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Addition of long-acting beta2-agonists to inhaled steroids versus higher dose inhaled steroids in adults and children with persistent asthma

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Abstract

Background—In asthmatic patients inadequately controlled on inhaled corticosteroids and/or those with moderate persistent asthma, two main options are recommended: the combination of a long-acting inhaled ß2 agonist (LABA) with inhaled corticosteroids (ICS) or use of a higher dose of inhaled corticosteroids.

Objectives—To determine the effect of the combination of long-acting $ß_2$ agonists and inhaled corticosteroids compared to a higher dose of inhaled corticosteroids on the risk of asthma

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CONTRIBUTIONS OF AUTHORS Dr Francine Ducharme revised the protocol, supervised the literature search, created the methodology and data extraction forms, reviewed all full-text publications for relevance, reviewed all included trials for methodology and data extraction, corresponded with authors and/or the pharmaceutical companies to identify other possibly relevant trials, to verify methodology and data extraction and request additional information, analysed and interpreted results of the meta-analysis and supervised the writing of the 2010 review.

Dr Ilana Greenstone, under the supervision of Francine Ducharme, conceived the protocol, requested the literature search (1999 to 2001), identified and reviewed the full-text publication of all citations of potential or potentially eligible RCTs, drafted the correspondence to authors and/or the pharmaceutical companies to solicit their collaboration in this review and in the identification of other possibly relevant trials, extracted the methodology and data, entered the description of studies and data entry in RevMan, verified all references, description of studies and data entry. She analysed and interpreted results of the meta-analysis and wrote the 2005 review.

Dr. Muireann Ni Chroinin, under the supervision of Dr. Francine Ducharme, reviewed the 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 in RevMan, interpreted the results and approved the final review.

Toby Lasserson participated in the 2009 update of the review by screening search results, assessing studies, extracting study characteristics and data, entering data in RevMan and writing up the review.

Four research assistants sequentially participated in some aspects of the review, under the supervision of Ilana Greenstone, Muireann Ni Chroinin and Francine Ducharme. From May to July 2001, Helen Magdalinos and from November 2001 to March 2002, Alya Danish, both supported by The Canadian Cochrane Network, entered the references, characteristics of included and excluded studies, revised the table of comparisons and corrected confirmed data from authors. Vincent Masse, medical student supervised by Ilana Greenstone and Muireann Ni Chroinin, participated in verification and organisation of data in RevMan and entered references and reasons for exclusion. Marilyse Julien performed and assisted in the interpretation of the 2009 meta-regression.

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exacerbations, pulmonary function and on other measures of asthma control, and to look for characteristics associated with greater benefit for either treatment option.

Search methods—We identified randomised controlled trials (RCTs) through electronic database searches (MEDLINE, EMBASE and CINAHL), bibliographies of RCTs, clinical trial registries and correspondence with manufacturers until May 2008.

Selection criteria—RCTs that compared the combination of inhaled LABA and ICS to a higher dose of inhaled corticosteroids, in children and adults with asthma.

Data collection and analysis—Two authors independently assessed methodological quality and extracted data. We obtained confirmation from the trialists when possible. The primary endpoint was the number of patients experiencing one or more asthma exacerbations requiring oral corticosteroids.

Main results—This review included 48 studies (15,155 participants including 1155 children and 14,000 adults). Participants were inadequately controlled on their current ICS regimen, experiencing ongoing symptoms and with generally moderate (FEV1 60% to 79% of predicted) airway obstruction. The studies tested the combination of salmeterol or formoterol with a median dose of 400 mcg/day of beclomethasone or equivalent (BDP-eq) compared to a median of 1000 mcg/day of BDP-eq, usually for 24 weeks or less. There was a statistically significantly lower risk of exacerbations requiring systemic corticosteroids in patients treated with LABA and ICS (RR 0.88, 95% CI 0.78 to 0.98, 27 studies, N = 10,578) from 11.45% to 10%, with a number needed to treat of 73 (median study duration: 12 weeks). The study results were dominated by adult studies; trial data from three paediatric studies showed a trend towards increased risk of rescue oral steroids (RR 1.24, 95% CI 0.58 to 2.66) and hospital admission (RR 2.21, 95% CI 0.74 to 6.64) associated with combination therapy. Overall, there was no statistically significant difference in the risk ratios for either hospital admission (RR 1.02, 95% CI 0.67 to 1.56) or serious adverse events (RR 1.12, 95% CI 0.91 to 1.37). The combination of LABA and ICS resulted in significantly greater but modest improvement from baseline in lung function, symptoms and rescue medication use than with higher ICS dose. Despite no significant group difference in the risk of overall adverse events (RR 0.99, 95% CI 0.95 to 1.03), there was an increase in the risk of tremor (RR 1.84, 95% CI 1.20 to 2.82) and a lower risk of oral thrush (RR 0.58, 95% CI 0.40 to 0.86)) in the LABA and ICS compared to the higher ICS group. There was no significant difference in hoarseness or headache between the treatment groups. The rate of withdrawals due to poor asthma control favoured the combination of LABA and ICS (RR 0.65, 95% CI 0.51 to 0.83).

Authors' conclusions—In adolescents and adults with sub-optimal control on low dose ICS monotherapy, the combination of LABA and ICS is modestly more effective in reducing the risk of exacerbations requiring oral corticosteroids than a higher dose of ICS. Combination therapy also led to modestly greater improvement in lung function, symptoms and use of rescue ß$_2$ agonists and to fewer withdrawals due to poor asthma control than with a higher dose of inhaled corticosteroids. Apart from an increased rate of tremor and less oral candidiasis with combination therapy, the two options appear relatively safe in adults although adverse effects associated with long-term ICS treatment were seldom monitored. In children, combination therapy did not lead to a significant reduction, but rather a trend towards an increased risk, of oral steroid-treated exacerbations and hospital admissions. These trends raised concern about the safety of combination therapy in view of modest improvement in children under the age of 12 years.

Medical Subject Headings (MeSH)

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

MeSH check words

Adolescent; Adult; Child; Child, Preschool; Humans

BACKGROUND

Beta-2 adrenergic agonists are the major class of medication used for the relief of asthma symptoms. They produce their effects through interaction with specific ß$_2$ adrenergic receptors located in the plasma membrane of virtually all types of cells, including bronchial wall smooth muscle (Nelson 1995). For several decades, short-acting inhaled ß$_2$ agonists have been the primary agents used to treat patients with asthma. Their benefits include rapid onset of bronchodilation within five to 15 minutes (D'Alonzo 1997), highly effective protection against exercise-induced asthma and protection against the early asthmatic response to allergen (Sears 1998). Their duration of action is only three to six hours (Nelson 1995). Short-acting ß$_2$ agonists do not seem to have any effect on overall severity of asthma, nor on inflammation (Sears 1998). Long-acting ß$_2$ agonists, such as salmeterol and formoterol, have been developed for more prolonged control of symptoms (D'Alonzo 1997). Slightly slower in onset of action than short-acting ß$_2$ agonists, inhaled salmeterol exerts its bronchodilating effect within ten to 20 minutes (Adkins 1997). This effect then lasts up to 12 hours due to high affinity binding of the molecule's side chain to a specific site within the ß$_2$ adrenergic receptor (Adkins 1997; D'Alonzo 1997; Nelson 1995). Formoterol, on the other hand, has an onset of bronchodilation within less than five minutes (Bartow 1998; Moore 1998) and a duration of action similar to that of salmeterol. Due to its ability to enter the cell's lipid bi-layer, it becomes available over a prolonged period to stimulate the receptor (Nelson 1995). These two long-acting ß$_2$ agonists have been shown to reduce daytime and nighttime symptoms, improve quality of sleep, reduce requirement for short-acting ß$_2$ agonists (D'Alonzo 1997; Sears 1998) and protect against methacholine-induced, cold air-induced and exercise-induced bronchoconstriction (D'Alonzo 1997; Nelson 1995; Moore 1998). Long-acting inhaled ß$_2$ agonists are currently used in the maintenance, rather than in the acute treatment, of children aged six years and older and adults with asthma. At time of publication, these drugs have not yet been marketed for children less than four years old, although such approval may currently be sought in several countries.

The need for frequent use of ß$_2$ agonists generally indicates a significant inflammatory process that should be controlled with anti-inflammatory drugs (Fireman 1995; Nelson 1995; Kemp 1998). Inhaled corticosteroids are currently the most effective anti-inflammatory drugs used for long-term control of asthma (Adams 2008; Manning 2008).

When asthma control is unsatisfactory despite low doses of inhaled corticosteroids, several options have been proposed: increasing the dose of inhaled corticosteroids or adding other agents such as long-acting ß$_2$ agonists, leukotriene receptor antagonists or theophylline. Of all add-on therapies, long-acting ß$_2$ agonists have emerged as the preferred option in terms of efficacy (BTS 2008 (updated June 09); GINA 2008; Lemiere 2004; NIH Publication 2007). Guidelines differ with regards to choosing between increasing the dose of inhaled corticosteroids or adding long-acting ß$_2$ agonists for adults, children, toddlers and infants/ toddlers.

In adults, all but the British guidelines prefer the addition of long-acting ß$_2$ agonists to inhaled corticosteroids in cases of sub-optimal control on inhaled corticosteroid monotherapy. The Canadian and Australian Consensus statement recommends the addition of long-acting ß$_2$ agonists if control is unsatisfactory with 400 mcg/day of CFC-beclomethasone dipropionate (BDP) or equivalent (Australia 2006; GINA 2008; Lemiere 2004,) while doses of 200 to 800 mcg/day are recommended by the British guidelines (BTS 2008 (updated June 09)). In contrast, the American guidelines give equal weight to adding long-acting ß$_2$ agonists or increasing the dose of inhaled corticosteroids (NIH Publication 2007). In children aged 5 years and older with poor control on 400 mcg/day of BDP-equivalent, it is recommended to first increase the dose of inhaled corticosteroids to a medium dose in the Australian (Australia 2006), Canadian (Lemiere 2004) and International (GINA 2008) statements, before adding long-acting ß$_2$ agonists, where the paediatric medium dose is 401 to 800 mcg/ day for all but the Gina guidelines where it is 201 to 400 mcg/ day. The American guidelines give equal weight to increasing the inhaled corticosteroid dose of a moderate dose or adding a long-acting ß$_2$ agonist. In contrast, the British (BTS 2008 (updated June 09)) guidelines recommend the addition of long-acting ß$_2$ agonists at an inhaled corticosteroid dose of 400 mcg/day before increasing the inhaled corticosteroid dose to 800 mcg/day. In infants and preschool-aged children, the American guidelines (NIH Publication 2007) recommend increasing the dose of ICS to a medium dose as the preferred option. The British Thoracic Society guidelines do not recommend the use of long-acting ß$_2$ agonists in this age group (BTS 2008 (updated June 09), while other guidelines have made no specific statement. Clearly, uncertainties persist regarding the severity of airway obstruction and the baseline dose of inhaled corticosteroids to which addition of long-acting ß$_2$ agonists may be preferable to increasing the dose of inhaled corticosteroids. The influence of age for optimising treatment strategies is also unclear.

Two published meta-analyses initially examined the combination of salmeterol with inhaled corticosteroids (Shrewsbury 2000) or with fluticasone specifically (Heyneman 2002) as compared to a double-dose inhaled corticosteroid. Both of these reviews demonstrated clear superiority of combination therapy with regards to lung function, symptoms and use of rescue ß$_2$ agonists. Shrewsbury 2000 also showed that combination therapy was superior in the prevention of asthma exacerbations. However, these meta-analyses were not systematic reviews in that they:

1. only included trials sponsored by GlaxoSmithKline;
2. tested only salmeterol as the long-acting ß$_2$ agonist; and

3. were limited to adult trials.

However, the safety of long-acting ß$_2$ agonists alone or in combination with inhaled corticosteroids has been challenged. There have been clear indications that the use of long-acting ß$_2$ agonists as monotherapy is worse than use in combination with inhaled corticosteroids (Warner 1998). A recent systematic review combining trials in which long-acting ß$_2$ agonists were used alone or in combination with inhaled corticosteroids reported an increase in the risk of serious adverse events associated with long-acting ß$_2$ agonists (Salpeter 2006). The possible protection offered by inhaled corticosteroids has led to recommendations from national and international asthma consensus statements that stipulate the use of long-acting ß$_2$ agonists only in combination with inhaled corticosteroids (Australia 2006; BTS 2008 (updated June 09); Georgitis 1999; GINA 2008; Lemiere 2004; NIH Publication 2007; Warner 1998). Yet concerns about the safety of long-acting ß$_2$ agonists must clearly be addressed in adults and particularly in children, in whom few data are available.

We published a Cochrane Review comparing the combination of any long-acting ß$_2$ agonist preparation and inhaled corticosteroids to increased inhaled corticosteroid dose and documented the beneficial effect of combination therapy on asthma exacerbations requiring systemic corticosteroids, lung function, symptoms and rescue bronchodilators (Greenstone 2005). With the publication of several additional trials since 2005, we believed a systematic review comparing the combination of long-acting ß$_2$ agonist and inhaled corticosteroids to a higher dose of inhaled corticosteroids in patients with a prior trial of inhaled corticosteroids would provide a more unbiased view of the evidence on safety and efficacy and, perhaps, greater insight as to the patient and treatment characteristics associated with greater benefit or harm from either treatment option. We believed this update would strengthen the evidence supporting the safety of long-acting ß$_2$ agonists when used in combination therapy (Ernst 2006).

OBJECTIVES

The objective of this review was to compare the relative benefit and safety profile of the combination of long-acting ß$_2$ agonists (LABAs) and inhaled corticosteroids (ICS) with a higher dose of inhaled corticosteroids in asthmatic patients with or without previous treatment with inhaled corticosteroids. We also wished to examine whether the benefit of either treatment option was influenced by the severity of airway obstruction, age, baseline dose of inhaled corticosteroids to which LABA was added, ICS dose difference between treatment options, use of one or two devices to deliver combination therapy, dose and type of long-acting ß$_2$ agonist and duration of intervention.

METHODS

Criteria for considering studies for this review

Types of studies—Only randomised controlled trials (RCTs) conducted in adults, adolescents and/or children in whom long-acting ß2 agonists were added to inhaled corticosteroids.

Types of participants—Children aged two years and above, adolescents or adults with recurrent or chronic asthma. We did not include studies where pre-treatment excluded inhaled corticosteroids. The comparison of combination therapy with higher dose steroids in steroid naive patients is covered in Ni Chroinin 2009a.

Types of interventions—Long-acting ß$_2$ agonist administered twice a day (e.g. salmeterol or formoterol) combined with inhaled corticosteroids compared to a higher dose of inhaled corticosteroids with or without placebo. Delivery of therapy could be either via one or two inhaler devices. Other co-interventions such as xanthines, anticholinergics and non-steroidal anti-inflammatory medications were accepted, provided that the dose remained unchanged throughout the study. The intervention must have been administered for at least 28 days at fixed doses. Inhaled short-acting ß$_2$ agonists and short courses of oral corticosteroids were permitted rescue interventions.

Types of outcome measures

Primary outcomes: The primary outcome was the proportion of participants with asthma exacerbations requiring a short course of systemic corticosteroids.

Secondary outcomes:

1. Proportion of participants in each group requiring hospital admission for asthma.
2. Withdrawals.
3. Serious adverse events.
4. Pulmonary function tests.
5. Symptoms (including days and nights without symptoms, and symptom scores.
6. Quality of life measured with validated scales.
7. Rescue use of short-acting ß2 agonists.
8. Measures of inflammation, such as serum eosinophils, serum eosinophil cationic protein and sputum eosinophils.
9. Clinical and biochemical adverse effects related to treatment were examined for all those that were systematically sought and documented.

