogeneity: $Tau^2 = 64.6$
						2.10 (P = 0.035)	Test for overall effect: $Z =$

Analysis 1.22. Comparison 1 Long-acting beta2 versus placebo: both groups receiving similar dose ICS, Outcome 22 Change in % symptom-free days at endpoint

Review: Addition of long-acting beta2-agonists to inhaled corticosteroids versus same dose inhaled corticosteroids for chronic asthma in adults and children

Comparison: 1 Long-acting beta2 versus placebo: both groups receiving similar dose ICS

Outcome: 22 Change in % symptom-free days at endpoint

Ci. I			100		Mean	142111	Mean
Study or subgroup	LABA + ICS N	Mean(SD)	ICS alone N	Mean(SD)	Difference IV,Random,95% CI	Weight	Difference IV.Random,95% CI
1 Mean baseline FEV1 >/			14	(rear (SP)	- manageriy soo Ci		nynandom,/3/6 Cl
Malone 2005	- 80% or predic	24.4 (41)	102	21.2 (41)	+	5.2 %	3.20 [-8.08, 14.48]
Subtotal (95% CI)	101		102		•	5.2 %	3.20 [-8.08, 14.48]
Heterogeneity: not applic Test for overall effect: Z =							
2 Mean baseline FEVI 61							
Bailey 2008	239	10.8 (38)	236	8.9 (34)	+	7.9 %	1.90 [-4.58, 8.38]
Boyd 1995	53	22 (30)	62	13 (22)	•	6.0 %	9.00 [-0.76, 18.76]
Jenkins 2006a	222	31.2 (32.42)	57	15.6 (32.42)	-	6.1 %	15.60 [6.16, 25.04]
Jenkins 2006b	114	32.2 (40.91)	58	15.6 (40.91)		4.5 %	16.60 [3.67, 29.53]
Kavaru 2000	87	22.6 (42.81)	85	7.2 (37.7)		4.9 %	15.40 [3.35, 27.45]
Kemp 1998	252	38.1 (36.5)	254	13.6 (28.69)	-	8.3 %	24.50 [18.78, 30.22]
Nathan 2006	94	18.5 (37.81)	91	15 (29.57)	-	6.0 %	3.50 [-6.26, 13.26]
Noonan 2006a	121	23.14 (31.97)	54	9.5 (31.97)		5.7 %	13.64 [3.39, 23.89]
Noonan 2006b	113	21.8 (31.44)	55	9.5 (31.97)	-	5.7 %	12.30 [2.05, 22.55]
SD 039 0728		. ,		. ,			
	441	19 (30.1)	132	5.9 (24.1)		8.8 %	13.10 [8.12, 18.08]
Shapiro 2000	81	33.8 (41.4)	81	15.4 (37.8)		4.8 %	18.40 [6.19, 30.61]
Zetterstrom 2001a	123	25 (31.39)	62	8 (31.85)	•	6.0 %	17.00 [7.32, 26.68]
Zetterstrom 2001b	115	22.3 (31.21)	62	8 (31.85)	•	6.0 %	14.30 [4.53, 24.07]
Subtotal (95% CI) Heterogeneity: Tau ² = 33 Test for overall effect: Z = 3 Mean baseline FEV1 no SAS40036	6.45 (P < 0.00		1289 .00095); I ² =0 158	-0.5 (34)	-	80.6 %	13.37 [9.31, 17.44] 6.20 [-1.27, 13.67]
SAS40037	154	5.1 (36)	157	-1.9 (36)	•	6.9 %	7.00 [-1.00, 15.00]
Subtotal (95% CI)	324		315		•	14.2 %	6.57 [1.11, 12.03]
Heterogeneity: Tau ² = 0.0); Chi ² = 0.02, d	f = 1 (P = 0.89);	12 =0.0%				
				-100 Favour) -50 0 50 10 s ICS alone Favours LAB/		
Study or subgroup	LABA + ICS N	Mean(SD)	ICS alone N	Mean(SD)	Mean Difference IV,Random,95% CI	Weight	Me Differer IV,Random,95%
Test for overall effect: Z = Total (95% CI) Heterogeneity: Tau ² = 32 Test for overall effect: Z =	2480 .55; Chi ² = 40.9	8, df = 15 (P = 0	1706 0.00032); I ² =	-63%	•	100.0 %	11.88 [8.25, 15.50
				-10	00 -50 0 50	100	
				Favou	irs ICS alone Favours LA	BA + ICS	

Analysis 1.23. Comparison 1 Long-acting beta2 versus placebo: both groups receiving similar dose ICS, Outcome 23 Change in # of symptom-free nights at endpoint

Review: Addition of long-acting beta2-agonists to inhaled corticosteroids versus same dose inhaled corticosteroids for chronic asthma in adults and children

Comparison: 1 Long-acting beta2 versus placebo: both groups receiving similar dose ICS

Outcome: 23 Change in # of symptom-free nights at endpoint

Study or subgroup	LABA + ICS N	Mean(SD)	ICS alone N	Mean(SD)			Mean erence			Mean Difference IV.Fixed,95% CI
I Mean baseline FEVI	61% to 79% of predic	ted		,						
Boyd 1995	53	0.33 (0.32)	62	0.13 (0.26)			ŀ			0.20 [0.09, 0.31]
					-10	-5	0	5	10	
				Fav	ours LABA -	+ ICS	Fav	ours IC	S alone	

Analysis 1.24. Comparison 1 Long-acting beta2 versus placebo: both groups receiving similar dose ICS, Outcome 24 % symptom-free nights at 12 +/- 4 weeks

Review: Addition of long-acting beta2-agonists to inhaled corticosteroids versus same dose inhaled corticosteroids for chronic asthma in adults and children

Comparison: 1 Long-acting beta2 versus placebo: both groups receiving similar dose ICS

Outcome: 24 % symptom-free nights at 12 +/- 4 weeks

Study or subgroup	LABA + ICS N	Mean(SD)	ICS alone N	Mean(SD)			iffere	lean ence 95% CI		Mean Difference IV,Fixed,95% CI
		(Job)		r ican(ob)		14,11		/ 5/0 Cl		14,1000,000 C
I Mean baseline FEVI	61% to 79% of predic	ted								
Molimard 2001	130	81.7 (28.4)	129	76.4 (29.7)			+			5.30 [-1.78, 12.38]
					-100	-50	0	50	100	
					Favours IC	S alone		Eavours	LABA + I	cs

Analysis 1.25. Comparison 1 Long-acting beta2 versus placebo: both groups receiving similar dose ICS, Outcome 25 Change in % symptom-free nights at endpoint

Review: Addition of long-acting beta2-agonists to inhaled corticosteroids versus same dose inhaled corticosteroids for chronic asthma in adults and children

Comparison: 1 Long-acting beta2 versus placebo: both groups receiving similar dose ICS

Outcome: 25 Change in % symptom-free nights at endpoint

Study or subgroup	LABA + ICS		ICS alone		Std. Mean Difference	Weight	Std. Mean Difference
	N	Mean(SD)	Ν	Mean(SD)	IV,Random,95% CI		IV,Random,95% CI
I Mean baseline FEVI	61% to 79% of pr	redicted					
Kavaru 2000	87	4.6 (16.14)	85	2.4 (21.5)		23.4 %	0.12 [-0.18, 0.41]
Boyd 1995	53	33 (32)	62	13 (26)		19.0 %	0.69 [0.31, 1.06]
Kemp 1998	252	29.2 (38.1)	254	9.5 (28.69)		31.1 %	0.58 [0.41, 0.76]
Molimard 2001	130	33 (53)	129	-1.6 (53)		26.5 %	0.65 [0.40, 0.90]
Total (95% CI)	522		530		+	100.0 %	0.51 [0.28, 0.74]
Heterogeneity: Tau ² =	0.04; Chi ² = 9.29	, df = 3 (P = 0.03)	; I ² =68%				
Test for overall effect:	Z = 4.30 (P = 0.0	00017)					
				-1			
				Favou	rs ICS alone Favours LAB	A + ICS	

Analysis 1.26. Comparison 1 Long-acting beta2 versus placebo: both groups receiving similar dose ICS, Outcome 26 Change in asthma control days %

Review: Addition of long-acting beta2-agonists to inhaled corticosteroids versus same dose inhaled corticosteroids for chronic asthma in adults and children

Comparison: 1 Long-acting beta2 versus placebo: both groups receiving similar dose ICS

Outcome: 26 Change in asthma control days %

Study or subgroup	LABA + ICS		ICS alone		Mean Difference	Weight	Mean Difference
	N	Mean(SD)	Ν	Mean(SD)	IV,Fixed,95% CI		IV,Fixed,95% CI
I Mean baseline FEVI 6	1% to 79% of pr	redicted					
Jenkins 2006b	114	32.2 (32.43)	58	16.3 (32.43)	•	23.4 %	15.90 [5.65, 26.15]
Zetterstrom 2001b	115	26.9 (32.06)	62	12.1 (32.96)	+	24.2 %	14.80 [4.72, 24.88]
Jenkins 2006a	222	32.4 (32.42)	57	16.3 (32.42)	-	27.7 %	16.10 [6.66, 25.54]
Zetterstrom 2001a	123	28.5 (32.27)	62	12.1 (32.96)	•	24.7 %	16.40 [6.41, 26.39]
Total (95% CI) Heterogeneity: $Chi^2 = C$ Test for overall effect: Z	= 6.24 (P < 0.0	0001)	239		•	100.0 %	15.81 [10.85, 20.77]
Test for subgroup differe	ences: Not applic	able					
				-100	-50 0 50	100	

Analysis 1.27. Comparison 1 Long-acting beta2 versus placebo: both groups receiving similar dose ICS, Outcome 27 Change in # overall daily rescue inhalations at endpoint

Review: Addition of long-acting beta2-agonists to inhaled corticosteroids versus same dose inhaled corticosteroids for chronic asthma in adults and children

Comparison: 1 Long-acting beta2 versus placebo: both groups receiving similar dose ICS

Outcome: 27 Change in # overall daily rescue inhalations at endpoint

Study or subgroup	LABA + ICS		ICS alone		Mean Difference	Weight	Mea Differenc
	N	Mean(SD)	N	Mean(SD)	IV,Random,95% CI		IV,Random,95% C
I Mean baseline FEVI >/=	80% of predicte	ed					
O'Byrne 2001a	323	-0.29 (0.79)	322	-0.06 (0.79)	•	9.8 %	-0.23 [-0.35, -0.11
O'Byme 2001b	315	-0.31 (0.78)	312	-0.2 (0.78)	-	9.8 %	-0.11 [-0.23, 0.01
Subtotal (95% CI)	638		634		•	19.6 %	-0.17 [-0.29, -0.05
Heterogeneity: Tau ² = 0.00		($ ^2 = 46\%$				
Test for overall effect: Z = 1 2 Mean baseline FEV1 61%							
Kavaru 2000	87	-1.9 (2.43)	85	-0.4 (1.94)	-	5.4 %	-1.50 [-2.16, -0.84
Tal 2002	148	-0.11 (0.7)	138	-0.09 (0.7)	+	9.6 %	-0.02 [-0.18, 0.14
Hultquist 2000	117	-1.86 (1.84)	115	-1.35 (1.83)		6.9 %	-0.51 [-0.98, -0.04
Noonan 2006a	121	-1 (2.09)	54	-0.78 (2.09)	-	5.3 %	-0.22 [-0.89, 0.45
Noonan 2006b	113	-1.5 (2.07)	55	-0.78 (2.09)		5.3 %	-0.72 [-1.39, -0.05
SD 039 0728	438	-0.8 (1.4)	130	-0.2 (1.3)	•	8.9 %	-0.60 [-0.86, -0.34
Shapiro 2000	81	-2.3 (3.6)	81	-0.9 (1.8)		3.9 %	-1.40 [-2.28, -0.52
Boyd 1995	53	-5.1 (4.7)	62	-2.5 (4)		1.6 %	-2.60 [-4.21, -0.99
Kemp 1998	252	-3.48 (3.02)	254	-1.25 (2.55)	+	6.8 %	-2.23 [-2.72, -1.74
Buhl 2003a	176	-0.27 (0.9)	86	0 (0.9)	-	9.1 %	-0.27 [-0.50, -0.04
Buhl 2003b	176	-0.35 (0.9)	85	0 (0.9)	•	9.1 %	-0.35 [-0.58, -0.12
Bailey 2008	239	-0.35 (1.5)	236	-0.15 (1.6)	-	8.7 %	-0.20 [-0.48, 0.08
Subtotal (95% CI)	2001		1381		•	80.4 %	-0.73 [-1.05, -0.41
Heterogeneity: $Tau^2 = 0.25$			0001); 2 =89	9%			
Test for overall effect: $Z = -$		01)					
Total (95% CI)	2639	10 10 10 00	2015	201	•	100.0 %	-0.58 [-0.80, -0.35
Heterogeneity: $Tau^2 = 0.13$ Test for a small effect: $Z = 1$			0001); 1* =8:	1%			
est for overall effect: $Z = $,				

Analysis 1.28. Comparison 1 Long-acting beta2 versus placebo: both groups receiving similar dose ICS, Outcome 28 Change in # daytime rescue inhalations at endpoint

Review: Addition of long-acting beta2-agonists to inhaled corticosteroids versus same dose inhaled corticosteroids for chronic asthma in adults and children

Comparison: 1 Long-acting beta2 versus placebo: both groups receiving similar dose ICS

Outcome: 28 Change in # daytime rescue inhalations at endpoint

Study or subgroup	puffs per day (SE)	puffs per day IV,Random,95% CI	Weight	puffs per day IV,Random,95% C
Mean baseline FEV >/= 80	% of predicted			
Koopmans 2006	-0.9 (0.3)	-	6.9 %	-0.90 [-1.49, -0.31]
Malone 2005	-0.1 (0.1887)	+	8.8 %	-0.10 [-0.47, 0.27]
SM540012	-0.12 (0.051)	•	10.5 %	-0.12 [-0.22, -0.02]
Subtotal (95% CI)		•	26.2 %	-0.27 [-0.62, 0.07]
Heterogeneity: $Tau^2 = 0.06$; C Test for overall effect: $Z = 1.5$		0%		
2 Mean baseline FEV1 61% to Kavaru 2000	79% of predicted -1.5 (0.3367)	-	6.3 %	-1.50 [-2.160.84
Kemp 1998	-1.67 (0.199)	•	8.6 %	-1.67 [-2.06, -1.28]
Molimard 2001	-0.9 (0.1378)	•	9.6 %	-0.90 [-1.17, -0.63]
Nathan 2006	-0.7 (0)			Not estimable
O'Byme 2001a	-0.23 (0.0612)	•	10.4 %	-0.23 [-0.35, -0.11]
Price 2002	-0.33 (0.1071)	•	10.0 %	-0.33 [-0.54, -0.12]
Russell 1995	-0.37 (0.2806)	-	7.2 %	-0.37 [-0.92, 0.18
van der Molen 1997	-1.3 (0.2092)	-	8.4 %	-1.30 [-1.71, -0.89]
Zetterstrom 2001 a	-0.55 (0.2704)	-	7.4 %	-0.55 [-1.08, -0.02]
Zetterstrom 2001b	-0.69 (0.3673)		5.9 %	-0.69 [-1.41, 0.03]
Subtotal (95% CI) Heterogeneity: Tau ² = 0.24; C Test for overall effect: Z = 4.5: 3 Mean baseline FEV1 not rep		=91%	73.8 %	-0.82 [-1.18, -0.46]
Subtotal (95% CI) Heterogeneity: not applicable	oned			Not estimable
Test for overall effect: not app Total (95% CI) Heterogeneity: Tau ² = 0.17; C	icable hi ² = 122.36, df = 11 (P<0.00001);	↓ 1 ² =91%	100.0 %	-0.68 [-0.94, -0.42]
Test for overall effect: $Z = 5.1$	8 (P < 0.00001)			
	Fav	-4 -2 0 2 4		

Analysis 1.29. Comparison 1 Long-acting beta2 versus placebo: both groups receiving similar dose ICS, Outcome 29 # daytime rescue inhalations (puffs per day) at endpoint

Review: Addition of long-acting beta2-agonists to inhaled corticosteroids versus same dose inhaled corticosteroids for chronic asthma in adults and children

Comparison: 1 Long-acting beta2 versus placebo: both groups receiving similar dose ICS

Outcome: 29 # daytime rescue inhalations (puffs per day) at endpoint

Study or subgroup	LABA + ICS		ICS alone		Mean Difference	Weight	Mear Difference
	N	Mean(SD)	N	Mean(SD)	IV,Random,95% CI		IV,Random,95% C
1 Mean baseline FEV1 61	% to 79% of pre	dicted					
Norhaya 1999	20	1.32 (1.12)	20	1.65 (1.5)		29.5 %	-0.33 [-1.15, 0.49
van der Molen 1997	124	0.9 (1.3)	113	1.8 (1.8)		70.5 %	-0.90 [-1.30, -0.50
Total (95% CI)	144		133		-	100.0 %	-0.73 [-1.24, -0.22
Heterogeneity: $Tau^2 = 0$.	05; Chi ² = 1.49,	df = 1 (P = 0.22);	I ² =33%				
Test for overall effect: Z	= 2.81 (P = 0.004	19)					
					2 -1 0 1	2	
				5	LABA + ICS Favours IC		

Analysis 1.30. Comparison 1 Long-acting beta2 versus placebo: both groups receiving similar dose ICS, Outcome 30 # night-time rescue inhalations (puffs per night) at endpoint

Review: Addition of long-acting beta2-agonists to inhaled corticosteroids versus same dose inhaled corticosteroids for chronic asthma in adults and children

Comparison: 1 Long-acting beta2 versus placebo: both groups receiving similar dose ICS

Outcome: 30 # night-time rescue inhalations (puffs per night) at endpoint

Study or subgroup	LABA + ICS		ICS alone		Mean Difference	Weight	Mear Difference
	Ν	Mean(SD)	Ν	Mean(SD)	IV,Random,95% C	l	IV,Random,95% C
I Mean baseline FEVI	61% to 79% of p	oredicted					
Northaya 1999	20	0.92 (0.89)	20	1.08 (0.8)		31.6 %	-0.16 [-0.68, 0.36
Kemp 1998	252	-0.75 (1.11)	254	-0.18 (1.11)		68.4 %	-0.57 [-0.76, -0.38
Total (95% CI)	272		274		-	100.0 %	-0.44 [-0.81, -0.07
Heterogeneity: Tau ² =	0.04; Chi ² = 2.0	7, df = 1 (P = 0.1	5); I ² =52%				
Test for overall effect:	Z = 2.31 (P = 0.0	021)					
					-1 -0.5 0 0.5	1	
				Favours	s LABA + ICS Favours	ICS alone	

Analysis 1.31. Comparison 1 Long-acting beta2 versus placebo: both groups receiving similar dose ICS, Outcome 31 Change in # night-time rescue inhalations at endpoint

Review: Addition of long-acting beta2-agonists to inhaled corticosteroids versus same dose inhaled corticosteroids for chronic asthma in adults and children

Comparison: 1 Long-acting beta2 versus placebo: both groups receiving similar dose ICS

Outcome: 31 Change in # night-time rescue inhalations at endpoint

			ICS alone		Difference	Weight	Difference
	N	Mean(SD)	N	Mean(SD)	IV,Random,95% CI	_	IV,Random,95% C
I Mean baseline FEVI >/= 80	% of predicte	ed					
SMS40012	83	-0.03 (0.18)	85	0.08 (0.37)		16.3 %	-0.11 [-0.20, -0.02
Subtotal (95% CI)	83		85		•	16.3 %	-0.11 [-0.20, -0.02
Heterogeneity: not applicable							
Test for overall effect: $Z = 2.4$	6 (P = 0.014))					
2 Mean baseline FEV1 61% to	79% of pred	icted					
Hultquist 2000	117	-0.47 (0.54)	115	-0.46 (0.54)	+	15.5 %	-0.01 [-0.15, 0.13
Russell 1995	70	-0.15 (1.05)	83	-0.11 (0.97)		11.1 %	-0.04 [-0.36, 0.28
Price 2002	332	-0.38 (0.73)	331	-0.26 (0.75)	-	16.0 %	-0.12 [-0.23, -0.01
Kemp 1998	252	-0.75 (1.11)	254	-0.18 (1.12)		14.2 %	-0.57 [-0.76, -0.38
Molimard 2001	130	-0.4 (0.72)	129	0.1 (0.69)		14.8 %	-0.50 [-0.67, -0.33
van der Molen 1997	125	-0.9 (1.1)	113	-0.1 (1.1)	·•-	12.1 %	-0.80 [-1.08, -0.52
Subtotal (95% CI)	1026		1025		-	83.7 %	-0.33 [-0.57, -0.10
Heterogeneity: Tau ² = 0.07; C	$Chi^2 = 51.59$,	df = 5 (P<0.0000)); l² =90%				
Test for overall effect: $Z = 2.7$	9 (P = 0.005	3)					
Total (95% CI)	1109		1110		+	100.0 %	-0.30 [-0.48, -0.11
Heterogeneity: Tau ² = 0.05; C	Chi ² = 57.38,	df = 6 (P<0.0000)); I² =90%				
Test for overall effect: $Z = 3.1$	7 (P = 0.001	5)					

Analysis 1.32. Comparison 1 Long-acting beta2 versus placebo: both groups receiving similar dose ICS, Outcome 32 Change in mean rescue-free days

Review: Addition of long-acting beta2-agonists to inhaled corticosteroids versus same dose inhaled corticosteroids for chronic asthma in adults and children

Comparison: 1 Long-acting beta2 versus placebo: both groups receiving similar dose ICS

Outcome: 32 Change in mean rescue-free days

Study or subgroup	LABA + ICS	ICS alone	% (SE)		%	Weight	9
	Ν	N		IV,Fixe	ed,95% CI		IV,Fixed,95% C
I Mean baseline FEVI 61%	to 79% of predicte	ed					
Jenkins 2006a	222	57	18.9 (4.6837)			12.9 %	18.90 [9.72, 28.08
Jenkins 2006b	114	58	21.4 (5.1071)			10.9 %	21.40 [11.39, 31.41
SD 039 0728	438	130	15.2 (2.7551)		_ - ••	37.3 %	15.20 [9.80, 20.60
Zetterstrom 2001a	123	62	19.1 (4.9745)			11.5 %	19.10 [9.35, 28.85
Zetterstrom 2001b	115	62	19.1 (5)			11.3 %	19.10 [9.30, 28.90
Subtotal (95% CI)	1012	369			-	83.9 %	17.63 [14.03, 21.23
Heterogeneity: Chi ² = 1.57	, df = 4 (P = 0.81)	; I ² =0.0%					
Test for overall effect: $Z = S$	9.59 (P < 0.00001)						
2 Mean baseline FEV1 not r	reported						
SAS40037	158	159	14 (4.199)			16.1 %	14.00 [5.77, 22.23
Subtotal (95% CI)	158	159			-	16.1 %	14.00 [5.77, 22.23
Heterogeneity: not applicab	de						
Test for overall effect: $Z = 3$	3.33 (P = 0.00086)						
Total (95% CI)	1170	528			+	100.0 %	17.05 [13.75, 20.35
Heterogeneity: Chi ² = 2.20	, df = 5 (P = 0.82)	; I ² =0.0%					
Test for overall effect: $Z =$	10.13 (P < 0.00001)					
Test for subgroup difference	es: $Chi^2 = 0.63$, df	= I (P = 0.43),	$ ^2 = 0.0\%$				
				-20 -10	0 10 20		
			En	ours ICS alone	Favours LABA	+ 105	

Analysis 1.33. Comparison 1 Long-acting beta2 versus placebo: both groups receiving similar dose ICS, Outcome 33 Rescue medication-free days

Review: Addition of long-acting beta2-agonists to inhaled corticosteroids versus same dose inhaled corticosteroids for chronic asthma in adults and children

Comparison: 1 Long-acting beta2 versus placebo: both groups receiving similar dose ICS

Outcome: 33 Rescue medication-free days

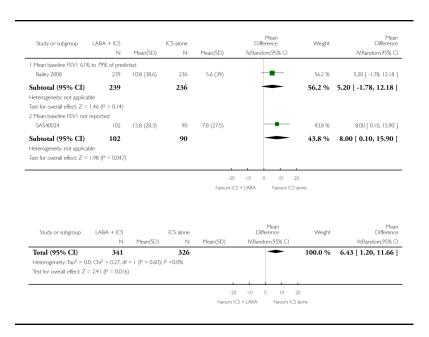
Study or subgroup	LABA + ICS		ICS alone			C	M Differe	lean Ince		Mear Difference
	N	Mean(SD)	N	Mean(SD)		IV,F	ixed,	95% CI		IV,Fixed,95% C
I Mean baseline FEVI	61% to 79% of predic	ted								
Kuna 2006	202	61.8 (26.5)	207	55.5 (26.1)			•			6.30 [1.20, 11.40
					-10	-5	0	5	10	
					Favours IC	IS alone		Favours	LABA + I	CS

Analysis 1.34. Comparison 1 Long-acting beta2 versus placebo: both groups receiving similar dose ICS, Outcome 34 Change in % rescue medication-free days

Review: Addition of long-acting beta2-agonists to inhaled corticosteroids versus same dose inhaled corticosteroids for chronic asthma in adults and children

Comparison: 1 Long-acting beta2 versus placebo: both groups receiving similar dose ICS

Outcome: 34 Change in % rescue medication-free days



Analysis 1.35. Comparison 1 Long-acting beta2 versus placebo: both groups receiving similar dose ICS, Outcome 35 Change in % nights with no awakening

Review: Addition of long-acting beta2-agonists to inhaled corticosteroids versus same dose inhaled corticosteroids for chronic asthma in adults and children

Comparison: 1 Long-acting beta2 versus placebo: both groups receiving similar dose ICS

Outcome: 35 Change in % nights with no awakening

Study or subgroup	LABA + ICS		ICS alone		Mean Difference	Weight	Mea Difference
	Ν	Mean(SD)	N	Mean(SD)	IV,Fixed,95% CI	-	IV,Fixed,95%
I Mean baseline FEVI	61% to 79% of p	predicted					
Kuna 2006	202	11.3 (16.7)	207	12 (16.5)		41.5 %	-0.70 [-3.92, 2.52
Kavaru 2000	87	4.6 (16.14)	85	2.4 (21.57)		13.2 %	2.20 [-3.50, 7.90
Noonan 2006a	121	-2.16 (20.17)	109	0 (20.17)		15.8 %	-2.16 [-7.38, 3.06
Nathan 2006	94	4.1 (13.57)	91	-0.6 (20.03)		17.6 %	4.70 [-0.25, 9.65
Shapiro 2000	81	7.2 (17.1)	81	2.8 (21.6)		11.9 %	4.40 [-1.60, 10.40
Total (95% CI) Heterogeneity: Chi ² =	585 6.03, df = 4 (P =	= 0.20); I ² =34%	573		-	100.0 %	1.01 [-1.06, 3.08
Test for overall effect:	Z = 0.96 (P = 0.1	34)					
	rences: Not appl	icable					

Analysis 1.36. Comparison 1 Long-acting beta2 versus placebo: both groups receiving similar dose ICS, Outcome 36 % nights with awakening

Review: Addition of long-acting beta2-agonists to inhaled corticosteroids versus same dose inhaled corticosteroids for chronic asthma in adults and children

Comparison: 1 Long-acting beta2 versus placebo: both groups receiving similar dose ICS

Outcome: 36 % nights with awakening

Study or subgroup	LABA + ICS		ICS alone		Mean Difference	Weight	Mea Differenc
	N	Mean(SD)	N	Mean(SD)	IV,Fixed,95% CI		IV,Fixed,95% (
Mean baseline FEV >/=	80% of predicte	d					
O'Byme 2001b	315	-4.3 (10.8)	312	-2.8 (10.8)	-	67.1 %	-1.50 [-3.19, 0.19
Subtotal (95% CI)	315		312		•	67.1 %	-1.50 [-3.19, 0.19
Heterogeneity: not applica	ble						
Test for overall effect: Z =	1.74 (P = 0.082)						
2 Mean baseline FEV1 619	6 to 79% of predi	cted					
Tal 2002	148	5.5 (10.4)	138	6.6 (10.4)		32.9 %	-1.10 [-3.51, 1.31
Subtotal (95% CI)	148		138		-	32.9 %	-1.10 [-3.51, 1.31
Heterogeneity: not applica	ble						
Test for overall effect: Z =	0.89 (P = 0.37)						
Total (95% CI)	463		450		+	100.0 %	-1.37 [-2.75, 0.02
Heterogeneity: $Chi^2 = 0.0$	7, df = 1 (P = 0.7	9); l ² =0.0%					
Test for overall effect: Z =	1.94 (P = 0.053)						
Test for subgroup difference	es: Chi ² = 0.07,	f = 1 (P = 0.79)	, I ² =0.0%				
				-10	-5 0 5	10	
				Favours LA	ABA + ICS Favours IC	5 alone	

Analysis 1.37. Comparison 1 Long-acting beta2 versus placebo: both groups receiving similar dose ICS, Outcome 37 Change in night-time awakening (number of nights) at endpoint

Review: Addition of long-acting beta2-agonists to inhaled corticosteroids versus same dose inhaled corticosteroids for chronic asthma in adults and children

Comparison: 1 Long-acting beta2 versus placebo: both groups receiving similar dose ICS

Outcome: 37 Change in night-time awakening (number of nights) at endpoint

Study or subgroup	LABA + ICS N	Mean(SD)	ICS alone N	Mean(SD)	Std. Mean Difference IV,Fixed,95% CI	Weight	Std Mear Difference IV,Fixed,95% C
			IN .	(JD)	14,1 Med,7 576 CI		14,1 Mcd,7 576 C
I Mean baseline FEVI 61							
Zetterstrom 2001b	115	-5.6 (16.94)	62	-5.8 (17.37)		12.7 %	0.01 [-0.30, 0.32
Zetterstrom 2001a	123	-8.4 (17)	62	-5.8 (17.37)		13.0 %	-0.15 [-0.46, 0.15
Tal 2002	148	-1.7 (10.4)	138	-1.9 (10.4)	-	22.5 %	0.02 [-0.21, 0.25
Nathan 2006	94	-0.04 (0.19)	91	0.02 (0.19)		14.4 %	-0.31 [-0.60, -0.02
Bailey 2008	239	-0.14 (0.7)	236	-0.06 (0.7)		37.4 %	-0.11 [-0.29, 0.07
Total (95% CI)	719		589		•	100.0 %	-0.10 [-0.21, 0.01]
Heterogeneity: Chi ² = 3.	.75, df = 4 (P = 1	0.44); l ² =0.0%					
Test for overall effect: Z	= 1.81 (P = 0.07	0)					
Test for subgroup differe	nces: Not applica	able					

Analysis 1.38. Comparison 1 Long-acting beta2 versus placebo: both groups receiving similar dose ICS, Outcome 38 Change in quality of life (AQLQ score) at endpoint

Review: Addition of long-acting beta2-agonists to inhaled corticosteroids versus same dose inhaled corticosteroids for chronic asthma in adults and children

Comparison: 1 Long-acting beta2 versus placebo: both groups receiving similar dose ICS

Outcome: 38 Change in quality of life (AQLQ score) at endpoint

Study or subgroup	Mean Difference (SE)	Mean Difference	Weight	Mear Difference
		IV,Random,95% CI		IV,Random,95% C
I Mean baseline FEVI 61%	to 79% of predicted			
Green 2006	0.1 (0.128)		29.8 %	0.10 [-0.15, 0.35
Kemp 1998	0.47 (0.1071)		34.0 %	0.47 [0.26, 0.68
Price 2002	0.19 (0.0969)		36.2 %	0.19 [0.00, 0.38
Total (95% CI)		-	100.0 %	0.26 [0.04, 0.47]
Heterogeneity: $Tau^2 = 0.02$	2; Chi ² = 5.92, df = 2 (P = 0.05); I ² =66%			
Test for overall effect: Z =	2.36 (P = 0.018)			
-				
	-0.	5 -0.25 0 0.25 0.5		
		Favours ICS Favours LABA + IC	~	

Analysis 1.39. Comparison 1 Long-acting beta2 versus placebo: both groups receiving similar dose ICS, Outcome 39 Total # adverse events

Review: Addition of long-acting beta2-agonists to inhaled corticosteroids versus same dose inhaled corticosteroids for chronic asthma in adults and children

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Comparison: 1 Long-acting beta2 versus placebo: both groups receiving similar dose ICS

Outcome: 39 Total # adverse events

Study or subgroup	LABA + ICS	ICS alone	Risk Ratio	Weight	Risk Rati
	n/N	n/N	M-H,Fixed,95% CI		M-H,Fixed,95% C
Mean baseline FEV1 >/= 80					
Langton Hewer 1995	10/11	9/12		0.3 %	1.21 [0.83, 1.77
Malone 2005	60/101	58/102		2.3 %	1.04 [0.83, 1.32
Morice 2008a	100/212	41/104		2.1 %	1.20 [0.91, 1.58
Morice 2008b	92/203	40/103		2.1 %	1.17 [0.88, 1.55
SD 039 0718	90/128	92/145		3.4 %	1.11 [0.94, 1.31
SD 039 0719	104/123	54/63	-	2.8 %	0.99 [0.87, 1.12
Verberne 1998	59/60	52/57		2.1 %	1.08 [0.99, 1.18
Subtotal (95% CI)	838	586	•	15.0 %	1.09 [1.01, 1.19
fotal events: 515 (LABA + IC	S), 346 (ICS alone)				
leterogeneity: Chi ² = 3.80, d	$f = 6 (P = 0.70); I^2 = 0.1$)%			
Fest for overall effect: $Z = 2.1$	8 (P = 0.029)				
2 Mean baseline FEV1 61% to	79% of predicted				
Aubier 1999a	124/171	58/82		3.1 %	1.03 [0.87, 1.21
Aubier 1999b	119/167	58/83		3.0 %	1.02 [0.86, 1.21
Bailey 2008	146/239	161/236		6.3 %	0.90 [0.78, 1.02
Boyd 1995	44/55	53/64		1.9 %	0.97 [0.81, 1.15
Buhl 2003a	60/176	39/86		2.0 %	0.75 [0.55, 1.02
Buhl 2003b	71/176	39/86		2.0 %	0.89 [0.66, 1.19
D5896C0001a	82/155	42/77		2.2 %	0.97 [0.75, 1.25
D5896C0001b	66/153	42/76		2.2 %	0.78 [0.59, 1.02
Fitzgerald 1999	13/89	9/91		0.3 %	1.48 [0.66, 3.28
Jenkins 2006a	68/226	13/57		0.8 %	1.32 [0.79, 2.21
Jenkins 2006b	31/115	14/58		0.7 %	1.12 [0.65, 1.93
Kemp 1998	134/252	130/254		5.1 %	1.04 [0.88, 1.23
Kuna 2006	76/202	74/207		2.9 %	1.05 [0.82, 1.36

0.5 0.7 I I.5 2 Favours LABA + ICS Favours ICS alone

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Study or subgroup	LABA + ICS	ICS alone	Risk Ratio	Weight	Risk Rati
Nathan 2006	n/N 65/94	n/N 63/91	M-H,Fixed,95% CI	2.5 %	M-H,Fixed,95% (
Norhaya 1999	2/30	3/30		0.1 %	0.67 [0.12, 3.71
Russell 1995	84/99	94/105	-	3.6 %	0.95 [0.85, 1.05
SD 039 0714	98/136	115/134		4.5 %	0.84 [0.74, 0.95
5D 039 0725a	120/184	50/84		2.7 %	1.10 [0.89, 1.35
5D 039 0725b	104/168	50/85		2.6 %	1.05 [0.85, 1.30
5D 039 0726a	90/154	38/73		2.0 %	1.12 [0.87, 1.45
SD 039 0726b	75/147	38/72		2.0 %	0.97 [0.74, 1.27
5D 039 0728	394/443	118/133	-	7.1 %	1.00 [0.94, 1.07
Shapiro 2000	0/81	0/81			Not estimab
van der Molen 1997	104/125	94/114		3.8 %	1.01 [0.90, 1.13
btotal (95% CI)	3967	2588	•	65.3 %	0.98 [0.94, 1.02
lean baseline FEV1 not report SAM40012	ed 99/181	111/181		4.3 %	0.89 [0.75, 1.0
erogeneity: $Chi^2 = 21.27$, df = t for overall effect: Z = 0.98 (F		0.0%			
5AM40012	99/181	111/181		4.3 %	0.89 [0.75, 1.06
5AS40024	28/102	24/90		1.0 %	1.03 [0.65, 1.64
5AS40036	100/172	77/159		3.1 %	1.20 [0.98, 1.47
SAS40037	77/161	84/161		3.3 %	0.92 [0.74, 1.14
SD 037 0344a	81/216	38/105		2.0 %	1.04 [0.76, 1.41
5D 037 0344b	74/213	37/105		1.9 %	0.99 [0.72, 1.35
SFA100314	37/124	35/124		1.4 %	1.06 [0.72, 1.56
SFA100316	20/113	25/118	·	1.0 %	0.84 [0.49, 1.42
5FCF4026	49/159	43/159		1.7 %	1.14 [0.81, 1.61
btotal (95% CI) al events: 565 (LABA + ICS), 4		1202	+	19.7 %	1.01 [0.92, 1.10
erogeneity: $Chi^2 = 6.46$, df = t for overall effect: Z = 0.12 (F	. ,	%			
tal (95% CI) al events: 3297 (LABA + ICS),	6246	4376	•	100.0 %	1.00 [0.97, 1.04
erogeneity: Chi ² = 37.79, df = t for overall effect: Z = 0.13 (F					

Analysis 1.40. Comparison 1 Long-acting beta2 versus placebo: both groups receiving similar dose ICS, Outcome 40 # patients with headache

Review: Addition of long-acting beta2-agonists to inhaled corticosteroids versus same dose inhaled corticosteroids for chronic asthma in adults and children

Comparison: 1 Long-acting beta2 versus placebo: both groups receiving similar dose ICS

Outcome: 40 # patients with headache

Study or subgroup	LABA + ICS n/N	ICS alone n/N	Risk Ratio M-H,Fixed,95% Cl	Weight	Risk Ratio M-H,Fixed,95% C
Mean baseline FEV >/= 80)% of predicted				
Malone 2005	20/101	20/102	-	5.5 %	1.01 [0.58, 1.76
SD 039 0718	19/128	20/145	-	5.2 %	1.08 [0.60, 1.92
SD 039 0719	26/123	14/63	+	5.1 %	0.95 [0.54, 1.69
Verberne 1998	25/60	23/57	+	6.6 %	1.03 [0.67, 1.60
Subtotal (95% CI)	412	367	•	22.5 %	1.02 [0.78, 1.33
Total events: 90 (LABA + ICS	5), 77 (ICS alone)				
Heterogeneity: $Chi^2 = 0.09$, c	$ff = 3 (P = 0.99); I^2 = 0.$	0%			
Test for overall effect: Z = 0.1	4 (P = 0.89)				
2 Mean baseline FEV1 61% to	o 79% of predicted				
Akpinarli 1999	0/16	0/16			Not estimable
Aubier 1999a	10/171	8/82		3.0 %	0.60 [0.25, 1.46
Aubier 1999b	11/167	8/83		3.0 %	0.68 [0.29, 1.63
Bailey 2008	34/239	41/236	-	11.5 %	0.82 [0.54, 1.24
Boyd 1995	17/55	17/64		4.4 %	1.16 [0.66, 2.05
D5896C0001a	14/155	7/77	-	2.6 %	0.99 [0.42, 2.36
D5896C0001b	7/153	6/76		2.2 %	0.58 [0.20, 1.66
Ind 2003	8/171	8/160	-	2.3 %	0.94 [0.36, 2.43
Jenkins 2006a	2/226	2/57		0.9 %	0.25 [0.04, 1.75
Jenkins 2006b	1/115	3/58		1.1 %	0.17 [0.02, 1.58
Kavaru 2000	2/92	0/90		0.1 %	4.89 [0.24, 100.51
Kemp 1998	8/261	14/264		3.9 %	0.58 [0.25, 1.35
Kuna 2006	4/202	2/207		0.5 %	2.05 [0.38, 11.07
Nathan 2006	14/94	15/91	-	4.2 %	0.90 [0.46, 1.76
Pauwels 1997a	1/210	0/213		0.1 %	3.04 [0.12, 74.27
Pauwels 1997b	0/215	0/214			Not estimable

0.01 0.1 1 10 100 Favours LABA + ICS Favours ICS alone

Study or subgroup	LABA + ICS n/N	ICS alone n/N	Risk Ratio M-H,Fixed,95% Cl	Weight	Risk Ratio M-H,Fixed,95% Cl
Russell 1995	20/99	9/107		2.4 %	2.40 [1.15, 5.02]
SD 039 0725a	21/184	8/84		3.1 %	1.20 [0.55, 2.59]
SD 039 0725b	13/168	9/85		3.3 %	0.73 [0.33, 1.64]
Tal 2002	9/148	6/138		1.7 %	1.40 [0.51, 3.83]
van der Molen 1997	37/125	27/114	+	7.9 %	1.25 [0.82, 1.91]
Weiler 2005	4/99	4/100		1.1 %	1.01 [0.26, 3.93]
Zetterstrom 2001a	3/123	3/62		1.1 %	0.50 [0.10, 2.43]
Zetterstrom 2001b	3/115	2/62		0.7 %	0.81 [0.14, 4.71
Zimmerman 2004a	10/95	7/50		2.5 %	0.75 [0.30, 1.86
Zimmerman 2004b	13/105	7/51	_	2.6 %	0.90 [0.38, 2.12
Subtotal (95% CI)	3803	2841		66.3 %	0.96 [0.81, 1.13]
3 Mean baseline FEV1 not rep D'Urzo 2001	1/455	2/456		0.6 %	0.50 [0.05, 5.51
Heterogeneity: Chi ² = 21.17, o Test for overall effect: Z = 0.48		0.0%			
SAM40012	14/181	10/181		2.8 %	1.40 [0.64, 3.07
SAS40024	6/102	4/90		1.2 %	1.32 [0.39, 4.54
SAS40036	10/172	5/159		1.4 %	1.85 [0.65, 5.29
SAS40037	5/161	8/161		2.2 %	0.63 [0.21, 1.87
SFA100314	4/124	6/124		1.7 %	0.67 [0.19, 2.30
SFA100316	6/113	5/118		1.4 %	1.25 [0.39, 3.99
Subtotal (95% CI) Total events: 46 (LABA + ICS) Heterogeneity: Chi ² = 3.48, df Test for overall effect: Z = 0.56	$f = 6 (P = 0.75); I^2 = 0.0$	1289	•	11.2 %	1.12 [0.74, 1.70
Total (95% CI) Total events: 402 (LABA + ICS Heterogeneity: Chi ² = 25.28, c Test for overall effect: $Z = 0.13$	5523 5), 330 (ICS alone) df = 34 (P = 0.86); I ² =	4497	•	100.0 %	0.99 [0.87, 1.13

Analysis 1.41. Comparison 1 Long-acting beta2 versus placebo: both groups receiving similar dose ICS, Outcome 41 # patients with hoarseness

Review: Addition of long-acting beta2-agonists to inhaled corticosteroids versus same dose inhaled corticosteroids for chronic asthma in adults and children

Comparison: 1 Long-acting beta2 versus placebo: both groups receiving similar dose ICS

Outcome: 41 # patients with hoarseness

Study or subgroup	LABA + ICS	ICS alone	Risk Ratio M- H.Random,95%	Weight	Risk Ratio M- H.Random,95
	n/N	n/N	CI		CI
I Mean baseline FEVI 61% to	o 79% of predicted				
Kuna 2006	4/202	5/207		29.7 %	0.82 [0.22, 3.01]
Zetterstrom 2001 a	0/123	3/62	•	9.3 %	0.07 [0.00, 1.38]
Zetterstrom 2001b	4/115	2/62		22.1 %	1.08 [0.20, 5.72]
Kavaru 2000	3/92	2/90		20.5 %	1.47 [0.25, 8.58]
Ind 2003	5/171	0/160		9.6 %	10.30 [0.57, 184.73]
Subtotal (95% CI)	703	581		91.1 %	1.02 [0.36, 2.88]
Total events: 16 (LABA + ICS	5), 12 (ICS alone)				
Heterogeneity: Tau ² = 0.43; 0	$Chi^2 = 5.84, df = 4 (P = 1)$	= 0.21); I ² =31%			
Test for overall effect: $Z = 0.0$)4 (P = 0.97)				
2 Mean baseline FEV1 not rep	ported				
SFCF4026	2/159	0/159		8.9 %	5.00 [0.24, 103.33]
Subtotal (95% CI)	159	159		8.9 %	5.00 [0.24, 103.33]
Total events: 2 (LABA + ICS).	, 0 (ICS alone)				
Heterogeneity: not applicable					
Test for overall effect: $Z = 1.0$	04 (P = 0.30)				
Total (95% CI)	862	740		100.0 %	1.17 [0.44, 3.10]
Total events: 18 (LABA + ICS	5), 12 (ICS alone)				
Heterogeneity: Tau ² = 0.39; 0	$Chi^2 = 6.85, df = 5 (P = 5)$	= 0.23); I ² =27%			
Test for overall effect: $Z = 0.3$	32 (P = 0.75)				
			0.1 0.2 0.5 1 2 5 10		

Analysis 1.42. Comparison 1 Long-acting beta2 versus placebo: both groups receiving similar dose ICS, Outcome 42 # patients with oral thrush

Review: Addition of long-acting beta2-agonists to inhaled corticosteroids versus same dose inhaled corticosteroids for chronic asthma in adults and children

Comparison: 1 Long-acting beta2 versus placebo: both groups receiving similar dose ICS

Outcome: 42 # patients with oral thrush

Risk Ra	Weight	Risk Ratio	ICS alone	LABA + ICS	Study or subgroup
M-H,Fixed,95%		M-H,Fixed,95% CI	n/N	n/N	
					FEV >/= 80% predicted
Not estimat			0/56	0/60	Verberne 1998
4.04 [0.46, 35.5]	11.4 %		1/102	4/101	Malone 2005
Not estimat			0/19	0/18	Wallin 2003
4.04 [0.46, 35.52	11.4 %		177	179	Subtotal (95% CI)
				, I (ICS alone)	Total events: 4 (LABA + ICS),
					Heterogeneity: not applicable
				6 (P = 0.21)	Test for overall effect: $Z = 1.26$
				79% of predicted	2 Mean baseline FEV1 61% to
0.49 [0.05, 5.3	23.2 %		2/90	1/92	Kavaru 2000
4.03 [0.22, 73.6	7.9 %		0/55	4/124	Noonan 2006a
3.24 [0.13, 78.6	5.5 %		0/107	1/99	Russell 1995
1.50 [0.26, 8.7	22.9 %		2/84	3/84	Shapiro 2000
0.58 [0.05, 6.24	21.2 %		2/64	1/55	Boyd 1995
1.42 [0.06, 34.3	7.8 %		0/54	1/115	Noonan 2006b
1.34 [0.52, 3.46	88.6 %	+	454	569	Subtotal (95% CI)
				i), 6 (ICS alone)	Total events: 11 (LABA + ICS)
			1%	If = 5 (P = 0.85); $I^2 = 0.0$	Heterogeneity: $Chi^2 = 2.03$, df
				I (P = 0.54)	Test for overall effect: $Z = 0.6$
1.65 [0.71, 3.86	100.0 %	•	631	748	Total (95% CI)
				i), 7 (ICS alone)	Total events: 15 (LABA + ICS)
)%	$ff = 6 (P = 0.82); I^2 = 0.0$	Heterogeneity: Chi ² = 2.95, df
				6 (P = 0.25)	Test for overall effect: $Z = 1.16$

Analysis 1.43. Comparison 1 Long-acting beta2 versus placebo: both groups receiving similar dose ICS, Outcome 43 # patients with tremor

Review: Addition of long-acting beta2-agonists to inhaled corticosteroids versus same dose inhaled corticosteroids for chronic asthma in adults and children

Comparison: 1 Long-acting beta2 versus placebo: both groups receiving similar dose ICS

Outcome: 43 # patients with tremor

Study or subgroup	LABA + ICS	ICS alone	Risk Ratio M-	Weight	Risk Ratio M-
	n/N	n/N	H,Random,95% Cl		H,Random,95 Cl
I Mean baseline FEVI >/= 8	0% of predicted				
Verberne 1998	0/60	0/56			Not estimable
Pohunek 2006b	2/201	0/213		6.8 %	5.30 [0.26, 109.66]
Subtotal (95% CI)	261	269	-	6.8 %	5.30 [0.26, 109.66]
Total events: 2 (LABA + ICS)	, 0 (ICS alone)				
Heterogeneity: not applicable					
Test for overall effect: $Z = 1.0$					
2 Mean baseline FEV1 61% to Pauwels 1997a	2/210	0/213		6.8 %	5.07 [0.24, 105.00]
Jenkins 2006b	1/115	2/58		9.8 %	0.25 [0.02, 2.72]
Jenkins 2006a	1/226	1/57		7.9 %	0.25 [0.02, 3.97]
Zimmerman 2004a	0/95	0/50			Not estimable
Zimmerman 2004b	1/106	0/51		6.3 %	1.46 [0.06, 35.18]
Noonan 2006b	1/115	0/55		6.3 %	1.45 [0.06, 34.99]
Noonan 2006a	0/121	0/54			Not estimable
Russell 1995	0/99	0/107			Not estimable
Pauwels 1997b	2/215	0/214		6.8 %	4.98 [0.24, 103.06]
Norhaya 1999	1/30	3/30		10.9 %	0.33 [0.04, 3.03]
Boyd 1995	3/55	3/64	-	16.7 %	1.16 [0.24, 5.53]
Kemp 1998	4/261	0/264		7.2 %	9.10 [0.49, 168.23]
van der Molen 1997	13/125	0/114		7.7 %	24.64 [1.48, 409.86]
Weiler 2005	2/99	0/100		6.8 %	5.05 [0.25, 103.87]
Subtotal (95% CI)	1872	1431	+	93.2 %	1.63 [0.64, 4.15]
Total events: 31 (LABA + ICS					
Heterogeneity: $Tau^2 = 0.70;$		° = 0.17); I ² =29%			
Test for overall effect: Z = 1.0 Total (95% CI)	2133 P = 0.31)	1700	•	100.0 %	1.74 [0.72, 4.20]
Total events: 33 (LABA + IC)		1,30		100.0 /0	1.7 1 [0.7 2, 4.20]
Heterogeneity: $Tau^2 = 0.57;$		P = 0.20); I ² =24%			
Test for overall effect: $Z = 1.2$	24 (P = 0.22)				

Analysis 1.44. Comparison 1 Long-acting beta2 versus placebo: both groups receiving similar dose ICS, Outcome 44 # patients with tachycardia or palpitations

Review: Addition of long-acting beta2-agonists to inhaled corticosteroids versus same dose inhaled corticosteroids for chronic asthma in adults and children

Comparison: 1 Long-acting beta2 versus placebo: both groups receiving similar dose ICS

