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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 ß$_2$-adrenergic agonists (LABAs) are recommended as 'add-on' 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.

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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 FEV_1 (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 ß$_2$-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 ß$_2$-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.

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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 ß$_2$-agonists are powerful agents used to relieve the bronchoconstriction associated with asthma. They act by stimulating the ß$_2$-receptors located in airway smooth muscle resulting in smooth muscle relaxation (Nelson 1995). Inhaled ß2-agonists can be differentiated by their onset and duration of action. Short-acting ß2-agonists, such as salbutamol and terbutaline, are hydrophilic and interact directly with ß$_2$-receptors, leading to a fast onset of action with a duration of effect of six hours or less (D'Alonzo 1997). Long-acting ß$_2$-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 ß2-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 ß$_2$-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 ß$_2$-agonists generally indicates a significant inflammatory process that should be controlled with anti-inflammatory drugs such as inhaled corticosteroids. The role of long-acting ß$_2$-agonists in the management of asthma has previously been debated (Ernst 2006; Salpeter 2006). At present, the use of long-acting ß$_2$-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 ß$_2$-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 ß2-agonists as monotherapy (Walters 2007). Although all national and international asthma consensus statements recommend the use of

long-acting ß2-agonists only in combination with inhaled corticosteroids (BTS 2007; Canadian Paediatric 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 Paediatric Asthma Guideline 2005); and 800 µg/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 Paediatric 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 Paediatric 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 $ß_2$-agonists to inhaled corticosteroids in asthmatic patients.

We also wished to examine whether the efficacy of long-acting $ß_2$-agonists was influenced by age, severity of airway obstruction, dose of inhaled corticosteroids to which long-acting $ß_2$-agonists were added, number of devices to deliver combination therapy, the dose and

type of long-acting ß$_2$-agonist and the duration of intervention. Additionally we wished to assess carefully the safety profile (and its possible determinants) of long-acting ß$_2$-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 ß2-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 ß$_2$-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 ß$_2$-agonists and short courses of oral steroids were permitted.

Types of outcome measures

Primary outcomes: 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 ß$_2$-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

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(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 μg of beclomethasone dipropionate equates to 1 μg of budesonide and 0.5 μg of fluticasone propionate (NAEPP 2007). All doses of inhaled medications were reported based on ex-valve 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 I^2 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 I^2, 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.

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 (FEV_1): classified as mild (FEV_1 80% or more), moderate (FEV_1 61% to 79%) or severe (FEV_1 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 CFC-propelled 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 ß2-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 Chi^2 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 FEV_1 (litres) and dose of inhaled corticosteroids (µg/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 ß$_2$-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 ß$_2$-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 ß$_2$-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 ß2-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 $ß_2$-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 $ß_2$-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 FEV_1 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 FEV_1 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), FEV_1 at endpoint in litres (0.12 L/sec, 95% CI 0.07 to 0.17, 10 studies) (Analysis 1.8), FEV_1 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 FEV_1 with respect to duration of study (P = 0.67) (Analysis 1.12) did not identify statistically significant differences, the change in FEV_1 was significantly influenced by baseline % predicted FEV_1 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) .

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 ß$_2$-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 ß$_2$-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 FEV_1 (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 FEV_1 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 (FEV_1 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 ß2-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 ß2-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 ß2-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 µg/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 FEV_1 with a $ß_2$-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 FEV_1.

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

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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 ß$_2$-agonists should be targeted for inclusion in future studies. Stratified subgroup analyses on baseline FEV_1 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;
2. 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 ß$_2$-agonists.

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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 (cross-over, 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

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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
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 FEV1 within the previous year EXCLUSION CRITERIA: Asthma exacerbation or respiratory infection in < month ELIGIBILITY CRITERIA DURING RUN-IN: Only patients requiring salbutamol 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
Allocation concealment?	Unclear	Information not available

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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 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 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

Item	Authors' judgement	Description
Adequate sequence generation?	Yes	See Appendix 2

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	PROTOCOL: Combination ICS and LABA versus ICS via one inhaler All other items listed under interventions 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 % 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; plus 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 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 preceding 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
Blinding? All outcomes	Yes	Identical placebo
Incomplete outcome data addressed? All outcomes	Unclear	Not enough information presented to determine how ITT population was defined: "The study was analysed on an intention-to-treat basis. All patients randomized to treatment were evaluable."
Free of selective reporting?	Yes	OCS-treated exacerbation data available

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 DOSE OF ICS mean: 600 mcg/day ASTHMA DURATION mean (range) in years: 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 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 intervals RUN-IN PERIOD: None DOSE OF ICS DURING RUN-IN: Not applicable DOSE OPTIMISATION PERIOD: None INTERVENTION PERIOD: 24 weeks TEST GROUP (LABA + SINGLE DOSE ICS): Usual ICS + salmeterol 50 mcg bid CONTROL GROUP: Placebo + usual dose of ICS DEVICE: MDI NUMBER OF DEVICES: 2 COMPLIANCE: Not reported CO-TREATMENT: Not reported
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, multicentre 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 DURING RUN-IN: 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 formoterol 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

	ASTHMA DURATION (years): Not reported ATOPY (%): Not reported ELIGIBILITY CRITERIA: Non-smoking adults with asthma as defined by ATS criteria; treated with ICS 400 to 1200 mcg/day for at least 1 month prior to screening; >= 15% reversibility after bronchodilator; during the last 7 days of run-in, had used albuterol on at least 5 days awakening on >= 1 night due to asthma symptoms; use of beta agonist >= 10 puffs as weekly mean; competence with turbuhaler; compliance with dairy cards and assessments EXCLUSION: Respiratory infection within 2 months of screening; acute asthma exacerbation requiring an ER visit in the previous 3 months CRITERIA FOR RANDOMISATION DURING RUN-IN: Had used rescue albuterol on at least 5 of the last 7 days of the run-in period. Excluded from randomisation if asthma was poorly controlled as defined by 2 or more awakenings per week or a visit 2 premedication FEV1 less than 50% predicted or less than 1 L
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

	AGE: median (range): 42 (23 to 64) GENDER: (% males): 60 SEVERITY: Moderate BASELINE % PREDICTED FEV1: Not reported BASELINE DOSE OF ICS (before start of run-in): 400 to 1000 BDP equivalent ASTHMA DURATION: Not reported ATOPY (%): 70 ELIGIBILITY CRITERIA: Non-smoking; asthma diagnosed by ATS criteria; 15% reversibility following bronchodilator EXCLUSION CRITERIA: Respiratory infection or asthma exacerbation in 2 months prior to study
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 OCS

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)

	WITHDRAWALS: FP/SAL: 162; FP: 215 AGE: mean (range) or mean (SD) 40 (16) GENDER: (% male) 42 SEVERITY: Moderate BASELINE % PREDICTEDFEV1: 77 BASELINE DOSE OF ICS: Divided into 3 strata: 0; 500 mcg/d or less; between 500 and 1000 mcg/d ASTHMA DURATION: 0 to 1 year: FP/SAL: 56; FP: 97- 1 to 10 years: FP/SAL: 649; FP: 647 -> 10 years: FP/SAL: 1004; FP: 992 ATOPY (%): 58 ELIGIBILITY CRITERIA: 12 to 80 years of age; 6-month history of asthma; FEV1 reversibility of 15%; smoking history of less than 10 pack-years; no use of LABA or oral beta-agonists in previous 2 weeks EXCLUSION CRITERIA: Not reported
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 a composite in a rate; data could not be extracted and used in metaanalysis

Green 2006

Methods	Cross-over, single-centre study in UK

Participants	N SCREENED: 66 N RANDOMISED: 49 N COMPLETED: 39 GENDER (% male): 52 MEAN AGE: 42 SEVERITY: Not stated BASELINE FEV1 PREDICTED: 74.8% ATOPY (%): 93% INCLUSION CRITERIA: 18 to 75 years, diagnosed with asthma; receiving treatment with 400 mcg/day beclomethasone dipropionate; one or more of 1) > 15% increase in FEV1 post-SABA; 2) > 20% within-day variability in PEF assessed twice daily over a 2-week period; 3) provocative concentration of methacholine causing a 20% fall in FEV1 (PC20) < 8 mg/mL-1; following run-in on 200 mcg day BUD, participants were eligible if they had recorded day- or night-time asthma symptoms on their diary cards on at least 4 days in the third or fourth baseline week EXCLUSION: Current smokers or smoking history of > 10 pack-years, significant comorbidity, treated with oral corticosteroids, long-acting ß2-agonists, leukotriene antagonists or theophylline; asthma exacerbation or lower respiratory tract infection within the 4 weeks prior to trial entry
Interventions	LABA + ICS versus SAME DOSE ICS OUTCOMES: End of phase TREATMENT PERIOD: 6 weeks RUN-IN PERIOD: 4 weeks TEST GROUP: Budesonide 100 mg bid + formoterol 12 mg bid CONTROL: Budesonide 100 mg bid NUMBER OF DEVICES: 2 COMPLIANCE: Not assessed CO-TREATMENT: prn SABA
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 (AZ provided active and placebo inhalers) Confirmation of methodology and data: Obtained User defined number: 200

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 a 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"
Allocation concealment?	Yes	Correspondence with investigator: "… this was indeed generated by a third party, namely the pharmacist responsible for dispensing the double blind medication."
Blinding? All outcomes	Yes	Identical placebos
Incomplete outcome data addressed? All outcomes	No	Completers used for analysis

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 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 centres in 6 countries; 3 groups of which 2 are considered for this review
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 % PREDICTED FEV1: 71 BASELINE DOSE 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 inhaled 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 to asthma symptoms; use of beta agonist >= 10 puffs as weekly mean; competence with turbuhaler; compliance with dairy cards and assessments
Interventions	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

All outcomes		
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 hospital 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 after 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**
Adequate sequence generation?	Yes	Computer-generated, blocks of 8

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 DOSE OF ICS (RANGE): BDP 300 to 500 mcg/day; triamcinolone acetate 600 to 1000 mcg/day; flunisolide 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 centres 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 DOSE 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."
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 DOSE 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 cationic 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

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	"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 in 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; been hospitalised for any aspect of their reversible airways disease within the past 12 months; required daily maintenance therapy with oral steroids within the past 3 months; required a booster course of oral prednisolone in excess 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 this clinical trial ELIGIBILITY CRITERIA FOR RANDOMISATION DURING RUN-IN: Not other criteria other than above reported
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

	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; had a variation of more than 15% in PEF over a 24-hour period on at least 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 Foundation and the NH & MRC of Australia Confirmation of methodology and data obtained User-defined number: 400

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
Incomplete outcome data addressed? All outcomes	No	Completers analysed
Free of selective reporting?	Yes	OCS-treated exacerbations available for meta-analysis

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 DOSE OF ICS (start of run-in): 166 mcg (FP stratum) ASTHMA DURATION: Not reported ATOPY(%): Not reported ELIGIBILITY CRITERIA: 4 to 11 years; ATS defined asthma for at least 2 months; ICS therapy (BDP equivalent 252 to 336 mcg /d) for 1 month prior to entry; participants aged 6 to 11 required to have FEV1% predicted; participants aged 4 to 5 required to have am PEF 50% to 95% predicted; >/= 12% response 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% predicted; daytime asthma (score at least 1)/use of SABA on 3+ days of last 7 days of run-in; 70% or greater diary card entry
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: "…all 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 study
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 DOSE 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

	% RUN-IN PARTICIPANTS RANDOMISED: 97 (of 7 patients who discontinued before randomisation 3 failed to fulfil the selection criteria, 2 withdrew their consent and 2 were lost to follow up) RANDOMISED: 259 (Form 12 mcg bid: 130; on-demand salbutamol (ODS): 129) WITHDRAWALS: 30 (Form 12 mcg bid: 12; ODS: 18) AGE: mean: Form 12 mcg bid: 39 years GENDER: (% male): 57 SEVERITY: Moderate BASELINE % PREDICTED FEV1: 73 BASELINE DOSE OF ICS (start of run-in): Not reported; maximum dose 1000 mcg BDP equivalent ASTHMA DURATION: 15 years ATOPY (%): Not reported ELIGIBILITY CRITERIA: 18 years or over; moderate persistent asthma; taking daily treatment with an ICS, same one for at least 1 month prior to first visit; require daily treatment with inhaled bronchodilators; asthma defined according to criteria of ATS; FEV1 >= 60% of predicted normal value for patient; reversibility test (increase in FEV1 >= 10% of predicted value) had to be documented at first visit within 3 months prior to visit; refrain from taking salbutamol 6 hours before each spirometry EXCLUSION CRITERIA: Known hypersensitivity to sympathetic amines or to lactose; pregnancy or breast-feeding; women of childbearing potential who did not use a reliable contraceptive method; significant change in the regular asthma medication; asthma exacerbation or respiratory tract infection in the month prior to the first visit; incapacity to use a metered-dose inhaler correctly or to complete patient diary; concomitant treatments with theophylline, anticholinergic bronchodilators and inhaled or oral B2 agonists other than the trial medications were not allowed CRITERIA FOR RANDOMISATION DURING RUN-IN: No additional criteria reported
Interventions	LABA + ICS versus SAME dose of ICS OUTCOMES: measured at 12 weeks RUN-IN PERIOD: 2 to 6 weeks DOSE OF ICS DURING RUN-IN: Same as usual DOSE OPTIMISATION PERIOD: None INTERVENTION PERIOD: 12 weeks TEST GROUP: (Form 12 + ICS) formoterol 12 mcg bid + ICS CONTROL GROUP: (ODS) On-demand salbutamol + usual ICS (up to 1000 ucg beclomethasone or 800 mcg budesonide or 500 mcg fluticasone per day) DEVICE: Dry powder Diskhaler NUMBER OF DEVICES: 2 (test group) COMPLIANCE: Not reported CO-TREATMENT: Salbutamol prn
Outcomes	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 and the NH&MRC of Australia Confirmation of methodology and data not obtained 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?	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 DOSE 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

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/d 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 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 bid 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	As for Noonan 2006a
Notes	As for Noonan 2006a

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 DOSE 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 ICS 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-agonist (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 dose 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

	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 used
Incomplete outcome data addressed? All outcomes	No	Completers used for analysis
Free of selective reporting?	Yes	Data available for OCS-treated exacerbations

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) 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 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

	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; 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: 1, 2, 3, 6, 9 and 12 months of treatment

	RUN-IN PERIOD: 4 weeks DOSE OF ICS DURING RUN-IN: BUD 800 bid DOSE OPTIMISATION PERIOD: None INTERVENTION PERIOD: 52 weeks TEST GROUP: Budesonide 100 mcg bid + formoterol 12 mcg bid CONTROL GROUP: Budesonide 100 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 day time 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 measure: 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	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 Middle 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 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; 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
Free of selective reporting?	Yes	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 DOSE OF ICS (start of run-in): 454 mcg/d ASTHMA DURATION: 3 ATOPY(%): Not reported

	ELIGIBILITY CRITERIA: 4 to 11 years; diagnosis of asthma (ATS) for a minimum period of 6 months; pre-SABA PEF >/= 50% predicted; ICS treatment for at least 12 weeks before entry into the study, at a constant dose of 375 to 1000 mcg/d during the 30 days prior to enrolment; history an average of >/= 1 clinically important exercise induced bronchoconstriction per week during the 12 weeks months leading up to the study; ability to use Turbuhaler device and peak flow meter EXCLUSION CRITERIA: Oral, parenteral or rectal corticosteroids within 30 days; respiratory infection affecting asthma control within 30 days; any significant coexisting disease/disorder; known/suspected hypersensitivity to study medication or inhaled lactose; inhaled anticholinergics, ß-blockers (including eye drops), xanthines and other anti-asthma agents not permitted during the study POST-RUN-IN: Total asthma-symptom score of at least one on a minimum of 4 of last 7 days of the run-in period; during last 7 days of the run-in, patients had to have a mean morning PEF of 50% to 85% of the post-SABA PEF
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: Combination budesonide/formoterol 200/6 mcg bid CONTROL GROUP: Budesonide 200 mcg bid DEVICE: Turbuhaler NUMBER OF DEVICES: 1 (double-dummy design used; second inhaler device to deliver) COMPLIANCE: Not reported CO-TREATMENT: prn SABA
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: 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

	OUTCOMES: 4 weeks RUN-IN PERIOD: 2 weeks DOSE OF ICS DURING RUN-IN: Usual ICS DOSE OPTIMISATION PERIOD: None INTERVENTION PERIOD: 4 weeks TEST GROUP (LABA + SINGLE DOSE ICS): Budesonide 400 mcg bid + formoterol 9 mcg bid CONTROL GROUP: Budesonide 400 mcg bid DEVICE: Turbuhaler NUMBER OF DEVICES: 2 COMPLIANCE: Missed doses recorded by patients in diary CO-TREATMENT: prn SABA
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 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)
Participants	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 one salbutamol blister per episode; recorded a diurnal variation in PEF of >= 15% 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
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

	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."
Free of selective reporting?	Yes	Data on OCS-exacerbations available for meta-analysis

SAM40008

Methods	Parallel-group, multicentre study (34 centres in Europe and New Zealand). Dose of 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 DOSE 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 DEVICES: 1 COMPLIANCE: Not assessed CO-TREATMENT: prn SABA
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
Blinding? All outcomes	Yes	Identical inhaler devices
Incomplete outcome data addressed? All outcomes	Unclear	"The Intent-To-Treat (ITT) Population, representing all subjects randomised to treatment who had taken at least one dose of study medication and had at least one post randomisation diary assessment, was the primary population for all safety and efficacy endpoints."
Free of selective reporting?	Yes	Exacerbations described in trial report available; OCS-treated exacerbations could not be used since data were reported across phases of the study

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 DOSE 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 DURING RUN-IN: Symptom score >/= 2 on 3 of last 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 reported CO-TREATMENT: prn SABA
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' 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	"To be 'evaluable', subjects had to meet the entry and randomisation criteria, receive at least one dose of study medication and have completed at least one day's post-randomisation diary information."
Free of selective reporting?	Yes	Exacerbations described in trial report available; OCS-treated exacerbations could not be identified from the data available

SAS40024

Methods	Parallel-group, 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 (range) or mean (SD): 29.3 (11.2) GENDER (% male): 39 SEVERITY: Moderate BASELINE % PREDICTED FEV1 (mean): Not reported BASELINE DOSE 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
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

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: FP/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 therapy 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

	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)
Participants	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 % PREDICTED FEV1 (mean): Not reported BASELINE DOSE OF ICS: Not reported ASTHMA DURATION: Not reported ATOPY (%): Not reported ELIGIBILITY 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
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*; pm 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
Participants	% 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 DOSE 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
Interventions	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 COMPLIANCE: Not reported CO-TREATMENT: prn SABA
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

	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 DOSE OF ICS (start of run-in): Not reported ASTHMA DURATION: Not reported ATOPY (%): Not reported

	ELIGIBILITY CRITERIA: ICS 375 to 1000 mcg BDP equivalent; FEV1 40% to 90% predicted normal; >= 12% improvement following inhalation of 1 mg of terbutaline EXCLUSION CRITERIA: Not reported CRITERIA FOR RANDOMISATION DURING RUN-IN: Symptomatic
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 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: prn 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 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

Methods	Parallel-group, multicentre study
Participants	% ELIGIBLE OF SCREENED POPULATION: Not stated % RUN-IN PARTICIPANTS RANDOMISED: 74 RANDOMISED: 186 (BUD/F: 123; BUD: 63) WITHDRAWALS: BUD/F: 13; BUD: 10 AGE mean (range) or mean (SD): 9 (1.7) SEVERITY: Not stated BASELINE % PREDICTED FEV1: 84% BASELINE DOSE OF ICS: 307 ASTHMA DURATION: 6 years ATOPY (%): Not stated ELIGIBILITY CRITERIA: 6 to 12 years; inhaled steroid-dependent asthma; FEV1 > 50% of predicted; history of PEF or FEV1 reversibility 12%; subjects without history of reversibility must have demonstrated FEV1 reversibility as above at any time before Visit 2 EXCLUSION CRITERIA: Not reported ELIGIBILITY CRITERIA DURING RUN-IN: Not reported
Interventions	LABA and ICS versus SAME dose ICS

	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 OCS

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 DOSE 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 OCS

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, 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 DOSE OF ICS: 382 ASTHMA DURATION: 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 DURING RUN-IN: Stable during run-in period
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

	Data and methodology: Not obtained User defined: 1600

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

SFA100314

Methods	Parallel-group, multicentre 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 asthma; experienced activity-induced bronchospasm EXCLUSION 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	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

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 DOSE OF ICS: 1000 mcg/d BDP ASTHMA DURATION: 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: prn 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 episode 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 into 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 % PREDICTED 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-leukotriene 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

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
Participants	% 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
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 DOSE 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: % SABA-free days INFLAMMATORY MARKERS: PC20 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: 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 DOSE 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 use peak flow meter. During study: non-compliance with respect to study

	medication, completing the diary cards, clinic visits; withdrawal at own or investigators discretion; total number of course of oral corticosteroids more than allowed in study CRITERIA FOR RANDOMISATION 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 period 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."
Free of selective reporting?	Yes	OCS-treated exacerbations available for meta-analysis

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

	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 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)

	GENDER (% male): 39 SEVERITY: Moderate BASELINE % PREDICTED FEV1 (mean): 78 BASELINE DOSE OF ICS: FP 500 mcg/day ASTHMA DURATION: 59% > 15 years ATOPY (%): Not reported ELIGIBILITY CRITERIA: 12 to 50 years; diagnosis of asthma for at least 6 months; treatment with FP 500 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
Interventions	PROTOCOL: LABA + ICS versus SAME dose ICS alone OUTCOMES: 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
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 % PREDICTED FEV1: 77.4 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 of 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: Usual ICS DOSE OPTIMISATION PERIOD: None INTERVENTION PERIOD: 12 weeks TEST GROUP: Usual dose ICS + formoterol 12 mcg bid CONTROL GROUP: Usual dose ICS + placebo bid DEVICE: Turbuhaler NUMBER OF DEVICES: 2 COMPLIANCE: Measured during run-in CO-TREATMENT: prn SABA
Outcomes	PULMONARY FUNCTION TEST: am PEF*; pm PEF; FEV1 (Note: mean value during treatment for 12 weeks reported rather than value at endpoint) SYMPTOM SCORES: Total asthma symptom score FUNCTIONAL STATUS: Rescue medication use; paediatric asthma quality of life score INFLAMMATORY MARKERS: Not described ADVERSE EFFECTS: Described WITHDRAWALS: Described Primary outcome measure*
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	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): 456

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 questionnaire

ATS = American Thoracic Society

AZ = AstraZeneca

BDP = beclomethasone

bid = twice a day

BUD = budesonide

COPD = chronic obstructive pulmonary 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 ß2 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 infection

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 . Co-intervention with other non-steroidal anti-asthmatic drugs not stable during the intervention 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
Brambilla 2003	Duration of intervention < 30 days

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 and 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 not 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 or 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 2001	Not 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 delivery 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 ß2 agonist

LTRA = leukotriene receptor antagonist

NEJM = New England Journal of Medicine

RCT = randomised controlled trial

Rx = 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 DOSE 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 = beclomethasone

FEV1 = forced expiratory volume in one second

FP = fluticasone

ICS = inhaled corticosteroids

mcg = microgram

PEFR = peak expiratory 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]

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Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
3.1 Mean baseline FEV1 >/= 80% of predicted	14	4219	Risk Ratio (M-H, Fixed, 95% CI)	0.88 [0.64, 1.21]
3.2 Mean baseline 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, 20.77]
26.1 Mean baseline FEV1 61% to 79% of predicted	4	813	Mean Difference (IV, Fixed, 95% CI)	15.81 [10.85, 20.77]
27 Change in # overall daily rescue inhalations at endpoint	14	4654	Mean Difference (IV, Random, 95% CI)	−0.58 [−0.80, −0.35]
27.1 Mean baseline FEV1 >/= 80% of predicted	2	1272	Mean Difference (IV, Random, 95% CI)	−0.17 [−0.29, −0.05]
27.2 Mean baseline FEV1 61% to 79% of predicted	12	3382	Mean Difference (IV, Random, 95% CI)	−0.73 [−1.05, −0.41]
28 Change in # daytime rescue inhalations at endpoint	13		puffs per day (Random, 95% CI)	−0.68 [−0.94, −0.42]

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]

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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

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

WMD archive

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

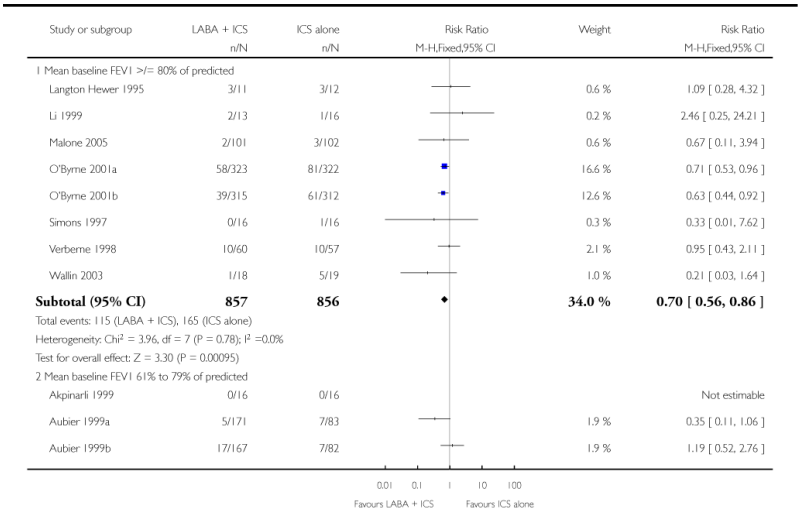
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
stratifying on baseline FEV1				
8 Change in # overall daily rescue inhalations at endpoint	10	3088	Mean Difference (IV, Random, 95% CI)	−0.74 [−1.07, −0.42]
8.1 Mean baseline FEV1 >/= 80% of predicted	2	1272	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]