Search methods for identification of studies

Electronic searches—A search was carried out in the Cochrane Airways Review Group's 'Asthma and Wheez* RCT' register, which is derived from a comprehensive search of EMBASE (1980 to May 2008), MEDLINE (1966 to May 2008) and CINAHL (1982 to May 2008). In addition, we handsearched 20 of the most productive respiratory care journals and added relevant randomised controlled trials to the register. This register also contains a variety of studies published in foreign languages. We did not exclude trials on the basis of language.

The search of the database used 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 (((corticosteroid* or corticosteroid* or corticosteroid*) and inhal*) or (budesonide or beclomethasone or fluticasone or triamcinolone or flunisolide)).

Searching other resources—We searched the clinical trials register of The Cochrane Collaboration (the Central Register of Controlled Trials (CENTRAL)) using the above search strategy. We reviewed 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 the pharmaceutical companies who manufacture the agents (GlaxoSmithKline, Astra Zeneca and Novartis). We searched registers of published and unpublished clinical trial data (http://www.ctr.gsk.co.uk; http://www.clinicalstudyresults.org; http://www.astrazenecaclinicaltrials.com; http://www.novartisclinicaltrials.com).

Data collection and analysis

Selection of studies—From the title, abstract or descriptors, one of the authors (IRG or MNC and FMD or TJL) 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 authors (IRG or MNC and FMD or TJL) reviewed all other citations independently in full text, assessing for inclusion based on study design, population, intervention and outcome.

Data extraction and management—Two authors (IRG or MNC and FMD or TJL) independently extracted data for the trials and entered data into the Cochrane Collaboration software program, Review Manager (RevMan) (RevMan 2008). For the 2008 update of the review, one author (TJL) extracted the data.

As a ‘user defined’ item, we recorded the difference in the daily dose of inhaled corticosteroids in the LABA and ICS versus higher ICS groups, reported in chlorofluorocarbon (CFC)-propelled ‘beclomethasone-equivalent’ , where 1 mcg of beclomethasone dipropionate = 1 mcg of budesonide = 0.5 mcg fluticasone propionate (NIH Publication 2007). All doses of inhaled medications are reported based on ex-VALVE, rather than ex-inhaler, values.

Assessment of risk of bias in included studies—We assessed the risk of bias for the allocation, blinding and the handling of missing data from the studies. This is in line with recommendations made in the *Cochrane Handbook for Systematic Reviews of Interventions* (Handbook 2008). The method for assessing study quality for previous versions of this review is given in Appendix 2.

Dealing with missing data—We contacted study investigators and/or study sponsors for trials with pharmaceutical company sponsorship to obtain verification of study design and

information on missing outcome data. We were particularly interested in obtaining verification and missing data for the two outcomes pertaining to exacerbations: those necessitating systemic corticosteroids and those leading to hospital admission. Where we could not determine whether these outcomes had been collected in the studies we contacted the investigators or study sponsors to ascertain whether this information was available for us to use in our analyses.

We sought additional outcome data (such as FEV1 or PEF) which was incompletely reported from the investigators or from the sponsors.

Assessment of heterogeneity—We assessed statistical heterogeneity with the I^2 statistic. This gives an estimate of the proportion of heterogeneity between the study results that exceeds what would be expected with the play of chance, expressed as a percentage (Higgins 2003).

Data synthesis—The analysis focused on the following comparison:

Long-acting ß2 agonist (LABA) and inhaled corticosteroids (ICS) versus a higher dose of inhaled corticosteroids as second-line treatment (i.e. in patients who were already taking inhaled corticosteroids at baseline).

Note that given the large size of this review, other comparisons originally stated in the protocol published in 1999 were assessed in two other reviews. This includes comparing the addition of LABA to similar (Ni Chroinin 2005; Ni Chroinin 2009a) and tapering doses of inhaled corticosteroids (Gibson 2005).

If a trial had more than one intervention or control group, we considered additional comparisons, if appropriate. If two comparisons used the same group twice as comparator (e.g. a three-arm study which had two ‘LABA + ICS’ arms but only one ‘higher ICS’ group) (Woolcock 1996a; Woolcock 1996b), we halved the number of participants in the control group (e.g. ICS alone group) to avoid over-representation. For dichotomous outcomes (such as hospitalisation) we halved the control group numerator and denominator.

We calculated treatment effects for dichotomous variables as relative risk (RR) and/or risk difference (RD) with 95% confidence intervals (CI). For continuous outcomes, such as pulmonary function tests, we calculated pooled statistics as mean differences (MD or generic inverse variance) or standardised mean differences (SMD), as indicated, and reported 95% confidence intervals. We tested homogeneity of effect sizes between studies being pooled with the I^2 statistic and the Dersimonian & Laird method, with values above 25% and a $P < 0.05$ being used, respectively, as the cut-off level for statistical significance. In the absence of heterogeneity we used a fixed-effect model (Greenland 1985). If heterogeneity was suggested, we applied the Dersimonian & Laird random-effects model (DerSimonian 1986) to the summary estimates. Unless otherwise specified, the pooled estimates are derived from the fixed-effect model.

We assumed equivalence if the relative risk estimate and its confidence interval were between 0.9 and 1.1. We derived numbers needed to treat (NNT) from the pooled relative risks using Visual Rx (Cates 2002).

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 benefit may change according to the value of characteristic (e.g. 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 group percent predicted forced expiratory volume in 1 second (FEV1) classified as mild (FEV1: >= 80%), moderate (FEV1 61% to 79%), or severe (FEV1 <= 60%) (GINA 2008).
2. Dose of inhaled corticosteroids examined as:
    i. mean dose (ex-valve) of inhaled corticosteroids in LABA group, reported in CFC-propelled beclomethasone-equivalent (mcg/day);
    ii. dose difference in dose of inhaled corticosteroids (in CFC-propelled beclomethasone equivalent) between the LABA and the higher ICS groups. When not reported, an estimate of the mean was made based on the provided range.
3. Long-acting ß2 agonist (salmeterol/formoterol).
4. Children (< 18 years) versus adults.
5. Use of one or two devices to deliver the combination of ICS + LABA.
6. Trial duration (in weeks).

We examined difference in the magnitude of effect attributable to these subgroups with the residual Chi^2 test from the Peto odds ratios (Deeks 2001). The number of trials allowed us to conduct a multivariate meta-regression to examine the simultaneous impact of, and interaction between the above-named variables on, the heterogeneity of patients with exacerbations requiring systemic corticosteroids. We built backward and forward models using these subgroups as well as using FEV1 (L), dose of inhaled corticosteroids in the LABA group (mcg/day), dose difference in ICS between LABA and control group (mcg/day) and trial duration as continuous variables, using $P < 0.10$ as entry and exit criteria (Stata, Version 8.2, Stata Corporation, Texas, USA).

Sensitivity analysis—We performed sensitivity analyses to investigate the potential impact of the following variables on the primary outcome:

1. risk of bias;
2. publication bias;
3. funding source.

We used funnel plots to examine the possibility of publication bias (Egger 1997). The fail-safe N test was used to estimate the number of unpublished studies required to reverse the observed group difference (Gleser 1996).

RESULTS

Description of studies

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

Results of the search—For an archive of previous search detail see Table 1. Literature searches conducted between April 2004 and May 2008 yielded 375 citations, from which we included 18 studies. Figure 1 illustrates the handling of literature search results and inclusion of studies in this update.

The current review aggregates 47 trials recruiting 15,155 participants. One trial contributed two intervention groups which were both compared to the same control group (Woolcock 1996a;Woolcock 1996b). Therefore we evaluated 48 different *studies* since we considered them as separate data sets in this review for ease of description. A total of 125 citations reported the 48 included studies.

Two studies are available as conference abstracts (Joshi 2005;Ortega-Cisneros 1998). We downloaded 12 studies from manufacturers' online trial results registries, and we have not been able to identify a full-text journal article for them: D5896C00001;SAM30013; SAM30022; SAM40012; SAM40090; SAM40120;SAS40013; SAS40026; SD 039 0726; SD 039 0728; SFCF4026;SLGA5021. From a further 12 reports identified from these web-sites, we were able to identify and include data previously unavailable from full-text trial reports (Bateman 2003; Bergmann 2004;Busse 2003; Condemi 1999; Greening 1994; Ind 2003; Jenkins 2000; Johansson 2001; Kelsen 1999; Murray 1999; Verberne 1998; Woolcock 1996a; Woolcock 1996b).

Included studies—Forty-six studies had a parallel design while two were cross-overs (Green 2006; Heuck 2000). Detailed descriptions of each study are given in the 'Characteristics of included studies' table. An overview of these studies is given below.

Participants: Forty studies focused on adults and six on children exclusively (Heuck 2000; Ortega-Cisneros 1998; SAM104926; SAM40012;SAM40100; Verberne 1998). Two studies included both children and adults (LOCCS; O'Byrne 2005). There were a total of 1155 children and 14,000 adults recruited to the studies.

Participants had inadequate control of their asthma at the time of enrolment in all but three studies (LOCCS; Pearlman 1999;Vermetten 1999). Severity of airway obstruction was generally moderate, with a baseline FEV1 or PEF 60% to 80% of predicted in 23 studies. Twelve studies recruited patients with minimal airway obstruction, with a mean baseline FEV1 or PEF of 80% of predicted or more (Busse 2003; Green 2006; Kips 2000;Lalloo 2003; Li 1999; LOCCS; O'Byrne 2001; SAM104926;SAM40012; SFCF4026; Verberne 1998; Vermetten 1999; Wallin 2003). Three of the paediatric trials failed to report baseline

severity (Heuck 2000; Ortega-Cisneros 1998; SAM40100). In the majority of manufacturer's study reports available from the Glaxo-SmithKline website, baseline FEV1 predicted was not available.

All but four studies required the intake of inhaled corticosteroids for a minimum of one to three months prior to randomisation.Condemi 1999 included a proportion of patients who were corticosteroid-naive prior to enrolment, but who remained symptomatic despite inhaled corticosteroids during the two to four-week run-in phase. We considered this study to have recruited patients with sub-optimal control on inhaled corticosteroids.

The presence of atopic disease at baseline was reported in four studies. Two of these trials reported atopy in more than 80% of its participants (Li 1999; Verberne 1998), while 60% were atopicin Wallin 2003.

Smoking status was reported in 22 trials. Thirteen trials specifically reported the absence or exclusion of active smokers (>= 10 cigarettes/day) (Baraniuk 1999; Bateman 2006; Bergmann 2004; Condemi 1999; Johansson 2001; Kelsen 1999; Lalloo 2003;Li 1999; Pearlman 1999; SAM40120; SAS40013; SAS40026;SFCF4026; SLGA5021). Six trials reported the proportion of active smokers as being between 1% to 10% (Bateman 2003;Mitchell 2003) and 15% to 33% (Greening 1994; Vermetten 1999; Woolcock 1996a; Woolcock 1996b).

Type of long-acting ß$_2$ agonist, delivery device, inhaled steroid and co-treatment: The long-acting ß$_2$ agonist preparation was salmeterol xinafoate in 35 studies and formoterol in the remaining 13. All but three tested the standard dose of the long-acting ß$_2$ agonist (salmeterol 50 mcg bid and formoterol 12 mcg bid). One study tested a double dose of salmeterol, i.e. 100 mcg bid (Woolcock 1996a), one study assessed a double dose of formoterol (SD 039 0728) and two studies tested a 6 mcg bid dose of formoterol (Bateman 2003; Lalloo 2003).

Twenty-five studies examined long-acting ß$_2$-agonists in combination with corticosteroids in the same device (Bateman 2003;Bateman 2006; Bergmann 2004; Busse 2003; D5896C00001; Ind 2003; Jenkins 2000; Johansson 2001; Joshi 2005; Lalloo 2003;LOCCS; O'Byrne 2005; SAM104926; SAM30013; SAM30022;SAM40012; SAM40090; SAM40100; SAM40120; SAS40013;SAS40026; SD 039 0726; SD 039 0728; SFCF4026; Zhong 2005). The remaining studies tested the delivery of LABA and ICS by separate devices. Adherence to study medication was monitored during the run-in and/or the treatment period in 13 studies (Baraniuk 1999; Bateman 2003; Busse 2003; Fowler 2002;Greening 1994; Heuck 2000; Kelsen 1999; Kips 2000; Lalloo 2003; Murray 1999; O'Byrne 2005; Pauwels 1997; Pearlman 1999), but adherence observed during the trial was seldom reported, nor used for efficacy or subgroup analyses.

The type of inhaled corticosteroid varied among the studies. Forty-three studies compared the same inhaled corticosteroid preparation in both the LABA and the control groups. Ten studies compared CFC-beclomethasone, 11 trials assessed budesonide and 22 assessed fluticasone.

Five studies compared the combination of fluticasone propionate and long acting ß$_2$ agonist to CFC-beclomethasone (Jenkins 2000; SAM30022), budesonide (Johansson 2001; Zhong 2005) or HFABDP (Fowler 2002) in the higher ICS group. One study compared the combination of LABA and the patients' own pre-study corticosteroid to additional fluticasone in the higher ICS group (Li 1999). Finally, one study compared budesonide and long acting ß$_2$ agonist to fluticasone propionate in the higher ICS group (Bateman 2003).

After conversion of all doses of inhaled corticosteroids in CFC-equivalent (NIH Publication 2007), the median dose (25th, 75th) of inhaled corticosteroids in the LABA group was 400 (400, 800) with a range of 200 to 1000 mcg/day, while the median dose in the higher ICS group was 1000 (800, 1000) with a range of 400 to 2000. The median absolute dose difference between the intervention and the control group was 600 (400, 600) mcg/day with a range of 200 to 1200. When stated as median relative ICS dose difference, the control group tested a quite homogenous 2.5-fold (2, 2.5) increase in ICS dose as compared to the LABA group. Of note, in absence of adequate details provided by the study by Van Noord 1999, we assumed that an equal proportion of patients of the intervention group received 100 and 250 mcg/ day of fluticasone, respectively, for an average daily intake of 700 mcg/day of beclomethasone-equivalent in the LABA + ICS group and double in the higher ICS group.

Co-interventions with other prophylactic medications, such as xanthines, sodium cromoglycate and anticholinergics, was permitted in nine studies provided that doses remained unchanged throughout the trial (Baraniuk 1999; Bergmann 2004; Greening 1994; Ind 2003; Johansson 2001; Murray 1999; Van Noord 1999;Woolcock 1996a; Woolcock 1996b). Inhaled short-acting ß$_2$ agonist was permitted in all the trials as rescue medication.

Study duration: The duration of the trials was variable: four weeks (Fowler 2002; Green 2006; Pearlman 1999), six weeks (Heuck 2000;SAM40100; Zhong 2005), 12 weeks (Baraniuk 1999; Bateman 2003; Bateman 2006; Bergmann 2004; Bouros 1999; Busse 2003;Johansson 2001; Joshi 2005; Lalloo 2003; Li 1999; Mitchell 2003;Ortega-Cisneros 1998; SAM30013; SAM30022; SAM40090;SAM40120; SAS40026; Van Noord 1999; Vermetten 1999;Wallin 2003), 24 weeks (Condemi 1999; Greening 1994; Ind 2003; Jenkins 2000; Kelsen 1999; Murray 1999; SAM40012;SFCF4026; SLGA5021; Woolcock 1996a; Woolcock 1996b); 52 weeks (Kips 2000; O'Byrne 2001; O'Byrne 2005; Pauwels 1997) and 54 weeks (SAS40013; Verberne 1998). In Busse 2003, to avoid over-representation of patients randomised to the 24-week arm and who contribute data both at 12 weeks and 24 weeks, we only used the 12-week data for all patients irrespective of whether they were randomised to the 12-week (part 1) or the 24-week (part 2) study.

Funding source: Most of the studies (44) were funded by producers of long-acting ß2 agonists. Thirty-three studies were supported by GlaxoSmithK-line, seven by Astra Zeneca (Bateman 2003; D5896C00001;Lalloo 2003, O'Byrne 2001; O'Byrne 2005; SD 039 0726; SD 039 0728), two by Astra Draco (Kips 2000; Pauwels 1997) and two by Novartis (Bouros 1999; Mitchell 2003). Source of funding was unspecified in three trials (Heuck 2000; Joshi 2005; Ortega-Cisneros 1998) and one trial was supported by an anonymous grant (Fowler 2002).