Outcome: 44 # patients with tachycardia or palpitations

Study or subgroup	LABA + ICS	ICS alone	Risk Ratio	Weight	Risk Ratio
	n/N	n/N	M-H,Fixed,95% CI		M-H,Fixed,95% CI
I Mean baseline FEVI >/= 8					
Verberne 1998	0/60	0/56			Not estimable
Subtotal (95% CI)	60	56			Not estimable
Total events: 0 (LABA + ICS					
Heterogeneity: not applicable Test for overall effect: not ap					
2 Mean baseline FEV1 61% t					
Pauwels 1997a	0/210	0/213			Not estimable
Zimmerman 2004b	1/105	1/51		21.2 %	0.49 [0.03, 7.61]
Zimmerman 2004a	0/95	0/50			Not estimable
Russell 1995	0/99	0/107			Not estimable
Pauwels 1997b	1/215	0/214		7.9 %	2.99 [0.12, 72.89]
Norhaya 1999	0/30	0/30			Not estimable
Shapiro 2000	0/81	0/81			Not estimable
Boyd 1995	1/55	1/64		14.5 %	1.16 [0.07, 18.17]
Kemp 1998	1/261	0/264		7.8 %	3.03 [0.12, 74.15]
van der Molen 1997	7/125	2/114		32.9 %	3.19 [0.68, 15.05]
Subtotal (95% CI)	1276	1188	•	84.3 %	2.13 [0.77, 5.88]
		1188	•	84.3 %	2.13 [0.77, 5.88]
Total events: 11 (LABA + IC	S), 4 (ICS alone)		•	84.3 %	2.13 [0.77, 5.88]
Total events: 11 (LABA + IC Heterogeneity: Chi ² = 1.65,	S), 4 (ICS alone) df = 4 (P = 0.80); I ² =0		-	84.3 %	2.13 [0.77, 5.88]
Total events: 11 (LABA + IC -leterogeneity: Chi ² = 1.65, Test for overall effect: Z = 1. 3 Mean baseline FEV1 not re	S), 4 (ICS alone) df = 4 (P = 0.80); I ² =0 46 (P = 0.14) eported	.0%	•		
Total events: 11 (LABA + IC Heterogeneity: $Chi^2 = 1.65$, Test for overall effect: Z = 1.	S), 4 (ICS alone) df = 4 (P = 0.80); I ² =0 46 (P = 0.14)			84.3 % 15.7 %	
Total events: 11 (LABA + IC Heterogeneity: Chi ² = 1.65, Test for overall effect: Z = 1. 3 Mean baseline FEV1 not re D'Urzo 2001	S), 4 (ICS alone) df = 4 (P = 0.80); I ² =0 46 (P = 0.14) eported	.0%	-		
Total events: 11 (LABA + IC Heterogeneity: Chi ² = 1.65, Test for overall effect: Z = 1. 3 Mean baseline FEV1 not re D'Urzo 2001 Subtotal (95% CI) Total events: 2 (LABA + ICS	(CS), 4 (ICS alone) df = 4 (P = 0.80); I ² =0 46 (P = 0.14) eported 2/455 455), 1 (ICS alone)	1/456	-	15.7 %	2.00 [0.18, 22.03]
Total events: 11 (LABA + IC Heterogeneity: Chi ² = 1.65, Test for overall effect: Z = 1. 3 Mean baseline FEV1 not re D'Urzo 2001 Subtotal (95% CI) Total events: 2 (LABA + ICS	(CS), 4 (ICS alone) df = 4 (P = 0.80); I ² =0 46 (P = 0.14) eported 2/455 455), 1 (ICS alone)	1/456	-	15.7 %	2.00 [0.18, 22.03]
Total events: 11 (LABA + IC Heterogeneity: Chi ² = 1.65, Test for overall effect: Z = 1. 3 Mean baseline FEV1 not re D'Urzo 2001 Subtotal (95% CI) Total events: 2 (LABA + ICS	(CS), 4 (ICS alone) df = 4 (P = 0.80); I ² =0 46 (P = 0.14) eported 2/455 455), 1 (ICS alone)	1/456		15.7 %	2.00 [0.18, 22.03]
Total events: 11 (LABA + IC Heterogeneity: Ch ² = 1.65, Test for overall effect: Z = 1. 3 Mean baseline FEV1 not re D'Urzo 2001 Subtotal (95% CI) Total events: 2 (LABA + ICS	(CS), 4 (ICS alone) df = 4 (P = 0.80); I ² =0 46 (P = 0.14) eported 2/455 455), 1 (ICS alone)	.0% 1/456 456	0.01 0.1 1 10 100 urs (ARA+ICS Travurs ICS ato	15.7 % 15.7 %	2.00 [0.18, 22.03]
Total events: 11 (LABA + IC Heterogeneity: Ch ² = 1.65, Test for overall effect: Z = 1. 3 Mean baseline FEV1 not re D'Urzo 2001 Subtotal (95% CI) Total events: 2 (LABA + ICS	(CS), 4 (ICS alone) df = 4 (P = 0.80); I ² =0 46 (P = 0.14) eported 2/455 455), 1 (ICS alone)	.0% 1/456 456	0.01 0.1 1 10 100 urs LABA + ICS Fabours ICS alor	15.7 % 15.7 %	2.00 [0.18, 22.03]
Total events: 11 (LABA + IC Heterogeneity: Chi ² = 1.65, Test for overall effect: Z = 1. 3 Mean baseline FEV1 not re D'Urzo 2001 Subtotal (95% CI) Total events: 2 (LABA + ICS	(CS), 4 (ICS alone) df = 4 (P = 0.80); I ² =0 46 (P = 0.14) eported 2/455 455), 1 (ICS alone)	.0% 1/456 456		15.7 % 15.7 %	2.00 [0.18, 22.03]
Total events: 11 (LABA + IC Heterogeneity: Chi ² = 1.65, 165 cfor overall effect: Z = 1. 3 Mean baseline FEV1 not re D'Uroo 2001 Subtotal (95% CI) Total events: 2 (LABA + ICS Heterogeneity: not applicable	5), 4 (ICS alone) df = 4 (P = 0.80); I ² = 0 46 (P = 0.14) sported 2/455 455), I (ICS alone) e	0% 1/456 456 Favo	urs LABA + ICS Favours ICS alor	157 % 15.7 % *	2.00 [0.18, 22.03] 2.00 [0.18, 22.03]
Subtoral (95% CI) Total events: II (ABA + IC Heterogeneity: Chi ² = 1.65, Test for overal effect; Z = 1.1 3 Mean baseline FEVI not re D'Uzo 2001 Subtoral (95% CI) Total events: Z (ABA + ICS Heterogeneity: not applicable Study or subgroup	(CS), 4 (ICS alone) df = 4 (P = 0.80); I ² =0 46 (P = 0.14) eported 2/455 455), 1 (ICS alone)	.0% 1/456 456		15.7 % 15.7 %	2.00 [0.18, 22.03]
Total events: 11 (LABA + IC Heterogeneity: Chi ² = 1.65, 15 effort overall effect: Z = 1. 3 Mean baseline FEV1 not re D'Uroo 2001 Subtotal (95% CI) Total events: 2 (LABA + ICS Heterogeneity: not applicable	5), 4 (ICS alone) df = 4 (P = 0.80); P = 0 46 (P = 0.14) ported 2/455 455), 1 (ICS alone) e LABA + ICS n/N	0% 1/456 456 Faro ICS alone	urs LABA + ICS Favours ICS alor Risk Ratio	157 % 15.7 % *	2.00 [0.18, 22.03] 2.00 [0.18, 22.03] Risk Ratio
Total events: 11 (LABA + IC Heterogeneity: Chi ² = 1.65, 18 Mean baseline FEV1 not re D'Urzo 2001 Subtroal (95% CI) Total events: 2 (LABA + ICS Heterogeneity: not applicable Study or subgroup Study or subgroup	S), 4 (ICS alone) df = 4 (P = 0.80); I ² = 0 46 (P = 0.14) ported 2/455 455), 1 (ICS alone) e LABA + ICS r/N 7 (P = 0.57) 1791	0% 1/456 456 Faro ICS alone	urs LABA + ICS Favours ICS alor Risk Ratio	157 % 15.7 % *	200 [0.18, 22.03] 2.00 [0.18, 22.03] Risk Ratio
Total events: 11 (LABA + IC Heterogeneity: Chi ² = 1.65, Test for overall effect. Z = 1. Mean baseline TeV1 not re D'Urzo 2001 Subtotal (95% CI) Total events: 2 (LABA + ICS Heterogeneity: not applicable Study or subgroup est for overall effect. Z = 0.5 foral (95% CI) foral events: 3 (LABA + ICS	5), 4 (ICS alone) df = 4 (P = 0.80); P = 0 46 (P = 0.14) pported 2/455 455), 1 (ICS alone) e LABA + ICS n/N 77 (P = 0.57) 1791 5), 5 (ICS alone)	0% 1/456 456 Faro ICS alone n/N 1700	urs LABA + ICS Favours ICS alor Risk Ratio	15.7 % 15.7 % we Weight	2.00 [0.18, 22.03] 2.00 [0.18, 22.03] Risk Ratio M-H.Fixed.95% CI
Total events: 11 (LABA + IC Heterogeneity: Ch ² = 1.65, 18 for overall effect: Z = 1. 3 Mean baseline FEV1 not re D'Uroo 2001 Subtotal (95% CI) Total events: 2 (LABA + ICS Heterogeneity: not applicable Study or subgroup est for overall effect: Z = 0.5 total events: 13 (LABA + ICS Heterogeneity: Ch ² = 1.65, c	S), 4 (ICS alone) df = 4 (P = 0.80); P = 0 46 (P = 0.14) ported 2/455 455), 1 (ICS alone) e LABA + ICS n/N 77 (P = 0.57) 1791 1791 j, 5 (ICS alone) if = 5 (P = 0.90); P = 01	0% 1/456 456 Faro ICS alone n/N 1700	urs LABA + ICS Favours ICS alor Risk Ratio	15.7 % 15.7 % we Weight	2.00 [0.18, 22.03] 2.00 [0.18, 22.03] Risk Ratio M-H.Fixed.95% CI
Total events: 11 (LABA + IC Heterogeneity: Ch ² = 1.65, 18 for overall effect: Z = 1. 3 Mean baseline FEV1 not re D'Uroo 2001 Subtotal (95% CI) Total events: 2 (LABA + ICS Heterogeneity: not applicable Study or subgroup est for overall effect: Z = 0.5 total events: 13 (LABA + ICS Heterogeneity: Ch ² = 1.65, c	S), 4 (ICS alone) df = 4 (P = 0.80); P = 0 46 (P = 0.14) ported 2/455 455), 1 (ICS alone) e LABA + ICS n/N 77 (P = 0.57) 1791 1791 j, 5 (ICS alone) if = 5 (P = 0.90); P = 01	0% 1/456 456 Faro ICS alone n/N 1700	urs LABA + ICS Favours ICS alor Risk Ratio	15.7 % 15.7 % we Weight	2.00 [0.18, 22.03] 2.00 [0.18, 22.03] Risk Ratio M-H.Fixed.95% CI
Total events: 11 (LABA + IC Heterogeneity: Chi ² = 1.65, Test for overall effect: Z = 1. Mean baseline FV1 not re D'Urzo 2001 Subtotal (95% CI) Total events: 2 (LABA + ICS Heterogeneity: not applicable Study or subgroup	S), 4 (ICS alone) df = 4 (P = 0.80); P = 0 46 (P = 0.14) ported 2/455 455), 1 (ICS alone) e LABA + ICS n/N 77 (P = 0.57) 1791 1791 j, 5 (ICS alone) if = 5 (P = 0.90); P = 01	0% 1/456 456 Fao ICS alone n/N 1700 %	urs LABA + ICS Favours ICS alor Risk Ratio	15.7 % 15.7 % we Weight	2.00 [0.18, 22.03] 2.00 [0.18, 22.03] Risk Ratio M-H-Fixed,95% CI

Analysis 1.45. Comparison 1 Long-acting beta2 versus placebo: both groups receiving similar dose ICS, Outcome 45 Deaths

Review: Addition of long-acting beta2-agonists to inhaled corticosteroids versus same dose inhaled corticosteroids for chronic asthma in adults and children

Comparison: 1 Long-acting beta2 versus placebo: both groups receiving similar dose ICS

Outcome: 45 Deaths

Study or subgroup	LABA + ICS	ICS alone	Risk Ratio	Weight	Risk Ratio
	n/N	n/N	M-H,Fixed,95% CI		M-H,Fixed,95% Cl
Mean baseline FEV1 61% to	79% of predicted				
Aubier 1999a	1/171	0/165		25.3 %	2.90 [0.12, 70.57]
Subtotal (95% CI)	171	165		25.3 %	2.90 [0.12, 70.57]
otal events: I (LABA + ICS),	0 (ICS alone)				
Heterogeneity: not applicable					
Test for overall effect: $Z = 0.6$	5 (P = 0.51)				
Mean baseline FEV1 not rep	orted				
D'Urzo 2001	2/455	1/456		49.6 %	2.00 [0.18, 22.03
SD 037 0344a	1/216	0/210		25.2 %	2.92 [0.12, 71.21
Subtotal (95% CI)	671	666		74.7 %	2.31 [0.34, 15.63]
otal events: 3 (LABA + ICS),	I (ICS alone)				
Heterogeneity: Chi ² = 0.03, dl	$f = 1 (P = 0.85); l^2 = 0.85$	0%			
Test for overall effect: $Z = 0.8$	6 (P = 0.39)				
Total (95% CI)	842	831	-	100.0 %	2.46 [0.48, 12.65]
"otal events: 4 (LABA + ICS),	I (ICS alone)				
leterogeneity: Chi² = 0.05, d	f = 2 (P = 0.98); I ² =0.	0%			
Test for overall effect: $Z = 1.01$	8 (P = 0.28)				

Analysis 1.46. Comparison 1 Long-acting beta2 versus placebo: both groups receiving similar dose ICS, Outcome 46 # patients with adverse cardiovascular events

Review: Addition of long-acting beta2-agonists to inhaled corticosteroids versus same dose inhaled corticosteroids for chronic asthma in adults and children

Comparison: 1 Long-acting beta2 versus placebo: both groups receiving similar dose ICS

Outcome: 46 # patients with adverse cardiovascular events

Study or subgroup	LABA + ICS	ICS alone	Risk Ratio	Weight	Risk Ratio
	n/N	n/N	M-H,Fixed,95% CI		M-H,Fixed,95% C
I Mean baseline FEVI >/= 80	1% of predicted				
Verberne 1998	0/60	1/56		21.0 %	0.31 [0.01, 7.49
Subtotal (95% CI)	60	56		21.0 %	0.31 [0.01, 7.49]
Total events: 0 (LABA + ICS),	I (ICS alone)				
Heterogeneity: not applicable					
Test for overall effect: Z = 0.7	2 (P = 0.47)				
2 Mean baseline FEVI 61% to	79% of predicted				
Akpinarli 1999	0/16	0/16			Not estimable
Boyd 1995	2/55	2/64		25.1 %	1.16 [0.17, 7.99
Kemp 1998	4/261	4/264		53.9 %	1.01 [0.26, 4.00
Subtotal (95% CI)	332	344	-	79.0 %	1.06 [0.35, 3.24
Total events: 6 (LABA + ICS),	6 (ICS alone)				
Heterogeneity: Chi ² = 0.01, d	$If = I (P = 0.9 I); I^2 = 0.9$	0%			
Test for overall effect: $Z = 0.1$	0 (P = 0.92)				
Total (95% CI)	392	400	+	100.0 %	0.90 [0.32, 2.54]
Total events: 6 (LABA + ICS),	7 (ICS alone)				
Heterogeneity: Chi ² = 0.52, d	If = 2 (P = 0.77); $ ^2 = 0.77$	0%			
Test for overall effect: $Z = 0.1$	9 (P = 0.85)				
			0.01 0.1 1 10 100		
		Favou	rs LABA + ICS Favours ICS alor	ie .	

Analysis 1.47. Comparison 1 Long-acting beta2 versus placebo: both groups receiving similar dose ICS, Outcome 47 # Worsening asthma

Review: Addition of long-acting beta2-agonists to inhaled corticosteroids versus same dose inhaled corticosteroids for chronic asthma in adults and children

Comparison: 1 Long-acting beta2 versus placebo: both groups receiving similar dose ICS

Outcome: 47 # Worsening asthma

Study or subgroup	LABA + ICS n/N	ICS alone n/N	Risk Ratio M-H,Fixed,95% Cl	Risk Ratio M-H,Fixed,95% C
I Mean baseline FEVI 61%	to 79% of predicted			
Molimard 2001	17/130	20/129		0.84 [0.46, 1.54
			0.1 0.2 0.5 1 2 5 10	
			Favours LABA + ICS Favours ICS alone	

Analysis 1.48. Comparison 1 Long-acting beta2 versus placebo: both groups receiving similar dose ICS, Outcome 48 Change in height (cm) as SD scores at 24 +/- 4 weeks

Review: Addition of long-acting beta2-agonists to inhaled corticosteroids versus same dose inhaled corticosteroids for chronic asthma in adults and children

Comparison: 1 Long-acting beta2 versus placebo: both groups receiving similar dose ICS

Outcome: 48 Change in height (cm) as SD scores at 24 +/- 4 weeks

Study or subgroup	LABA + ICS		ICS alone			[1ean ence		Mear Difference
	Ν	Mean(SD)	Ν	Mean(SD)		IV,	ixed,	,95% CI		IV,Fixed,95% C
I Mean baseline FEVI	>/= 80% of predicted									
Verberne 1998	60	-0.1 (0.31)	57	-0.16 (0.3)			+		_	0.06 [-0.05, 0.17
					-0.2	-0.1	0	0.1	0.2	
					Favours				LABA +	ICS.

Analysis 1.49. Comparison 1 Long-acting beta2 versus placebo: both groups receiving similar dose ICS, Outcome 49 PC20 Methacholineadjusted odds ratio increase from baseline

Review: Addition of long-acting beta2-agonists to inhaled corticosteroids versus same dose inhaled corticosteroids for chronic asthma in adults and children

Comparison: 1 Long-acting beta2 versus placebo: both groups receiving similar dose ICS

Outcome: 49 PC20 Methacholine-adjusted odds ratio increase from baseline

Study or subgroup	LABA + ICS		ICS alone		Mean Difference	Mean Difference
	Ν	Mean(SD)	Ν	Mean(SD)	IV,Random,95% CI	IV,Random,95% CI
I Mean baseline FEVI	61% to 79% of predi	cted				
Fitzgerald 1999	89	2.39 (5.19)	91	1.74 (3.82)		0.65 [-0.68, 1.98]
					-10 -5 0 5 10	
				Fa	avours LABA + ICS Favours ICS alone	

Analysis 1.50. Comparison 1 Long-acting beta2 versus placebo: both groups receiving similar dose ICS, Outcome 50 ACTH induced cortisol < 18 microg/dl at endpoint

Review: Addition of long-acting beta2-agonists to inhaled corticosteroids versus same dose inhaled corticosteroids for chronic asthma in adults and children

Comparison: 1 Long-acting beta2 versus placebo: both groups receiving similar dose ICS

Outcome: 50 ACTH induced cortisol < 18 microg/dl at endpoint

Study or subgroup	LABA + ICS n/N	ICS alone n/N	Risk Ratio M-H,Fixed,95% Cl	Risk Ratio M-H,Fixed,95% C
I Mean baseline FEVI 61%	to 79% of predicted			
Shapiro 2000	1/84	2/84	• • • • • • • • • • • • • • • • • • • •	0.50 [0.05, 5.41
			0.1 0.2 0.5 1 2 5 10	
			Favours LABA + ICS Favours ICS alone	

Analysis 1.51. Comparison 1 Long-acting beta2 versus placebo: both groups receiving similar dose ICS, Outcome 51 am cortisol < 5 microg/dl at endpoint

Review: Addition of long-acting beta2-agonists to inhaled corticosteroids versus same dose inhaled corticosteroids for chronic asthma in adults and children

Comparison: 1 Long-acting beta2 versus placebo: both groups receiving similar dose ICS

Outcome: 51 am cortisol < 5 microg/dl at endpoint

	LABA + ICS n/N	ICS alone n/N	Risk. Ratio M-H,Fixed,95% Cl	Risk Ratio M-H,Fixed,95% C
I Mean baseline FEVI 61% to 7	79% of predicted			
Shapiro 2000 1/84	1/84	2/84	·	0.50 [0.05, 5.41
			0.1 0.2 0.5 1 2 5 10	

Analysis 1.52. Comparison 1 Long-acting beta2 versus placebo: both groups receiving similar dose ICS, Outcome 52 Change in % PC20 at endpoint

Review: Addition of long-acting beta2-agonists to inhaled corticosteroids versus same dose inhaled corticosteroids for chronic asthma in adults and children

Comparison: 1 Long-acting beta2 versus placebo: both groups receiving similar dose ICS

Outcome: 52 Change in % PC20 at endpoint

Study or subgroup	LABA + ICS		ICS alone			Mean erence	Weight	Mear Difference
	N	Mean(SD)	N	Mean(SD)	IV,Fixe	:d,95% CI		IV,Fixed,95% C
I Mean baseline FEVI	>/= 80% of predi	cted						
Meijer 1995	20	1.1 (1.34)	19	0.8 (1.74)	I		100.0 %	0.30 [-0.68, 1.28
Total (95% CI)	20		19			•	100.0 %	0.30 [-0.68, 1.28]
Heterogeneity: not app	olicable							
Test for overall effect:	Z = 0.60 (P = 0.55	5)						
Test for subgroup diffe	rences: Not applic	able						
					10 -5	0 5	10	
					urs ICS alone		LABA + ICS	

Analysis 1.53. Comparison 1 Long-acting beta2 versus placebo: both groups receiving similar dose ICS, Outcome 53 PC20 histamine

Review: Addition of long-acting beta2-agonists to inhaled corticosteroids versus same dose inhaled corticosteroids for chronic asthma in adults and children

Comparison: 1 Long-acting beta2 versus placebo: both groups receiving similar dose ICS

Outcome: 53 PC20 histamine

Study or subgroup	Doub'g doses (SE)	Doub'g doses IV,Fixed,95% Cl	Doub'g doses IV,Fixed,95% CI	
I Mean baseline FEVI >/= 80% Koopmans 2006	of predicted 0.7 (0.3)		0.70 [0.11, 1.29]	
		-4 -2 0 2 4 Favours ICS alone Favours LABA+ICS		

Analysis 2.1. Comparison 2 Additional comparisons for same dose, Outcome 1 # patients with exacerbations requiring oral steroids by baseline predicted FEV1

Review: Addition of long-acting beta2-agonists to inhaled corticosteroids versus same dose inhaled corticosteroids for chronic asthma in adults and children

Comparison: 2 Additional comparisons for same dose

Outcome: 1 # patients with exacerbations requiring oral steroids by baseline predicted FEV1

Study or subgroup	LABA + ICS n/N	ICS alone n/N	Risk Ratio IV.Fixed,95% CI	Weight	Risk Ratio IV.Fixed.95% C
Mean baseline FEV1 >/= 80			10000000		11,000,000
Langton Hewer 1995	3/11	3/12		2.5 %	1.09 [0.28, 4.32
Li 1999	2/13	1/16		0.9 %	2.46 [0.25, 24.21
Malone 2005	2/101	3/102		1.5 %	0.67 [0.11, 3.94
O'Byrne 2001a	58/323	81/322	-	52.1 %	0.71 [0.53, 0.96
O'Byrne 2001b	39/315	61/312	•	34.1 %	0.63 [0.44, 0.92
Simons 1997	0/16	1/16	•	0.5 %	0.33 [0.01, 7.62
Verberne 1998	10/60	10/57	_	7.3 %	0.95 [0.43, 2.11
Wallin 2003	1/18	5/19		1.1 %	0.21 [0.03, 1.64

Study or subgroup	LABA + ICS	ICS alone	Risk Ratio	Weight	Risk Ratio	
Subtotal (95% CI)	n/N 857	n/N 856	N,Fixed,95% CI	100.0 %	N/Fixed,95% C 0.70 [0.57, 0.87	
Total events: 115 (LABA + IC		020	•	100.0 %	0./0[0.5/,0.8/	1
Heterogeneity: Chi ² = 3.96, d	$f = 7 (P = 0.78); I^2 = 0.0$	1%				
Test for overall effect: $Z = 3.2$						
2 Mean baseline FEV1 61% to Akpinarli 1999	79% of predicted 0/16	0/16			Not estimable	e
Aubier 1999a	5/171	7/83		1.7 %	0.35 [0.11, 1.06	
Aubier 1999b	17/167	7/82		3.0 %	1.19 [0.52, 2.76	
Boyd 1995	19/55	15/64	•	6.5 %	1.47 [0.83, 2.61	
Fitzgerald 1999	3/89	6/91		1.2 %	0.51 [0.13, 1.98	1
Kavaru 2000	0/92	0/90			Not estimable	e
Kemp 1998	53/252	59/254	•	19.8 %	0.91 [0.65, 1.26	1
Nathan 2006	1/94	3/91		0.4 %	0.32 [0.03, 3.05	1
Noonan 2006a	5/124	2/55		0.8 %	1.11 [0.22, 5.54	1
Noonan 2006b	4/115	2/54		0.8 %	0.94 [0.18, 4.97	1
Norhaya 1999	1/30	3/30		0.4 %	0.33 [0.04, 3.03	
Pauwels 1997a	62/210	82/213		29.3 %	0.77 { 0.59, 1.00	
Pauwels 1997b	41/215	60/214		17.4 %	0.68 [0.48, 0.96	
Russell 1995	16/99	18/99		5.7 %	0.89 [0.48, 1.64	
Shapiro 2000	1/84	2/84		0.4 %	0.50 [0.05, 5.41	
van der Molen 1997	33/125	32/114	+	12.4 %	0.94 [0.62, 1.42	1
Weiler 2005	1/102	0/90		0.2 %	2.65 [0.11, 64.26	1
Subtotal (95% CI)	2040	1724	•	100.0 %	0.83 [0.72, 0.96]
Total events: 262 (LABA + IC Heterogeneity: Chi ² = 11.82,		0.097				
Test for overall effect: $Z = 2.4$		0.0%				
3 Mean baseline FEV1 not rep						
SAS40024	0/99	2/100	· •	8.0 %	0.20 [0.01, 4.15	1
SAS40036	2/172	7/159		30.3 %	0.26 [0.06, 1.25	1
SAS40037	3/161	6/161		39.2 %	0.50 [0.13, 1.96]
SFA100314	1/124	1/124		9.6 %	1.00 [0.06, 15.81	1
SFA100316	2/113	1/118		12.9 %	2.09 [0.19, 22.71	1
Subtotal (95% CI)	669	662	-	100.0 %	0.49 [0.21, 1.16	1
Total events: 8 (LABA + ICS),					16 A 16 A	
Heterogeneity: Chi ² = 2.61, d	f = 4 (P = 0.63); P = 0.0	1%				
<u> </u>			0.02 0.1 1 10 50	3 3	1 <u>1</u> 1	
		F	avours LABA + ICS Favours ICS alor	ie.		
				397		
ubgroup LAB		ICS alone	Risk Ratio	W	eight	Risk I
	n/N	n/N	IV,Fixed,95% CI			IV,Fixed,95
all effect: $Z = 1.62$ (P = 0.						
roup differences: $Chi^2 = 2$.	76, df = 2 (P = 0.2	5), I ² =28%				
			0.02 0.1 1 10	50		

Analysis 2.2. Comparison 2 Additional comparisons for same dose, Outcome 2 # patients with exacerbations requiring oral steroids children versus adults

Review: Addition of long-acting beta2-agonists to inhaled corticosteroids versus same dose inhaled corticosteroids for chronic asthma in adults and children

Comparison: 2 Additional comparisons for same dose

Outcome: 2 # patients with exacerbations requiring oral steroids children versus adults

Study or subgroup	LABA + ICS n/N	ICS alone n/N	Risk Ratio IV,Fixed,95% Cl	Weight	Risk Rat IV,Fixed,95% (
I Children					
Akpinarli 1999	0/16	0/16			Not estimab
Langton Hewer 1995	3/11	3/12	_	10.2 %	1.09 [0.28, 4.32
Malone 2005	2/101	3/102		6.2 %	0.67 [0.11, 3.94
Russell 1995	16/99	18/99	+	51.3 %	0.89 [0.48, 1.64
Simons 1997	0/16	1/16		2.0 %	0.33 [0.01, 7.62
Verberne 1998	10/60	10/57	-	30.3 %	0.95 [0.43, 2.11
Subtotal (95% CI)	303	302	•	100.0 %	0.89 [0.58, 1.39
Total events: 31 (LABA + ICS) Heterogeneity: Chi ² = 0.58, d Test for overall effect: Z = 0.5 2 Adults	$f = 4 (P = 0.96); I^2 = 0.96$	0%			
Aubier 1999a	5/171	7/83		1.2 %	0.35 [0.11, 1.06
Aubier 1999b	17/167	7/82	- - -	2.2 %	1.19 [0.52, 2.76
Boyd 1995	19/55	15/64	+	4.7 %	1.47 [0.83, 2.61
Fitzgerald 1999	3/89	6/91		0.8 %	0.51 [0.13, 1.98

0.01 0.1 I IO IOO Favours LABA + ICS Favours ICS alone

Risk Ri IV.Fixed.95%	Weight	Risk Ratio IV.Fixed.95% Cl	ICS alone n/N	LABA + ICS n/N	Study or subgroup
IV,FIXed,95% Not estima		IV,FIXEU,95% CI	0/90	0/92	Kavaru 2000
0.91 [0.65, 1.2	14.4 %	+	59/254	53/252	Kemp 1998
2.46 [0.25, 24.2	0.3 %		1/16	2/13	Li 1999
0.32 [0.03, 3.0	0.3 %		3/91	1/94	Nathan 2006
1.11 [0.22, 5.5	0.6 %		2/55	5/124	Noonan 2006a
0.94 [0.18, 4.5	0.6 %		2/54	4/115	Noonan 2006b
0.33 [0.04, 3.0	0.3 %		3/30	1/30	Norhaya 1999
0.71 [0.53, 0.5	17.2 %	-	81/322	58/323	O'Byrne 2001a
0.63 [0.44, 0.5	11.3 %	•	61/312	39/315	O'Byme 2001b
0.77 [0.59, 1.0	21.4 %	-	82/213	62/210	Pauwels 1997a
0.68 [0.48, 0.5	12.7 %	-	60/214	41/215	Pauwels 1997b
0.20 [0.01, 4.1	0.2 %		2/100	0/99	SAS40024
0.26 [0.06, 1.2	0.6 %		7/159	2/172	SAS40036
0.50 [0.13, 1.5	0.8 %		6/161	3/161	SAS40037
1.00 [0.06, 15.8	0.2 %		1/124	1/124	SFA100314
2.09 [0.19, 22.7	0.3 %		1/118	2/113	SFA100316
0.50 [0.05, 5.4	0.3 %		2/84	1/84	Shapiro 2000
0.94 [0.62, 1.4	9.0 %	+	32/114	33/125	van der Molen 1997
0.21 [0.03, 1.6	0.4 %		5/19	1/18	Wallin 2003
2.65 [0.11, 64.2	0.2 %		0/90	1/102	Weiler 2005
0.77 [0.68, 0.8	100.0 %		2940	3263	ubtotal (95% CI)
2.65 [0.11, 64.2	0.2 % 100.0 %	•	2940	3263 5), 445 (ICS alone) df = 22 (P = 0.57); I ² = 5 (P = 0.000052)	

Analysis 2.3. Comparison 2 Additional comparisons for same dose, Outcome 3 # patients with exacerbations requiring oral steroids by dose of ICS in both groups

Review: Addition of long-acting beta2-agonists to inhaled corticosteroids versus same dose inhaled corticosteroids for chronic asthma in adults and children

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Comparison: 2 Additional comparisons for same dose

Outcome: 3 # patients with exacerbations requiring oral steroids by dose of ICS in both groups

Study or subgroup	LABA + ICS	ICS alone	Peto Odds Ratio	Weight	Pet Odds Rati
	n/N	n/N	Peto,Fixed,95% CI		Peto,Fixed,95% (
Low dose of ICS (<= 400 mcg/	day of BDP-eq)				
Kavaru 2000	0/92	0/90			Not estimab
Malone 2005	2/101	3/102		0.7 %	0.67 [0.11, 3.95
O'Byrne 2001a	58/323	81/322	-	16.2 %	0.65 [0.45, 0.95
O'Byme 2001b	39/315	61/312		12.5 %	0.59 [0.38, 0.90
Pauwels 1997a	62/210	82/213	-	14.1 %	0.67 [0.45, 1.00
SAS40036	2/172	7/159		1.3 %	0.29 [0.08, 1.11
SAS40037	3/161	6/161		1.3 %	0.50 [0.13, 1.90
SFA100314	1/124	1/124		0.3 %	1.00 [0.06, 16.08
SFA100316	2/113	1/118		0.4 %	2.05 [0.21, 19.89
Simons 1997	0/16	1/16	•	0.1 %	0.14 [0.00, 6.82
Verberne 1998	10/60	10/57		2.5 %	0.94 [0.36, 2.45
Wallin 2003	1/18	5/19	•	0.8 %	0.23 [0.04, 1.27
ubtotal (95% CI)	1705	1693	•	50.3 %	0.63 [0.51, 0.78
tal events: 180 (LABA + ICS), eterogeneity: Chi ² = 5.37, df = st for overall effect: Z = 4.25 (F Moderate dose of ICS (401 to 1	10 (P = 0.86); I ² =0 P = 0.000021)				
Akpinarli 1999	0/16	0/16			Not estimab
Noonan 2006a	5/124	2/55		0.9 %	1.11 [0.22, 5.69
Noonan 2006b	4/115	2/54		0.8 %	0.94 [0.16, 5.35
Norhaya 1999	1/30	3/30		0.6 %	0.35 [0.05, 2.61
Pauwels 1997b	41/215	60/214		11.5 %	0.61 [0.39, 0.95
Russell 1995	16/99	18/99		4.2 %	0.87 [0.42, 1.81
ubtotal (95% CI)	599	468	•	17.9 %	0.68 [0.48, 0.97
tal events: 67 (LABA + ICS), 8 eterogeneity: Chi ² = 1.56, df =		0%			

Favours LABA + ICS Favours ICS alone

Study or subgroup	LABA + ICS	ICS alone	Peto Odds Ratio	Weight	Pete Odds Ratio
	n/N	n/N	Peto,Fixed,95% CI		Peto,Fixed,95% C
Test for overall effect: $Z = 2.11$	(P = 0.035)				
3 High dose of ICS (>800 mcg	/day of BDP-eq)				
Aubier 1999a	5/171	7/83		1.5 %	0.30 [0.09, 1.01
Aubier 1999b	17/167	7/82		2.9 %	1.21 [0.49, 2.95
Boyd 1995	19/55	15/64		3.6 %	1.72 [0.78, 3.80
Nathan 2006	1/94	3/91		0.6 %	0.35 [0.05, 2.53
SAS40024	0/99	2/100	·	0.3 %	0.14 [0.01, 2.18
Shapiro 2000	1/84	2/84		0.4 %	0.51 [0.05, 4.96
Weiler 2005	1/102	0/90		0.1 %	6.57 [0.13, 333.61
Subtotal (95% CI)	772	594	+	9.4 %	0.94 [0.58, 1.54
Heterogeneity: $Chi^2 = 9.93$, df Test for overall effect: $Z = 0.24$ 4 Unspecified dose of ICS or ra	(P = 0.81)				
Fitzgerald 1999	3/89	6/91		1.3 %	0.51 [0.13, 1.94
Kemp 1998	53/252	59/254	-	13.0 %	0.88 [0.58, 1.34
Langton Hewer 1995	3/11	3/12		0.7 %	1.12 [0.18, 6.92
Li 1999	2/13	1/16		0.4 %	2.59 [0.24, 27.45
van der Molen 1997	33/125	32/114	-	7.0 %	0.92 [0.52, 1.62
Subtotal (95% CI)	490	487	•	22.4 %	0.89 [0.65, 1.22
Total events: 94 (LABA + ICS), Heterogeneity: $Chi^2 = 1.53$, df Test for overall effect: $Z = 0.72$	= 4 (P = 0.82); I ² =0.	0%			
Total (95% CI)	3566	3242	•	100.0 %	0.72 [0.62, 0.83
Total events: 385 (LABA + ICS), 480 (ICS alone)				
Heterogeneity: Chi ² = 22.82, d	$f = 27 (P = 0.69); I^2 =$	0.0%			
Test for overall effect: $Z = 4.32$					
Tast for subgroup differences (Chi ² = 4.42, df = 3 (P	= 0.22), I ² =32%			

Analysis 2.4. Comparison 2 Additional comparisons for same dose, Outcome 4 # patients with exacerbations requiring oral steroids by combination inhaler or separate inhaler for LABA

Review: Addition of long-acting beta2-agonists to inhaled corticosteroids versus same dose inhaled corticosteroids for chronic asthma in adults and children

Comparison: 2 Additional comparisons for same dose

Outcome: 4 # patients with exacerbations requiring oral steroids by combination inhaler or separate inhaler for LABA

Study or subgroup	LABA + ICS n/N	ICS alone n/N	Risk Ratio IV.Fixed,95% Cl	Weight	Risk Ratio IV.Fixed.95% C
Combination inhaler	1014	1014	N, NG, 2376 CI		14,1 Xed,7 576 C
Aubier 1999b	17/167	7/82		34.2 %	1.19 [0.52, 2.76
Kavaru 2000	0/92	0/90			Not estimable
Li 1999	2/13	1/16		4.6 %	2.46 [0.25, 24.21
Malone 2005	2/101	3/102		7.7 %	0.67 [0.11, 3.94
Nathan 2006	1/94	3/91		4.8 %	0.32 [0.03, 3.05
Noonan 2006a	5/124	2/55		9.3 %	1.11 [0.22, 5.54
SAS40024	0/99	2/100	·	2.6 %	0.20 [0.01, 4.15
SAS40036	2/172	7/159		9.9 %	0.26 [0.06, 1.25
SAS40037	3/161	6/161		12.9 %	0.50 [0.13, 1.96
SFA100314	1/124	1/124		3.2 %	1.00 [0.06, 15.81
SFA100316	2/113	1/118		4.2 %	2.09 [0.19, 22.71
Shapiro 2000	1/84	2/84		4.2 %	0.50 [0.05, 5.41
Weiler 2005	1/102	0/90		2.4 %	2.65 [0.11, 64.26
leterogeneity: $Chi^2 = 7.15$, d est for overall effect: $Z = 0.8$ Separate inhaler	5 (P = 0.40)				
Akpinarli 1999	0/16	0/16			Not estimable
Aubier 1999a	5/171	7/83		1.2 %	0.35 [0.11, 1.06
Boyd 1995	19/55	15/64		4.7 %	1.47 [0.83, 2.61
Fitzgerald 1999	3/89	6/91		0.8 %	0.51 [0.13, 1.98
Kemp 1998	53/252	59/254	+	14.3 %	0.91 [0.65, 1.26
Langton Hewer 1995	3/11	3/12		0.8 %	1.09 [0.28, 4.32
Noonan 2006b	4/115	2/54		0.6 %	0.94 [0.18, 4.97
Norhaya 1999	1/30	3/30		0.3 %	0.33 [0.04, 3.03
			0.02 0.1 1 10 50 s LABA + ICS Favours ICS alo	ne	
Study or subgroup	LABA + ICS n/N	ICS alone n/N	Risk Ratio IV,Fixed,95% Cl	Weight	Risk Rat IV,Fixed,95%
O'Byrne 2001a	58/323	81/322	•	17.0 %	0.71 [0.53, 0.9

	n/N	n/N	IV,Fixed,95% CI		IV,Fixed,95% CI
O'Byrne 2001a	58/323	81/322	•	17.0 %	0.71 [0.53, 0.96]
O'Byrne 2001b	39/315	61/312	+	11.2 %	0.63 [0.44, 0.92]
Pauwels 1997a	62/210	82/213	•	21.1 %	0.77 [0.59, 1.00]
Pauwels 1997b	41/215	60/214	-	12.5 %	0.68 [0.48, 0.96]
Russell 1995	16/99	18/99		4.1 %	0.89 [0.48, 1.64]
Simons 1997	0/16	1/16	·	0.2 %	0.33 [0.01, 7.62]
van der Molen 1997	33/125	32/114	+	8.9 %	0.94 [0.62, 1.42]
Verberne 1998	10/60	10/57		2.4 %	0.95 [0.43, 2.11]
Subtotal (95% CI)	2102	1951	•	100.0 %	0.78 [0.69, 0.89]
otal events: 347 (LABA + ICS), 4	140 (ICS alone)				
leterogeneity: Chi ² = 12.41, df =	14 (P = 0.57); I ² =	0.0%			
est for overall effect: Z = 3.86 (P	= 0.00011)				
Not reported					
Wallin 2003	1/18	5/19		100.0 %	0.21 [0.03, 1.64]
Subtotal (95% CI)	18	19		100.0 %	0.21 [0.03, 1.64]
otal events: I (LABA + ICS), 5 (I	CS alone)				
leterogeneity: not applicable					
est for overall effect: Z = 1.49 (P	= 0.14)				
est for subgroup differences: Chi	² = 1.59, df = 2 (P =	= 0.45), I ² =0.0%			
est for subgroup differences: Chi	² = 1.59, df = 2 (P =		0.02 0.1 I ID 50 s LABA + ICS Favours ICS alc	one	

Analysis 2.5. Comparison 2 Additional comparisons for same dose, Outcome 5 # patients with exacerbations requiring oral steroids by whether LABA dose is usual or higher than usual

Review: Addition of long-acting beta2-agonists to inhaled corticosteroids versus same dose inhaled corticosteroids for chronic asthma in adults and children

Comparison: 2 Additional comparisons for same dose

Outcome: 5 # patients with exacerbations requiring oral steroids by whether LABA dose is usual or higher than usual

Risk Ra IV.Fixed.95%	Weight	Risk Ratio IV.Fixed.95% CI	ICS alone n/N	LABA + ICS n/N	Study or subgroup
					LABA at usual dose
Not estima			0/16	0/16	Akpinarli 1999
0.35 [0.11, 1.0	1.3 %		7/83	5/171	Aubier 1999a
1.19 [0.52, 2.7	2.3 %		7/82	17/167	Aubier 1999b
0.51 [0.13, 1.9	0.9 %		6/91	3/89	Fitzgerald 1999
Not estima			0/90	0/92	Kavaru 2000
0.91 [0.65, 1.2	15.4 %	+	59/254	53/252	Kemp 1998
2.46 [0.25, 24.2	0.3 %		1/16	2/13	Li 1999
0.67 [0.11, 3.9	0.5 %		3/102	2/101	Malone 2005
0.32 [0.03, 3.0	0.3 %		3/91	1/94	Nathan 2006
1.11 [0.22, 5.5	0.6 %		2/55	5/124	Noonan 2006a
0.94 [0.18, 4.9	0.6 %		2/54	4/115	Noonan 2006b
0.33 [0.04, 3.0	0.3 %		3/30	1/30	Norhaya 1999
0.71 [0.53, 0.9	18.4 %	•	81/322	58/323	O'Byme 2001a
0.63 [0.44, 0.9	12.1 %	•	61/312	39/315	O'Byme 2001b
0.77 [0.59, 1.0	22.8 %	-	82/213	62/210	Pauwels 1997a
0.68 [0.48, 0.9	13.6 %	-	60/214	41/215	Pauwels 1997b
0.89 [0.48, 1.6	4.4 %		18/99	16/99	Russell 1995
0.20 [0.01, 4.1	0.2 %	•	2/100	0/99	SAS40024
0.26 [0.06, 1.2	0.7 %		7/159	2/172	SAS40036
0.50 [0.13, 1.9	0.9 %		6/161	3/161	SAS40037
1.00 [0.06, 15.8	0.2 %		1/124	1/124	SFA100314
2.09 [0.19, 22.7	0.3 %		1/118	2/113	SFA100316
0.50 [0.05, 5.4	0.3 %		2/84	1/84	Shapiro 2000
0.33 [0.01, 7.6	0.2 %	•	1/16	0/16	Simons 1997

Risk Ratio	Weight	Risk Ratio	ICS alone	LABA + ICS	Study or subgroup
IV,Fixed,95% C		IV,Fixed,95% CI	n/N	n/N	
0.95 [0.43, 2.11	2.6 %		10/57	10/60	Verberne 1998
0.21 [0.03, 1.64	0.4 %		5/19	1/18	Wallin 2003
2.65 [0.11, 64.26	0.2 %		0/90	1/102	Weiler 2005
0.74 [0.65, 0.84]	100.0 %	•	3052	3375	Subtotal (95% CI)
), 430 (ICS alone)	liotal events: 330 (LABA + ICS)
			0.0%	$f = 24 (P = 0.93); I^2 = 0$	Heterogeneity: Chi ² = 14.81, d
				(P < 0.00001)	lest for overall effect: Z = 4.55
				ose	2 LABA at higher than usual do
1.47 [0.83, 2.61	32.4 %		15/64	19/55	Boyd 1995
1.09 [0.28, 4.32	5.6 %		3/12	3/11	Langton Hewer 1995
0.94 [0.62, 1.42	61.9 %	+	32/114	33/125	van der Molen 1997
1.10 [0.79, 1.52]	100.0 %	•	190	191	Subtotal (95% CI)
				50 (ICS alone)	Fotal events: 55 (LABA + ICS),
			%	= 2 (P = 0.46); I ² =0.0	Heterogeneity: Chi ² = 1.55, df
				(P = 0.58)	Test for overall effect: $Z = 0.56$
			= 0.03), I ² =79%	$Chi^2 = 4.79, df = 1 (P =$	Fest for subgroup differences: C
		0.02 0.1 1 10 50			
		s LABA + ICS Favours ICS alone	Favou		

Analysis 2.6. Comparison 2 Additional comparisons for same dose, Outcome 6 # patients with exacerbations requiring oral steroids by type of LABA

Review: Addition of long-acting beta2-agonists to inhaled corticosteroids versus same dose inhaled corticosteroids for chronic asthma in adults and children

Comparison: 2 Additional comparisons for same dose

Outcome: 6 # patients with exacerbations requiring oral steroids by type of LABA

Study or subgroup	LABA + ICS n/N	ICS alone n/N	Risk Ratio IV,Fixed,95% CI	Weight	Risk Rat IV,Fixed,95% (
I Formoterol					
Akpinarli 1999	0/16	0/16			Not estimab
Fitzgerald 1999	3/89	6/91		1.1 %	0.51 [0.13, 1.98
Noonan 2006a	5/124	2/55	·	0.8 %	1.11 [0.22, 5.54
Noonan 2006b	4/115	2/54		0.8 %	0.94 [0.18, 4.97
O'Byme 2001a	58/323	81/322	-	23.4 %	0.71 [0.53, 0.96
O'Byme 2001b	39/315	61/312	•	15.4 %	0.63 [0.44, 0.92
Pauwels 1997a	62/210	82/213	-	29.0 %	0.77 [0.59, 1.00
Pauwels 1997b	41/215	60/214	-	17.3 %	0.68 [0.48, 0.96
van der Molen 1997	33/125	32/114	+	12.2 %	0.94 [0.62, 1.42
Subtotal (95% CI)	1532	1391	•	100.0 %	0.74 [0.64, 0.85
Test for overall effect: Z = 4.16 2 Salmeterol	(P = 0.000033)				
Test for overall effect: $Z = 4.16$	(P = 0.000033)				
Aubier 1999a	5/171	7/83		3.6 %	0.35 [0.11, 1.06
Aubier 1999b	17/167	7/82	-	6.4 %	1.19 [0.52, 2.76
Boyd 1995	19/55	15/64	-	13.7 %	1.47 [0.83, 2.61
Kavaru 2000	0/92	0/90		1011 10	Not estimab
Kemp 1998	53/252	59/254	-	41.9 %	0.91 [0.65, 1.26
Langton Hewer 1995	3/11	3/12		2.4 %	1.09 [0.28, 4.32
Li 1999	2/13	1/16		0.9 %	2.46 [0.25, 24.21
Malone 2005	2/101	3/102		1.4 %	0.67 [0.11, 3.94
Nathan 2006	1/94	3/91		0.9 %	0.32 [0.03, 3.05
Norhaya 1999	1/30	3/30		0.9 %	0.33 [0.04, 3.03
Russell 1995	16/99	18/99	_	12.0 %	0.89 [0.48, 1.64

Favours LABA + ICS Favours ICS alone

Risk Rat	Weight	Risk Ratio	ICS alone	LABA + ICS	Study or subgroup
IV,Fixed,95%		IV,Fixed,95% CI	n/N	n/N	
0.26 [0.06, 1.25	1.9 %		7/159	2/172	SAS40036
0.50 [0.13, 1.96	2.4 %		6/161	3/161	SAS40037
1.00 [0.06, 15.81	0.6 %		1/124	1/124	SFA100314
2.09 [0.19, 22.71	0.8 %		1/118	2/113	SFA100316
0.50 [0.05, 5.4]	0.8 %		2/84	1/84	Shapiro 2000
0.33 [0.01, 7.62	0.5 %	·	1/16	0/16	Simons 1997
0.95 [0.43, 2.1]	7.1 %	-	10/57	10/60	Verberne 1998
0.21 [0.03, 1.64	1.1 %		5/19	1/18	Wallin 2003
2.65 [0.11, 64.26	0.4 %		0/90	1/102	Weiler 2005
0.89 [0.72, 1.10	100.0 %	•	1851	2034	Subtotal (95% CI)
), 154 (ICS alone)	otal events: 140 (LABA + ICS
).0%	If = 19 (P = 0.65); I ² =(-leterogeneity: Chi ² = 16.09, o
				(P = 0.29)	lest for overall effect: $Z = 1.03$
			= 0.14), I ² =53%	$Chi^2 = 2.14$, df = 1 (P =	Test for subgroup differences:
		0.02 0.1 1 10 50			
		s LABA + ICS Favours ICS alo	C		

Analysis 2.7. Comparison 2 Additional comparisons for same dose, Outcome 7 # patients with exacerbations requiring oral steroids by trial duration

Review: Addition of long-acting beta2-agonists to inhaled corticosteroids versus same dose inhaled corticosteroids for chronic asthma in adults and children

Comparison: 2 Additional comparisons for same dose

Outcome: 7 # patients with exacerbations requiring oral steroids by trial duration

Study or subgroup	LABA + ICS n/N	ICS alone n/N	Risk Ratio IV.Fixed.95% CI	Weight	Risk Rati IV.Fixed,95% (
<= 6 weeks	1014	1014	Na Mady 570 Cr		141 1464/2 220 0
Akpinarli 1999	0/16	0/16			Not estimabl
Boyd 1995	19/55	15/64	-	15.9 %	1.47 [0.83, 2.61
Kavaru 2000	0/92	0/90			Not estimab
Kemp 1998	53/252	59/254	-	48.6 %	0.91 [0.65, 1.26
Langton Hewer 1995	3/11	3/12		2.8 %	1.09 [0.28, 4.32
Li 1999	2/13	1/16		1.0 %	2.46 [0.25, 24.21
Malone 2005	2/101	3/102		1.7 %	0.67 [0.11, 3.94
Nathan 2006	1/94	3/91		1.0 %	0.32 [0.03, 3.05
Noonan 2006a	5/124	2/55		2.0 %	1.11 [0.22, 5.54
Noonan 2006b	4/115	2/54		1.9 %	0.94 [0.18, 4.97
Norhaya 1999	1/30	3/30		1.1 %	0.33 [0.04, 3.03
Russell 1995	16/99	18/99	+	13.9 %	0.89 [0.48, 1.64
SAS40024	0/99	2/100		0.6 %	0.20 [0.01, 4.15
SAS40036	2/172	7/159		2.1 %	0.26 [0.06, 1.25
SAS40037	3/161	6/161		2.8 %	0.50 [0.13, 1.96
SFA100314	1/124	1/124		0.7 %	1.00 [0.06, 15.81
SFA100316	2/113	1/118		0.9 %	2.09 [0.19, 22.71
Shapiro 2000	1/84	2/84		0.9 %	0.50 [0.05, 5.4]
Simons 1997	0/16	1/16		0.5 %	0.33 [0.01, 7.62
Wallin 2003	1/18	5/19		1.2 %	0.21 [0.03, 1.64
Weiler 2005	1/102	0/90		0.5 %	2.65 [0.11, 64.26
Subtotal (95% CI) Total events: 117 (LABA + ICS) Heterogeneity: Chi ² = 12.92, d Test for overall effect: Z = 0.84	$f = 18 (P = 0.80); I^2 =$	1754 0.0%	·	100.0 %	0.91 [0.72, 1.14

Favours LABA + ICS Favours ICS alone

Study or subgroup	LABA + ICS n/N	ICS alone n/N	Risk Ratio IV.Fixed.95% CI	Weight	Risk Ratio IV.Fixed.95% C
2 > 16 weeks	1015	Intern	IV,FIXEU,7576 CI		IV,FIXE0,7576 C
2 > 16 weeks Aubier 1999a	5/171	7/83		1.6 %	0.35 [0.11, 1.06
Aubier 1999b	17/167	7/82		2.8 %	1.19 [0.52, 2.76
	3/89				
Fitzgerald 1999	3/89	6/91		1.1 %	0.51 [0.13, 1.98
O'Byrne 2001a	58/323	81/322	•	22.0 %	0.71 [0.53, 0.96
O'Byrne 2001b	39/315	61/312	•	14.4 %	0.63 [0.44, 0.92
Pauwels 1997a	62/210	82/213	-	27.3 %	0.77 [0.59, 1.00
Pauwels 1997b	41/215	60/214	•	16.2 %	0.68 [0.48, 0.96
van der Molen 1997	33/125	32/114	+	11.5 %	0.94 [0.62, 1.42
Verberne 1998	10/60	10/57	+	3.1 %	0.95 [0.43, 2.11
Subtotal (95% CI)	1675	1488	•	100.0 %	0.74 [0.64, 0.85
Total events: 268 (LABA + IC	S), 346 (ICS alone)				
Heterogeneity: Chi ² = 5.98, d	$f = 8 (P = 0.65); ^2 = 0.05$	0%			
Test for overall effect: $Z = 4.2$	2 (P = 0.000024)				
Test for subgroup differences:	$Chi^2 = 2.25, df = 1$ (P	= 0.13), I ² =56%			
			0.01 0.1 1 10 100		
		Favou	irs LABA + ICS Favours ICS alo	ne	