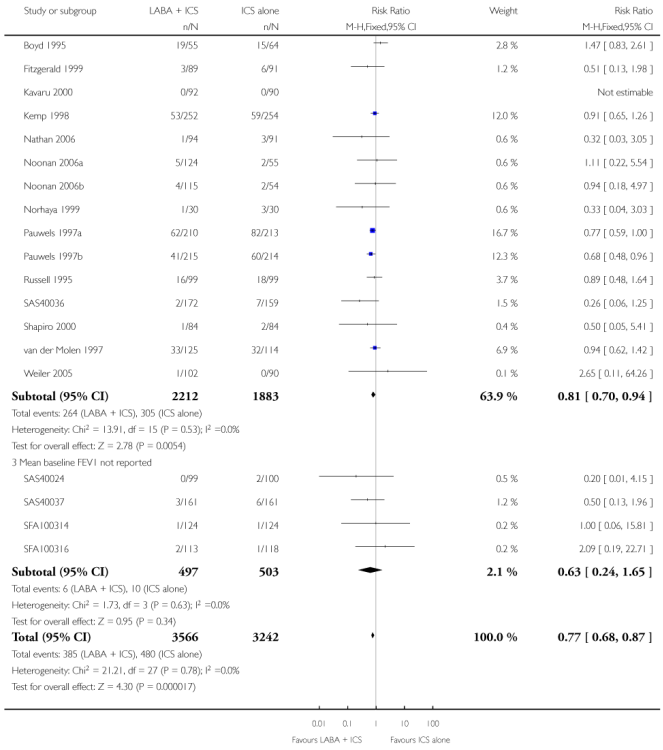
Analysis 1.1. Comparison 1 Long-acting beta2 versus placebo: both groups receiving similar dose ICS, Outcome 1 # patients with exacerbations requiring oral steroids

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





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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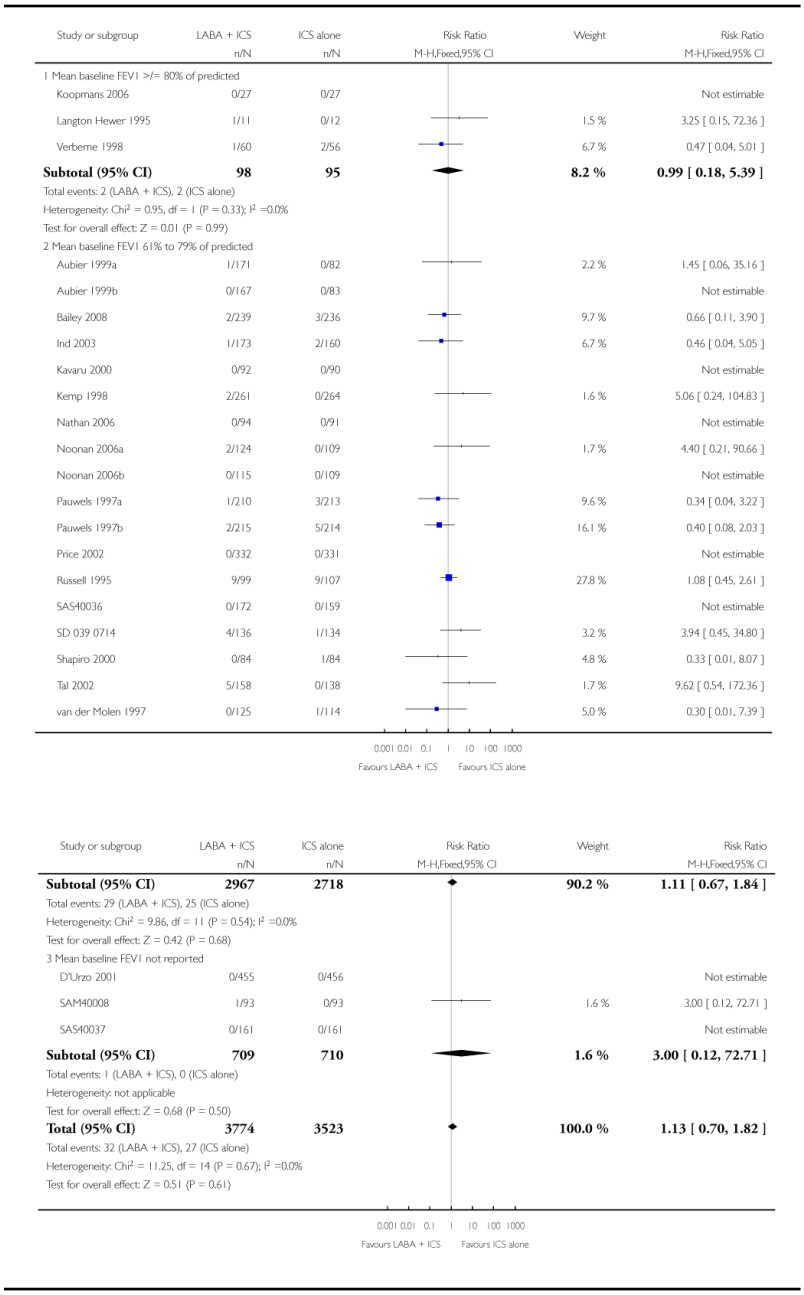
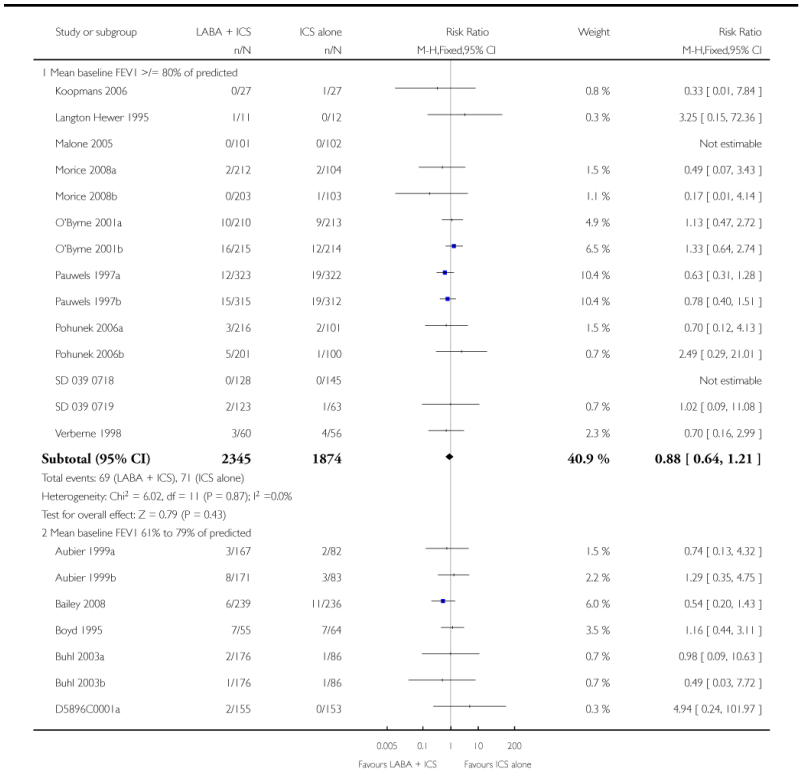


Analysis 1.3. Comparison 1 Long-acting beta2 versus placebo: both groups receiving similar dose ICS, Outcome 3 Serious adverse event including respiratory

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



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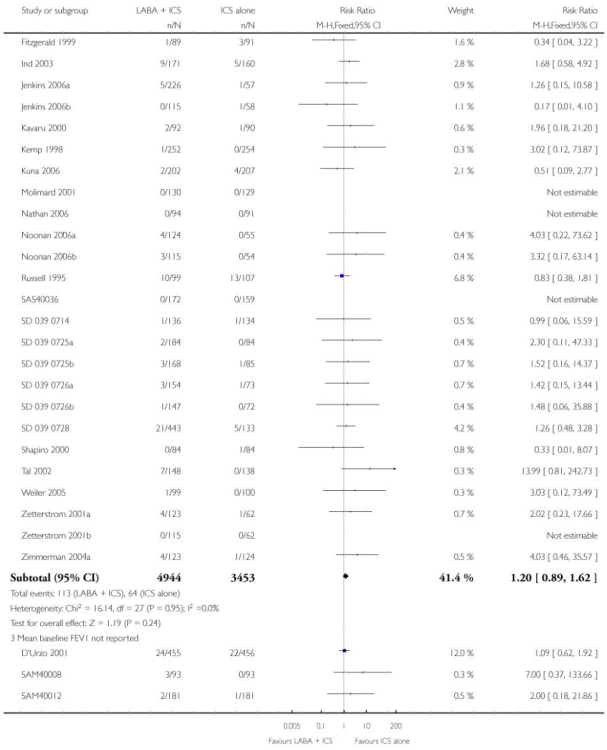
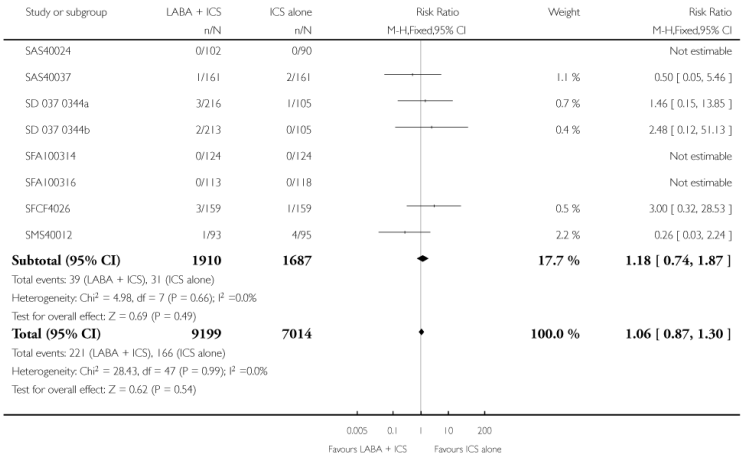


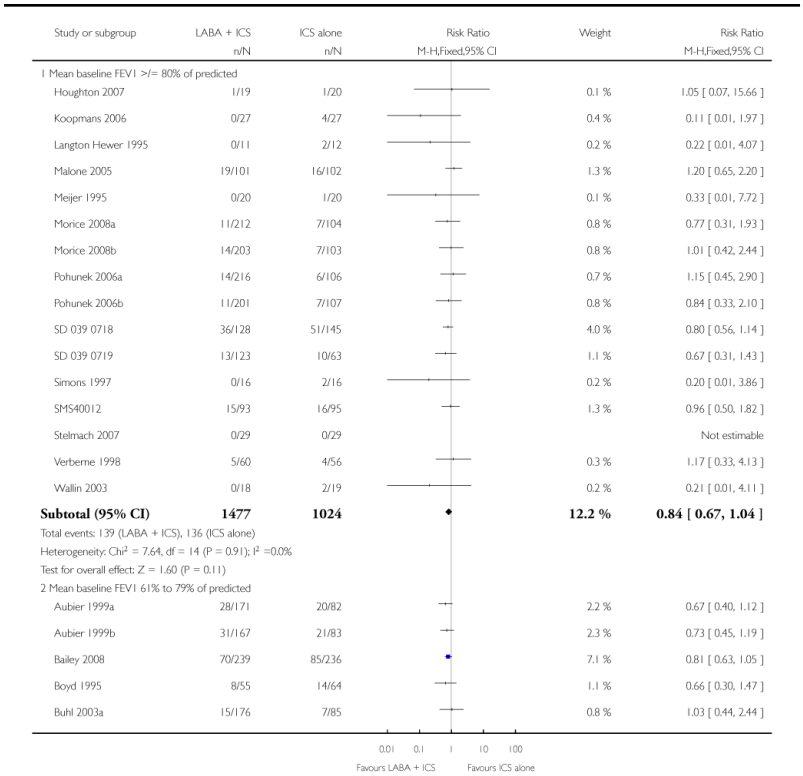


Analysis 1.4. Comparison 1 Long-acting beta2 versus placebo: both groups receiving similar dose ICS, Outcome 4 Total # withdrawals

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



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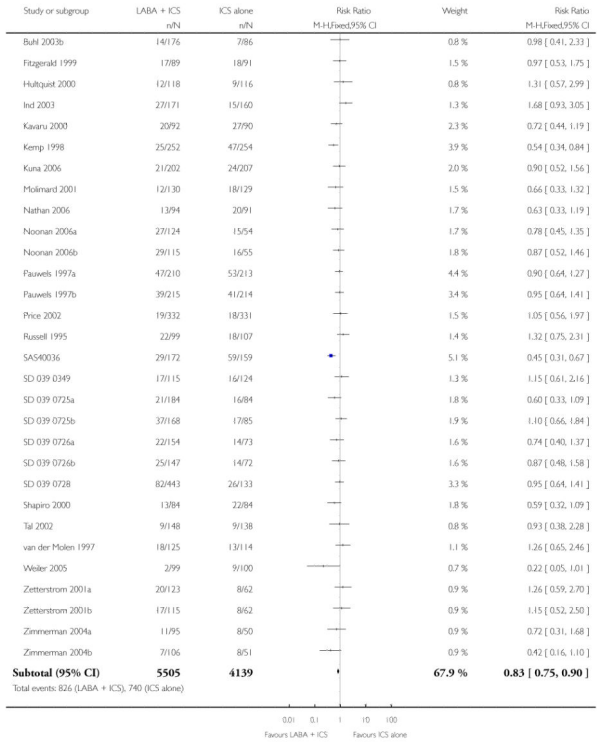
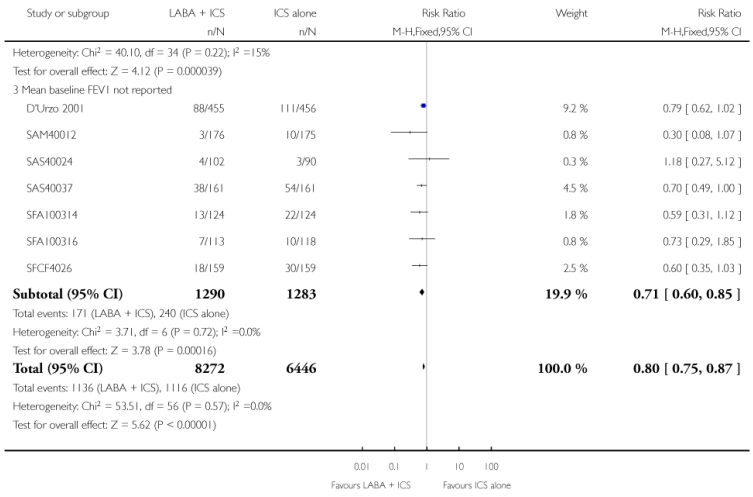


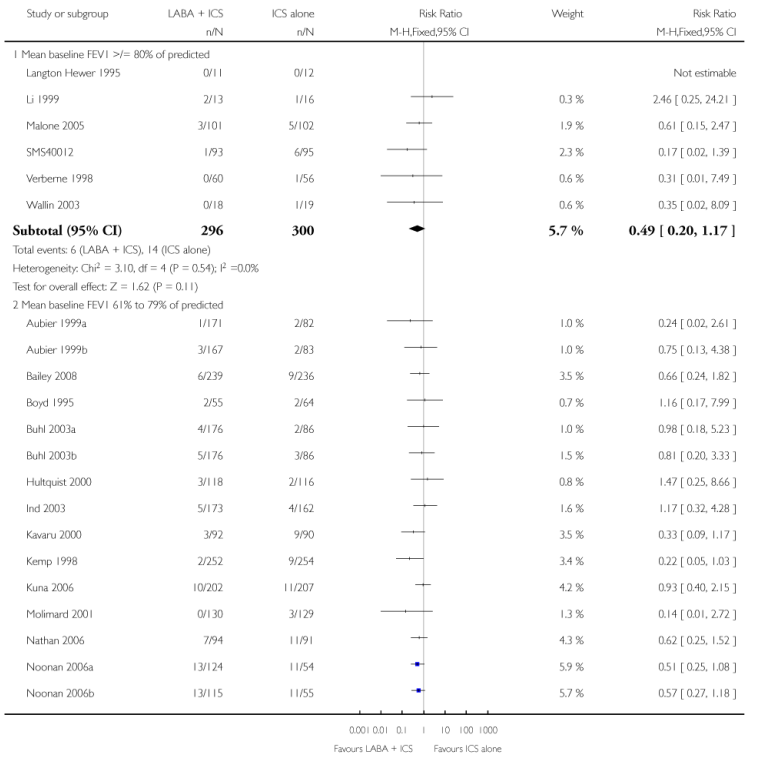


Analysis 1.5. Comparison 1 Long-acting beta2 versus placebo: both groups receiving similar dose ICS, Outcome 5 # withdrawals due to poor asthma control or exacerbation

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



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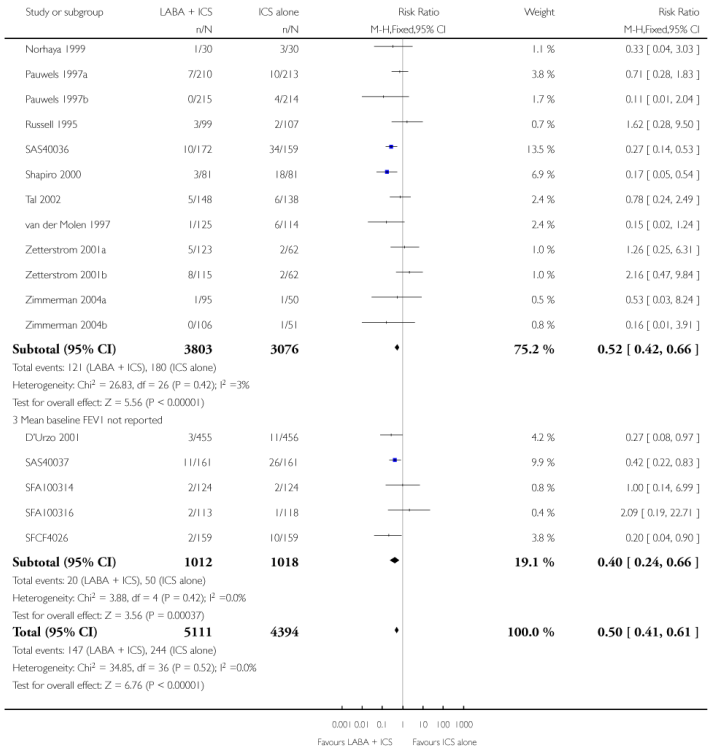

Analysis 1.6. Comparison 1 Long-acting beta2 versus placebo: both groups receiving similar dose ICS, Outcome 6 # withdrawals due to adverse events

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

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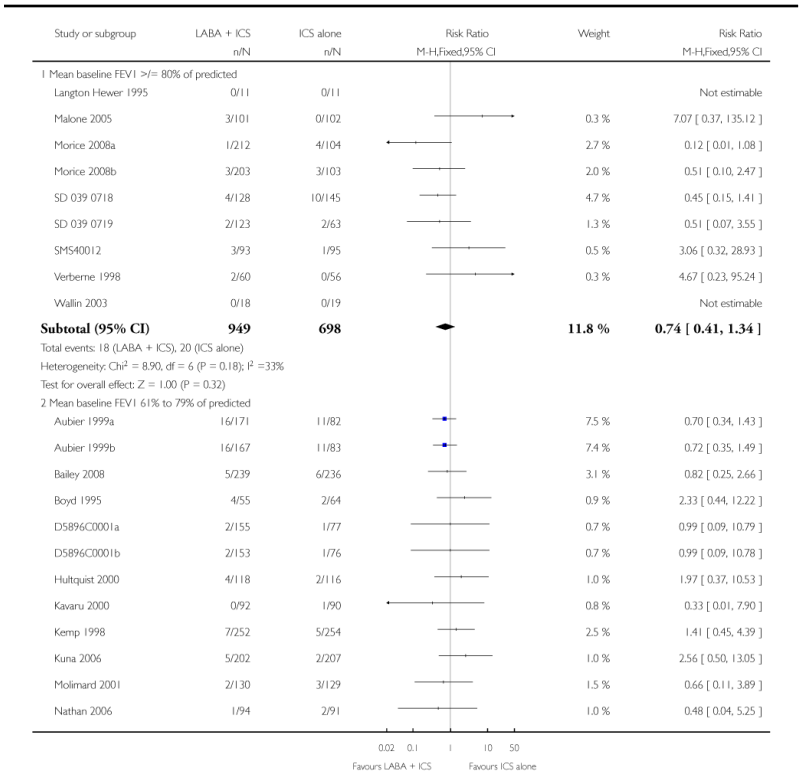

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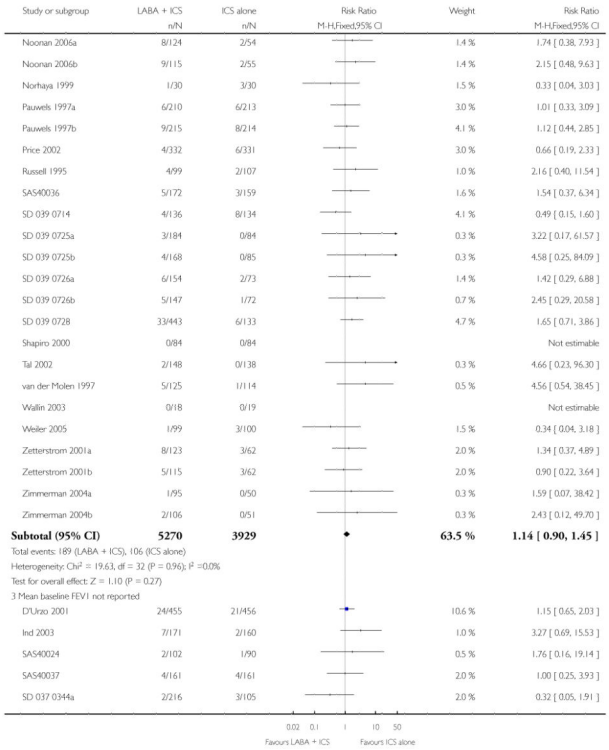

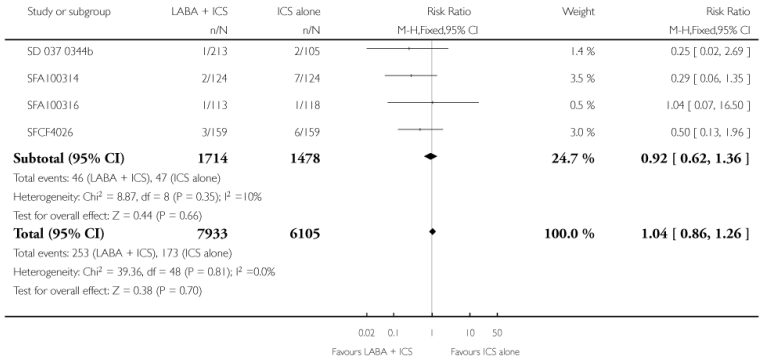

Analysis 1.7. Comparison 1 Long-acting beta2 versus placebo: both groups receiving similar dose ICS, Outcome 7 # withdrawals due to serious non-respiratory event

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

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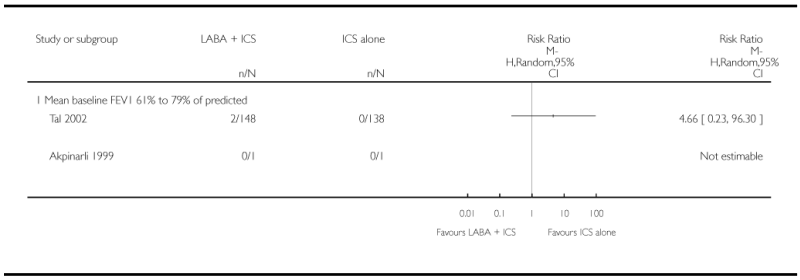
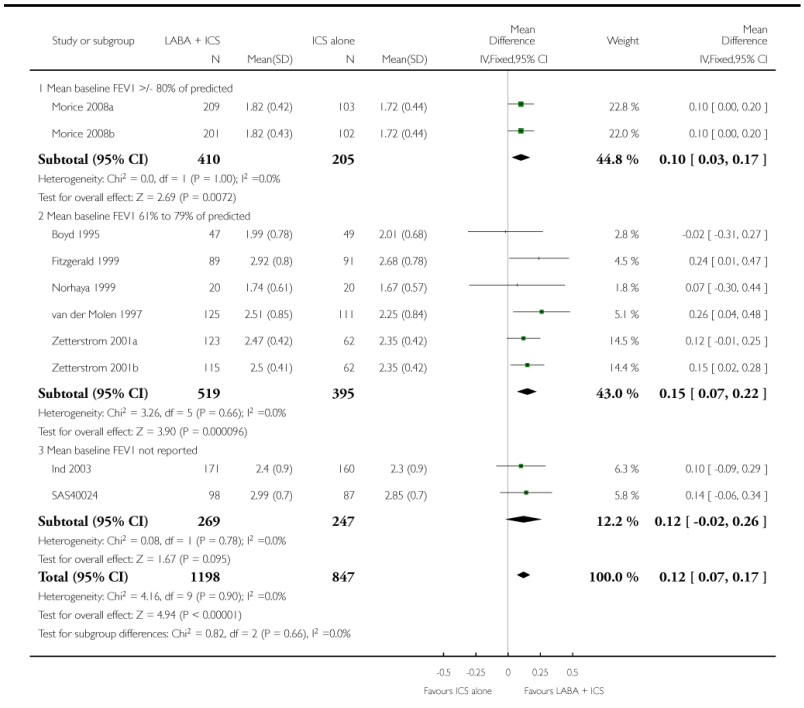


Analysis 1.8. Comparison 1 Long-acting beta2 versus placebo: both groups receiving similar dose ICS, Outcome 8 FEV1 (L) at endpoint