Excluded studies—A total of 286 studies (392 citations) failed to meet the eligibility criteria of this review. The reasons for their exclusion are detailed in the 'Characteristics of excluded studies' table.

Risk of bias in included studies

An overview of our judgements of bias protection for each study is given in Figure 2. We confirmed the methodology of 15 trials directly with the authors of the published trial reports.

Allocation—Following correspondence we have ascertained the randomisation procedure for a number of GlaxoSmithKline-sponsored studies. We have judged that the procedures for generating and concealing allocation put the GlaxoSmithKline-sponsored studies at a low risk of selection bias (Appendix 3).

Blinding—With the exception of three studies, blinding with identical inhaler devices to deliver therapy, or a double-dummy design as a means of protecting against detection bias, was used in the studies. The remaining study designs were open label (Bouros 1999; Ortega-Cisneros 1998; Zhong 2005).

Incomplete outcome data—The meaning of 'intention-to-treat' populations was left undefined in all the studies where this was mentioned. In nine studies the population analysed was either restricted to completers or the last observation was carried forward (see Figure 2). In the remaining trials we could not ascertain how the population analysed was composed.

Other potential sources of bias—One small study stated how many patients were screened for eligibility. Eighteen trials reported the percentage of run-in participants that were successfully randomised. This ranged from 35% (Busse 2003) to 100% (Fowler 2002) of recruited patients.

Effects of interventions

Primary outcome: oral steroid-treated exacerbations—Beta-2 adrenergic agonist (LABA) + inhaled corticosteroid (ICS) treatment led to a lower risk of oral steroid-treated exacerbations than higher doses of ICS (RR 0.88, 95% CI 0.78 to 0.98, P = 0.02; Figure 3, N = 25 studies, 9833 participants). There was no evidence of publication bias as the Egger's test for bias was −0.23(95% CI −1.95 to 1.48). There was no evidence of statistical heterogeneity between studies (I^2 = 2%).

The risk difference was −0.01 (−0.02 to −0.00). Based on the total number of participants with oral steroid-treated exacerbations, the effect of LABA was to reduce the risk of exacerbations from 11.45% in the higher ICS group to 10% in the combination groups. This is compatible with a number needed to treat (NNT) of 73(95% CI 42 to 437) from studies with a median duration of 12 weeks. However, due to variation in the rate of rescue oral corticosteroids in the control groups, we also calculated NNTs for four different control group risks based on control group risk quartiles (see Table 2):

Risk status	Median control group risk (%) [range]	Median study duration (weeks) [range]	Mean FEV1 [range]	NNT (benefit)
Low	1.24 [0 to 3.03]	12 [12 to 12]	81.7 [70 to 102]	673
Low to medium	7.89 [2.86 to 9.43]	12 [12 to 24]	83.8 [74 to 92]	106
Medium to high	12.11 [11.11 to 13.78]	18 [12 to 54]	72 [61 to 88]	69
High	18.87 [14.35 to 38.71]	52 [24 to 52]	73.4 [61 to 87]	45

Visual inspection of the funnel plot did not suggest any significant asymmetry in the analyses we assembled (Figure 4). The fail-safe N test estimated that 154 studies would be needed to reverse the observed group difference.

Sensitivity analysis by allocation sequence generation, allocation concealment and blinding did not materially affect the strength or direction of the results (Analysis 2.9; Analysis 2.10; Analysis 2.11).

Among studies contributing data to the main outcome, the median dose (interquartile range) of inhaled corticosteroids in the LABA group was quite homogeneous at 400 (400 to 400) with a range of 200 to 1000 mcg/day, while the median dose in the higher ICS group was 1000 (800 to 1000). The median absolute dose difference between the intervention and the control group was 600 (400 to 600) mcg/day. The median FEV1 was 77 (71 to 85)% of predicted and the median treatment duration was 12 (12 to 24) weeks. All studies were funded by the manufacturer.

We had planned *a priori* analyses to explore the influence of the a number of variables on the magnitude of effect (effect modification or confounding). From the subgroup analyses both LABA type and study duration gave statistically significant results. Studies testing salmeterol show a significantly greater group difference in favour of combination therapy than those testing formoterol (RR 0.75 versus 1.00). The ratio of these risk ratios (RRR) was 1.33, 95% CI 1.07 to 1.67 (Analysis 2.4). Studies of six months duration or less were also significantly more likely to be associated with a reduced risk of rescue oral steroids (i.e. a larger effect size) than longer duration trials (RR 0.72 versus 1.00; RRR 1.37, 95% CI 1.05 to 1.78, Analysis 2.6). Both variables were highly correlated ($r = -0.70$), and the correlation made it impossible to disentangle the relative contribution of either LABA type or duration of study to the size of effect. It is noteworthy that the dose of LABA, dose of ICS dose combined with LABA, ICS dose difference between the two groups, number of devices to deliver combination therapy, and publication status were not important effect modifiers. The majority of studies recruited adults: the subgroup estimate for these studies favoured the use of LABA in reducing the risk of oral steroid treatment (RR 0.87, 95% CI 0.78 to 0.97). In children the result was not statistically significant (RR 1.28, 95% CI 0.58 to 2.66, Figure 5). Although the test for interaction between these subgroup analyses gave a non-statistically significant result ($P = 0.29$), the RRR included the possibility that children could be almost three times more likely than adults to require oral-steroids when treated with a LABA than they were when treated with increased steroids (RRR 1.42, 95% CI 0.73 to 2.77).

The meta-regression provided additional information. Since one study included a group with zero events (Li 1999), we entered 0.1 for missing data to allow the meta-regression to be performed on all 27 studies contributing to the main outcome: sensitivity analysis excluding Li 1999 did not affect the results. The multivariate regression suggested that higher baseline FEV_1, children and formoterol were associated with increased risk of poor response to combination therapy.

Secondary outcomes

Hospital admission and withdrawal: There was no significant group difference in the risk of patients with exacerbation requiring hospitalisation (RR 1.02, 95% CI 0.67 to 1.56, N = 33) (Analysis 1.2). In 10 studies there were no confirmed events.

A post-hoc subgroup analysis on age gave two non-statistically significant subgroup results, but where the effect was in opposite directions (adults: RR 0.87, 95% CI 0.54 to 1.38; children: RR 2.21, 95% CI 0.74 to 6.64) (Analysis 2.12). The confidence interval around the RRR included unity, but does not rule out a greater than eight-fold greater risk of hospitalisation with LABA in children when compared with adults (RRR 2.66, 95% CI 0.81 to 8.78).

The use of LABA significantly reduced the number of withdrawals due to poor asthma control (RR 0.71, 95% CI 0.56 to 0.91, 29 studies) (Analysis 1.3). There was a borderline difference favouring combination therapy in the number of overall withdrawals (RR 0.92, 95% CI 0.84 to 1.00, 39 studies) (Analysis 1.4). There was no significant difference in the risk of withdrawals due to adverse events (RR 0.99, 95% CI 0.78 to 1.26, 30 studies) (Analysis 1.5).

Lung function - end of treatment values: The combination of LABA and ICS provided significantly higher lung function at endpoint compared to increased dose of ICS for: FEV1 (0.08 L, 95% CI 0.03 to 0.13, 11 studies)(Analysis 1.6); % predicted FEV1 (1.78%, 95% CI 0.39 to 3.18, seven studies) (Analysis 1.7), morning PEF (23.31 L/min, 95% CI 18.09 to 28.52, random-effects model, 14 studies) (Analysis 1.11) or in % predicted (3.45%, 95% CI 1.28 to 5.63, five studies)(Analysis 1.13); and evening PEF (16.79 L/min, 95% CI 10.72 to 22.85, four studies) (Analysis 1.14). There were insufficient data (less than two trials) to aggregate the PEF variability at endpoint.

Lung function - change from baseline: The combination of LABA and ICS provided significantly greater improvement in lung function compared to increased dose of ICS for: FEV1 (0.08 L, 95% CI 0.06 to 0.09, 22 studies) (Analysis 1.8), in morning or clinic PEF in L/min at endpoint (16.30 L/ min, 95% CI 13.48 to 19.11, random-effects model, 30 studies) (Analysis 1.12), and in evening PEF in L/min at endpoint ((13.70 L/min, 95% CI 10.28 to 17.12, random-effects model, 22 studies) (Analysis 1.16). The change in PEF variability also supported the use of combination therapy (−4.55, 95% CI −6.32 to −2.78, seven studies) (Analysis 1.19).

Change from baseline in % predicted FEV1 was not significant (0.35%, 95% CI −0.18 to 0.87, random-effects model, four studies) (Analysis 1.10). The improvement in FEV1

observed within six weeks (+ 90 mL) is sustained until 12 (+ 100 mL), 24 weeks (+ 90 mL) and 52 weeks (+ 70 mL), with no significant effect of timing (P = 0.75) (Analysis 1.9).

Symptoms: The change in daytime symptom score (SMD −0.26, 95% CI −0.35 to −0.17, five studies) (Analysis 1.20); overall (24 hours) symptom score (SMD −0.23, 95% CI −0.37 to −0.08, random-effects model, six studies) (Analysis 1.21); change in percent symptom-free days at endpoint (9.18%, 95% CI 6.02 to 12.33, random-effects model, 12 studies) (Analysis 1.22) and % nighttime awakenings at endpoint (−0.40; 95% CI −0.55 to −0.25, fixed-effect model, two studies) (Analysis 1.29); all favoured combination therapy. However, there was no significant group difference in percentage of symptom-free days at endpoint (5.81%, 95% CI −1.14 to 12.76, random-effects model, eight studies) (Analysis 1.23); daytime symptoms at endpoint (SMD −0.28, 95% CI −0.67 to 0.11, random-effects model, five studies) (Analysis 1.24); nighttime symptoms at endpoint (SMD −0.24, 95% CI −0.49 to 0.01, three studies) (Analysis 1.25); change in nighttime symptoms (SMD −0.01, 95% CI −0.04 to 0.01, two studies) (Analysis 1.26); percentage of symptom-free nights at endpoint (−2.10%; 95% CI −7.98 to 3.79, two studies) (Analysis 1.27), and in the change from baseline in nighttime awakenings (SMD −0.03, 95% CI −0.10 to 0.04, seven studies) (Analysis 1.28). Because of insufficient data, the following outcomes could not be pooled: % nights with no awakenings at endpoint (Analysis 1.30) and change in % nights with no awakenings (Analysis 1.30).

Rescue medication use: The change in daytime rescue inhalations of short-acting ß$_2$ agonist favoured the combination of LABA and ICS (−0.48 puffs/ d, 95% CI −0.77 to −0.20, random-effects model, five studies) (Analysis 1.32) as did the change in nighttime inhalations (SMD −0.13, 95% CI −0.21 to −0.05, random-effects model, four studies) (Analysis 1.33), the change in rescue inhalations over 24 hours (−0.20, 95% CI −0.29 to −0.11, 12 studies) (Analysis 1.34) and the change in mean percent of rescue-free days at endpoint (11.48%, 95% CI 7.98 to 14.98, fixed-effect model, three studies) (Analysis 1.39). There was no group difference at endpoint in the number of daytime rescue inhalations (−0.44, 95% CI −0.94 to 0.06, five studies) (Analysis 1.35); nighttime rescue inhalations (−0.09, 95% CI −0.23 to 0.04, random-effects model, four studies) (Analysis 1.36); % overall rescue-free days (5.14%, 95% CI −2.79 to 13.08, random-effects model, three studies (Analysis 1.37). No pooling was possible for the change in asthma control days (Analysis 1.40), percent asthma control days at endpoint (Analysis 1.44) and the change in percent symptom-free days (Analysis 1.38).

Quality of life: There was no group difference in the change from baseline in quality of life measured by the Juniper Questionnaire (0.10, 95% CI −0.06 to 0.26, four studies) (Analysis 1.41).

Inflammatory markers: Few trials reported inflammatory markers. There was no group difference in the change from baseline in serum ECP (0.62 mcg/ L, 95% CI −2.45 to 3.70, two studies) (Analysis 1.45). Only one trial reported total exhaled nitric oxide at endpoint, preventing pooling.

Adverse events: The risk ratio of serious adverse events (including all cause hospital admission) was 1.12 (95% CI 0.91 to 1.37) (Analysis 1.52). This estimate is based on data from 35 studies.

There was significantly more tremor in the LABA group (RR 1.84, 95% CI 1.20 to 2.82, 11 studies) (Analysis 1.53), although this result became non-significant when the one study using a higher dose of LABA was excluded (Woolcock 1996a). There was significantly less oral thrush on LABA and ICS compared with the higher dose of ICS (RR 0.58, 95% CI 0.40 to 0.86, 14 studies) (Analysis 1.54).

One study assessed growth in children, with a significantly better short-term rate of growth in the LABA and ICS group over 12 months (0.9 cm, 95% CI 0.20 to 1.60). There were insufficient trials reporting these outcomes to aggregate adrenal suppression and osteopenia.

There was no group difference in the following.

1. Overall side effects (RR 0.99, 95% CI 0.95 to 1.03, 30 studies) (Analysis 1.55).
2. Adverse cardiovascular events (RR 0.99, 95% CI 0.49 to 2.01, random-effects model, nine studies) (Analysis 1.56).
3. Headache (RR 1.02, 95% CI 0.92 to 1.12, 25 studies) (Analysis 1.57).
4. Hoarseness (RR 0.95, 95% CI 0.79 to 1.14, nine studies) (Analysis 1.58).
5. Tachycardia/palpitations (RR 1.20, 95% CI 0.78 to 1.84, 15 studies) (Analysis 1.59).

DISCUSSION

The review demonstrates that the addition of long-acting inhaled ß2 agonists (LABA) to moderate doses of inhaled steroids (ICS) reduces the relative risk of oral steroid-treated exacerbations by around 12% and the absolute risk by about 1%. The evidence that forms the basis of this result is predominantly from adults. In children the evidence for the use of LABAs over increased doses of inhaled steroids is less favourable towards LABA, and includes the possibility that increased steroids is superior in reducing the requirement for oral steroids and hospital admissions. Overall 73 patients need to be treated with combination therapy to prevent one use of rescue oral corticosteroids. Based on number needed to treat (NNT) calculations for the different control group risks in the studies included in our analyses, this would mean that 45 patients in the high-risk trials (where study duration was between six and 12 months and study populations had significant airway obstruction), and 673 patients in the low-risk trials (where study duration was between three and six months and study populations had less severe airway obstruction) would need to be treated with a LABA instead of increased dose of ICS in order to prevent one experiencing an exacerbation requiring oral steroids. Although neither the dose of ICS to which LABA was added nor the difference in ICS dose between groups influenced the effect size. These findings predominantly apply to patients who remained symptomatic at baseline despite a median ICS dose of 400 mcg/day.

Neither the dose of ICS to which LABA was added nor the number of devices to administer combination therapy appear to affect the magnitude of protection conferred by LABA, as supported by the subgroup analyses and meta-regression. While no definitive conclusions can be derived from the subgroup analyses and the meta-regression, the findings highlight several factors that appear to influence the magnitude of response to combination therapy compared to higher doses of ICS. These factors, difficult to disentangle due to their correlation, are the LABA used, the duration of treatment, the mean FEV1 and the age group: formoterol, longer duration of treatment, higher mean FEV_1 at baseline, and children (versus adults) appear to decrease the efficacy of combination therapy. These apparent effect modifiers should be explored in future studies with a long-term duration (of one year and beyond), to provide confirmatory evidence of the findings our primary analysis.