Analysis 2.8. Comparison 2 Additional comparisons for same dose, Outcome 8 # patients with exacerbations requiring oral steroids study unsupported by pharmaceutical industry excluded

Review: Addition of long-acting beta2-agonists to inhaled corticosteroids versus same dose inhaled corticosteroids for chronic asthma in adults and children

Comparison: 2 Additional comparisons for same dose

Outcome: 8 # patients with exacerbations requiring oral steroids study unsupported by pharmaceutical industry excluded

Study or subgroup	LABA + ICS	ICS alone	Risk Ratio IV.Fixed.95% CI	Weight	Risk Rat
	n/N	n/N	IV,Fixed,95% C.I		IV,Fixed,95%
I Charity funded Langton Hewer 1995	3/11	3/12	_	100.0 %	1.09 [0.28, 4.32
Subtotal (95% CI)	11	12		100.0 %	1.09 [0.28, 4.32
Total events: 3 (LABA + ICS),					
Heterogeneity: not applicable					
Test for overall effect: $Z = 0.1$					
 Funded by pharmaceutical in Akpinarli 1999 	0/16	0/16			Not estimat
Aubier 1999a	5/171	7/83		1.2 %	0.35 [0.11, 1.06
Aubier 1999b	17/167	7/82		2.0 %	1.19 [0.52, 2.76
Boyd 1995	19/55	15/64		4.4 %	1.47 [0.83, 2.6
Fitzgerald 1999	3/89	6/91		0.8 %	0.51 [0.13, 1.98
Kavaru 2000	0/92	0/90			Not estimat
Kemp 1998	53/252	59/254	-	13.5 %	0.91 [0.65, 1.26
Li 1999	2/13	1/16		0.3 %	2.46 [0.25, 24.2
Malone 2005	2/101	3/102		0.5 %	0.67 [0.11, 3.94
Nathan 2006	1/94	3/91	• • • • • • • • • • • • • • • • • • • •	0.3 %	0.32 [0.03, 3.0
Noonan 2006a	5/124	2/55		0.6 %	1.11 [0.22, 5.5
Noonan 2006b	4/115	2/54		0.5 %	0.94 [0.18, 4.9]
Norhaya 1999	1/30	3/30	•	0.3 %	0.33 [0.04, 3.03
O'Byrne 2001a	58/323	81/322		16.1 %	0.71 [0.53, 0.96
O'Byme 2001b	39/315	61/312		10.5 %	0.63 [0.44, 0.92
Pauwels 1997a	62/210	82/213	-	19.9 %	0.77 [0.59, 1.00
Pauwels 1997b	41/215	60/214	-	11.8 %	0.68 [0.48, 0.96
Russell 1995	16/99	18/99		3.8 %	0.89 [0.48, 1.64
SAS40024	0/99	2/100	•	0.2 %	0.20 [0.01, 4.15
SAS40036	2/172	7/159	•	0.6 %	0.26 [0.06, 1.25

0.1 0.2 0.5 I 2 5 I0 Favours LABA + ICS Favours ICS alone

Study or subgroup	LABA + ICS n/N	ICS alone n/N	Risk Ratio IV,Fixed,95% CI	Weight	Risk Ratio IV,Fixed,95% CI
SAS40037	3/161	6/161		0.8 %	0.50 [0.13, 1.96]
SFA100314	1/124	1/124	·	0.2 %	1.00 [0.06, 15.81]
SFA100316	2/113	1/118		0.3 %	2.09 [0.19, 22.71]
Shapiro 2000	1/84	2/84	•	0.3 %	0.50 [0.05, 5.41]
Simons 1997	0/16	1/16	•	0.1 %	0.33 [0.01, 7.62]
van der Molen 1997	33/125	32/114	-	8.4 %	0.94 [0.62, 1.42]
Verberne 1998	10/60	10/57		2.3 %	0.95 [0.43, 2.11]
Wallin 2003	1/18	5/19	·	0.3 %	0.21 [0.03, 1.64]
Weiler 2005	1/102	0/90		0.1 %	2.65 [0.11, 64.26]
Subtotal (95% CI) Total events: 382 (LABA + IC Heterogeneity: Chi ² = 20.92, Test for overall effect: Z = 4.0	df = 26 (P = 0.75); $I^2 =$	3230	•	100.0 %	0.78 [0.69, 0.88]
Test for subgroup differences:	Chi ² = 0.23, df = 1 (P =	= 0.63), I ² =0.0%			
			0.1 0.2 0.5 1 2 5 10 Favours LABA + ICS Favours ICS alone		

Analysis 2.9. Comparison 2 Additional comparisons for same dose, Outcome 9 Sensitivity analysis: exacerbations requiring oral steroids: studies with low risk of bias of selection bias (adequate allocation sequence generation)

Review: Addition of long-acting beta2-agonists to inhaled corticosteroids versus same dose inhaled corticosteroids for chronic asthma in adults and children

Comparison: 2 Additional comparisons for same dose

Outcome: 9 Sensitivity analysis: exacerbations requiring oral steroids: studies with low risk of bias of selection bias (adequate allocation sequence generation)

Risk Rati M-H,Fixed,95% (Weight	Risk Ratio M-H,Fixed,95% CI	ICS alone n/N	LABA + ICS n/N	Study or subgroup
0.35 [0.11, 1.06	2.0 %		7/83	5/171	Aubier 1999b
1.47 [0.83, 2.61	2.9 %		15/64	19/55	Boyd 1995
0.94 [0.18, 4.97	0.6 %		2/54	4/115	Noonan 2006b
2.09 [0.19, 22.71	0.2 %		1/118	2/113	SFA100316
0.32 [0.03, 3.05	0.6 %		3/91	1/94	Nathan 2006
0.71 [0.53, 0.96	17.0 %	•	81/322	58/323	O'Byrne 2001a
1.11 [0.22, 5.54	0.6 %		2/55	5/124	Noonan 2006a
0.68 [0.48, 0.96	12.6 %	•	60/214	41/215	Pauwels 1997b
1.00 [0.06, 15.81	0.2 %		1/124	1/124	SFA100314
0.94 [0.62, 1.42	7.0 %	+	32/114	33/125	van der Molen 1997
2.46 [0.25, 24.21	0.2 %		1/16	2/13	Li 1999
0.91 [0.65, 1.26	12.3 %	+	59/254	53/252	Kemp 1998
0.20 [0.01, 4.15	0.5 %		2/100	0/99	SAS40024
0.21 [0.03, 1.64	1.0 %		5/19	1/18	Wallin 2003
0.89 [0.48, 1.64	3.8 %		18/99	16/99	Russell 1995
0.26 [0.06, 1.25	1.5 %		7/159	2/172	SAS40036
0.33 [0.01, 7.62	0.3 %		1/16	0/16	Simons 1997
Not estimab			0/90	0/92	Kavaru 2000
0.50 [0.13, 1.96	1.3 %		6/161	3/161	SAS40037
0.95 [0.43, 2.11	2.2 %		10/57	10/60	Verberne 1998
0.67 [0.11, 3.94	0.6 %		3/102	2/101	Malone 2005
0.50 [0.05, 5.41	0.4 %		2/84	1/84	Shapiro 2000
2.65 [0.11, 64.26	0.1 %		0/90	1/102	Weiler 2005
0.77 [0.59, 1.00	17.1 %	-	82/213	62/210	Pauwels 1997a

Study or subgroup	LABA + ICS	ICS alone	Risk Ratio	Weight	Risk Ratio
	n/N	n/N	M-H,Fixed,95% CI		M-H,Fixed,95% CI
O'Byrne 2001b	39/315	61/312	-	12.9 %	0.63 [0.44, 0.92]
Aubier 1999a	17/167	7/82		2.0 %	1.19 [0.52, 2.76]
Total (95% CI)	3420	3093	•	100.0 %	0.77 [0.69, 0.87]
Total events: 378 (LABA + I	ICS), 468 (ICS alone)				
Heterogeneity: Chi ² = 20.02	2, df = 24 (P = 0.70); l ²	=0.0%			
Test for overall effect: $Z = 4$	IT (P = 0.000030)				
			0.01 0.1 1 10 100		
		Fa	vours LABA + ICS Favours ICS alo	one	

Analysis 2.10. Comparison 2 Additional comparisons for same dose, Outcome 10 Sensitivity analysis: exacerbations requiring oral steroids: studies with low risk of bias of selection bias (adequate allocation concealment)

Review: Addition of long-acting beta2-agonists to inhaled corticosteroids versus same dose inhaled corticosteroids for chronic asthma in adults and children

Comparison: 2 Additional comparisons for same dose

Outcome: 10 Sensitivity analysis: exacerbations requiring oral steroids: studies with low risk of bias of selection bias (adequate allocation concealment)

Study or subgroup	LABA + ICS	ICS alone	Risk Ratio	Weight	Risk Ra
Nathan 2006	n/N	n/N 3/91	M-H,Fixed,95% CI	1.0 %	M-H,Fixed,95%
					0.32 [0.03, 3.0
SFA100314	1/124	1/124		0.3 %	1.00 [0.06, 15.8
Russell 1995	16/99	18/99	-	6.1 %	0.89 [0.48, 1.6
O'Byrne 2001b	39/315	61/312	•	20.8 %	0.63 [0.44, 0.9
Boyd 1995	19/55	15/64		4.7 %	1.47 [0.83, 2.6
Shapiro 2000	1/84	2/84		0.7 %	0.50 [0.05, 5.4
Aubier 1999b	5/171	7/83		3.2 %	0.35 [0.11, 1.0
Li 1999	2/13	1/16		0.3 %	2.46 [0.25, 24.2
SFA100316	2/113	1/118		0.3 %	2.09 [0.19, 22.7
Verberne 1998	10/60	10/57	_	3.5 %	0.95 [0.43, 2.1
Study or subgroup	LABA + ICS n/N	ICS alone n/N	Risk Ratio MH.Fixed,95% Cl	Weight	Risk Rat M-H,Fixed,95% (
Study or subgroup Kemp 1998				Weight 20.0 %	
	n/N	n/N	M-H,Fixed,95% CI		M-H,Fixed,95%
Kemp 1998	n/N 53/252	n/N 59/254	M-H,Fixed,95% CI	20.0 %	M-H,Fixed,95% 0.91 [0.65, 1.26
Kemp 1998 Weiler 2005	n/N 53/252 1/102	n/N 59/254 0/90	M-H,Fixed,95% CI	20.0 %	M-H,Fixed,95% (0.91 [0.65, 1.26 2.65 [0.11, 64.26
Kemp 1998 Weiler 2005 SAS40024	n/N 53/252 1/102 0/99	n/N 59/254 0/90 2/100	M-H,Fixed,95% CI	20.0 %	M-H,Fixed,95% (0.91 [0.65, 1.26 2.65 [0.11, 64.26 0.20 [0.01, 4.15
Kemp 1998 Weiler 2005 SAS40024 Kavaru 2000	n/N 53/252 1/102 0/99 0/92	n/N 59/254 0/90 2/100 0/90	M-H,Fixed,95% CI	20.0 % 0.2 % 0.8 %	M.H.Fixed,95% 0.91 [0.65, 1.26 2.65 [0.11, 64.26 0.20 [0.01, 4.15 Not estimab
Kemp 1998 Weiler 2005 SAS40024 Kavaru 2000 O'Byrne 2001a	n/N 53/252 1/102 0/99 0/92 58/323	n/N 59/254 0/90 2/100 0/90 81/322	M-H,Fixed,95% CI	20.0 % 0.2 % 0.8 % 27.6 %	M-H-Foxed,9536 0.91 [0.65, 1.26 2.65 [0.11, 64.26 0.20 [0.01, 4.15 Not estimab 0.71 [0.53, 0.96
Kemp 1998 Weiler 2005 SAS40024 Kavaru 2000 O'Byrne 2001a SAS40037	n/N 53/252 1/102 0/99 0/92 58/323 3/161	n/N 59/254 0/90 2/100 0/90 81/322 6/161	M-H,Fixed,95% CI	20.0 % 0.2 % 0.8 % 27.6 % 2.0 %	M-H_Fixed95% (0.91 [0.65, 1.26 2.65 [0.11, 64.26 0.20 [0.01, 4.15 Not estimat 0.71 [0.53, 0.96 0.50 [0.13, 1.96
Kemp 1998 Weiler 2005 SAS40024 Kavaru 2000 O'Byrne 2001a SAS40037 Wallin 2003	n/N 53/252 1/102 0/99 0/92 58/323 3/161 1/18	n/N 59/254 0/90 2/100 0/90 81/322 6/161 5/19	M-H,Fixed,95% CI	20.0 % 0.2 % 0.8 % 27.6 % 2.0 % 1.7 %	M.H.Fiseed.95% (0.91 [0.65, 1.26 2.65 [0.11, 64.26 0.20 [0.01, 4.15 Not estimati 0.71 [0.53, 0.96 0.50 [0.13, 1.96 0.21 [0.03, 1.64
Kemp 1998 Weiler 2005 SAS40024 Kavaru 2000 O'Byrne 2001 a SAS40037 Walin 2003 Aubier 1999a	n/N 53/252 1/102 0/99 0/92 58/323 3/161 1/18 1/18	n/N 59/254 0/90 2/100 81/322 6/161 5/19 7/82	M-H,Fixed,95% CI	200 % 0.2 % 0.8 % 27.6 % 2.0 % 1.7 % 3.2 %	M.H.Fixed.95% (0.91 [0.65, 1.26 2.65 [0.11, 64.26 0.20 [0.01, 4.15 Not estimati 0.71 [0.53, 0.96 0.50 [0.13, 1.96 0.21 [0.03, 1.64 1.19 [0.52, 2.76]

Analysis 2.11. Comparison 2 Additional comparisons for same dose, Outcome 11 Sensitivity analysis: exacerbations requiring oral steroids: studies with low risk of detection bias (adequate blinding)

Review: Addition of long-acting beta2-agonists to inhaled corticosteroids versus same dose inhaled corticosteroids for chronic asthma in adults and children

Comparison: 2 Additional comparisons for same dose

Outcome: 11 Sensitivity analysis: exacerbations requiring oral steroids: studies with low risk of detection bias (adequate blinding)

Aubier 1999b O'Byrne 2001b Pauwels 1997b SAS40036	n/N 5/171 39/315	n/N 7/83	M-H,Fixed,95% CI		M-H,Fixed,95% C
O'Byrne 2001b Pauwels 1997b		//83		10.00	0.35 5.0 11
Pauwels 1997b	39/315			1.9 %	0.35 [0.11, 1.06]
		61/312	•	12.5 %	0.63 [0.44, 0.92]
SAS40036	41/215	60/214	•	12.3 %	0.68 [0.48, 0.96]
	2/172	7/159		1.5 %	0.26 [0.06, 1.25]
Aubier 1999a	17/167	7/82		1.9 %	1.19 [0.52, 2.76]
Noonan 2006a	5/124	2/55		0.6 %	1.11 [0.22, 5.54]
Kemp 1998	53/252	59/254	•	12.0 %	0.91 [0.65, 1.26]
SFA100316	2/113	1/118		0.2 %	2.09 [0.19, 22.71]
Norhaya 1999	1/30	3/30		0.6 %	0.33 [0.04, 3.03]
Noonan 2006b	4/115	2/54		0.6 %	0.94 [0.18, 4.97]
Weiler 2005	1/102	0/90		0.1 %	2.65 [0.11, 64.26]
Pauwels 1997a	62/210	82/213	-	16.6 %	0.77 [0.59, 1.00]
O'Byrne 2001a	58/323	81/322	•	16.6 %	0.71 [0.53, 0.96]
SAS40037	3/161	7/161		1.4 %	0.43 [0.11, 1.63]
Simons 1997	0/16	1/16		0.3 %	0.33 [0.01, 7.62]
Fitzgerald 1999	3/89	6/91		1.2 %	0.51 [0.13, 1.98]
Verberne 1998	10/60	10/57		2.1 %	0.95 [0.43, 2.11]
Nathan 2006	1/94	3/91		0.6 %	0.32 [0.03, 3.05]
Boyd 1995	19/55	15/64		2.8 %	1.47 [0.83, 2.61]
Li 1999	2/13	1/16		0.2 %	2.46 [0.25, 24.21]
SAS40024	0/99	2/100		0.5 %	0.20 [0.01, 4.15]
Langton Hewer 1995	3/11	3/12		0.6 %	1.09 [0.28, 4.32]
Russell 1995	16/99	18/99		3.7 %	0.89 [0.48, 1.64]
Malone 2005	2/101	3/102		0.6 %	0.67 [0.11, 3.94]
Akpinarli 1999	0/16	0/16			Not estimable
Malone 2005	2/101	3/102 0/16	0.01 0.1 1 10 100 s LABA + ICS Favours ICS alon	0.6 %	0.67 [0.11, 3.94
Study or subgroup	LABA + ICS n/N	ICS alone n/N	Risk Ratio M-H,Fixed,95% Cl	Weight	Risk Ratio M-H,Fixed,95% C
Wallin 2003	1/18	5/19		1.0 %	0.21 [0.03, 1.64
Shapiro 2000	1/84	2/84		0.4 %	0.50 [0.05, 5.41
van der Molen 1997	33/125	32/114	+	6.8 %	0.94 [0.62, 1.42
SFA100314	1/124	1/124		0.2 %	1.00 [0.06, 15.81
Kavaru 2000	0/92	0/90			Not estimabl
Total (95% CI)	3566	3242	•	100.0 %	0.77 [0.68, 0.87
Total events: 385 (LABA + ICS Heterogeneity: $Ch^2 = 21.58$, d Test for overall effect: $Z = 4.33$	$ff = 27 (P = 0.76); I^2$	=0.0%			

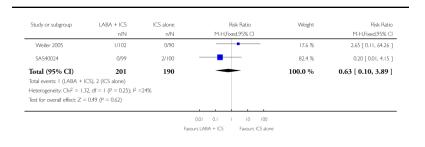
Analysis 2.12. Comparison 2 Additional comparisons for same dose, Outcome 12 Sensitivity analysis: exacerbations requiring oral steroids: studies with low risk of bias of attrition bias (complete follow up of study participants)

Review: Addition of long-acting beta2-agonists to inhaled corticosteroids versus same dose inhaled corticosteroids for chronic asthma in adults and children

Comparison: 2 Additional comparisons for same dose

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Outcome: 12 Sensitivity analysis: exacerbations requiring oral steroids: studies with low risk of bias of attrition bias (complete follow up of study participants)



Analysis 2.13. Comparison 2 Additional comparisons for same dose, Outcome 13 Sensitivity analysis: exacerbations requiring oral steroids by data publication status (data available from published source)

Review: Addition of long-acting beta2-agonists to inhaled corticosteroids versus same dose inhaled corticosteroids for chronic asthma in adults and children

Comparison: 2 Additional comparisons for same dose

Outcome: 13 Sensitivity analysis: exacerbations requiring oral steroids by data publication status (data available from published source)

Study or subgroup	LABA + ICS	ICS alone	Risk Ratio	Weight	Risk Ratio
	n/N	n/N	IV,Fixed,95% CI		IV,Fixed,95% C
Akpinarli 1999	0/16	0/16			Not estimable
Boyd 1995	19/55	15/64		5.5 %	1.47 [0.83, 2.61
Fitzgerald 1999	3/89	6/91		1.0 %	0.51 [0.13, 1.98
Langton Hewer 1995	3/11	3/12		1.0 %	1.09 [0.28, 4.32
Norhaya 1999	1/30	3/30		0.4 %	0.33 [0.04, 3.03
O'Byrne 2001a	58/323	81/322	•	20.2 %	0.71 [0.53, 0.96
O'Byrne 2001b	39/315	61/312	+	13.2 %	0.63 [0.44, 0.92
Pauwels 1997a	62/210	82/213	-	25.0 %	0.77 [0.59, 1.00
Pauwels 1997b	41/215	60/214	+	14.9 %	0.68 [0.48, 0.96
Russell 1995	16/99	18/99		4.8 %	0.89 [0.48, 1.64
Simons 1997	0/16	1/16	•	0.2 %	0.33 [0.01, 7.62
van der Molen 1997	33/125	32/114	-	10.5 %	0.94 [0.62, 1.42
Verberne 1998	10/60	10/57		2.8 %	0.95 [0.43, 2.11
Wallin 2003	1/18	5/19		0.4 %	0.21 [0.03, 1.64
Total (95% CI) Total events: 286 (LABA + IC) Heterogeneity: Ch ² = 11.06, r Test for overall effect: Z = 3.8 Test for subgroup differences:	df = 12 (P = 0.52); I ² = 3 (P = 0.00013)	1579	•	100.0 %	0.77 [0.67, 0.88]
			0.02 0.1 1 10 50		
			0.02 0.1 I I0 50 rs LABA + ICS Favours ICS ak		

Analysis 2.14. Comparison 2 Additional comparisons for same dose, Outcome 14 Change in FEV1 at endpoint stratifying on age (children versus adults)

Review: Addition of long-acting beta2-agonists to inhaled corticosteroids versus same dose inhaled corticosteroids for chronic asthma in adults and children

Comparison: 2 Additional comparisons for same dose

Outcome: 14 Change in FEV1 at endpoint stratifying on age (children versus adults)

Study or subgroup	L (SE)	L IV,Random,95% CI	Weight	IV,Random,95% C
I Children				
Langton Hewer 1995	0.42 (0.1071)		1.8 %	0.42 [0.21, 0.63
Malone 2005	0.06 (0.0357)	-	11.4 %	0.06 [-0.01, 0.13
Pohunek 2006a	0.08 (0.0306)	•	13.8 %	0.08 [0.02, 0.14
Pohunek 2006b	0.05 (0.0306)	-	13.8 %	0.05 [-0.01, 0.11
Russell 1995	0.09 (0.0612)	-	5.0 %	0.09 [-0.03, 0.21
SD 039 0714	0.13 (0.05)	-	7.0 %	0.13 [0.03, 0.23
SD 039 0719	0.08 (0.0306)	•	13.8 %	0.08 [0.02, 0.14
SD 039 0725a	0.07 (0.0255)	-	16.7 %	0.07 [0.02, 0.12
SD 039 0725b	0.08 (0.0255)	•	16.7 %	0.08 [0.03, 0.13
	i ² = 12.52, df = 8 (P = 0.13); l ² = 3	36%	100.0 %	0100 [0109, 0111
Test for overall effect: Z = 5.51 2 Adults				
Heterogeneity: Tau ² = 0.00; Ch Test for overall effect: Z = 5.51 2 Adults Aubier 1999a	(P < 0.00001) 0.03 (0.0561)		3.7 %	0.08 [0.05, 0.11
Heterogeneity: Tau ² = 0.00; Ch Test for overall effect: Z = 5.51 2 Adults Aubier 1999a Aubier 1999b	(P < 0.00001) 0.03 (0.0561) 0.04 (0.0561)	-	3.7 % 3.7 %	0.03 [-0.08, 0.14
Heterogeneity: Tau ² = 0.00; Ch Test for overall effect: Z = 5.51 2 Adults Aubier 1999a Aubier 1999b Bailey 2008	(P < 0.00001) 0.03 (0.0561) 0.04 (0.0561) 0.11 (0.0332)		3.7 % 3.7 % 6.3 %	0.03 [-0.08, 0.14 0.04 [-0.07, 0.15 0.11 [0.04, 0.18
Heterogeneity: Tau ² = 0.00; Ch Test for overall effect: Z = 5.51 2 Adults Aubier 1999a Aubier 1999b Bailey 2008 Boyd 1995	(P < 0.00001) 0.03 (0.0561) 0.04 (0.0561) 0.11 (0.0332) 0.04 (0.0816)		3.7 % 3.7 % 6.3 % 2.2 %	0.03 [-0.08, 0.14 0.04 [-0.07, 0.15 0.11 [0.04, 0.18 0.04 [-0.12, 0.20
Heterogeneity: Tau ² = 0.00; Ch Test for overall effect: Z = 5.51 2 Aduts Aubier 1999a Aubier 1999b Bailey 2008 Boyd 1995 D5896C0001a	(P < 0.00001) 0.03 (0.0561) 0.04 (0.0561) 0.11 (0.0332) 0.04 (0.0816) 0.19 (0.0306)		3.7 % 3.7 % 6.3 % 2.2 % 6.7 %	0.03 [-0.08, 0.14 0.04 [-0.07, 0.15 0.11 [0.04, 0.18 0.04 [-0.12, 0.20 0.19 [0.13, 0.25
Heterogeneity: Tau ² = 0.00; Ch Test for overall effect: Z = 5.51 2 Aduts Aubier 1999a Bailey 2008 Boyd 1995 D5896CD001 a D5896CD001 b	(P < 0.00001) 0.03 (0.0561) 0.04 (0.0561) 0.11 (0.0332) 0.04 (0.0816) 0.19 (0.0306) 0.1 (0.0306)		3.7 % 3.7 % 6.3 % 2.2 % 6.7 %	0.03 [-0.08, 0.14 0.04 [-0.07, 0.15 0.11 [0.04, 0.18 0.04 [-0.12, 0.20 0.19 [0.13, 0.25 0.10 [0.04, 0.16
Heterogeneity: Tau ² = 0.00; Ch Test for overall effect: Z = 5.51 2 Aduts Aubier 1999a Bailey 2008 Boyd 1995 D5896CD001 a D5896CD001 b GOAL	(P < 0.00001) 0.03 (0.0561) 0.04 (0.0561) 0.11 (0.0332) 0.04 (0.0816) 0.19 (0.0306) 0.1 (0.0306) 0.12 (0.0204)		37 % 37 % 63 % 22 % 67 % 67 % 83 %	0.03 [-0.08, 0.14 0.04 [-0.07, 0.15 0.11 [0.04, 0.18 0.04 [-0.12, 0.20 0.19 [0.13, 0.25 0.10 [0.04, 0.16 0.12 [0.08, 0.16
Heterogeneity: Tau ² = 0.00; Ch Test for overall effect: Z = 5.51 2 Aduts Aubier 1999a Bailey 2008 Boyd 1995 D5896C0001 a D5896C0001 b GGAL Green 2006	(P < 0.00001) 0.03 (0.0561) 0.04 (0.0561) 0.11 (0.0332) 0.04 (0.0816) 0.19 (0.0306) 0.1 (0.0306) 0.12 (0.0204) 0.02 (0.047449)		37 % 37 % 63 % 22 % 67 % 83 % 45 %	0.03 [-0.08, 0.14 0.04 [-0.07, 0.15 0.11 [0.04, 0.18 0.04 [-0.12, 0.20 0.19 [0.13, 0.25 0.10 [0.04, 0.16 0.12 [0.08, 0.16 0.02 [-0.07, 0.11]
Heterogeneity: Tau ² = 0.00; Ch Test for overall effect: Z = 5.51 2 Adults: Aubier 1999a Bailey 2008 Boyd 1995 D58%6C0001 a D58%6C0001 b GOAL Green 2006 Hultquist 2000	(P < 0.00001) 0.03 (0.0561) 0.04 (0.0561) 0.11 (0.0332) 0.04 (0.0816) 0.19 (0.0306) 0.19 (0.0306) 0.12 (0.0204) 0.02 (0.047449) 0.12 (0.0714)		37 % 37 % 63 % 22 % 67 % 67 % 83 % 45 % 27 %	0.03 [-0.08, 0.14 0.04 [-0.07, 0.15 0.11 [0.04, 0.18 0.04 [-0.12, 0.20 0.19 [0.13, 0.25 0.10 [0.04, 0.16 0.12 [0.08, 0.16 0.02 [-0.07, 0.11 0.12 [-0.02, 0.26
Heterogeneity: Tau ² = 0.00; Ch Test for overall effect: Z = 5.51 2 Aduts Aubier 1999a Bailey 2008 Boyd 1995 D5896C0001 a D5896C0001 b GGAL Green 2006	(P < 0.00001) 0.03 (0.0561) 0.04 (0.0561) 0.11 (0.0332) 0.04 (0.0816) 0.19 (0.0306) 0.1 (0.0306) 0.12 (0.0204) 0.02 (0.047449)	46% 	37 % 37 % 63 % 22 % 67 % 83 % 45 %	0.03 [-0.08, 0.14 0.04 [-0.07, 0.15 0.11 [0.04, 0.18 0.04 [-0.12, 0.20 0.19 [0.13, 0.25 0.10 [0.04, 0.16 0.12 [0.08, 0.16 0.02 [-0.07, 0.11]

Favours ICS alone Favours LABA+ICS

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Study or subgroup	L (SE)	L	Weight	L
		IV,Random,95% CI		IV,Random,95% C
Nathan 2006	0.22 (0.0561)		3.7 %	0.22 [0.11, 0.33]
Noonan 2006a	0.09 (0.0663)		3.0 %	0.09 [-0.04, 0.22]
Noonan 2006b	0.04 (0.0663)		3.0 %	0.04 [-0.09, 0.17]
SAM40008	0.15 (0.099)		1.6 %	0.15 [-0.04, 0.34]
SAS40036	0.18 (0.0459)	+	4.7 %	0.18 [0.09, 0.27]
SAS40037	0.07 (0.0459)	-	4.7 %	0.07 [-0.02, 0.16]
SD 039 0726a	0.16 (0.051)		4.2 %	0.16 [0.06, 0.26]
SD 039 0726b	0.13 (0.051)		4.2 %	0.13 [0.03, 0.23]
SD 039 0728	0.1 (0.0255)	•	7.5 %	0.10 [0.05, 0.15]
Shapiro 2000	0.23 (0.0714)		2.7 %	0.23 [0.09, 0.37]
van der Molen 1997	0.12 (0.051)		4.2 %	0.12 [0.02, 0.22]
Subtotal (95% CI)		•	100.0 %	0.13 [0.10, 0.15]
-leterogeneity: Tau ² = 0.00; Chi	² = 42.80, df = 22 (P = 0.005); l ² =	=49%		
Test for overall effect: Z = 9.28 ((P < 0.00001)			
		-1 -0.5 0 0.5 1		
	F	avours ICS alone Favours LABA+ICS	5	

Analysis 2.15. Comparison 2 Additional comparisons for same dose, Outcome 15 Change in FEV1 at endpoint stratifying on LABA (formoterol versus salmeterol)

Review: Addition of long-acting beta2-agonists to inhaled corticosteroids versus same dose inhaled corticosteroids for chronic asthma in adults and children

Comparison: 2 Additional comparisons for same dose

Outcome: 15 Change in FEV1 at endpoint stratifying on LABA (formoterol versus salmeterol)

Study or subgroup	LABA + ICS N	ICS N	L (SE)	L IV.Random.95% CI	Weight	IV,Random,95% C
I Formoterol	14	14		representatility/370 Cl		14, 41 (DOT 1, 2076 C
D5896C0001a	151	75	0.19 (0.0306)	+	4.5 %	0.19 [0.13, 0.25
D5896C0001b	152	76	0.1 (0.0306)	-+-	4.5 %	0.10 [0.04, 0.16
Green 2006	39	39	0.02 (0.047449)	-	3.0 %	0.02 [-0.07, 0.11
Hultquist 2000	117	116	0.12 (0.0714)		1.8 %	0.12 [-0.02, 0.26
Molimard 2001	130	129	0.11 (0.0561)		2.5 %	0.11 [0.00, 0.22
Noonan 2006a	117	54	0.09 (0.0663)		2.0 %	0.09 [-0.04, 0.22
Noonan 2006b	111	54	0.04 (0.0663)		2.0 %	0.04 [-0.09, 0.17
Pohunek 2006a	216	106	0.08 (0.0306)	+	4.5 %	0.08 [0.02, 0.14
Pohunek 2006b	201	107	0.04 (0.0306)	+	4.5 %	0.04 [-0.02, 0.10
SD 039 0714	133	131	0.13 (0.05)		2.9 %	0.13 [0.03, 0.23
SD 039 0719	119	63	0.08 (0.0306)	+	4.5 %	0.08 [0.02, 0.14
SD 039 0725a	131	60	0.07 (0.0255)	-	5.0 %	0.07 [0.02, 0.12
SD 039 0725b	124	60	0.08 (0.0255)	+	5.0 %	0.08 [0.03, 0.13
SD 039 0726a	152	72	0.16 (0.051)		2.8 %	0.16 [0.06, 0.26
SD 039 0726b	147	72	0.13 (0.051)		2.8 %	0.13 [0.03, 0.23
SD 039 0728	436	132	0.1 (0.0255)	-	5.0 %	0.10 [0.05, 0.15
van der Molen 1997	124		0.12 (0.051)		2.8 %	0.12 [0.02, 0.22
Subtotal (95% CI)	2600	1457			59.8 %	0.09 [0.07, 0.12
Heterogeneity: $Tau^2 = 0.00$;	Chi ² = 20.92, df =	16 (P = 0.18	s); I² =24%			
Test for overall effect: $Z = 9$.06 (P < 0.00001)					
2 Salmeterol			0.00 (0.05 (1))		0.5.04	
Aubier 1999a	171	165	0.03 (0.0561)		2.5 %	0.03 [-0.08, 0.14
Aubier 1999b	167	82	0.04 (0.0561)		2.5 %	0.04 [-0.07, 0.15
Bailey 2008	239	236	0.11 (0.0332)	-+-	4.2 %	0.11 [0.04, 0.18
Boyd 1995	47	49	0.04 (0.0816)		1.5 %	0.04 [-0.12, 0.20

-I -0.5 0 0.5 I Favours ICS alone Favours LABA+ICS

Meight		1 (SE)	105		Study or subgroup
www.gint	IV,Random,95% CI	L (JL)	N	N	Study of subgroup
5.5 %	•	0.12 (0.0204)	1199	1133	GOAL
1.8 %		0.23 (0.0714)	85	87	Kavaru 2000
3.5 %	+	0.27 (0.0408)	254	252	Kemp 1998
0.9 %		0.42 (0.1071)	10	11	Langton Hewer 1995
4.0 %	+	0.06 (0.0357)	102	101	Malone 2005
2.5 %	-	0.22 (0.0561)	89	92	Nathan 2006
2.2 %		0.09 (0.0612)	87	76	Russell 1995
1.1 %		0.15 (0.099)	93	93	SAM40008
3.1 %		0.18 (0.0459)	158	170	SAS40036
3.1 %	+-	0.07 (0.0459)	159	158	SAS40037
1.8 %		0.23 (0.0714)	81	81	Shapiro 2000
40.2 %	•		2849	2878	Subtotal (95% CI)
		122); I ² =65%	14 (P = 0.000)		D , .
					Test for overall effect: $Z = 6.34$
100.0 %	'			p - , -	Total (95% CI)
		18); 14 =54%	31 (P = 0.000		0 /
					Test for overall effect: $Z = 10.0^4$
	1.8 % 3.5 % 0.9 % 4.0 % 2.5 % 2.2 % 1.1 % 3.1 % 3.1 % 1.8 %	NRandom/95% Cl 55 % 18 % 35 % 09 % 40 % 25 % 22 % 11 % 31 % 31 % 18 % 18 % 40.2 %	NRandom/95% Cl 0.12 (0.0204) 5.5 % 0.23 (0.0714) - 1.8 % 0.27 (0.0408) 0.22 (0.0408) - 0.22 (0.0408) - 0.22 (0.0408) - 0.9 % 0.06 (0.0357) 0.22 (0.0561) - 0.22 (0.0561) - 0.18 (0.0459) - 0.18 (0.0459) - 0.18 (0.0459) - 0.22 ().14 () - 0.23 (0.0714) - 0.22 ().2 () - 0.22 ().2 () - 0.18 (0.0459) - 0.23 (0.0714) - 0.22 ().2 () - 0.22 () - 0.23 () - 0.22 () - 0.22 () - 0.22 () - 0.23 () - 0.22 () - 0.22 () - 0.22 () - 0.3 () - 0.4 () <td< td=""><td>N IVRandom/95% CI 1199 0.12 (0.0204) • 5.5 % 85 0.23 (0.0714) • 1.8 % 254 0.27 (0.0408) • 3.5 % 10 0.42 (0.1071) • 0.9 % 102 0.06 (0.0357) • 4.0 % 89 0.22 (0.0561) • 2.2 % 87 0.09 (0.0612) • 2.2 % 93 0.18 (0.0459) • 3.1 % 159 0.07 (0.0459) • 3.1 % 81 0.23 (0.0714) • 1.8 % 81 0.23 (0.0714) • 40.2 % 14 (P = 0.00022); P = 65% • 40.2 % 4306 • 100.0 %</td><td>N N MRandom/95% CI 1133 1199 0.12 (0.0204) • 55.% 87 85 0.23 (0.0714) • 1.8 % 252 254 0.27 (0.0408) • 35.% 11 10 0.42 (0.1071) 0.9 % 101 102 0.06 (0.0357) • 4.0 % 92 89 0.22 (0.0561) • 2.5 % 76 87 0.09 (0.0612) - 2.2 % 93 93 0.15 (0.099) • 1.1 % 170 158 0.18 (0.0459) • 3.1 % 170 158 0.18 (0.0459) • 3.1 % 8.8 % 18.8 % 2878 2849 • 40.2 % 81 81 0.23 (0.0714) • 18.8 % 40.2 % • 40.2 % • 40.2 % • 40.2 % • 40.2 % • 40.2 % • 40.2 % • 100.0 % • 100.0 % 67.18, df = 31 (P = 0.00018); P = 54% •</td></td<>	N IVRandom/95% CI 1199 0.12 (0.0204) • 5.5 % 85 0.23 (0.0714) • 1.8 % 254 0.27 (0.0408) • 3.5 % 10 0.42 (0.1071) • 0.9 % 102 0.06 (0.0357) • 4.0 % 89 0.22 (0.0561) • 2.2 % 87 0.09 (0.0612) • 2.2 % 93 0.18 (0.0459) • 3.1 % 159 0.07 (0.0459) • 3.1 % 81 0.23 (0.0714) • 1.8 % 81 0.23 (0.0714) • 40.2 % 14 (P = 0.00022); P = 65% • 40.2 % 4306 • 100.0 %	N N MRandom/95% CI 1133 1199 0.12 (0.0204) • 55.% 87 85 0.23 (0.0714) • 1.8 % 252 254 0.27 (0.0408) • 35.% 11 10 0.42 (0.1071) 0.9 % 101 102 0.06 (0.0357) • 4.0 % 92 89 0.22 (0.0561) • 2.5 % 76 87 0.09 (0.0612) - 2.2 % 93 93 0.15 (0.099) • 1.1 % 170 158 0.18 (0.0459) • 3.1 % 170 158 0.18 (0.0459) • 3.1 % 8.8 % 18.8 % 2878 2849 • 40.2 % 81 81 0.23 (0.0714) • 18.8 % 40.2 % • 40.2 % • 40.2 % • 40.2 % • 40.2 % • 40.2 % • 40.2 % • 100.0 % • 100.0 % 67.18, df = 31 (P = 0.00018); P = 54% •

Analysis 2.16. Comparison 2 Additional comparisons for same dose, Outcome 16 Change in FEV1 at endpoint stratifying on baseline FEV1

Review: Addition of long-acting beta2-agonists to inhaled corticosteroids versus same dose inhaled corticosteroids for chronic asthma in adults and children

Comparison: 2 Additional comparisons for same dose

Outcome: 16 Change in FEV1 at endpoint stratifying on baseline FEV1

Study or subgroup	L (SE)	L IV,Random,95% CI	Weight	IV,Random,95% (
<= 16 weeks				
Boyd 1995	0.04 (0.0816)		2.0 %	0.04 [-0.12, 0.20
D5896C0001a	0.19 (0.0306)	•	5.4 %	0.19 [0.13, 0.25
D5896C0001b	0.1 (0.0306)	•	5.4 %	0.10 [0.04, 0.14
GOAL	0.12 (0.0204)	•	6.4 %	0.12 [0.08, 0.1
Green 2006	0.02 (0.047449)	-	3.9 %	0.02 [-0.07, 0.1
Kavaru 2000	0.23 (0.0714)		2.4 %	0.23 [0.09, 0.3
Kemp 1998	0.27 (0.0408)	+	4.4 %	0.27 [0.19, 0.3
Langton Hewer 1995	0.42 (0.1071)		1.3 %	0.42 [0.21, 0.6
Malone 2005	0.06 (0.0357)		4.9 %	0.06 [-0.01, 0.1
Molimard 2001	0.11 (0.0561)		3.3 %	0.11 [0.00, 0.2
Nathan 2006	0.22 (0.0561)		3.3 %	0.22 [0.11, 0.3
Noonan 2006a	0.09 (0.0663)		2.7 %	0.09 [-0.04, 0.2
Noonan 2006b	0.04 (0.0663)		2.7 %	0.04 [-0.09, 0.1
Pohunek 2006a	0.08 (0.0306)	•	5.4 %	0.08 [0.02, 0.1
Pohunek 2006b	0.05 (0.0306)	•	5.4 %	0.05 [-0.01, 0.1
Russell 1995	0.09 (0.0612)		2.9 %	0.09 [-0.03, 0.2
SAS40036	0.18 (0.0459)	-	4.0 %	0.18 [0.09, 0.2
SAS40037	0.07 (0.0459)		4.0 %	0.07 [-0.02, 0.1
SD 039 0714	0.13 (0.05)		3.7 %	0.13 [0.03, 0.2
SD 039 0719	0.08 (0.0306)	•	5.4 %	0.08 [0.02, 0.1
SD 039 0725a	0.07 (0.0255)	-	5.9 %	0.07 [0.02, 0.1
SD 039 0725b	0.08 (0.0255)	•	5.9 %	0.08 [0.03, 0.1
SD 039 0726a	0.16 (0.051)		3.6 %	0.16 [0.06, 0.2
SD 039 0726b	0.13 (0.051)		3.6 %	0.13 [0.03, 0.2

Favours ICS alone Favours LABA+ICS

Study or subgroup	L (SE)	L	Weight	L
		IV,Random,95% CI	-	IV,Random,95% CI
Shapiro 2000	0.23 (0.0714)		2.4 %	0.23 [0.09, 0.37]
Subtotal (95% CI)		•	100.0 %	0.12 [0.09, 0.14]
Heterogeneity: $Tau^2 = 0.00$; Chi	² = 62.01, df = 24 (P = 0.00003);	12 =61%		
Test for overall effect: $Z = 8.80$	(P < 0.00001)			
2 > 16 weeks				
Aubier 1999a	0.03 (0.0561)	+	8.4 %	0.03 [-0.08, 0.14]
Aubier 1999b	0.04 (0.0561)	+	8.4 %	0.04 [-0.07, 0.15]
Bailey 2008	0.11 (0.0332)	•	24.1 %	0.11 [0.04, 0.18]
Hultquist 2000	0.12 (0.0714)	•	5.2 %	0.12 [-0.02, 0.26]
SAM40008	0.15 (0.099)		2.7 %	0.15 [-0.04, 0.34]
SD 039 0728	0.1 (0.0255)	-	40.9 %	0.10 [0.05, 0.15]
van der Molen 1997	0.12 (0.051)	•	10.2 %	0.12 [0.02, 0.22]
Subtotal (95% CI)		•	100.0 %	0.10 [0.06, 0.13]
0 ,	= 3.21, df = 6 (P = 0.78); l ² =0.09	6		
Test for overall effect: $Z = 5.88$	(P < 0.00001)			
		-I -0.5 0 0.5 I		
	F	avours ICS alone Favours LABA+IC	25	

Analysis 3.1. Comparison 3 WMD archive, Outcome 1 Change in morning PEF (L/min) at endpoint stratifying on baseline FEV1

Review: Addition of long-acting beta2-agonists to inhaled corticosteroids versus same dose inhaled corticosteroids for chronic asthma in adults and children

Comparison: 3 WMD archive

Outcome: 1 Change in morning PEF (L/min) at endpoint stratifying on baseline FEV1

Study or subgroup	LABA + ICS		ICS alone		Mean Difference	Mi Differe
	N	Mean(SD)	N	Mean(SD)	IV,Random,95% CI	IV,Random,95%
Aubier 1999a	171	33 (40.54)	82	15 (39.8)		18.00 [7.46, 28.5
Aubier 1999b	167	35 (40.1)	83	15 (39.8)	-	20.00 [9.50, 30.5
Bailey 2008	239	15.6 (53.8)	236	1.4 (52.5)		14.20 [4.64, 23.7
Boyd 1995	48	54 (41.6)	52	28 (50.1)		26.00 [8.00, 44.0
Buhl 2003a	176	22.8 (76.88)	86	0 (76.88)		22.80 [2.98, 42.6
Buhl 2003b	176	27.4 (76.88)	85	0 (76.88)		27.40 [7.50, 47.3
Hultquist 2000	117	33.86 (63.71)	116	16.25 (63.22)		17.61 [1.31, 33.9
Ind 2003	171	47.7 (47.4)	160	23.4 (38.3)		24.30 [15.04, 33.5
Jenkins 2006a	222	37.4 (41.7)	57	4.5 (41.7)		32.90 [20.76, 45.0
Jenkins 2006b	114	36.2 (41.5)	58	4.5 (41.5)		31.70 [18.58, 44.8
Kavaru 2000	87	52.5 (49.44)	85	17.3 (40.57)		35.20 [21.70, 48.7
Kemp 1998	252	47 (58.73)	254	14 (52.59)	-	33.00 [23.28, 42.7
Kuna 2006	202	23.4 (38.1)	207	5.5 (37.8)	+	17.90 [10.54, 25.2
Langton Hewer 1995	11	26 (49)	10	-35 (63)		61.00 [12.39, 109.6
Molimard 2001	130	25.7 (36.5)	129	4.5 (32.7)		21.20 [12.76, 29.6
Nathan 2006	94	49.6 (54.29)	91	13.9 (39.11)		35.70 [22.10, 49.3
Noonan 2006a	121	35 (42.5)	54	9 (42.5)		26.00 [12.37, 39.6
Noonan 2006b	113	28 (42.5)	55	9 (42.5)		19.00 [5.30, 32.7
O'Byrne 2001a	323	12.89 (44.4)	322	2.78 (44.3)	-	10.11 [3.26, 16.9
O'Byrne 2001b	315	18.5 (44.4)	312	1.73 (44.2)	+	16.77 [9.83, 23.7
Pohunek 2006a	216	29 (31.28)	106	19 (31.28)	+	10.00 [2.73, 17.2
Pohunek 2006b	201	34 (31.28)	107	19 (31.28)	-+-	15.00 [7.66, 22.3
Price 2002	332	36.8 (61.95)	331	17.8 (61.85)	-+-	19.00 [9.58, 28.4
Russell 1995	75	27 (36)	88	18.5 (43)		8.50 [-3.63, 20.6

-100 -50 0 50 100 Favours ICS alone Favours LABA + ICS

Study or subgroup	LABA + ICS		ICS alone		Mean Difference	Mean Difference
	N	Mean(SD)	N	Mean(SD)	IV,Random,95% CI	IV,Random,95% CI
SAS40024	102	19.2 (34.3)	90	6.3 (38.9)	-+-	12.90 [2.46, 23.34]
SAS40036	169	4.4 (44)	158	-16.8 (43)	+	21.20 [11.77, 30.63]
SAS40037	158	6.1 (44)	159	-15 (43)	+	21.10 [11.52, 30.68]
SD 037 0344a	215	18.9 (37.2)	104	4.3 (35.1)	-	14.60 [6.22, 22.98]
SD 037 0344b	209	17.1 (36.8)	103	4.3 (35.1)	+	12.80 [4.38, 21.22]
SD 039 0718	128	23.56 (32.78)	145	7.95 (27)	+	15.61 [8.43, 22.79]
SD 039 0726a	152	I (67)	72	-32 (67)		33.00 [14.21, 51.79]
SD 039 0726b	147	-4 (67)	72	-32 (67)		28.00 [9.11, 46.89]
SD 039 0728	441	40.3 (41.1)	132	5.61 (35.5)		34.69 [27.52, 41.86]
SFCF4026	154	5.54 (34.25)	154	-14.56 (34.62)	+	20.10 [12.41, 27.79]
Shapiro 2000	81	53.5 (50.4)	81	15.2 (41.4)		38.30 [24.10, 52.50]
SMS40012	83	12.1 (46.3)	85	-0.9 (38)		13.00 [0.18, 25.82]
Tal 2002	148	23.1 (28.5)	138	11.1 (28.5)	+	12.00 [5.39, 18.61]
van der Molen 1997	125	26.7 (41.6)	113	-5.7 (30.7)		32.40 [23.17, 41.63]
Verberne 1998	60	30.92 (33)	57	15.89 (43.41)		15.03 [1.00, 29.06]
Weiler 2005	99	32 (39.8)	100	9 (30)	+	23.00 [13.20, 32.80]
Zetterstrom 2001a	123	35.7 (41.26)	62	0.2 (41.76)		35.50 [22.80, 48.20]
Zetterstrom 2001b	115	32 (40.75)	62	0.2 (41.76)		31.80 [19.01, 44.59]
					-100 -50 0 50 IC Favours ICS alone Favours LAB	

Analysis 3.2. Comparison 3 WMD archive, Outcome 2 Change in evening PEF (L/min) at endpoint

Review: Addition of long-acting beta2-agonists to inhaled corticosteroids versus same dose inhaled corticosteroids for chronic asthma in adults and children

Comparison: 3 WMD archive

Outcome: 2 Change in evening PEF (L/min) at endpoint

Study or subgroup	LABA + ICS N	Mean(SD)	ICS alone N	Mean(SD)	Mean Difference IV.Random,95% CI	Mear Differenci IV.Random.95% C
Aubier 1999a	171	23 (39.23)	82	9 (39.8)	IV,Kandom,95% CI	14.00 [3.57, 24.43
Aubier 1999b	167	29 (40.1)	83	9 (39.8)		20.00 [9.50, 30.50
Bailey 2008	239	18.3 (54.3)	236	4.7 (58.2)	_	13.60 [3.47, 23.73
Buhl 2003a	176	23.6 (33.26)	86	0 (33.26)	-	23.60 [15.02, 32.18
		. ,		. ,	-	
Buhl 2003b	176	16.6 (33.26)	85	0 (33.26)	L.	16.60 [7.99, 25.21
Hultquist 2000	117	24.02 (62.63)	116	11.39 (62.04)		12.63 [-3.38, 28.64
Ind 2003	171	31.6 (57.6)	160	15.4 (38.3)		16.20 [5.72, 26.68
Jenkins 2006a	222	31.3 (39)	57	-0.1 (39)	-	31.40 [20.05, 42.75
Jenkins 2006b	114	30.7 (39)	58	-0.1 (39)		30.80 [18.47, 43.13
Kavaru 2000	87	35 (43.84)	85	18 (12.4)		17.00 [7.42, 26.58
Kuna 2006	202	9.6 (37.7)	207	-1.7 (37.8)	+	11.30 [3.98, 18.62
Langton Hewer 1995	11	48 (52)	10	-42 (64)		90.00 [39.82, 140.18
Nathan 2006	94	36.1 (48.48)	91	9 (33.39)		27.10 [15.14, 39.06
Noonan 2006a	121	34 (42.5)	54	7 (42.5)		27.00 [13.37, 40.63
Noonan 2006b	112	26 (40.86)	55	7 (42.5)		19.00 [5.46, 32.54
Price 2002	332	26 (59.04)	331	10.2 (58.95)	+	15.80 [6.82, 24.78
SD 039 0718	128	21.4 (40.62)	145	5.79 (35.3)	+	15.61 [6.53, 24.69
SD 039 0726a	152	1.14 (28)	72	-31.88 (34.6)	-	33.02 [23.87, 42.17
SD 039 0726b	147	-14.28 (35.4)	72	-31.88 (34.6)		17.60 [7.77, 27.43
SFCF4026	154	1.1 (30.28)	154	-16.33 (29.91)	-+-	17.43 [10.71, 24.15
Shapiro 2000	81	45.4 (46.8)	81	7.9 (40.5)		37.50 [24.02, 50.98
SMS40012	83	9.5 (46.2)	85	0.9 (37.4)		8.60 [-4.13, 21.33
Tal 2002	148	20 (27.7)	138	8.3 (27.7)	-+-	11.70 [5.28, 18.12
Zetterstrom 2001a	123	24.8 (37.38)	62	-3.7 (37.75)		28.50 [17.01, 39.99
Zetterstrom 2001b	115	22.3 (36.88)	62	-3.7 (37.75)		26.00 [14.44, 37.56
					00 -50 0 50 100	