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



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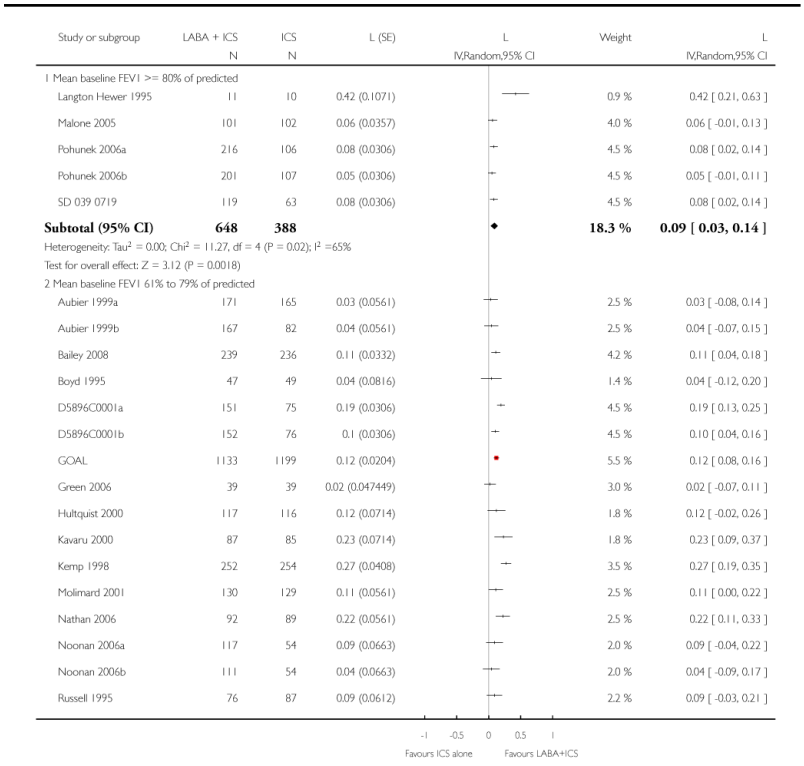
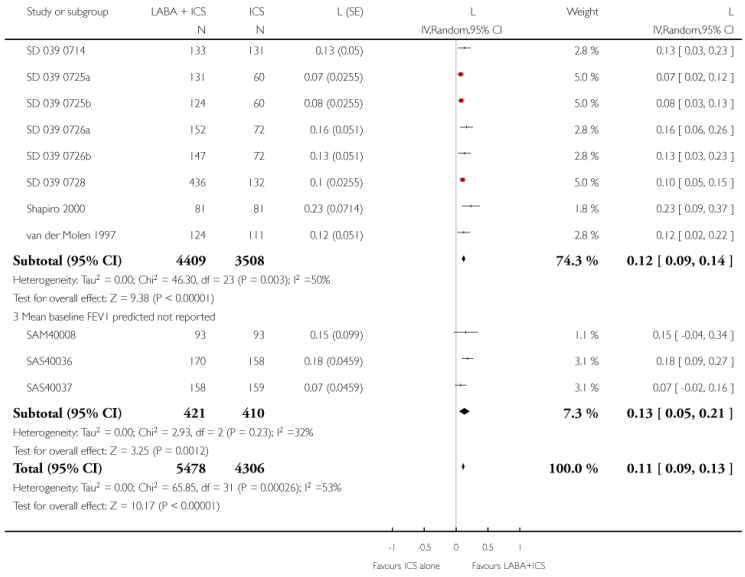
Analysis 1.9. Comparison 1 Long-acting beta2 versus placebo: both groups receiving similar dose ICS, Outcome 9 Change in FEV1 at endpoint stratifying on baseline FEV1

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





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

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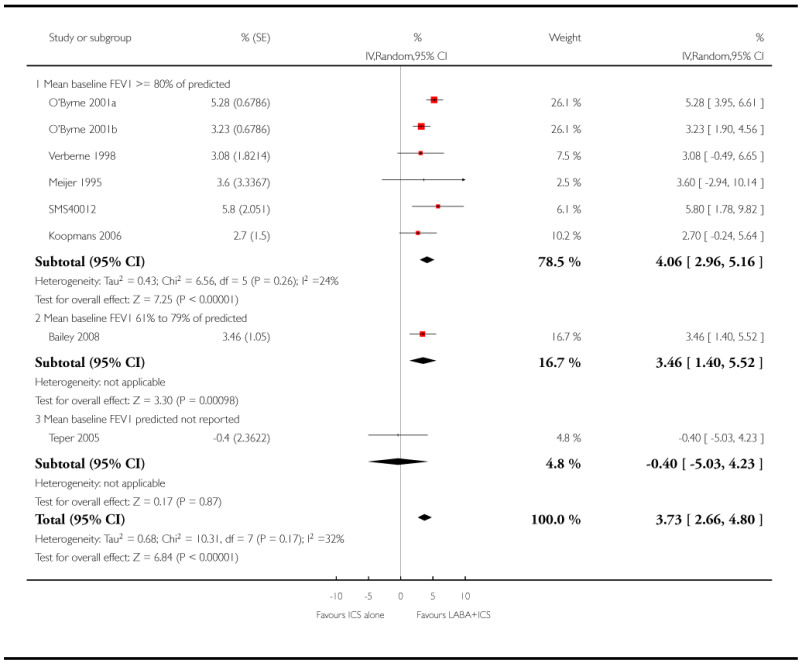

Analysis 1.11. Comparison 1 Long-acting beta2 versus placebo: both groups receiving similar dose ICS, Outcome 11 FEV1 % predicted at endpoint

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

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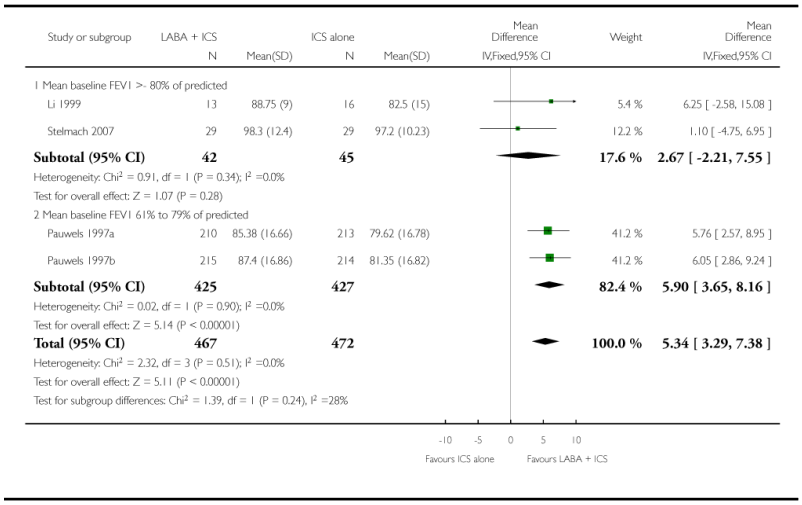

Analysis 1.12. Comparison 1 Long-acting beta2 versus placebo: both groups receiving similar dose ICS, Outcome 12 Change in FEV1 (L or % predicted) stratifying on trial duration

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

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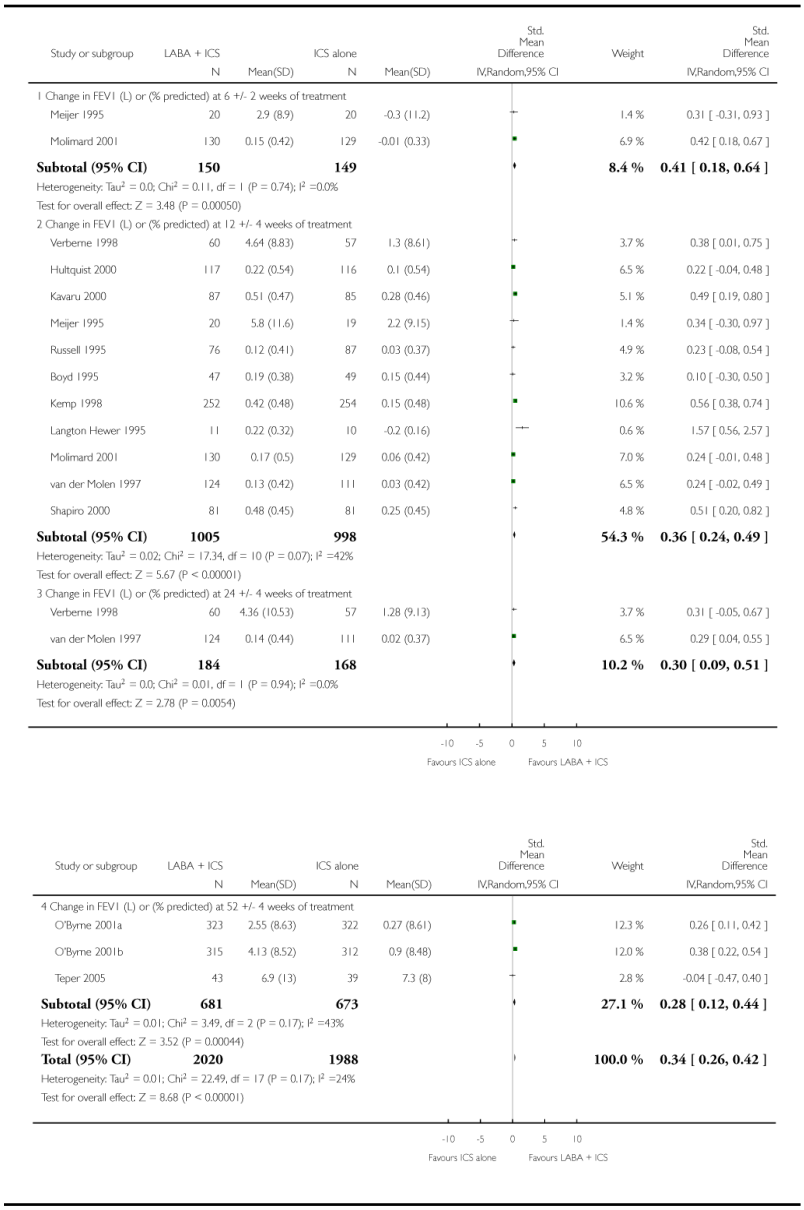

Analysis 1.13. Comparison 1 Long-acting beta2 versus placebo: both groups receiving similar dose ICS, Outcome 13 Morning PEF (L/min) at endpoint

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

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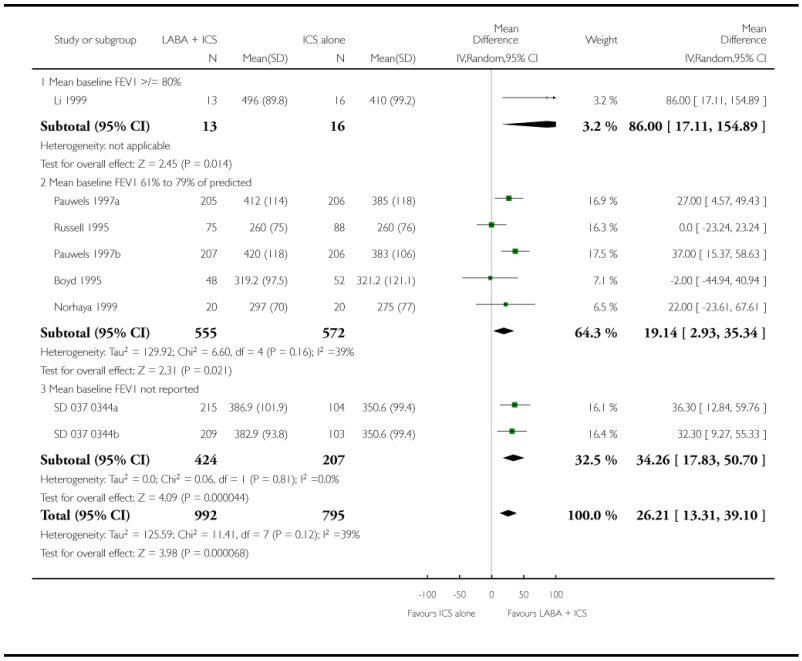
Outcome: 13 Morning PEF (L/min) at endpoint



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

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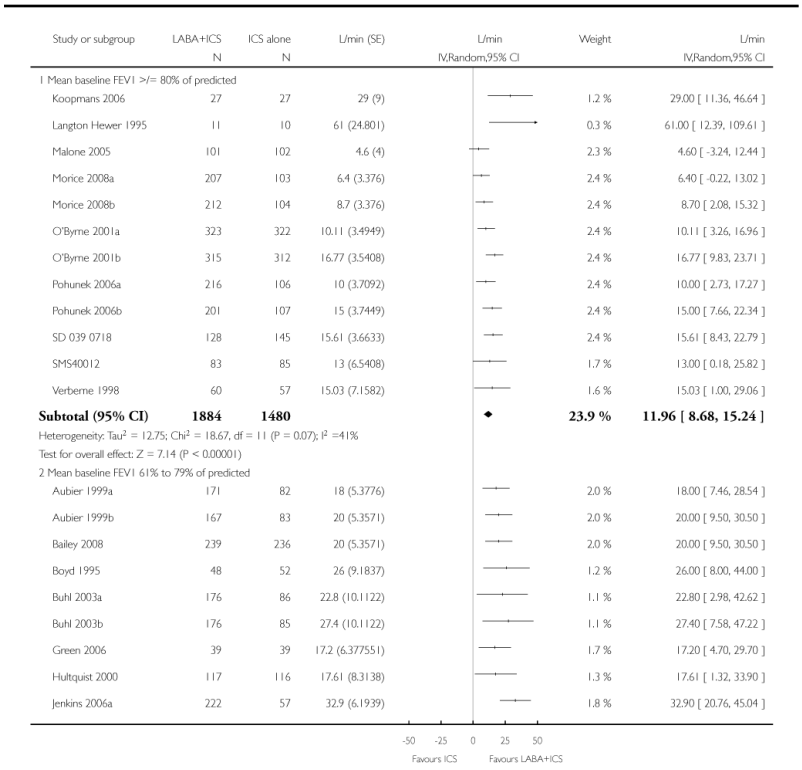

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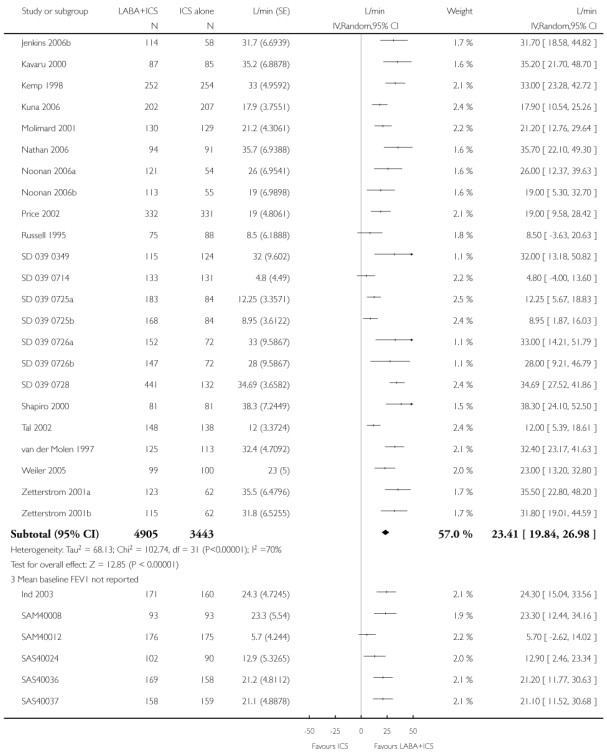

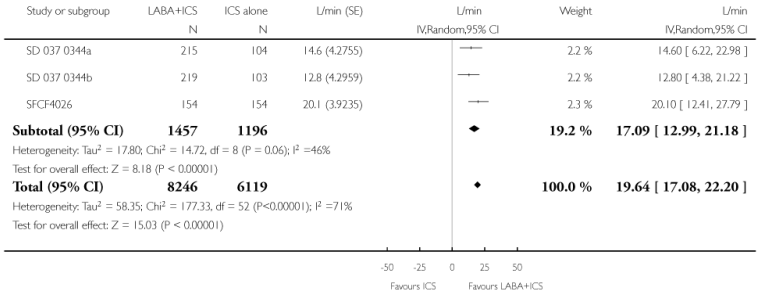

Analysis 1.15. Comparison 1 Long-acting beta2 versus placebo: both groups receiving similar dose ICS, Outcome 15 Evening PEF (L/min) at endpoint

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

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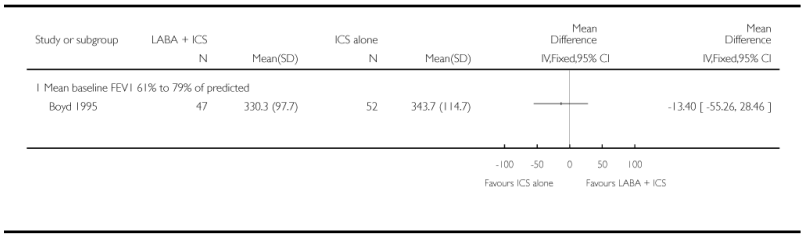
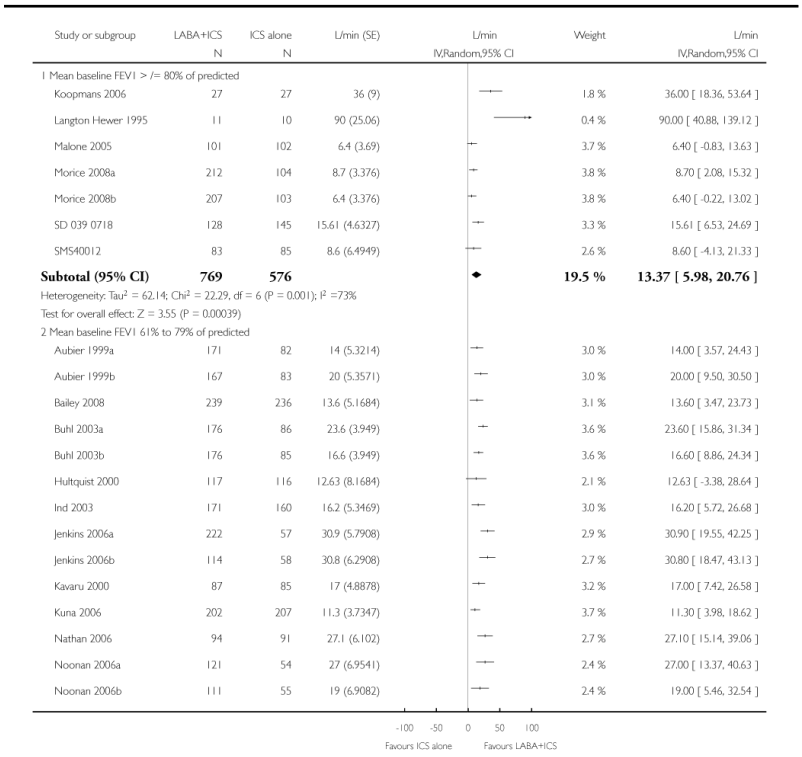


Analysis 1.16. Comparison 1 Long-acting beta2 versus placebo: both groups receiving similar dose ICS, Outcome 16 Change in evening PEF at endpoint

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



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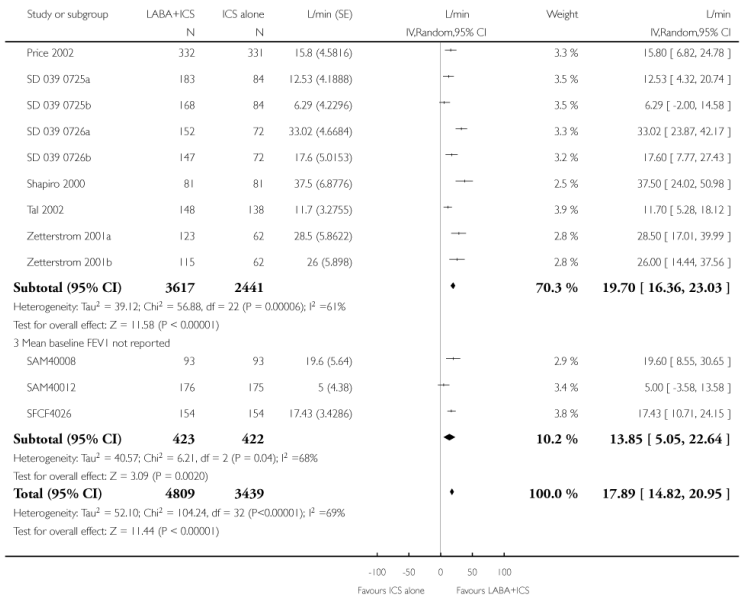
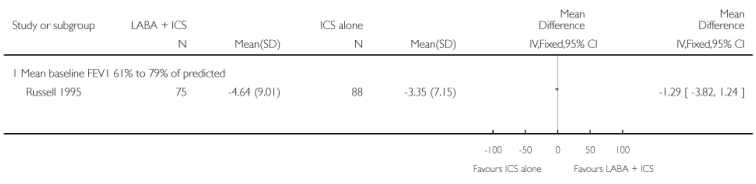


Analysis 1.17. Comparison 1 Long-acting beta2 versus placebo: both groups receiving similar dose ICS, Outcome 17 Change in PEF variability at endpoint

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



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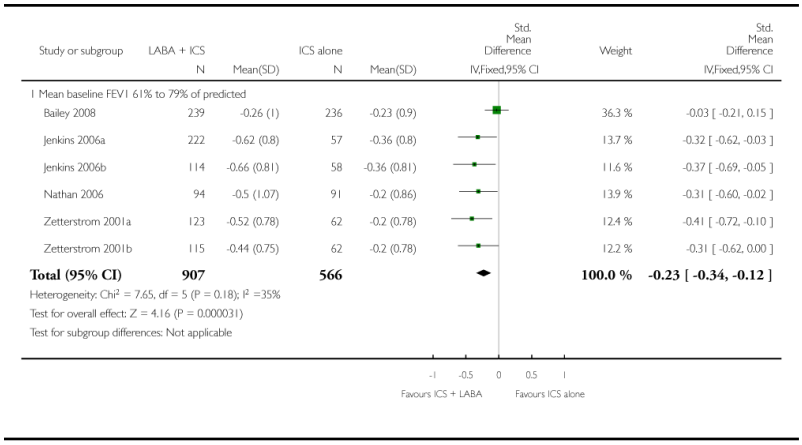
Analysis 1.18. Comparison 1 Long-acting beta2 versus placebo: both groups receiving similar dose ICS, Outcome 18 Change in 24-hour symptom score at endpoint

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



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

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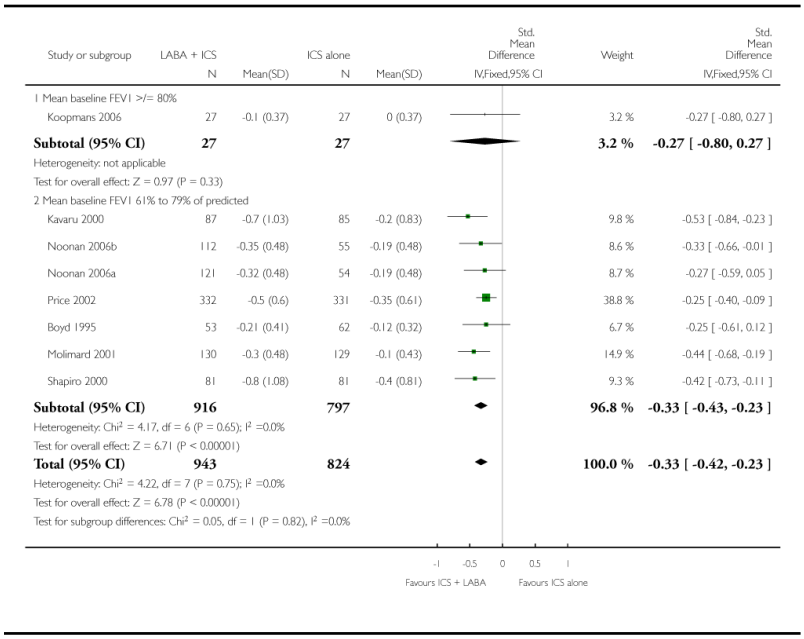

Analysis 1.20. Comparison 1 Long-acting beta2 versus placebo: both groups receiving similar dose ICS, Outcome 20 Change in night-time symptom score at endpoint

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

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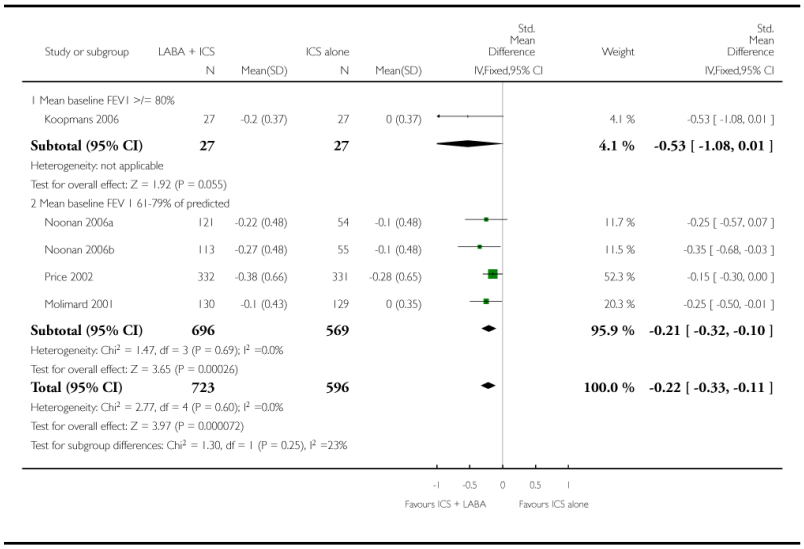

Analysis 1.21. Comparison 1 Long-acting beta2 versus placebo: both groups receiving similar dose ICS, Outcome 21 % symptom-free days

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

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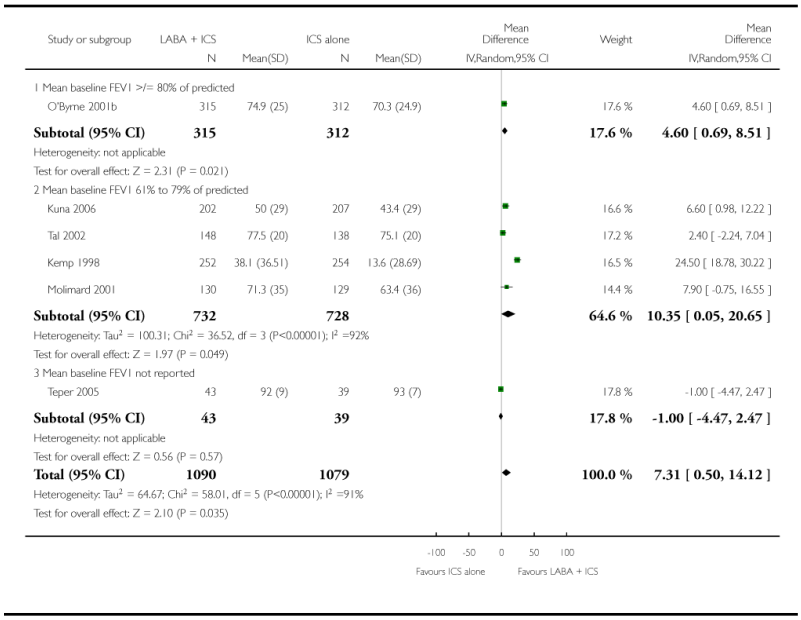