There is a theoretical possibility that in the long-run higher doses of ICS may be superior to lower doses of ICS in combination with LABA for preventing exacerbations. One cannot rule out the possibility that the addition of LABA to corticosteroids allows the progression or the ongoing presence of airway inflammation, a factor that could become more evident with prolonged exposure to treatment (Reddel 2000). Despite several trials investigating inflammation, most inflammatory markers could not be aggregated due to the various markers measured in different media (serum (Heuck 2000; Fowler 2002), sputum (Li 1999; Kips 2000), bronchoalveolar lavage and bronchial biopsy (Wallin 2003), urine (Heuck 2000) and expired air (Fowler 2002)). This prevented us from examining the impact of either treatment option on most inflammatory markers. Serum ECP (measured in two trials) revealed no group difference after four to six weeks of treatment with 200 to 400 mcg/day of beclomethasone-equivalent combined with LABA. Moreover, the absence of characterisation of the type and amount of airway inflammation, measured for example by sputum analysis, prevented the identification of the best therapy (and the amount of inhaled corticosteroids) needed for individual patients.

Could the beneficial effect of combination therapy be explained by an initial better compliance with combination therapy that tapers down with time to that observed with inhaled corticosteroids alone? Surprisingly, although 13 trials monitored it during the treatment period, compliance was seldom reported, nor were analyses stratified based on compliance. In the absence of these data this hypothesis cannot be tested. Conversely, LABA may have a more rapid effect on lung function and symptoms than ICS and be more effective when needed, that is, when baseline FEV1 is lower. Moreover, the dose of ICS and duration of treatment may differentially affect different manifestations of asthma. Indeed, rapid improvement in lung function and symptoms have been documented with a higher ICS dose (Currie 2003b; Reddel 2000), while the beneficial effect of low doses of ICS on airway hyperreactivity, severe exacerbations and death requires prolonged (more than one year) treatment (Suissa 2001).

With only limited data for our primary outcome available from the seven small paediatric trials and two which recruited adults and children (accounting for 2% of the weight in the results) together with the unreported proportion of adolescents in recruited to the adult studies, there are insufficient data to comment firmly on a differential effect associated with age. However, the trends toward an increased risk of rescue oral corticosteroids and hospital

admissions in children on combination therapy merits caution. Careful risk-benefit assessment should be done before using combination therapy instead of higher dose ICS in children aged 12 years or less with due consideration of the uncertain impact on the severity of exacerbations, against the known risk of growth retardation associated with steroids (Sharek 1999). One study measured linear growth in children in this review, and reported a significantly lower growth rate over one year in the higher dose steroid group compared with combination therapy (Analysis 1.60).

Secondary outcomes were uniformly supportive of the beneficial effect of LABA, although the magnitude of benefit on lung function, symptoms and rescue ß$_2$ agonists use appears modest. It is of note that two of the 52-week trials graphically displayed the change in lung function over time and identified an initial improvement favouring combination therapy over higher ICS in the first 24 weeks, with gradually overlapping values thereafter (Kips 2000;Verberne 1998). These downward trends after 24 weeks were less pronounced in the other two trials (O'Byrne 2001; Pauwels 1997). Yet the sustained improvement in FEV1 observed over time makes tachyphylaxis a difficult explanation for the apparent waning protection against exacerbations, particularly since it has been described as occurring within a few weeks of treatment. Morning and evening PEF, whether reported as change or value at endpoint, also favour the use of LABA. The 12% increase in symptom-free days favoured the addition of LABA to ICS. Surprisingly, the use of LABA only reduced the use of rescue ß$_2$ agonists by less than half a puff per day, with a non-significant group difference in nighttime use of rescue medication. No *post hoc* subgroup analyses on trial duration or dose of ICS were done on secondary outcomes to avoid multiple comparisons. The representation of long-term studies in most secondary outcomes was minimal. In this review the addition of LABA appears somewhat superior to increased ICS in controlling day-to-day symptoms and improving lung function.

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With the exception of tremor, the addition of LABA was not associated with any difference compared with higher doses of ICS in overall or specific adverse effects. Removing the study using a higher than licensed dose of LABA yielded a non-statistically significant result between the treatments in tremor. As might be expected, oral candidiasis was more frequent in patients treated with a higher dose of ICS than in those treated with combination therapy. The safety of LABAs remains a question of some controversy since the uncertainty around the pooled effect from combination studies has not ruled important differences in the likelihood of serious adverse events from clinical trial data (Cates 2009a; Cates 2009b). Similarly, our review does not provide conclusive proof of the safety of LABAs when compared with high-dose steroids alone, even though the pooled result includes unity. In the absence of systematic documentation of the adverse effects specific to inhaled corticosteroids (i.e. adrenal dysfunction, osteopenia and growth in children) or LABAs, the long-term safety of either strategy, particularly in children remains to be demonstrated. There is an urgent need to conduct studies addressing this question with systematic assessment of these potential adverse effects. In summary, while the data provide some reassurance, there is some uncertainty around the risk of severe adverse health events associated with the use of LABA even in presence of inhaled corticosteroids, and particularly so in children.

To whom can these results be generalised? Patients included in the eligible trials were largely adults, who were symptomatic on their current inhaled corticosteroids dose, demonstrated significant (>= 12% or 15%) reversibility in FEV1 with ß$_2$ agonist and did not have severe airway obstruction or recent asthma exacerbations. The reversibility to bronchodilator tends to favour the LABA option over inhaled corticosteroids and may seriously limit generalisability since reversibility to bronchodilator is a criteria met in less than 10% of patients at a given point in time (Storms 2003). Since pregnant or lactating women as well as those of childbearing age without appropriate contraception were generally not eligible, a large proportion of females were probably excluded. Few studies reported the smoking status of their patients. This raises an important question regarding applicability of findings to smokers, a group that has been shown to display significant resistance to both oral (Chaudhuri 2003) and inhaled (Chalmers 2002) corticosteroids. Recognising the possibility of patient selection bias, the findings may be applied to adult asthmatics who remain symptomatic on 400 mcg/day of beclomethasone or equivalent, with a mild or moderate airway obstruction reversible with bronchodilator. With the small weight carried by paediatric trials, generalising these results to children would be inappropriate (Ni Chroinin 2009b). No data are available for preschool-aged children.

To our knowledge, this systematic review is the largest meta-analysis comparing the relative benefit and harms of the combination of LABA and inhaled corticosteroids to a higher dose of inhaled corticosteroids. It provides complementary information to another Cochrane Review examining the relative benefit of adding LABA or a leukotriene receptor antagonist to inhaled corticosteroids (Ducharme 2006). The three options currently recommended by international consensus statements in the face of sub-optimal asthma control on inhaled corticosteroids have now been covered by Cochrane Reviews. The results of this review are strengthened by the overall high methodological quality of the included trials and confirmation of methodology and data by authors or sponsors of several trials, including the provision of unpublished data. The present review had sufficient power to explore variables associated with the effectiveness of either treatment option. In future research priority should be given to addressing the large gap in knowledge related to these two treatment options in children and adolescents.

AUTHORS' CONCLUSIONS

Implications for practice

In adult patients who remain symptomatic on 400 mcg/day of beclomethasone or equivalent, two strategies may be considered: adding a long-acting ß2 agonist (LABA) or increasing the dose of inhaled corticosteroids (ICS) to 800 or 1000 mcg/day. There is a slight but significant difference favouring LABA in offering protection against the risk of exacerbations requiring systemic corticosteroids. The reduction in the relative risk is 12% while the absolute reduction is about 1%, with an overall number needed to treat to prevent an exacerbation of 72, which varies from 45 from high-event studies(predominantly long-term ones) to 772 in low-event studies. Baseline FEV1, treatment duration and type of LABA may modify the magnitude of effect, although we can only speculate about their true relationship to the overall effect as the latter two are themselves highly correlated with each

other. The combination of long-acting ß2 agonists with inhaled corticosteroids leads to greater but modest improvement in FEV1 (+ 80 mL), symptoms and rescue ß2 agonists (−0.5 puff/day) than a 2 to 2.5-fold higher dose of inhaled corticosteroids, although most of the data come from trials of six months or less. Studies conducted in school-aged children contributed few data to the primary outcome and we cannot comment firmly on the relative treatment effect in children and adolescents. Due to the apparent trend toward higher risk of exacerbations requiring systemic steroids and hospital admission, caution should be advised when considering use of combination therapy in children as higher ICS dose may be preferable. However, impaired growth in children treated with higher doses of inhaled steroids has been identified in one study, and this should be weighed against the uncertain (and possibly unfavourable) effects of combination therapy on oral steroid requirement in children. The lack of group difference in reported side effects should be interpreted with caution in the absence of systematic documentation of airway inflammation parameters, as well as adverse effects typically associated with long-term use of inhaled corticosteroids (osteopenia, growth and adrenal suppression), particularly in children.

Implications for research

To address the current gaps in knowledge, future trials should focus on the paediatric and adolescent populations, in whom the gap in knowledge is particularly pressing, and investigate the impact of treatment duration of LABA of the effect size. Moreover, there is a need to characterise patients at baseline better (in terms of type and amount of airway inflammation, phenotype, genotype, smoking status, etc.) to examine the relative efficacy of each treatment strategy for individual patient characteristics.

Studies should consider the following design characteristics.

1. Long-term interventions >= 52 weeks.
2. Stratifying on, and providing subgroup analyses for, children and adolescents.
3. Stratifying on, and providing subgroup analyses for, patients with mild, moderate and severe obstruction.
4. Stratifying on, and providing subgroup analyses for, smoking status.
5. Characterising patients in terms of type and amount of airway inflammation by induced sputum (genotype, smoking status, etc.) and perform randomisation stratified on these characteristics.
6. Providing subgroup analyses for the effect size at different points in time during the trial.
7. Relaxing eligibility criteria to allow the inclusion of patients in whom the diagnosis of asthma has been confirmed in the past (either by provocation or documented reversibility to bronchodilator or corticosteroids), even if the patients do not exhibit reversibility to bronchodilator at enrolment.
8. Monitoring, reporting and providing subgroup analyses on compliance.

9. Stratifying, providing subgroup analyses using different dose of ICS to which LABA is added.
10. Examining inflammatory markers.
11. Monitoring and reporting side effects that may be associated with the long-term use of inhaled corticosteroids (osteopenia, adrenal suppression and, in children, growth).

Future trials should aim for the following design characteristics.

1. Double-blinding, adequate randomisation and complete reporting of withdrawals and drop-outs with intention-to-treat analysis.
2. Intervention period of 52 weeks or more to assess the impact on patients with exacerbations requiring oral corticosteroids properly.
3. Clear reporting of the percentage and reasons for 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 include are as follows.

1. Proportion of patients with one or more exacerbations requiring systemic corticosteroids.
2. Change in symptoms, symptom-free days and nights, pulmonary function tests, use of rescue ß2 agonists, quality of life.
3. Change in inflammatory markers.
4. Safety, particularly regarding long-term side effects of inhaled corticosteroids (growth, osteopenia, adrenal suppression) and/or long-acting ß2 agonists (severe adverse effects and mortality).

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CHARACTERISTICS OF STUDIES

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

Baraniuk 1999

Methods	Parallel-group, multicentre study (50 centres). Three groups of which 2 considered here, namely: FP 250 bid; FP 100 + SL 50 bid Jadad quality score = 5
Participants	Symptomatic asthmatic children >= 12 years and adults % ELIGIBLE OF SCREENED POPULATION: Not reported % RUN-IN PARTICIPANTS RANDOMISED: Not reported RANDOMISED: 454 (FP100 + Salm50: 231; FP250: 223) WITHDRAWALS: FP100 + Salm50: 16; FP250: 13 AGE: mean (range): 41 (12 to 79) GENDER (% male): 40 SEVERITY: Moderate BASELINE % PREDICTED FEV1: 63.1 BASELINE DOSE OF ICS (start of run-in): Not reported ASTHMA DURATION: Not reported ATOPY (%): Not reported ELIGIBILITY CRITERIA: Non-smokers; >= 12 years of age who had asthma defined in accordance with American Thoracic Society criteria; low dose of beclomethasone dipropionate or fluticasone for at least 3 months preceding the study; the daily dosing schedule for the inhaled corticosteroid had to be constant for the 14-day run-in period prior to the study; FEV1 of 40% to 85% of predicted normal values for age, gender and height; reversibility of airway obstruction was demonstrated by >= 15% increase in FEV1 within 30 minutes after 2 puffs of albuterol EXCLUSION CRITERIA: Pregnant/lactating mothers; use of methotrexate, gold, cyclosporine or azathioprine for control of asthma within 30 days prior to study; use of inhaled cromolyn or inhaled nedocromil within weeks prior to the study; use of oral or injectable corticosteroids within 4 weeks prior to the study; significant concomitant illness or concurrent use of any other prescription or over-the-counter medication that might affect the course of asthma or interact with sympathomimetic amines CRITERIA FOR RANDOMISATION DURING RUN-IN: FEV1 between 40% to 65%, if FEV1 65.1% to 85% had to have asthma symptoms; demonstrate compliance and complete diary cards; not to have experienced clinical exacerbation during screening period
Interventions	LABA + ICS versus INCREASED dose of ICS OUTCOMES: Reported at 1, 2, 4, 6, 8 and 12 weeks RUN-IN PERIOD: 2 weeks DOSE OF ICS DURING RUN-IN: Usual ICS DOSE OPTIMISATION PERIOD: None INTERVENTION PERIOD: 12 weeks TEST GROUP: (FP 100 + Salm 50) fluticasone 100 mcg bid + salmeterol 50 mcg bid CONTROL GROUP: (FP 250) fluticasone 250 mcg bid DEVICE: MDI NUMBER OF DEVICES: 2 COMPLIANCE: Assessed CO-TREATMENT: prn SABA and theophylline as needed
Outcomes	PULMONARY FUNCTION TEST: FEV1*; am PEF; pm PEF SYMPTOM SCORES: Symptom scores (score of 0 to 5) FUNCTIONAL STATUS: Rescue medication use; nocturnal awakenings; symptom-free days; physician global assessment INFLAMMATORY MARKERS: Not described ADVERSE EFFECTS: Described WITHDRAWALS: Described Primary outcome measure*
Notes	Full-text publication Funded by Glaxo Wellcome Confirmation of methodology and data obtained User-defined number: 1000
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	Double-dummy design; use of identical placebo
Incomplete outcome data addressed? All outcomes	Unclear	"Analyses were based on data from the intent-to-treat population, consisting of all patients exposed to the study drug."
Free of selective reporting?	Yes	Data available for meta-analysis

Bateman 2003

Methods	Parallel-group, multicentre (37 centres in 6 countries) Jadad quality score = 5
Participants	Patients with asthma >= 18 years % ELIGIBLE OF SCREENED POPULATION: Not reported % RUN-IN PARTICIPANTS RANDOMISED: 92 RANDOMISED: 344 (BUD 200 + Form 6: 168; FP250: 176) WITHDRAWALS: BUD 200 + Form 12: 3; FP250: 8 AGE: mean (range): 42 (17 to 75) GENDER (% male): BUD 200/Form 6: 42; FP250: 44 SEVERITY: Moderate BASELINE % PREDICTED FEV1(mean): 78 BASELINE DOSE OF ICS: Mean mcg/day BDP equivalent: 594 ASTHMA DURATION mean (range) years: 16.3 (0 to 66) ATOPY (%): Not reported SMOKERS (%): 6 ELIGIBILITY CRITERIA: >= 18 years of age with a diagnosis of persistent asthma (minimum duration 6 months) as defined by the Global Initiative for Asthma (GINA) guidelines; using any inhaled glucocorticoid at a constant dose of 200 to 1000 mcg/day for at least 30 days before study entry; FEV1 of 60% to 90% of predicted normal values; reversibility of airway obstruction was demonstrated by >= 12% increase in FEV1 within 30 minutes after bronchodilator EXCLUSION CRITERIA: Female patients of childbearing potential not using adequate contraception; use of oral, parenteral or rectal corticosteroids or respiratory tract infection within 30 days prior to the study; heavy smoking (>= 10 pack years) CRITERIA FOR RANDOMISATION DURING RUN-IN: Required to have diary data for at least 7 of the last 10 days of run-in period
Interventions	LABA + ICS vs INCREASED dose of ICS OUTCOMES: Reported at 4, 8 and 12 weeks RUN-IN PERIOD: 2 weeks DOSE OF ICS DURING RUN-IN: BUD 200 bid DOSE OPTIMISATION PERIOD: None INTERVENTION PERIOD: 12 weeks TEST GROUP: (BUD 200 + Fom 6) budesonide 200 mcg bid + formoterol 6 mcg bid CONTROL GROUP: (FP 250) fluticasone 250 mcg bid DEVICE: Diskhaler NUMBER OF DEVICES: 1 COMPLIANCE: Assessed using diary cards CO-TREATMENT: prn SABA
Outcomes	PULMONARY FUNCTION TEST: FEV1; am PEF*; pm PEF SYMPTOM SCORES: Change in symptom score (score of 0 to 3) FUNCTIONAL STATUS: Rescue medication use; % nocturnal awakenings; % of symptom-free days; % asthma-control days INFLAMMATORY MARKERS: Not described ADVERSE EFFECTS: Described WITHDRAWALS: Described Primary outcome measure*
Notes	Full-text publication Funded by Astra Zeneca