Analysis 3.3. Comparison 3 WMD archive, Outcome 3 Change in % symptom-free days at endpoint

Review: Addition of long-acting beta2-agonists to inhaled corticosteroids versus same dose inhaled corticosteroids for chronic asthma in adults and children

Comparison: 3 WMD archive

Outcome: 3 Change in % symptom-free days at endpoint

-

Study or subgroup	LABA + ICS		ICS alone		Mean Difference	Weight	Mean Difference
	N	Mean(SD)	Ν	Mean(SD)	IV,Random,95% CI	_	IV,Random,95% CI
I Mean baseline FEVI >/		ted					
Subtotal (95% CI)	0		0				Not estimable
Heterogeneity: not applic Test for overall effect: no							
2 Mean baseline FEV1 61		dicted					
Zetterstrom 2001a	123	25 (31.39)	62	8 (31.85)	-	7.7 %	17.00 [7.32, 26.68]
Kavaru 2000	87	22.6 (42.81)	85	7.2 (37.7)	-	6.1 %	15.40 [3.35, 27.45]
Zetterstrom 2001b	115	22.3 (31.21)	62	8 (31.85)	+	7.6 %	14.30 [4.53, 24.07]
Jenkins 2006b	114	32.2 (40.91)	58	15.6 (40.91)		5.6 %	16.60 [3.67, 29.53]
Jenkins 2006a	222	31.2 (32.42)	57	15.6 (32.42)	*	7.8 %	15.60 [6.16, 25.04]
Noonan 2006a	121	23.14 (31.97)	54	9.5 (31.97)	-	7.2 %	13.64 [3.39, 23.89]
Noonan 2006b	113	21.8 (31.44)	55	9.5 (31.97)	•	7.3 %	12.30 [2.05, 22.55]
Nathan 2006	94	18.5 (37.81)	91	15 (29.57)	+	7.6 %	3.50 [-6.26, 13.26]
Shapiro 2000	81	33.8 (41.4)	81	15.4 (37.8)		6.0 %	18.40 [6.19, 30.61]
Boyd 1995	53	22 (30)	62	13 (22)	*	7.6 %	9.00 [-0.76, 18.76]
Kemp 1998	252	38.1 (36.5)	254	13.6 (28.69)		11.0 %	24.50 [18.78, 30.22]
Subtotal (95% CI)	1375		921		•	81.5 %	14.98 [11.03, 18.92]
Heterogeneity: Tau ² = 11 Fest for overall effect: Z 3 Mean baseline FEV1 no	= 7.44 (P < 0.00		0.06); I ² =449	6			
SAS40036	170	5.7 (35)	158	-0.5 (34)	•	9.5 %	6.20 [-1.27, 13.67]
SAS40037	154	5.1 (36)	157	-1.9 (36)	•	9.0 %	7.00 [-1.00, 15.00]
Subtotal (95% CI)	324		315		•	18.5 %	6.57 [1.11, 12.03]
Heterogeneity: $Tau^2 = 0$.			$ ^2 = 0.0\%$				
Fest for overall effect: Z	= 2.36 (P = 0.01	8)					
				-10	0 -50 0 50 1	00	
					s ICS alone Favours LAI		
Study or subgroup	LABA + ICS		ICS alone		Mean Difference	Weight	Mean Difference
	N	Mean(SD)	Ν	Mean(SD)	IV,Random,95% CI		IV,Random,95% CI
Total (95% CI)	1699		1236		•	100.0 %	13.34 [9.43, 17.24]
Heterogeneity: Tau ² = 2			.01); I ² =55%				
Test for overall effect: Z =	= 6.70 (P < 0.000)01)					
				-100	-50 0 50 10	0	

Analysis 3.4. Comparison 3 WMD archive, Outcome 4 Change in mean % rescue free days at 12 +/- 4 weeks

Review: Addition of long-acting beta2-agonists to inhaled corticosteroids versus same dose inhaled corticosteroids for chronic asthma in adults and children

Comparison: 3 WMD archive

Outcome: 4 Change in mean % rescue free days at 12 +/- 4 weeks

Study or subgroup	LABA + ICS		ICS alone		Mean Difference	Weight	Mear Difference
	N	Mean(SD)	N	Mean(SD)	IV,Fixed,95% CI		IV,Fixed,95% C
I Mean baseline FEVI 61%	to 79% of pre	dicted					
Zetterstrom 2001a	123	31.9 (31.72)	62	12.8 (32.07)		11.4 %	19.10 [9.35, 28.85
Jenkins 2006b	114	38.6 (31.65)	58	17.2 (31.65)	+	10.9 %	21.40 [11.39, 31.41
Jenkins 2006a	222	36.1 (31.53)	57	17.2 (31.53)	•	12.9 %	18.90 [9.72, 28.08
Zetterstrom 2001b	115	31.9 (31.1)	62	12.8 (32.07)	-	11.3 %	19.10 [9.30, 28.90
SD 039 0728	438	22.8 (30.9)	130	7.6 (26.5)	-	37.4 %	15.20 [9.80, 20.60
Subtotal (95% CI)	1012		369		•	83.9 %	17.63 [14.03, 21.23
Heterogeneity: Chi ² = 1.57	7, df = 4 (P = 0	.81); I ² =0.0%					
Test for overall effect: $Z =$	9.60 (P < 0.000	01)					
2 Mean baseline FEV1 not	reported						
SAS40037	158	7 (37.5)	159	-7 (37.3)	•	16.1 %	14.00 [5.77, 22.23
Subtotal (95% CI)	158		159		•	16.1 %	14.00 [5.77, 22.23
Heterogeneity: not applical	ble						
Test for overall effect: Z =	3.33 (P = 0.000	086)					
Total (95% CI)	1170		528		•	100.0 %	17.05 [13.75, 20.35
Heterogeneity: Chi ² = 2.20), df = 5 (P = 0	.82); 12 =0.0%					
Test for overall effect: $Z =$	10.13 (P < 0.00	0001)					
Test for subgroup difference	es: Chi ² = 0.63	df = 1 (P = 0.4)	13), I ² =0.0%				
				-100	-50 0 50	100	
				F	ICS alone Eavour	LABA + ICS	

Analysis 3.5. Comparison 3 WMD archive, Outcome 5 Change in FEV1 at endpoint (L) stratifying on baseline FEV1

Review: Addition of long-acting beta2-agonists to inhaled corticosteroids versus same dose inhaled corticosteroids for chronic asthma in adults and children

Comparison: 3 WMD archive

Outcome: 5 Change in FEV1 at endpoint (L) stratifying on baseline FEV1

Study or subgroup	LABA + ICS N	Mean(SD)	ICS alone N	Mean(SD)	Difference IV.Random.95% CI	Diffen IV.Random.95
Aubier 1999a	167	0.04 (0.51)	83	0 (0.51)		0.04 [-0.09, 0.
Aubier 1999b	165	0.03 (0.51)	82	0 (0.51)		0.03 [-0.11, 0
Bailey 2008	239	0.045 (0.4)	236	-0.06 (0.3)		0.11 [0.04, 0
Boyd 1995	47	0.19 (0.38)	49	0.15 (0.44)		0.04 [-0.12, 0
D5896C0001a	151	0.01 (0.18)	75	-0.18 (0.21)	+	0.19 [0.13, 0
D5896C0001b	152	-0.08 (0.25)	76	-0.18 (0.21)	-+-	0.10 [0.04, 0
GOAL	1133	0.32 (0.48)	1119	0.2 (0.47)	+	0.12 [0.08, 0
Hultquist 2000	117	0.22 (0.54)	116	0.1 (0.54)		0.12 [-0.02, 0
Kavaru 2000	87	0.51 (0.46)	85	0.28 (0.46)		0.23 [0.09, 0
Kemp 1998	252	0.42 (0.48)	254	0.15 (0.48)	+	0.27 [0.19, 0
Langton Hewer 1995	11	0.22 (0.32)	10	-0.2 (0.16)		0.42 [0.21, 0
Molimard 2001	130	0.17 (0.5)	129	0.06 (0.42)		0.11 [0.00, 0
Nathan 2006	92	0.41 (0.38)	89	0.19 (0.38)		0.22 [0.11, 0
Noonan 2006a	117	0.19 (0.4)	54	0.1 (0.4)		0.09 [-0.04, 0
Noonan 2006b	111	0.14 (0.39)	54	0.1 (0.4)	-+-	0.04 [-0.09, 0
Pohunek 2006a	216	0.16 (0.25)	106	0.08 (0.25)		0.08 [0.02, 0
Pohunek 2006b	201	0.13 (0.25)	107	0.08 (0.25)	+	0.05 [-0.01, 0
Russell 1995	76	0.12 (0.41)	87	0.03 (0.37)	+-	0.09 [-0.03, 0
SAS40036	170	0.03 (0.4)	158	-0.15 (0.4)	-	0.18 [0.09, 0
SAS40037	158	-0.04 (0.4)	159	-0.11 (0.4)	-	0.07 [-0.02, 0

Favours LABA + ICS Favours ICS alone

Study or subgroup	LABA + ICS		ICS alone		Mean Difference	Mean Difference
	N	Mean(SD)	N	Mean(SD)	IV,Random,95% CI	IV,Random,95% CI
SD 039 0719	119	0.21 (0.2)	63	0.13 (0.2)	+	0.08 [0.02, 0.14]
SD 039 0726a	152	-0.04 (0.34)	72	-0.2 (0.34)		0.16 [0.06, 0.26]
SD 039 0726b	147	-0.07 (0.34)	72	-0.2 (0.34)		0.13 [0.03, 0.23]
SD 039 0728	436	0.18 (0.2)	132	0.08 (0.28)	+	0.10 [0.05, 0.15]
Shapiro 2000	81	0.48 (0.45)	81	0.25 (0.45)		0.23 [0.09, 0.37]
van der Molen 1997	124	0.14 (0.44)	111	0.02 (0.37)		0.12 [0.02, 0.22]
					-I -0.5 0 0.5 I	
				Fav	ours ICS alone Favours LABA	+ ICS

Analysis 3.6. Comparison 3 WMD archive, Outcome 6 Change in # daytime rescue inhalations (puffs per day) at endpoint

Review: Addition of long-acting beta2-agonists to inhaled corticosteroids versus same dose inhaled corticosteroids for chronic asthma in adults and children

Comparison: 3 WMD archive

Outcome: 6 Change in # daytime rescue inhalations (puffs per day) at endpoint

	Study or subgroup	LABA + ICS		ICS alone		Mean Difference	Mean Difference
Kemp 1998 252 -2.73 (2.54) 254 -1.66 (1.91) + -1.67 [-2.06, -1.28] Malone 2005 101 -0.5 (0.22) 102 -0.4 (1.9) + -0.10 [-0.47, 0.27] Molimard 2001 130 -0.8 (1.32) 129 0.1 (0.85) ** -0.00 [-1.17, -0.63] Nathan 2006 94 -1.6 (0) 91 -0.9 (0) Not estimable O'Byrne 2001a 323 -0.29 (0.79) 322 -0.06 (0.79) • -0.23 [-0.54, 0.12] Price 2002 332 -1.18 (1.45) 331 -0.85 (1.26) * -0.33 [-0.54, 0.12]		N	Mean(SD)	Ν	Mean(SD)	IV,Random,95% CI	IV,Random,95% Cl
Malone 2005 101 -0.5 (0.22) 102 -0.4 (1.9) -0.10 [-0.47, 0.27] Molimard 2001 130 -0.8 (1.32) 129 0.1 (0.85) ** -0.00 [-1.17, -0.63] Nathan 2006 94 -1.6 (0) 91 -0.9 (0) Not estimable O'Byrne 2001a 323 -0.29 (0.79) 322 -0.06 (0.79) -0.23 [-0.35, -0.11] Price 2002 332 -1.18 (1.45) 331 -0.85 (1.26) * -0.33 [-0.54, -0.12]	Kavaru 2000	87	-1.9 (2.43)	85	-0.4 (1.94)		-1.50 [-2.16, -0.84
Molimard 2001 130 -0.8 (1.32) 129 0.1 (0.85) ** -0.90 [-1.17, -0.63] Nathan 2006 94 -1.6 (0) 91 -0.90 (0) Not estimable O'Byme 2001a 323 -0.29 (0.79) 322 -0.06 (0.79) * -0.23 [-0.35, -0.11] Price 2002 332 -1.18 (1.45) 331 -0.85 (1.26) * -0.33 [-0.54, -0.12]	Kemp 1998	252	-2.73 (2.54)	254	-1.06 (1.91)	-	-1.67 [-2.06, -1.28]
Holmmard 2001 1.30 -0.6 (1.32) 1.29 0.1 (0.85) -0.9 (0.1 Nathan 2006 94 -1.6 (0) 91 -0.9 (0) Not estimable O'Byrne 2001a 323 -0.29 (0.79) 322 -0.06 (0.79) -0.23 [-0.35, -0.11] Price 2002 332 -1.18 (1.45) 331 -0.85 (1.26) -0.33 [-0.54, -0.12]	Malone 2005	101	-0.5 (0.22)	102	-0.4 (1.9)	+	-0.10 [-0.47, 0.27]
O'Byme 2001a 323 -0.29 (0.79) 322 -0.06 (0.79) • -0.23 [-0.35, -0.11] Price 2002 332 -1.18 (1.45) 331 -0.85 (1.26) • -0.33 [-0.54, -0.12]	Molimard 2001	130	-0.8 (1.32)	129	0.1 (0.85)	+	-0.90 [-1.17, -0.63
Price 2002 332 -1.18 (1.45) 331 -0.85 (1.26) + -0.33 [-0.54,-0.12]	Nathan 2006	94	-1.6 (0)	91	-0.9 (0)		Not estimable
	O'Byrne 2001a	323	-0.29 (0.79)	322	-0.06 (0.79)	•	-0.23 [-0.35, -0.11]
Russell 1995 73 -0.75 (1.78) 86 -0.38 (1.73) -0.37 (-0.92, 0.18.1	Price 2002	332	-1.18 (1.45)	331	-0.85 (1.26)	+	-0.33 [-0.54, -0.12]
	Russell 1995	73	-0.75 (1.78)	86	-0.38 (1.73)		-0.37 [-0.92, 0.18]
-4 -2 0 2 4 Facurs ICS alone Facurs LABA + ICS							+ ICS
Facurs ICS alone Facurs IABA + ICS Mean Mea						nurs ICS alone Favours LABA Mean	Mea
Favours ICS alone Favours LABA + ICS Study or subgroup LABA + ICS ICS alone Difference Difference Difference	Study or subgroup				Favo	Mean Difference	Mea Differenc
Favours ICS alone Favours ICS alone Mean Mean Study or subgroup LABA + ICS ICS alone Difference Difference Difference N Mean(SD) N Mean(SD) IVRandom.95% CI IV.Random.95% CI	, , ,	N	()	Ν	Favo Mean(SD)	Mean Difference	Mea Differenc IV.Random,95% (
Facurs ICS alone Mean Difference Mean Difference Mean Difference N Mean(SD) N Mean(SD) N/Random.95% CI N/Random.95% CI \$M540012 83 -0.01 (0.26) 85 0.11 (0.38) -0.12 [-0.22, -0.02	SM540012	N 83	-0.01 (0.26)	N 85	Fax: Mean(SD) 0.11 (0.38)	Urs ICS alone Favours LABA Difference IV/Random/95% CI	Mea Differenc IV,Random,95% (-0.12 [-0.22, -0.02
Facurs ICS alone Mean Difference Mean Difference Mean Difference N Mean(SD) N Mean(SD) N/Random.95% CI N/Random.95% CI \$M540012 83 -0.01 (0.26) 85 0.11 (0.38) -0.12 [-0.22, -0.02	SM540012	N 83	-0.01 (0.26)	N 85	Fax: Mean(SD) 0.11 (0.38)	Urs ICS alone Favours LABA Difference IV/Random/95% CI	Mea Differenc IV,Random,95% (-0.12 [-0.22, -0.02
Favors ICS alone Favors ICS alone Mean Difference Difference Difference </td <td>SM540012 van der Molen 1997</td> <td>N 83 124</td> <td>-0.01 (0.26) -1.5 (1.7)</td> <td>N 85 113</td> <td>Fave Mean(SD) 0.11 (0.38) -0.2 (1.5)</td> <td>Urs ICS alone Favours LABA Difference IV/Random/95% CI</td> <td>Mea Differenc IV.Random.95% (-0.12 [-0.22, -0.02 -1.30 [-1.71, -0.89</td>	SM540012 van der Molen 1997	N 83 124	-0.01 (0.26) -1.5 (1.7)	N 85 113	Fave Mean(SD) 0.11 (0.38) -0.2 (1.5)	Urs ICS alone Favours LABA Difference IV/Random/95% CI	Mea Differenc IV.Random.95% (-0.12 [-0.22, -0.02 -1.30 [-1.71, -0.89
Facurs ICS alone Facurs ICS alone Facurs ICS alone Mean Mean Study or subgroup LABA + ICS ICS alone Difference Difference Difference N Mean(SD) N Mean(SD) IVRandom,95% CI IVRandom.95% CI IVRandom.95% CI IVRandom.95% CI IVRandom.95% CI -0.12 [-0.22, -0.02 van der Molen 1997 124 -1.5 (1.7) 113 -0.2 (1.5) -1.30 [-1.7], -0.89	SM540012 van der Molen 1997 Zetterstrom 2001a	N 83 124 123	-0.01 (0.26) -1.5 (1.7) -0.99 (1.66)	N 85 113 62	Fave Mean(SD) 0.11 (0.38) -0.2 (1.5) -0.44 (1.78)	Urs ICS alone Favours LABA Difference IV/Random/95% CI	Mea Differenc IV.Random/558 (-0.12 [-0.22, -0.02 -1.30 [-1.71, -0.89 -0.55 [-1.08, -0.02
		73	-0.75 (1.78)	86	-0.38 (1.73)		-0.37 [-0.92, 0.18]
	Russell 1995	73	-0.75 (1.78)	86	-0.38 (1.73)		-0.37 [-0.92, 0.18]
Russell 1995 73 -0.75 (1.78) 86 -0.38 (1.73)	Price 2002	332	-1.18 (1.45)	331	-0.85 (1.26)	+	-0.33 [-0.54, -0.12]
	r				. ,	Ī	
	O'Byrne 2001a	323	-0.29 (0.79)	322	-0.06 (0.79)	•	-0.23 [-0.35, -0.11]
Price 2002 332 -1.18 (1.45) 331 -0.85 (1.26)0.33 [-0.54, -0.12]	Nathan 2006	94	-1.6 (0)	91	-0.9 (0)		Not estimable
C/Byme 2001a 323 -0.29 (0.79) 322 -0.06 (0.79) • -0.23 [-0.35, -0.11] Price 2002 332 -1.18 (1.45) 331 -0.85 (1.26) • -0.33 [-0.54, -0.12]	Molimard 2001	130	-0.8 (1.32)	129	0.1 (0.85)	-+-	-0.90 [-1.17, -0.63]
Pointand 2001 1.30 -0.6 (1.3.2) 1.29 0.1 (0.85) -0.90 (1.1.7, -0.83) Nathan 2006 94 -1.6 (0) 91 -0.9 (0) Not estimable O'Byrne 2001a 323 -0.29 (0.79) 322 -0.06 (0.79) -0.23 [-0.35, -0.11] Price 2002 332 -1.18 (1.45) 331 -0.85 (1.26) -0.33 [-0.54, -0.12]	Malone 2005	101	-0.5 (0.22)	102	-0.4 (1.9)	+	-0.10 [-0.47, 0.27]
Molimard 2001 130 -0.8 (1.32) 129 0.1 (0.85) ** -0.90 [-1.17, -0.63] Nathan 2006 94 -1.6 (0) 91 -0.90 (0) Not estimable O'Byme 2001a 323 -0.29 (0.79) 322 -0.06 (0.79) * -0.23 [-0.35, -0.11] Price 2002 332 -1.18 (1.45) 331 -0.85 (1.26) * -0.33 [-0.54, -0.12]	Kemp 1998	252	-2.73 (2.54)	254	-1.06 (1.91)	+	-1.67 [-2.06, -1.28]
Malone 2005 101 -0.5 (0.22) 102 -0.4 (1.9) -0.10 [-0.47, 0.27] Molimard 2001 130 -0.8 (1.32) 129 0.1 (0.85) ** -0.00 [-1.17, -0.63] Nathan 2006 94 -1.6 (0) 91 -0.9 (0) Not estimable O'Byrne 2001a 323 -0.29 (0.79) 322 -0.06 (0.79) -0.23 [-0.35, 0.11] Price 2002 332 -1.18 (1.45) 331 -0.85 (1.26) * -0.33 [-0.54, 0.12]							
Kemp 1998 252 -2.73 (2.54) 254 -1.66 (1.91)	Kayanu 2000		. ,		. ,		
Kemp 1998 252 -2.73 (2.54) 254 -1.66 (1.91)	stady of subgroup		Mean(SD)		Mean(SD)		
Kavaru 2000 87 -1.9 (2.43) 85 -0.4 (1.94) -1.50 [-2.16, -0.84 Kemp 1998 252 -2.73 (2.54) 2.54 -1.06 (1.91) -1.67 [-2.06, -1.28 Malone 2005 101 -0.5 (0.22) 102 -0.4 (1.9) -1.67 [-2.06, -1.28 Molmard 2001 130 -0.8 (1.32) 129 0.1 (0.85) ++ -0.09 [-1.17, -0.63 Nathan 2006 9.4 -1.6 (0) 9.1 -0.9 (0) Not estimable O'Byrne 2001a 323 -0.29 (0.79) 322 -0.06 (0.79) - -0.33 [-0.54, -0.12 Price 2002 332 -1.18 (1.45) 331 -0.85 (1.26) - -	Study or subgroup	LABA + ICS		ICS alone			

Analysis 3.7. Comparison 3 WMD archive, Outcome 7 Change in FEV1 at endpoint (% predicted) stratifying on baseline FEV1

Review: Addition of long-acting beta2-agonists to inhaled corticosteroids versus same dose inhaled corticosteroids for chronic asthma in adults and children

Comparison: 3 WMD archive

Outcome: 7 Change in FEV1 at endpoint (% predicted) stratifying on baseline FEV1

Mea Differeno	Mean erence	Dif		ICS alone		LABA + ICS	study or subgroup
IV,Fixed,95% C	d,95% CI	IV,Fix	Mean(SD)	Ν	Mean(SD)	N	
-0.40 [-5.03, 4.23			7.3 (8)	39	6.9 (13)	43	Teper 2005
3.23 [1.90, 4.56			0.9 (8.48)	312	4.13 (8.52)	315	O'Byrne 2001b
3.08 [-0.49, 6.65			1.28 (9.13)	57	4.36 (10.53)	60	Verberne 1998
2.28 [0.95, 3.61			0.27 (8.61)	322	2.55 (8.63)	323	O'Byrne 2001a
5.80 [1.78, 9.82			-0.3 (13.7)	85	5.5 (12.9)	83	SMS40012
3.60 [-2.94, 10.14		_	2.2 (9.15)	19	5.8 (11.6)	20	Meijer 1995
3.46 [1.40, 5.52			-1.84 (10.6)	236	1.62 (12.3)	239	Bailey 2008
	0 5 10	-10 -5					
ABA	Favours ICS + L	Favours ICS alone					

Analysis 3.8. Comparison 3 WMD archive, Outcome 8 Change in # overall daily rescue inhalations at endpoint

Review: Addition of long-acting beta2-agonists to inhaled corticosteroids versus same dose inhaled corticosteroids for chronic asthma in adults and children

Comparison: 3 WMD archive

Outcome: 8 Change in # overall daily rescue inhalations at endpoint

Study or subgroup	LABA + ICS		ICS alone		Mean Difference	Weight	Mear Difference
	N	Mean(SD)	N	Mean(SD)	IV,Random,95% CI		IV,Random,95% C
I Mean baseline FEVI >/=	80% of predicte	ed					
O'Byme 2001a	323	-0.29 (0.79)	322	-0.06 (0.79)	•	13.9 %	-0.23 [-0.35, -0.11
O'Byrne 2001b	315	-0.31 (0.78)	312	-0.2 (0.78)	÷	13.9 %	-0.11 [-0.23, 0.01]
Subtotal (95% CI)	638		634			27.9 %	-0.17 [-0.29, -0.05]
Heterogeneity: $Tau^2 = 0.00$;	Chi ² = 1.86, d	f = I (P = 0.17);	l ² =46%				
Test for overall effect: $Z = 2$.83 (P = 0.004	6)					
2 Mean baseline FEV1 61%	to 79% of pred	licted					
Hultquist 2000	117	-1.86 (1.84)	115	-1.35 (1.83)	•	10.9 %	-0.51 [-0.98, -0.04
Kavaru 2000	87	-1.9 (2.43)	85	-0.4 (1.94)	•	9.0 %	-1.50 [-2.16, -0.84]
Tal 2002	148	-0.11 (0.7)	138	-0.09 (0.7)	÷	13.7 %	-0.02 [-0.18, 0.14
Noonan 2006b	113	-1.5 (2.07)	55	-0.78 (2.09)	•	8.8 %	-0.72 [-1.39, -0.05
Noonan 2006a	121	-1 (2.09)	54	-0.78 (2.09)	+	8.8 %	-0.22 [-0.89, 0.45
Shapiro 2000	81	-2.3 (3.6)	81	-0.9 (1.8)	•	7.0 %	-1.40 [-2.28, -0.52]
Boyd 1995	53	-5.1 (4.7)	62	-2.5 (4)		3.1 %	-2.60 [-4.21, -0.99
Kemp 1998	252	-3.48 (3.02)	254	-1.25 (2.55)	•	10.8 %	-2.23 [-2.72, -1.74]
Subtotal (95% CI)	972		844		•	72.1 %	-1.06 [-1.76, -0.37]
Heterogeneity: Tau ² = 0.86;	Chi ² = 99.46,	df = 7 (P<0.0000	11); I ² =93%				
Test for overall effect: $Z = 3$.01 (P = 0.002	6)					
Total (95% CI)	1610		1478		•	100.0 %	-0.74 [-1.07, -0.42]
Heterogeneity: Tau ² = 0.19;	$Chi^2 = 107.82$, df = 9 (P<0.000	001); I ² =92%	5			
Test for overall effect: $Z = 4$.49 (P < 0.000	01)					
				-10	-5 0 5	0	

Analysis 3.9. Comparison 3 WMD archive, Outcome 9 Change in quality of life (AQLQ score) at endpoint

Review: Addition of long-acting beta2-agonists to inhaled corticosteroids versus same dose inhaled corticosteroids for chronic asthma in adults and children

Comparison: 3 WMD archive

Outcome: 9 Change in quality of life (AQLQ score) at endpoint

Study or subgroup	LABA + ICS N	Mean(SD)	ICS alone N	Mean(SD)	Mean Difference IV.Random,95% CI	Weight	Mean Difference IV.Random,95% CI
Nathan 2006	94	0.89 (0)	91	0.43 (0)			Not estimable
Price 2002	332	0.67 (1.28)	331	0.48 (1.27)		50.9 %	0.19 [0.00, 0.38]
Kemp 1998	252	1.08 (1.27)	254	0.61 (1.11)		49.1 %	0.47 [0.26, 0.68]
Total (95% CI) Heterogeneity: Tau ² =	678 = 0.03; Chi ² = 3.72	, df = 1 (P = 0.0	676 5); I ² =73%		+	100.0 %	0.33 [0.05, 0.60]
Test for overall effect:	Z = 2.34 (P = 0.0	19)					
					-1 -0.5 0 0.5 I burs ICS alone Favours LAB/	+ ICS	

HISTORY

Protocol first published: Issue 1, 2000

Review first published: Issue 4, 2005

Date	Event	Description
30 April 2008	Amended	Converted to new review format.
24 June 2005	New citation required and conclusions have changed	Substantive amendment.

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

Given the large size of the review other comparisons originally stated in the protocol (published in 1999) are now assessed in separate reviews; this includes comparing the addition of LABA to inhaled corticosteroids to increased doses of inhaled corticosteroids (Ducharme 2010) and tapering doses of inhaled corticosteroids (Gibson 2005). A similar comparison focusing only on steroid-naive patients is the object of another Cochrane Review (Ni Chroinin 2009a) and a recent review focused on the role of LABA in paediatrics.(Ni Chroinin 2009b) Finally, the question of serious asthma-related events with the use of long-acting beta-agonists has been addressed in a series of linked reviews (Cates 2008a; Cates 2009b).

We have incorporated a new method to assess the risk of bias in line with recommendations described in the *Cochrane Handbook for Systematic Reviews of Interventions* (Cochrane Handbook).

WHAT'S NEW

Last assessed as up-to-date: 15 June 2008.

Date	Event	Description
19 June 2008	New citation required and conclusions have changed	44 new studies included; additional unpublished data available for primary outcome which had the effect of narrowing the confidence intervals in adults
2 May 2008	New search has been performed	New literature search performed.

References to studies included in this review

- Akpinarli 1999 {published data only} . Akpinarli A, Tuncer A, Saraclar Y, Sekerel BE, Kalayci O.
 Effect of formoterol on clinical parameters and lung functions in patients with bronchial asthma: a randomised controlled trial. Archives of Disease in Childhood. 1999; 81:45–8. [PubMed: 10373134]
- Aubier 1999a {published data only} . Aubier M, Pieters WR, Schlosser NJ, Steinmetz KO. Salmeterol/fluticasone propionate (50/500 mug) in combination in a Diskus(TM) inhaler (Seretide(TM)) is effective and safe in the treatment of steroid-dependent asthma. Respiratory Medicine. 1999; 93(12):876-84. [PubMed: 10653049] Pieters W, Ringdal N, Aubier M, Chapman KR, Huskisson SC. A new inhaler combination containing salmeterol and fluticasone propionate is well-tolerated in long-term use. European Respiratory Journal. 1998; Vol. 12(issue Suppl 29):P164.Pieters WR, Lundback B, Sondhi S, Price MJ. Cost effectiveness analysis of salmeterol/fluticasone propionate 50/500mcg vs fluticasone propionate 500mcg in patients with corticosteroid-dependent asthma. Pharmacoeconomics. 1999; 16(Suppl 2):29-34.Pieters, WR.: Sondhi, S.; Price, MJ.; Thwaites, RM.; Nyth, A. The cost effectiveness of salmeterol/fluticasone propionate 50/500 microgram combination inhaler versus fluticasone propionate 500 microgram in patients with chronic asthma. European Respiratory Society; Madrid, Spain: Oct 9-13. 1999 1999 p. P2458Pieters WR, Steinmetz KO, Aubier M, Johnson L, Gomez E, Bogolubov M. Effectiveness of a new salmeterol/fluticasone propionate (50/500µg) combination inhaler in patients with reversible airways obstruction. European Respiratory Journal. 1998; Vol. 12(issue Suppl 28):35s.Pieters, WR.; Wilson, KK.; Smith, HCE.; Tamminga, JJ. Cost-effectiveness of fluticasone propionate/salmeterol combination product and fluticasone propionate/montelukast in asthma. Annual Thoracic Society 97th International Conference; San Francisco CA. May 18-23. 2001; Schlosser NJ, Steinmetz KO, Aubier M, Gomez E, Wixon C. Evaluation of long-term safety of salmeterol/fluticasone propionate (50/500µg) combination inhaler in patients with reversible airways obstruction. European Respiratory Journal. 1998; Vol. 12(issue Suppl 28): 35s.*SFCB30019. A multicentre randomized, double-blind, double-dummy, parallel-group comparison of the salmeterol/fluticasone propionate combination product (50/500mcg strength) BD via one DISKUS/Accuhaler inhaler with salmeterol 50mcg BD via one DISKUS/Accuhaler and fluticasone propionate 500mcg BD via another DISKUS/Accuhaler and with fluticasone propionate 500mcg BD via one DISKUS/Accuhaler in adolescents and adults with reversible airways obstruction. 2004. http://www.ctr.gsk.co.uk
- Aubier 1999b {published data only} . Aubier M, Pieters WR, Schlosser NJ, Steinmetz KO.
 Salmeterol/fluticasone propionate (50/500 mug) in combination in a Diskus(TM) inhaler (Seretide(TM)) is effective and safe in the treatment of steroid-dependent asthma. Respiratory Medicine. 1999; 93(12):876–84. [PubMed: 10653049] Pieters W, Ringdal N, Aubier M, Chapman KR, Huskisson SC. A new inhaler combination containing salmeterol and fluticasone propionate is well-tolerated in long-term use. European Respiratory Journal. 1998; Vol. 12(issue Suppl29):P164.Pieters WR, Lundback B, Sondhi S, Price MJ. Cost effectiveness analysis of salmeterol/fluticasone propionate 50/500mcg vs fluticasone propionate 500mcg in patients with corticosteroid-dependent asthma. Pharmacoeconomics. 1999; 16(Suppl 2):29–34.Pieters, WR.; Sondhi, S.; Price, MJ.; Thwaites, RM.; Nyth, A. The cost effectiveness of salmeterol/fluticasone propionate 50/500 microgram combination inhaler versus fluticasone propionate 500 microgram in patients with chronic asthma. European Respiratory Society; Madrid, Spain: Oct 9-13. 1999 p. P24581999Pieters WR, Steinmetz KO, Aubier M, Johnson L, Gomez E, Bogolubov M. Effectiveness of a new salmeterol/fluticasone propionate (50/500µg) combination inhaler in

patients with reversible airways obstruction. European Respiratory Journal. 1998; Vol. 12(issue Suppl 28):35s.Pieters, WR.; Wilson, KK.; Smith, HCE.; Tamminga, JJ. Cost-effectiveness of fluticasone propionate/salmeterol combination product and fluticasone propionate/montelukast in asthma. Annual Thoracic Society 97th International Conference; San Francisco CA. May 18-23. 2001; Schlosser NJ, Steinmetz KO, Aubier M, Gomez E, Wixon C. Evaluation of long-term safety of salmeterol/fluticasone propionate (50/500µg) combination inhaler in patients with reversible airways obstruction. European Respiratory Journal. 1998; Vol. 12(issue Suppl 28): 35s.*SFCB30019. A multicentre randomized, double-blind, double-dummy, parallel-group comparison of the salmeterol/fluticasone propionate combination product (50/500mcg strength) BD via one DISKUS/Accuhaler inhaler with salmeterol 50mcg BD via one DISKUS/Accuhaler and with fluticasone propionate 500mcg BD via one DISKUS/Accuhaler in adolescents and adults with reversible airways obstruction. 2004. http://www.ctr.gsk.co.uk

- Bailey 2008 {unpublished data only} . Bailey W, Castro M, Matz J, White M, Dransfield M, Yancey S, et al. Asthma exacerbations in African Americans treated for 1 year with combination fluticasone propionate and salmeterol or fluticasone propionate alone. Current Medical Research and Opinion. 2008; 24(6):1669–82. [PubMed: 18462564] * [accessed 30 April 2008] Glaxo Smith Kline (SFA103153). A multicenter, randomized, double-blind, parallel group, 52-week comparison of asthma control and measures of airway inflammation in subjects of African descent receiving fluticasone propionate/salmeterol 100/50mcg DISKUS[™] BID or fluticasone propionate 100mcg DISKUS[™] BID alone. 2007. http://www.gsk.ctr.co.uk
- Boyd 1995 {published data only} . Boyd G. Salmeterol xinafoate in asthmatic patients under consideration for maintenance oral corticosteroid therapy. European Respiratory Journal. 1995; 8:1494–8. [PubMed: 8575574]
- Buhl 2003a {published data only} . Buhl R, Creemers JPHM, Vondra V, Martelli NA. Improved and maintained asthma control with once-daily budesonide/formoterol single inhaler in mild-tomoderate persistent asthma. European Respiratory Journal. 2001; Vol. 18(issue Suppl 33): 21s.Buhl R, Creemers JPHM, Vondra V, Martelli NA. Once-daily budesonide/formoterol via a single inhaler is effective in mild-to-moderate persistent asthma. European Respiratory Journal. 2001; Vol. 18(issue Suppl 33):21s.Buhl R, Creemers JPHM, Vondra V, Martelli NA. Once daily Symbicort (budesonide/eformoterol in a single inhaler) is effective in moderate-persistent asthma. Thorax. 2001; 56(Suppl 3):iii62.Buhl R, Creemers JPHM, Vondra V, Martelli NA, Naya IP, Eksstrom T. Once daily budesonide /formoterol in a single inhaler in adults with moderate persistent asthma. Respiratory Medicine. 2003; 97(4):323-30. [PubMed: 12693793] Buhl R, Zetterstrom O, Mellem H, Perpina M, Hedman J, O'Neill S, et al. Improved asthma control with budesonide/formoterol via a single inhaler compared with budesonide alone, in moderate persistent asthma. European Respiratory Journal. 2001; Vol. 18(issue Suppl 33):48s.Buhl, R.; Creemers, JPHM.; Vondra, V.; Martelli, NA. Symbicort® (budesonide and formoterol in a single inhaler) administered once daily is effective in mild to moderate asthma. Annual Thoracic Society 97th International Conference; San Francisco CA. May 18-23. 2001; *SD 039 0666. Symbicort high dose once daily in mild to moderate asthmatic patients. 2005. http:// www.astrazenecaclinicaltrials.com
- Buhl 2003b {published data only} . Buhl R, Creemers JPHM, Vondra V, Martelli NA. Improved and maintained asthma control with once-daily budesonide/formoterol single inhaler in mild-to-moderate persistent asthma. European Respiratory Journal. 2001; Vol. 18(issue Suppl 33): 21s.Buhl R, Creemers JPHM, Vondra V, Martelli NA. Once-daily budesonide/formoterol via a single inhaler is effective in mild-to-moderate persistent asthma. European Respiratory Journal. 2001; Vol. 18(issue Suppl 33):21s.Buhl R, Creemers JPHM, Vondra V, Martelli NA. Once daily Symbicort (budesonide/formoterol in a single inhaler) is effective in moderate-persistent asthma. Thorax. 2001; 56(Suppl 3):iii 62.Buhl R, Creemers JPHM, Vondra V, Martelli NA, Naya IP, Eksstrom T. Once daily budesonide /formoterol in a single inhaler in adults with moderate persistent asthma. Respiratory Medicine. 2003; 97:323–30. [PubMed: 12693793] Buhl R, Zetterstrom O, Mellem H, Perpina M, Hedman J, O'Neill S, et al. Improved asthma control with budesonide/formoterol via a single inhaler compared with budesonide alone, in moderate persistent asthma. European Respiratory Journal. 2001; Vol. 18(issue Suppl 33):48s.Buhl, R.; Creemers, JPHM.; Vondra, V.; Martelli, NA. Symbicort® (budesonide and formoterol in a single inhaler) administered once daily is effective in mild to moderate asthma. Annual Thoracic

Society 97th International Conference; San Francisco CA. May 18-23. 2001; *SD 039 0666. Symbicort high dose once daily in mild to moderate asthmatic patients. 2005. http://www.astrazenecaclinicaltrials.com

- D'Urzo 2001 {published data only} . D'Urzo AD, Chapman KR, Cartier A, Hargreave FE, Fitzgeerald M, Tesarowski D. Effectiveness and safety of salmeterol in non-specialist practice settings. Chest. 2001; 119:714–9. [PubMed: 11243947] * [accessed 20 June 2008] SLGQ94 (521/180) (GSK). A multicenter, randomized, double-blind, parallel-group trial to evaluate the long-term efficacy and safety of inhaled salmeterol 50µg BID compared to short-acting 2agonists as-needed in adult patients with asthma. 2007. http://ctr.gsk.co.uk
- D5896C0001a {unpublished data only} . [accessed 30 April 2008] AstraZeneca (D5896C00001). A randomized, double-blind, active-controlled, parallel-group, single-dummy, multicenter, 12 week study to assess the efficacy and safety of SYMBICORT® pMDI 160/4.5 μg x 2 actuations once-daily (qd) compared to SYMBICORT pMDI 80/4.5 μg x 2 actuations qd, SYMBICORT pMDI80/4.5 μg x 2 actuations twice-daily (bid) and to budesonide pMDI 160 μgx 2 actuations qd in asthmatic subjects 12 years of age and older. 2005. http://www.astrazenecaclinicaltrials.com
- D5896C0001b {unpublished data only} . [accessed 30 April 2008] AstraZeneca (D5896C00001). A randomized, double-blind, active-controlled, parallel-group, single-dummy, multicenter, 12 week study to assess the efficacy and safety of SYMBICORT® pMDI 160/4.5 μg x 2 actuations once-daily (qd) compared to SYMBICORT pMDI 80/4.5 μg x 2 actuations qd, SYMBICORT pMDI80/4.5 μg x 2 actuations twice-daily (bid) and to budesonide pMDI 160 μgx 2 actuations qd in asthmatic subjects 12 years of age and older. 2005. http://www.astrazenecaclinicaltrials.com
- Fitzgerald 1999 {published data only} . FitzGerald JM, Chapman KR, Della Cioppa G, Stubbing D, Fairbarn MS, Till MD, et al. Sustained bronchoprotection, bronchodilatation, and symptom control during regular formoterol use in asthma of moderate or greater severity. The Canadian FO/OD1 Study Group. Journal of Allergy & Clinical Immunology. 1999; 103(3 pt 1):427–35. [PubMed: 10069876]
- Gardiner 1994 {published data only} . Gardiner PV, Ward C, Booth H, Allison A, Hendrick DJ, Walters EH. Bronchoalveolar lavage inflammatory indices in asthmatics. American Journal of Respiratory & Critical Care Medicine. 1994; 150(4):1006–11. [PubMed: 7921429]
- GOAL {published and unpublished data} . Anonymous. GSK asthma trial suggests total control is possible. Pharmaceutical Journal. 2004; 273(7322):594. Arthurs R. Gaining optimal asthma control. Practice Nurse. 2004; (Suppl):3-8.Bateman, E.; Boushey, H.; Bousquet, J.; Busse, W.; Clark, T.; Pauwels, R., et al. Achievement for guideline based asthma control with salmeterol/ fluticasone propionate compared with fluticasone propionate alone; results of Goal study. Triennial World Asthma Meeting, Thailand; (16-19 February). 2004; Bateman E, Boushey H, Bousquet J, Busse W, Clark T, Pauwels R, et al. Achieving and maintaining guideline defined asthma control with salmeterol/fluticasone propionate versus fluticasone propionate alone: the results of the GOAL study. American Journal of Respiratory & Critical Care Medicine. 2004; 169(7):A87.Bateman E, Pauwels R, Boushey H, Bousquet J, Busse W, Clark T, et al. Aiming for total control of asthma significantly improves asthma-related quality of life: salmeterol/ fluticasone propionate versus fluticasone propionate alone. American Journal of Respiratory & Critical Care Medicine. 2004; 169(7):A87.Bateman ED, Boushey HA, Bousquet J, Busse WW, Clark TJ, Pauwels RA, et al. GOAL Investigators Group. Can guideline-defined asthma control be achieved? The Gaining Optimal Asthma ControL study. American Journal of Respiratory & Critical Care Medicine. 2004; 170(8):836-44.Bateman ED, Boushey HA, Bousquet J, Busse WW, Clark TJ, Pauwels RA, et al. GOAL Investigators Group. Can guideline-defined asthma control be achieved? The Gaining Optimal Asthma ControL study. American Respiratory & Critical Care Medicine. 2004; (Online data supplement)Bateman ED, Bousquet J, Keech ML, Busse WW, Clark TJ, Pedersen SE. The correlation between asthma control and health status: the GOAL study. European Resspiratory Journal. 2006 Epub ahead of print. Bateman ED, Edin HM, Sondhi S, Gul N. Asthma-related quality of life in the GOAL study: baseline results. European Respiratory Journal. 2002; 20(Suppl 38):46s.Bons J, Cordier JF, Godard P, Prud'Homme A, Celli I, Bousquet J. Aiming for total control of asthma: the GOAL study design. Revue Française d'Allergologie et d'Immunologie Clinique. 2004; 44(367):TT13.Boushey, H.; Bateman, E.; Bousquet, J.; Busse, W.; Clark, T.; Pauwels, R., et al. Achieving total control of asthma with salmeterol/fluticasone propionate versus fluticasone propionate alone: Goal study results.