Analysis 1.22. Comparison 1 Long-acting beta2 versus placebo: both groups receiving similar dose ICS, Outcome 22 Change in % symptom-free days at endpoint

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

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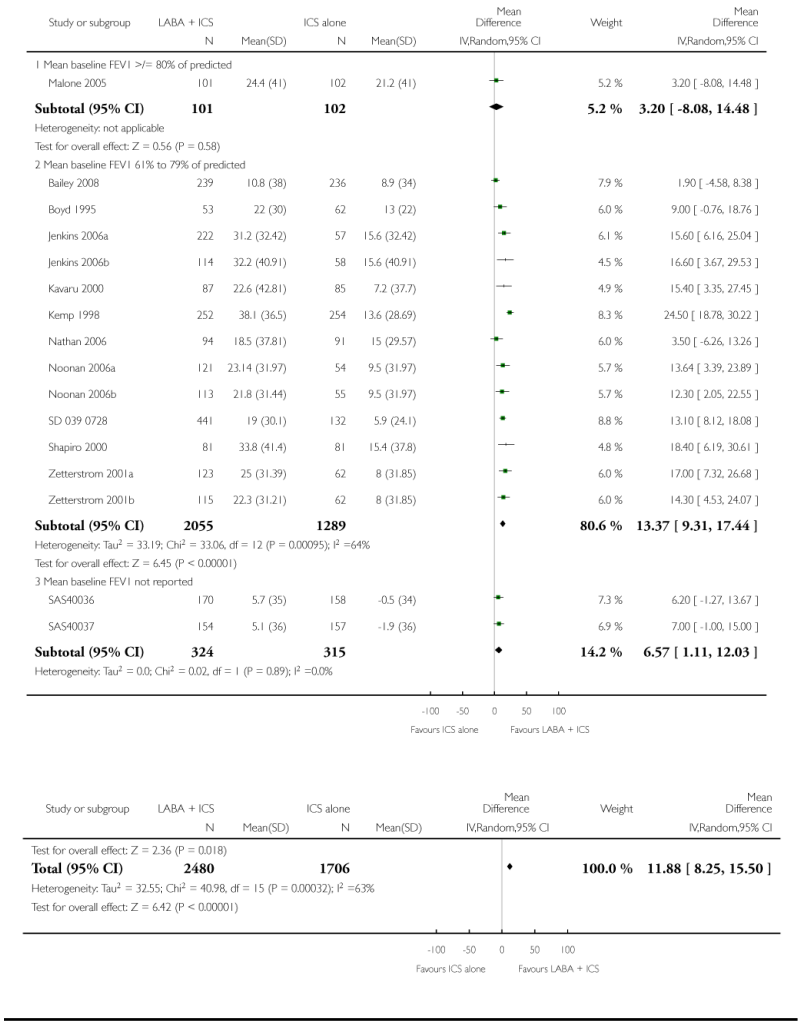

Analysis 1.23. Comparison 1 Long-acting beta2 versus placebo: both groups receiving similar dose ICS, Outcome 23 Change in # of symptom-free nights at endpoint

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

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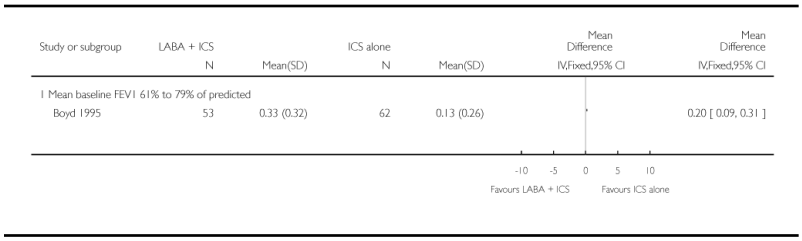
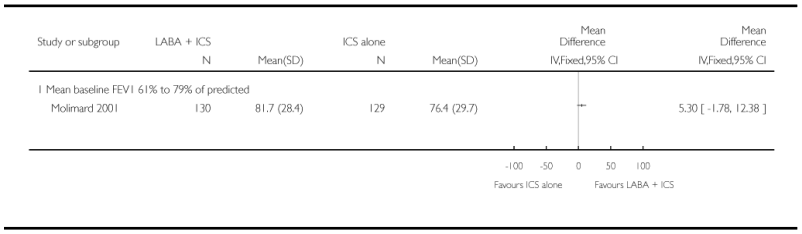


Analysis 1.24. Comparison 1 Long-acting beta2 versus placebo: both groups receiving similar dose ICS, Outcome 24 % symptom-free nights at 12 +/- 4 weeks

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



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

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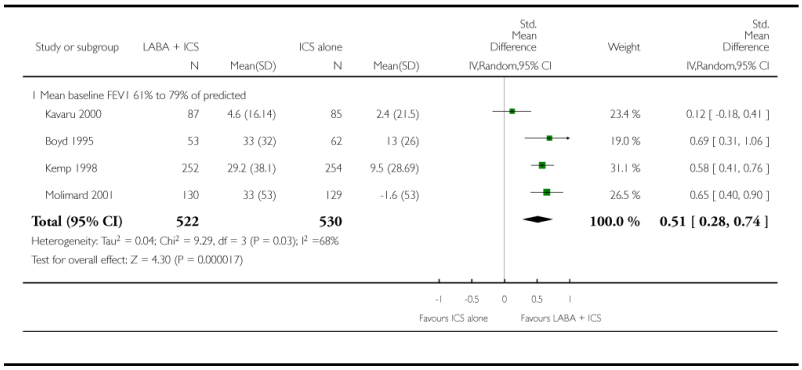
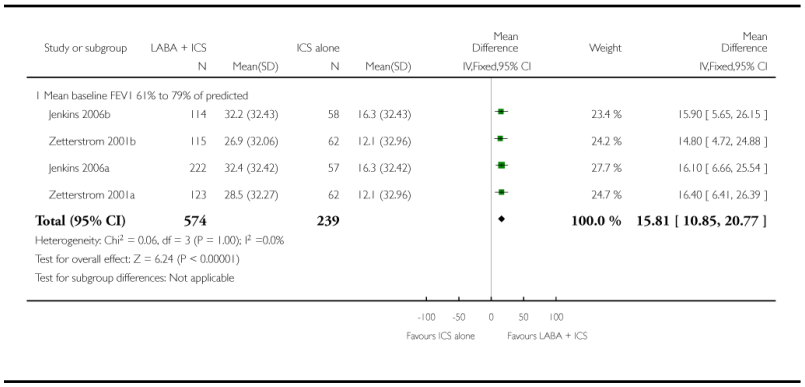


Analysis 1.26. Comparison 1 Long-acting beta2 versus placebo: both groups receiving similar dose ICS, Outcome 26 Change in asthma control days %

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 %



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

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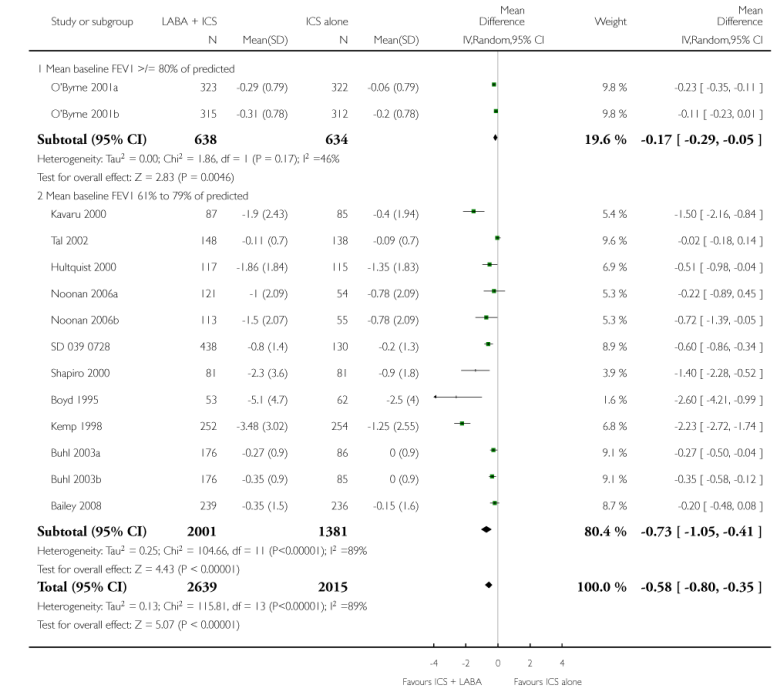
Outcome: 27 Change in # overall daily rescue inhalations at endpoint



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

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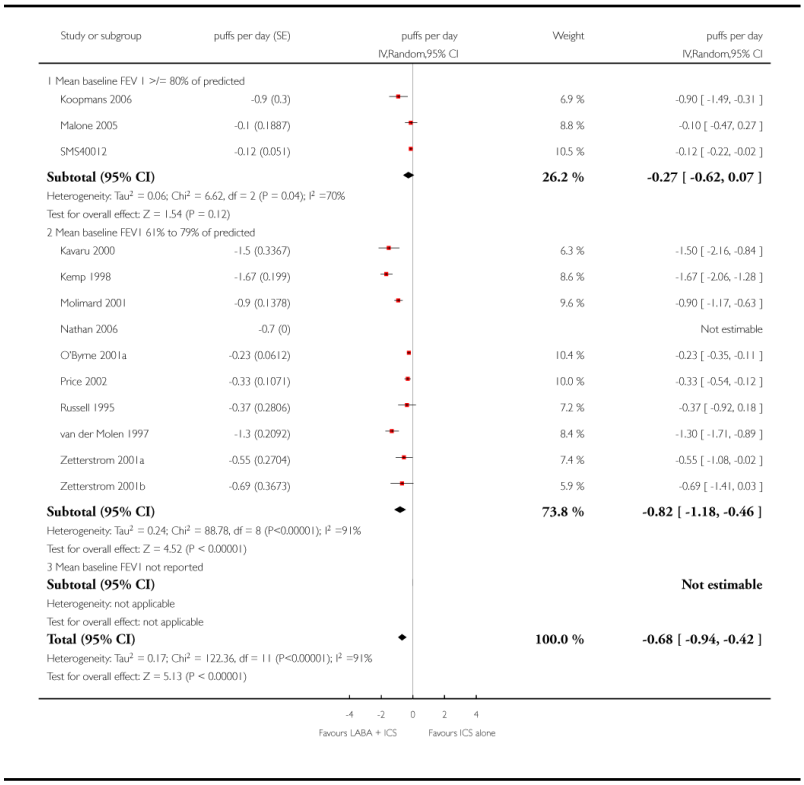
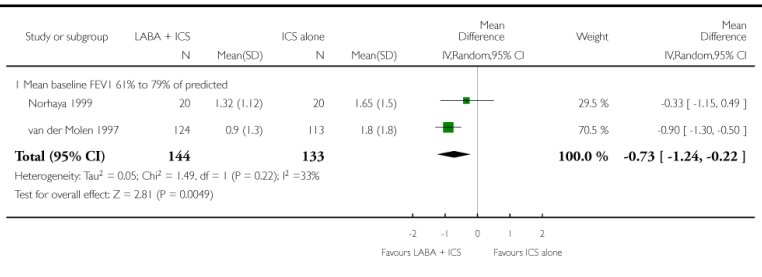


Analysis 1.29. Comparison 1 Long-acting beta2 versus placebo: both groups receiving similar dose ICS, Outcome 29 # daytime rescue inhalations (puffs per day) at endpoint

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



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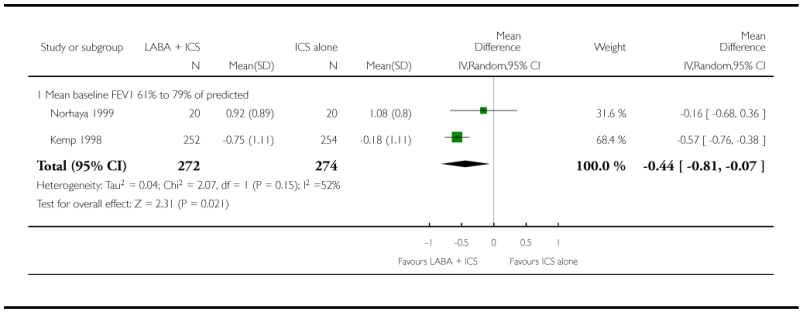
Analysis 1.30. Comparison 1 Long-acting beta2 versus placebo: both groups receiving similar dose ICS, Outcome 30 # night-time rescue inhalations (puffs per night) at endpoint

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

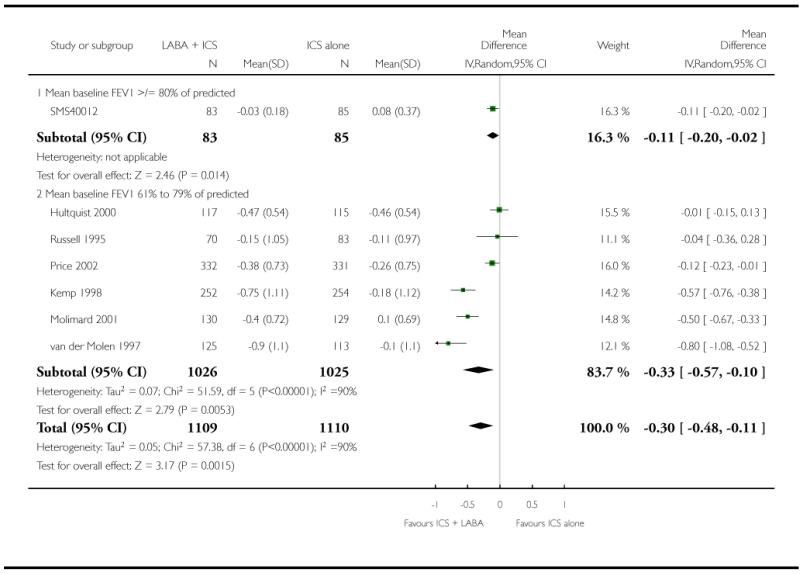


Analysis 1.31. Comparison 1 Long-acting beta2 versus placebo: both groups receiving similar dose ICS, Outcome 31 Change in # night-time rescue inhalations at endpoint

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



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

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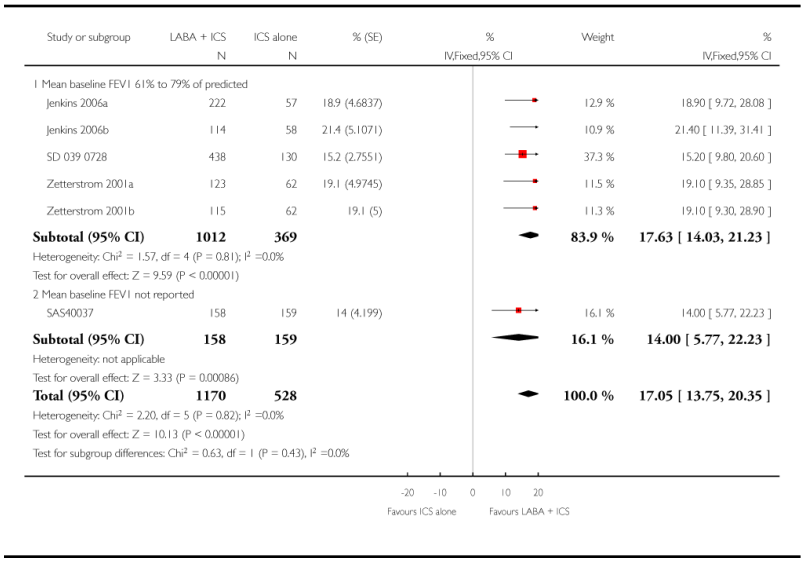
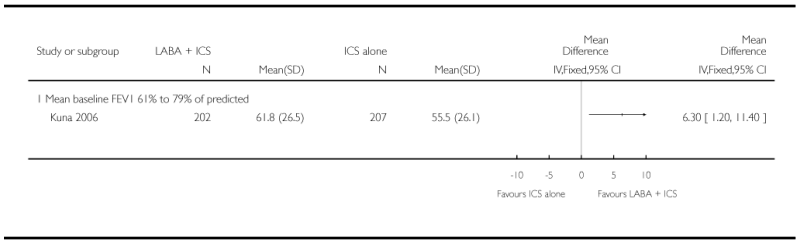


Analysis 1.33. Comparison 1 Long-acting beta2 versus placebo: both groups receiving similar dose ICS, Outcome 33 Rescue medication-free days

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



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

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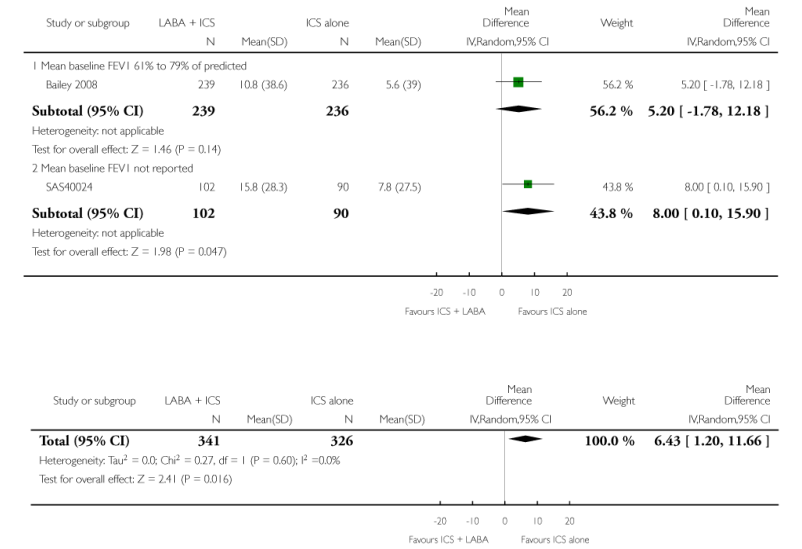
Comparison: 1 Long-acting beta2 versus placebo: both groups receiving similar dose ICS

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

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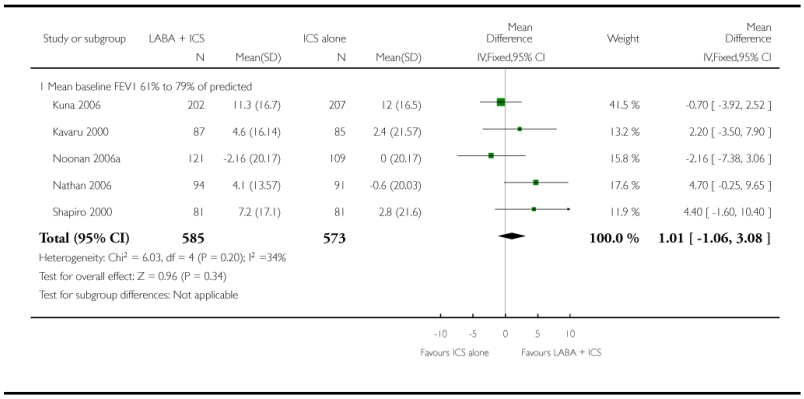
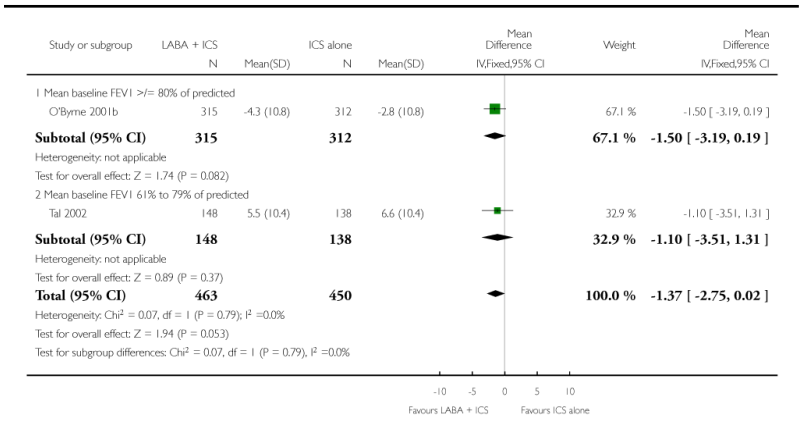


Analysis 1.36. Comparison 1 Long-acting beta2 versus placebo: both groups receiving similar dose ICS, Outcome 36 % nights with awakening

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



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

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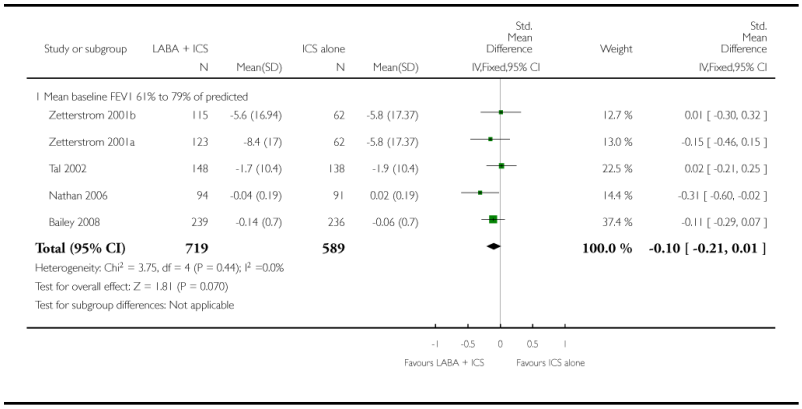
Comparison: 1 Long-acting beta2 versus placebo: both groups receiving similar dose ICS

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

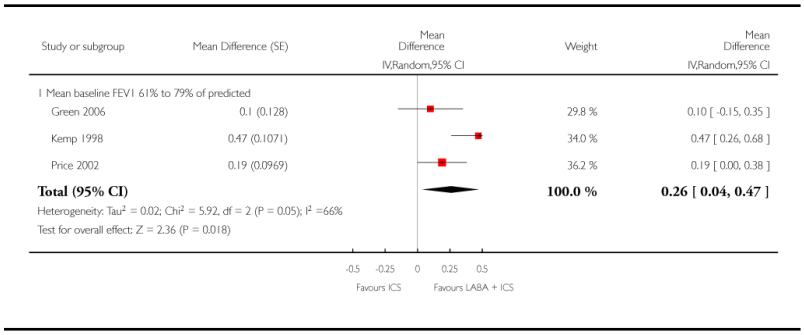


Analysis 1.38. Comparison 1 Long-acting beta2 versus placebo: both groups receiving similar dose ICS, Outcome 38 Change in quality of life (AQLQ score) at endpoint

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



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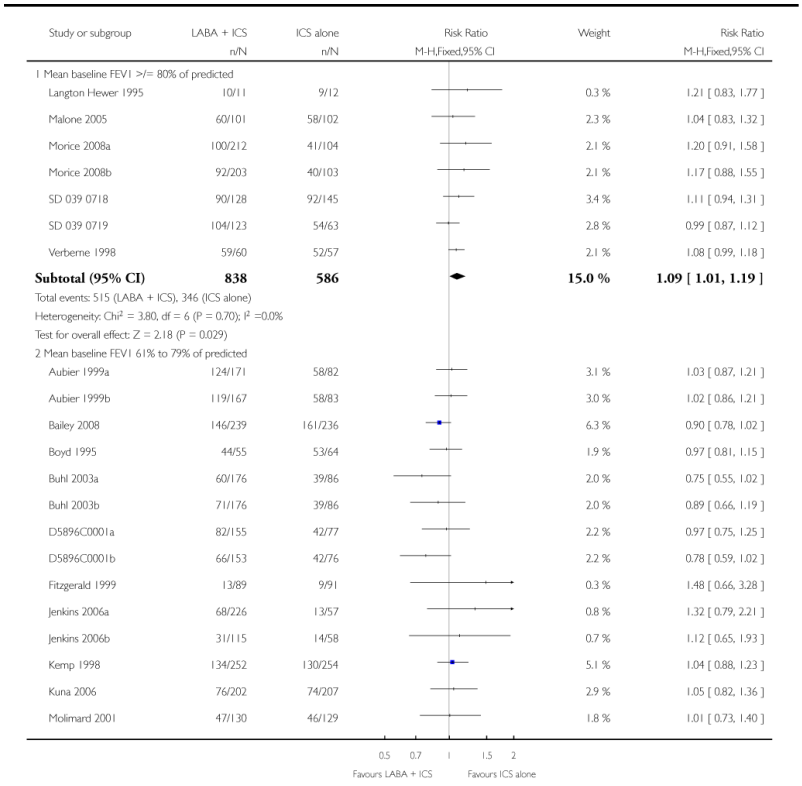
Comparison: 1 Long-acting beta2 versus placebo: both groups receiving similar dose ICS

Outcome: 39 Total # adverse events



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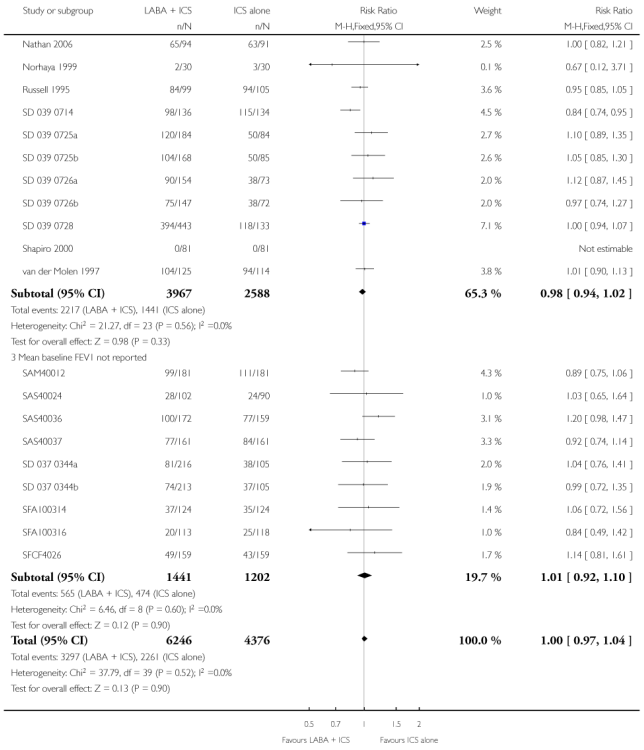