	Confirmation of methodology and data: Not obtained User-defined number: 1000

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; identical placebo
Incomplete outcome data addressed? All outcomes	Unclear	Described as intention-to-treat analysis; explicit details of how missing data were handled not reported
Free of selective reporting?	Yes	Severe exacerbations (including OCS treated exacerbations) extracted as proxy for OCS-treated exacerbations (see Analysis 3.1)

Bateman 2006

Methods	Parallel-group, multicentre study (37 centres: 36 in USA, 1 in Puerto Rico) Jadad quality score = 4
Participants	Persistent symptomatic asthmatic adults % ELIGIBLE OF SCREENED POPULATION: Not reported % RUN-IN PARTICIPANTS RANDOMISED: Not reported RANDOMISED: 484 (FP/SAL: 246; FP: 238) WITHDRAWALS: FP/SAL: 6; FP: 4 AGE: mean: 41 GENDER: (% male): 41 SEVERITY: Moderate BASELINE % PRED FEV1 (mean): 70 BASELINE DOSE OF ICS: FP500 ASTHMA DURATION: Not reported ATOPY (%): Not reported ELIGIBILITY CRITERIA: > 12 and < 80 years; diagnosis of persistent (non-seasonal) asthma for more than 6 months; treated with short-acting beta-agonists; FEV1 > 60 and < 80% predicted; reversibility to SABA of 15% OR PEF < 85% predicted; achievement of good asthma control in last 4 weeks of open label period; score of >= 2 on combined day and nighttime score on 4 of last 7 days of run-in period EXCLUSION CRITERIA: Treatment with corticosteroids (within 12 weeks) antileukotriene agents, sodium cromoglycate, long-acting beta-agonists, nedocromil sodium, ketotifen, methylxanthines, anti-cholinergic agents (within 4 weeks); participants with acute asthma exacerbation in 6 weeks prior to study; participants with respiratory tract infection within 4 weeks prior to study; significant smoking history
Interventions	LABA/ICS versus INCREASED dose of ICS OUTCOMES: TIMING 12 weeks RUN-IN: 2 weeks on SABA; −12 weeks open label with combination FP/SAL DOSE OF ICS DURING RUN-IN: 250 mcg bid INTERVENTION PERIOD: 12 weeks TEST GROUP: Combination fluticasone 100 mcg and salmeterol 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: Daytime symptoms; nighttime symptoms; % symptom-free days; % symptom-free nights FUNCTIONAL STATUS: Rescue medication use; exacerbations (moderate: OCS treatment; severe: hospitalisation) INFLAMMATORY MARKERS: Not reported ADVERSE EFFECTS: Reported

	WITHDRAWALS: Reported Primary outcome measure*
Notes	Full-text article (additional data from 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 3
Allocation concealment?	Yes	See Appendix 3
Blinding? All outcomes	Yes	Identical devices
Incomplete outcome data addressed? All outcomes	Unclear	"The Intent-to-Treat (ITT) population (all subjects who were randomised to treatment and received ≥ 1 dose of double-blind study medication) were used for the safety and efficacy analyses."
Free of selective reporting?	Yes	OCS-treated exacerbations available on request from study sponsors

Bergmann 2004

Methods	Parallel-group, multicentre study (76 centres) Jadad quality score = 4
Participants	Patients with asthma 18 to 70 years % ELIGIBLE OF SCREENED POPULATION: Not reported % RUN-IN PARTICIPANTS RANDOMISED: 91 RANDOMISED: 365 (FP250/SM 50 bid: 179; FP500 bid: 186) WITHDRAWALS: FP250/SM 50 bid: 13; FP500 bid: 18 AGE mean: 49 GENDER (% male): 47 SEVERITY: Moderate BASELINE % PREDICTED FEV1 mean: 75 BASELINE DOSE OF ICS: Mean mcg/day BDP equivalent: 800 to 1000 of BDP or BUD ASTHMA DURATION (mean (range) years): Not reported ATOPY (%): Not reported SMOKERS: 0 ELIGIBILITY CRITERIA: 18 to 70 years of age with a diagnosis of persistent asthma (minimum duration 6 months) as defined by the German asthma guidelines; asthma of moderate severity (i.e., symptoms < 1/day but no more than 2/week during daytime, or symptoms >= 2/month but less than 1/week at night; FEV1 50% to 80% of predicted; reversibility of airway obstruction was demonstrated by >= 15% increase in FEV1 after 200 mcg salbutamol; non- or ex-smoker; asthma treated with 800 to 1000 mcg/day of BUD or BDP (or 500 FP) per day for at least 3 months prior to study EXCLUSION CRITERIA: Previous therapy with inhaled LABA, oral beta-agonists, oral or parental steroids in preceding 4 weeks; change in asthma medication, treatment with other study medication, respiratory tract infection or hospital stay due to respiratory problems in receding 4 weeks; inability to correctly administer study drugs, known allergy to components of study drugs; severe concomitant illness or other chronic respiratory diseases (such as cystic fibrosis or interstitial fibrosis); in women, inadequate contraception, pregnancy or lactation CRITERIA FOR RANDOMISATION DURING RUN-IN: At least one of the following criteria: use of rescue medication >= 7 of 14 days; total asthma symptoms score >= 10 points (sums of scores from 14 days and nights); excluded if incomplete diary or considered not reliable or respiratory tract infection during run-in
Interventions	LABA + ICS vs INCREASED dose of ICS OUTCOMES: Reported at 4, 8 and 12 weeks RUN-IN PERIOD: 2 weeks DOSE OF ICS DURING RUN-IN: BUD 200 bid

	DOSE OPTIMISATION PERIOD: None INTERVENTION PERIOD: 12 weeks TEST GROUP: (FLUT 200 + SALM50) fluticasone 200 mcg bid + salmeterol 50 mcg bid (1 inhaler) CONTROL GROUP: (FP 500) fluticasone 500 mcg bid DEVICE: Diskus NUMBER OF DEVICES: 1 COMPLIANCE: Assessed using diary cards CO-TREATMENT: Theophylline, cholinergic drugs or leukotrienes if dose was not changed during the trial. Prn SABA
Outcomes	PULMONARY FUNCTION TEST: FEV1; am PEF*; pm PEF SYMPTOM SCORES: Change in daytime and nighttime symptom score (score of 0 to 4) FUNCTIONAL STATUS: Rescue medication use; % of symptom-free days INFLAMMATORY MARKERS: Not described ADVERSE EFFECTS: Described WITHDRAWALS: Described Primary outcome measure*
Notes	Full-text publication Funded by Glaxo Welcome Germany Confirmation of methodology and data: Not obtained User-defined number: 1000

Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	Yes	See Appendix 3
Allocation concealment?	Yes	See Appendix 3
Blinding? All outcomes	Yes	Identical inhaler devices
Incomplete outcome data addressed? All outcomes	No	"The full analysis set (FAS) consisted of those patients who inhaled at least one dose of study medication and had no critical protocol violation (e.g. a missing diary from the screening period). The last observation carried forward (LOCF) principle was applied to the efficacy variables."
Free of selective reporting?	Unclear	Unclear whether exacerbations were recorded in the study

Bouros 1999

Methods	Parallel-group, multicentre study (11 centres) Jadad quality score = 2
Participants	Symptomatic asthmatic adults % ELIGIBLE OF SCREENED POPULATION: Not reported % RUN-IN PARTICIPANTS RANDOMISED: 84 RANDOMISED: 134 (BDP250 + Form 12: 69; BDP500: 65) WITHDRAWALS: BDP250 + Form 12: 4; BDP500: 6 AGE mean: 43 Gender (% male): 35 SEVERITY: Moderate BASELINE % PREDICTED FEV1: 60% to 79% (estimated) BASELINE DOSE OF ICS: BDP 500 mcg/day ASTHMA DURATION: Not described ATOPY (%): Not described SMOKING STATUS: Not described ELIGIBILITY CRITERIA: >= 18 years old; use of inhaled BDP aerosol for at least 1 month prior to enrolment, at a constant daily dose of 500 mg EXCLUSION CRITERIA: Other clinically significant diseases; pregnant or lactating women; patients on B-blocker therapy or hypersensitivity of sympathomimetic amines; received a short course of oral corticosteroid in the 6

	weeks prior to enrolment; more then 3 oral corticosteroid short courses during the year prior to enrolment CRITERIA FOR RANDOMISATION DURING RUN-IN: A symptom score of 2 or greater on at least 4 of the 7 days during the second week of the run-in; FEV1 before administration of an inhaler agonist 40% to 85% of the predicted value; a reversibility test with 200 mg salbutamol demonstrating an increase in FEV1 of at least 15% from baseline value
Interventions	LABA + ICS vs INCREASED dose of ICS OUTCOMES: Reported at 4, 8 and 12 weeks RUN-IN PERIOD: 2 weeks to document symptoms and beta2 use DOSE OF ICS DURING RUN-IN: BDP 500 mcg/day DOSE OPTIMISATION PERIOD: None INTERVENTION PERIOD: 12 weeks TEST GROUP: (BDP500 + Form 12) beclomethasone 250 mcg bid + formoterol fumarate 12 mcg bid CONTROL GROUP: (BDP1000) beclomethasone 500 mcg bid DEVICE: MDI NUMBER OF DEVICES: 2 COMPLIANCE: Not reported CO-TREATMENT: prn SABA (used with a spacer device)
Outcomes	PULMONARY FUNCTION TEST: am PEF*; pm PEF; FEV1 SYMPTOM SCORE: Morning and evening score (score of 0 to 4) FUNCTIONAL STATUS: Mean rescue B2-agonist (inhalations per day or night); exacerbations requiring systemic steroids 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: 500 (1000-500)

Risk of bias

Item	**Authors' judgement**	**Description**
Adequate sequence generation?	Yes	See Appendix 3
Allocation concealment?	Yes	See Appendix 3
Blinding? All outcomes	No	Open label
Incomplete outcome data addressed? All outcomes	No	Completers analysed
Free of selective reporting?	Yes	OCS-treated exacerbations available

Busse 2003

Methods	Parallel-group, multicentre study (90 centres in US). Study had 2 treatment periods: fixed dosing during period 1 (up to week 12), and variable dosing in period 2 (weeks 12 to 24) Jadad quality score = 3
Participants	Stable asthmatic patients 12 years and over % ELIGIBLE OF SCREENED POPULATION: Not reported % RUN-IN PATIENTS RANDOMISED: 558/1596 = 35% RANDOMISED: 558 (Salmeterol 50 bid + ICS: 281; ICS + placebo: 277) WITHDRAWALS: S + ICS: 35; ICS: 42 AGE mean (range): 39 (12 to 77) GENDER (% male): 42 BASELINE % PREDICTED FEV1 mean: 80.5 BASELINE DOSE OF ICS (mean): Not reported by treatment groups BDP 400 to 800 mcgs/day; triamcinolone acetate 1200 to 1600 mcgs/day; flunisolide 1000 to 1500 mcgs/day; FP 440 to 660 mcgs/day ASTHMA DURATION: Not reported

	ATOPY (%): Not described SMOKING STATUS: Not reported ELIGIBILITY CRITERIA: Asthma for at least 6 months and treated with medium dose ICS for at least 30 days before screening; baseline FEV1 of 65% to 95% normal; >= 12% improvement from baseline in lung function following inhaled bronchodilator; best FEV1 within +/− 15% of the best predose FEV1 obtained at screening; no more than 1 nighttime awakening requiring albuterol and fewer than 18 puffs albuterol during the previous week EXCLUSION CRITERIA: Pregnancy and/or lactating; life-threatening asthma; asthma hospitalisation within 3 months of screening; change in asthma regimen 30 days before screening; significant concurrent diseases including recent URTI; systemic corticosteroids in 30 days before screening CRITERIA TO ENTER RUN-IN PERIOD 2: 20% decrease from the screening visit pre-dose FEV1; >= 20% decrease from the mean morning baseline PEF on any one of the 7 days immediately preceding the visit; total symptom score of >= 8 during any week before run-in visit; 2 or more nighttime awakenings due to asthma requiring treatment with albuterol during any week period before run-in visit CRITERIA FOR RANDOMISATION FOLLOWING RUN-IN PERIODS: Patients who regained asthma control following step-up treatment during run-in period 2; best FEV1 >= 65% of predicted and >= 15% of the best predose FEV1 obtained at visit IA
Interventions	LABA + ICS vs INCREASED dose of ICS OUTCOMES: Reported at 1, 4, 8 and 12 and 24 weeks (only those at 12 weeks used) DOSEOPTIMISATION PERIOD: 10 weeks; patients commenced on FP 250 mcg bid or equivalent for 2 weeks. Stable patients had their dose dropped to FP 100 bid. Patients who became unstable on this were eligible to continue. FP 250 bid was commenced and patients stable on this were eligible to continue INTERVENTION PERIOD: 12 to 24 weeks (data at 12 weeks used) TEST GROUP: (FP 100 bid + S 50 bid) salmeterol 50 mcg bid + fluticasone propionate 100 bid CONTROL GROUP: Fluticasone propionate 250 bid DEVICE: Diskhaler NUMBER OF DEVICES: 1 COMPLIANCE: Monitored during study CO-TREATMENT: prn SABA
Outcomes	PULMONARY FUNCTION TEST: FEV1; am PEF; pm PEF SYMPTOMSCORE: Mean change in daily symptom score (score of 0 to 5 Likert scale) FUNCTIONAL STATUS: Exacerbations (defined as any worsening of asthma that required asthma medication beyond blinded study drugs or albuterol); rescue medication use; nocturnal awakening; % rescue-free days; % symptom-free days INFLAMMATORY MARKERS: Not assessed ADVERSE EFFECTS: Reported WITHDRAWALS: Reported Primary outcome measure: proportion of patients who remained in study after 12 weeks and who did not withdraw due to lack of efficacy
Notes	Full-text publication. Additional data available from GSK trials register Funded by Glaxo Wellcome Confirmation of methodology and data obtained User-defined number: 600 (1000-400)

Risk of bias

Item	**Authors' judgement**	**Description**
Adequate sequence generation?	Yes	See Appendix 3
Allocation concealment?	Yes	See Appendix 3
Blinding? All outcomes	Yes	Identical inhaler devices
Incomplete outcome data addressed? All outcomes	No	Last observation carried forward: "All analyses for efficacy and safety were conducted through use of the intent-to-treat population (all randomised patients). All data from patients who were withdrawn from the study early were included in the analyses, data available up to the time of study discontinuation being used. No interpolation was used for missing data."