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Triennial World Asthma Meeting; Thailand. 16-19 February; 2004. Boushey H, Bateman E, Bousquet J, Busse W, Clark T, Pauwels R, et al. Improvements in asthma outcomes following 1 year of treatment with salmeterol/fluticasone or fluticasone alone when stepped up to achieve guideline-defined total control. Journal Allergy and Clinical Immunology. 2004; 113(2 (Suppl 1): 114s-5s.Boushey HA, Pedersen S, Bateman E, Clark T, Busse W, Bousquet J, et al. Improved exacerbation rates and asthma control in current and former smokers treated with salmeterol/ fluticasone propionate: results of the GOAL study. Journal of Allergy & Clinical Immunology. 2005; 115(Suppl 2):S59.Bousquet J. Is asthma control achievable? European Respiratory Review. 2004; 13(92):102-4.Bousquet J, Bateman E, Boushey H, Busse W, Clark T, Pauwels R, et al. The effect of oral corticosteroids and high-dose combination therapy on achieving control of refractory asthma. Journal Allergy and Clinical Immunology. 2004; 113(2 (Suppl 1): 113s.Bousquet J, Bons J, Godard P, Cordier JF, Desfougeres JL, Prud'Homme A. Aiming for total control of asthma: the GOAL study results. Revue Française d'Allergologie et d'Immunologie Clinique. 2004; 44(367):TT16.Briggs AH, Bousquet J, Wallace MV, Busse WW, Clark TJH, Pedersen SE, et al. Cost-effectiveness of asthma control: an economic appraisal of the GOAL study. Allergy. 2006; 61(5):531-6. [PubMed: 16629780] Busse W, Bateman E, Boushey H, Bousquet J, Clark T, Pauwels R, et al. Achieving GINA/NIH guideline-based asthma control with salmeterol/fluticasone compared with fluticasone alone: the results of the GOAL study. Journal of Allergy and Clinical Immunology. 2004; 113(2 (Suppl 1):114s.Busse, W.; Bateman, E.; Boushey, H.; Bousquet, J.; Clark, T.; Pauwels, R., et al. Aiming to achieve total control of asthma with salmeterol/fluticasone propionate and fluticasone propionate alone is well tolerated: Goal 1 year safety data. Triennial World Asthma Meeting; Thailand. 16-19 February; 2004. Clark T, Bateman E, Boushey H, Bousquet J, Busse W, Pauwels R, et al. Time course of achievement of individual clinical goals of asthma treatment: the results of the GOAL study. American Journal of Respiratory & Critical Care Medicine. 2004; 169(7):A318.Clark T, Bateman E, Boushey H, Bousquet J, Busse W, Pauwels R, Pedersen S. Salmeterol/fluticasone and fluticasone alone are well tolerated over 1 year of treatment stepped-up to achieve total control: safety results of the GOAL study. Journal Allergy and Clinical Immunology. 2004; 113(2 (Suppl 1):115s.Clark TJ, Bousquet J, Bateman ED, James MH. GOAL (gaining optimal asthma control): a study to assess asthma control. European Respiratory Journal. 2001; 18(Suppl 33):175-6s.Clark TJH, Bateman ED, James MH, on behalf of the GOAL Steering Committee. Assessing asthma control using a composite measure based on GINA/NIH guidelines: an analysis of GOAL baseline data. European Respiratory Journal. 2002; 20(Suppl 38):47s.Clark, TJH.; Bateman, ED.; on behalf of the GOAL Steering Committee. Aiming for Total Control of asthma in ICS-free patients improves traditional outcomes: results of the Gaining Optimal Asthma controL (GOAL) study [abstract]. 23rd European Academy of Allergology and Clinical Immunology Meeting Abstract Book; Amsterdam, The Netherlands. June 12-16; 2004. p. 669Cordier JF, Bousquet J, Boucot I, Prud'Homme A, Godard P. Which dose for achieving total control of asthma? The results of the GOAL study. Revue Française d'Allergologie et d'Immunologie Clinique. 2004; 44(367): TT14.Godard P, Prud'Homme A, Cordier JF, Sohier B, Bousquet J. Time course of achievement of asthma control: the results of the GOAL study. Revue Française d'Allergologie et d'Immunologie Clinique. 2004; 44(367):TT15.Juniper EF, Bateman ED, Sondhi S, Gul N. Asthma Control Questionnaire (ACQ) differentiates between levels of clinical control in a large scale trial. American Journal of Respiratory & Critical Care Medicine. 2003; 167(7):A37.Pauwels, R.; Bateman, E.; Boushey, H.; Bousquet, J.; Busse, W.; Clark, T., et al. Addition of oral corticosteroids to combination therapy has little impact on achieving total control of asthma. 4th Triennial World Asthma Meeting Abstract Book; Bangkok, Thailand. February 16-19; 2004. p. 135Pauwels R, Bateman E, Boushey H, Bousquet J, Busse W, Clark T, et al. Aiming for total control of asthma reduces the risk of exacerbations: a comparison of salmeterol/fluticasone propionate versus fluticasone propionate alone. American Journal of Respiratory and Critical Care Medicine. 2004; 169(7):A87.Pauwels R, Bateman E, Boushey H, Bousquet J, Busse W, Clark T, et al. Can total control of asthma be achieved?: the results of the GOAL study. Journal of Allergy and Clinical Immunology. 2004; 113(2 (Suppl 1): 114s.Pedersen SE. Is guideline-defined asthma control achievable? The Gaining Optimal Asthma ControL (GOAL) Study [Er guideline-defineret astmakontrol opnaelig?]. Ugeskrift for Laeger. 2005; 167(38):3595-7. [PubMed: 16219190] Pedersen, SE.; Bateman, ED.; on behalf of the GOAL Steering Committee. Aiming for Total Control of asthma in patients taking inhaled

corticosteroids improves traditional outcomes: Results of the Gaining Optimal Asthma controL (GOAL) study. [abstract]. 3rd European Academy of Allergology and Clinical Immunology Meeting Abstract Book; Amsterdam, The Netherlands. June 12-16; 2004. p. 670Pederson, S.; Bateman, E.; Boushey, H.; Bousquet, J.; Busse, W.; Clark, T., et al. Aiming for guideline defined total control of asthma improves one-year asthma outcomes: results of Goal study. Triennial World Asthma Meeting; Thailand. 16-19 February; 2004. *SAM40027. Gaining Optimal Asthma ControL (GOAL): A multi-centre, stratified, randomised, double-blind, parallel-group, step-up comparison of the level of asthma control achieved with salmeterol/fluticasone propionate combination DISKUS (ACCUHALER) dry powder inhaler compared with fluticasone propionate DISKUS (ACCUHALER) alone in adults and adolescents. 2004. http://

- Green 2006 {published data only} . Green RH, Brightling CE, McKenna S, Hargadon B, Neale N, Parker D, et al. Comparison of asthma treatment given in addition to inhaled corticosteroids on airway inflammation and responsiveness. European Respiratory Journal. 2006; 27(6):1144–51. [PubMed: 16455831] Green, RH.; Brightling, CE.; McKenna, S.; Hargadon, B.; Parker, D.; Pavord, ID. A placebo controlled comparison of formoterol, montelukast or higher dose of inhaled budesonide in subjects with symptomatic asthma despite treatment with low dose inhaled budesonide. American Thoracic Society 99th International Conference; 2003. B036 Poster H82
- Houghton 2007 {published data only} . Houghton CM, Lawson N, Borrill ZL, Wixon CL, Yoxall S, Langley SJ, et al. Comparison of the effects of salmeterol/fluticasone propionate with fluticasone propionate on airway physiology in adults with mild persistent asthma. Respiratory Research. 2007; 8(1):52. [PubMed: 17629923]
- Hultquist 2000 {unpublished data only} . [accessed 30 April 2008] AstraZeneca (SD 004 0216). Oxis turbuhaler® (formoterol), Accolate® (zafirlukast) or placebo as add on treatment to Pulmicort Turbuhaler® (budesonide) in asthmatic patients on inhaled steroids. 2000. http:// www.astrazenecaclinicaltrials.comHultquist, C. Unpublished data. Personal communication
- Ind 2003 {published data only} . Ind P, Haughney J, Price D, Rosen J-P, Kennelly J. Four months adjustable or fixed BD dosing with budesonide /Formoterol in a single inhaler reduces symptom severity. Thorax. 2002; Vol. 57(issue Suppl 3):iii88.Ind PW, Dal Negro R, Colman N, Fletcher CP, Browning DC, James MH. Inhaled fluticasone propionate and salmeterol in moderate adult asthma I: lung function and symptoms. American Journal of Respiratory and Critical Care Medicine. 1998; Vol. 157(issue Suppl 3):A416.Ind PW, Dal Negro R, Colman N, Fletcher CP, Browning DC, James MH. Inhaled fluticasone propionate and salmeterol in moderate adult asthma II: exacerbations. American Journal of Respiratory and Critical Care Medicine. 1998; Vol. 157(issue Suppl 3):A415.Ind PW, Dal Negro R, Colman NC, Fletcher CP, Browning D, James MH. Addition of salmeterol to fluticasone propionate treatment in moderate to severe asthma. Respiratory Medicine. 2003; 97(5):555–62. [PubMed: 12735675] *SLGQ97. A multicentre double-blind, parallel group study to evaluate the relative clinical benefits of three treatment interventions: i) salmeterol xinafoate 50 mcg bd plus fluticasone propionate 250 mcg bd; ii) fluticasone propionate 250 mcg bd, in adult asthmatic subjects poorly controlled on current inhaled corticosteroids. 2005. http://ctr.gsk.co.uk
- Jenkins 2006a {published and unpublished data} . Jenkins C, Kolarikova R, Kuna P, Caillaud D, Sanchis J, Popp W, et al. Efficacy and safety of high-dose budesonide/formoterol (Symbicort(R)) compared with budesonide administered either concomitantly with formoterol or alone in patients with persistent symptomatic asthma. Respirology. 2006; 11(3):276–86. [PubMed: 16635085] *SD 039 0689. Efficacy and safety of Symbicort® (budesonide/formoterol) 1280/36 mcg daily delivered dose compared to Pulmicort® (budesonide) 1600 mcg metered dose and Pulmicort (budesonide) 1600 mcg metered dose plus Oxis® (formoterol) 36 mcg delivered dose all delivered via Turbuhaler® in steroid-using asthmatic adolescents and adults. A double-blind, double-dummy, randomized, parallel group, phase III, multicentre study. 2005. http://www.astrazeneca.com
- Jenkins 2006b {published data only} . Jenkins C, Kolarikova R, Kuna P, Caillaud D, Sanchis J, Popp W, et al. Efficacy and safety of high-dose budesonide/formoterol (Symbicort(R)) compared with budesonide administered either concomitantly with formoterol or alone in patients with persistent symptomatic asthma. Respirology. 2006; 11(3):276–86. [PubMed: 16635085] *SD 039 0689. Efficacy and safety of Symbicort® (budesonide/formoterol) 1280/36 mcg daily delivered

dose compared to Pulmicort® (budesonide) 1600 mcg metered dose and Pulmicort (budesonide) 1600 mcg metered dose plus Oxis® (formoterol) 36 mcg delivered dose all delivered via Turbuhaler® in steroid-using asthmatic adolescents and adults. A double-blind, double-dummy, randomized, parallel group, phase III, multicentre study. 2005. http://www.astrazeneca.com

- Kavaru 2000 {published and unpublished data} . Edin HM, Payne E, Herrle MR, Schoaf L, Mather DB, Scott CA, et al. Salmeterol/fluticasone propionate combination via HFA MDI improves quality of life in asthma patients. Journal of Allergy and Clinical Immunology. 2001; Vol. 107(issue 2):S246.Edin HM, Prillaman B, Baitinger LA, House K, Shah TP. Improved ability to perform strenuous activities after treatment with fluticasone propionate-salmeterol combination. American Journal of Respiratory & Critical Care Medicine. 2002; Vol. 165(issue Suppl 8):A112.Edwards T, Gross G, Mitchell D, Chervinsky P, Woodring A, Baitinger L, et al. The salmeterol xinafoate/fluticasone propionate dry powder combination product via diskus® inhaler improves asthma control compared to salmeterol xinafoate or fluticasone propionate dry powder alone. American Journal of Respiratory and Critical Care Medicine. 1998; Vol. 157(issue Suppl 3):A414.Johansson G. Price MJ. Sondhi S. Cost-effectiveness analysis of salmeterol/fluticasone propionate 50/100mug vs fluticasone propionate 100mug in adults and adolescents with asthma III. Pharmacoeconomics. 1999; 16(Suppl 2):15-21.Kavuru M, Melamed J, Gross G, Laforce C, House K, Prillaman B, et al. Salmeterol and fluticasone propionate combined in a new powder inhalation device for the treatment of asthma: a randomised, double blind, placebo controlled trial. Journal of Allergy and Clinical Immunology. 2000; 105(6):1108–16. [PubMed: 10856143] Nathan RA, Dorinsky P, Rosenzweig JR, Shah T, Edin H, Prillaman B. Improved ability to perform strenuous activities after treatment with fluticasone propionate/salmeterol combination in patients with persistent asthma. Journal of Asthma. 2003; 40(7):815-22. [PubMed: 14626338] *SFCA3002. A randomized, double-blind, parallel-group trial evaluating safety and efficacy of salmeterol 50mcg BID and fluticasone propionate 100mcg BID individually and in combination and placebo in subjects with asthma. 2005. http://www.clinicalstudyresults.org
- Kemp 1998 {published data only} . Kemp JP, Cook DA, Incaudo GA, Corren J, Kalberg C, Emmett A, et al. Salmeterol improves quality of life in patients with asthma requiring inhaled corticosteroids. Journal of Allergy & Clinical Immunology. 1998; 101:188–95. [PubMed: 9500751]
- Koopmans 2006 {published data only} . Koopmans JG, Lutter R, Jansen HM, van der Zee JS. Adding salmeterol to an inhaled corticosteroid: long term effects on bronchial inflammation in asthma. Thorax. 2006; 61(4):306–12. [PubMed: 16449264] *SAS30013. A study to compare the long term effects on airway inflammation of Seretide versus Flixotide in adult subjects with asthma. 2004. http://www.ctr.gsk.co.uk
- Kuna 2006 {published data only} . [accessed 30 April 2008] AstraZeneca (SD 039 0665). Symbicort low dose once daily in mild to moderate asthmatic patients. 2000. http:// www.astrazenecaclinicaltrials.com*Kuna P, Creemers JPHM, Vondra V, Black PN, Lindqvist A, Nihlen U, et al. Once-daily dosing with budesonide/formoterol compared with twice-daily budesonide/formoterol and once-daily budesonide in adults with mild to moderate asthma. Respiratory Medicine. 2006; 100(12):2151–9. [PubMed: 16701989]
- Langton Hewer 1995 {published data only} . Langton Hewer S, Hobbs J, French D, Lenney W. Pilgrims progress: the effect of salmeterol in older children with chronic severe asthma. Respiratory Medicine. 1995; 89:435–40. [PubMed: 7644775]
- Leblanc 1996 {published data only} . Leblanc P, Knight A, Kreisman H, Borkhoff CM, Johnston PR. A placebo-controlled, crossover comparison of salmeterol and salbutamol in patients with asthma. American Journal of Respiratory & Critical Care Medicine. 1996; 154:324–8. [PubMed: 8756801]
- Li 1999 {published data only} . Li X, Ward C, Thien F, Bish R, Bamford T, Bao X, et al. An antiinflammatory effect of salmeterol, a long-acting B2-agonist, assessed in airway biopsies and bronchoalveolar lavage in asthma. American Journal of Respiratory & Critical Care Medicine. 1999; 160:1493–9. [PubMed: 10556111] *Reid DW, Ward C, Wang N, Zheng L, Bish R, Orsida B, et al. Possible anti-inflammatory effect of salmeterol against interleukin-8 and neutrophil activation in asthma in vivo. European Respiratory Journal. 2003; 21(6):994–9. [PubMed: 12797494]

Ducharme et al.

- Malone 2005 {published and unpublished data}. Dorinsky P, Emmett A, Sutton L. Reduced risk for asthma exacerbations in pediatric patients receiving salmeterol plus inhaled corticosteroids (ICS) vs ICS alone [Abstract]. European Respiratory Journal. 2004; 24(Suppl 48):308s.House K, Dorinsky PM, Stauffer J, Schoaf L, Ellsworth A. The safety of fluticasone propionate/salmeterol Diskus (R) in pediatric patients ages 4 –11 with asthma [Abstract]. Chest. 2004; 126(Suppl 4): 911S.Malone R, LaForce C, Nimmagadda S, Schoaf L, House K, Ellsworth A, et al. The safety of twice-daily treatment with fluticasone propionate and salmeterol in pediatric patients with persistent asthma. Annals of Allergy, Asthma, and Immunology. 2005; 95(1):66–71. [accessed 30 April 2008] SAS30031(GSK). A randomized, double-blind, 12-week trial evaluating the safety of the fluticasone propionate/salmeterol DISKUS combination product 100/50mcg BID versus fluticasone propionate DISKUS 100mcg BID in symptomatic pediatric subjects (4-11 years) with asthma. 2005. http://www.ctr.gsk.co.uk*Scott C, Wu W, Ellsworth A, Crim C. Efficacy and safety of fluticasone propionate/salmeterol DISKUS and fluticasone propionate DISKUS and HFA in children [Abstract]. European Respiratory Journal. 2005; 26(Suppl 49) Abstract No. 1057.
- Meijer 1995 {published data only} . Meijer GG, Postma DS, Mulder PG, van Aalderen WM.
 Long-term circadian effects of salmeterol in asthmatic children treated with inhaled corticosteroids. American Journal of Respiratory & Critical Care Medicine. 1995; 152:1887–92.
 [PubMed: 8520751]
- Molimard 2001 {published data only} .*Molimard M, Bourcereau J, Le Gros V, Bourdeix I, Leynadier F, Duroux P. Comparison between formoterol 12 ug bid and on-demand salbutamol in moderate persistent asthma. Respiratory Medicine. 2001; 95(1):64–70. [PubMed: 11207020]
- Morice 2008a {published and unpublished data} . AstraZeneca, A. [accessed 4 January 2008] 12week randomised, double-blind, parallel-group, multicentre phase-III study to compare the efficacy and safety of Symbicort® pMDI (budesonide/formoterol 80/4.5 mcg 2 actuations b.i.d., delivered dose) with that of Pulmicort® pMDI (budesonide 100 mcg 2 actuations b.i.d., metered dose) and Symbicort Turbuhaler® (budesonide/formoterol 80/4.5 mcg 2 actuations b.i.d., delivered dose) in children with asthma. 2007. http://www.astrazenecaclinicaltrials.comMorice AH, Peterson S, Beckman O, Kukova Z. Efficacy and safety of a new pressurised metered-dose inhaler formulation of budesonide/formoterol in children with asthma: A superiority and therapeutic equivalence study. Pulmonology Pharmacology Therapeutics. 2008; 21(1):152–9.
- Morice 2008b {published data only} . AstraZeneca. [accessed 4 January 2008] A 12-week randomised, double-blind, parallel-group, multicentre phase-III study to compare the efficacy and safety of Symbicort®pMDI (budesonide/formoterol 80/4.5 mcg 2 actuations b.i.d., delivered dose) with that of Pulmicort®pMDI (budesonide 100 mcg 2 actuations b.i.d., metered dose) and Symbicort Turbuhaler® (budesonide/formoterol 80/4.5 mcg 2 actuations b.i.d., delivered dose) in children with asthma. 2007. http://www.astrazenecaclinicaltrials.comMorice AH, Peterson S, Beckman O, Kukova Z. Efficacy and safety of a new pressurised metered-dose inhaler formulation of budesonide/formoterol in children with asthma: a superiority and therapeutic equivalence study. Pulmonology Pharmacology Therapeutics. 2008; Vol. 21(issue 1):152–9.
- Nathan 2006 {published and unpublished data} . Edin HM, Payne E, Herrle MR, Schoaf L, Mather DB, Scott CA, et al. Salmeterol/fluticasone propionate combination via HFA MDI improves quality of life. Journal of Allergy & Clinical Immunology. 2001; 107(2):S246.Nathan RA, Mitchell D, Condemi J, Heller A, Schoaf L, Herrle M, et al. Cardiovascular and hypothalamicpituitary-adrenal axis safety of fluticasone propionate/salmeterol HFA MDI in adolescent and adult patients with asthma. American Journal for Respiratory & Critical Care Medicine. 2001; 163(5):A863.Nathan RA, Rooklin A, Schoaf L, Scott C, Ellsworth A, House K, et al. Efficacy and tolerability of fluticasone propionate/salmeterol administered twice daily via hydrofluoroalkane 134a metered-dose inhaler in adolescent and adult patients with persistent asthma: a randomized, double-blind, placebo-controlled, 12-week study. Clinical Therapeutics. 2006; 28(1):73-85. [PubMed: 16490581] Pearlman DS, Kent E, Lanz MJ, Peden D, Baitinger L, Herrle M, et al. Fluticasone propionate/salmeterol HFA MDI has a rapid onset of effect in asthmatics treated with short or long-acting beta-agonists (BA) or inhaled corticosteroids (ICS). American Journal of Respiratory & Critical Care Medicine. 2001; 163(5):A865.Rooklin A, Elkayam D, Weiler J, Windom H, Schoaf L, Scott C, et al. The fluticasone propionate/salmeterol HFA MDI is significantly more efficacious in treating asthma than placebo HFA MDI,

fluticasone propionate CFC MDI or salmeterol CFC MDI. Journal of Allergy and Clinical Immunology. 2001; 107(2):100s.*SAS30004. A randomized, double-blind, placebo-controlled, parallel-group 12-week trial evaluating the safety and efficacy of the salmeterol/fluticasone propionate combination in GR106642X MDI, 50/250mcg BID, and salmeterol in propellant 11/12 MDI, 50mcg BID, fluticasone propionate in propellant 11/12 MDI, 250mcg BID, and placebo propellant GR106642X MDI in adult and adolescent subjects with asthma. 2005. http:// ctr.gsk.co.uk

- Noonan 2006a {published data only} . Noonan M, Rosenwasser LJ, Martin P, O'Brien CD, O'Dowd L. Efficacy and safety of budesonide and formoterol in one pressurised metered-dose inhaler in adults and adolescents with moderate to severe asthma: a randomised clinical trial. Drugs. 2006; 66(17):2235–54. [PubMed: 17137405] * [accessed 13 June 2008] SD 039 0717 (AstraZeneca). A twelve-week, randomized, double-blind, double-dummy, placebo-controlled trial of Symbicort® (160/4.5 µg) versus its mono- products (budesonide and formoterol) in adolescents (12 years of age) and adults with asthma. 2004. http:// www.astrazenecaclinicaltrials.com
- Noonan 2006b {published data only} . Noonan M, Rosenwasser LJ, Martin P, O'Brien CD, O'Dowd L. Efficacy and safety of budesonide and formoterol in one pressurised metered-dose inhaler in adults and adolescents with moderate to severe asthma: a randomised clinical trial. Drugs. 2006; 66(17):2235–54. [PubMed: 17137405] * [accessed 13 June 2008] SD 039 0717 (AstraZeneca). A twelve-week, randomized, double-blind, double-dummy, placebo-controlled trial of Symbicort® (160/4.5 µg) versus its mono-products (budesonide and formoterol) in adolescents (12 years of age) and adults with asthma. 2004. http://www.astrazenecaclinicaltrials.com
- Norhaya 1999 {published data only} .*Norhaya MR, Yap TM, Zainudin BMZ. Addition of inhaled salmeterol to inhaled corticosteroids in patients with poorly controlled nocturnal asthma. Repirology. 1999; 4(1):77–81.
- O'Byrne 2001a {published data only} . Barnes PJ, O'Byrne PM, Rodriguez-Roisin R, Runnerstrom E, Sandstrom T, Svensson K, et al. Oxis and Pulmicort turbuhaler in the management of asthma OPTIMA international study group. Treatment of mild persistent asthma with low doses of inhaled budesonide alone or in combination with formoterol. Thorax. 2000; 55(Suppl 3):A4.Barnes PJ, O'Byrne PM, Rodriguez-Roisin R, Runnerstrom E, Sandstrom T, Svensson K, et al. Treatment of mild persistent asthma with low doses of inhaled budesonide alone or in combination with formoterol. For the Oxis and Pulmicort Turbuhaler in the Management of Asthma (OPTIMA) international study group. Thorax. 2000; Vol. 55(issue Suppl 3):s5.Jönsson BG, Berggren FE, Svensson K, O'Byrne PM. Budesonide and formoterol in mild persistent asthma compared with doubling the dose of budesonide - a cost-effectiveness analysis. European Respiratory Journal. 2001; Vol. 18(issue Suppl 33):517s.Jönsson BG, Berggren FE, Svensson K, O'Byrne PM. Economic results of adding formoterol to budesonide in mild persistent asthma. European Respiratory Journal. 2001; Vol. 18(issue Suppl 33):331s.O'Byrne PM, Barnes PJ, Rodriguez-Roisin R, Runnerstrom E, Sandstrom T, Svensson K, et al. Low dose inhaled budesonide and formoterol in mild persistent asthma: The OPTIMA randomized trial. American Journal of Respiratory & Critical Care Medicine. 2001; 164(8 pt 1):1392-7. [PubMed: 11704584] *O'Byrne PM, Barnes PJ, Rodriguez-Roisin R, Sandtröm T, Tattersfield AE, Runnerström EM, et al. Addition of formoterol Turbuhaler® to budesonide Tubuhaler® is safe and well tolerated in the long-term treatment of mild asthma: results from the OPTIMA trial. European Respiratory Journal. 2001; Vol. 18(issue Suppl 33):330s.
- O'Byrne 2001b {published data only} . Barnes PJ, O'Byrne PM, Rodriguez-Roisin R, Runnerstrom E, Sandstrom T, Svensson K, et al. Oxis and Pulmicort turbuhaler in the management of asthma OPTIMA international study group. Treatment of mild persistent asthma with low doses of inhaled budesonide alone or in combination with formoterol. Thorax. 2000; 55(Suppl 3):A4.Barnes PJ, O'Byrne PM, Rodriguez-Roisin R, Runnerstrom E, Sandstrom T, Svensson K, et al. Treatment of mild persistent asthma with low doses of inhaled budesonide alone or in combination with formoterol. For the Oxis and Pulmicort Turbuhaler in the Management of Asthma (OPTIMA) international study group. Thorax. 2000; Vol. 55(issue Suppl 3):s5.Jönsson BG, Berggren FE, Svensson K, O'Byrne PM. Budesonide and formoterol in mild persistent asthma compared with doubling the dose of budesonide - a cost-effectiveness analysis.

European Respiratory Journal. 2001; Vol. 18(issue Suppl 33):517s.Jönsson BG, Berggren FE, Svensson K, O'Byrne PM. Economic results of adding formoterol to budesonide in mild persistent asthma. European Respiratory Journal. 2001; Vol. 18(issue Suppl 33):331s.O'Byrne PM, Barnes PJ, Rodriguez-Roisin R, Runnerstrom E, Sandstrom T, Svensson K, et al. Low dose inhaled budesonide and formoterol in mild persistent asthma: the OPTIMA randomized trial. American Journal of Respiratory & Critical Care Medicine. 2001; 164(8 pt 1):1392–7. [PubMed: 11704584] *O'Byrne PM, Barnes PJ, Rodriguez-Roisin R, Sandtröm T, Tattersfield AE, Runnerström EM, et al. Addition of formoterol Turbuhaler® to budesonide Tubuhaler® is safe and well tolerated in the long-term treatment of mild asthma: results from the OPTIMA trial. European Respiratory Journal. 2001; Vol. 18(issue Suppl 33):330s.

- Pauwels 1997a {published data only} . Pauwels R. Additive effects of inhaled formoterol and budesonide in reducing asthma exacerbations. Allergy. 1998; 53:20–3. [PubMed: 9615842]
 *Pauwels RA, Lofdahl CG, Postma DA, Tattersfield AE, O'Byrne P, Barnes PJ, et al. Effect of inhaled formoterol and budesonide on exacerbations of asthma. New England Journal of Medicine. 1997; 337(20):1405–11. [PubMed: 9358137]
- Pauwels 1997b {published data only}. Pauwels R. Additive effects of inhaled formoterol and budesonide in reducing asthma exacerbations. Allergy. 1998; 53:20–3. [PubMed: 9615842]
 Pauwels RA, Lofdahl CG, Postma DA, Tattersfield AE, O'Byrne P, Barnes PJ, et al. Effect of inhaled formoterol and budesonide on exacerbations of asthma. New England Journal of Medicine. 1997; 337(20):1405–11. [PubMed: 9358137]
- Pohunek 2006a {published data only} . Pohunek P, Kuna P, De Boeck K. Budesonide/formoterol improves lung function compared with budesonide alone in children with asthma [Abstract]. European Respiratory Journal. 2004; 24(Suppl 48):379s.Pohunek P, Kuna P, Jorup C, De Boeck K. Budesonide/formoterol improves lung function compared with budesonide alone in children with asthma. Pediatric Allergy and Immunology. 2006; 17(6):458–65. [PubMed: 16925692]
 *Pohunek P, Matulka M, Rybnicek O, Kopriva F, Honomichlova H, Svobodova T. Dose-related efficacy and safety of formoterol (Oxis) Turbuhaler compared with salmeterol Diskhaler in children with asthma. Pediatric Allergy & Immunology. 2004; 15(1):32–9. [PubMed: 14998380]
- Pohunek 2006b {published data only} . Pohunek P, Kuna P, De Boeck K. Budesonide/formoterol improves lung function compared with budesonide alone in children with asthma [Abstract]. European Respiratory Journal. 2004; 24(Suppl 48):379s.Pohunek P, Kuna P, Jorup C, De Boeck K. Budesonide/formoterol improves lung function compared with budesonide alone in children with asthma. Pediatric Allergy and Immunology. 2006; 17(6):458–65. [PubMed: 16925692]
 *Pohunek P, Matulka M, Rybnicek O, Kopriva F, Honomichlova H, Svobodova T. Dose-related efficacy and safety of formoterol (Oxis) Turbuhaler compared with salmeterol Diskhaler in children with asthma. Pediatric Allergy & Immunology. 2004; 15(1):32–9. [PubMed: 14998380]
- Price 2002 {published data only} . Price D, Dutchman D, Mawson A, Bodalia B, Duggan S, Todd P, FLOW (Eformoterol in the management of mild asthma-eformoterol Turboinhaler with budesonide Turbohaler) research group. Early asthma control and maintenance with eformoterol following reduction of inhaled corticosteroid dose. Thorax. 2002; 57(9):791–8. [PubMed: 12200524] Price MJ, Briggs AH. Development of an economic model to assess the cost effectiveness of asthma management strategies. Pharmacoeconomics. 2002; Vol. 20(issue 3): 183–94. [PubMed: 11929348] *Price, MJ.; Sondhi, S.; Yan, S.; Nyth, A.; House, K. Salmeterol/ fluticasone propionate combination inhaler is more cost effective than fluticasone propionate in patients with asthma. European Respiratory Society 1999 Annual Congress; Madrid, Spain. Oct 9-13; 1999.
- Reddel 2007 {unpublished data only} . Reddel HK, Peyters MJ, Wark PA, Sand IB, Jenkins CR. Comparison of the efficacy of Seretide and Flixotide when down-titrating the inhaled corticosteroid dose. Respirology. 2007; 12(Suppl 1):A40.
- Russell 1995 {published data only} . Russell G, Williams DAJ, Weller P, Price JF. Salmeterol xinafoate on children on high dose inhaled steroids. Annals of Allergy, Asthma, and Immunology. 1995; 75:423–8.* [accessed 20 June 2008] SALMP/AH91/D89 (GSK). A phase III, multi-centre, double-blind, placebo controlled, parallel group study assessing the efficacy and safety of inhaled salmeterol xinafoate (SereventTM) 50 micrograms BD via the DiskhalerTM when added to the existing treatment of moderate to severe asthmatic children. 2006. http:// ctr.gsk.co.uk

Ducharme et al.

- SAM40008 {unpublished data only} . SAM40008. A multicentre, randomised, double-blind, parallel group comparison of the efficacy of Seretide bd and fluticasone propionate bd (both via diskus/accuhaler inhaler) when tapering the inhaled corticosteroid dose in asthmatic adults. 2004. http://www.ctr.gsk.co.uk
- SAM40012 {unpublished data only} . Dorinsky P, Emmett A, Sutton L. Reduced risk for asthma exacerbations in pediatric patients receiving salmeterol plus inhaled corticosteroids (ICS) versus ICS alone [Abstract]. European Respiratory Journal. 2004; 24(Suppl 48):308s.SAM40012. A multicentre, randomised, double-blind, double-dummy, parallel group comparison of three treatments: 1) salmeterol/fluticasone propionate (SFC) (50/100mcg strength) bd via DISKUS/ACCUHALER inhaler, 2) fluticasone propionate 200mcg bd via DISKUS/ACCUHALER inhaler, 3) fluticasone propionate 100mcg bd via DISKUS/ACCUHALER inhaler in children aged 4-11 years with asthma. 2005. http://www.ctr.gsk.co.uk
- SAS40024 {unpublished data only} . Dorinsky P, Jones S, Kalberg C, Emmett A, Rickard K.
 Sustained protection against activity-induced bronchospasm (AIB) during chronic treatment with the fluticasone propionate/salmeterol combination (FSC). American Journal of Respiratory and Critical Care Medicine. 2002; Vol. 165(issue Suppl 8):A568.Dorinsky P, Kalberg C, Emmett A, Rickard K. Sustained protection against activity-induced bronchospasm during chronic treatment with fluticasone/salmeterol combination. European Respiratory Journal. 2002; 20(Suppl 38): 308s.SAS40024. A randomized, double-blind, parallel-group study evaluating the protective effects of the fluticasone propionate/salmeterol combination product (FSC, 100/50mcg BID via diskus) against bronchospasms induced by activity as measured by exercise challenge testing in adolescent and adult subjects who require chronic inhaled corticosteroid therapy for the treatment of persistent asthma. 2005. http://www.ctr.gsk.co.uk
- SAS40036 {unpublished data only} . Keonig S, Waitkus-Edwards K, Yancey S, Prillaman B, Dorinsky P. Loss of asthma control when patients receiving fluticasone propionate/salmeterol 100/50 mcg Diskus® are stepped-down to fluticasone propionate, salmeterol or montelukast alone. Journal of Allergy and Clinical Immunology. 2004; 113(2 (Suppl 1)):S94. [DOI: 10.1016/ j.jaci.2003.12.325]. *SAS40036. A multicenter, randomized, double-blind, double-dummy, parallel group, 16-week comparison of asthma control in adolescents and adults receiving either fluticasone propionate/salmeterol Diskus combination product 100/50mcg BID, fluticasone propionate Diskus 100mcg BID, salmeterol xinafoate Diskus 50mcg BID, or oral montelukast 10mg QD. 2005. http://www.ctr.gsk.co.uk
- SAS40037 {unpublished data only} . SAS40037. A multicenter, randomized, double-blind, double-dummy, parallel group, 16-week comparison of asthma control in adolescents and adults receiving either fluticasone propionate/salmeterol Diskus (combination product 100/50mcg BID, fluticasone propionate Diskus 100mcg BID, salmeterol xinafoate Diskus 50mcg BID, or oral montelukast 10mg QD. 2005. http://www.ctr.gsk.co.uk
- SD 037 0344a {unpublished data only} . [accessed 30 April 2008] AstraZeneca (SD 037 0344). A 3-month, multi-centre, double-blind, double-dummy, randomised, parallel group, phase III study to investigate the efficacy and safety of formoterol HFA pMDI compared with placebo and Oxis® Turbuhaler® in subjects with asthma. 2003. http://www.astrazenecaclinicaltrials.com
- SD 037 0344b {unpublished data only} . [accessed 30 April 2008] AstraZeneca (SD 037 0344). A 3-month, multi-centre, double-blind, double-dummy, randomised, parallel group, phase III study to investigate the efficacy and safety of Formoterol HFA pMDI compared with placebo and Oxis® Turbuhaler® in subjects with asthma. 2003. http://www.astrazenecaclinicaltrials.com
- SD 039 0349 {unpublished data only} . [accessed 30 April 2008] AstraZeneca (SD 039 0349). Efficacy and safety of a fixed combination of budesonide/formoterol Turbuhaler® in inhaled steroid-using asthmatic adults. 1999. http://www.astrazenecaclinicaltrials.com
- SD 039 0714 {unpublished data only} . [accessed 21 February 2006] AstraZeneca Pharmaceuticals. Efficacy and safety of budesonide/formoterol Turbuhaler® (160/4.5 mcg b.i.d. delivered dose) compared to budesonide Turbuhaler® (200 mcg b.i.d. metered dose) in steroidusing asthmatic adolescent patients. A double-blind, double-dummy, randomised, parallel group, phase III, multicentre study. 2005. www.astrazenecaclinicaltrials.com
- SD 039 0718 {unpublished data only} . [accessed 4 January 2008] AstraZeneca Pharmaceuticals (SD 039 0718). A twelve-week, randomized, double-blind, double-dummy trial of Symbicort®

(40/4.5 mcg) versus its mono-products (budesonide and formoterol) in asthmatic children aged six to fifteen years. 2005. http://www.astrazenecaclinicaltrials.com

- SD 039 0719 {unpublished data only} . [accessed 4 January 2008] AstraZeneca Pharmaceuticals (SD 039 0719). A six-month, randomized, open-label safety study of Symbicort® (160/4.5 mcg) compared to Pulmicort Turbuhaler® in asthmatic children aged 6 to 11 years. 2005. http:// www.astrazenecaclinicaltrials.com
- SD 039 0725a {unpublished data only} . [accessed 4 January 2008] AstraZeneca Pharmaceuticals (SD 039 0725). A twelve-week, randomized, double-blind, double-dummy, active-controlled study of Symbicort® pMDI administered once daily in children and adolescents 6 to 15 years of age with asthma. 2005. http://www.astrazenecaclinicaltrials.com
- SD 039 0725b {unpublished data only} . [accessed 4 January 2008] AstraZeneca Pharmaceuticals (SD 039 0725). A twelve-week, randomized, double-blind, double-dummy, active-controlled study of Symbicort® pMDI administered once daily in children and adolescents 6 to 15 years of age with asthma. 2005. http://www.astrazenecaclinicaltrials.com
- SD 039 0726a {unpublished data only} . Ambrose, H.; Lawrance, R.; Goldman, M. [accessed 27 June 2008] Beta-adrenergic receptor Gly16Arg variation: effect on response to budesonide/ formoterol or budesonide (post-formoterol) in asthma patients. 2007. http:// meeting.chestjournal.orgBerger, WE.; Bleecker, ER.; O'Dowd, L.; Miller, CJ. [accessed 26 June 2008] Asthma control with once-daily budesonide/formoterol (BUD/FM) pressurized metered-dose inhaler. 2007. http://www.abstracts2view.comBleecker, ER.; Berger, WE.; O'Dowd, L.; Miller, CJ. [accessed 27 June 2008] Safety of once-daily budesonide (BUD) and formoterol (FM) administered via one pressurized metered-dose inhaler (pMDI) in patients with asthma. 2007. http://www.abstracts2view.com* [accessed 26 June 2008] SD 039 0726 (AstraZeneca). A twelve-week, randomized, double-blind, double-dummy, placebo- and active-controlled study of SYMBICORT® pMDI administered once daily in adults and adolescents with asthma. 2005. www.astrazenecaclinicaltrials.com
- SD 039 0726b {unpublished data only} . Ambrose, H.; Lawrance, R.; Goldman, M. [accessed 27 June 2008] Beta-adrenergic receptor Gly16Arg variation: Effect on response to budesonide/ formoterol or budesonide (post-formoterol) in asthma patients. 2007. http:// meeting.chestjournal.orgBerger, WE.; Bleecker, ER.; O'Dowd, L.; Miller, CJ. [accessed 26 June 2008] Asthma control with once-daily budesonide/formoterol (BUD/FM) pressurized metered-dose inhaler. 2007. http://www.abstracts2view.comBleecker, ER.; Berger, WE.; O'Dowd, L.; Miller, CJ. [accessed 27 June 2008] Safety of once-daily budesonide (BUD) and formoterol (FM) administered via one pressurized metered-dose inhaler (pMDI) in patients with asthma. 2007. http://www.abstracts2view.com [accessed 26 June 2008] SD 039 0726 (AstraZeneca). A twelve-week, randomized, double-blind, double-dummy, placebo- and active-controlled study of SYMBICORT® pMDI administered once daily in adults and adolescents with asthma. 2005. www.astrazenecaclinicaltrials.com
- SD 039 0728 {unpublished data only} . O'Brien, CD.; Peters, SP.; Prenner, BM.; Martin, P. [accessed 26 June 2008] Long-term safety of budesonide/formoterol pressurized metered-dose inhaler (BUD/FM pMDI) in asthma patients: adverse events and asthma exacerbations. 2007. http://www.abstracts2view.comO'Brien, CD.; Peters, SP.; Prenner, BM.; Martin, P. [accessed 26 June 2008] Resource use with budesonide/formoterol pressurized metered-dose inhaler (BUD/FM pMDI) versus BUD pMDI in asthma patients. 2007. www.astrazenecaclinicaltrials.comPeters, SP.; Prenner, BM.; Martin, P.; O'Brien, CD. [accessed 26 June 2008] Long-term effects on lung function of budesonide (BUD) and formoterol (FM) in one pressurized metered-dose inhaler (BUD/FM pMDI) and BUD pMDI in patients with asthma. 2007. http://www.abstracts2view.comPrenner, BM.; Peters, SP.; Martin, P.; O'Brien, CD. [accessed 26 June 2008] Long-term control of asthma symptoms with budesonide/formoterol pressurized metered-dose inhaler (BUD/FM pMDI) versus BUD pMDI. 2007. http:// www.abstracts2view.comPrenner, BM.; Peters, SP.; Martin, P.; O'Brien, CD. [accessed 26 June 2008] Safety pharmacodynamics (PD) of budesonide/formoterol (BUD/FM) pMDI in asthma patients. 2007. http://www.abstracts2view.com* [accessed 26 June 2008] SD 039 0728 (AstraZeneca). A 52-week, randomized, double-blind, single-dummy, parallel-group, multicenter Phase III study comparing the long-term safety of SYMBICORT® pMDI 160/4.5 µg x 4 actuations twice daily to SYMBICORT® pMDI 160/4.5 µg x 2 actuations twice daily and

budesonide HFA pMDI 160 μ g x 4 actuations twice daily in adult and adolescent subjects with asthma. 2006. www.astrazenecaclinicaltrials.com

- SFA100314 {unpublished data only} . [accessed 16 May 2008] GlaxoSmithKline (SFA100314). A stratified, multicenter, randomized, double-blind, parallel group, 4-week comparison of fluticasone propionate/salmeterol DISKUS combination product 100/50mcg BID versus fluticasone propionate DISKUS 100mcg BID in pediatric and in adolescent subjects with activity-induced bronchospasm. 2007. http://www.ctr.gsk.co.uk
- SFA100316 {unpublished data only} . [accessed 30 April 2008] GlaxoSmithKline (SFA100316). A stratified, multicenter, randomized, double-blind, parallel group, 4-week comparison of fluticasone propionate/salmeterol DISKUS combination product 100/50mcg BID versus fluticasone propionate DISKUS 100mcg BID in pediatric and in adolescent subjects with activity-induced bronchospasm. 2006. http://ctr.gsk.co.uk
- SFCF4026 {unpublished data only} . SFCF4026. Maintenance of asthma control in adults: comparison of three therapeutic strategies in patients whose asthma is controlled by a medium dose of inhaled corticosteroid and a long-acting inhaled beta2-agonist. 2005. http:// www.ctr.gsk.co.uk
- Shapiro 2000 {published data only} . [accessed 4 June 2008] SFCA3003. A randomized, doubleblind, parallel-group trial evaluating safety and efficacy of salmeterol 50mcg BID and fluticasone propionate 250mcg BID individually and in combination and placebo in subjects with asthma. 2004. http://ctr.gsk.co.uk*Shapiro G, Lumry W, Wolfe J, Given J, White MV, Woodring A, et al. Combined salmeterol 50mcg and fluticasone propionate 350mcg in the Diskus device for the treatment of asthma. American Journal of Respiratory & Critical Care Medicine. 2000; 161:527– 34. [PubMed: 10673196]
- Simons 1997 {published data only} . Simons FE, Gerstner TV, Cheang MS. Tolerance to the bronchoprotective effect of salmeterol in adolescents with exercise-induced asthma using concurrent inhaled glucocorticoid treatment. Pediatrics. 1997; 99(5):655–9. [PubMed: 9113940]
- SMS40012 {unpublished data only} . SLMF 4002 (SMS40012). Efficacy and safety of salmeterol in patients with asthma controlled with inhaled corticosteroids. 2005. http://www.ctr.gsk.co.uk
- Stelmach 2007 {published data only (unpublished sought but not used)} . Stelmach I, Grzelewskia T, Bobrowska-Korzeniowska M, Stelmach P, Kuna P. A randomized, double-blind trial of the effect of anti-asthma treatment on lung function in children with asthma. Pulmonary Pharmacology & Therapeutics. 2007; 20:691–700. [PubMed: 17046300]
- Tal 2002 {published data only} . [accessed 30 April 2008] AstraZeneca (SD 039 0353). Efficacy and safety of budesonide/formoterol Turbuhaler® in a fixed combination in steroid-using asthmatic children. 1999. http://www.astrazenecaclinicaltrials.comTal, A.; Simon, G.; Vermeulen, JH. Symbicort® (budesonide and formoterol in a single inhaler) is effective and well tolerated in children with asthma. Annual Thoracic Society 97th International Conference; San Francisco CA. May 18-23. 2001; Tal A, Simon G, Vermeulen JH, Petru V, Cobos N, Everard ML, et al. Budesonide/formoterol in a single inhaler versus inhaled corticosteroids alone in the treatment of asthma. Pediatric Pulmonology. 2002; 34(5):342-50. [PubMed: 12357478] Tal A, Simon G, Vermeulen JH, Petru V, Cobos N, Everard ML, et al. Rapid and sustained improvements in lung function and symptom control with budesonide/formoterol in adolescent asthma. European Respiratory Journal. 2001; Vol. 18(issue Suppl 33):494s.Tal, A.; Simon, G.; Vermeulen, JH.; Petru, V.; Cobos, N.; Everard, ML., et al. Symbicort (budesonide and formoterol in a single inhaler) improves lung function in children with asthma. International Paediatric Respiratory and Allergy Congress; Prague. April 1-4; 2001. p. 85Tal, A.; Simon, G.; Vermeulen, JH.; Petru, V.; Cobos, N.; Everard, ML., et al. Symbicort (budesonide and formoterol in a single inhaler) is more effective that budesonide alone in children with asthma. International Paediatric Respiratory and Allergy Congress; Prague. April 1-4; 2001. p. 84-5.*Vermeulen, JH.; Simon, G.; Tal, A. Symbicort® (budesonide and formoterol in a single inhaler) improves lung function in asthmatic children aged 4-17 years. Annual Thoracic Society 97th International Conference; San Francisco CA. May 18-23; 2001.
- Teper 2005 {published data only} . Teper, AM.; Zaragoza, SM.; Lubovich, S.; Rodriguez, VA.; Venalago, C.; Kofman, CD., et al. Effect of fluticasone propionate (FP) with or without salmeterol (S) on bronchial reactivity (BR) in children with mild to moderate persistent asthma

[Abstract]. American Thoracic Society 2005 International Conference; San Diego, California. May 20-25; 2005. [C47] [Poster: A5]

- van der Molen 1997 {published data only} . van de Molen T, Postma DS, Kraan J, Chapman K, Grossman R, Turner MO, et al. No influence of six months treatment with formoterol on airway hyperresponsiveness in asthma subjects using inhaled corticosteroids. American Journal of Respiratory & Critical Care Medicine. 1998; 157(3 Suppl):A400.van der Molen T, Postma DS, Turner MO, Meyboomde Jong B, Malo JL, Chapman K, et al. Effects of the long acting beta agonist formoterol on asthma control in asthmatic patients using inhaled corticosteroids. Thorax. 1997; 52:535–9. [PubMed: 9227720] *van der Molen T, Sears MR, de Graaff CS, Postma DS, Meyboom-de Jong B. Quality of life during formoterol treatment: comparison between asthmaspecific and generic questionnaires. European Respiratory Journal. 1998; 12(1):30–4. [PubMed: 9701410]
- Verberne 1998 {published data only} . [accessed 20 June 2008] SLGB4014 (SLPT15). Placebo controlled study during one year comparing the addition of salmeterol with an increase of the dose of the inhaled corticosteroid in asthmatic children already on treatment with inhaled corticosteroids. 2006. http://ctr.gsk.co.uk*Verberne AAPH, Frost C, Duiverman EJ, Grol MH, Kerribijn KF. Addition of salmeterol versus doubling the dose of beclomethasone in children with asthma. American Journal of Respiratory & Critical Care Medicine. 1998; 158:213–19. [PubMed: 9655732]
- Wallin 2003 {published data only} . Sue-Chu, M.; Wallin, A.; Wilson, S.; Ward, J.; Sandstrom, T.; Djukanovic, R., et al. Bronchial biopsy study in asthmatics treated with low and high dose fluticasone propionate (FP) compared to low dose FP combined with salmeterol. European Respiratory Society 1999 Annual Congress; Madrid, Spain. Oct 9-13; 1999. Wallin A, Sandstrom T, Cioppa GD, Holgate S, Wilson S. The effects of regular inhaled formoterol and budesonide on preformed Th-2 cytokines in mild asthmatics. Respiratory Medicine. 2002; 96(12):1021–5. [PubMed: 12477218] Wallin A, Sue-Chu M, Bjermer L, Ward J, Sandstrom T, Lindberg A, et al. Effect of inhaled fluticasone with and without salmeterol on airway inflammation in asthma. Journal of Allergy & Clinical Immunology. 2003; 112(1):72–8. [PubMed: 12847482]
- Weiler 2005 {published and unpublished data} . [accessed 4 November 2008] SAS40025. A randomized, double-blind, parallel-group study evaluating the protective effects of the fluticasone propionate/salmeterol combination product (FSC 250/50mcg BID via diskus) against bronchospasms induced by activity as measured by exercise challenge testing in adolescent and adult subjects who require chronic inhaled corticosteroid therapy for the treatment of persistent asthma. 2005. http://www.clinicalstudyresults.org*Weiler JM, Nathan RA, Rupp NT, Kalberg CJ, Emmett A, Dorinsky P. Effect of fluticasone/salmeterol via a single device on exercise-induced bronchospasm in patients with persistent asthma. Annals of Allergy Asthma and Immunology. 2005; 94(1):65–72.
- Zetterstrom 2001a {published data only} . Zetterstrom, O.; Buhl, R.; Mellem, H. Efficacy and safety of Symbicort® (budesonide and formoterol in a single inhaler) in adults with asthma. Annual Thoracic Society 97th International Conference; San Francisco CA. May 18-23; 2001. Zetterstrom O, Buhl R, Mellem H, Perpina M, Hedman J, O'Neill S, et al. Improved asthma control with budesonide/formoterol in a single inhaler, compared with budesonide alone. European Respiratory Journal. 2001; 18(2):262–8. [PubMed: 11529282] Zetterstrom O, Buhl R, Mellem H, Perpina M, Hedman J, O'Neill S, et al. The new single inhaler product containing both budesonide/formoterol improves asthma control in adults. European Respiratory Journal. 2000; Vol. 16(issue Suppl 31):455s.*Zetterström O, Buhl R, Mellem H, Perpiñá M, Hedman J, O'Neill S, et al. Efficacy and safety of a new single inhaler product containing both budesonide and formoterol in adult asthma. European Respiratory Journal. 2000; Vol. 16(issue 31):455s.
- Zetterstrom 2001b {published data only} . Zetterstrom, O.; Buhl, R.; Mellem, H. Efficacy and safety of Symbicort® (budesonide and formoterol in a single inhaler) in adults with asthma. Annual Thoracic Society 97th International Conference; San Francisco CA. May 18-23; 2001. Zetterstrom O, Buhl R, Mellem H, Perpina M, Hedman J, O'Neill S, et al. Improved asthma control with budesonide/formoterol in a single inhaler, compared with budesonide alone. European Respiratory Journal. 2001; 18(2):262–8. [PubMed: 11529282] Zetterstrom O, Buhl R, Mellem H, Perpina M, Hedman J, O'Neill S, et al. The new single inhaler product containing both budesonide/formoterol improves asthma control in adults. European Respiratory Journal.

2000; 16(Suppl 31):455s.*Zetterström O, Buhl R, Mellem H, Perpiñá M, Hedman J, O'Neill S, et al. Efficacy and safety of a new single inhaler product containing both budesonide and formoterol in adult asthma. European Respiratory Journal. 2000; Vol. 16(issue 31):455s.

- Zimmerman 2004a {published data only}. Zimmerman B, D'Urzo A, Berube D. Efficacy and safety of formoterol turbuhaler(R) when added to inhaled corticosteroid treatment in children with asthma. Pediatric Pulmonology. 2004; 37(2):122–7. [PubMed: 14730657] Zimmerman B, D'Urzo A, Berube D. Efficacy and tolerability of formoterol turbuhaler(r) compared with placebo, in children (6-11 yr) with asthma poorly controlled with inhaled corticosteroids [abstract]. American Journal of Respiratory and Critical Care Medicine. 2002; Vol. 165(issue 8 Suppl):A746.*Zimmerman, B.; D'Urzo, A.; Berube, D. Efficacy and tolerability of formoterol Turbuhaler in 6-11 year old children with asthma, not adequately controlled with inhaled corticosteroids. European Respiratory Society Annual Congress; 2002. p. P2734
- Zimmerman 2004b {published data only} . Zimmerman B, D'Urzo A, Berube D. Efficacy and safety of formoterol turbuhaler(R) when added to inhaled corticosteroid treatment in children with asthma. Pediatric Pulmonology. 2004; 37(2):122–7. [PubMed: 14730657] Zimmerman B, D'Urzo A, Berube D. Efficacy and tolerability of formoterol turbuhaler(r) compared with placebo, in children (6-11 yr) with asthma poorly controlled with inhaled corticosteroids [abstract]. American Journal of Respiratory and Critical Care Medicine. 2002; Vol. 165(issue 8 Suppl):A746.*Zimmerman, B.; D'Urzo, A.; Berube, D. Efficacy and tolerability of formoterol Turbuhaler in 6-11 year old children with asthma, not adequately controlled with inhaled corticosteroids. European Respiratory Society Annual Congress; 2002. p. P2734

References to studies excluded from this review

- Aalbers 2004 {published data only} . 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. [PubMed: 15006018] Aalbers R, Backer V, Kava TT, Welte T, Omenaas ER, Bergqvist PB, et al. Adjustable dosing with budesonide/formoterol reduces the rate of asthma exacerbations compared with fixed dosing salmeterol/fluticasone. European Respiratory Society. 2003:2–20.Aalbers, R.; Backer, V.; Kava, TT.; Welte, T.; Omenaas, ER.; Bergqvist, PB., et al. Improvements in FEV1 are greater with budesonide/formoterol than with salmeterol/fluticasone. European Respiratory Society Annual Congress; 2003. p. 2-19.*Aalbers R, Backer V, Kava TT, Welte T, Omenaas ER, Bergqvist PBF, et al. Is well controlled asthma weeks a useful measure? Fewer exacerbations in patients treated with budesonide/formoterol than salmeterol/fluticasone. European Respiratory Society. 2003:2–18.
- Adinoff 1998 {published data only} . Adinoff AD, Schwartz HJ, Rickard KA, Yancey SW, Swearingen BE. Salmeterol compared with current therapies in chronic asthma. Journal of Family Practice. 1998; 47(4):278–84. [PubMed: 9789513]
- Ankerst 2003 {published data only} . Ankerst J, Persson G, Weibull E. Cardiovascular effects of a high dose of the budesonide/formoterol single inhaler in asthmatic patients. European Respiratory Journal. 2001; Vol. 18(issue Suppl 33):53s.Ankerst J, Persson G, Weibull E. Tolerability of a high dose of budesonide/formoterol in a single inhaler in patients with asthma. Pulmonary Pharmacology & Therapeutics. 2003; 16:147–51. [PubMed: 12749830]
- Anonymous 2003 {published data only} . Anonymous. Flexible dosing of combination inhaler cuts asthma exacerbations. Pharmaceutical Journal. 2003; 271(7271):535.
- Arvidsson 1991 {published data only} . Arvidsson P, Larsson S, Lofdahl CG, Melander B, Svedmyr N, Wahlander L. Inhaled formoterol during one year in asthma: a comparison with salbutamol. European Respiratory Journal. 1991; 4(10):1168–73. [PubMed: 1687129]
- Aziz 1998 {published data only} . Aziz I, Hall IP, McFarlane LC, Lipworth BJ. Beta2adrenoceptor regulation and bronchodilator sensitivity after regular treatment with formoterol in subjects with stable asthma. Journal of Allergy & Clinical Immunology. 1998; 101(3):337–41. [PubMed: 9525449]
- Aziz 1999a {published data only} . Aziz I, Lipworth BJ. A bolus of inhaled budesonide rapidly reverses airway subsensitivity and beta2-adrenoceptor down-regulation after regular inhaled formoterol. Chest. 1999; 115(3):623–8. [PubMed: 10084466]

- Aziz 1999b {published data only} . Aziz I, Lipworth BJ. In vivo effect of albuterol on methacholine-contracted bronchi in conjunction with salmeterol and formoterol. Journal of Allergy & Clinical Immunology. 1999; 103(5 pt 1):816–22. [PubMed: 10329815]
- Aziz 2000 {published data only} . Aziz, I.; Wilson, AM.; Lipworth, BJ. Effects of formoterol (FM) and budesonide (BUD) alone or in combination (FM+BUD) on inflammatory markers in asthmatic patients. European Respiratory Society; Madrid, Spain: Oct 9-13. 1999 1999 p. 2854Aziz I, Wilson AM, Lipworth BJ. Effects of once-daily formoterol and budesonide given alone or in combination on surrogate inflammatory markers in asthmatic adults. Chest. 2000; 118(4):1049–58. [PubMed: 11035676]
- Bacci 2002 {published data only} . Bacci E, Di Franco A, Bartoli ML, Carnevali S, Cianchetti S, Dente FL, et al. Comparison of anti-inflammatory and clinical effects of beclomethasone dipropionate and salmeterol in moderate asthma. European Respiratory Journal. 2002; 20(1):66– 72. [PubMed: 12166584]
- Baker 1998 {published data only} . Baker J, Yancey S, Kalberg C, Petrocella V, Emmett A, Bowers B, et al. Added salmeterol versus increased-dose fluticasone in patients symptomatic on low-dose fluticasone. American Journal of Respiratory and Critical Care Medicine. 1998; 157(Suppl 3):A406.
- Baki 1998 {published data only} . Baki A, Karaguzel G. Short-term effects of budesonide, nedocromil sodium and salmeterol on bronchial hyperresponsiveness in childhood asthma. Acta Paediatrica Japonica. 1998; 40(3):247–51. [PubMed: 9695299]
- Baraniuk 1999 {published data only} . Baraniuk J, Murray JJ, Nathan RA, Berger WE, Johnson M, Edwards LD, et al. Fluticasone alone or in combination with salmeterol vs triamcinolone in asthma. Chest. 1999; 116(3):625–32. [PubMed: 10492263] Cook D, Srebro SH, Rogenes PR, Rickard K, Edwards L, Johnson MC. A comparison of the safety and efficacy of fluticasone, triamcinolone, and fluticasone plus salmeterol in patients with mild to moderate asthma. American Journal of Respiratory & Critical Care Medicine. 1998; Vol. 157(issue Suppl 3):A416.*Johnson MC, Srebro SH, Rogenes PR, Rickard K, Edwards L. A comparison of physician-rated and patient-rated outcomes in a study with fluticasone, triamcinolone, and fluticasone plus salmeterol. American Journal of Respiratory & Critical Care Medicine. 1998; Vol. 157(issue Suppl 3):A414.
- Bateman 1998 {published data only} . Bateman ED, Britton M, Carrillo J, Almeida J, Wixon C. Salmeterol/fluticasone combination inhaler. A new, effective and well tolerated treatment for asthma. Clinical Drug Investigation. 1998; 16(3):193–201. [PubMed: 18370540]
- Bateman 2003a {published data only} . Bateman, ED.; Bantje, TA.; Gomes, M.; Toumbis, M.; Huber, R.; Eliraz, A., et al. Symbicort (budesonide and formoterol in a single inhaler) is a more effective treatment than fluticasone in asthma patients. Annual Thoracic Society 97th International Conference; 2001. Bateman ED, Bantje TA, Gomes MJ, Toumbis MG, Huber RM, Naya I, et al. Combination therapy with a single inhaler budesonide/formoterol compared with high dose fluticasone propionate alone in patients with moderate persistent asthma. American Journal of Respiratory Medicine. 2003; 2(3):275-81. [PubMed: 14720008] Bateman ED, Bantje TA, Joao Gomes M, Toumbis M, Huber R, Eliraz A. Early and sustained benefits of budesonide and formoterol in a single inhaler vs fluticasone in moderate asthma. European Respiratory Journal. 2001; Vol. 18(issue Suppl 33):157s.Bateman ED, Bantje TA, Joao Gomes M, Toumbis M, Huber R, Eliraz A. Early and sustained benefits of budesonide and formoterol in a single inhaler vs fluticasone in moderate asthma. European Respiratory Journal. 2001; Vol. 18(issue Suppl 33):157s.Bateman ED, Bantje TA, Joao Gomes M, Toumbis M, Huber R, Eliraz A, et al. Symbicort (budesonide/eformoterol) Turbohaler controls asthma more effectively than fluticasone Diskus. Thorax. 2001; Vol. 56(issue Suppl 3):iii, 63.Ericsson, K.; Bantje, TA.; Huber, H.; Borg, S. Symbicort® Turbuhaler® is more cost effective than fluticasone Diskus[™] in the treatment of asthma. Annual Thoracic Society 97th International Conference; San Francisco CA. May 18-23; 2001. Ericsson K, Bantje TA, Huber R, Borg S, Anderson F. Cost-effectiveness of budesonide and formoterol in a single inhaler compared to fluticasone in the treatment of asthma. European Respiratory Journal. 2001; Vol. 18(issue Suppl 33):157s.*Ericsson K, Bantje TA, Huber R, Borg S, Andersson F. Symbicort Turbohaler is more effective than fluticasone Diskus in the treatment of asthma. Thorax. 2001; Vol. 56(issue Suppl 3):iii63.