Analysis 1.40. Comparison 1 Long-acting beta2 versus placebo: both groups receiving similar dose ICS, Outcome 40 # patients with headache

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

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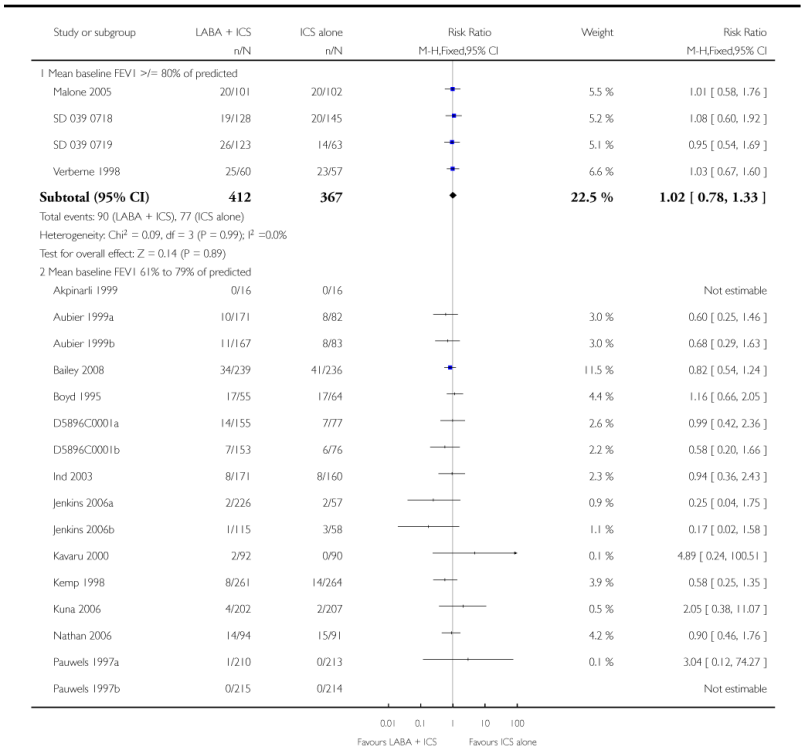

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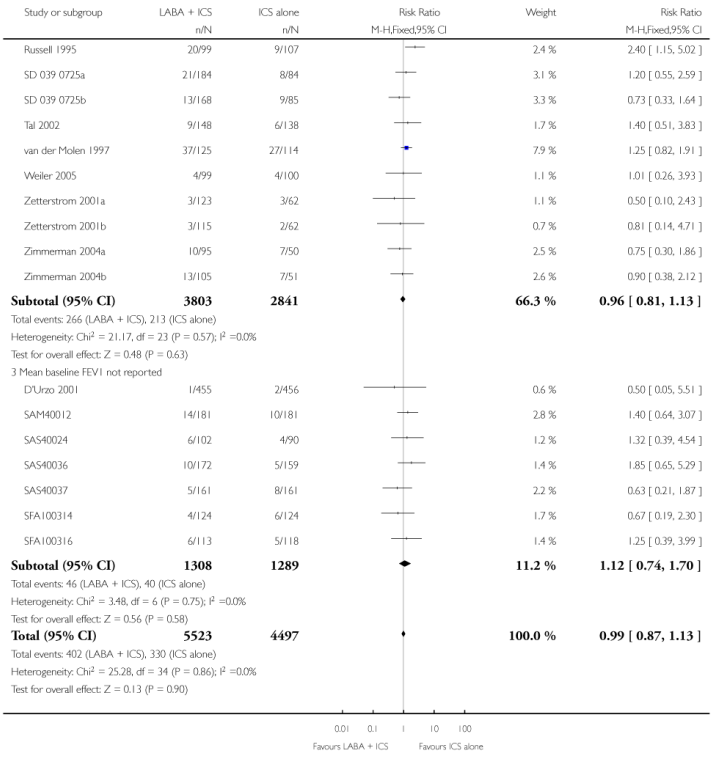

Analysis 1.41. Comparison 1 Long-acting beta2 versus placebo: both groups receiving similar dose ICS, Outcome 41 # patients with hoarseness

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

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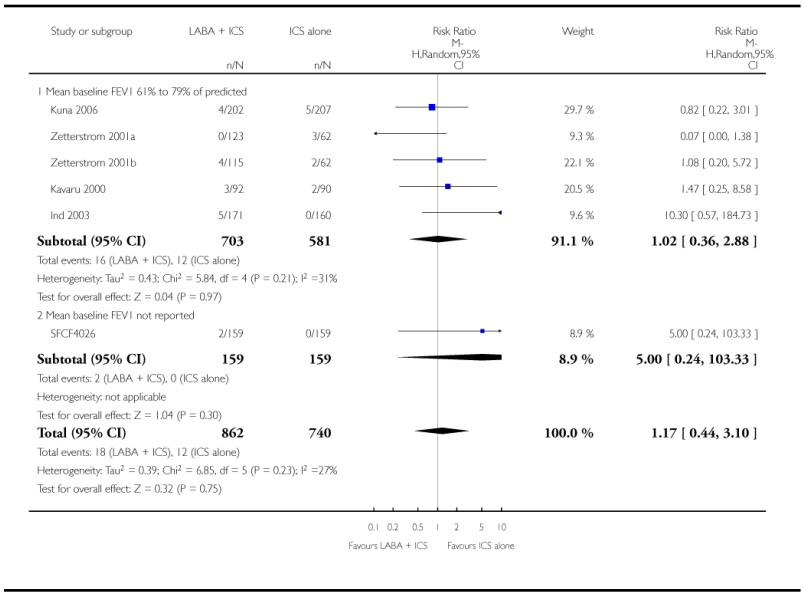

Analysis 1.42. Comparison 1 Long-acting beta2 versus placebo: both groups receiving similar dose ICS, Outcome 42 # patients with oral thrush

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

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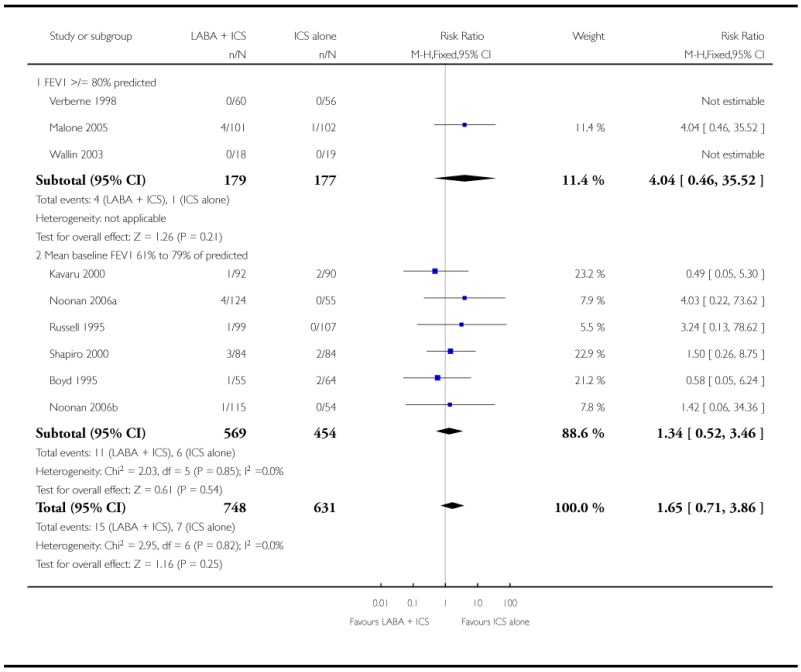

Analysis 1.43. Comparison 1 Long-acting beta2 versus placebo: both groups receiving similar dose ICS, Outcome 43 # patients with tremor

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

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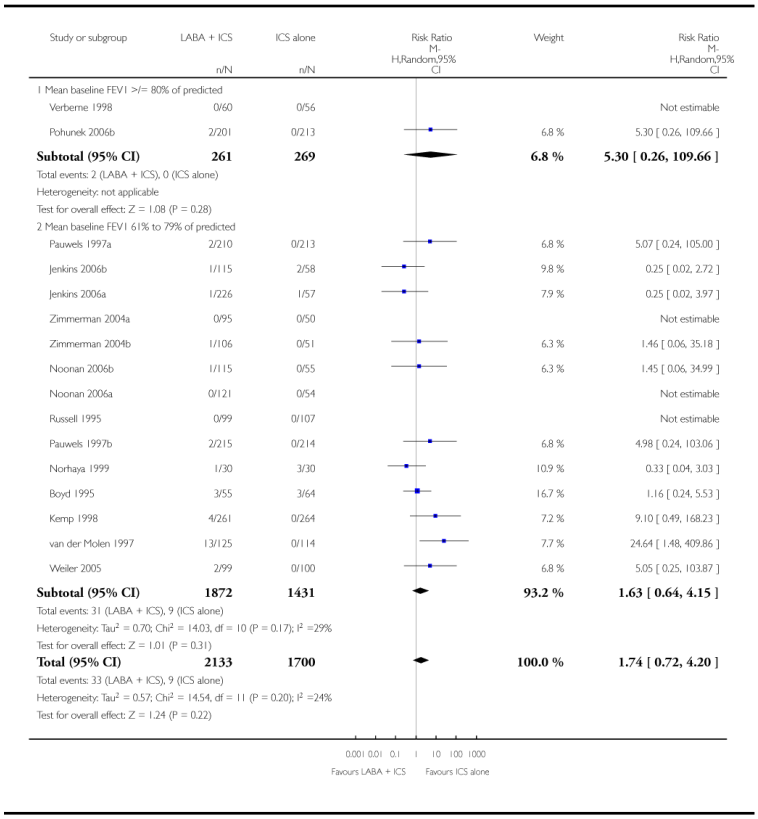

Analysis 1.44. Comparison 1 Long-acting beta2 versus placebo: both groups receiving similar dose ICS, Outcome 44 # patients with tachycardia or palpitations

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

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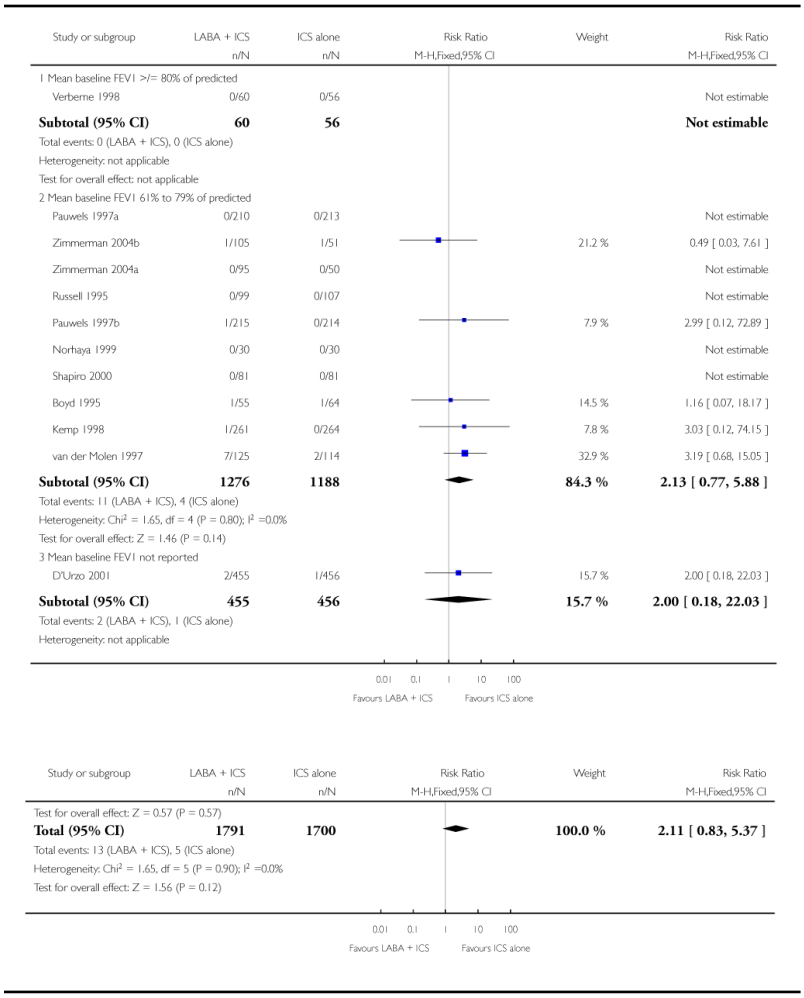

Analysis 1.45. Comparison 1 Long-acting beta2 versus placebo: both groups receiving similar dose ICS, Outcome 45 Deaths

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

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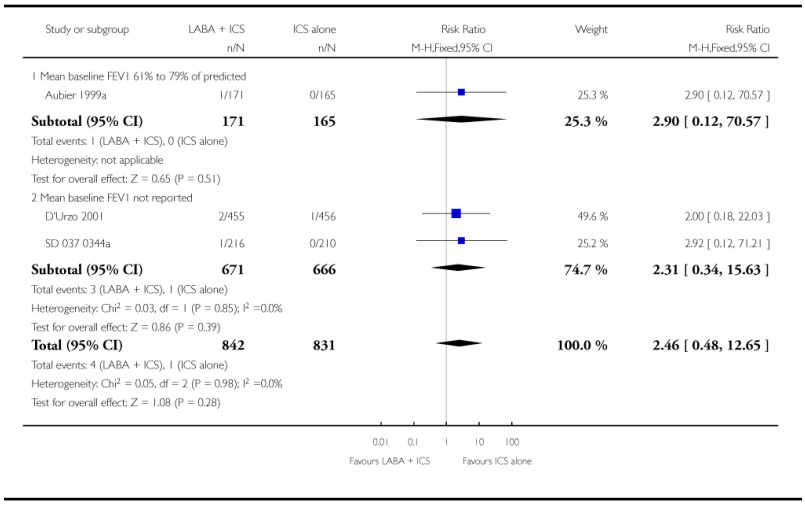
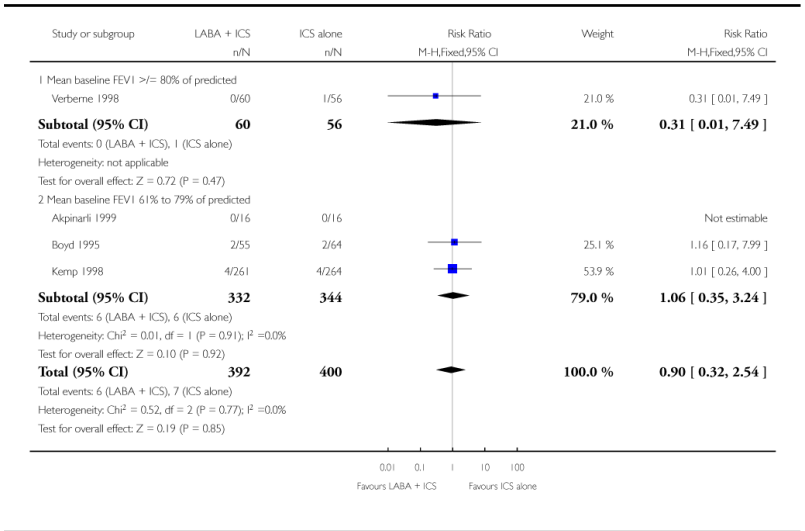


Analysis 1.46. Comparison 1 Long-acting beta2 versus placebo: both groups receiving similar dose ICS, Outcome 46 # patients with adverse cardiovascular events

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



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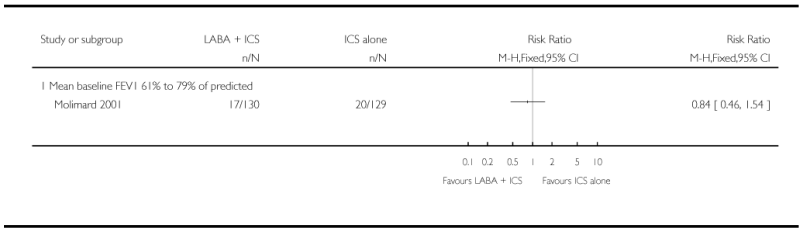
Analysis 1.47. Comparison 1 Long-acting beta2 versus placebo: both groups receiving similar dose ICS, Outcome 47 # Worsening asthma

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

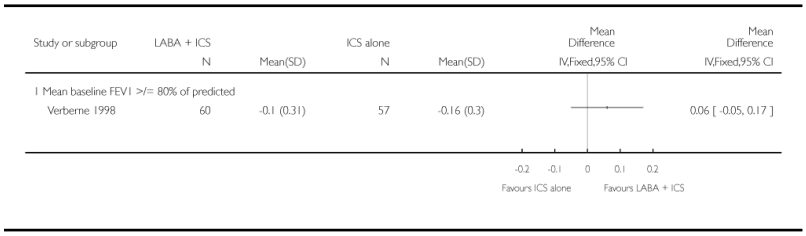


Analysis 1.48. Comparison 1 Long-acting beta2 versus placebo: both groups receiving similar dose ICS, Outcome 48 Change in height (cm) as SD scores at 24 +/- 4 weeks

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

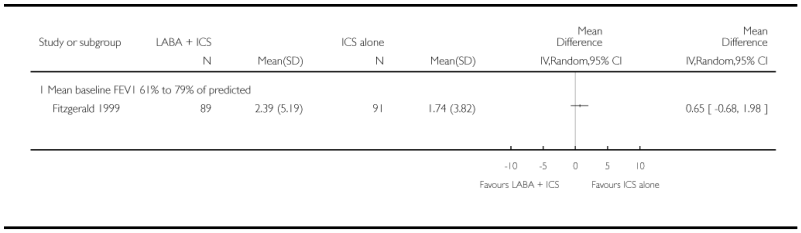


Analysis 1.49. Comparison 1 Long-acting beta2 versus placebo: both groups receiving similar dose ICS, Outcome 49 PC20 Methacholine-adjusted odds ratio increase from baseline

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

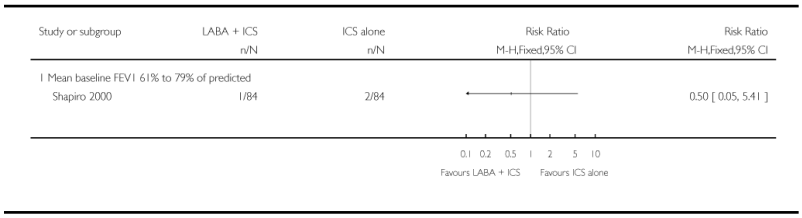


Analysis 1.50. Comparison 1 Long-acting beta2 versus placebo: both groups receiving similar dose ICS, Outcome 50 ACTH induced cortisol < 18 microg/dl at endpoint

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

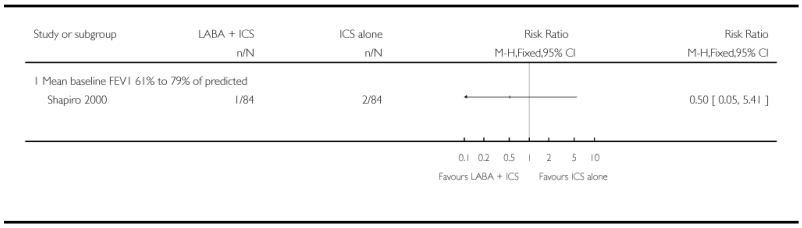


Analysis 1.51. Comparison 1 Long-acting beta2 versus placebo: both groups receiving similar dose ICS, Outcome 51 am cortisol < 5 microg/dl at endpoint

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

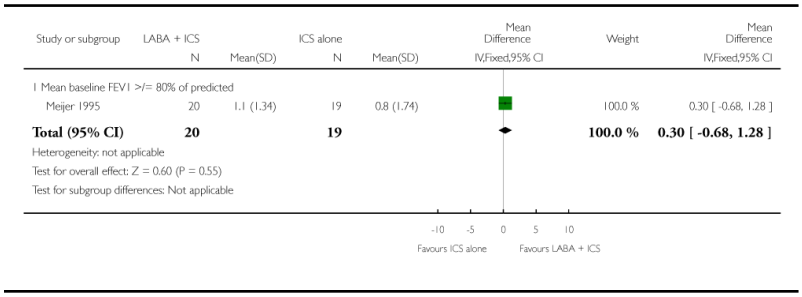


Analysis 1.52. Comparison 1 Long-acting beta2 versus placebo: both groups receiving similar dose ICS, Outcome 52 Change in % PC20 at endpoint

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



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

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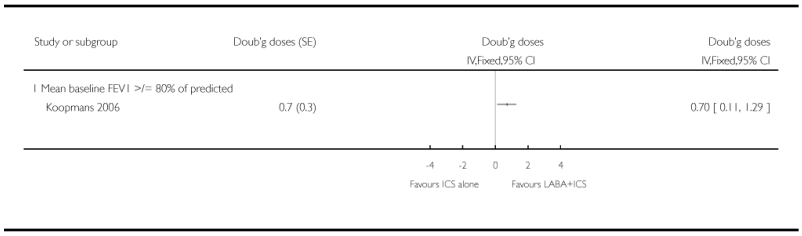
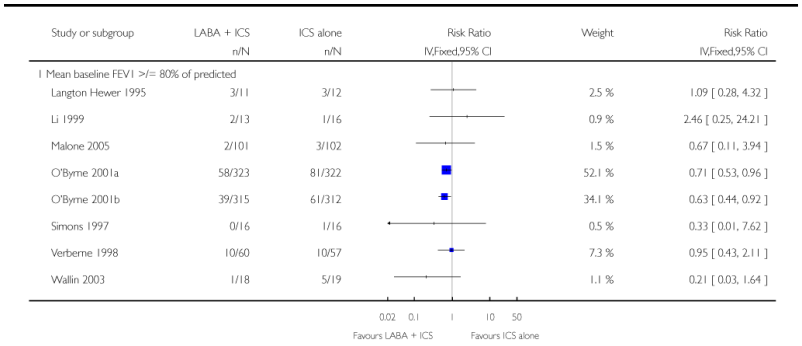


Analysis 2.1. Comparison 2 Additional comparisons for same dose, Outcome 1 # patients with exacerbations requiring oral steroids by baseline predicted FEV1

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



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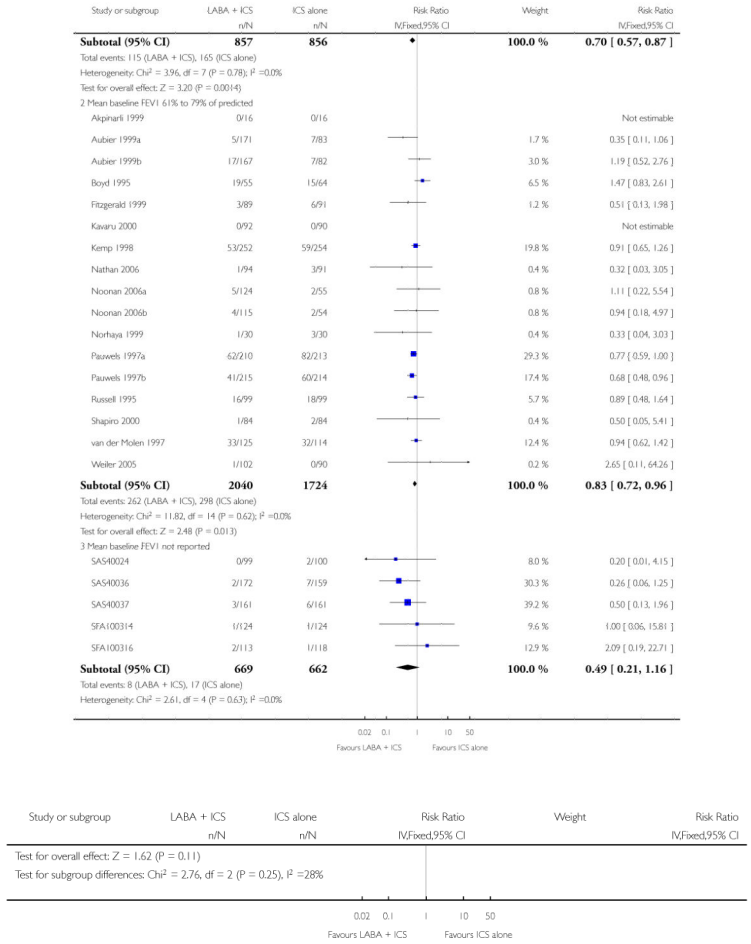

Analysis 2.2. Comparison 2 Additional comparisons for same dose, Outcome 2 # patients with exacerbations requiring oral steroids children versus adults