Free of selective reporting?	Yes	OCS-treated exacerbations available on request from GSK

Condemi 1999

Methods	Parallel-group, multicentre study (36 research centres) Jadad quality score = 5 Confirmation of methodology obtained
Participants	Symptomatic asthmatic adults % ELIGIBLE OF SCREENED POPULATION: Not reported % RUN-IN PARTICIPANTS RANDOMISED: 85 RANDOMISED: 437 (FP100 + Salm50: 221; FP250: 216) WITHDRAWALS: FP100 + Salm50: 19; F250: 30 AGE mean: 36.9 years GENDER (% male): 39 SEVERITY: Moderate BASELINE % PREDICTED FEV1: 61 BASELINE DOSE OF ICS: Not reported ASTHMA DURATION: < 10 years: 23%; >= 10 years: 87% ATOPY(%): Not reported SMOKERS: None ELIGIBILITY CRITERIA: >= 12 years old; asthma for at least 6 months; increase in FEV1 by 15% or greater after the inhalation of 200 mg of albuterol; FEV1 of 40% to 80% of predicted value; used short-acting bronchodilator on a regular basis for 3 months EXCLUSION CRITERIA: Current tobacco use; hospital admissions for asthma in the past 30 days; upper or lower respiratory infection within 30 days; positive pregnancy test or lactating; excluded during screening if they had an asthma exacerbation CRITERIA FOR RANDOMISATION FOLLOWING RUN-IN: FEV1 40% to 65% of predicted normal; at least one of the following over the 7 days prior to randomisation: an average of >= 4 puffs of albuterol per day; 2 or more days when evening PEF variation was >= 20%; 2 or more nights with awakenings due to asthma; 3 or more days with scores of >= 2 for any of the daytime symptoms of wheeze, chest tightness, shortness of breath or cough
Interventions	LABA + ICS vs INCREASED dose of ICS OUTCOMES: Reported at 2,4,8,12,16,20 and 24 weeks RUN-IN: 2 to 4 weeks DOSE OF ICS DURING RUN-IN: FP 100 bid INTERVENTION PERIOD: 24 weeks TEST GROUP: (FP100 + Sal50) fluticasone propionate 100 mg bid + salmeterol 50 mg bid CONTROL GROUP: (FP250) fluticasone propionate 250 mg bid DEVICE: Metered-dose inhalers NUMBER OF DEVICES: 2 COMPLIANCE: Not reported CO-TREATMENT: Albuterol on an as-needed basis
Outcomes	PULMONARY FUNCTION TEST: Change in morning* and evening PEF; change in FEV1(L) SYMPTOM SCORES: Change in daytime symptom scores (scores of 0 to 5) FUNCTIONAL STATUS: Change in mean rescue B2-agonist use (number of puffs); change in number of nighttime awakenings; change in % nights with no awakenings; exacerbations requiring systemic steroids INFLAMMATORY MARKERS: Not reported ADVERSE EFFECTS: Reported WITHDRAWALS: Described Primary outcome measure*
Notes	Full-text publication Funded by Glaxo Wellcome Confirmation of methodology and data obtained User defined number: 600 (1000-400)

Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	Yes	Random computer-generated numbers

Allocation concealment?	Yes	Letter coded inhalers supplied by pharmacy
Blinding? All outcomes	Yes	Double-dummy design; identical placebo
Incomplete outcome data addressed? All outcomes	Unclear	"All statistical analyses were performed on the intent-to-treat (ITT) population consisting of all subjects who were randomised to blinded study drug."
Free of selective reporting?	Yes	OCS-treated exacerbations available for meta-analysis

D5896C00001

Methods	Parallel-group, multicentre 4-arm trial, 2 of which are considered in this review
Participants	% ELIGIBLE OF SCREENED POPULATION: 44 % RUN-IN PARTICIPANTS RANDOMISED: 63 RANDOMISED: 306 (BUD/F: 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	LABA and ICS versus HIGHER 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 qd CONTROL GROUP: Budesonide 400 mcg qd NUMBER OF DEVICES: 1 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 randomised 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 randomised 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

Fowler 2002

Methods	Parallel-group, single centre study Jadad quality score = 4 Confirmation of methodology not obtained
Participants	Symptomatic asthmatic adults % ELIGIBLE OF SCREENED POPULATION: Not reported % RUN-IN PARTICIPANTS RANDOMISED: 100 RANDOMISED: 39 (Salm50/FP: 19; HFA BDP: 20) WITHDRAWALS: 0 AGE mean: 44 GENDER (% male): 51 SEVERITY: Moderate-severe BASELINE FEV1% predicted: 69% BASELINE DOSE OF ICS: >= 800 mcg CFC-BDP or equivalent or >= 200 mcg CFC-BDP as second-line therapy ASTHMA DURATION: Not reported ATOPY (%): Not reported SMOKING STATUS: Not reported ELIGIBILITY CRITERIA: FEV1 55% to 85% predicted; >= 15% improvement from baseline in PEF or FEV1 following an inhaled beta2-agonist; PD 20 methacholine < 200 mcg; use of > 2 puffs of rescue medication/ day and symptoms at least 5 days per week; at least 80% compliance with dose prescribed as per dose counters EXCLUSION CRITERIA: Patients receiving oral corticosteroids; asthma exacerbation in the 3 months before study entry CRITERIA FOR RANDOMISATION FOLLOWING RUN-IN: Diary card evidence over the previous month of using at lease 2 puffs per day of rescue medication and having symptoms at least 5 days per week; patients who did not meet these criteria had their treatment tapered in a stepwise fashion at 1 to 2-week intervals until they were taking less than 200 mcg CFC-BDP or equivalent at which point they were withdrawn from the study or their beta-2 agonist use met the above criteria
Interventions	LABA + ICS vs INCREASED dose of ICS OUTCOMES: Reported 1, 2 and 4 weeks RUN-IN PERIOD: 4 weeks DOSE OF ICS DURING RUN-IN: BDP 2000 mcg/day TREATMENT DURATION: 4 weeks DOSE OPTIMISATION PERIOD: None INTERVENTION PERIOD: 4 weeks TEST GROUP: (FP 100 mg + SAL50 mg): Fluticasone dipropionate 100 mcg bid + salmeterol 50 mcg bid CONTROLGROUP: (HFA BDP 200 mcg bid) beclomethasone dipropionate 200 mcg bid DEVICE: FP + S via diskhaler; HFA-BDP via metered dose inhaler NUMBER OF DEVICES: 2 COMPLIANCE: Dose counters used to check compliance CO-TREATMENT: Albuterol DPI via clickhaler
Outcomes	PULMONARY FUNCTION TEST: Diurnal variation in PEF (%); FEV1 % predicted; PD 20 SYMPTOM SCORES: Not reported FUNCTIONAL STATUS: AQLQ 32 questions with 7-point scale; rescue B2-agonist use INFLAMMATORY MARKERS: Serum ECP; nitric oxide OTHER: Plasma cortisol ADVERSE EFFECTS: Reported WITHDRAWALS: Described Primary outcome: Not reported

Notes	Full-text publication Funded by anonymous research grant and received HFA-BDP and placebo free from 3M healthcare Confirmation of methodology and data not obtained User defined number: 400 (800-400)

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	Yes	Double-dummy study
Incomplete outcome data addressed? All outcomes	Unclear	Described as intention-to-treat
Free of selective reporting?	Unclear	Not clear whether the study collected information on exacerbations treated with OCS

Green 2006

Methods	Cross-over, single centre study in UK
Participants	% ELIGIBLE OF SCREENED POPULATION: Not specified % RUN-IN PARTICIPANTS RANDOMISED: 74 RANDOMISED: 49 WITHDRAWALS: 10 GENDER: (% male): 51 MEAN AGE: 42 SEVERITY: Not stated BASELINE FEV1 % PREDICTED: 74.8 BASELINE DOSE OF ICS: </−400 BDP ASTHMA DURATION: Not available ATOPIC: 93% SMOKING STATUS: Non or ex-smokers eligible 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) < 8mg/mL-1; following run-in on 200 mcg day BUD, participants were eligible if they had recorded day or nighttime 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 b2-agonists, leukotriene antagonists or theophylline; asthma exacerbation or lower respiratory tract infection within the 4 weeks prior to trial entry
Interventions	LABA + ICS vs INCREASED dose of ICS OUTCOMES: 4 weeks RUN-IN PERIOD: 4 weeks DOSE OF ICS DURING RUN-IN: BUD 100 mcg bid TREATMENT DURATION: 4 weeks DOSE OPTIMISATION PERIOD: None TEST GROUP: Budesonide 100 mg bid + formoterol 12 mg bid CONTROL GROUP: Budesonide 400 mg bid DEVICE: Turbohaler NUMBER OF DEVICES: 2 (double-dummy) 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: Stated (not by treatment group) Primary outcome measure*
Notes	Full-text article Funding source: Not disclosed Methodology and data: TJL emailed 17 April 2008. Response from RG with details of randomisation and data User defined: 800

Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	Yes	"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."
Allocation concealment?	Yes	"…this was indeed generated by a third party, namely the pharmacist responsible for dispensing the double blind medication (…) None of the study investigators were aware of the randomisation schedule until the last patient had completed the cross-over study"
Blinding? All outcomes	Yes	Double-dummy
Incomplete outcome data addressed? All outcomes	No	Completers used for analysis
Free of selective reporting?	Yes	OCS-treated exacerbations reported. Data could not be extracted as only data on events and not number of participants were made available

Greening 1994

Methods	Parallel-group, multicentre study Jadad quality score = 5
Participants	Symptomatic asthmatic adults % ELIGIBLE OF SCREENED POPULATION: Not reported % RUN-IN PARTICIPANTS RANDOMISED: Not reported RANDOMISED: 426 (Salm50/BDP: 220; BDP: 206) WITHDRAWALS: Salm50/BDP: 71; BDP: 65 AGE mean: 48 years GENDER (% male): 44 SEVERITY: Moderate BASELINE FEV1: 2.13 Litres/sec Baseline % predicted PEF: 74 BASELINE DOSE OF ICS: Not reported ASTHMA DURATION: 11 years ATOPY (%): Information not available SMOKING STATUS: Current/previous smokers: 50% ELIGIBILITY CRITERIA: FEV1 >= 50% predicted; >= 15% improvement from baseline in PEF or FEV1 following an inhaled beta2-agonist; no courses of oral steroids during the previous 6 weeks or <= 4 short courses during the past year EXCLUSION CRITERIA: Patients receiving regular oral corticosteroids or who had received short course of oral corticosteroids in the 6 weeks prior to start of study or

	who had received 4 or more short courses in the last year. Patients who had received newly prescribed asthma therapy or who had changed asthma therapy in the 6 weeks prior to entering the study. Patients with FEV1 < 50% or predicted at the start of baseline. Patients who had a medical or physiological condition which in the investigator's opinion should preclude them from the study, or one or more of the concurrent medical conditions: severe cardiac disease, clinically significant hepatic or renal dysfunction, thyrotoxicosis, uncontrolled diabetes mellitus, history of active neoplastic disease, tuberculosis, acute respiratory infection which required prescribed therapy 2 weeks prior to study, patients receiving beta-blockers, patients currently receiving other long-acting B2-adrenoreceptor agonists, female patients who were pregnant or lactating or were not taking adequate contraceptive precautions, patients whose history over the previous year was not documented, patients who were receiving or had received research medication in the previous month, patients previously enrolled in this study, patients with evidence of alcohol abuse, known hypersensitivity to salbutamol, salmeterol or beclomethasone dipropionate CRITERIA FOR RANDOMISATION DURING RUN-IN: Period variation in PEF over 1 week of >= 15% (highest evening PEF minus lowest morning PEF as a percentage of highest value); symptoms on >= 4 of 7 days during the second baseline week
Interventions	LABA + ICS vs INCREASED dose of ICS OUTCOMES: 1, 3, 6 months RUN-IN PERIOD: 2 weeks DOSE OF ICS DURING RUN-IN: BDP 200 bid DOSE OPTIMISATION PERIOD: None INTERVENTION PERIOD: 6 months TEST GROUP: Beclomethasone (MDI) 200 mcg bid + salmeterol (Diskhaler) 50 mcg bid CONTROL GROUP: Beclomethasone (MDI) 500 mcg bid + placebo DEVICE: Diskhaler and MDI NUMBER OF DEVICES: 2 COMPLIANCE: Evaluated CO-TREATMENT: prn SABA. Other asthma drugs (xanthines) if already started prior to study
Outcomes	PULMONARY FUNCTION TEST: am PEF; pm PEF SYMPTOM SCORES: Not given FUNCTIONAL STATUS: Nighttime disturbance (% patients with disturbance every night, >= 50% nights , < 50% nights and no night disturbance); daytime symptoms (% patients with symptoms every day, >= 50% of days, < 50% days, and no symptoms); rescue medication use; exacerbations mild (increase in relief medication); moderate (requiring a short course in oral corticosteroids); or severe (requiring hospital admission) INFLAMMATORY MARKERS: Not described ADVERSE EFFECTS: Reported WITHDRAWALS: Reported Primary outcome measure*
Notes	Full-text publication Supported by Allen & Hanburys Ltd, Uxbridge, Glaxo Pharmaceuticals Ltd, Uxbridge and Access Ltd, London (data and statistical advice) Confirmation of methodology and data extraction obtained User defined number: 600 (1000-400)

Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	Yes	Computer-generated random numbers
Allocation concealment?	Yes	Numbered coded medication allocated on sequential basis
Blinding? All outcomes	Yes	Use of identical placebo
Incomplete outcome data addressed? All outcomes	Unclear	"All analyses were performed on an intention-to-treat (ITT) basis, i.e. all subjects randomised and who had verifiable data."
Free of selective reporting?	Yes	OCS-treated exacerbations available for meta-analysis

Heuck 2000

Methods	Cross-over study, single treatment centre Jadad quality score:4
Participants	Asthmatic children % ELIGIBLE OF SCREENED POPULATION: Not reported % RUN-IN PARTICIPANTS RANDOMISED: Not reported RANDOMISED: 27 WITHDRAWALS: 2 MEAN AGE (RANGE): 9.6 (6.1 to 13.5) GENDER (% male): 52 SEVERITY: Mild to moderate BASELINE FEV1 L (range): Not reported BASELINE PEF L/min (range): 280 l/min BASELINE DOSE OF ICS Mean: BUD 200 bid or equivalent ASTHMA DURATION (range in years): 4.5 (1.4 to 9.5) ATOPY (%): Not reported ELIGIBILITY CRITERIA: Not described EXCLUSION CRITERIA: Not described
Interventions	LABA + ICS versus INCREASED DOSE ICS OUTCOMES: Reported weekly RUN-IN: None DOSE OF ICS DURING RUN-IN: N/A INTERVENTION PERIOD: 12 weeks TEST GROUP: (Form + ICS) formoterol 12 mcg bid + budesonide 100 bid CONTROL GROUP: Placebo + budesonide 200 bid DEVICE: Turbuhaler (ICS); Aerolizer (formoterol) NUMBER OF DEVICES: 2 COMPLIANCE: Turbuhalers weighed and number of formoterol capsules counted CO-TREATMENT: Terbutaline via turbuhaler but no other co-treatments allowed
Outcomes	PULMONARY FUNCTION TEST: FEV1; am PEF; pm PEF SYMPTOM SCORE: Daytime and nighttime score (score of 0 to 4) FUNCTIONAL STATUS: Exacerbations; rescue medication use; lower leg growth; serum and urinary markers of type I and III collagen turnover INFLAMMATORY MARKERS: Inflammatory markers in serum ADVERSE EFFECTS: Reported WITHDRAWALS: Reported Primary outcome measure: Not reported
Notes	Full-text publication Source of funding not stated Confirmation of methodology and data not obtained User-defined number: 200 (400-200)

Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	Yes	"Treatment order was allocated by a computerised randomisation scheme prepared in balanced blocks."
Allocation concealment?	Unclear	Information on concealment of allocation not provided
Blinding? All outcomes	Yes	Double-blind; double-dummy
Incomplete outcome data addressed? All outcomes	No	Completers used for analysis
Free of selective reporting?	Yes	Data on OCS-treated exacerbations available

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%; of 859 recruited 357 not randomised (improved during run-in period) RANDOMISED: 502 (496 with completed case report forms included in intention-to-treat population). 336 for this review: FP/SAL: 171; FP: 165 WITHDRAWALS: FP/SAL: 27; FP: 22 Mean AGE years: 44.4 GENDER (% male): 45 SEVERITY: Moderate to severe BASELINE FEV1: 2.3 L % PREDICTED PEF am: 75 BASELINE DOSE OF ICS (median): 1000 mcg ASTHMA DURATION (range in years): 0.2 to 68 ATOPY (%): Information not available SMOKING STATUS: Not reported 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 systemic disease; participation was deemed unsuitable by their physician from the study
Interventions	LABA + ICS vs INCREASED 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: 6 months TEST GROUP: Combination fluticasone propionate/salmeterol 250/50 mcgs bid (in one device) INCREASED DOSE: FP 500 mcgs bid DEVICE: MDI NUMBER OF DEVICES: 1 COMPLIANCE: Not reported CO-TREATMENT: prn SABA. Other asthma drugs as needed except LABA
Outcomes	PULMONARY FUNCTION TEST: am PEF*; pm PEF SYMPTOM SCORES: Nighttime scores 0 to 4; day-time 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 Glaxo Wellcome Research and Development Confirmation of methodology and data extraction not obtained User defined number: 1000 (2000-1000)

Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	Yes	See Appendix 3
Allocation concealment?	Yes	See Appendix 3
Blinding? All outcomes	Yes	Identical placebo
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 (see Analysis 3.1)

Jenkins 2000

Methods	Parallel-group, multicentre study (44 centres) Jadad quality score = 4
Participants	Symptomatic asthmatic adults % ELIGIBLE OF SCREENED POPULATION: Not reported % RUN-IN PARTICIPANTS RANDOMISED: Not reported RANDOMISED: 353 (FP/SAL: 180; BUD: 173) WITHDRAWALS: FP/SAL: 29; BUD: 30 Mean AGE years: 47 GENDER (% male): 50 SEVERITY: Moderate to severe BASELINE FEV1 % PRED: 70 BASELINE DOSE OF ICS median mcg/day prior to randomisation (n): FP500 (85*); BUD 800 (168); BDP 1000 (101*) *One patient was receiving both FP and BDP prior to study entry ASTHMA DURATION: < 1 year: 6%; 1 to 5 =18%; 5 to 10 = 16%; > 10: 60% ATOPY (%): Information unavailable SMOKING STATUS: Not reported ELIGIBILITY CRITERIA: > 12 years; documented reversible airways obstruction receiving ICS (BUD or BDP 800 to 1600 mcg/day or FP 400 to 600 mcg/day for > 4 weeks); baseline FEV1 or PEF 50% to 85% of normal; 15% increase in FEV1 or PEF 85% of maximum after bronchodilator; using rescue bronchodilator more than twice per day or total symptom score > 2 on > 4 of 7 days EXCLUSION CRITERIA: Acute exacerbation requiring hospitalisation, systemic corticosteroids, lower respiratory tract infection or change in asthma medication in 4 weeks prior to recruitment; LABA treatment or slow release bronchodilator in 2 weeks before recruitment; smoking history > 10 pack-years; pregnant or lactating females; regular oral corticosteroid treatment; serious uncontrolled systemic disease CRITERIA FOR RANDOMISATION DURING RUN-IN: No other additional criteria
Interventions	LABA + ICS versus INCREASED dose of ICS OUTCOMES: 4, 12 and 24 weeks RUN-IN PERIOD: 2 weeks DOSE OF ICS DURING RUN-IN: Usual ICS DOSE OPTIMISATION PERIOD: None INTERVENTION PERIOD: 24 weeks TEST GROUP: (FP/SAL) Combination fluticasone and salmeterol 250/50 mcg bid in single device, plus placebo turbuhaler INCREASED dose: BUD (DPI): Budesonide 800 mcg bid by turbuhaler + placebo Diskus DEVICE: Diskus (FP/SAL) and Turbuhaler (BUD) NUMBER OF DEVICES: 1 COMPLIANCE: Not reported CO-TREATMENT: prn SABA
Outcomes	PULMONARY FUNCTION TEST: am PEF*; pm PEF; FEV1 SYMPTOM SCORES: Not reported FUNCTIONAL STATUS: Symptom-free days and nights; % salbutamol-free days in each group; % symptom-free days in each group; exacerbations severe (requiring emergency hospital treatment); moderate (requiring additional inhaled corticosteroids); mild (requiring increase in use of relief medication which physician considered to be clinically relevant) INFLAMMATORY MARKERS: Not described ADVERSE EFFECTS: Reported WITHDRAWALS: Reported Primary outcome measure*
Notes	Full-text publication Supported by Glaxo Wellcome Research and Development Confirmation of methodology and data extraction not obtained User defined number: 600 (1600-1000)

Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	Yes	See Appendix 3
Allocation concealment?	Yes	See Appendix 3
Blinding? All outcomes	Yes	Double-dummy design
Incomplete outcome data addressed? All outcomes	Unclear	"The Intent-to-Treat (ITT) population was defined as all patients who entered the study, were randomised, and received at least one dose of study treatment, was used for assessment of safety data as well as for all efficacy analyses."
Free of selective reporting?	Yes	Moderate exacerbations extracted as proxy for OCS-treated exacerbations (see Analysis 3.1)

Johansson 2001

Methods	Parallel-group, multicentre study (39 centres in North America, Europe and South Africa) Jadad quality score = 5
Participants	Symptomatic asthmatic patients % ELIGIBLE OF SCREENED POPULATION: Not reported % RUN-IN PARTICIPANTS RANDOMISED: 80 RANDOMISED: 349 (FP/SAL: 176; BUD: 173) WITHDRAWALS: FP/SAL: 23; BUD: 15 AGE mean (years): 36 GENDER (% male): 43 SEVERITY: moderate BASELINE % PREDICTED FEV1: 77 BASELINE DOSE OF ICS: mean in mcg (note: 19% of Sal FP group and 40% of BUD group on no corticosteroids before randomisation): FP 375; BUD 400; BDP 500 ASTHMA DURATION: Not reported ATOPY (%): Not reported SMOKING STATUS: Not reported ELIGIBILITY CRITERIA (including run-in criteria for randomisation): Mild to moderate asthma; symptomatic patients determined either by use of rescue salbutamol (on more than 2 occasions per 24 hours) or symptoms (total daytime and nighttime diary card symptom score of >= 2) on at least 4 of the last 7 days of the run-in period EXCLUSION CRITERIA: If patients had changed their regular asthma medication or received any long-acting or slow-release bronchodilators within the previous 2 weeks, had had a lower respiratory tract infection within the previous 4 weeks, or were smokers with a history of 10 pack years or more; if in the previous 4 weeks patients had had an asthma exacerbation requiring hospitalisation and/or treatment with oral, parenteral or depot corticosteroids; patients with serious uncontrolled diseases likely to interfere with the study or who showed evidence of alcohol or drug abuse; pregnant or lactating females, or those likely to become pregnant
Interventions	LABA + ICS versus INCREASED dose of ICS OUTCOMES: Reported at 12 weeks RUN-IN PERIOD: 2 weeks DOSE OF ICS DURING RUN-IN: Usual ICS DOSE OPTIMISATION PERIOD: None INTERVENTION PERIOD: 12 weeks TEST GROUP: Combination fluticasone/salmeterol 100/50 mcg bid CONTROL GROUP: Budesonide 400 mcg bid DEVICE: FP/SAL: Diskus, BUD: Turbuhaler NUMBER OF DEVICES: 1 COMPLIANCE: Not reported CO-TREATMENT: prn SABA (use of stable asthma medications permitted)

Outcomes	PULMONARY FUNCTION TEST: am PEF*; pm PEF; diurnal variation in PEF post-treatment in each group SYMPTOM SCORES: % days and nights when symptom score < 2 (daytime 0 to 5; nighttime 0 to 4) FUNCTIONAL STATUS: Rescue medication use; symptom-free days/nights INFLAMMATORY MARKERS: Not reported ADVERSE EFFECTS: Reported WITHDRAWALS: Reported Primary outcome measure*
Notes	Full-text publication Funded by GlaxoSmithKline Confirmation of methodology and data extraction: Not obtained User defined number: 400 (800-400)

Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	Yes	See Appendix 3
Allocation concealment?	Yes	See Appendix 3
Blinding? All outcomes	Yes	Use of identical placebo
Incomplete outcome data addressed? All outcomes	Unclear	"The Intent-to-Treat (ITT) population was defined as all patients who entered the study, were randomised, and received at least one dose of study treatment: it was used for assessment of safety data as well as for all efficacy analyses."
Free of selective reporting?	Yes	OCS-treated exacerbations available on request from study sponsor

Joshi 2005

Methods	Parallel-group study. Other details not available. Jadad quality score = 2
Participants	Unclear severity % ELIGIBLE OF SCREENED POPULATION: Not reported % RUN-IN PARTICIPANTS RANDOMISED: Not reported RANDOMISED: 115 (FP/SAL: 59; FP: 56) WITHDRAWALS: Not stated AGE mean: Not reported GENDER (% male): Not reported SEVERITY: Not reported BASELINE % PREDICTED FEV1 (mean): Not reported BASELINE DOSE OF ICS: Not reported ASTHMA DURATION: Not reported ATOPY (%): Not reported ELIGIBILITY CRITERIA: >= 18 years of age EXCLUSION CRITERIA: Not stated
Interventions	LABA + ICS versus INCREASED dose ICS OUTCOME TIMING: 12 weeks RUN-IN: 4 weeks DOSE OF ICS DURING RUN-IN: Not stated INTERVENTION PERIOD: 12 weeks TEST GROUP: Combination fluticasone and salmeterol 100/50 mcg bid CONTROL GROUP: Fluticasone 200 mcg bid DEVICE: Rotahaler NUMBER OF DEVICES: 1 COMPLIANCE: Not reported CO-TREATMENT: prn SABA
Outcomes	PULMONARY FUNCTION TEST: am PEF; FEV1 SYMPTOM SCORES: Daily symptom scores; nighttime symptom scores FUNCTIONAL STATUS: Rescue-free days

	INFLAMMATORY MARKERS: Not stated ADVERSE EFFECTS: Not stated WITHDRAWALS: Not stated Primary outcome measure*
Notes	Conference abstract publication Source of funding: Not stated Confirmation of methodology and data: Not obtained User defined number: 800

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	Identical inhaler devices used
Incomplete outcome data addressed? All outcomes	Unclear	Information not available
Free of selective reporting?	Unclear	Unclear whether exacerbations were recorded in the study

Kelsen 1999

Methods	Parallel-group, multicentre study (34 centres) Jadad quality score: 5
Participants	Symptomatic asthmatic adults % ELIGIBLE OF SCREENED POPULATION: Not reported % RUN-IN PARTICIPANTS RANDOMISED: 483/639 = 76% RANDOMISED: 483 (BDP + Sal: 239; BDP: 244) WITHDRAWALS: BDP + Sal: 48; BDP: 49 AGE mean (years): 42 GENDER (% male): 39 SEVERITY: Moderate BASELINE % PREDICTED FEV1: 64.5 BASELINE DOSE OF ICS: at least 400 mcg BDP or 800 mcg triamcinolone acetonide ASTHMA DURATION: Not reported ATOPY(%): Not reported SMOKING STATUS: No smokers ELIGIBILITY CRITERIA: Non-smokers; >= 18 years and up; baseline FEV1 of 45% to 80% of predicted value; FEV1 of >= 12 % after inhalation of 2 puffs of albuterol; using inhaled corticosteroids regularly for at least 3 months prior to enrolment; 14 days prior to enrolment must have taken 400 mg of beclomethasone daily or 800 mg of triamcinolone EXCLUSION CRITERIA: Not described CRITERIA FOR RANDOMISATION DURING RUN-IN: Must have symptomatic asthma defined as: >= 3 nights with nighttime awakening; >= 3 days with daytime symptoms; >= 3 days with albuterol used as a rescue medication occurring during the 7 days prior to randomisation
Interventions	LABA + ICS vs INCREASED dose of ICS OUTCOMES: Reported at 4, 12 and 24 weeks RUN-IN PERIOD: 2 weeks DOSE OF ICS DURING RUN-IN: BDP 200 bid DOSE OPTIMISATION PERIOD: None INTERVENTION PERIOD: 24 weeks TEST GROUP: (BDP 200 + Salm50) beclomethasone 200 mcg + salmeterol 50 mcg bid CONTROL GROUP: (BDP 400) beclomethasone 400 mcg bid DEVICE: Inhalation aerosol NUMBER OF DEVICES: 2 COMPLIANCE: Recorded in diary cards CO-TREATMENT: prn SABA

Outcomes	PULMONARY FUNCTION TEST: FEV1; am PEF*; pm PEF SYMPTOM SCORES: Mean symptom score (score of 0 to 4) FUNCTIONAL STATUS: Rescue medication use; symptom-free days; nocturnal disturbance; severe exacerbation (requiring systemic steroids) INFLAMMATORY MARKERS: Not reported ADVERSE EFFECTS: Reported WITHDRAWALS: Reported Primary outcome measure*
Notes	Full-text publication Funded by Glaxo Wellcome Confirmation of methodology and data: obtained User-defined number: 400 (800-400)

Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	Yes	See Appendix 3
Allocation concealment?	Yes	See Appendix 3
Blinding? All outcomes	Yes	Use of identical placebo
Incomplete outcome data addressed? All outcomes	Unclear	Analysis population described as all participants randomised to double-blind treatment
Free of selective reporting?	Yes	OCS-treated exacerbations available for meta-analysis (from GSK; study data included non-OCS exacerbations)

Kips 2000

Methods	Parallel-group, multicentre study (3 centres) Jadad quality score = 4
Participants	Well-controlled asthmatic adults (acute ICS reduction): considered as SYMPTOMATIC % ELIGIBLE OF SCREENED POPULATION: Not reported % RUN-IN PARTICIPANTS RANDOMISED: 86 RANDOMISED: 60 BUD + F: 29; BUD: 31 WITHDRAWALS: Not described AGE mean years (range): 36 (19 to 69) GENDER (% male): 40 SEVERITY: Mild BASELINE % PREDICTED FEV1 mean: 79 BASELINE DOSE OF ICS (start of run-in) mean (range): 691 (50 to 1500) mcg ASTHMA DURATION: Not described ATOPY (%): Not described SMOKING STATUS: Not described ELIGIBILITY CRITERIA: Established diagnosis of asthma for 6 months; treated with inhaled corticosteroids (ICS) for at least 3 months; baseline FEV1 > 50% of predicted; >= 15% increase in FEV1 or >= 9% in % predicted FEV1 after 1 mg of inhaled terbutaline EXCLUSION CRITERIA: Treated daily with >= 2000 mg of beclomethasone, >= 1600 mg of budesonide via pressure metered dose inhaler, >= 800 mg of budesonide via Turbuhaler, >= 800 mg of fluticasone; 3 courses of oral steroids in < 6 months; hospital admission due to asthma < 6 months CRITERIA FOR RANDOMISATION DURING RUN-IN: Compliance between 75% and 125% of recommended doses stable asthma for the last 10 days of run-in period; unstable asthma defined as: diurnal variation in PEF exceeded 20% on 2 consecutive days; B2 agonist use exceeded 4 inhalations per day; awakenings due to asthma occurred on 2 consecutive nights; patient needed oral corticosteroids
Interventions	LABA + ICS vs INCREASED dose of ICS OUTCOMES reported at 6, 12, 24 and 52 weeks RUN-IN PERIOD: 4 weeks with budesonide 800 mcg bid to monitor compliance and document asthma stability