- Bateman 2003b {published data only} . Bateman, ED.; Akveld, M.; Ho, M. Greater responder rate to fluticasone propionate/salmeterol combination over montelukast plus fluticasone in asthma. American Thoracic Society 99th International Conference; 2003. B036 Poster H90
- Behling 1999 {published data only} . Behling, B.; Matthys, H. Comparison of efficacy and safety of formoterol with terbutaline in children with mild to moderate asthma. European Respiratory Society; Madrid, Spain: Oct 9-13. 1999 1999 p. 369
- Bensch 2002 {published data only} . Bensch G, Berger WE, Blokhnn M, Socolovshy AL, Thomson MH, Till MD, et al. One year efficacy and safety of inhaled formoterol dry powder in children with persistent asthma. Annals of Allergy, Asthma, and Immunology. 2002; 89:180–90.
- Berger 2001 {published data only} . Berger, W.; Bensch, G.; Blokhin, BM.; Socolovsky, AL.; Thompson, MH.; Till, D. Addition of formoterol (Foradil®) improves lung function and symptoms in children with persistent asthma not controlled by inhaled corticosteroids. Annual Thoracic Society 97th International Conference; San Francisco CA. May 18-23; 2001.
- Berggren 2001 {published data only} . Berggren F, Ekstrom T. A cost-effectiveness study comparing the as-needed use of formoterol (Oxis) and terbutaline (Bricanyl) in patients with moderate to severe asthma. Respiratory Medicine. 2001; 95(9):753–8. [PubMed: 11575897]
- Bergmann 2004 {published data only} . Bergmann KC, Lindemann L, Braun R, Steinkamp G. Salmeterol/fluticasone propionate (50/250 mug) combination is superior to double dose fluticasone (500 mug) for the treatment of symptomatic moderate asthma: a prospective, doubleblind trial. Swiss Medical Weekly. 2004; 134(3-4):50–8. [PubMed: 14745658]
- Bernstein 2002 {published data only} . Bernstein IL. Beta2-agonists: Deja vu all over again: the second-generation controversy. Chest. 2002; Vol. 122(issue 3):763–5. [PubMed: 12226008]
- Bessmertny 2002 {published data only} . Bessmertny O, DiGregorio RV, Cohen H, Becker E, Looney D, Golden J, et al. A randomized clinical trial of nebulized magnesium sulfate in addition to albuterol in the treatment of acute mild-to-moderate asthma exacerbations in adults. Annals of Emergency Medicine. 2002; 39(6):585–91. [PubMed: 12023699]
- Bijl-Hofland 2001 {published data only} . Bijl-Hofland ID, Cloosterman SG, Folgering HT, van den Elshout FJ, van Weel C, van Schayck CP. Inhaled corticosteroids, combined with longacting beta(2)-agonists, improve the perception of bronchoconstriction in asthma. American Journal of Respiratory & Critical Care Medicine. 2001; 164(5):764–9. [PubMed: 11549530]
- Bjermer 2000 {published data only} . Bjermer L, Bisgaard H, Bousquet J, Fabbri LM, Greening A, Haahtela T, et al. Montelukast or salmeterol combined with an inhaled steroid in adult asthma: design and rationale of a randomized, double-blind comparative study (the IMPACT Investigation of Montelukast as a Partner Agent for Complementary Therapy-trial). Respiratory Medicine. 2000; 94(6):612–21. [PubMed: 10921768]
- Bjermer 2002 {published data only} . Bjermer, L.; Greening, A.; Haahtela, T.; Bousquet, J.; Holgate, ST.; Picado, C., et al. Chest. San Diego, CA: 2002. Addition of montelukast or salmeterol to fluticasone in patients with uncontrolled asthma: results of the IMPACT trial; p. 4342002
- Bjermer 2003 {published data only} . Bjermer L, Bisgaard H, Bousquet J, Fabbri LM, Greening AP, Haahtela T, et al. Montelukast and fluticasone compared with salmeterol and fluticasone in protecting against asthma exacerbation in adults: one year, double blind, randomised, comparative trial. BMJ. 2003; 327(7420):891. [PubMed: 14563743]
- Bloom 2003 {published data only} . Bloom, J.; Calhoun, W.; Koenig, S.; Yancey, S.; Reilly, D.; Edwards, L., et al. Fluticasone propionate/salmeterol 100/50mcg is inhaled steroid sparing in patients who require fluticasone propionate 250mcg for asthma stability. American Thoracic Society 99th International Conference; 2003. D034 Poster C33
- Boonsawat 2003 {published data only} . Boonsawat W, Charoenratanakul S, Pothirat C, Sawanyawisuth K, Seearamroongruang T, Bengtsson T, et al. Formoterol (OXIS) Turbuhaler as a rescue therapy compared with salbutamol pMDI plus spacer in patients with acute severe asthma. Respiratory Medicine. 2003; 97(9):1067–74. [PubMed: 14509562]
- Booth 1993 {published data only} . Booth H, Fishwick K, Harkawat R, Devereux G, Hendrick DJ, Walters EH. Changes in methacholine induced bronchoconstriction with the long acting beta 2 agonist salmeterol in mild to moderate asthmatic patients. Thorax. 1993; 48(11):1121–4. [PubMed: 8296255]

- Boskovska 2001 {published data only} . Boskovska MI, Dokic D, Busletic-Bozinovska K, Arbutina S, Goseva Z. Concomitant use of low-dose inhaled corticosteroids and a long-acting bronchodilator vis a vis doubling the dose of inhaled corticosteroid in asthma patients. European Respiratory Journal. 2001; (issue Suppl 33):98s.
- Bouchard 2000 {published data only} . Bouchard J, Arkinstall W, Tesarowski D. Efficacy of salmeterol and fluticasone propionate (FP) combination therapy versus FP alone in mild/ moderate asthma. American Journal of Respiratory and Critical Care Medicine. 2000; Vol. 161(issue Suppl 3):A197.
- Boulet 2003 {unpublished data only} . Boulet, LP.; Chapman, K.; Roberts, J.; Watson, EG. Efficacy of salmeterol/fluticasone propionate HFA MDI versus high dose fluticasone propionate HFA MDI in adolescent and adult asthma. European Respiratory Society Meeting; 2003.
- Bouros 1999 {published data only} . Bouros D, Bachlitzanakis N, Kottakis J, Pfister P,
 Polychronopoulos V, Papadakis E, et al. Foromoterol and beclomethasone versus higher dose
 beclomethasone as maintenance therapy in adult asthma. European Respiratory Journal. 1999; 14:627–32. [PubMed: 10543286]
- Brambilla 1994 {published data only} . Brambilla C, Chastang C, Georges D, Bertin L. Salmeterol compared with slow-release terbutaline in nocturnal asthma. A multicenter, randomized, doubleblind, double-dummy, sequential clinical trial. French Multicenter Study Group. Allergy. 1994; 49(6):421–6. [PubMed: 7915501]
- Brambilla 2003 {published data only} . Brambilla C, Le Gros V, Bourdeix I. Formoterol 12 mcg bid administered via single dry powder inhaler in adults with asthma suboptimally controlled with salmeterol or on demand salbutamol. Clinical Therapeutics. 2003; 25(7):2022–36. [PubMed: 12946548]
- Braniuk 1999 {published data only} . Braniuk J, Murray JJ, Nathan RA, Berger WE, Johnson M, Edwards LD, et al. Fluticasone alone or in combination with salmeterol vs triamcinolone in asthma. Chest. 1999; 116(3):625–32. [PubMed: 10492263]
- Brenner 1988 {published data only} . Brenner M, Berkowitz R, Marshall N, Strunk RC. Need for theophylline in severe steroid-requiring asthmatics. Clinical Allergy. 1988; 18(2):143–50. [PubMed: 3365858]
- Britton 1992 {published data only} . Britton MG, Earnshaw JS, Palmer JBD. A twelve month comparison of salmeterol with salbutamol in asthmatic patients. European Respiratory Journal. 1992; 5(9):1062–7. [PubMed: 1426215]
- Britton 1998 {published data only} . Britton MG, Carrillo T, Almeida J, Wixon C. Combined Serevent[™] and fluticasone propionate (50/100µg strength) bd via one Diskus[™] (Accuhaler[™]) inhaler compared with salmeterol 50µg and fluticasone propionate 100µg bd via two separate Diskus inhalers. American Journal of Respiratory & Critical Care Medicine. 1998; Vol. 157(issue Suppl 3):A415.
- Brogden 1991 {published data only} . Brogden RN, Faulds D. Salmeterol xinafoate. A review of its pharmacological properties and therapeutic potential in reversible obstructive airways disease. Drugs. 1991; 42(5):895–912. [PubMed: 1723379]
- Buchvald 2003 {published data only} . Buchvald F, Bisgaard H. Comparisons of the complementary effect on exhaled nitric oside of salmeterol vs montelukast in asthmatic children taking regular budesonide. Annals of Allergy, Asthma & Immunology. 2003; 91(3):309–13.
- Busse 1999 {published data only} . Busse W, Nelson H, Wolfe J, Kalberg C, Yancey SW, Rickard KA. Comparison of inhaled salmeterol and oral zafirlukast in patients with asthma. Journal of Allergy & Clinical Immunology. 1999; 103(6):1075–80. [PubMed: 10359889]
- Busse 2003a {published data only} . Busse W, Koenig SM, Oppenheimer J, Sahn SA, Yancey SW, Reilly D, et al. Steroid-sparing effects of fluticasone propionate 100mcg and salmeterol 50mcg administered twice daily in a single product in patients previously controlled with fluticasone propionate 250mcg administered twice daily. Journal of Allergy & Clinical Immunology. 2003; 111(2):57–65. [PubMed: 12532097] *Sahn, S.; Yancey, S.; Reilly, D.; Edwards, L.; Rickard, K.; Dorinsky, P. Chest. San Diego, CA: 2002. 2002. The fluticasone propionate/salmeterol (FSC) combination product 100/50 mcg BID is steroid sparing in patients who require FP250 mcg BID for asthma stability.

- Busse 2003b {published data only} .*Busse W, Koenig SM, Oppenheimer J, Sahn SA, Yancey SW, Reilly D, et al. Steroid-sparing effects of fluticasone propionate 100mcg and salmeterol 50mcg administered twice daily in a single product in patients previously controlled with fluticasone propionate 250mcg administered twice daily. Journal of Allergy & Clinical Immunology. 2003; 111(2):57–65. [PubMed: 12532097]
- Byrnes 2000 {published data only} . Byrnes C, Shrewsbury S, Barnes PJ, Bush A. Salmeterol in paediatric asthma. Thorax. 2000; 55(9):780–4. [PubMed: 10950898]
- Calhoun 2001 {published data only} . Calhoun WJ, Nelson HS, Nathan RA, Pepsin PJ, Kalberg C, Emmett A, et al. Comparison of fluticasone propionate-salmeterol combination therapy and montelukast in patients who are symptomatic on short-acting 2-agonists alone. American Journal of Respiratory & Critical Care Medicine. 2001; 164(5):759–63. [PubMed: 11549529]
- Calverley 2002 {published data only} . Calverley PMA, Pauwels RA, Vestbo J, Jones PW, Pride NB, Gulsvik A, et al. Salmeterol/fluticasone propionate combination for one year provides greater clinical benefit than its individual components in COPD. American Journal of Respiratory & Critical Care Medicine. 2002; Vol. 165(issue Suppl 8):A226.
- Castle 1993 {published data only} . Castle W, Fuller R, Hall J, Palmer J. Serevent nationwide surveillance study: comparison of salmeterol with salbutamol in asthmatic patients who require regular bronchodilator treatment. BMJ. 1993; 306(6884):1034–7. [PubMed: 8098238]
- Cazzola 2000 {published data only} . Cazzola M, Di Lorenzo G, Di Perna F, Calderaro F, Testi R, Centanni S. Additive effects of salmeterol and fluticasone or theophylline in COPD. Chest. 2000; 118(6):1576–81. [PubMed: 11115442]
- Chan 2001 {published data only} . Chan JS, Cowie RL, Lazarenko GC, Little C, Scott S, Ford GT. Comparison of intramuscular betamethasone and oral prednisone in the prevention of relapse of acute asthma. Canadian Respiratory Journal. 2001; 8(3):147–52. [PubMed: 11420590]
- Chapman 1999 {published data only} . Chapman KR, Ringdal N, Backer V, Palmqvist M, Saarelainen S, Briggs M. Salmeterol and fluticasone propionate (50/250 mug) administered via combination Diskus inhaler: as effective as when given via separate Diskus inhalers. Canadian Respiratory Journal. 1999; 6(1):45–51. [PubMed: 10202220]
- Cheer 2003 {published data only} . Cheer SM, Warner GT, Easthope SE. Formoterol delivered by Turbuhaler: in pediatric asthma. Paediatric Drugs. 2003; 5(1):63–8. [PubMed: 12513109]
- Cloosterman 2001 {published data only} . Cloosterman SG, Bijl-Hofland ID, van Herwaarden CL, Akkermans RP, van Den Elshout FJ, Folgering HT, et al. A placebo-controlled clinical trial of regular monotherapy with short-acting and long-acting beta(2)-agonists in allergic asthmatic patients. Chest. 2001; 119(5):1306–15. [PubMed: 11348933]
- Condemi 1999 {published data only} . Condemi JJ, Goldstein S, Kalberg C, Yancey S, Emmett A, Rickard K. The addition of salmeterol to fluticasone propionate versus increasing the dose of fluticasone propionate in patients with persistent asthma. Annals of Allergy, Asthma, and Immunology. 1999; 82:383–9.
- Condemi 2001 {published data only} . Condemi JJ. Comparison of the efficacy of formoterol and salmeterol in patients with reversible obstructive airway disease: a multicenter, randomized, open-label trial. Clinical Therapeutics. 2001; 23(9):1529–41. [PubMed: 11589265]
- Cook 2001 {published data only} . Cook CK, Prillaman BA, House KW, Rickard KA, Shah TP. Concurrent use of salmeterol/fluticasone propionate Diskus® powder combination product and fluticasone propionate aqueous nasal spray does not adversely affect HPA-axis function. Annals of Allergy, Asthma, and Immunology. 2001; 86:98.
- Corren 2007 {published and unpublished data} . AstraZeneca (SD 039 0617). A twelve week, randomized, double-blind, double-dummy, placebo-controlled trial of SYMBICORT® pMDI (80/4.5 mcg) versus its mono-products (budesonide and formoterol) in children and adults with asthma. 2007. www.astrazenecaclinicaltrials.comaccessed 15 May 2008Corren J, Korenblat PE, Miller CJ, O'Brien CD, Mezzanotte WS. Twelve-week, randomized, placebo-controlled, multicenter study of the efficacy and tolerability of budesonide and formoterol in one metered-dose inhaler compared with budesonide alone and formoterol alone in adolescents and adults with asthma. Clinical Therapeutics. 2007; 29(5):823–43. [PubMed: 17697902]

- Crompton 1999 {published data only} . Crompton GK, Ayres JG, Basran G, Schiraldi G, Brusasco V, Eivindson A, et al. Comparison of oral bambuterol and inhaled salmeterol. American Journal of Respiratory & Critical Care Medicine. 1999; 159(3):824–8. [PubMed: 10051257]
- Currie 2002 {published data only} . Currie, GP.; Stenback, S.; Lipworth, BJ. Dissociation in effects of fluticasone but not fluticasone/salmeterol on lung function and airway hyperresponsiveness in mild persistent asthma. European Respiratory Society Annual Congress; 2002. p. P2391
- Currie 2003a {published data only} . Currie GP, Lee DK, Haggart K, Bates CE, Lipworth BJ. Effects of montelukast on surrogate inflammatory markers in corticosteroid-treated patients with asthma. American Journal of Respiratory and Critical Care Medicine. 2003; 167(9):1232–8. [PubMed: 12456382]
- Currie 2003b {published data only} . Currie GP, Bates CE, Lee DK, Jackson CM, Lipworth BJ. Effects of fluticasone plus salmeterol versus twice the dose of fluticasone in asthmatic patients. European Journal of Clinical Pharmacology. 2003; 59(1):11–15. [PubMed: 12743669]
- Currie 2003c {published data only} . Currie GP, Stenback S, Lipworth BJ. Effects of fluticasone vs. fluticasone/salmeterol on airway calibre and airway hyperresponsiveness in mild persistent asthma. British Journal of Clinical Pharmacology. 2003; 56(1):11–7. [PubMed: 12848770]
- D'Alonzo 1994 {published data only} . D'Alonzo GE, Nathan RA, Henochowicz, Morris RJ, Ratner P, Rennard SI. Salmetrol xinafoate as maintenance therapy compared with albuterol in patients with asthma. JAMA. 1994; 271:1412–16. [PubMed: 7909853]
- Dahl 1989 {published data only} . Dahl R, Pedersen B, Hagglof B. Nocturnal asthma: effect of treatment with oral sustained-release terbutaline, inhaled budesonide, and the two in combination. Journal of Allergy & Clinical Immunology. 1989; 83(4):811–5. [PubMed: 2651509]
- Dahl 1991 {published data only} . Dahl R, Earnshaw JS, Palmer JBD. Salmeterol: a four week study of a long-acting beta-adrenoceptor agonist for the treatment of reversible airways disease. European Respiratory Journal. 1991; 4(10):1178–84. [PubMed: 1687131]
- Dal Negro 2001a {published data only} . Dal Negro, R.; Micheletto, C.; Tognella, S.; Trevisan, F.; Pomari, C. Short-term bronchodilation following salmeterol 50mcg and combined salmeterol + fluticasone p(50/250mcg) via Diskus: a randomized, double blind cross-over study in reversible airway obstruction. Annual Thoracic Society 97th International Conference; San Francisco CA. May 18-23; 2001.
- Dal Negro 2001b {published data only} . Dal Negro RW, Micheletto C, Pomari C, Trevisan F, Tognella S. The combination salmeterol (S) + fluticasone propionate (F) in mild-to-moderate asthma. European Respiratory Journal. 2001; Vol. 18(issue Suppl 33):426s.
- Dal Negro 2002a {published data only} . Dal Negro R, Micheletto C, Trevison F, Tognells S, Pomari C, Spencer S. Salmeterol & fluticasone 50µg/250µg bid vs salmeterol 50µg bid and vs placebo in the long-term treatment of COPD. American Journal of Respiratory & Critical Care Medicine. 2002; (issue Suppl 8):A228.
- Dal Negro 2002b {published data only} . Dal Negro, RW.; Micheletto, C.; Tognella, S.; Trevisan, F.; Pomari, C. Is the sequence of salmeterol (SM) and fluticasone p. (FP) dry powder inhalation crucial in persistent mild asthma?. European Respiratory Society Annual Congress; 2002. p. P396
- Davis 2001 {published data only} . Davis, ES.; Bowers, B.; Pepsin, P.; Kalberg, C.; Dorinsky, P. The impact of fluticasone propionate/salmeterol combination product compared to oral montelukast on asthma related quality of life. Annual Thoracic Society 97th International Conference; San Francisco CA. May 18-23; 2001.
- Del Rio-Navarro 2001a {published data only} . Del-Rio-Navarro BE, Sienra-Monge JJL, Alvarez-Amador M, Reyes-Ruiz N, Arevalo-Salas A, Berber A. Serum potassium levels, CPK-MB and ECG in children suffering asthma treated with beclomethasone or beclomethasone-salmeterol. Allergologia et Immunopathologia. 2001; 29(1):16–21. [PubMed: 11449530]
- Del-Rio-Navarro 2001b {published data only} . Del Rio BE, Corona L, Fregosa R, Berber A, Magana J, Sienra-Monge JL. Effect of salmeterol and salmeterol plus beclomethasone on the saliva flow and saliva IgA levels on patients with chronic moderate persistent asthma (CMPA). Journal of Allergy and Clinical Immunology. 2001; Vol. 107(issue 2):s11.Del-Rio-Navarro BE,

Coron-Hernandez L, Fragoso-Rios R, Berber A, Torres-Alcantara S, Cuairan-Ruidiaz V, et al. Effect of salmeterol and salmeterol plus beclomethasone on saliva flow and IgA in patients with moderate-persistent chronic asthma. Annals of Allergy, Asthma and Immunology. 2001; 87(5): 420–3.

- Dempsey 2000a {published data only} . Dempsey OJ, Wilson AM, Sims EJ, Lipworth BJ. Additive anti-inflammatory effects of montelukast but not salmeterol in asthmatics suboptimally controlled on inhaled steroids. American Journal of Respiratory and Critical Care Medicine. 2000; Vol. 161(issue Suppl 3):A198.
- Dempsey 2000b {published data only} . Dempsey OJ, Wilson AM, Sims EJ, Mistry C, Lipworth BJ. Additive bronchoprotective and bronchodilator effects with single doses of salmeterol and montelukast in asthmatic patients receiving inhaled corticosteroids. Chest. 2000; 117(4):950–3. [PubMed: 10767223]
- Dente 2001a {published data only} . Dente FL, Scuotri L, Bacci E, Di Franco A, Giannini D, Taccola M, et al. Effects of combined treatment -fluticasone plus salmeterol - on allergeninduced asthmatic responses. American Journal of Respiratory and Critical Care Medicine. 2001; Vol. 463(issue Suppl 5):A419.
- Dente 2001b {published data only} . Dente FL, Scuotri L, Bacci E, DeSanctis M, Di Franco A, Giannini D, et al. Combined treatment with fluticasone plus salmeterol protects against allergeninduced asthmatic responses better than each drug alone. European Respiratory Journal. 2001; Vol. 18(issue Suppl 33):349s.
- Dicpinigaitis 2002 {published data only} . Dicpinigaitis PV, Dobkin JB, Reichel J. Antitussive effect of the leukotriene receptor antagonist zafirlukast in subjects with cough-variant asthma. Journal of Asthma. 2002; 39(4):291–7. [PubMed: 12095178]
- Didier 1997 {published data only} . Didier A, Campos Oriola R. A two-month comparison of salmeterol/beclomethasone and slow-release terbutaline/budesonide in moderate asthma management. Clinical Drug Investigation. 1997; 14(1):1–11.
- Djordjevic 1999 {published data only} . Djordjevic, D.; Zickovic, D.; Stankovic, I.; Pejcic, T.; Ducic, J.; Rancic, M., et al. Comparative study of three months treatment in combination of salmeterol and beclomethasone dipropionate (BDP) with doubling the dose of BDP in mild asthma. European Respiratory Society; Madrid, Spain: Oct 9-13. 1999 p. p8491999
- Dorinsky 2001a {published data only} . Dorinsky, PM.; Kalberg, C.; Pepsin, P.; Emmett, A.; Rickard, K. Greater onset of improvement in clinical efficacy measures with first line use of the fluticasone/salmeterol combination product compared to montelukast. Annual Thoracic Society 97th International Conference; San Francisco CA. May 18-23; 2001.
- Dorinsky 2001b {published data only} . Dorinsky P, Kalberg C, Pepsin P, Emmett A, Bowers B, Rickard K. The fluticasone/salmeterol combination product is superior to montelukast as first-line asthma control. European Respiratory Journal. 2001; Vol. 18(issue Suppl 33):263s.
- Eliraz 2001 {published data only} . Eliraz A, Ramirez-Rivera A, Ferranti P, Holzer R, Garcia JM, Turcotte C, et al. Similar efficacy following four weeks treatment of asthmatics with formoterol 12 mcg BD delivered by two different dry powder inhalers; differences in inhaler handling. International Journal of Clinical Practice. 2001; 55(3):164–70. [PubMed: 11351769]
- Eliraz 2002a {published data only} . Eliraz A, Fritscher CC, Perez CMR, Boonsawat W, Nang AN, Bardin P, et al. Symbicort® (budesonide/formoterol) achieves more rapid control of asthma that fluticasone in patients with mild asthma. American Journal of Respiratory & Critical Care Medicine. 2002; Vol. 165(issue Suppl 8):A567.
- Eliraz 2002b {published data only} . Eliraz A, Fritscher CC, Perez CMR, Boonsawat W, Nang AN, Bardin P, et al. Budesonide and formoterol in a single inhaler quickly gains asthma control compared with fluticasone propionate in mild asthma. European Respiratory Journal. 2001; Vol. 18(issue Suppl 33):48s.
- Ericsson 2001a {published data only} . Ericsson, K.; Bantje, TA.; Huber, H.; Borg, S. Symbicort® Turbuhaler® is more cost effective than fluticasone Diskus[™] in the treatment of asthma. Annual Thoracic Society 97th International Conference; San Francisco CA. May 18-23; 2001.
- Ericsson2001b {published data only} . Ericsson K, Bantje TA, Huber R, Borg S, Anderson F. Cost-effectiveness of budesonide and formoterol in a single inhaler compared to fluticasone in the treatment of asthma. European Respiratory Journal. 2001; Vol. 18(issue Suppl 33):157s.

- Everden 2002 {published data only} . Everden P, Lloyd A, Hutchinson J, Plumb J. Costeffectiveness of eformoterol Turbohaler(R) versus salmeterol Accuhaler(R) in children with symptomatic asthma. Respiratory Medicine. 2002; 96(4):250–8. [PubMed: 12000004]
- Faurschou 1994 {published data only} . Faurschou P, Engel AM, Haanaes OC. Salmeterol in two different doses in the treatment of nocturnal bronchial asthma poorly controlled by other therapies. Allergy. 1994; 49(40):827–32. [PubMed: 7709991]
- Faurschou 1996 {published data only} . Faurschou P, Steffensen I, Jacques L. Effect of addition of inhaled salmeterol to the treatment of moderate-to-severe asthmatics uncontrolled on high-dose inhaled steroids. European Respiratory Journal. 1996; 9(9):1885–90. [PubMed: 8880107]
- Fish 2000 {published data only} . Fish J, Boone R, Emmett A, Yancey S, Knobil K, Rickard K. Salmeterol added to inhaled corticosteroids (ICS) provides greater asthma control compared to montelukast. American Journal of Respiratory & Critical Care Medicine. 2000; Vol. 161(issue Suppl 3):A203.
- Fish 2001 {published data only} . Fish JE, Israel E, Murray JJ, Emmett A, Boone R, Yancey SW, et al. Salmeterol powder provides significantly better benefit than montelukast in asthmatic patients receiving concomitant inhaled corticosteroid therapy. Chest. 2001; 120(2):423–30. [PubMed: 11502639]
- Fitzpatrick 1990 {published data only} . Fitzpatrick MF, Mackay T, Driver H, Douglas NJ. Salmeterol in nocturnal asthma: a double-blind, placebo controlled trial of long-acting inhaled beta2 agonist. BMJ. 1990; 301:1365–8. [PubMed: 1980220]
- Fowler 2002 {published data only} . Fowler SJ, Currie PC, Lipworth BJ. Step down therapy with low dose fluticasone-salmeterol combination or medium dose hydrofluoroalkane 134abeclomethasone alone. Journal of Allergy & Clinical Immunology. 2002; 109(6):929–35. [PubMed: 12063520]
- Fuglsang 1995 {published data only} . Fuglsang G, Agertoft L, Vikre-Jorgensen J, Pedersen S. Influence of budesonide on the response to inhaled terbutaline in children with mild asthma. Pediatric Allergy and Immunology. 1995; 6(2):103–8. [PubMed: 7581719]
- Gabrijelcic 2004 {published data only} . Gabrijelcic J, Casas A, Rabinovich RA, Roca J, Barbera JA, Chung KF, et al. Formoterol protects against platelet-activating factor-induced effects in asthma. European Respiratory Journal. 2004; 23(1):71–5. [PubMed: 14738234]
- Giannini 1996 {published data only} . Giannini D, Carletti A, Dente FL, Testi R, Bacci D,
 Bancalari L, et al. Effect of inhaled beclomethasone dipropionate (BDP) on tolerance to
 salmeterol (S) in allergen induced bronchoconstriction. European Respiratory Journal. 1996; Vol. 9(issue Suppl 23):272s.
- Giannini 1998a {published data only} . Giannini D, Di Franco A, Bacci E, Conti I, Dente FL, Kotopulos C, et al. Long-term treatment with salmeterol and inhaled corticosteroids does not induce tolerance to the protective effect of salmeterol on allergen challenge. American Journal of Respiratory & Critical Care Medicine. 1998; Vol. 157(issue Suppl 3):A414.
- Giannini 1998b {published data only} . Giannini D, di Franco A, Bacci E, Conti I, Dente FL, Kotopulos C, et al. One-week regular treatment with salmeterol induces tolerance to the protective effect of salmeterol on allergen challenge only in subjects not regularly treated with salmeterol and inhaled corticosteroid. European Respiratory Journal. 1998; 12(Suppl 28):156s.
- Giannini 1999 {published data only} . Giannini D, Bacci E, Dente FL, Di Franco A, Vagaggini B, Testi R, et al. Inhaled beclomethasone dipropionate reverts tolerance to the protective effect of salmeterol on allergen challenge. Chest. 1999; 115(3):629–34. [PubMed: 10084467]
- Giannini 2000 {published data only} . Giannini D, Di Franco A, Bacci E, Dente FL, Taccola M, Vagaggini B, et al. The protective effect of salbutamol inhaled using different devices on methacholine bronchoconstriction. Chest. 2000; 117(5):1319–23. [PubMed: 10807817]
- Giannini 2001 {published data only} . Giannini D, Tonelli M, Di Franco A, Bacci E, Conti I, Dente FL, et al. Tolerance to the protective effect of salmeterol on allergen challenge in mild untreated asthmatics and in moderate asthmatics on inhaled corticosteroid treatment. European Respiratory Journal. 2001; Vol. 18(issue Suppl 33):103s.
- Giannini 2002a {published data only} . Giannini D, Tonelli M, Di Franco A, Bacci E, Conti I, Dente FL, et al. Tolerance to the protective effect of salmeterol + fluticasone combination

(50/250 µg) on allergen challenge in mild untreated asthmatics. American Journal of Respiratory and Critical Care Medicine. 2002; Vol. 165(issue Suppl 8):A566.

- Giannini 2002b {published data only} . Giannini D, di Franco A, Bacci E, Conti I, Dente FL, Kotopulos C, et al. One-week regular treatment with salmeterol induces tolerance to the protective effect of salmeterol on allergen challenge only in subjects not regularly treated with salmeterol and inhaled corticosteroid. European Respiratory Journal. 1998; 12(Suppl 28):156s.
- Gizycki 2000 {published data only} . Gizycki MJ, Venge P, Dahl R, Jeffery PK. Comparison of the effects of six weeks treatment with fluticasone or salmeterol on the late phase response (LPR) in mild asthma - a bronchial biopsy study. American Journal of Respiratory and Critical Care Medicine. 2000; Vol. 161(issue Suppl 3):A203.
- Gold 2001 {published data only} . Gold M, Jõgi R, Mulder PGH, Akveld MLM. Salmeterol/ fluticasone propionate combination 50/100µg bid is more effective than fluticasone propionate 100µg bid plus montelukast 10 mg once daily in reducing exacerbations. European Respiratory Journal. 2001; Vol. 18(issue Suppl 33):262s.
- Green 2002 {published data only} . Green RH, Brightling CE, McKenna S, Hargadon B, Parker D, Wardlaw AJ, et al. A placebo controlled comparison of formoterol, montelukast or higher dose of inhaled corticosteroids in subjects with symptomatic asthma despite treatment with low dose inhaled corticosteroids. Thorax. 2002; Vol. 57(issue Suppl III):iii–11.
- Greening 1994 {published data only} . Greening AP, Ind PW, Northfield M, Shaw G. Added salmeterol versus higher-dose corticosteroid in asthma patients with symptoms on existing inhaled corticosteroid. Lancet. 1994; 344:219–24. [PubMed: 7913155]
- Grosclaude 2003 {published data only} . Grosclaude M, Cerruti JL, Delannay B, Herent M, Spilthooren F, Desfougeres JL. The fixed fluticasone/salmeterol gives better control of asthma than the association of beclomethasone dipropionate-montelukast. Allergie et Immunologie. 2003; 35(9):356–62.
- Grzelewska-Rzymowska 2003 {published data only} . Grzelewska-Rzymowska I, Malolepszy J, de Molina M, Sladek K, Zarkovic J, Siergiejko Z. Equivalent asthma control and systemic safety of inhaled budesonide delivered via HFA-134a or CFC propellant in a broad range of doses. Respiratory Medicine. 2003; 97(Suppl D):S10–S19. [PubMed: 14753247]
- Gustafsson 1994 {published data only} . Gustafsson PM, Von BA, Jenkins MM. Salmeterol 50 mug twice daily in the treatment of mild-to-moderate asthma in childhood - a comparison of two inhalation devices. European Journal of Clinical Research. 1994; 5:63–73.
- Hasani 2003 {published data only} . Hasani A, Toms N, O'Connor J, Dilworth JP, Agnew JE. Effect of salmeterol xinafoate on lung mucociliary clearance in patients with asthma. Respiratory Medicine. 2003; 97(6):667–71. [PubMed: 12814152]
- Haughney 2002 {published data only} . Haughney, J.; Price, D.; Rosen, JP.; Kennelly, J. Adjustable maintenance treatment with budesonide/formoterol combination rapidly improves and maintains quality of life in asthma patients. European Respiratory Society Annual Congress; 2002. p. P379
- Heuck 1999 {published data only} . Heuck, C.; Heickendorff, L.; Wolthers, OD.; Sygehus, S.
 Short term growth and collagen turnover in asthmatics treated inhaled formoterol and budesonide. European Respiratory Society; Madrid, Spain: Oct 9-13. 1999 p. 364
- Heuck 2000 {published data only} . Heuck C, Heickendorff L, Wolthers OD. A randomized controlled trial of short term growth and collagen turnover in asthmatics with inhaled formoterol and budesonide. Archives of Disease in Childhood. 2000; 83:334–9. [PubMed: 10999872]
- Hyland 1995 {published data only} . Hyland ME, Crocker GR. Validation of an asthma quality of life diary in a clinical trial. Thorax. 1995; 50(7):724–30. [PubMed: 7570405]
- Ind 2002a {published data only} . Ind, P.; Haughney, J.; Price, D.; Rosen, JP.; Kennelly, J. Managed adjustable dosing of budesonide/formoterol combination provides equivalent asthma control to fixed dosing at a lower overall dose. European Respiratory Society Annual Congress; 2002. p. P2450
- Ind 2002b {published data only} . Ind PW, Villasante C, Shiner RJ, Pietinalho A, Boszormenyi NG, Soliman S, et al. Safety of formoterol by Turbuhaler as reliever medication compared with terbutaline in moderate asthma. European Respiratory Journal. 2002; 20(4):859–66. [PubMed: 12412676]

- Ind 2003a {published data only} . Haughney, J.; Price, D.; Rosen, JP.; Kennelly, J. Adjustable maintenance treatment with budesonide/formoterol combination rapidly improves and maintains quality of life in asthma patients. European Respiratory Society Annual Congress; 2002. p. P379Ind, PW.; Price, D.; Haughney, J.; Rosen, JP. Adjustable dosing with budesonide/formoterol in a single inhaler (Symbicort (r)) provides similarly effective treatment of asthma compared with fixed dosing but at a lower overall dose. American Thoracic Society 99th International Conference; 2003. D034 Poster C38
- Isabelle 2001 {published data only} . Isabelle, P.; Bjamer, D.; Neuparth, N.; Desfougeres, JL. Efficacy and safety of salmeterol/fluticasone combination 50/100mug bd via two different powder devices in children. Annual Thoracic Society 97th International Conference; San Francisco CA. May 18-23; 2001.
- Jeffery 2002 {published data only} . Jeffery PK, Venge P, Gizycki MJ, Egerod I, Dahl R, Faurschou P. Effects of salmeterol on mucosal inflammation in asthma: a placebo-controlled study. European Respiratory Journal. 2002; 20(6):1378–85. [PubMed: 12503692]
- Jenkins 1995 {published data only} . Jenkins M. Clinical evaluation of CFC-free metered dose inhalers. Journal of Aerosol Medicine: Deposition, Clearance, and Effects in the Lung. 1995; 8(Suppl 1):s41–s47.
- Jenkins 2000 {published data only} . Becker, I.; Kielborn, A.; Price, MJ.; Volmer, T.; Lloyd, AC. Cost-effectiveness of salmeterol/fluticasone combination product and budesonide in asthma patients in Germany; Madrid, Spain. European Respiratory Society; Oct 9-13. 1999 p. 8541999Jenkins 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 threefold-higher dose of budesonide (800mcg bd). European Respiratory Journal. 2000; Vol. 16(issue Suppl 31):456s.Jenkins C, Woolcock AJ, Saarelainen P, Lundbaack B, James MH. Salmeterol/ fluticasone propionate combination therapy 50/250 mcgs twice daily is more effective than budesonide 800 twice daily in treating moderate to severe asthma. Respiratory Medicine. 2000; 94:715-23. [PubMed: 10926345] Lundback B, Jenkins C, Price MJ, Thwaites RM. Costeffectiveness of salmeterol/fluticasone propionate combination product 50/250 microgram twice daily and budesonide 800 microgram twice daily in the treatment of adults and adolescents with asthma. Respiratory Medicine. 2000; 94(7):724–32. [PubMed: 10926346] 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.*Parnaby A, Lloyd A, Browning D, McCarthy TP. A comparison of the cost-effectiveness of salmeterol/fluticasone combination inhaler and budesonide in the management of asthma. Thorax. 2000; Vol. 55(issue Suppl 3):A64.
- Jenkins 2002 {published data only} . Jenkins C. Combination therapy with fluticasone and salmeterol for symptomatic asthma produces similar benefits when given by Accuhaler in a single or two separate devices over 24 weeks. Respirology. 2002; Vol. 7(issue Suppl:A20):22.
- Johansson 2001 {published data only} . Johansson G, McIvor RA, D'Ambrosio FP, Gratziou C, James MH. Comparison of salmeterol/fluticasone propionate combination with budesonide in patients with mild-to-moderate asthma. Clinical Drug Investigation. 2001; 21(9):633–42.
- Jones 1994 {published data only} . Jones KP. Salmeterol xinafoate in the treatment of mild to moderate asthma in primary care. Thorax. 1994; 49:971–5. [PubMed: 7974313]
- Juniper 1995 {published data only} . Juniper EF, Johnston PR, Borkhoff CM, Guyatt GH, Boulet LP, Haukioja A. Quality of life in asthma clinical trials: comparison of salmeterol and salbutamol. American Journal of Respiratory & Critical Care Medicine. 1995; 151(1):66–70. [PubMed: 7812574]
- Juniper 1999 {published data only} . Juniper EF, Svenson K, O'Byrne PM, Barnes PJ, Bauer CA, Lofdahl CG, et al. Asthma quality of life during 1 year of treatment with budesonide with or without formoterol. European Respiratory Journal. 1999; 14:1038–43. [PubMed: 10596687]
- 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(r)) plus budesonide (Miflonide(r)) versus a fixed combination of salmeterol and fluticasone (Seretide(r)) in asthma self-management. European Respiratory Society Annual Congress; 2002.

- Kalberg 1998 {published data only} . Kalberg CJ, Nelson H, Yancey S, Petrocella V, Emmett AH, Rickard KA, et al. A comparison of added salmeterol versus increased-dose fluticasone in patients symptomatic on low-dose fluticasone [Abstract]. Journal of Allergy & Clinical Immunology. 1998; 101(Suppl):S6.Knobil K, Kalberg C, Emmett A, Rickard K. Adding salmeterol is more effective than increasing the dose of fluticasone for patients with asthma who are symptomatic on low dose fluticasone. European Respiratory Journal. 1998; Vol. 12(issue Suppl 29):19s, P160.
- Kalra 1996 {published data only} . Kalra S, Swystun VA, Bhagat R, Cockcroft DW. Inhaled corticosteroids do not prevent the development of tolerance to the bronchoprotective effect of salmeterol. Chest. 1996; 109(4):953–6. [PubMed: 8635376]
- Karaman 2007 {published data only (unpublished sought but not used)} . Karaman O, Arli O, Uzuner N, Islekel H, Babayigit A, Olmez D, et al. The effectiveness of asthma therapy alternatives and evaluating the effectiveness of asthma therapy by interleukin-13 and interferon gamma levels in children. Allergy & Asthma Proceedings. 2007; 28(2):204–9. [PubMed: 17479606]
- Kardos 2001 {published data only} . Kardos P, Bruggenjurgen B, Martin A, Meyer-Sabellek W, Richter K, Vogelmeier C, et al. Treatment of bronchial asthma using a new adjustable combination treatment plan: Asthma Control Plan (ATACO). Pneumologie. 2001; 55(5):253–7. [PubMed: 11449612]
- Keith 2001 {published data only} . Keith P, D' Urzo A, Stepner N, et al. Fluticasone/salmeterol combination (FSC) is safe and provides effective long-term (52 week) control in the management of patients with persistent asthma (PA). European Respiratory Journal. 2001; Vol. 18(issue Suppl 33):176s.
- Kelsen 1999 {published data only} . Kelsen SG, Church NL, Gillman SA, Lanier BQ, Emmett AH, Rickard KA, et al. Salmeterol added to inhaled corticosteroids therapy is superior to doubling the dose of inhaled corticosteroids: a randomized clinical trial. Journal of Asthma. 1999; 36(8):703– 15. [PubMed: 10609625]
- Kerwin 2001 {published data only} . Kerwin E, Srebro S, Church N, Emmett A, Rickard K, Knobil K. Salmeterol added to low-dose fluticasone propionate (fp) improves pulmonary function and albuterol use more rapidly than adding montelukast. Annals of Allergy, Asthma & Immunology. 2001; 86:99.
- Ketchell 2002 {published data only} . Ketchell RI, Jensen MW, Spina D, O'Connor BJ. Doserelated effects of formoterol on airway responsiveness to adenosine 5'-monophosphate and histamine. European Respiratory Journal. 2002; 19(4):611–16. [PubMed: 11998988]
- Kidney 1995 {published data only} . Kidney J, Pizzichini MMM, Wong B, Morris MM, Efthimadis A, Dolovich J, et al. Salmeterol compared with beclomethasone and placebo on allergen induced asthmatic and inflammatory responses. European Respiratory Journal. 1995; Vol. 8(issue Suppl 19):336s.
- Kips 2000 {published data only} . Kips JC, O'Connor BJ, Inman MD, Svenson K, Pauwels RA, O'Byrne PM. A long-term study of the antiinflammatory effect of low-dose budesonide plus formoterol versus high-dose budesonide in asthma. American Journal Respiratory Critical Care Medicine. 2000; 161:996–1001.
- Kirby 2000 {published data only} . Kirby S, Falcoz C, Daniel MJ, Milleri S, Squassante L, Ziviani L, et al. Salmeterol and fluticasone propionate given as a combination: lack of systemic pharmacodynamic and pharmacokinetic interactions. European Journal of Clinical Pharmacology. 2000; 56(11):781–91. [PubMed: 11294367]
- Knobil 2000 {published data only} . Knobil K, Dorinsky P, Yancey S, Emmett A, Rickard K. Salmeterol is superior to montelukast as add-on therapy to inhaled corticosteroids. European Respiratory Journal. 2000; Vol. 16(issue Suppl 31):457s.
- Knorr 2001 {published data only} . Knorr B, Franchi LM, Bisgaard H, Vermeulen JH, LeSouef P, Santanello N, et al. Montelukast, a leukotriene receptor antagonist, for the treatment of persistent asthma in children aged 2 to 5 years. Pediatrics. 2001; 108(3):E48. [PubMed: 11533366]
- Kraft 2003 {published data only} . Kraft M, Martin RJ, Lazarus SC, Lemanske RF, Szefler SJ. Airway tissue mast cells in persistent asthma: predictor of treatment failure when patients discontinue inhaled corticosteroids. Chest. 2003; 124(1):42–50. [PubMed: 12853500]

- LaForce 1994 {published data only} . LaForce C, Liddle RF, Yancey SW. Salmeterol response in asthmatic patients using inhaled corticosteroids and in those not using inhaled corticosteroids. Annals of Allergy. 1994; Vol. 72:100.
- Lai 1995 {published data only} . Lai CKW, Chan CHS, Ho SS, Hui ACF, Lai KN. Inhaled salmeterol and albuterol in asthmatic patients receiving high-dose inhaled corticosteroids. Chest. 1995; 108:36–40. [PubMed: 7606988]
- Lalloo 2000 {published data only} . Lalloo UG, Bantje TA, Kozma D, Krofta K, Ankerst J, Johansen B, et al. Low-dose Symbicort (budesonide/formoterol) is more effective than doubledose inhaled corticosteroid in mild asthma. Allergy Clinical Immunology Int. 2000; (Vol. Suppl 2):122.
- Lalloo 2001a {published data only} . Lalloo, UG.; Malolepszy, J.; Kozma, D.; Krofta, K.; Ankerst, J.; Johansen, B., et al. Symbicort® (budesonide and formoterol in a single inhaler) is more effective than increasing the dose of inhaled corticosteroids in mild asthma; Annual Thoracic Society 97th International Conference. San Francisco CA. May 18-23; 2001.
- Lalloo 2001b {published data only} . Lalloo UG, Malolepszy J, Kozma D, Krofta K, Ankerst J, Johansen B, et al. Budesonide and formoterol in a single inhaler is more effective than a higher dose of inhaled corticosteroid in mild-moderate persistent asthma. European Respiratory Journal. 2001; 18(Suppl 33):159s.
- Lalloo 2001c {published data only} . Lalloo UG, Malolepsky J, Kozma D, Krofta K, Ankerst J, Johansen B, et al. Budesonide and formoterol in a single inhaler controls exacerbations more effectively than a higher dose of inhaled corticosteroids alone, in mild-moderate persistent asthma. European Respiratory Journal. 2001; 18(Suppl 33):43s.
- Lalloo 2003 {published data only} . Lalloo UG, Malolepszy D, Kozma K, Krofta J, Ankerst B, Johansen NC, et al. Budesonide and formoterol in a single inhaler improves asthma control compared with increasing the dose of corticosteroid in adults with mild to moderate asthma. Chest. 2003; 123(5):1480–7. [PubMed: 12740264]
- Lange 2001 {published data only} . Lange ML, House KW, Scott CA, Shah TP, Akveld MLM. The salmeterol/fluticasone propionate combination 50/100µg bid is effective as initial maintenance therapy in mild and moderate asthmatics. European Respiratory Journal. 2001; Vol. 18(issue Suppl 33):176s.
- Lazarus 2001 {published data only} . Lazarus SC, Boushey HA, Fahy JV, Chinchilli VM, Lemanske RF Jr, Sorkness CA, et al. Long-acting beta2 agonist monotherapy vs continued therapy with inhaled corticosteroids in patients with persistent asthma: a randomized controlled trial. JAMA. 2001; 285(20):2583–93. [PubMed: 11368732]
- Lee 2003 {published data only} . Lee DK, Jackson CM, Currie GP, Cockburn WJ, Lipworth BJ. Comparison of combination inhalers vs inhaled corticosteroids alone in moderate persistent asthma. British Journal of Clinical Pharmacology. 2003; 56(5):494–500. [PubMed: 14651722]
- Lemanske 2001 {published data only} . Lemanske RF Jr, Sorkness CA, Mauger EA, Lazarus SC, Boushey HA, Fahy JV, et al. Inhaled corticosteroid reduction and elimination in patients with persistent asthma receiving salmeterol: a randomized controlled trial. JAMA. 2001; 285(20): 2594–603. [PubMed: 11368733]
- Lenney 1995 {published data only} . Lenney W, Pedersen S, Boner AL, Ebbutt A, Jenkins MM. Efficacy and safety of salmeterol in childhood asthma. European Journal of Pediatrics. 1995; 154:983–90. [PubMed: 8801107]
- Leuppi 2003 {published data only} . Leuppi FD, Salzberg M, Meyer L, Bucher SE, Nief M, Brutsche MH, et al. An individualized, adjustable maintenance regimen of budesonide/ formoterol provides effective asthma symptom control at a lower overall dose than fixed dosing. Swiss Medical Weekly. 2003; 133(21-2):302–9. [PubMed: 12861468]
- LHSRG 2000 {published data only} . The Lung Health Study Research Group. Effect of inhaled triamcinolone on the decline in pulmonary function in chronic obstructive pulmonary disease. New England Journal of Medicine. 2000; 343(26):1902–9. [PubMed: 11136260]
- Lindqvist 2001 {published data only} . Lindqvist, AE.; Karjalainen, EM.; Laitinen, LA.; Kava, T.; Altraja, A.; Pulkkinen, M., et al. Salmeterol (SLM), fluticasone propionate (FP) or disodium cromoglycate (DSCG) in the treatment of newly diagnosed asthma. Annual Thoracic Society 97th International Conference; San Francisco CA. May 18-23; 2001.