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

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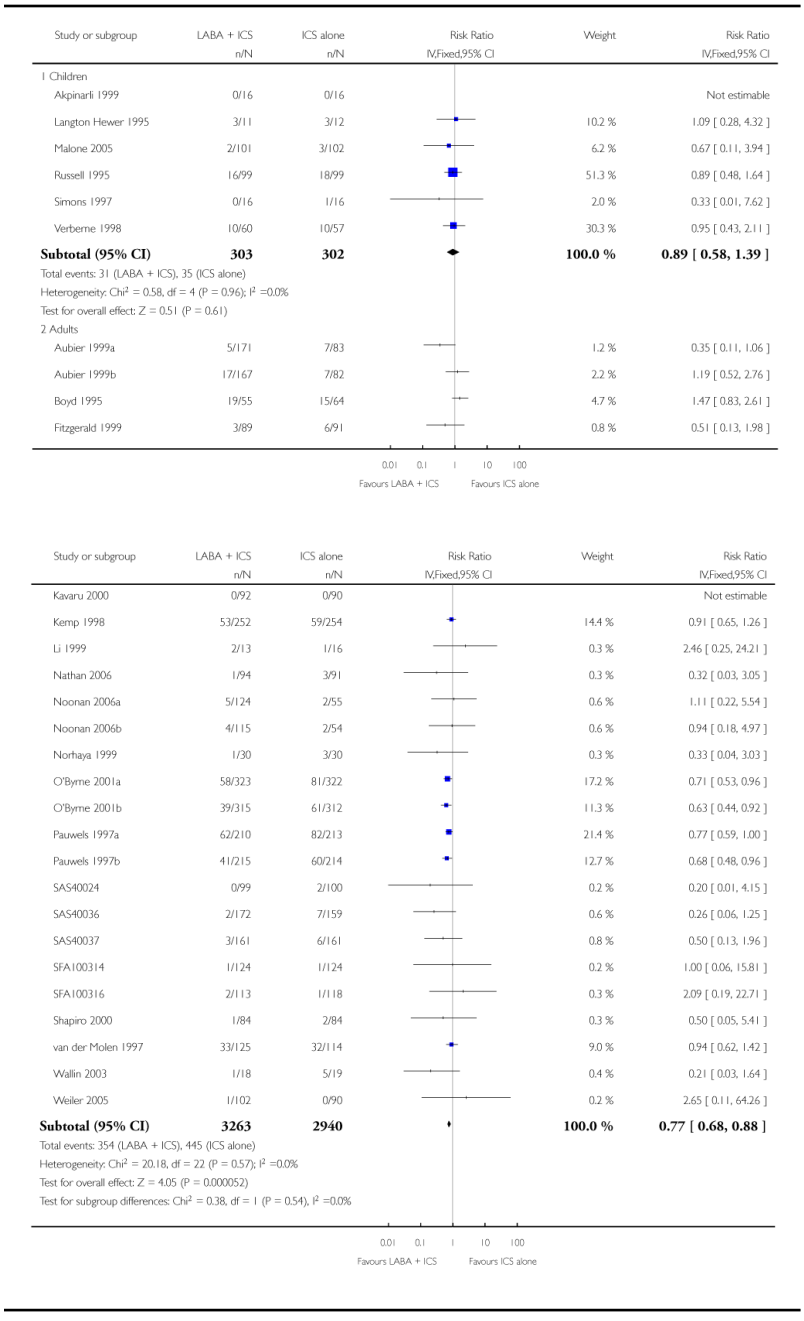

Analysis 2.3. Comparison 2 Additional comparisons for same dose, Outcome 3 # patients with exacerbations requiring oral steroids by dose of ICS in both groups

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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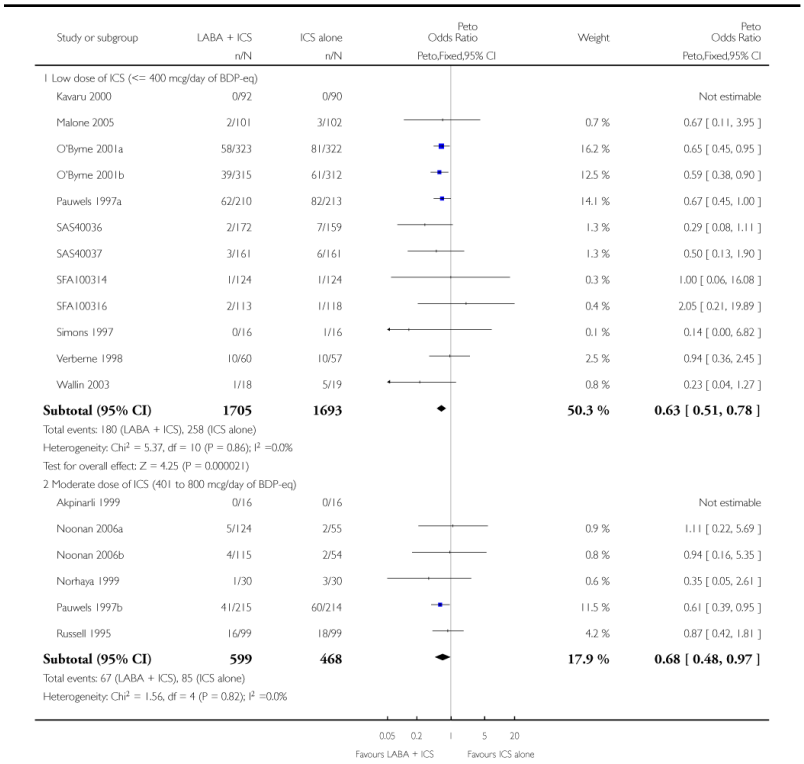
Comparison: 2 Additional comparisons for same dose

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



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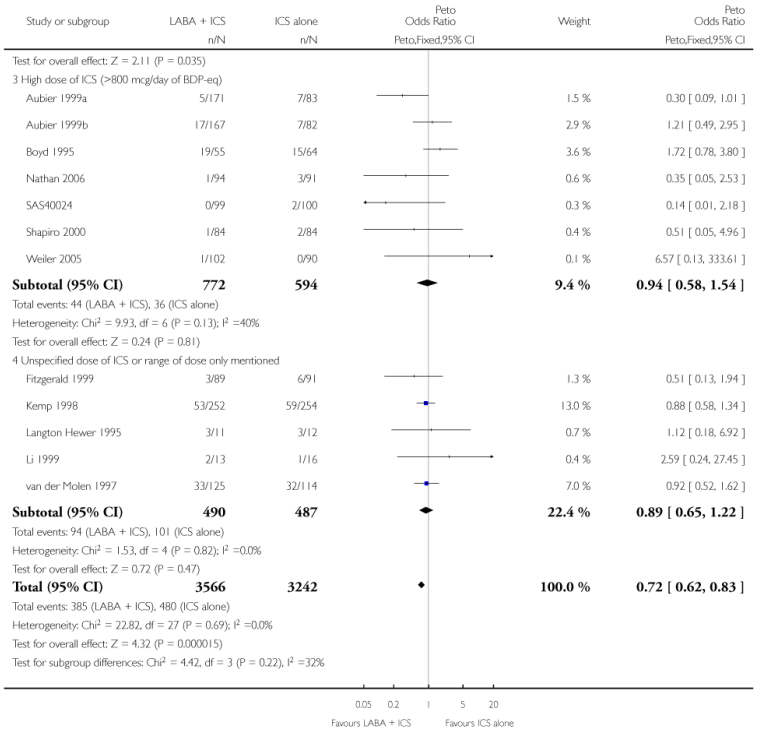

Analysis 2.4. Comparison 2 Additional comparisons for same dose, Outcome 4 # patients with exacerbations requiring oral steroids by combination inhaler or separate inhaler for LABA

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

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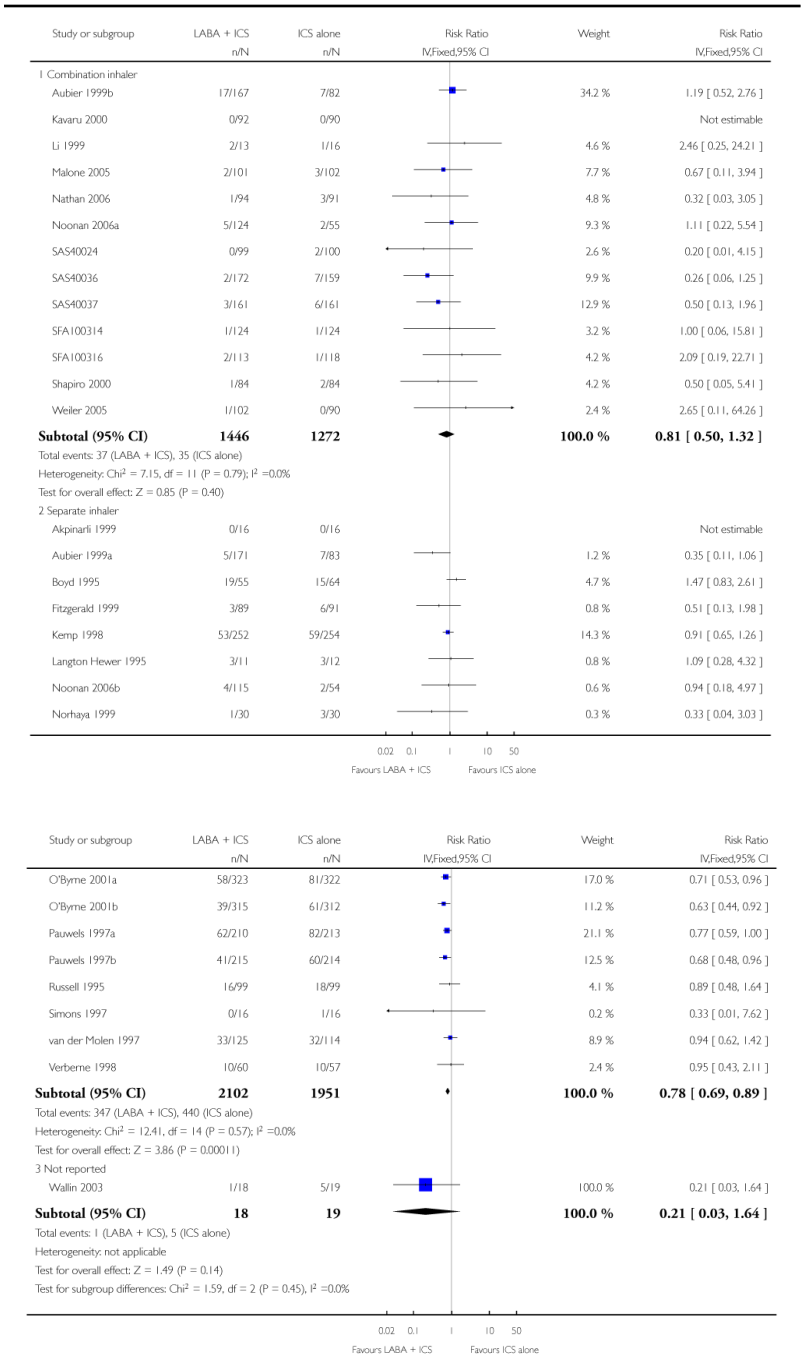
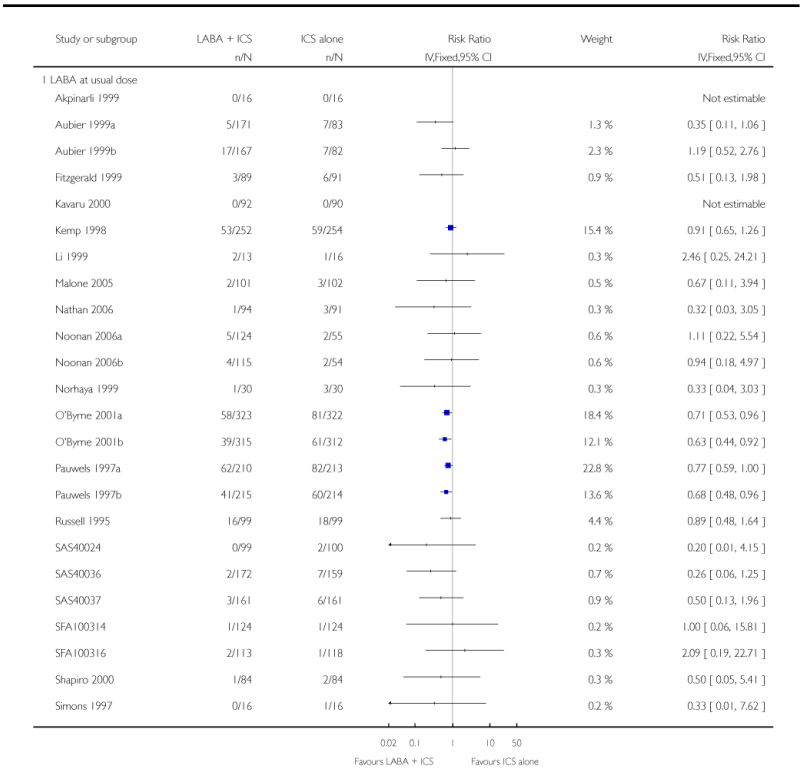


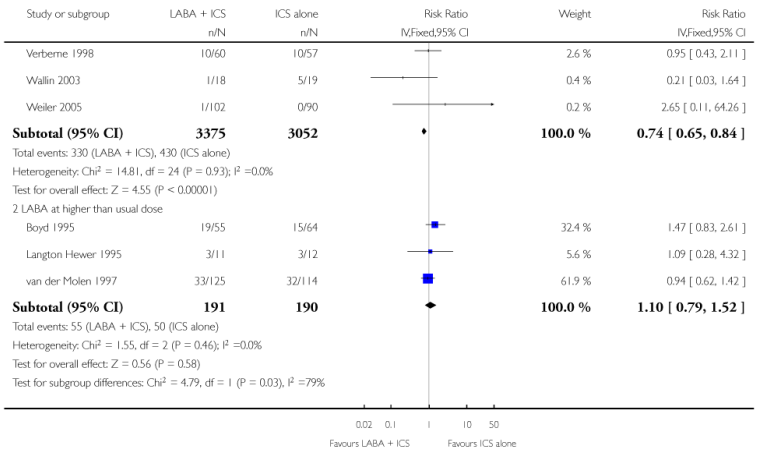
Analysis 2.5. Comparison 2 Additional comparisons for same dose, Outcome 5 # patients with exacerbations requiring oral steroids by whether LABA dose is usual or higher than usual

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





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

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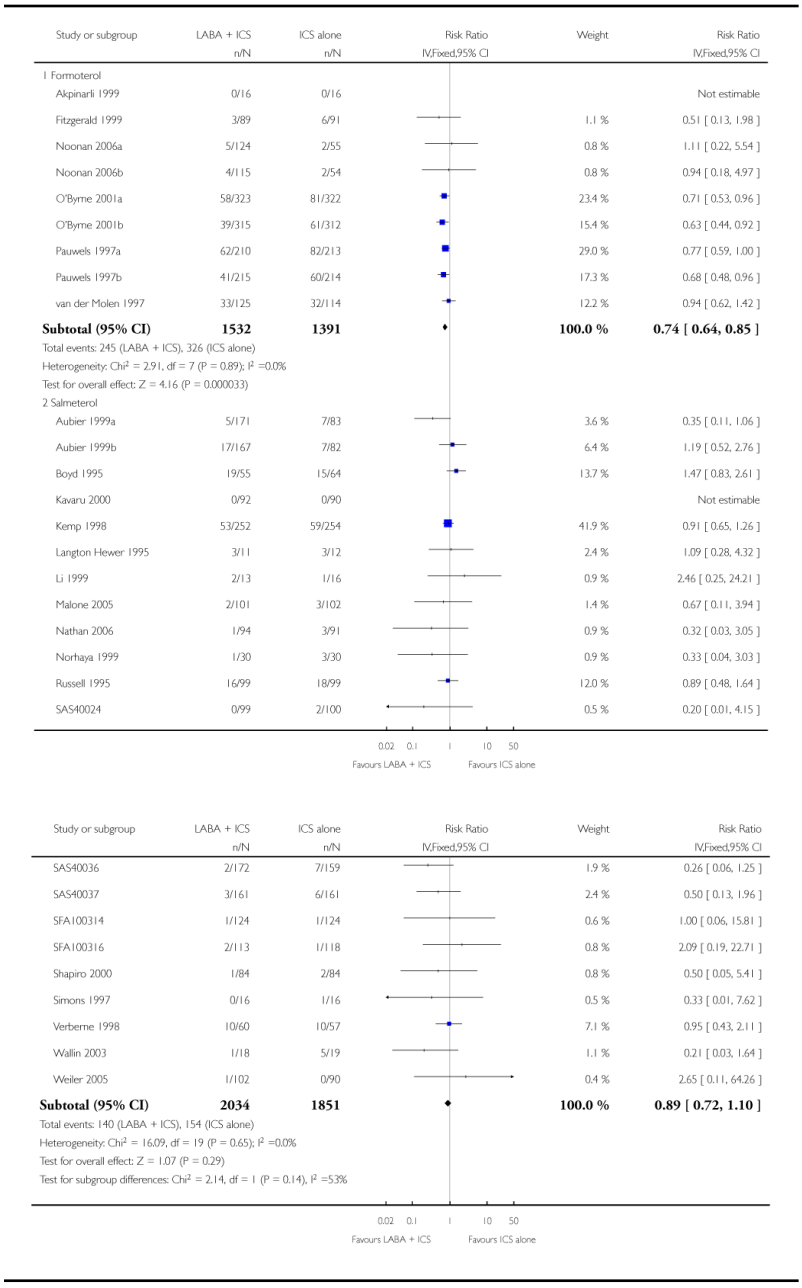

Analysis 2.7. Comparison 2 Additional comparisons for same dose, Outcome 7 # patients with exacerbations requiring oral steroids by trial duration

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

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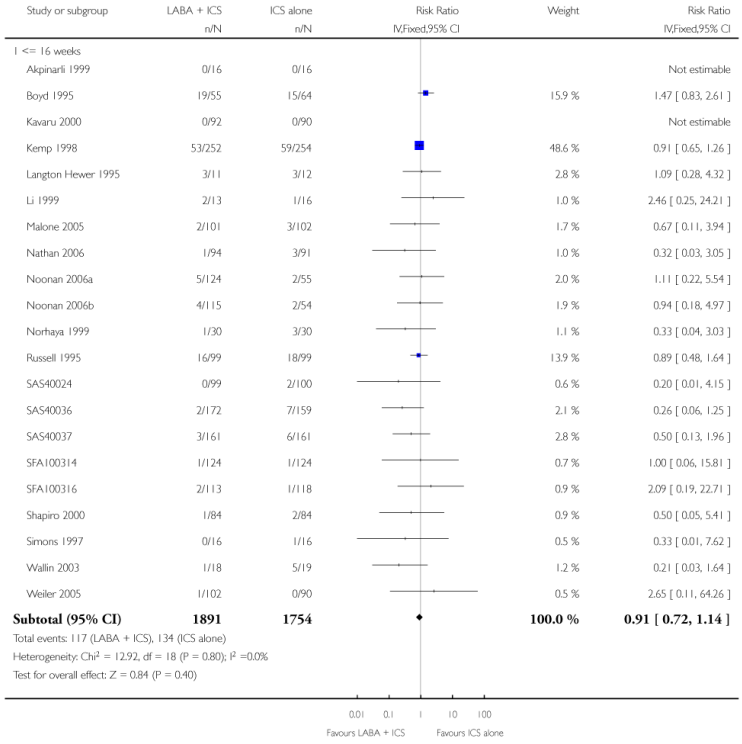
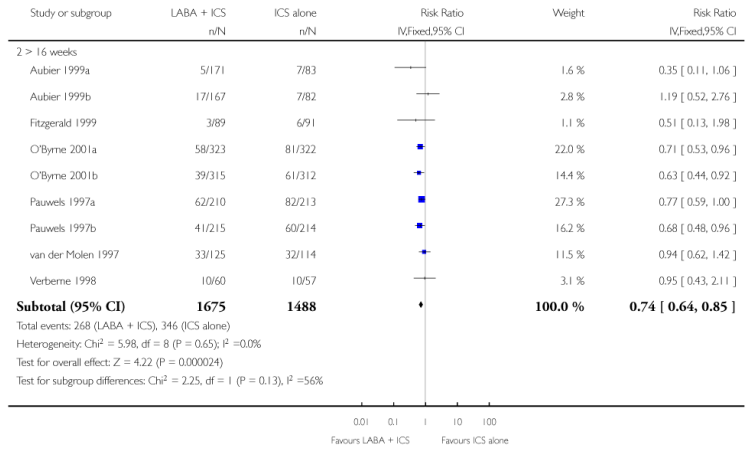
Comparison: 2 Additional comparisons for same dose

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





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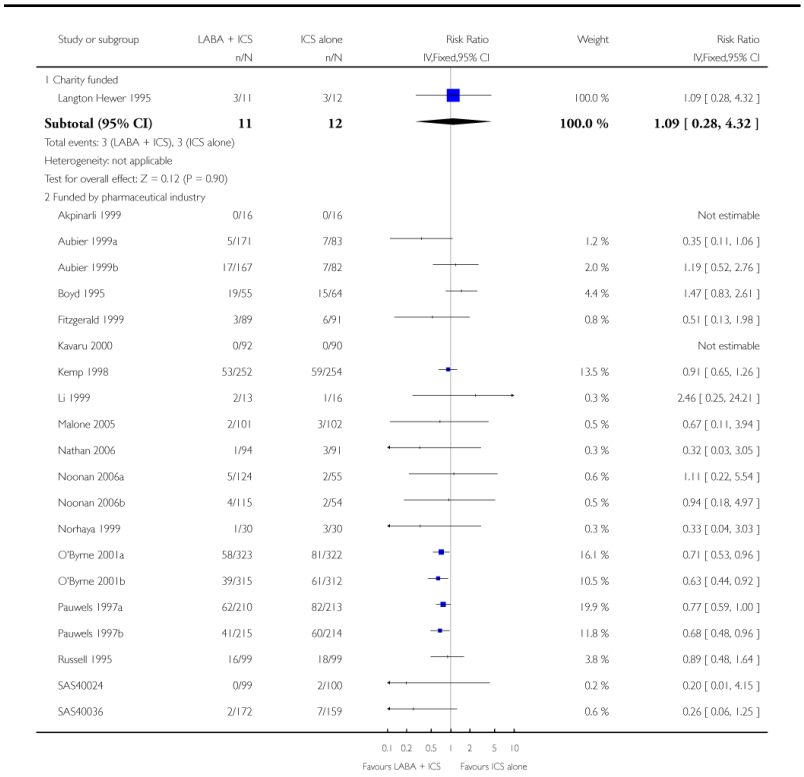
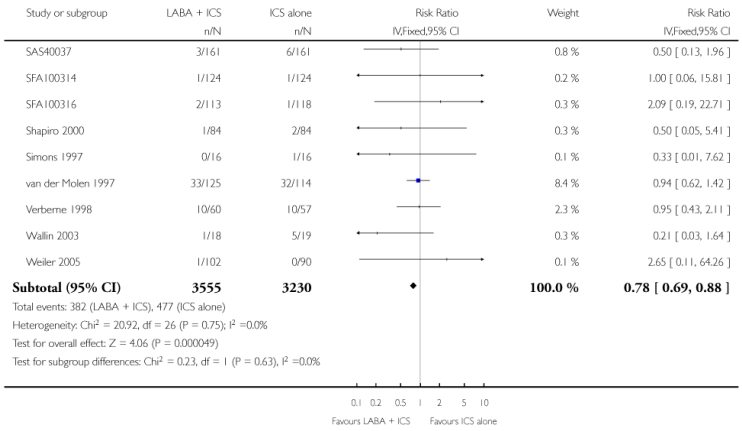
Analysis 2.8. Comparison 2 Additional comparisons for same dose, Outcome 8 # patients with exacerbations requiring oral steroids study unsupported by pharmaceutical industry excluded

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





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)

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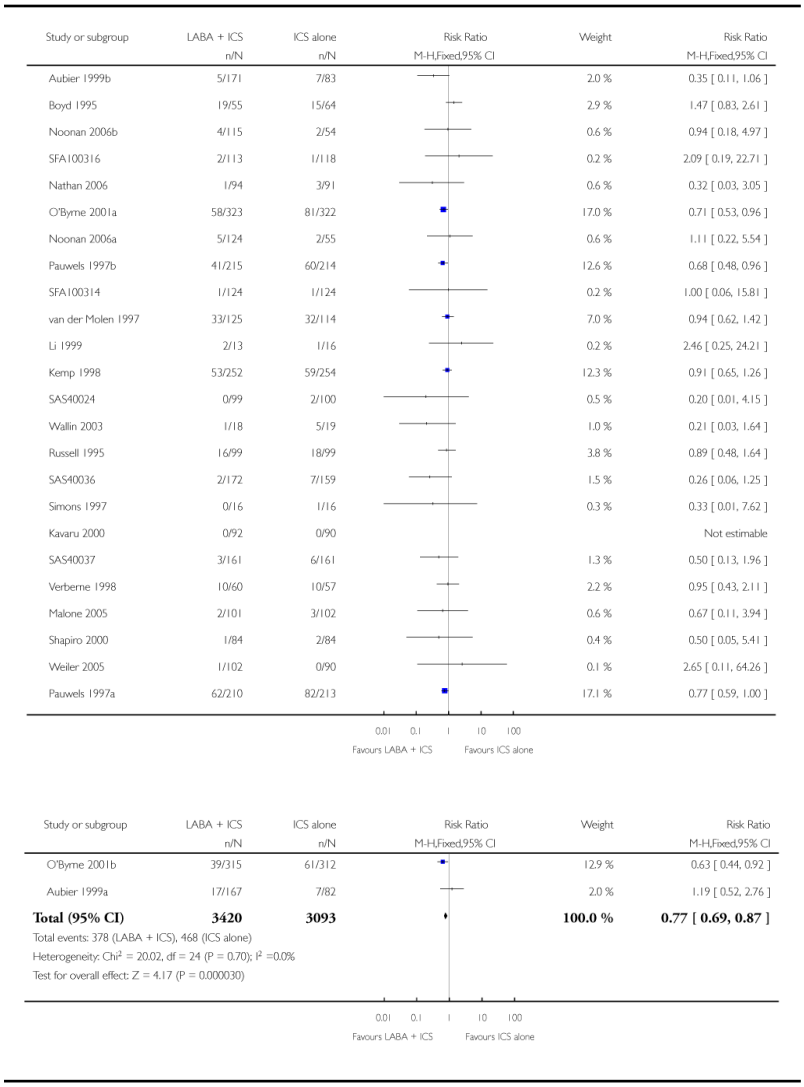

Analysis 2.10. Comparison 2 Additional comparisons for same dose, Outcome 10 Sensitivity analysis: exacerbations requiring oral steroids: studies with low risk of bias of selection bias (adequate allocation concealment)

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)

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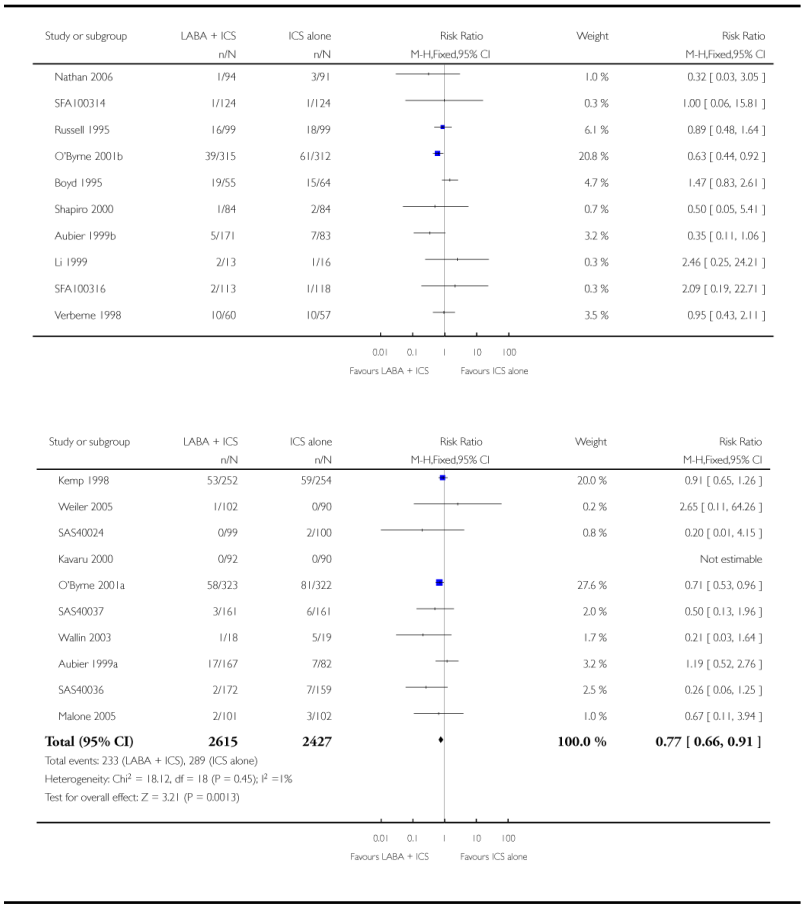

Analysis 2.11. Comparison 2 Additional comparisons for same dose, Outcome 11 Sensitivity analysis: exacerbations requiring oral steroids: studies with low risk of detection bias (adequate blinding)

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)

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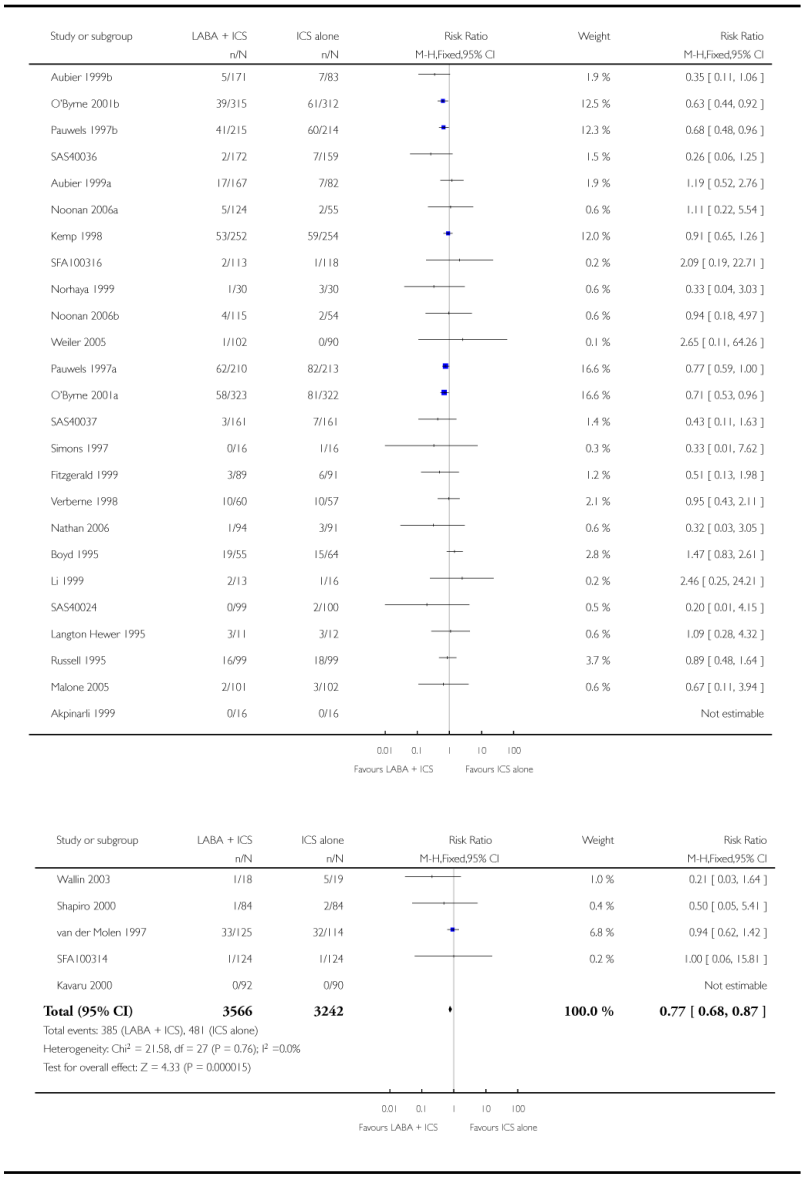

Analysis 2.12. Comparison 2 Additional comparisons for same dose, Outcome 12 Sensitivity analysis: exacerbations requiring oral steroids: studies with low risk of bias of attrition bias (complete follow up of study participants)

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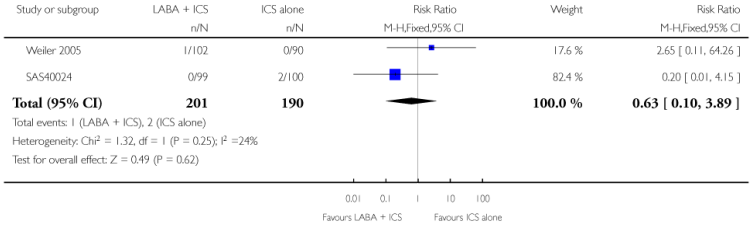
Outcome: 12 Sensitivity analysis: exacerbations requiring oral steroids: studies with low risk of bias of attrition bias (complete follow up of study participants)

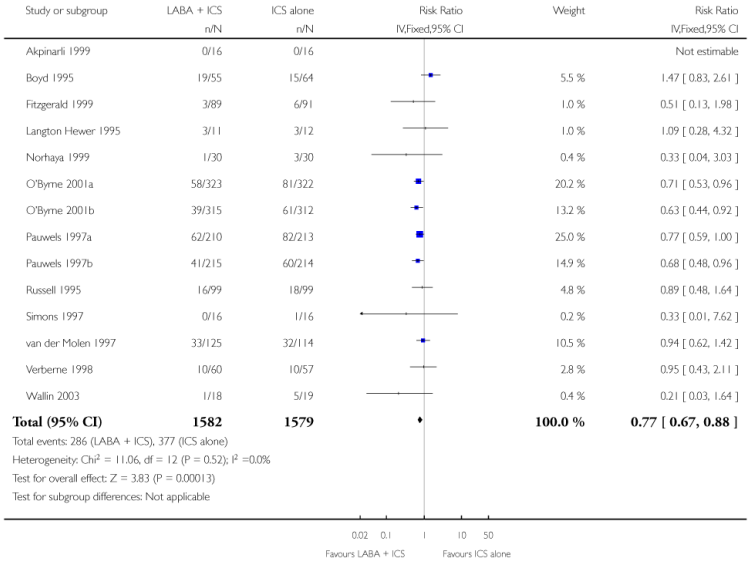


Analysis 2.13. Comparison 2 Additional comparisons for same dose, Outcome 13 Sensitivity analysis: exacerbations requiring oral steroids by data publication status (data available from published source)

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)



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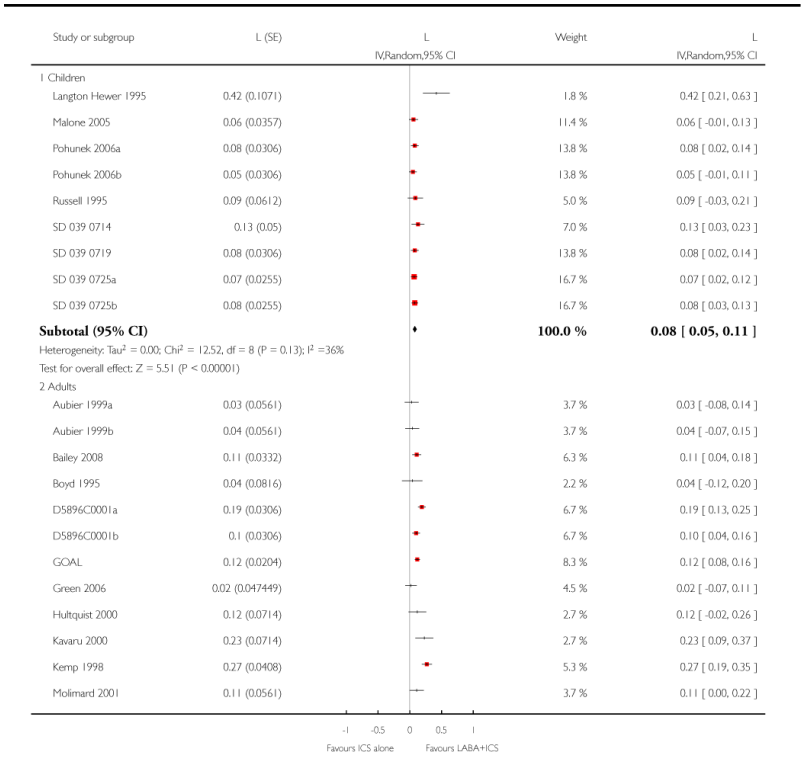
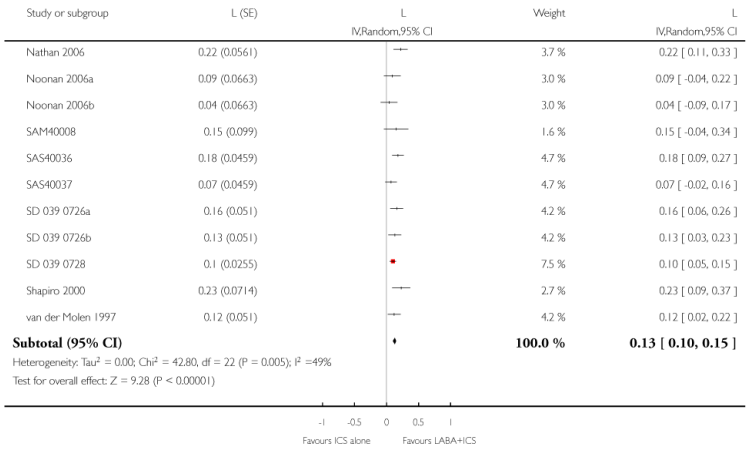
Analysis 2.14. Comparison 2 Additional comparisons for same dose, Outcome 14 Change in FEV1 at endpoint stratifying on age (children versus adults)

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)





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)

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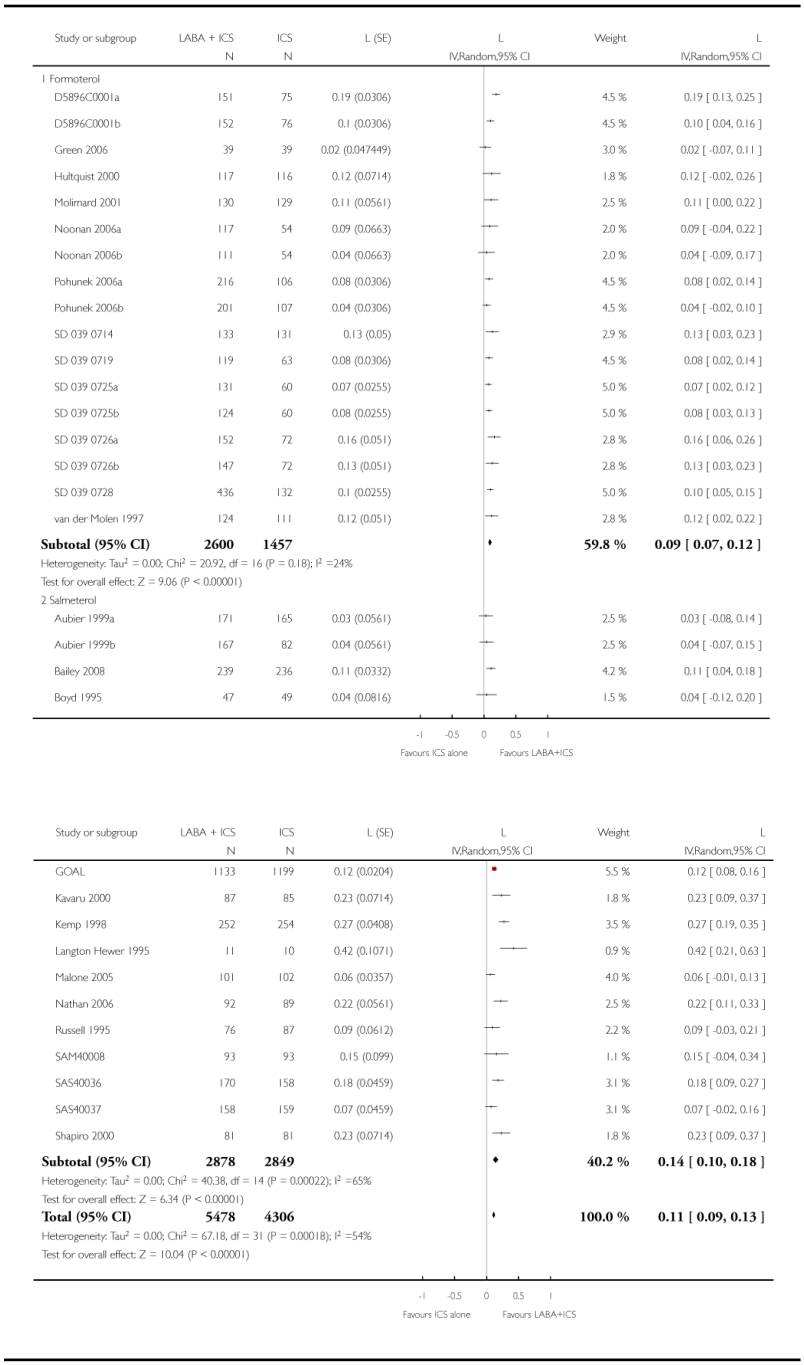
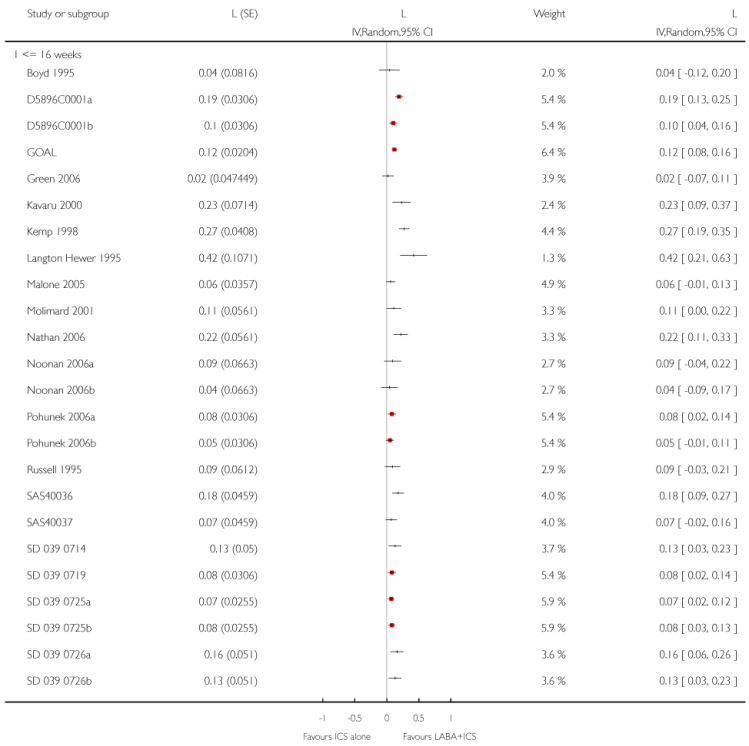


Analysis 2.16. Comparison 2 Additional comparisons for same dose, Outcome 16 Change in FEV1 at endpoint stratifying on baseline FEV1

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



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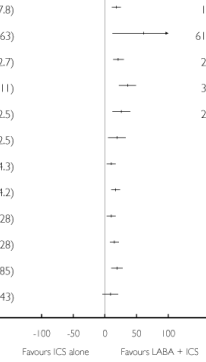
Analysis 3.1. Comparison 3 WMD archive, Outcome 1 Change in morning PEF (L/min) at endpoint stratifying on baseline FEV1

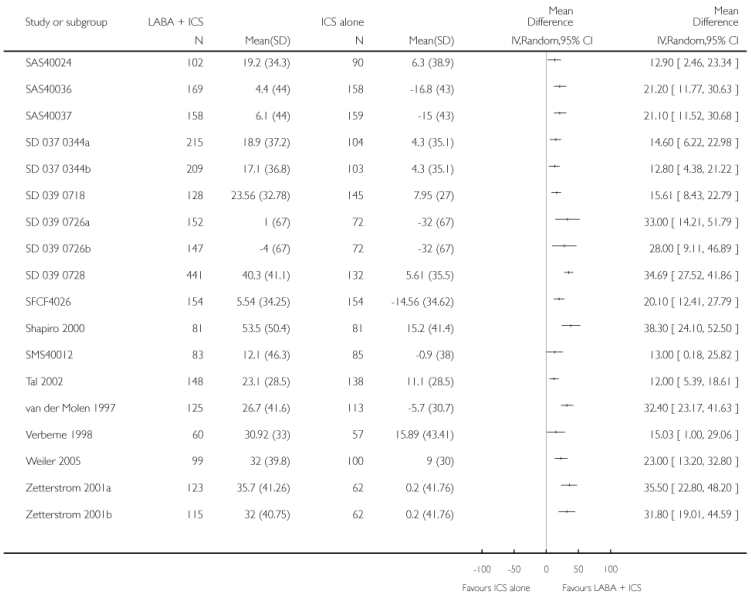
Review: Addition of long-acting beta2-agonists to inhaled corticosteroids versus same dose inhaled corticosteroids for chronic asthma in adults and children

Comparison: 3 WMD archive

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

Study or subgroup	LABA + ICS N	Mean(SD)	ICS alone N	Mean(SD)	Mean Difference IV,Random,95% CI	Mean Difference IV,Random,95% CI
Aubier 1999a	171	33 (40.54)	82	15 (39.8)		18.00 [7.46, 28.54]
Aubier 1999b	167	35 (40.1)	83	15 (39.8)		20.00 [9.50, 30.50]
Bailey 2008	239	15.6 (53.8)	236	1.4 (52.5)		14.20 [4.64, 23.76]
Boyd 1995	48	54 (41.6)	52	28 (50.1)		26.00 [8.00, 44.00]
Buhl 2003a	176	22.8 (76.88)	86	0 (76.88)		22.80 [2.98, 42.62]
Buhl 2003b	176	27.4 (76.88)	85	0 (76.88)		27.40 [7.50, 47.30]
Hultquist 2000	117	33.86 (63.71)	116	16.25 (63.22)		17.61 [1.31, 33.91]
Ind 2003	171	47.7 (47.4)	160	23.4 (38.3)		24.30 [15.04, 33.56]
Jenkins 2006a	222	37.4 (41.7)	57	4.5 (41.7)		32.90 [20.76, 45.04]
Jenkins 2006b	114	36.2 (41.5)	58	4.5 (41.5)		31.70 [18.58, 44.82]
Kavaru 2000	87	52.5 (49.44)	85	17.3 (40.57)		35.20 [21.70, 48.70]
Kemp 1998	252	47 (58.73)	254	14 (52.59)		33.00 [23.28, 42.72]
Kuna 2006	202	23.4 (38.1)	207	5.5 (37.8)		17.90 [10.54, 25.26]
Langton Hewer 1995	11	26 (49)	10	-35 (63)		61.00 [12.39, 109.61]
Molimard 2001	130	25.7 (36.5)	129	4.5 (32.7)		21.20 [12.76, 29.64]
Nathan 2006	94	49.6 (54.29)	91	13.9 (39.11)		35.70 [22.10, 49.30]
Noonan 2006a	121	35 (42.5)	54	9 (42.5)		26.00 [12.37, 39.63]
Noonan 2006b	113	28 (42.5)	55	9 (42.5)		19.00 [5.30, 32.70]
O'Byrne 2001a	323	12.89 (44.4)	322	2.78 (44.3)		10.11 [3.26, 16.96]
O'Byrne 2001b	315	18.5 (44.4)	312	1.73 (44.2)		16.77 [9.83, 23.71]
Pohunek 2006a	216	29 (31.28)	106	19 (31.28)		10.00 [2.73, 17.27]
Pohunek 2006b	201	34 (31.28)	107	19 (31.28)		15.00 [7.66, 22.34]
Price 2002	332	36.8 (61.95)	331	17.8 (61.85)		19.00 [9.58, 28.42]
Russell 1995	75	27 (36)	88	18.5 (43)		8.50 [-3.63, 20.63]





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

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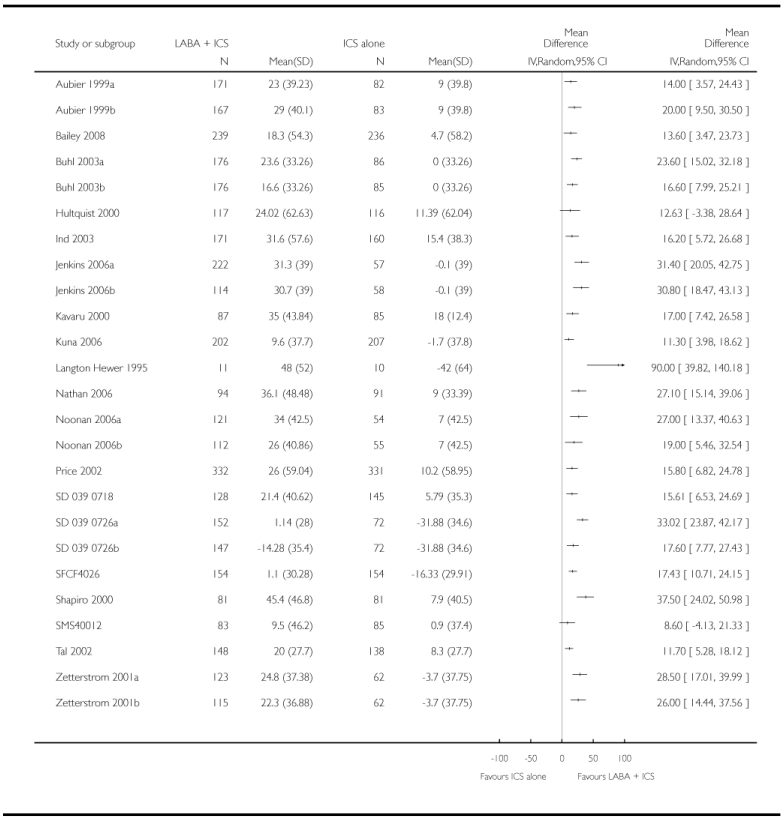

Analysis 3.3. Comparison 3 WMD archive, Outcome 3 Change in % symptom-free days at endpoint

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

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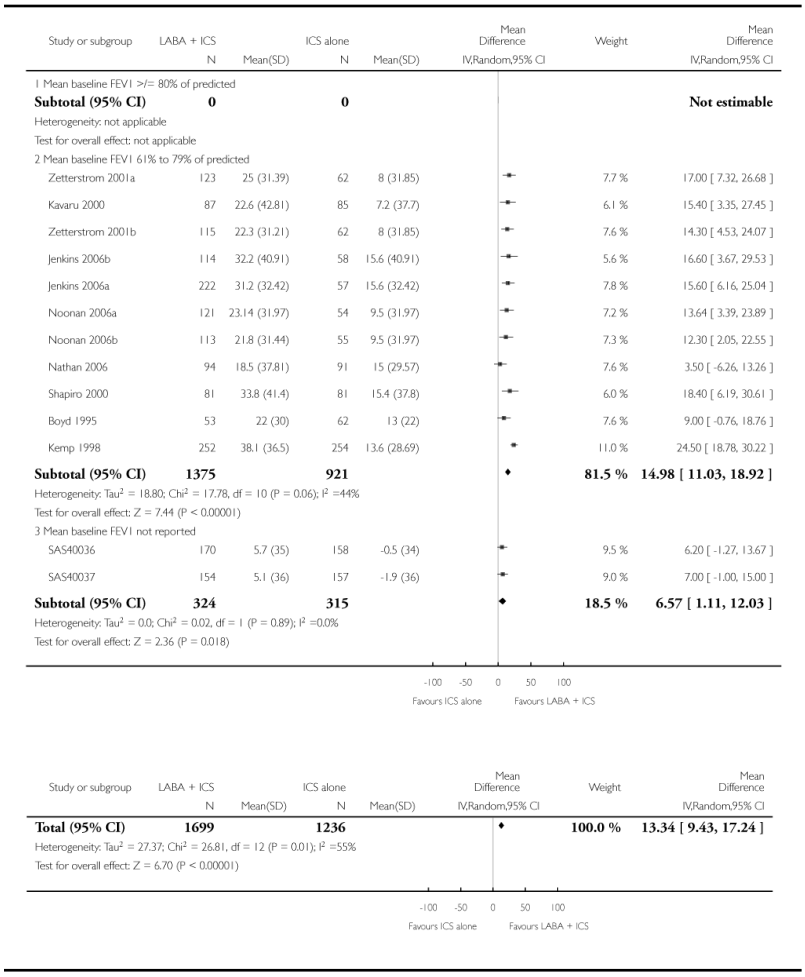