- Lindqvist 2003 {published data only} . Lindqvist A, Karjalainen EM, Laitinen LA, Kava T, Altraja A, Pulkkinen M, et al. Salmeterol resolves airway obstruction but does not possess antieosinophil efficacy in newly diagnosed asthma: a randomized, double-blind, parallel group biopsy study comparing the effects of salmeterol, fluticasone propionate, and disodium cromoglycate. Journal of Allergy & Clinical Immunology. 2003; 112(1):23–8. [PubMed: 12847475]
- Lipworth {published data only} . Lipworth, BJ. Does genetic polymorphism of b2-adrenoceptors determine airway sensitivity to regular long-acting b2-agonist therapy?. National Research Register (UK); [: N0405016375]
- Lipworth 1996 {published data only} . Lipworth BJ, Hall IP, Aziz I, Tan KS, Wheatley A. Beta2adrenoceptor polymorphism and bronchoprotective sensitivity with regular short- and long-acting beta2-agonist therapy. Clinical Science. 1996; 3:253–9.
- Lipworth 1998 {published data only} . Lipworth B, Tan S, Devlin M, Aiken T, Baker R, Hendrick D. Effects of treatment with formoterol on bronchoprotection against methacholine. American Journal of Medicine. 1998; 104(5):431–8. [PubMed: 9626025]
- Lipworth 1999a {published data only} . Lipworth BJ, Aziz I. A high dose of albuterol does not overcome bronchoprotective subsensitivity in asthmatic subjects receiving regular salmeterol or formoterol. Journal of Allergy & Clinical Immunology. 1999; 103(1 part 1):88–92. [PubMed: 9893190]
- Lipworth 1999b {published data only} . Lipworth BJ, Hall IP, Aziz I, Tan KS, Wheatley A. Beta2adrenoceptor polymorphism and bronchoprotective sensitivity with regular short- and long-acting beta2-agonist therapy. Clinical Science. 1996; 3:253–9.
- Lipworth 2000a {published data only} . Lipworth BJ, Dempsey OJ, Aziz I. Functional antagonism with formoterol and salmeterol in asthmatic patients expressing the homozygous glycine-16 beta(2)-adrenoceptor polymorphism. Chest. 2000; 118(2):321–8. [PubMed: 10936119]
- Lipworth 2000b {published data only} . Lipworth BJ, Dempsey OJ, Aziz I, Wilson AM. Effects of adding a leukotriene antagonist or a long-acting beta(2)-agonist in asthmatic patients with the glycine-16 beta(2)-adrenoceptor genotype. American Journal of Medicine. 2000; 109(2):114–21. [PubMed: 10967152]
- Lockey 1999 {published data only} . Lockey RF, DuBuske LM, Friedman B, Petrocella V, Cox F, Rickard K. Nocturnal asthma: effect of salmeterol on quality of life and clinical outcomes. Chest. 1999; 115(3):666–73. [PubMed: 10084473]
- Lowhagen 2002 {published data only} . Lowhagen O, Wever AM, Lusuardi M, Moscato G, De Backer WA, Gandola L, et al. The inflammatory marker serum eosinophil cationic protein (ECP) compared with PEF as a tool to decide inhaled corticosteroid dose in asthmatic patients. Respiratory Medicine. 2002; 96(2):95–101. [PubMed: 11862965]
- Lundback 2002 {published data only} . Lundback, B.; Ronmark, E.; Jonsson, AC.; Larsson, LG.; Petavy, F.; James, MH. Airway hyperresponsiveness and treatment effectiveness during a one year study of the combination of salmeterol and fluticasone propionate (FP) compared with FP and salmeterol alone in mild to moderate asthma. European Respiratory Society Annual Congress; 2002. p. P2397
- Lyseng-Williamson 2003 {published data only} . Lyseng-Williamson KA, Plosker GL. Inhaled salmeterol/fluticasone propionate combination: a pharmacoeconomic review of its use in the management of asthma. Pharmacoeconomics. 2003; 21(13):951–89. [PubMed: 12959627]
- Lötvall 2002 {published data only} . Lötvall J, van der Woude HJ, Palmqvist M, Arvidsson P, Beckman O, Boorsma M, et al. More rapid onset of action of budesonide/formoterol (Symbicort®) than salmeterol/fluticasone (SeretideTM). American Journal of Respiratory & Critical Care Medicine. 2002; Vol. 165(issue Suppl 8):A567.
- Magadle 2001 {published data only} . Magadle R, Berar-Yanay N, Weiner P. Long-acting bronchodilators in premenstrual exacerbation of asthma. Respiratory Medicine. 2001; 95(9):740– 3. [PubMed: 11575895]
- Malmqvist-Granlund 2000 {published data only} . Malmqvist-Granlund K, Asking L, Lindbald T, Rollwage U, Steckel H. An in vitro comparison of budesonide/formoterol and fluticasone/ salmeterol in dry powder inhalers. European Respiratory Journal. 2000; Vol. 16(issue Suppl 31): 455s.

- Malolepszy 2001 {published data only} . Malolepszy J, Boszormenyi Nagy G, Selroos O, Larsson P, Brander R. Safety of formoterol turbuhaler at cumulative dose of 90 mug in patients with acute bronchial obstruction. European Respiratory Journal. 2001; 18(6):928–34. [PubMed: 11829098]
- Malolepszy 2002 {published data only} . Malolepszy J. Efficacy and tolerability of oral theophylline slow-release versus inhaled formoterol in moderate asthma poorly controlled on low-dose steroids. Atemwegs- und Lungenkrankheiten. 2002; 28(2):78–87.
- Martinat 2003 {published data only} . Martinat Y, Desfougeres JL. Fixed-dose fluticasonesalmeterol combination: at least effective and better tolerated than open-dose combinations. Revue De Pneumologie Clinique. 2003; 59(3):139–48. [PubMed: 13130200]
- Matz 2001 {published data only} . Matz J, Emmett A, Rickard K, Kalberg C. Addition of salmeterol to low-dose fluticasone versus higher-dose fluticasone: an analysis of asthma exacerbations. Journal of Allergy and Clinical Immunology. 2001; 107(5):783–9. [PubMed: 11344343]
- McCarthy 2000 {published data only} . McCarthy TP, Boone R, Yancey S, Rickard K. Salmeterol compared to montelukast as adjunctive therapy to inhaled corticosteroids. Thorax. 2000; Vol. 55(issue Suppl 3):A63.
- McCarthy 2001a {published data only} . McCarthy TP, Russell D, Baxter LE, et al. A comparison of the efficacy of salmeterol/fluticasone propionate combination (SF) with beclometasone dipropionate (BDP) delivered via metered dose inhaler (MDI) in patients not well controlled on bronchodilators alone. European Respiratory Journal. 2001; Vol. 18(issue Suppl 33):53–54s.
- McCarthy 2001b {published data only} . McCarthy TP, Greening AP, Holgate SK, Whitehead C, Rice L. The efficacy of salmeterol/fluticasone propionate combination (SFC) metered dose inhaler compared with beclomethasone dipropionate (BDP) in patients not well controlled at step 1 of the British guidelines on asthma management (BGAM). Thorax. 2001; Vol. 56(issue Suppl 3):iii62.
- McCarthy 2002 {published data only} . McCarthy TP, Grening AP, Holgate SK, Whitehead C, Rice L. Salmeterol/fluticasone propionate combination (SFC) is more effective that beclometasone dipropionate (BDP) in patients not well controlled on bronchodilators alone. American Journal of Respiratory & Critical Care Medicine. 2002; Vol. 165(issue Suppl 8):A566.
- McCarthy 2003 {published data only} . McCarthy, TP.; Woodcock, AA.; Pavord, ID.; Allen, DJ.; Parker, D.; Rice, L. A comparison of the anti-inflammatory and clinical effects of salmeterol 25mcg/fluticasone propionate 50mcg combination (SFC 50) with fluticasone propionate (FP) plus montelukast (M) in patients with mild to moderate asthma. American Thoracic Society 99th International Conference; 2003. B036 Poster H89
- Mcivor 1998 {published data only} . Mcivor RA, Pizzichini E, Turner MO, Hussack P, Hargreave FE, Sears MR. Potential masking effects of salmeterol on airway inflammation in asthma. American Journal of Respiratory & Critical Care Medicine. 1998; 158(3):924–30. [PubMed: 9731027]
- Michel 2000 {published data only} . Michel O, Olbrecht J, Moulard D, Sergysels R. Effect of antiasthmatic drugs on the response to inhaled endotoxin. Annals of Allergy, Asthma, & Immunology. 2000; 85(4):305–10.
- Midgren 1992 {published data only} . Midgren B, Melander B, Persson G. Formoterol, a new long-acting beta 2 agonist, inhaled twice daily, in stable asthmatic subjects. Chest. 1992; 101(4): 1019–22. [PubMed: 1348219]
- Miraglia del Giudice 2007 {published data only} . Miraglia del Giudice, M. Capristo M, Amelio R, Rocco A, Fusco N, Brunese FP. Combined fluticasone propionate/salmeterol (Diskus) vs fluticasone propionate (Diskus) in the control of persistent asthma in children. American Thoracic Society 99th International Conference; 2003. A117 Poster D78Miraglia del Giudice M, Piacentini GL, Capasso M, Capristo C, Maiello N, Boner AL, et al. Formoterol, montelukast, and budesonide in asthmatic children: effect on lung function and exhaled nitric oxide. Respiratory Medicine. 2007; 101(8):1809–13. [PubMed: 17418554]
- Mitchell 2000 {published data only} . Mitchell C, Jenkins C, Scicchitano R, Rubinfeld A. Adding formoterol is more effective and safer than doubling the dose of inhaled steroids in moderately severe asthma. American Journal of Respiratory & Critical Care Medicine. 2000; Vol. 161(issue Suppl 3):A197.

- Mitchell 2003 {published data only} . Mitchell C, Jenkins C, Scicchitano R, Rubinfeld A, Kottakis J. Formoterol (Foradil) and medium-high doses of inhaled corticosteroids are more effective than high doses of corticosteroids in moderate-to-severe asthma. Pulmonary Pharmacology & Therapeutics. 2003; 16(5):229–306.
- Murray 1998 {published data only} . Murray JJ, Hagaman DD, Dworski R, Keane B, Sheller JR. Inhibition by salmeterol and beclomethasone of late phase response to segmental antigen challenge in asthmatics. American Journal of Respiratory & Critical Care Medicine. 1998; Vol. 157(issue Suppl 3):A872.
- Murray 1999 {published data only} . Murray JJ, Church NL, Anderson WH, Bernstein DI, Wenzel SE, Emmett A, et al. Concurrent use of salmeterol with inhaled corticosteroids is more effective than inhaled corticosteroid dose increases. Allergy & Asthma Proceedings. 1999; 20(3):173–80. [PubMed: 10389550]
- Nathan 1995 {published data only} . Nathan RA, Seltzer JM, Kemp JP, Chervinsky P, Alexander WJ, Liddle R, et al. Safety of salmeterol in the maintenance treatment of asthma. Annals of Allergy, Asthma and Immunology. 1995; 75:243–8.
- Nathan 1999a {published data only} . Nathan RA, Pinnas JL, Schwartz HJ, Grossman J, Yancey SW, Emmett AH, et al. A six-month, placebo-controlled comparison of the safety and efficacy of salmeterol or beclomethasone for persistent asthma. Annals of Allergy, Asthma, & Immunology. 1999; 82:521–9.
- Nathan 1999b {published data only} . Nathan, R.; Woodring, A.; Baitinger, L.; Prillaman, B.; Faris, M.; House, K., et al. The salmeterol/fluticasone propionate Diskus combination decreases the incidence of exacerbations compared to treatment with salmeterol or fluticasone propionate alone. European Respiratory Society; Madrid, Spain: Oct 9-13. 1999 p. 8481999
- Nathan 2001 {published data only} . Nathan, RA.; Mitchell, D.; Condemi, J.; Heller, A.; Schoaf, L.; Herrle, M., et al. Cardiovascular and hypothalamic-pituitary-adrenal axis safety of fluticasone propionate/salmeterol HFA MDI in adolescent and adult patients with asthma. Annual Thoracic Society 97th International Conference; San Francisco CA. May 18-23; 2001.
- Nelson 1999 {published data only} . Nelson HS, Berkowitz RB, Tinkelman DA, Emmett AH, Rickard KA, Yancey SW. Lack of sub-sensitivity to albuterol after treatment with salmeterol in patients with asthma. American Journal of Respiratory and Critical Care Medicine. 1999; 159(5 part 1):1556–61. [PubMed: 10228126]
- Nelson 2000a {published data only} . Nelson H, Chervinsky P, Greos L, Pelskow W, Baitinger L, Scott C, et al. The salmeterol/fluticasone propionate combination product improves asthma control compared with the individual products in asthmatics treated with prn short-acting beta2-agonists alone. American Journal of Respiratory & Critical Care Medicine. 2000; Vol. 161(issue Suppl 3):A196.Nelson HS, Baitinger L, Scott C, House K, Payne E, Shah T. Salmeterol/ fluticasone propionate (50/100µg dose) non-CFC metered dose inhaler is safe and effective in in patients with asthma using short-acting β₂-agonists alone. European Respiratory Journal. 2000; Vol. 16(issue 31):53s.Nelson HS, Busse WW, Kerwin E, Church N, Emmett A, Rickard K, et al. Fluticasone propionate/salmeterol combination provides more effective asthma control than low-dose inhaled corticosteroid plus montelukast. Journal of Allergy and Clinical Immunology. 2000; 106(6):1088–95. [PubMed: 11112891]
- Nelson 2000b {published data only} . Nelson HS, Chervinsky P, Greos L, Pleskow W, Baitinger L, Scott C, et al. The salmeterol/fluticasone propionate combination product improves asthma control compared with the individual products in asthmatics treated with PRN short-acting beta2agonists alone. American Journal of Respiratory & Critical Care Medicine. 2000; Vol. 161(issue Suppl 3):A196.
- Nelson 2001 {published data only} . Nelson HS, Nathan RA, Kalberg C, Yancey SW, Rickard KA. Comparison of inhaled salmeterol and oral zafirlukast in asthmatic patients using concomitant inhaled corticosteroids. Medscape General Medicine. 2001; Vol. 3(issue 4):3. [PubMed: 11549982]
- Newnham 1995 {published data only} . Newnham DM, Grove A, McDevitt DG, Lipworth BJ. Subsensitivity of bronchodilator and systemic beta 2 adrenoceptor responses after regular twice daily treatment with eformoterol dry powder in asthmatic patients. Thorax. 1995; 50(5):497–504. [PubMed: 7597661]

- Nielsen 1999 {published data only} . Nielsen LP, Pedersen B, Faurschou P, Madsen F, Wilcke JTR, Dahl R. Salmeterol reduces the need for inhaled corticosteroids in steroid-dependent asthmatics. Respiratory Medicine. 1999; 93:863–8. [PubMed: 10653047]
- Nightingale 2002 {published data only} . Nightingale JA, Rogers DF, Barnes PJ. Comparison of the effects of salmeterol and formoterol in patients with severe asthma. Chest. 2002; 121(5): 1401–6. [PubMed: 12006420]
- Nsouli 2001 {published data only} . Nsouli SM, McNutt WJ. The additive effects of montelukast and salmeterol in moderate asthmatics who are uncontrolled on a low dose on inhaled corticosteroids. Annals of Allergy, Asthma & Immunology. 2001; 86:81.
- O'Brian 2001 {published data only} . O'Brian, J.; Carlos-Palma, A.; Bogolubov, M.; Davies, P.; Payne, E. Benefits of fluticasone propionate/salmeterol [fp/s] HFAMDI are apparent on the first day of dosing. Annual Thoracic Society 97th International Conference; San Francisco CA. May 18-23; 2001.
- Odeback 1998 {published data only} . Odeback P. Is the addition of salmeterol more effective than doubling the dose of budesonide in mild asthma? American Journal of Respiratory & Critical Care Medicine. 1998; Vol. 157(issue Suppl 3):A417.
- Olsson 2002 {published data only} . Olsson, P.; Stallberg, B.; Ekstrom, T.; Lindarck, N.; Jorgensen, LA. Adjustable maintenance treatment of asthma with budesonide and formoterol in a single inhaler. European Respiratory Society Annual Congress; 2002. p. P2451
- Ortega-Cisnero 1998 {published data only} . Ortega-Cisnero M, Maldonado-Alaniz ML, Rosas Vargas MA, Sierra-Monge JJL. Salmeterol and inhaled beclomethasone versus high dose inhaled beclomethasone in the control of pediatric patients with moderate asthma. Annals of Allergy, Asthma and Immunology. 1998; 80:131.
- Overbeck 2003 {published data only} . Overbeck, SE.; Mulder, PG.; Baelemans, SM.; Hoogsteden, HC.; Prins, JB. Comparison of budesonide plus formoterol with budesonide alone on airway inflammation in mild asthmatics. American Thoracic Society 99th International Conference; 2003. D034 Poster C36
- Ozkaya 1999 {published data only} . Ozkaya, O.; Turktas, I.; Cengizlier, R. Low dose budesonide plus formoterol versus high dose budesonide in children with bronchial asthma. European Respiratory Society; Madrid, Spain: Oct 9-13. 1999 1999
- Palmer 1992 {published data only} . Palmer JBD, Stuart AM, Shepherd GL, Viskum K. Inhaled salmeterol in the treatment of patients with moderate to severe reversible obstructive airways disease a 3 month comparison of the efficacy and safety of twice-daily salmeterol (100 mcg) with salmeterol (50 mcg). Respiratory Medicine. 1992; 86:409–17. [PubMed: 1361068]
- Palmqvist 2001 {published data only} . Palmqvist M, Arvidsson P, Beckman O, Peterson S, Lotvall J. Onset of bronchodilation of budesonide/formoterol vs salmeterol/fluticasone in single inhalers. Pulmonary Pharmacology & Therapeutics. 2001; 14(1):29–34. [PubMed: 11162416]
- Paterson 1999 {published data only} . Paterson, MC.; Wilson, AM.; Dempsey, OJ.; Sims, EJ.; Lipworth, BJ. The effect of combination therapy with salmeterol and montelukast in asthmatic patients receiving inhaled corticosteroids. European Respiratory Society; Madrid, Spain: Oct 9-13. 1999 p. P34901999
- Pauwels 1998 {published data only} . Pauwels RA, Yernault JC, Demedts MG, Geusens P. Safety and efficacy of fluticasone and beclomethasone in moderate to severe asthma. American Journal of Respiratory & Critical Care Medicine. 1998; 157(3 pt 1):827–32. [PubMed: 9517598]
- Pearlman 1992 {published data only} . Pearlman DA, Chervinsky P, LaForce C, Seltzer JM, Southern DL, Kemp JP, et al. A comparison of salmeterol with albuterol in the treatment of mild to moderate asthma. New England Journal of Medicine. 1992; 327:1420–5. [PubMed: 1357554]
- Pearlman 1994 {published data only} . Pearlman DS, Liddle R. Controlling asthma symptoms: salmeterol compared with salbutamol in large-scale multicentre studies. European Respiratory Review. 1994; 4(21):301–5.
- Pearlman 1999a {published data only} . Pearlman DS, Stricker W, Weistein S, Gross G, Chervinsky P, Woodring A, et al. Inhaled salmeterol and fluticasone: a study comparing monotherapy and combination therapy in asthma. Annals of Allergy, Asthma, & Immunology. 1999; 82:257–65.

- Pearlman 1999b {published data only} . Pearlman DS, Stricker W, Weistein S, Gross G, Chervinsky P, Woodring A, et al. Inhaled salmeterol and fluticasone: a study comparing monotherapy and combination therapy in asthma. Annals of Allergy, Asthma, & Immunology. 1999; 82:257–65.
- Pearlman 2001 {published data only} . Pearlman, DS.; Kent, E.; Lanz, MJ.; Peden, D.; Baitinger, L.; Herrle, M., et al. Fluticasone propionate/salmeterol HFAMDI has a rapid onset of effect in asthmatics treated with short or long-acting beta2-agonists (ba) or inhaled corticosteroids. Annual Thoracic Society 97th International Conference; San Francisco CA. May 18-23; 2001.
- Pearlman 2002 {published data only} . Pearlman DS, White MV, Lieberman AK, Pepsin PJ, Kalberg C, Emmett A, et al. Fluticasone propionate/salmeterol combination compared with montelukast for the treatment of persistent asthma. Annals of Allergy, Asthma and Immunology. 2002; 88(2):227–35.
- Peters 2000 {published data only} . Peters JI, Shelledy DC, Jones AP Jr, Lawson RW, Davis CP, LeGrand TS. A randomized, placebo-controlled study to evaluate the role of salmeterol in the inhospital management of asthma. Chest. 2000; 118(2):313–20. [PubMed: 10936118]
- Pieters 1999b {published data only} . Pieters WR, Lundback B, Sondhi S, Price MJ. Cost effectiveness analysis of salmeterol/fluticasone propionate 50/500mcg vs fluticasone propionate 500mcg in patients with corticosteroid-dependent asthma. Pharmacoeconomics. 1999; 16(Suppl 2):29–34.
- Pieters 2001 {published data only} . Pieters, WR.; Wilson, KK.; Smith, HCE.; Tamminga, JJ. Cost-effectiveness of fluticasone propionate/salmeterol combination product and fluticasone propionate/montelukast in asthma. Annual Thoracic Society 97th International Conference; San Francisco CA. May 18-23. 2001;
- Pinnas 1998 {published data only} . Pinnas JL, Schwartz H, Yancey SW, Rickard K. Six month comparison of beclomethasone versus salmeterol or placebo in adults with asthma. American Journal of Respiratory & Critical Care Medicine. 1998; Vol. 157(issue Suppl 3):A417.
- Pizzichini 1996 {published data only} . Pizzichini MM, Kidney JC, Wong BJ, Morris MM, Efthimiadis A, Dolovich J, et al. Effect of salmeterol compared with beclomethasone on allergen-induced asthmatic and inflammatory responses. European Respiratory Journal. 1996; 9(3):449–55. [PubMed: 8730003]
- Pljaskic-Kamenov 2000 {published data only} . Pljaskic-Kamenov SS, Filipovic MD, Kamenov BA. Comparison of addition of salmeterol xinafoate to budesonide with budesonide alone on symptoms and quality of life in asthmatic children. European Respiratory Journal. 2000; Vol. 16(issue Suppl 31):518s.
- Price 2003 {published data only} . Price, D.; Haughney, J.; Rosen, JP.; Morrison, K. Switching to Symbicort(r) from beclomethasone dipropionate (BDP) with or without salmeterol significantly improved symptom severity in patients with moderate asthma. American Thoracic Society 99th International Conference; 2003. Vol. D034 Poster C40
- Pujet 1995 {published data only} . Pujet JC, Evano CI. A randomized double-blind study comparing inhaled beclomethasone with long-acting theophylline for the first-line treatment of moderate asthma. Semaine Des Hopitaux. 1995; 71(27-8):865–72.
- Pyke 2001 {published data only} . Pyke SD. Synergy with salmeterol and fluticasone propionate after administration from a single inhaler (Seretide(tm)). European Respiratory Journal. 2001; Vol. 18(issue Suppl 33):176s.
- Rance 2002 {published data only} . Rance, L.; Musin, L. Chest. San Diego, CA: 2002. Asthma management costs in Canada are lower with combination fluticasone propionate/salmeterol (250/50mcg BID) in as single inhaler than with budesonide 800mcg BID plus eformoterol 12 mcg BID via separate inhalers; p. S62002
- Rickard 1999 {published data only} . Rickard, KA.; Yancey, S.; Emmett, AH.; Kalberg, CJ. Salmeterol compared to zafirlukast when added to inhaled corticosteroid therapy in patients with persistent asthma. European Respiratory Society; Madrid, Spain: Oct 9-13. 1999 p. P8391999
- Rickard 2001 {published data only} . Rickard K, Dorinsky PM, Knobil K, Pepsin P, Akveld ML. The salmeterol/fluticasone propionate combination 50/100µg bid is more effective than oral montelukast 10mg of as a first line therapy in mild and moderate asthmatics. European Respiratory Journal. 2001; Vol. 18(issue Suppl 33):262s.

- Rijssenbeek-Nouwens 2002 {published data only} . Rijssenbeek-Nouwens LH, Oosting AJ, De Monchy JG, Bregman I, Postma DS, De Bruin-Weller MS. The effect of anti-allergic mattress encasings on house dust mite-induced early- and late-airway reactions in asthmatic patients. A double-blind, placebo-controlled study. Clinical & Experimental Allergy. 2002; 32(1):117–25. [PubMed: 12002728]
- Ringbaek 1996 {published data only} . Ringbaek TJ, Soes-Petersen U, Christensen M, Iversen ET, Rasmussen FV. Salmeterol improves the control of disease in patients with moderate asthma. A comparative study of inhaled salmeterol 50 mg and salbutamol depot tablets 8 mg, both administered twice daily]. Ugeskrift for Laeger. 1996; 158(27):3940–3. [PubMed: 8701511]
- Ringdal 1997 {published data only} . Ringdal N, Eliraz A, Pruzinec R, Weber HH, Mulder PG, Akveld M, et al. The salmeterol/fluticasone combination is more effective than fluticasone plus oral montelukast in asthma. Respiratory Medicine. 3:234–4. 97.
- Ringdal 2002 {published data only} . Alonso JF, Badiola C, Kielhorn A. Economic evaluation of salmeterol/fluticasone combination vs budesonide plus formoterol in Spain. European Respiratory Journal. 2001; 18(Suppl 33):49s.Chuchalin, AG.; Chovan, L.; Ringdal, N.; Whitehead, PJ. AdvairTM seretideTM (250/50 mcg bid) shows nocturnal benefit over budesonide 800mu-g + formoterol 12mu-g bid in moderate to severe asthma. Annual Thoracic Society 97th International Conference; San Francisco CA. May 18-23. 2001; 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; Vol. 7(issue Suppl):A20. [: P23]. Martin, AA.; Whitehead, PJ.; McCarthy, TP. Asthma costs with salmeterol/fluticasone combination 50/250mcg bd compared to budesonide 800mcg bd plus formoterol 12mcg bd. American Thoracic Society 99th International Conference; 2003. D034 Poster C43Ringdal N, Chuchalin A, Chovan L, Tudoric N, Maggi E, Whitehead PJ. Evaluation of different inhaled combination therapies (EDICT): a randomised, double-blind comparison of Seretide (50/250 microgram bd Diskus vs. formoterol (12 microgram bd) and budesonide (800 microgram bd) given concurrently (both via Turbuhaler) in patients with moderate-to-severe asthma. Respiratory Medicine. 2002; 96(11):851-61. [PubMed: 12418582] Ringdal N, Chuchalin AG, Chovan L, Whitehead PJ. A comparison of AdvairTM/SeretideTM (salmeterol 50 mcg/fluticasone propionate 250 mcg bid) with formoterol 12 mcg + budesonide 800 mcg bid in moderate-severe asthma. American Journal of Respiratory & Critical Care Medicine. 2000; Vol. 161(issue 3 part 2 (Supp1)):A196.*Ringdal, NR.; Chovan, L.; Chuchalin, AG.; Whitehead, PJ. AdvairTM/SeretideTM (250/50mu-g bid) shows exacerbation benefit over budesonide plus formoterol bid in moderatesevere asthma. Annual Thoracic Society 97th International Conference; San Francisco CA. May 18-23. 2001;
- Ringdal 2003 {published data only} . Ringdal N, Eliraz A, Pruzinec R, Weber HH, Mulder PG, Akveld M, et al. The salmeterol/fluticasone combination is more effective than fluticasone plus oral montelukast in asthma. Respiratory Medicine. 3:234–4. 97.
- Rocca-Serra 2002 {published data only} . Rocca-Serra JP, Vicaut E, Lefrancois G, Umile A. Efficacy and tolerability of a new non-extrafine formulation of beclomethasone HFA-134a in patients with asthma: comparison with beclomethasone CFC. Clinical Drug Investigation. 2002; 22(10):653–65.
- Rooklin 2001 {published data only} . Rooklin A, Elkayam D, Weiler J, Windom H, Schoaf L, Scott C, et al. The fluticasone propionate/salmeterol HFA MDI is significantly more efficacious in treating asthma than placebo HFA MDI, fluticasone propionate CFC MDI or salmeterol CFC MDI. Journal of Allergy and Clinical Immunology. 2001; Vol. 107(issue 2):S100.
- Rosenhall 2001a {published data only} . Rosenhall, L.; Stahl, E.; Heinig, JH.; Lindquist, A.; Leegard, J.; Bergqvist, PBF. Health-related quality of life and asthma control in patients using Symbicort® (budesonide and formoterol in a single inhaler). Annual Thoracic Society 97th International Conference; San Francisco CA. May 18-23. 2001;
- Rosenhall 2001b {published data only} . Rosenhall L, Heinig JH, Lindqvist A, Leegard J, Bergqvist PB. Budesonide and formoterol in a single inhaler is safe and effective in the treatment of asthma. European Respiratory Journal. 2001; 18(33):159s.
- Rosenhall 2001c {published data only} . Rosenhall L, Stahl E, Heinig JH, Lindqvist A, Leegard J, Bergqvist PB. Health-related quality of life and asthma control in patients treated with

budesonide and formoterol in a single inhaler. European Respiratory Journal. 2001; Vol. 18(issue Suppl 33):46s.

- Rosenhall 2002 {published data only} . Rosenhall L, Heinig JH, Lindqvist A, Leegaard J, Stahl E, Bergqvist PB. Budesonide/formoterol (Symbicort) is well tolerated and effective in patients with moderate persistent asthma. International Journal of Clinical Practice. 2002; 56(6):427–33. [PubMed: 12166540]
- Rosenhall 2003 {published data only}. Rosenhall L, Elvstrand A, Tilling B, Vinge I, Jemsby P, Stahl E, et al. One-year safety and efficacy of budesonide/formoterol in a single inhaler (Symbicort Turbuhaler) for the treatment of asthma. Respiratory Medicine. 2003; 97(6):702–8. [PubMed: 12814158]
- Rosenhall 56 {published data only} . Rosenhall L, Heinig JH, Lindqvist A, Leegard J, Bergqvist PB. Symbicort (budesonide/eformoterol in a single inhaler) is safe and effective in the treatment of asthma. Thorax. 56(Vol. Suppl 3):iii, 63.
- Rosenthal 1999 {published data only} . Rosenthal RR, Busse WW, Kemp JP, Baker JW, Kalberg C, Emmett A, Rickard KA. Effect of long-term salmeterol therapy compared with as-needed albuterol use on airway hyperresponsiveness. Chest. 1999; 116(3):595–602. [PubMed: 10492259]
- Rumbak 1998 {published data only} . Rumbak M, Self T, Kelso T, Eberle L, Abou-Shala N, Learned S, et al. Moderate to high dose inhaled corticosteroids in adult asthmatics: does salmeterol facilitate step down therapy? European Respiratory Journal. 1998; 12(Suppl 29):19s.
- Sahn 2002 {published data only} . Sahn, S.; Yancey, S.; Reilly, D.; Edwards, L.; Rickard, K.; Dorinsky, P. Chest. San Diego, CA: 2002. 2002. The fluticasone propionate/salmeterol (FSC) combination product 100/50 mcg BID is steroid sparing in patients who require FP250 mcg BID for asthma stability. (conference)
- SAM30007 {unpublished data only} . [accessed 5 June 2008] SAM30007. A multicentre, randomised, double-blind, controlled, parallel-group, comparative investigation of the corticosteroid-saving potential of the combination therapy fluticasone propionate and salmeterol (SERETIDE) compared with fluticasone propionate alone, given to adult asthmatic subjects, when reducing the inhaled corticosteroid dose from an initially high level of 500µg bd. 2005. www.ctr.gsk.co.uk
- SAM40004 {published data only} . Beckett, P.; Hewitt, L.; Woodcock, A.; Smith, J.; Seghal, N.; Rice, L., et al. Improvement in airway hyper-responsiveness (AHR) and lung function with salmeterol/fluticasone propionate combination (SFC) in persistent asthma [abstract]. American Thoracic Society 99th International Conference; 2003. D034 Poster C27 [accessed 30 April 2008] SAM40004. A multi-centre, randomised, double-blind, placebo-controlled parallel group study to compare the effect on airway inflammation and remodelling of treatment with salmeterol/fluticasone propionate combination product (50/100µg strength) bd via the Accuhaler inhaler, or fluticasone propionate 100µg bd via the Accuhaler inhaler or placebo via the Accuhaler inhaler for 16 weeks, followed by double-blind treatment for 52 weeks with the salmeterol/fluticasone propionate 100µg bd via the Accuhaler inhaler, in adults with reversible airways obstruction (SIRIAS - Seretide in Inflammation and Remodelling In Asthma Study). 2006. http://www.gsk.ctr.co.uk
- Schreurs 1996 {published data only} . Schreurs AJ, Sinninghe Damste HE, de Graaff CS, Greefhorst AP. A dose-response study with formoterol Turbuhaler as maintenance therapy in asthmatic patients. European Respiratory Journal. 1996; 9:1678–83. [PubMed: 8866594]
- Sears 2003 {published data only} . Sears MR, McIvor A, Becker A, Fitzgearld JM, Boulet LP, Ernsy P, et al. Budesonide/formoterol adjustable maintenance dosing effectively improves asthma symptom severity: a multicentre Canadian study. European Respiratory Journal. 2003; 22(Suppl 45):P1695.
- Serrier 2003 {published data only} . Serrier P, Roche N, Pello JY, Larguier JS, Mezzi K. Asthma control achieved with inhaled corticosteroids and long-acting beta2-agonists in a free or fixed combination: results of the ALISE survey. Presse Medicale. 2003; 32(11):493–7.
- Shapiro 2001 {published data only} . Shapiro GG, Mendelson LM, Pearlman DS. Once-daily budesonide inhalation powder (Pulmicort Turbuhaler) maintains pulmonary function and

symptoms of asthmatic children previously receiving inhaled corticosteroids. Annals of Allergy, Asthma, and Immunology. 2001; 86(6):633–40.

- Sheth 2002 {published data only} . Sheth K, Borker R, Emmett A, Rickard K, Dorinsky P. Costeffectiveness comparison of salmeterol/fluticasone propionate versus montelukast in the treatment of adults with persistent asthma. Pharmacoeconomics. 2002; 20(13):909–18. [PubMed: 12381242]
- Shrewsbury 2002 {published data only} . Shrewsbury SB, Pyke S. MIASMA: asthma exacerbation reduction with salmeterol [Letter]. Chest. 2002; 121(3):1002–4. [PubMed: 11888994]
- Sienra-Monge 2001 {published data only} . Sienra-Monge JJL, Del Rio BE, Alvarez ME, Magana AJ. Comparison of quality of life and pulmonary function on moderate asthmatic children treated with beclomethasone and beclomethasone plus salmeterol. Journal of Allergy and Clinical Immunology. 2001; Vol. 107(issue 2):s263.
- Simons 1997b {published data only} . Simons FER. A comparison of beclomethasone, salmeterol and placebo in children with asthma. New England Journal of Medicine. 1997; 337:1659–65. [PubMed: 9385125]
- Sims 2003 {published data only} . Sims EJ, Jackson CM, Lipworth BJ. Add-on therapy with montelukast or formoterol in patients with the glycine-16 beta2-receptor genotype. British Journal of Clinical Pharmacology. 2003; 56(1):104–11. [PubMed: 12848782]
- Staehr 1995 {published data only} . Staehr P, Vestbo I. Salmeterol improves control in asthmatic patients treated in general practice. A comparative study of salmeterol (Serevent) and salbutamol. Ugeskr-Laeger. 1995; 157(1):36–40. [PubMed: 7839545]
- Stahl 2003 {published data only} . Stahl E, Postma DS, Svensson K, Tattersfield AE, Eivindson A, Schreurs A, et al. Formoterol used as needed improves health-related quality of life in asthmatic patients uncontrolled with inhaled corticosteroids. Respiratory Medicine. 2003; 97(9):1061–6. [PubMed: 14509561]
- Stallberg 2003 {published data only} . Stallberg B, Olsson P, Jorgensen LA, Lindarck N, Ekstrom T. Budesonide/formoterol adjustable maintenance dosing reduces asthma exacerbations versus fixed dosing. International Journal of Clinical Practice. 2003; 57(8):656–61. [PubMed: 14627173]
- Stanford 2002 {published data only} . Stanford, RH.; Borker, R.; Dorinsky, P.; Pepsin, P.; Kalberg, C.; Emmett, A. Chest. San Diego, CA: 2002. The costs and efficacy of fluticasone propionate/salmeterol combination versus montelukast in the treatment of adults with persistent asthma; p. 4222002
- Stankovic 2000 {published data only} . Stankovic IJ, Djordjevic DV, Pejcic TA, Zivkovic DS, Rancic MR, et al. Formoterol and beclomethasone dipropionate versus higher dose beclomethasone dipropionate in asthma patients. European Respiratory Journal. 2000; 16(Suppl 31):455s.
- Stelmach 2001 {published data only} . Stelmach I, Grzelewski T, Majak P, Majak J, Bobrowska M, Jerzynska J, et al. The effect of triamcinolone, montelukast and formoterol on serum levels of il-4, IgE and clinical parameters in children with asthma. Polski Merkuriusz Lekarski. 2001; 11(63):247–51. [PubMed: 11761821]
- Stelmach 2002a {published data only} . Stelmach I, Jerzynska J, Majak P, Grzelewski T, Gorski P, Stelmach W, Kuna P. Effect of triamcinolone acetonide, montelukast, nedocromil sodium, formoterol on serum levels of sICAM-1, sIL-2R and clinical parameters of asthma in children. Polski Merkuriusz Lekarsk. 2002; 12(68):99–103.
- Stelmach 2002b {published data only} . Stelmach I, Jerzynska J, Kuna P. A randomized, doubleblind trial of the effect of glucocorticoid, antileukotriene and [beta]-agonist treatment on IL-10 serum levels in children with asthma. Clinical & Experimental Allergy. 2002; 32(2):264–9. [PubMed: 11929492]
- Stelmach 2008 {published data only (unpublished sought but not used)} . Stelmach I, Grzelewski T, Jerzynska J, Kuna P. A randomized, double-blind trial on the effect of treatment with montelukast, budesonide, montelukast with budesonide, formoterol with budesonide on lung function and clinical symptoms in children with asthma [Abstract]. Journal of Allergy & Clinical Immunology. 2005; 115(Suppl 2):S151.Stelmach I, Grzelewski T, Majak P, Jerzynska J, Stelmach W, Kuna P. Effect of different antiasthmatic treatments on exercise-induced

bronchoconstriction in children with asthma. Journal of Allergy and Clinical Immunology. 2007 Epub ahead of print.

- Stojkovic-Andjelkovi 2001 {published data only} . Stojkovic-Andjelkovic AK, Pajovic DM, Protrka OJ, Ugrinovic BS, Obradovic SM, Pavicevic MD. Effect of combination fluticasone propionate and salmeterol diskhaler in treatment of moderate to severe asthma: comparison of initial high dose, constant medium dose and placebo. European Respiratory Journal. 2001; Vol. 18(issue Suppl 33):123s.
- Stoloff 2002 {published data only} . Stoloff S, Poinsett-Holmes K, Dorinsky PM. Combination therapy with inhaled long-acting beta(2)-agonists and inhaled corticosteroids: a paradigm shift in asthma management. Pharmacotherapy. 2002; 22(2):212–6. [PubMed: 11837559]
- Tan 1997 {published data only} . Tan S, Hall IP, Dewar J, Dow E, Lipworth B. Association between beta 2-adrenoceptor polymorphism and susceptibility to bronchodilator desensitisation in moderately severe stable asthmatics. Lancet. 1997; 350(9083):995–9. [PubMed: 9329515]
- Tattersfield 1999 {published data only} . Tattersfield AE, Postma DS, Barnes PJ, Svensson K, Bauer CA, O'Byrne PM, et al. Exacerbations of asthma: a descriptive study of 425 severe exacerbations. The FACET International Study Group. American Journal of Respiratory & Critical Care Medicine. 1999; 160(2):594–9. [PubMed: 10430734]
- Tattersfield 2001 {published data only} . Tattersfield AE, Lofdahl CG, Postma DS, Eivindson A, Schreurs AG, Rasidakis A, et al. Comparions of formoterol and terbutaline for as-needed treatment of asthma: a randomised trial. Lancet. 2001; 357(9252):257–61. [PubMed: 11214127]
- Tolley 2002 {published data only} . Tolley K, Martin A, Rice L, McCarthy TP. Salmeterol/ fluticasone propionate combination (SFC) demonstrates improved health outcomes and good cost effectiveness compared with beclometasone dipropionate. American Journal of Respiratory & Critical Care Medicine. 2002; 165(Suppl 8):A112.
- Tonelli 2001 {published data only} . Tonelli M, Giannini D, Di Franco A, Carnevali S, Bartoli ML, Cianchetti S, et al. Symptoms, induced sputum eosinophil percentages and treatment with salmeterol or fluticasone in mild asthmatics. European Respiratory Journal. 2001; (issue Suppl 33):336s.
- Trautmann 2001 {published data only} . Trautmann M. Treatment with salmeterol/fluticasone propionate (50/250g) inhaler improves lung function, asthma symptoms and quality of life in a large group of patients with mild to moderate asthma. American Journal of Respiratory & Critical Care Medicine. 2001; Vol. 163(issue 5):A864.
- Turner 1998 {published data only} . Turner MO, Johnston PR, Pizzichini E, Pizzichini MM, Hussack PA, Hargreave FE. Anti-inflammatory effects of salmeterol compared with beclomethasone in eosinophilic mild exacerbations of asthma: a randomized, placebo controlled trial. Canadian Respiratory Journal. 1998; 5(4):261–8. [PubMed: 9753527]
- Ullman 1990 {published data only} . Ullman A, Hedner J, Svedmyr N. Inhaled salmeterol and salbutamol in asthmatic patients. An evaluation of asthma symptoms and the possible development of tachyphylaxis. American Review of Respiratory Disease. 1990; 142(3):571–5. [PubMed: 1975162]
- Van den Berg 2000 {published data only} . Van den Berg NJ, Ossip MS, Hederos CA, Anttila H, Ribeiro BL, Davies PI. Salmeterol/fluticasone propionate (50/100 ug) in combination in Diskus inhaler (Seretide) is effective and safe in children with asthma. Pediatric Pulmonology. 2000; 30:97–105. [PubMed: 10922131]
- van der Woude 2001 {published data only} . van der Woude HJ, Winter TH, Boorsma M, Bergqvist PBF, Aalbers R. More rapid relief of methacholine-induced bronchoconstriction with budesonide/formoterol than with salmeterol/fluticasone. European Respiratory Journal. 2001; Vol. 18(issue Suppl 33):53s.
- Van der Woude 2004 {published data only} . Van Der Woude HJ, Boorsma M, Bergqvist PBF, Winter TH, Aalbers RH. Budesonide/formoterol in a single inhaler rapidly relieves methacholine-induced moderate-to-severe bronchoconstriction. Pulmonary Pharmacology & Therapeutics. 2004; 17(2):89–95. [PubMed: 15123230]
- Van Der Woude 2004 {published data only} . Van der Woude HJ, Boorsma M, Bergqvist PB, Winter TH, Aalbers R. Budesonide/formoterol in a single inhaler rapidly relieves methacholine-

induced moderate-to-severe bronchoconstriction. Pulmonary Pharmacology & Therapeutics. 2004; 17(2):89–95. [PubMed: 15123230]

- Van Noord 1999 {published data only} . Schreurs AJ, van Noord JA, Mulder PG. Fluticasone propionate (FP) and salmeterol xinafoate (SLM) in patients with mild to moderate asthma. European Respiratory Journal. 1998; Vol. 12(issue Suppl 29):19s, F159.Van Noord JA, Schreurs AJM, Mol SJM, Mulder PGH. Addition of salmeterol versus doubling the dose of fluticasone propionate in patients with mild to moderate asthma. Thorax. 1999; 54:207–12. [PubMed: 10325895]
- van Noord 2001 {published data only} . SFCB3023. A multicentre, randomised, double-blind, double-dummy, parallel-group, three-month comparison of the salmeterol/fluticasone propionate combination product (2×25/250mcg strength) bd via the pressurised metered dose inhaler with salmeterol/fluticasone propionate combination product (1×50/500mcg strength) bd via the Diskus/Accuhaler[™] inhaler and with fluticasone propionate (2x 250mcg strength) alone bd via the pressurised metered dose inhaler in adolescents and adults with reversible airways obstruction. 2004. http://www.ctr.gsk.co.ukvan Noord JA, Lill H, Carrillo Diaz T, Greefhorst AP, Davies P. Clinical equivalence of a salmeterol/fluticasone propionate combination product delivered via a chlorofluorocarbon-free metered-dose inhaler with the Diskus in patients with moderate to severe asthma. Clinical Drug Investigation. 2001; 21(4):243–55.*van Noord JA, Lill H, Carrillo T, Davies P. Clinical equivalence of salmeterol/fluticasone propionate combination 50/500 bid delivered via metered dose inhaler (MDI) or diskus[™] in patients with reversible airways obstruction. American Journal of Respiratory & Critical Care Medicine. 2000; Vol. 161(issue Suppl 3):A197.
- Van Schayck 2002 {published data only} . van Schayck CP, Cloosterman SG, Bijl-Hofland ID, van den Hoogen H, Folgering HT, van Weel C. Is the increase in bronchial responsiveness or FEV1 shortly after cessation of beta2-agonists reflecting a real deterioration of the disease in allergic asthmatic patients? A comparison between short-acting and long-acting beta2-agonists. Respiratory Medicine. 2002; 96(3):155–62. [PubMed: 11908511]
- Vastagh 2003 {published data only} . Vastagh E, Kuna P, Calistru P, Bogdan MA. Efficacy and safety of inhaled budesonide delivered once or twice daily via HFA-134a in mild to moderate persistent asthma in adult patients. Comparison with budesonide CFC. Respiratory Medicine. 2003; 97(Suppl D):S20–S28. [PubMed: 14753248]
- Verberne 1997 {published data only} . Verberne AA, Frost C, Roorda RJ, van der Laag H, Kerrebijn KF. One year treatment with salmeterol compared with beclomethasone in children with asthma. American Journal of Respiratory & Critical Care Medicine. 1997; 156:688–95. [PubMed: 9309980]
- Vermetten 1999 {published data only} . Vermetten AM, Boermans JM, Luiten WDVF, Mulder PGH, Vermue NA. Comparison of salmeterol with beclomethasone in adult patients with mild persistent asthma who are already on low-dose inhaled steroids. Journal of Asthma. 1999; 36(1): 97–106. [PubMed: 10077139]
- Vestbo 2000 {published data only} . Vestbo J, Sorensen T, Lange P, Brix A, Torre P, Viskum K. Long-term effect of inhaled budesonide in patients with mild to moderate chronic obstructive lung disease. Ugeskr-Laeger. 2000; 162(4):493–7. [PubMed: 10697447]
- Vickers 2000 {published data only} . Vickers, M. Assessment of long-term efficacy of early introduction of inhaled steroids in asthma. National Health Technology Assessment (NCCHTA);
- Vilsvik 2001 {published data only} . Vilsvik J, Ankerst J, Palmqvist M, Persson G, Schaanning J, Schwabe G, et al. Protection against cold air and exercise-induced bronchoconstriction while on regular treatment with Oxis. Respiratory Medicine. 2001; 95(6):484–90. [PubMed: 11421506]
- Virchow 2002 {published data only} . Virchow JC. Salmeterol powder provides significantly better benefit than montelukast in asthmatic patients receiving concomitant inhaled corticosteroid therapy. Chest. 2002; 121(6):2083–4. [PubMed: 12065391]
- Von Berg 1989 {published data only} . von-Berg A, Berdel D. Formoterol and salbutamol metered aerosols: comparison of a new and an established beta-2-agonist for their bronchodilating efficacy in the treatment of childhood bronchial asthma. Pediatric Pulmonology. 1989; 7(2):89– 93. [PubMed: 2797925]

- Von Berg 2003 {published data only} . Von Berg A, Papageorgiou Saxoni F, Wille S, Carrillo T, Kattamis C, Helms PJ. Efficacy and tolerability of formoterol Turbuhaler in children. International Journal of Clinical Practice. 2003; 57(10):852–6. [PubMed: 14712884]
- Wallaert 1999 {published data only} . Wallaert B, Brun P, Ostinelli J, Murciano D, Champel F, Blaive B, et al. A comparison of two long-acting beta-agonists, oral bambuterol and inhaled salmeterol, in the treatment of moderate to severe asthmatic patients with nocturnal symptoms. The French Bambuterol Study Group. Respiratory Medicine. 1999; 93(1):33–8.
- Wallin 1990 {published data only} . Wallin A, Melander B, Rosenhall L, Sandstrom T, Wahlander L. Formoterol, a new long acting beta 2 agonist for inhalation twice daily, compared with salbutamol in the treatment of asthma. Thorax. 1990; 45(4):259–61. [PubMed: 1972599]
- Wallin 1998 {published data only} . Wallin A, Sandstrom T, Soderberg M, Howarth P, Djukanovic R, Wilson S, et al. Effects of formoterol, budesonide and placebo treatment on asthmatic airway inflammation. Annals of Allergy, Asthma, and Immunology. 1998; Vol. 80:88.
- Wallin 1999 {published data only} . Wallin A, Sandstrom T, Soderberg M, Howarth P, Lundback B, Della-Cioppa G, et al. The effects of regular inhaled formoterol, budesonide, and placebo on mucosal inflammation and clinical indices in mild asthma. American Journal of Respiratory & Critical Care Medicine. 1999; 159(1):79–86. [PubMed: 9872822]
- Weinberger 2004 {published data only} . Weinberger M. Innovative therapies for asthma: Anti-IgE -the future? Paediatric Respiratory Reviews. 2004; 5(Suppl A):S115–18. [PubMed: 14980255]
- Weinstein 1998 {published data only} . Weinstein SF, Pearlman DS, Bronsky EA, Byrne A, Arledge T, Liddle R, et al. Efficacy of salmeterol xinafoate powder in children with chronic persistent asthma. Annals of Allergy, Asthma and Immunology. 1998; 81:51–8.
- Weinstein 2001 {published data only} . Weinstein SF, Pearlman DS, Condemi JJ, Herrle MR, Scott CA, Payne JE, et al. Superior efficacy of the fluticasone propionate/salmeterol (88/42mcg) HFA-MDI combination product versus the individual components in asthmatics previously treated with either short- or long-acting beta2-agonists or inhaled corticosteroids. Journal of Allergy and Clinical Immunology. 2001; 107(2):S102.
- Wempe 1992 {published data only} . Wempe JB, Tammeling EP, Koeter GH, Hakansson L, Venge P, Postma DS. Blood eosinophil numbers and activity during 24 hours: effects of treatment with budesonide and bambuterol. Journal of Allergy and Clinical Immunology. 1992; 90(5):757–65. [PubMed: 1430701]
- White 2001 {published data only} . White M, Scott C, Herrle MR, Pearlman D, Payne E, House K, et al. Salmeterol/fluticasone propionate (42/88mcg) HFA-MDI improves asthma control in asthmatics previously treated with short- or long-acting beta2-agonists or inhaled corticosteroids. Annals of Allergy, Asthma & Immunology. 2001; Vol. 86:81.
- Wilcke 1998 {published data only} . Wilcke JT, Iversen ET, Kok-Jensen A. Effect of salmeterol is independent of previously inhaled salbutamol: a clinical controlled study. Lung. 1998; 176(2): 133–9. [PubMed: 9500298]
- Wilding 1997 {published data only} . Wilding P, Clark M, Thompson Coon J, Lewis S, Rushton L, Bennett J, et al. Effect of long term treatment with salmeterol on asthma control: a double-blind, randomised crossover study. BMJ. 1997; 314:1441–6. [PubMed: 9167559]
- Wilson 1999 {published data only} . Wilson AM, Dempsey OJ, Sims EJ, Lipworth BJ. A comparison of salmeterol and montelukast as second-line therapy in asthmatic patients not controlled on inhaled corticosteroids. Thorax. 1999; Vol. 54(issue Suppl 3):A66, P189.
- Wilson 2000 {published data only} . Wilson SJ, Ward JA, Djukanovic R, Wallin A, Sue-Chu M, Sandstrom T, et al. Effects of high and low dose inhaled fluticasone propionate (FP) compared to low dose FP combined with salmeterol (SAL) on airway inflammation in asthma. American Journal of Respiratory & Critical Care Medicine. 2000; Vol. 161(issue Suppl 3):A196.
- Wilson 2001a {published data only} . Wilson AM, Dempsey OJ, Sims EJ, Lipworth BJ. Evaluation of salmeterol or montelukast as second-line therapy for asthma not controlled with inhaled corticosteroids. Chest. 2001; 119(4):1021–6. [PubMed: 11296164]
- Wilson 2001b {published data only} . Wilson SJ, Wallin A, Della-Cioppa G, Sandstrom T, Holgate ST. Effects of budesonide and formoterol on NF-kappaB, adhesion molecules, and

cytokines in asthma. American Journal of Respiratory & Critical Care Medicine. 2001; 164(6): 1047–52. [PubMed: 11587995]

- Wong 1992 {published data only} . Wong BJ, Dolovich J, Ramsdale EH, O'Byrne P, Gontovnick L, Denburg JA, et al. Formoterol compared with beclomethasone and placebo on allergen-induced asthmatic responses. American Review of Respiratory Disease. 1992; 146(5 pt 1):1156–60. [PubMed: 1443864]
- Woolcock 1995 {published data only} . Woolcock A. Continuing patient care with metered-dose inhalers. Journal of Aerosol Medicine: Deposition, Clearance, and Effects in the Lung. 1995; 8(Suppl 2):s5–s10.
- Woolcock 1996 {published data only} . Woolcock A, Lunback B, Ringdal N, Jacques LA.
 Comparison of addition of salmeterol to inhaled steroids with doubling the dose of inhaled steroids. American Journal of Respiratory & Critical Care Medicine. 1996; 153:1481–8.
 [PubMed: 8630590]
- Yates 1995 {published data only} . Yates DH, Sussman HS, Shaw MJ, Barnes PJ, Chung KF. Regular formoterol treatment in mild asthma: effect on bronchial responsiveness during and after treatment. American Journal of Respiratory & Critical Care Medicine. 1995; 152(41):1170–4. [PubMed: 7551366]
- Yates 1996 {published data only} . Yates DH, Kharitonov SA, Barnes PJ. An inhaled glucocorticoid does not prevent tolerance to the bronchoprotective effect of a long-acting inhaled beta 2-agonist. American Journal of Respiratory & Critical Care Medicine. 1996; 154(6 pt 1): 1603–7. [PubMed: 8970342]
- Youngchaiyud 1995 {published data only} . Youngchaiyud P, Permpikul C, Suthamsmai T, Wong E. A double-blind comparison of inhaled budesonide, long-acting theophylline, and their combination in treatment of nocturnal asthma. Allergy. 1995; 50:28–33. [PubMed: 7741186]
- Yurdakul 2002 {published data only} . Yurdakul AS, Calisir HC, Tunctan B, Ogretensoy M. Comparison of second controller medications in addition to inhaled corticosteroid in patients with moderate asthma. Respiratory Medicine. 2002; 96(5):322–9. [PubMed: 12113382]
- Zarkovic 1998 {published data only} . Zarkovic J, Gotz MH, Holgate ST, Taak NK. Effect of long-term regular salmeterol treatment in children with moderate asthma. Clinical Drug Investigation. 1998; 15(3):169–75.