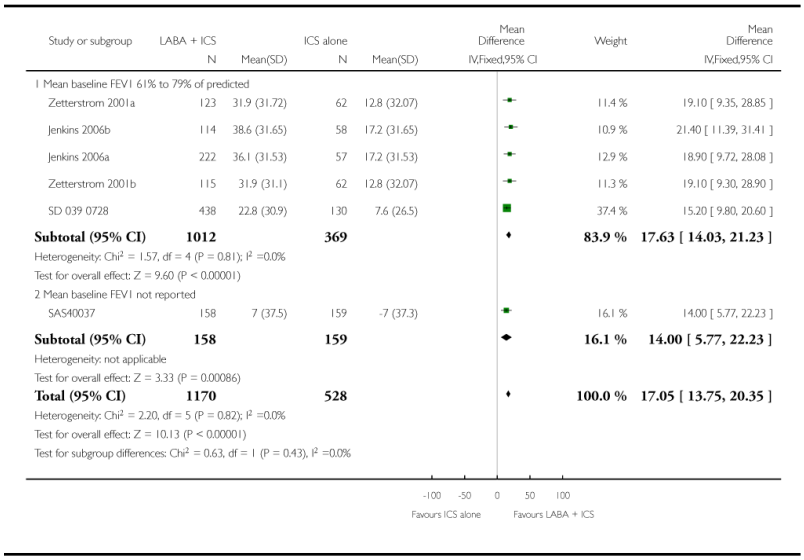
Analysis 3.4. Comparison 3 WMD archive, Outcome 4 Change in mean % rescue free days at 12 +/- 4 weeks

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

Europe PMC Funders Author Manuscripts



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

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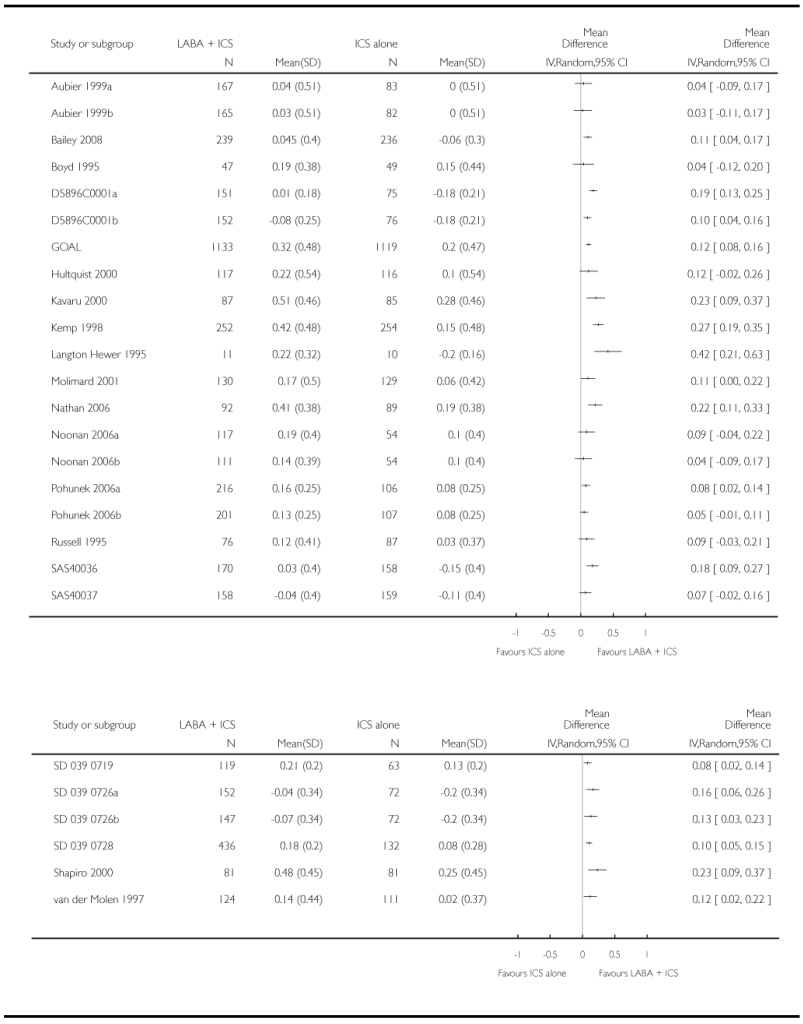

Analysis 3.6. Comparison 3 WMD archive, Outcome 6 Change in # daytime rescue inhalations (puffs per day) at endpoint

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

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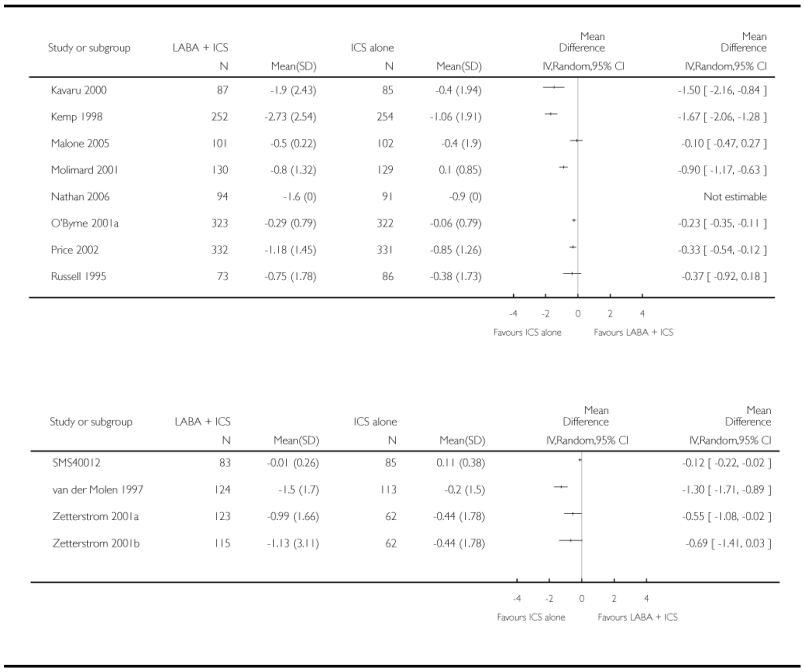
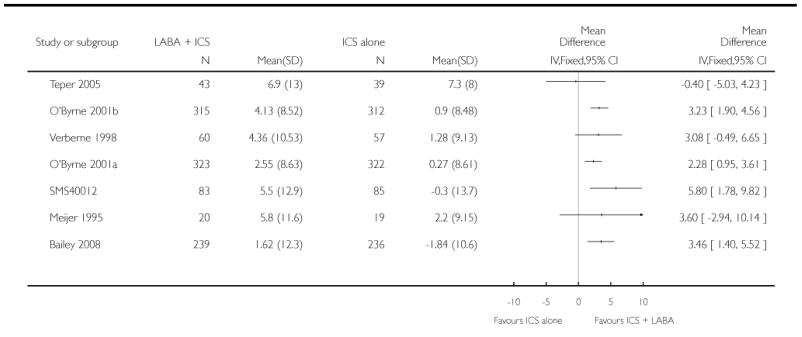


Analysis 3.7. Comparison 3 WMD archive, Outcome 7 Change in FEV1 at endpoint (% predicted) stratifying on baseline FEV1

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



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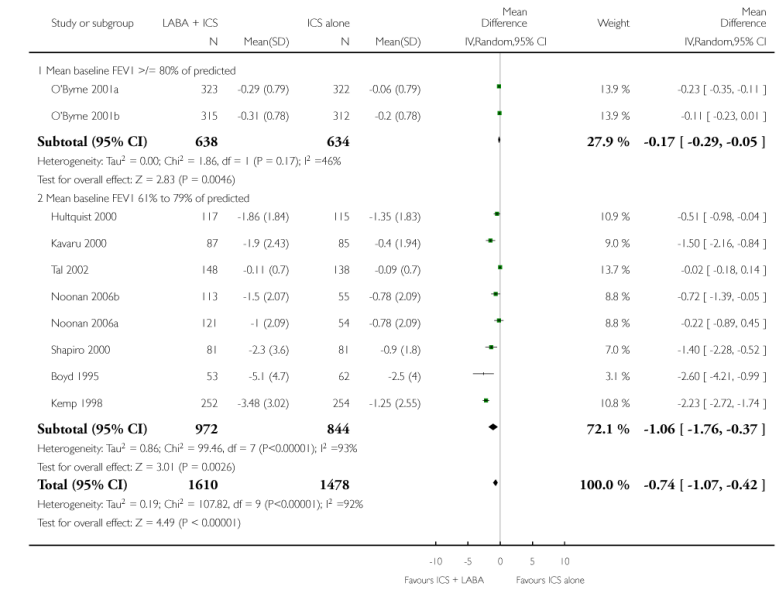
Analysis 3.8. Comparison 3 WMD archive, Outcome 8 Change in # overall daily rescue inhalations at endpoint

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

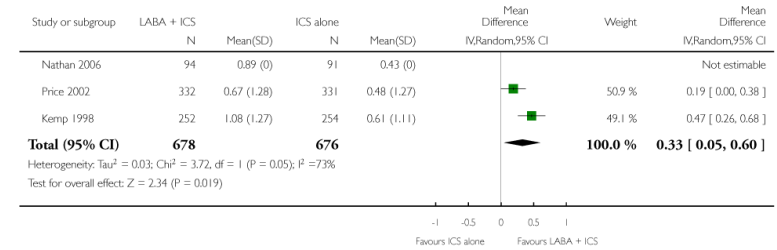


Analysis 3.9. Comparison 3 WMD archive, Outcome 9 Change in quality of life (AQLQ score) at endpoint

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



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 2009a; 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.

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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.

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* *Indicates the major publication for the study*

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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 ß$_2$-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 ß$_2$-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 ß$_2$-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 ß2-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.

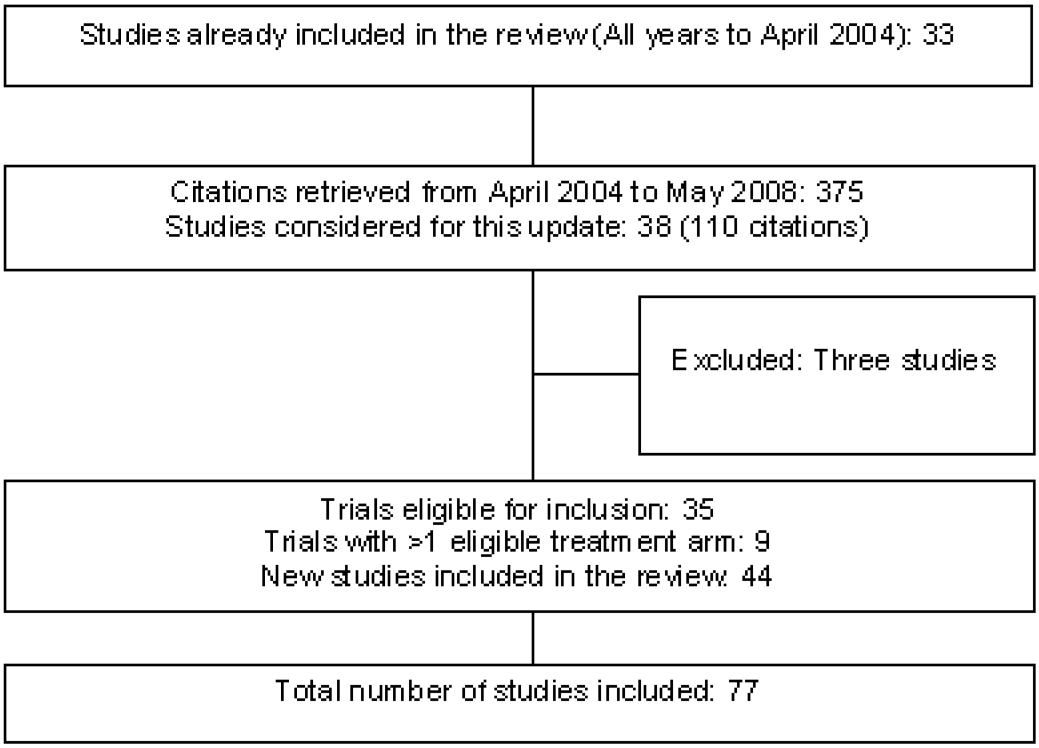

Figure 1.
Flow diagram for literature search results April 2004 to May 2008.

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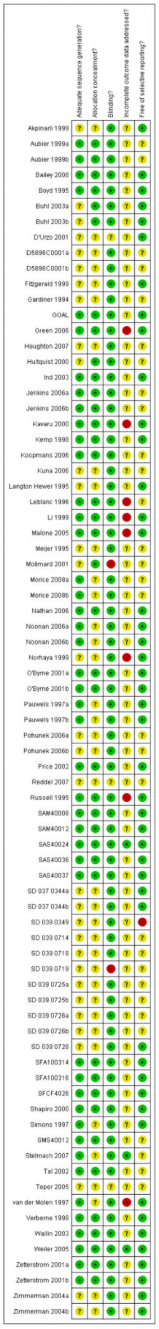

Figure 2.

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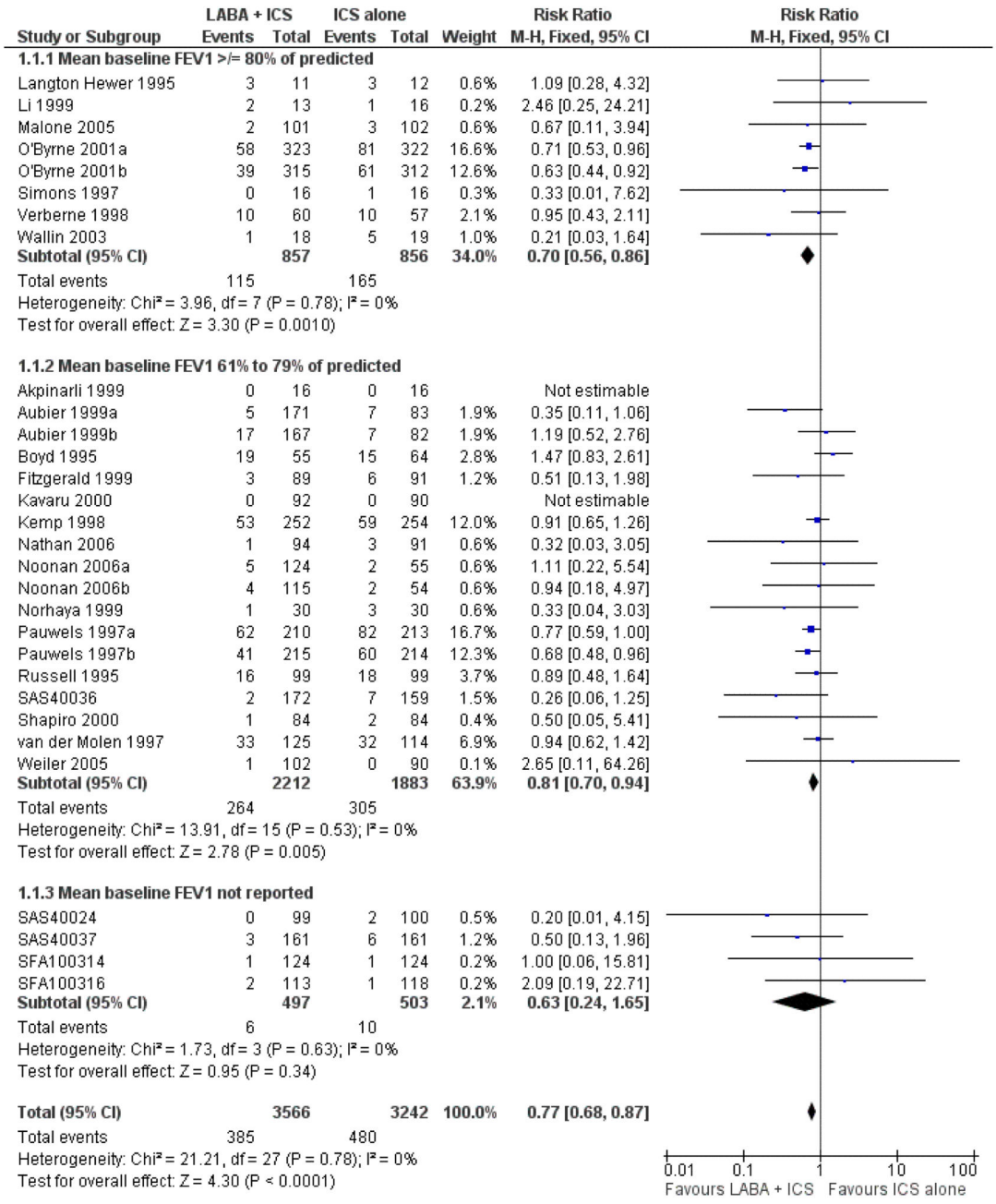

Figure 3.

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.

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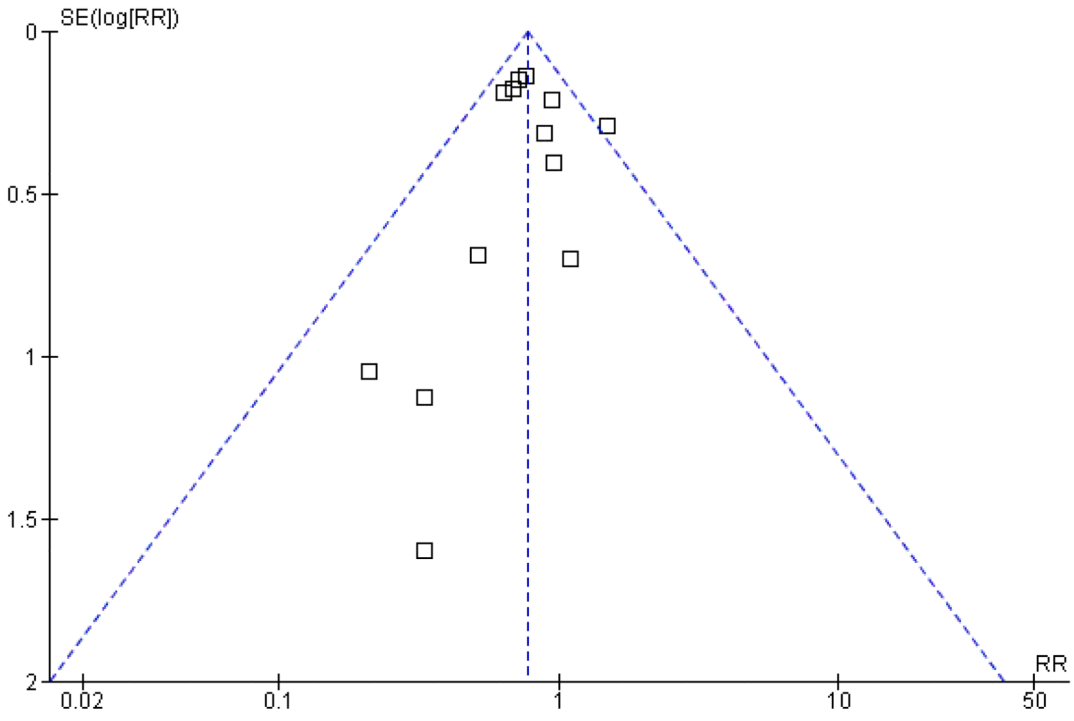

Figure 4.

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

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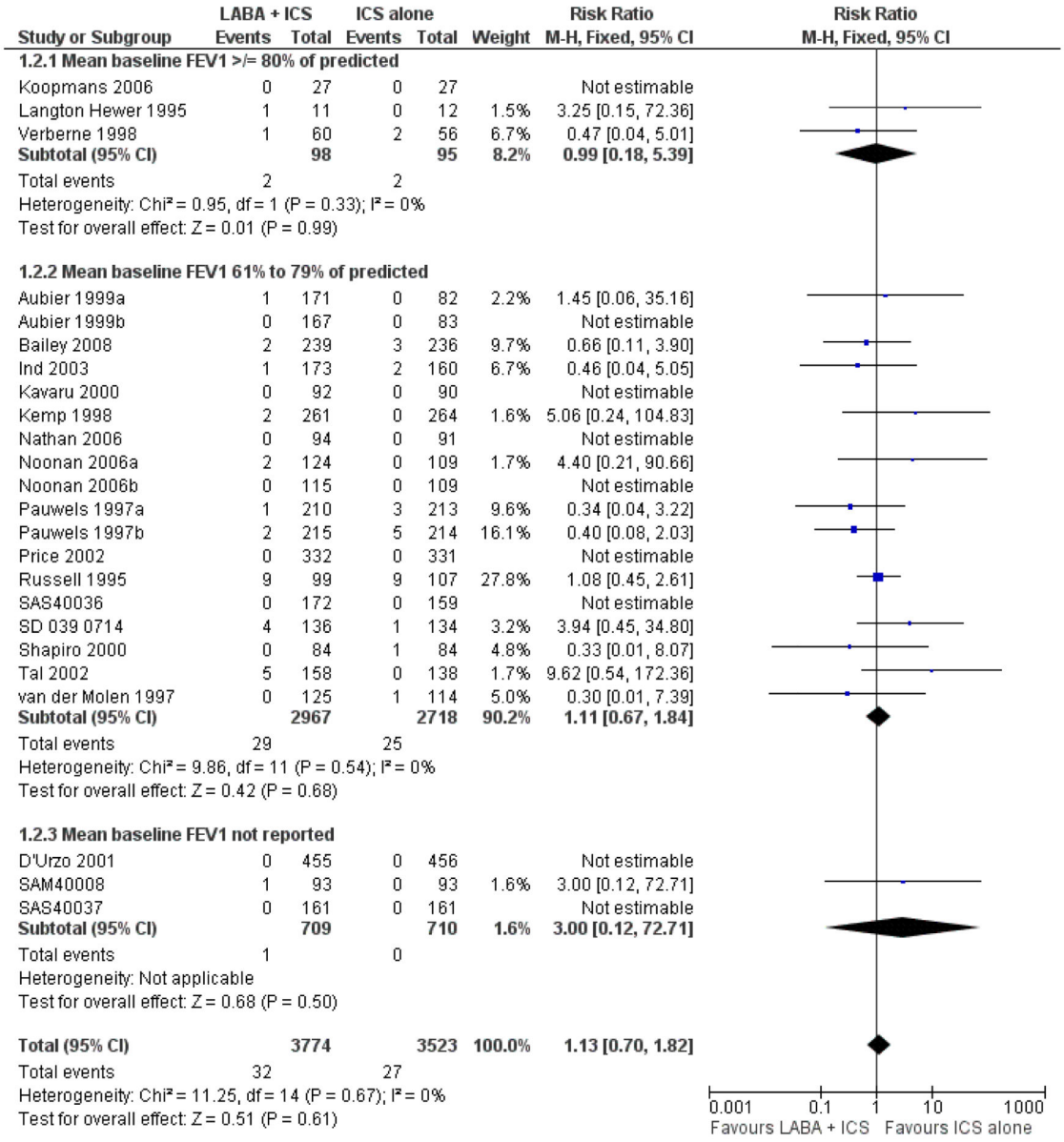

Figure 5.

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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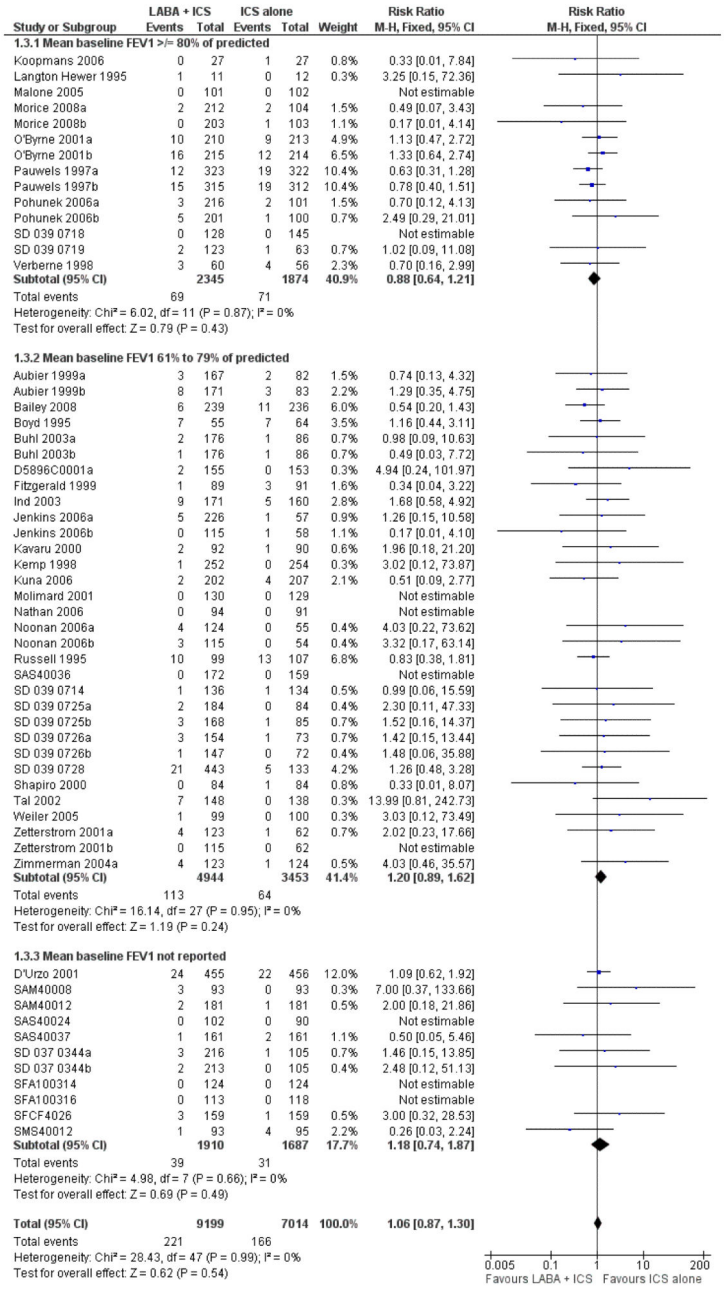

Figure 6.

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

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Table 1

Search history

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 ß2-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

Study ID	Control group % event rate	Control group N	Duration (wk)
Akpinarli 1999	0	16	6
Kavaru 2000	0	90	12
Weiler 2005	0	90	4
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
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
Pauwels 1997a	38	213	52