References to studies awaiting assessment

- Bateman 2001 {published data only} . Bateman ED, Beasley R, Silins V, Bogolubov M. Comparison of salmeterol/fluticasone propionate combination 50/100 bid delivered via metered dose inhaler or diskus in patients with reversible airways obstruction. American Journal of Respiratory & Critical Care Medicine. 2000; 161(Suppl 3):A197.Bateman ED, Silins V, Bogolubov M. Clinical equivalence of salmeterol/fluticasone propionate in combination (50/100 mcg twice daily) when administered via a chlorofluorocarbon-free metered dose inhaler or dry powder inhaler to patients with mild-to-moderate asthma. Respiratory Medicine. 2001; 95(2): 136–46. [PubMed: 11217910] * [accessed 12 June 2008] SFCB3022. A multicentre, randomised, double-blind, double-dummy, parallel-group, three-month comparison of the salmeterol/ fluticasone propionate combination product (2×25/50mcg strength) bd via the pressurised metered dose inhaler with salmeterol/fluticasone propionate combination product (1×50/100mcg strength) bd via the Diskus/AccuhalerTM inhaler and with fluticasone propionate (2x 50mcg strength) alone bd via the pressurised metered dose inhaler in adolescents and adults with reversible airways obstruction. 2004. www.ctr.gsk.co.uk
- Yancey 1997 {published data only} . Yancey SW, Rickard KA, Emmett A, Cox F. The response to salmeterol or theophylline in asthmatics either receiving or not-receiving inhaled corticosteroids. Annals of Allergy, Asthma and Immunology. 1997; Vol. 78:110.

References to ongoing studies

Aziz {published data only} . Aziz, I. Clinical Pharmacology. Ninewells Hospital and Medical School, University of Dundee; Dundee, DD1 9SY, Scotland, UK: Comparison of anti

inflammatory effect of once daily inhaled formoterol and once daily inhaled budesonide on inflammatory markers in asthmatic patients.

- Barnes a {published data only} . Barnes, NC. Respiratory Medicine. London Chest Hospital, Bonner Road; London, E2 9JX, United Kingdom: A randomized parallel 3 arm study to assess asthma control, lung function, costs and quality of life in patients with asthma treated with formoterol twice daily and either budesonide once or twice daily from a novel multidisc dry powder inhaler.
- Barnes b {published data only} . Barnes, PJ. Royal Brompton and Harefield NHS Trust; Effect of low dose formoterol and budesonide on exhaled breath in asthma.
- Bush {published data only} . Bush, A. Efficacy and safety of budesonide/formoterol Turbuhaler , compared to budesonide turbuhaler metered dose, in steroid using asthmatic adolescent patients, double blind, double dummy parallel group, Phase III, multicentre study. Department of Paediatrics, Imperial College School of Medicine, Brompton Campus, Dovehouse Street; Royal Brompton and Harefield NHS Trust; London, SW3 6LY, United Kingdom:
- Currie {published data only} . Currie, GP. Are there additional anti-inflammatory effects of leukotriene receptor antagonists in persistent asthmatics receiving inhaled steroid alone and combined inhaled steroid/long acting B2-agonists?. Academic Publications;
- Goves {published data only} . Goves, JR. Eformoterol in the management of mild asthma eformoterol Turbohaler R with budesonide Turbohaler R. Department of Paediatrics, Level 4 John Radcliffe Hospital; Headley Way, Headington, Oxford, OX3 9DU:
- Hill {published data only} . Hill, J. The ASSURE Study the effectiveness and safety of an individualised Symbicort Turbohaler maintenance dosing regimen (Symbicort Asthma Control Plan) versus Symbicort Turbohaler given as standard regular twice daily therapy. Northern General Hospital NHS Trust;
- Kharitonov {published data only} . Kharitonov, SA. Effect of inhaled corticosteroids (budesonide 100 micrograms/400 micrograms vs placebo) and formoterol on localisation of glucocorticoid receptor and exhaled markers in asthma. Royal Brompton and Harefield NHS Trust;
- Lipworth 2001 {unpublished data only} . Lipworth, BJ. Relative lung bioavailability with fluticasone via dry powder inhaler versus: (a) fluticasone/salmeterol combination vis dry powder inhaler; (b) fluticasone/salmeterol combination via HFA-pMDI plus spacer, in patients with moderate persistent asthma. Academic Publications; 2001.
- Millar {published data only} . Millar, AB. A randomised double-blind multi-centre study to evaluate the effect of adding alternative agents to inhaled steroids in adult asthmatics. Lung Research Unit, Southmead Hospital, Southmead Road, Westbury-on-Trym; Bristol, BS10 5NB, UK:
- Ruggins {published data only} . Ruggins, N. Pragmatic trial of add-on therapy in paediatric asthma. Southern Derbyshire Acute Hospitals NHS Trust, Consultant Paediatrician, Children's Hospital, Uttoxeter Road; Derby, DE22 3NE, England: 2003.
- Thomson {published data only} . Thomson, NC. Respiratory Medicine. Gartnavel General Hospital, Great Western Road; Glasgow, G12 0YN, Scotland: Bundesonide/formoterol fixed combination in adults with asthma.
- Young {published data only} . Young, KM. Budesonide/formoterol fixed combination in adults with asthma. Cambridge Consortium -Addenbrookes;

Additional references

- Adams 2008 . Adams NP, Bestall JC, Lasserson TJ, Jones P, Cates CJ. Fluticasone versus placebo for chronic asthma in adults and children. Cochrane Database of Systematic Reviews. 2008; Issue 4 [DOI: 10.1002/14651858.CD003135.pub4].
- Bateman 2008 Bateman E, Nelson H, Bousquet J, Kral K, Sutton L, Ortega H, et al. Meta-analysis: effects of adding salmeterol to inhaled corticosteroids on serious asthma-related events. 2008; Vol. 149(issue 1) www.annals.org. Epub.
- Bisgaard 2003 . Bisgaard H. Effect of long acting beta 2 agonists on exacerbation rates of asthma in children. Pediatric Pulmonology. 2003; 36:391–8. [PubMed: 14520721]

- BTS 2007 . British Thoracic Society. British Guideline on the Management of Asthma. 2007. www.brit-thoracic.org.uk
- Canadian Paediatic Asthma Guideline 2005 . Becker A, Bérubé D, Chad Z, Dolovich M, Ducharme F, D'Urzo T, et al. Canadian Pediatric Asthma Consensus Guidelines, 2003 (updated to December 2004). Canadian Medical Association Journal. 2005; Vol. 173(issue Suppl 6)
- Cates 2002 . Cates, CJ. BioMed Central. Vol. 2. BMC Medical Research Methodology; 2002. Simpson's paradox and calculation of number needed to treat from meta-analysis; p. 1
- 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].
- Cates 2009a . Cates CJ, Lasserson T, Cates MJ. Regular treatment with formoterol and inhaled steroids for chronic asthma: serious adverse events. Cochrane Database of Systematic Reviews. 2009; (Issue 2) [DOI: 10.1002/14651858.CD006924.pub2].
- Cates 2009b . Cates CJ, Cates MJ, Lasserson T. Regular treatment with salmeterol and inhaled steroids for chronic asthma: serious adverse events. Cochrane Database of Systematic Reviews. 2009; (Issue 3) [DOI: 10.1002/14651858.CD006922.pub2].
- Cochrane Handbook . Higgins, JPT.; Green, S., editors. Cochrane Handbook for Systematic Reviews of Interventions. Version 5.0.0. The Cochrane Collaboration; www.cochrane-handbook.org [updated February 2008]
- D'Alonzo 1997 D'Alonzo GE, Tolep KA. Salmeterol in the treatment of chronic asthma. American Family Physician. 1997; 56(2):558–62. [PubMed: 9262535]
- Deeks 2001 . Deeks, JJ.; Altman, DG.; Bradburn, MJ. Statistical methods for examining heterogeneity and combining results from several studies in meta-analysis. In: Egger, M.; Smith, GD.; Altman, DG., editors. Systematic reviews in health care: meta-analysis in context. BMJ Publishing; London: 2001. p. 285-312.
- DerSimonian 1986 . DerSimonian R, Laird N. Meta-analysis in clinical trials. Controlled Clinical Trials. 1986; 7:177–88. [PubMed: 3802833]
- Ducharme 2006 . Ducharme FM, Lasserson TJ, Cates CJ. Long-acting beta2-agonists versus antileukotrienes as add-on therapy to inhaled corticosteroids for chronic asthma. Cochrane Database of Systematic Reviews. 2006; (Issue 4) [DOI: 10.1002/14651858.CD003137.pub3].
- Ducharme 2010 . Ducharme FM, Ni Chroinin M, Greenstone I, Lasserson TJ. 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. 2010; (Issue 1) [DOI: 10.1002/14651858.CD005533.pub2].
- Egger 1997 . Egger M, Smith GD, Schneider M, Minder C. Bias in meta-analysis detected by a simple, graphical test. BMJ. 1997; 315:629–34. [PubMed: 9310563]
- Ernst 2006 . Ernst P, McIvor A, Ducharme FM, Boulet L-P, FitzGerald M, Chapman K, et al. Longacting inhaled beta-agonist bronchodilators are safe and effective in conjunction with inhaled corticosteroids. Annals of Internal Medicine. 2006; 145(9):693–4.
- 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) [DOI: 10.1002/14651858.CD005076.pub2].
- GINA 2007 . Global Initiative for Asthma. Global Strategy for Asthma Management and Prevention (NIH publication). 2007. http://www.ginasthma.com
- Gleser 1996 . Gleser LJ, Olkin I. Models for estimating the number of unpublished studies. Statistics in Medicine. 1996; 15:2493–507. [PubMed: 8961459]
- Greenland 1985 . Greenland S, Robins JM. Estimation of a common effect parameter from sparse follow-up data. Biometrics. 1985; 41:55–68. [PubMed: 4005387]
- Higgins 2003 . Higgins JPT. Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. BMJ. 2003; 327(557):560.

- Manning 2008 . Manning P, Gibson PG, Lasserson TJ. Ciclesonide versus placebo for chronic asthma in adults and children. Cochrane Database of Systematic Reviews. 2008; (Issue 2) [DOI: 10.1002/14651858.CD006217.pub2].
- NAC 2006 . National Asthma Council. Asthma Management Handbook. 5th Edition. National Asthma Campaign; Melbourne: 2006. Australia. http://www.nationalasthma.org.au/publications/amh/amhcont.htm
- NAEPP 2007 . National Asthma Education and Prevention Program. NIH Publication. National Heart, Lung and Blood Institute; National Heart, Lung and Blood Institute; Bethesda, MD: Bethesda, MD: 2007. Expert Panel Report 3 (EPR 3) Guidelines for the Diagnosis and Management of Asthma. http://www.nhlbi.nih.gov/guidelines/asthma/index.htm
- Nelson 1995 . Nelson HS. Beta-adrenergic bronchodilators. New England Journal of Medicine. 1995; 333(8):499–506. [PubMed: 7623883]
- Nelson 2003 . Nelson HS, Chapman KR, Pyke SD, Johnson M, Pritchard JN. Enhanced synergy between fluticasone propionate and salmeterol inhaled from a single inhaler versus separate inhalers. Journal of Allergy and Clinical Immunology. 2003; 112(1):29–36. [PubMed: 12847476]
- Ni Chroinin 2009a . Ni Chroinin M, Greenstone I, Lasserson TJ, Ducharme FM. Addition of inhaled long acting beta2-agonists to inhaled steroids as first line therapy for persistent asthma in steroid naive adults. Cochrane Database of Systematic Reviews. 2009; (Issue 4) [Art. No.: CD005307. DOI: 10.1002/14651858.CD005307.pub2].
- Ni Chroinin 2009b . Ni Chroinin M, Lasserson TJ, Greenstone I, Ducharme FM. Addition of longacting beta-agonists to inhaled corticosteroids for chronic asthma in children. Cochrane Database of Systematic Reviews. 2009; (Issue 3) [DOI: 10.1002/14651858.CD007949].
- RevMan 2008 . The Nordic Cochrane Centre. The Cochrane Collaboration. Review Manager (RevMan). 5.0. The Nordic Cochrane Centre, The Cochrane Collaboration; Copenhagen: 2008.
- Salpeter 2006 . Salpeter SR, Buckley NS, Ormiston TM, Salpeter EE. Meta-analysis: effect of longacting ß-agonists on severe asthma exacerbations and asthma-related deaths. Annals of Internal Medicine. 2006; 144(12):904–12. [PubMed: 16754916]
- SMART . FDA. [accessed 18 May 2009] Smart study site. www.fda.gov/bbs/topics/ANSWERS/ 2003/ANS01192.html
- Storms 2003 . Storms W. Clinical trials: are these your patients? Journal of Allergy & Clinical Immunology. 2003; 5(Suppl):S107–S111. [PubMed: 14586395]
- Walters 2007 . Walters EH, Gibson PG, Lasserson TJ, Walters JAE. 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) [DOI: 10.1002/14651858.CD001385.pub2].
- Warner 1998 . Warner JO, Naspitz CK. Third International Pediatric Consensus statement on the management of childhood asthma. International Pediatric Asthma Consensus Group. Pediatric Pulmonology. 1998; 25(1):1–17. [PubMed: 9475326]

References to other published versions of this review

- Ni Chroinin 2005 . Ni Chroinin M, Greenstone IIG, Ducharme F. Long-acting beta2-agonists versus placebo in addition to inhaled corticosteroids for chronic asthma in adults and children. Cochrane Database of Systematic Reviews. 2005; (Issue 4) [DOI: 10.1002/14651858.CD005535].
- * Indicates the major publication for the study

PLAIN LANGUAGE SUMMARY

Long-acting beta2-agonists versus placebo in addition to inhaled corticosteroids in children and adults with chronic asthma

The use of long-acting β_2 -agonists (LABAs) as 'add-on' medication to inhaled corticosteroids is recommended for poorly-controlled asthma where asthma exacerbations may require additional treatment with oral steroids. The purpose of this review was to assess the efficacy and safety of adding long-acting β_2 -agonists to inhaled corticosteroids in asthmatic children and adults. Based on the identified randomised trials, in people who remain symptomatic while on inhaled corticosteroids, the addition of long-acting β_2 -agonists improves lung function and reduces the risk of asthma exacerbations compared to ongoing treatment with a similar dose of inhaled corticosteroids alone in adults. We could not find evidence of increased serious adverse events or withdrawal rates due to adverse health events with the combination of long-acting β_2 -agonists at usual doses and inhaled corticosteroids in adults. This provides some indirect evidence, but not total reassurance, regarding the short- and medium-term safety of this treatment strategy. There have not been enough children studied to assess the risks and benefits of adding LABAs in this age group.

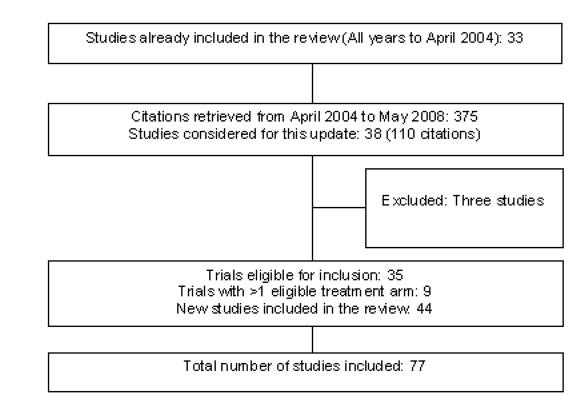


Figure 1.

Flow diagram for literature search results April 2004 to May 2008.

	Adequate sequence generation?	Allocation concealment?	 3 4 5 6 6 6 6 6 7 8 8 10 10	Incomplete outcome data addressed?	
Akpinarli 1999		?	٠	7	٠
Aubier 1999a				2	2
Authier 1000h				2	2
Auster 19390	-	-	-		
Balley 2008	•	•	•	ø	•
Boyd 1995	۰	۰	•	?	۰
Buhl 2003a	7	۲	٠	7	٠
Buhl 2003b	?	•	•	?	۰
D1Urzo 2001	?	•	2	8	•
D5896C0001a	?	2		2	2
D5896C0001b	7	2		7	2
Fitmarals 1999	2	2		7 7 7 0 7	
Outstand 1004	-	-	-	-	-
Gardiner 1994			-		
OOAL	•	•	•		•
Green 2005	۲	۲	٠	٠	۲
Haughton 2007	?	2	۲	7	7
Hultquist 2000	?	•	•	7	2
Ind 2003				2	
Jerkins 2006a				2	2
162 2033 Jarrines 2006. Karanz 2007 Karanz 2007 Karan	-	-	é		
Jennins 20060	-	-	-	-	-
Kavaru 2000	•	•	•	•	•
Kemp 1998	٠	٠	٠	?	۲
Koopmans 2006	•	•	•	1	7
Kuna 2005	?	2	•	?	?
Langton Hewer 1995	?	2		2	
Lehlanc 1996					2
111000	-		-	-	
LI 1995	-				-
Malone 2005	•	•	•	•	•
Meijer 1995	?	?	•	?	?
Molimard 2001	?	۲	٠	7	?
Morice 2008a	•	?	•	?	?
Morice 2008b	•	2	۲	1	2
Nethen 2006				2	
Noonan 2006a		2		2	
Norman 2000s	-		-		-
Noonan 20065	•				
Norhaya 1999	8	2	•	•	•
O'Byrne 2001a	•	•	٠	0	•
O'Eyrne 2001b	•	٠	۲	?	۲
Pauwels 1997a	•	2	٠	7	۲
Pauwels 1997b	•	2	•	?	
Pohunek 2006a	?	2		2	2
Potwoek 2006b	2	2		2	2
0444 2002			-		
Price 2002	-		•		-
Reddel 2007					
Russell 1995	٠	•	٠	•	٠
SAM40008	•	۲	۲	?	۲
SAM40012	•	•	•	?	•
SAS40024	•	٠	۲	•	۰
SAS40036				2	
SAS40037				2	
20.027.02444	-		-		-
30 037 03448	-			-	-
BU 037 0344b	0	1		1	
SD 039 0349	0	3	•	3	•
SD 039 0714	?	?	٠	?	?
SD 039 0718	?	2	•	7	?
SD 039 0719	?	2	•	?	?
SD 039 0725a	?	?	•	?	?
SD 039 0725b	2	2		2	2
SD 039 0776a				2	2
6D 029 07365	2			2	2
80 038 07200	-		-		
80 039 0728			•	·	•
SFA100314	۲	٠	۲	2	٠
SFA100316	٠	۲	۲	3	۰
SFCF4026	•	•	•	8	•
Shapiro 2000	•			2	•
Simons 1997		2		2	
SMS40012				7 9 7 7 7	2
Otelmach 2007	-	1	-		-
ownmeen 2007	-	-		-	-
Tal 2002	•		•		
Teper 2005	1	2	2	1	1
van der Molen 1997	•	8	•	•	•
Verberne 1998	•	•	•	?	•
Wallin 2003	•	•	•	• 7 7	•
Weiler 2005			۲		
Zetterstrom 2001=				2	
Zeterstrom 2001b				2	
Temporar 000	÷			-	-
Jimmenhan 2004a	-	1		-	-
⊿mmerman 2004b	1	1	۲	1	٠

Figure 2.

	LABA +	ICS	ICS ald	one		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% Cl	M-H, Fixed, 95% Cl
1.1.1 Mean baseline FE	V1 >/= 80	% of pr	edicted				
Langton Hewer 1995	3	11	3	12	0.6%	1.09 [0.28, 4.32]	
Li 1999	2	13	1	16	0.2%	2.46 [0.25, 24.21]	
Malone 2005	2	101	3	102	0.6%	0.67 [0.11, 3.94]	
O'Byrne 2001a	58	323	81	322	16.6%	0.71 [0.53, 0.96]	-
O'Byrne 2001b	39	315	61	312	12.6%	0.63 [0.44, 0.92]	
Simons 1997	0	16	1	16	0.3%	0.33 [0.01, 7.62]	
Verberne 1998	10	60	10	57	2.1%	0.95 [0.43, 2.11]	
Wallin 2003	1	18	5	19	1.0%	0.21 [0.03, 1.64]	
Subtotal (95% CI)		857		856	34.0%	0.70 [0.56, 0.86]	◆
Total events	115		165				
Heterogeneity: Chi ² = 3	.96, df = 7	(P = 0.1)	78); I ^z = 0	%			
Test for overall effect: Z	= 3.30 (P	= 0.001	0)				
1.1.2 Mean baseline FE	V1 61% to	o 79% o	f predict	ed			
Akpinarli 1999	0	16	0	16		Not estimable	
Aubier 1999a	5	171	7	83	1.9%	0.35 [0.11, 1.06]	
Aubier 1999b	17	167	7	82	1.9%	1.19 [0.52, 2.76]	
Boyd 1995	19	55	15	64	2.8%	1.47 [0.83, 2.61]	+
Fitzgerald 1999	3	89	6	91	1.2%	0.51 [0.13, 1.98]	
Kavaru 2000	0	92	0	90		Not estimable	
Kemp 1998	53	252	59	254	12.0%	0.91 [0.65, 1.26]	-
Nathan 2006	1	94	3	91	0.6%	0.32 [0.03, 3.05]	
Noonan 2006a	5	124	2	55	0.6%	1.11 [0.22, 5.54]	
Noonan 2006b	4	115	2	54	0.6%	0.94 [0.18, 4.97]	
Norhaya 1999	1	30	3	30	0.6%	0.33 [0.04, 3.03]	
Pauwels 1997a	62	210	82	213	16.7%	0.77 [0.59, 1.00]	
Pauwels 1997b	41	215	60	214	12.3%	0.68 [0.48, 0.96]	
Russell 1995	16	99	18	99	3.7%	0.89 [0.48, 1.64]	
SAS40036	2	172	7	159	1.5%	0.26 [0.06, 1.25]	
Shapiro 2000	1	84	2	84	0.4%	0.50 [0.05, 5.41]	
van der Molen 1997	33	125	32	114	6.9%	0.94 [0.62, 1.42]	-
Weiler 2005	1	102	0	90	0.1%	2.65 [0.11, 64.26]	
Subtotal (95% CI)		2212	-	1883	63.9%	0.81 [0.70, 0.94]	•
Total events	264		305				
Heterogeneity: Chi ² = 1		15 (P =		= 0%			
Test for overall effect: Z							
			·				
1.1.3 Mean baseline FE	V1 not re	ported					
SAS40024	0	99	2	100	0.5%	0.20 [0.01, 4.15]	
SAS40037	3	161	6	161	1.2%	0.50 [0.13, 1.96]	
SFA100314	1	124	1	124	0.2%	1.00 [0.06, 15.81]	
SFA100316	2	113	1	118	0.2%	2.09 [0.19, 22.71]	
Subtotal (95% CI)	_	497		503	2.1%	0.63 [0.24, 1.65]	
Total events	6		10				
Heterogeneity: Chi ² = 1	.73, df = 3	(P = 0.	63); I ^z = 0	%			
Test for overall effect: Z							
Total (95% CI)		3566		3242	100.0%	0.77 [0.68, 0.87]	•
Total events	385		480				
Heterogeneity: Chi ² = 2	1.21, df=	27 (P =	0.78); l² =	= 0%			0.01 0.1 1 10 100
Test for overall effect: Z	= 4.30 (P	< 0.000	01)				Favours LABA + ICS Favours ICS alone
			0.001				Tavouis LADA TIGS Favouis IGS alone

Figure 3.

Forest plot of comparison: 1 Long-acting beta2 vs placebo: both groups receiving similar dose ICS, outcome: 1.1 # patients with exacerbations requiring oral steroids.

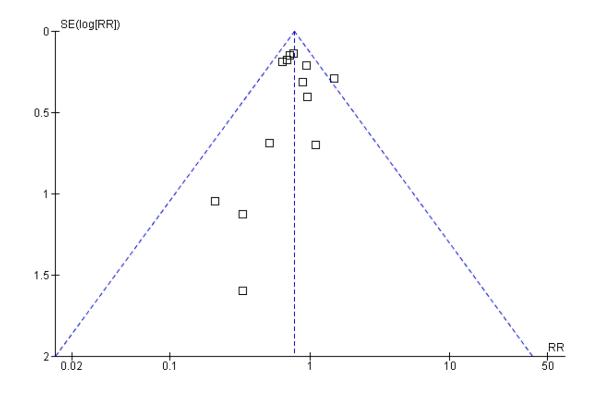


Figure 4.

Funnel plot of outcome: 2.9 Sensitivity analysis: exacerbations requiring oral steroids by data publication status (data available from published source).

Ducharme et al.

	LABA +		ICS ald			Risk Ratio	Risk Ratio
Study or Subgroup				Total	Weight	M-H, Fixed, 95% Cl	M-H, Fixed, 95% Cl
1.2.1 Mean baseline FE							
<oopmans 2006<="" td=""><td>0</td><td>27</td><td>0</td><td>27</td><td></td><td>Not estimable</td><td></td></oopmans>	0	27	0	27		Not estimable	
angton Hewer 1995	1	11	0	12	1.5%	3.25 [0.15, 72.36]	
/erberne 1998	1	60	2	56	6.7%	0.47 [0.04, 5.01]	
Subtotal (95% CI)		98		95	8.2%	0.99 [0.18, 5.39]	
Fotal events	2		2				
Heterogeneity: Chi ² = 0.		•		%			
Fest for overall effect: Z	= 0.01 (P =	= 0.99)					
1.2.2 Mean baseline FE	V1 61% to	79% o	f predict	ed			
Aubier 1999a	1	171	0	82	2.2%	1.45 [0.06, 35.16]	
Aubier 1999b	0	167	0	83		Not estimable	
Bailey 2008	2	239	3	236	9.7%	0.66 [0.11, 3.90]	
nd 2003	1	173	2	160	6.7%	0.46 [0.04, 5.05]	
Kavaru 2000	0	92	0	90		Not estimable	
<emp 1998<="" td=""><td>2</td><td>261</td><td>0</td><td>264</td><td>1.6%</td><td>5.06 [0.24, 104.83]</td><td></td></emp>	2	261	0	264	1.6%	5.06 [0.24, 104.83]	
Vathan 2006	0	94	0	91		Not estimable	
Noonan 2006a	2	124	0	109	1.7%	4.40 [0.21, 90.66]	
Noonan 2006b	0	115	0	109		Not estimable	
Pauwels 1997a	1	210	3	213	9.6%	0.34 [0.04, 3.22]	
Pauwels 1997b	2	215	5	214	16.1%	0.40 [0.08, 2.03]	
Price 2002	0	332	0	331		Not estimable	
Russell 1995	9	99	9	107	27.8%	1.08 [0.45, 2.61]	-+-
SAS40036	0	172	0	159		Not estimable	
3D 039 0714	4	136	1	134	3.2%	3.94 [0.45, 34.80]	
Shapiro 2000	0	84	1	84	4.8%	0.33 [0.01, 8.07]	
Гаl 2002	5	158	0	138	1.7%	9.62 [0.54, 172.36]	+
an der Molen 1997	0	125	1	114	5.0%	0.30 [0.01, 7.39]	
Subtotal (95% CI)		2967		2718	90.2%	1.11 [0.67, 1.84]	•
Fotal events	29		25				
Heterogeneity: Chi² = 9. Fest for overall effect: Z				0%			
restion overall ellect. Z	– 0.42 (F -	- 0.00)					
1.2.3 Mean baseline FE							
D'Urzo 2001	0	455	0	456		Not estimable	
3AM40008	1	93	0	93	1.6%	3.00 [0.12, 72.71]	
SAS40037 Subtotol (05% CI)	0	161	0	161	4 60/	Not estimable	
Subtotal (95% CI)		709	-	710	1.6%	3.00 [0.12, 72.71]	
Fotal events	1		0				
Heterogeneity: Not appl Fest for overall effect: Z		= 0,50)					
	(i						L
fotal (95% CI)		3774		3523	100.0%	1.13 [0.70, 1.82]	•
Fotal events	32		27				
	1.26 df = 1	4 (P =	0.67\:12-	- 0%			
Heterogeneity: Chi² = 1 Fest for overall effect: Z				- 0 /0			0.001 0.1 1 10 10

Figure 5.

Forest plot of comparison: 1 Long-acting beta2 versus placebo: both groups receiving similar dose ICS, outcome: 1.2 # patients with exacerbations requiring hospitalisation.

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Study or Subgroup		Total	ICS ale Events		Weight	Risk Ratio M-H, Fixed, 95% Cl	Risk Ratio M-H, Fixed, 95% Cl
1.3.1 Mean baseline FE			edicted				
Koopmans 2006	0	27	1	27	0.8%	0.33 [0.01, 7.84]	
Langton Hewer 1995	1	11	0	12	0.3%	3.25 [0.15, 72.36]	
Malone 2005	0	101	0	102		Not estimable	
Morice 2008a	2	212	2	104	1.5%	0.49 [0.07, 3.43]	
Morice 2008b	0	203	1	103	1.1%	0.17 [0.01, 4.14]	
O'Byrne 2001a	10	210	9	213	4.9%	1.13 [0.47, 2.72]	
O'Byrne 2001b	16	215	12	214	6.5%	1.33 [0.64, 2.74]	
,				322			
Pauwels 1997a	12	323	19	~~~	10.4%	0.63 [0.31, 1.28]	
Pauwels 1997b	15	315	19	312	10.4%	0.78 [0.40, 1.51]	
Pohunek 2006a	3	216	2	101	1.5%	0.70 [0.12, 4.13]	
Pohunek 2006b	5	201	1	100	0.7%	2.49 [0.29, 21.01]	
SD 039 0718	0	128	0	145		Not estimable	
SD 039 0719	2	123	1	63	0.7%	1.02 [0.09, 11.08]	
Verberne 1998	3	60	4	56	2.3%	0.70 [0.16, 2.99]	
Subtotal (95% CI)	2	2345	4	1874	40.9%	0.70 [0.10, 2.99]	
		2345		18/4	40.9%	0.88 [0.64, 1.21]	
Total events	69		71				
Heterogeneity: Chi ² = 6.	02, df = 1	1 (P = 0)).87); I ² =	0%			
Test for overall effect: Z							
1.3.2 Mean baseline FE	V1 61% t	0 79% 0	f prodict	ho			
					1 -~~	0.7410.40.4.55	
Aubier 1999a	3	167	2	82	1.5%	0.74 [0.13, 4.32]	
Aubier 1999b	8	171	3	83	2.2%	1.29 [0.35, 4.75]	
Bailey 2008	6	239	11	236	6.0%	0.54 [0.20, 1.43]	
Boyd 1995	7	55	7	64	3.5%	1.16 [0.44, 3.11]	
Buhl 2003a	2	176	1	86	0.7%	0.98 [0.09, 10.63]	
Buhl 2003b	1	176	1	86	0.7%	0.49 [0.03, 7.72]	
D5896C0001a	2	155	0	153	0.3%	4.94 [0.24, 101.97]	
Fitzgerald 1999	1	89	3	91	1.6%	0.34 [0.04, 3.22]	
Ind 2003	9	171	5	160	2.8%	1.68 [0.58, 4.92]	
Jenkins 2006a	5	226	1	57	0.9%	1.26 [0.15, 10.58]	
Jenkins 2006b	Ő	115	1	58	1.1%	0.17 [0.01, 4.10]	
Kavaru 2000	2	92	1	90	0.6%		
						1.96 [0.18, 21.20]	
Kemp 1998	1	252	0	254	0.3%	3.02 [0.12, 73.87]	
Kuna 2006	2	202	4	207	2.1%	0.51 [0.09, 2.77]	
Molimard 2001	0	130	0	129		Not estimable	
Nathan 2006	0	94	0	91		Not estimable	
Noonan 2006a	4	124	Ő	55	0.4%	4.03 [0.22, 73.62]	
Noonan 2006b	3	115	0	54	0.4%		
iteentani keessa						3.32 [0.17, 63.14]	
Russell 1995	10	99	13	107	6.8%	0.83 [0.38, 1.81]	
SAS40036	0	172	0	159		Not estimable	
SD 039 0714	1	136	1	134	0.5%	0.99 [0.06, 15.59]	
SD 039 0725a	2	184	0	84	0.4%	2.30 [0.11, 47.33]	
SD 039 0725b	3	168	1	85	0.7%	1.52 [0.16, 14.37]	
SD 039 0726a	3	154	1	73	0.7%		
	-					1.42 [0.15, 13.44]	
SD 039 0726b	1	147	0	72	0.4%	1.48 [0.06, 35.88]	
SD 039 0728	21	443	5	133	4.2%	1.26 [0.48, 3.28]	
Shapiro 2000	0	84	1	84	0.8%	0.33 [0.01, 8.07]	
Tal 2002	7	148	0	138	0.3%	13.99 [0.81, 242.73]	
Weiler 2005	1	99	0	100	0.3%	3.03 [0.12, 73.49]	
Zetterstrom 2001a	4	123	1	62	0.7%	2.02 [0.23, 17.66]	
Zetterstrom 2001b	0	115	0	62		Not estimable	
Zimmerman 2004a	4	123	1	124	0.5%	4.03 [0.46, 35.57]	
Subtotal (95% CI)		4944		3453	41.4%	1.20 [0.89, 1.62]	*
Total events	113		64			-	
Heterogeneity: Chi ² = 18		27 (P -		= 0%			
Test for overall effect: Z:				0.0			
1.3.3 Mean baseline FE						111	
D'Urzo 2001	24	455	22	456	12.0%	1.09 [0.62, 1.92]	
SAM40008	3	93	0	93	0.3%	7.00 [0.37, 133.66]	
SAM40012	2	181	1	181	0.5%	2.00 (0.18, 21,86)	
SAS40024	ô	102	o	90	2.0070	Not estimable	
SAS40024	1	161	2	161	1.1%		
						0.50 [0.05, 5.46]	
SD 037 0344a	3	216	1	105	0.7%	1.46 [0.15, 13.85]	
SD 037 0344b	2	213	0	105	0.4%	2.48 [0.12, 51.13]	
SFA100314	0	124	0	124		Not estimable	
SFA100316	0	113	0	118		Not estimable	
	3	159	1	159	0.5%	3.00 [0.32, 28.53]	
	1	93	4	95			
SFCF4026	1		4		2.2%	0.26 [0.03, 2.24]	
SFCF4026 SMS40012		1910		1687	17.7%	1.18 [0.74, 1.87]	-
SFCF4026 SMS40012 Subtotal (95% CI)			31				
SFCF4026 SMS40012 Subtotal (95% CI) Total events	39	(D. C		or			
SFCF4026 SMS40012 Subtotal (95% CI) Total events Heterogeneity: Chi ² = 4.	98, df = 7		66); I ² = 0	1%			
SFCF4026 SMS40012 Subtotal (95% CI) Total events Heterogeneity: Chi ² = 4. Test for overall effect: Z :	98, df = 7	= 0.49)	66); I ² = 0				
SFCF4026 SMS40012 Subtotal (95% CI) Total events Heterogeneity: Chi ² = 4. Test for overall effect: Z : Total (95% CI)	98, df = 7 = 0.69 (P		66); I² = 0		100.0%	1.06 [0.87, 1.30]	•
SFCF4026 SMS40012 Subtotal (95% CI) Total events Heterogeneity: Chi ² = 4. Test for overall effect: Z : Total (95% CI) Total events	98, df = 7 = 0.69 (P 221	= 0.49) 9199	66); I² = 0 166	7014	100.0%	1.06 [0.87, 1.30]	•
SFCF4026 SMS40012 Subtotal (95% CI) Total events Heterogeneity: Chi ² = 4. Test for overall effect: Z : Total (95% CI)	98, df = 7 = 0.69 (P 221 3.43, df =	= 0.49) 9199 47 (P =	66); I ² = 0 166 0.99); I ² :	7014	100.0%	1.06 [0.87, 1.30]	0.005 0.1 1 10 2

Figure 6.

Forest plot of comparison: 1 Long-acting beta2 versus placebo: both groups receiving similar dose ICS, outcome: 1.3 Serious adverse event including respiratory.

Table 1

Search history

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Year	Detail
All years to April 2004	Citations identified: 594 Of these, 545 reports were excluded for the following mutually exclusive reasons: (1) duplicate references (N = 208) (2) not a randomised controlled trial (N = 68) or an ongoing trial (N = 14) (3) participants were not asthmatics (N = 4) (4) no consistent intervention with inhaled corticosteroids in all participants (N = 41) (5) intervention was not daily inhaled long-acting β2-agonists (N = 19) (6) control intervention was not inhaled corticosteroids alone (N = 63) (7) duration of intervention was less than 30 days (N = 45) (8) outcome measures did not reflect asthma control (N = 8) (9) the treatment and intervention groups compared the same medications either in combination or with different delivery devices (N = 30) (10) co-intervention with a non-permitted agent (N = 1) (11) patients were steroid-naive on study entry (N = 20) (12) control group had a higher dose of inhaled corticosteroid than the intervention group (N = 21) (13) the dose of inhaled corticosteroid did not remain stable during the trial (N = 3) Due to the large number of citations considered, the reasons for exclusion are provided only for published randomised controlled trials 33 treatment-control comparisons derived from 28 trials met the entry criteria of the review

Table 2

Control group risk status for primary outcome

Akpinarli 1999 0 16 6 Kavaru 2000 0 90 12 Weiler 2005 0 90 4 SFA100314 1 124 4 SFA100316 1 118 4 SA540024 2 100 4 Shapiro 2000 2 84 12 Malone 2005 3 102 12 Noonan 2006 4 55 12 Noonan 2006 4 54 12 SAS40037 4 161 16 SAS40036 4 159 16 Li 1999 6 16 12 Simons 1997 6 16 12 Aubier 1999 9 82 28 Norhaya 1999 10 30 4 Verberne 1998 18 57 54 Russell 1995 18 99 12 O'Byrne 2001b 20 312 52 Kemp 1998 23 64 12 Boyd 1995 25	Study ID	Control group % event rate	Control group N	Duration (wk)
Weiler 2005 0 90 4 SFA100314 1 124 4 SFA100316 1 118 4 SA40024 2 100 4 Shapiro 2000 2 84 12 Malone 2005 3 102 12 Nathan 2006 3 91 12 Noonan 2006a 4 55 12 Noonan 2006b 4 54 12 SAS40037 4 161 16 SAS40036 4 159 16 Li 1999 6 16 12 Simons 1997 6 16 12 Simons 1997 9 82 28 Aubier 1999b 8 83 28 Norhaya 1999 10 30 4 Verberne 1998 18 57 54 Russell 1995 18 99 12 O'Byrne 2001b 20 312 52	Akpinarli 1999	0	16	6
SFA100314 1 124 4 SFA100316 1 118 4 SAS40024 2 100 4 Shapiro 2000 2 84 12 Malone 2005 3 102 12 Nathan 2006 3 91 12 Noonan 2006a 4 55 12 Noonan 2006b 4 54 12 SAS40037 4 161 16 SAS40036 4 159 16 Li 1999 6 16 12 Simons 1997 6 16 4 Fitzgerald 1999 7 91 24 Aubier 1999b 8 83 28 Norhaya 1999 10 30 4 Verberne 1998 18 57 54 Russell 1995 18 99 12 O'Byrne 2001b 20 312 52 Kemp 1998 23 254 12 Boyd 1995 23 64 12 Langton Hewer 1995 <td< td=""><td>Kavaru 2000</td><td>0</td><td>90</td><td>12</td></td<>	Kavaru 2000	0	90	12
SFA100316 1 118 4 SAS40024 2 100 4 Shapiro 2000 2 84 12 Malone 2005 3 102 12 Nathan 2006 3 91 12 Noonan 2006a 4 55 12 Noonan 2006b 4 54 12 SAS40037 4 161 16 SAS40036 4 159 16 Li 1999 6 16 12 Simons 1997 6 16 4 Fitzgerald 1999 7 91 24 Aubier 1999b 8 83 28 Aubier 1999p 10 30 4 Verberne 1998 18 57 54 Russell 1995 18 99 12 O'Byrne 2001b 20 312 52 Kemp 1998 23 254 12 Boyd 1995 23 64 12 Langton Hewer 1995 25 12 8 O'Byrne 2001a	Weiler 2005	0	90	4
SAS40024 2 100 4 Shapiro 2000 2 84 12 Malone 2005 3 102 12 Nathan 2006 3 91 12 Noonan 2006a 4 55 12 Noonan 2006b 4 54 12 SAS40037 4 161 16 SAS40036 4 159 16 Li 1999 6 16 12 Simons 1997 6 16 4 Fitzgerald 1999 7 91 24 Aubier 1999b 8 83 28 Norhaya 1999 10 30 4 Verberne 1998 18 57 54 Russell 1995 18 99 12 O'Byrne 2001b 20 312 52 Kemp 1998 23 254 12 Boyd 1995 23 64 12 Langton Hewer 1995 25 12 8 O'Byrne 2001a 25 322 52 Wallin 2003	SFA100314	1	124	4
Shapiro 2000 2 84 12 Malone 2005 3 102 12 Nathan 2006 3 91 12 Noonan 2006a 4 55 12 Noonan 2006b 4 54 12 SAS40037 4 161 16 SAS40036 4 159 16 Li 1999 6 16 12 Simons 1997 6 16 4 Fitzgerald 1999 7 91 24 Aubier 1999b 8 83 28 Norhaya 1999 10 30 4 Verberne 1998 18 57 54 Russell 1995 18 99 12 O'Byrne 2001b 20 312 52 Kemp 1998 23 254 12 Boyd 1995 25 12 8 O'Byrne 2001a 25 322 52 Wallin 2003 26 19 12 Pauwels 1997b 28 214 52 van der Molen 1997	SFA100316	1	118	4
Malone 2005 3 102 12 Nathan 2006 3 91 12 Noonan 2006a 4 55 12 Noonan 2006b 4 54 12 SAS40037 4 161 16 SAS40036 4 159 16 Li 1999 6 16 12 Simons 1997 6 16 4 Fitzgerald 1999 7 91 24 Aubier 1999b 8 83 28 Norhaya 1999 10 30 4 Verberne 1998 18 57 54 Russell 1995 18 99 12 O'Byrne 2001b 20 312 52 Kemp 1998 23 254 12 Boyd 1995 23 64 12 Langton Hewer 1995 25 12 8 O'Byrne 2001a 25 322 52 Wallin 2003 26 19 12 Pauwels 1997b 28 114 24 <td>SAS40024</td> <td>2</td> <td>100</td> <td>4</td>	SAS40024	2	100	4
Nathan 2006 3 91 12 Noonan 2006a 4 55 12 Noonan 2006b 4 54 12 SAS40037 4 161 16 SAS40036 4 159 16 Li 1999 6 16 12 Simons 1997 6 16 4 Fitzgerald 1999 7 91 24 Aubier 1999b 8 83 28 Aubier 1999b 8 83 28 Norhaya 1999 10 30 4 Verberne 1998 18 57 54 Russell 1995 18 99 12 O'Byrne 2001b 20 312 52 Kemp 1998 23 254 12 Boyd 1995 23 64 12 Langton Hewer 1995 25 12 8 O'Byrne 2001a 25 322 52 Wallin 2003 26 19 12	Shapiro 2000	2	84	12
Noonan 2006a 4 55 12 Noonan 2006b 4 54 12 SAS40037 4 161 16 SAS40036 4 159 16 Li 1999 6 16 12 Simons 1997 6 16 12 Simons 1997 6 16 4 Fitzgerald 1999 7 91 24 Aubier 1999b 8 83 28 Norhaya 1999 10 30 4 Verberne 1998 18 57 54 Russell 1995 18 99 12 O'Byrne 2001b 20 312 52 Kemp 1998 23 254 12 Boyd 1995 25 12 8 O'Byrne 2001a 25 322 52 Wallin 2003 26 19 12 Pauwels 1997b 28 214 52 van der Molen 1997 28 14 24 <td>Malone 2005</td> <td>3</td> <td>102</td> <td>12</td>	Malone 2005	3	102	12
Noonan 2006b 4 54 12 SAS40037 4 161 16 SAS40036 4 159 16 Li 1999 6 16 12 Simons 1997 6 16 4 Fitzgerald 1999 7 91 24 Aubier 1999b 8 83 28 Aubier 1999a 9 82 28 Norhaya 1999 10 30 4 Verberne 1998 18 57 54 Russell 1995 18 99 12 O'Byrne 2001b 20 312 52 Kemp 1998 23 254 12 Boyd 1995 23 64 12 Langton Hewer 1995 25 12 8 O'Byrne 2001a 25 322 52 Wallin 2003 26 19 12 Pauwels 1997b 28 214 52 van der Molen 1997 28 114 <	Nathan 2006	3	91	12
SAS40037 4 161 16 SAS40036 4 159 16 Li 1999 6 16 12 Simons 1997 6 16 4 Fitzgerald 1999 7 91 24 Aubier 1999b 8 83 28 Aubier 1999a 9 82 28 Norhaya 1999 10 30 4 Verberne 1998 18 57 54 Russell 1995 18 99 12 O'Byrne 2001b 20 312 52 Kemp 1998 23 254 12 Boyd 1995 23 64 12 Langton Hewer 1995 25 12 8 O'Byrne 2001a 25 322 52 Wallin 2003 26 19 12 Pauwels 1997b 28 214 52 van der Molen 1997 28 114 24	Noonan 2006a	4	55	12
SAS40036 4 159 16 Li 1999 6 16 12 Simons 1997 6 16 4 Fitzgerald 1999 7 91 24 Aubier 1999b 8 83 28 Aubier 1999a 9 82 28 Norhaya 1999 10 30 4 Verberne 1998 18 57 54 Russell 1995 18 99 12 O'Byrne 2001b 20 312 52 Kemp 1998 23 64 12 Boyd 1995 25 12 8 O'Byrne 2001a 25 322 52 Wallin 2003 26 19 12 Pauwels 1997b 28 214 52 van der Molen 1997 28 114 24	Noonan 2006b	4	54	12
Li 199961612Simons 19976164Fitzgerald 199979124Aubier 1999b88328Aubier 1999b88228Norhaya 199910304Verberne 1998185754Russell 1995189912O'Byrne 2001b2031252Kemp 19982325412Boyd 1995236412Langton Hewer 19952532252Wallin 2003261912Pauwels 1997b2821452van der Molen 19972811424	SAS40037	4	161	16
Simons 19976164Fitzgerald 199979124Aubier 1999b88328Aubier 1999a98228Norhaya 199910304Verberne 1998185754Russell 1995189912O'Byrne 2001b2031252Kemp 1998236412Boyd 199525128O'Byrne 2001a2532252Wallin 2003261912Pauwels 1997b2821452van der Molen 19972811424	SAS40036	4	159	16
Fitzgerald 1999 7 91 24 Aubier 1999b 8 83 28 Aubier 1999a 9 82 28 Norhaya 1999 10 30 4 Verberne 1998 18 57 54 Russell 1995 18 99 12 O'Byrne 2001b 20 312 52 Kemp 1998 23 254 12 Boyd 1995 23 64 12 Langton Hewer 1995 25 12 8 O'Byrne 2001a 25 322 52 Wallin 2003 26 19 12 Pauwels 1997b 28 214 52 van der Molen 1997 28 114 24	Li 1999	6	16	12
Aubier 1999b 8 83 28 Aubier 1999a 9 82 28 Norhaya 1999 10 30 4 Verberne 1998 18 57 54 Russell 1995 18 99 12 O'Byrne 2001b 20 312 52 Kemp 1998 23 254 12 Boyd 1995 23 64 12 Langton Hewer 1995 25 12 8 O'Byrne 2001a 25 322 52 Wallin 2003 26 19 12 Pauwels 1997b 28 214 52 van der Molen 1997 28 114 24	Simons 1997	6	16	4
Aubier 1999a98228Norhaya 199910304Verberne 1998185754Russell 1995189912O'Byrne 2001b2031252Kemp 19982325412Boyd 1995236412Langton Hewer 199525128O'Byrne 2001a2532252Wallin 2003261912Pauwels 1997b2821452van der Molen 19972811424	Fitzgerald 1999	7	91	24
Norhaya 1999 10 30 4 Verberne 1998 18 57 54 Russell 1995 18 99 12 O'Byrne 2001b 20 312 52 Kemp 1998 23 254 12 Boyd 1995 23 64 12 Langton Hewer 1995 25 12 8 O'Byrne 2001a 25 322 52 Wallin 2003 26 19 12 Pauwels 1997b 28 214 52 van der Molen 1997 28 114 24	Aubier 1999b	8	83	28
Verberne 1998 18 57 54 Russell 1995 18 99 12 O'Byrne 2001b 20 312 52 Kemp 1998 23 254 12 Boyd 1995 23 64 12 Langton Hewer 1995 25 12 8 O'Byrne 2001a 25 322 52 Wallin 2003 26 19 12 Pauwels 1997b 28 214 52 van der Molen 1997 28 114 24	Aubier 1999a	9	82	28
Russell 1995 18 99 12 O'Byrne 2001b 20 312 52 Kemp 1998 23 254 12 Boyd 1995 23 64 12 Langton Hewer 1995 25 12 8 O'Byrne 2001a 25 322 52 Wallin 2003 26 19 12 Pauwels 1997b 28 214 52 van der Molen 1997 28 114 24	Norhaya 1999	10	30	4
O'Byrne 2001b 20 312 52 Kemp 1998 23 254 12 Boyd 1995 23 64 12 Langton Hewer 1995 25 12 8 O'Byrne 2001a 25 322 52 Wallin 2003 26 19 12 Pauwels 1997b 28 214 52 van der Molen 1997 28 114 24	Verberne 1998	18	57	54
Kemp 19982325412Boyd 1995236412Langton Hewer 199525128O'Byrne 2001a2532252Wallin 2003261912Pauwels 1997b2821452van der Molen 19972811424	Russell 1995	18	99	12
Boyd 1995 23 64 12 Langton Hewer 1995 25 12 8 O'Byrne 2001a 25 322 52 Wallin 2003 26 19 12 Pauwels 1997b 28 214 52 van der Molen 1997 28 114 24	O'Byrne 2001b	20	312	52
Langton Hewer 1995 25 12 8 O'Byrne 2001a 25 322 52 Wallin 2003 26 19 12 Pauwels 1997b 28 214 52 van der Molen 1997 28 114 24	Kemp 1998	23	254	12
O'Byrne 2001a 25 322 52 Wallin 2003 26 19 12 Pauwels 1997b 28 214 52 van der Molen 1997 28 114 24	Boyd 1995	23	64	12
Wallin 2003 26 19 12 Pauwels 1997b 28 214 52 van der Molen 1997 28 114 24	Langton Hewer 1995	25	12	8
Pauwels 1997b 28 214 52 van der Molen 1997 28 114 24	O'Byrne 2001a	25	322	52
van der Molen 1997 28 114 24	Wallin 2003	26	19	12
	Pauwels 1997b	28	214	52
Pauwels 1997a 38 213 52	van der Molen 1997	28	114	24
	Pauwels 1997a	38	213	52