	DOSE OPTIMISATION PERIOD: None INTERVENTION PERIOD: 12 months TEST GROUP: (BUD200 + F) budesonide 100 mcg + formoterol 12 mcg bid CONTROL GROUP: (BUD800) budesonide 400 mcg + placebo bid DEVICE: Turbuhaler NUMBER OF DEVICES: 2 COMPLIANCE: Measured by means of hidden counter in inhaler CO-TREATMENT: prn SABA
Outcomes	PULMONARY FUNCTION TEST: FEV1 predicted; PEF SYMPTOM SCORES: Change in symptom score (score of 0 to 3) FUNCTIONAL STATUS: Rescue medication use; nocturnal awakenings in each group; severe exacerbation (requiring systemic steroids); episode-free days INFLAMMATORY MARKERS: sputum eosinophils*; sputum EG2 + cells; sputum eosinophil cationic protein; sputum differential cell count ADVERSE EFFECTS: Not described WITHDRAWALS: Not described Primary outcome measure*
Notes	Full-text publication Funded by Astra Draco Confirmation of methodology and data obtained User-defined number: 600 (800-200)

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 used
Incomplete outcome data addressed? All outcomes	No	"The analysis is based on a "per protocol" approach. Data from patients violating the protocol were included up to the violation time."
Free of selective reporting?	Yes	OCS-treated exacerbations available for meta-analysis

Lalloo 2003

Methods	Parallel-group, multicentre study (51 centres in 7 countries) Jadad quality score: 3
Participants	Symptomatic asthmatic adults % ELIGIBLE OF SCREENED POPULATION: Not reported % RUN-IN PARTICIPANTS RANDOMISED: 94 RANDOMISED: 467 (BDP + F: 230; BDP: 237) WITHDRAWALS: BDP + F: 15; BUD: 22 Mean AGE years (range): 41 (18 to 78) GENDER (% male): 43 SEVERITY: Mild to moderate BASELINE FEV1 % predicted (range): 81 (38 to 157) BASELINE DOSE OF ICS mean (range): 387 (200 to 500) ASTHMA DURATION (range in years): 0 to 53 years ATOPY (%): Information not available ELIGIBILITY CRITERIA: Aged >= 18; diagnosis of asthma minimum 6 months; FEV1 60% to 90% predicted normal; 12% reversibility post-bronchodilator; ICS at constant dose 200 to 500 mcgs /day for at least 1 month prior to study entry EXCLUSION CRITERIA: Patients receiving systemic corticosteroids within 30 days of study entry; respiratory infection within previous 4 weeks; known hypersensitivity to study medication or inhaled lactose; patients with severe cardiovascular disorders or other serious diseases; current or previous smokers with a history of smoking > or = 10 pack years; all female patients were required to be postmenopausal, sterile or using contraception CRITERIA FOR RANDOMISATION DURING RUN-IN: No other additional criteria

Interventions	LABA + ICS vs INCREASED dose of ICS OUTCOMES reported at 4, 8 and 12 weeks RUN-IN PERIOD: 2 weeks DOSE OF ICS DURING RUN-IN: BDP 100 bid DOSE OPTIMISATION PERIOD: None INTERVENTION PERIOD: 12 weeks TEST GROUP: Combination budesonide and formoterol 100/6 mcg bid in a single inhaler CONTROL GROUP: Budesonide 200 mcg bid DEVICE: Turbuhaler NUMBER OF DEVICES: 1 COMPLIANCE: Not reported CO-TREATMENT: prn SABA
Outcomes	PULMONARY FUNCTION TEST: FEV1 predicted; am PEF; pm PEF SYMPTOM SCORES: Score of 0 to 3 FUNCTIONAL STATUS: Rescue medication use; % symptom-free days; nighttime awakening; asthma control days; exacerbations (defined as requirement for OCS or fall in PEF of > 30%) INFLAMMATORY MARKERS: None ADVERSE EFFECTS: Reported WITHDRAWALS: Described Primary outcome measure: Not described
Notes	Full-text publication Funded by Astra Zeneca 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; other information not available
Allocation concealment?	Unclear	Information not available
Blinding? All outcomes	Yes	Identical inhaler devices
Incomplete outcome data addressed? All outcomes	Unclear	"Efficacy analyses were carried out on all randomised patients (intention-to-treat approach)."
Free of selective reporting?	Yes	Severe exacerbations included OCS exacerbations; added as additional study to sensitivity analysis

Li 1999

Methods	Parallel-group study. Three treatment arms, 2 of which are considered for this review Jadad quality score = 5
Participants	Symptomatic asthmatic adults % ELIGIBLE OF SCREENED POPULATION: Not reported % RUN-IN PARTICIPANTS RANDOMISED: 70 RANDOMISED: 32 Sal + usual ICS: 16; FP + usual ICS: 16 WITHDRAWALS: Sal + usual ICS: 3; FP + usual ICS: 0 AGE mean years: 40 GENDER (% male): 66 SEVERITY: Mild to moderate BASELINE FEV1 % predicted median (range): 82 BASELINE DOSE OF ICS: Mean (range): 400 (200 to 500) ASTHMA DURATION (range in years): Not reported ATOPY (%): 83 ELIGIBILITY CRITERIA: Aged 20 to 70 years; diagnosis of asthma; FEV1 >= 60 % predicted normal; treated with ICS for minimum 12 months in dose up to 500 mcg / day of BDP or BUD

	EXCLUSION CRITERIA: Respiratory infection within previous 4 weeks; any change in asthma medication in previous 4 weeks; hospital admission with airway disease in previous 4 weeks CRITERIA FOR RANDOMISATION DURING RUN-IN: At least one of the following: symptom score >= 2 on 7 of last 14 days; prn SABA >= 7 of 14 last days variation > 15% in PEF over a 24 hour period on >= 7 of last 14 days with some degrees of symptoms and rescue medication use during that time
Interventions	LABA + ICS vs INCREASED dose 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: (Salm50 + ICS) Salmeterol 50 mg bid + usual ICS CONTROL GROUP: (FP100 + usual ICS) fluticasone 100 mcg bid + usual ICS (‘double dose’) DEVICE: Dry powder diskhaler NUMBER OF DEVICES: 2 COMPLIANCE: Not reported CO-TREATMENT: prn SABA
Outcomes	PULMONARY FUNCTION TEST: am PEF; FEV1 SYMPTOM SCORES: score of 0 to 4 (mean/day) FUNCTIONAL STATUS: Rescue medication use; nocturnal awakenings; exacerbations requiring OCS 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 Glaxo Wellcome, 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	Unclear	Identical inhaler devices
Incomplete outcome data addressed? All outcomes	No	Completers analysed
Free of selective reporting?	Yes	OCS-treated exacerbations available for meta-analysis

LOCCS

Methods	Parallel-group, multicentre 3-arm study conducted in USA
Participants	% ELIGIBLE OF SCREENED POPULATION: 60 % RUN-IN PARTICIPANTS RANDOMISED: 63 RANDOMISED: 334 (FP 169; FP/SAL:165) WITHDRAWALS: 29 (FP 13; FP/SAL 16) AGE mean (range) or mean (SD): 30 (14) SEVERITY: Mild BASELINE % PRED FEV1: 92 BASELINE DOSE OF ICS: 400 mcg BDP equivalent ASTHMA DURATION: Not reported

	ATOPY (%): Not reported ELIGIBILITY CRITERIA: physician-diagnosed asthma; > 6 years; FEV1 predicted 60% or more; > 12% reversibility to SABA or a pc20 of 8 mg per millilitre or less within previous 2 years EXCLUSION CRITERIA: hospitalisation, urgent medical care, oral corticosteroid use, or use of additional asthma medication during run-in; presence of temperature exceeding 38.0 °C, or 100.4 °F) within previous 24 hours ELIGIBILITY CRITERIA DURING RUN-IN: adequate adherence with diary card; FEV1 > 80% predicted; Asthma Control Questionnaire score < 1.5; < 16 puffs of a rescue beta-agonist per week during final 2 weeks of run-in
Interventions	LABA + ICS versus HIGHER dose ICS OUTCOMES: 16 weeks RUN-IN PERIOD: 4 to 6 weeks DOSE OPTIMISATION PERIOD: NA TEST GROUP: Combination fluticasone and salmeterol 100/50 mcg (once daily, evening) CONTROL GROUP: Fluticasone 100 mcg bid NUMBER OF DEVICES: 1 (double-dummy design as combination given twice daily) COMPLIANCE: Assessed by counters on inhalers and counts of pills CO-TREATMENT: prn SABA
Outcomes	PULMONARY FUNCTION TEST: FEV1 predicted; FVC predicted; PEF predicted SYMPTOM SCORES: Daytime symptoms FUNCTIONAL STATUS: Treatment failure*; oral steroid use; quality of life (AQLQ); rescue medication use INFLAMMATORY MARKERS: Not reported ADVERSE EFFECTS: Stated
Notes	Full-text publication Funding source: GSK Confirmation of data and methodology: Not obtained. TJL contacted for separate OCS requirement between adults and children User defined: 400

Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	Yes	"The randomization schedule was a permuted block design stratified by clinic and pediatric status"
Allocation concealment?	Yes	Central randomisation
Blinding? All outcomes	Yes	Treble dummy: "At randomization each participant was instructed to use two Diskus inhalers each day, one in the morning and the other in the evening. The inhalers either were two containing fluticasone for the fluticasone group, one containing fluticasone and salmeterol and one placebo inhaler for the fluticasone/salmeterol group, or two placebo inhalers for the montelukast group. Inhalers were labelled AM or PM and had yellow or blue dots, respectively, to ensure compliance to the protocol. Each participant also took a capsule (or chewable tablet for 5 mg dose) containing montelukast or placebo once a day in the evening."
Incomplete outcome data addressed? All outcomes	Unclear	"Analyses were performed on the basis of the intention-to-treat principle; all available data from all patients were included in all analyses."
Free of selective reporting?	Yes	OCS-treated exacerbations available for meta-analysis

Mitchell 2003

Methods	Parallel-group, multicentre trial (16 centres) Jadad quality score: 4
Participants	Symptomatic asthmatic adults

	% ELIGIBLE OF SCREENED POPULATION: Not reported % RUN-IN PARTICIPANTS RANDOMISED: 203/274 (74%) RANDOMISED: 203 (BDP/F: 102; BDP: 101) WITHDRAWALS: BDP/F: 7; BDP: 12 AGE mean: 43.9 GENDER (% males): 44.6 SEVERITY: Moderate to severe BASELINE % PREDICTED FEV1 mean: 72 BASELINE DOSE OF ICS: Not reported ASTHMA DURATION mean: 27 years ATOPY (%): Not reported SMOKING STATUS: Current smokers: 8%; previous smokers: 40 ELIGIBILITY CRITERIA: Aged 18 years or more; moderate to severe asthma; FEV1 >= of predicted and increased by 15% or more within 30 minutes after beta2 agonists or historical evidence of reversibility; had to have received Rx with ICS (metered dose inhaler) at a constant daily dose of 1000 mcg beclomethasone dipropionate or 800 mcg budesonide for at least 1 month before screening EXCLUSION CRITERIA: Change in daily dose of ICS in the previous month; use of a LABA or having received a course of oral corticosteroid in the month before the screening; problems using the Aeroliser (R) despite proper instruction CRITERIA FOR RANDOMISATION DURING RUN-IN: Presence of at least 2 of the following on at least 2 of the last 7 days of the run-in period: waking at least once/night because of asthma; asthma interfering with daily activities on at least 1 day; at least 4 puffs of salbutamol rescue medication a day; diurnal variation in PEF of at least 15%
Interventions	LABA + ICS vs INCREASED dose ICS OUTCOMES: measured at 4, 8 and 12 weeks RUN-IN PERIOD: 2 to 4 weeks DOSE OF ICS DURING RUN-IN: 500 BDP bid DOSE OPTIMISATION PERIOD: Not reported INTERVENTION PERIOD: 12 weeks TEST GROUP: (BDP/F) beclomethasone 500 mcg bid and formoterol 12 mcg bid CONTROL GROUP: (BDP) beclomethasone 1000 mcg bid and placebo INHALER DEVICE: Formoterol: Aerolizer; BDP: dry powder inhaler NUMBER OF DEVICES: 2 COMPLIANCE: Not reported CO-TREATMENT: prn SABA
Outcomes	PULMONARY FUNCTION TEST: am PEF*; FEV1 SYMPTOM SCORES: Score of 0 to 4 (day and night) FUNCTIONAL STATUS: Rescue medication use; exacerbations INFLAMMATORY MARKERS: None ADVERSE EFFECTS: Reported WITHDRAWALS: Described *Primary outcome measure
Notes	Full-text publication Funded by Novartis Pharmaceutical Australia Pty Ltd Confirmation of methodology and data: not obtained User-defined number: 1000

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	Yes	Double-dummy design
Incomplete outcome data addressed? All outcomes	Unclear	"The analysis of efficacy was carried out in the intention-to-treat analysis and, in addition, a confirmatory analysis was carried out on the mean morning pre-medication PEF measured during the last 7 days of treatment in the patients who had completed the whole treatment period."
Free of selective reporting?	Unclear	Moderate exacerbations included OCS exacerbations; added as additional study to sensitivity analysis (see Analysis 3.1)

Murray 1999

Methods	Parallel-group, multicentre study (35 centres) Jadad quality score: 5
Participants	Symptomatic asthmatic patients % ELIGIBLE OF SCREENED POPULATION: Not reported % RUN-IN PARTICIPANTS RANDOMISED: Not reported RANDOMISED: 514 (BDP + Sal: 260; BDP: 254) WITHDRAWAL: BDP + Sal: 50; BDP: 57 AGE: mean (range): 42 (18 to 82) GENDER (% males): 43 SEVERITY: Moderate BASELINE % PREDICTED FEV1 mean: 65 BASELINE DOSE OF ICS: BDP 400 mcg daily or triamcinolone 800 mcg daily at study entry ASTHMA DURATION: Not reported ATOPY (%): Not reported ELIGIBILITY CRITERIA: FEV1 of 45% to 80% of the predicted value based on Capro standards adjusted for race; increase in FEV1 of at least 12% following the inhalation of 200 mg of albuterol; symptomatic while taking 400 mg of inhaled beclomethasone dipropionate or 800 mg triamcinolone acetonide daily EXCLUSION CRITERIA: Pregnant females or those planning a pregnancy; concurrent use of any medication affecting the course of asthma; interacting with sympathomimetic amines or corticosteroids; immunotherapy allowed if patient had received a constant dose for at least 12 weeks before enrolment with a continuation of the same regimen during the study CRITERIA FOR RANDOMISATION DURING RUN-IN: >= 3 nocturnal awakenings due to asthma symptoms during the 7 days before randomisation; >= 3 days with daytime symptoms during the 7 days before randomisation; >= 3 days with albuterol used as a relief medication during the 7 days before randomisation
Interventions	LABA + ICS vs INCREASED dose of ICS OUTCOMES reported at 4, 12 and 24 weeks RUN-IN PERIOD: 2 weeks DOSE OF ICS DURING RUN-IN: BDP 200 bid DOSE OPTIMISATION PERIOD: None INTERVENTION PERIOD: 24 weeks TEST GROUP: Beclomethasone 200 mg plus salmeterol 50 mg twice daily CONTROL GROUP: Beclomethasone 400 mg twice daily DEVICE: MDI NUMBER OF DEVICES: 2 COMPLIANCE: Evaluated CO-TREATMENT: prn SABA; maintenance theophylline
Outcomes	PULMONARY FUNCTION TEST: FEV1 predicted; am PEF*; pm PEF SYMPTOM SCORES: Change in symptom score (score of 0 to 4) FUNCTIONAL STATUS: Rescue medication use; nocturnal awakening; exacerbation (defined as events requiring treatment with any asthma medication excluded during study participation); mean % symptom-free days INFLAMMATORY MARKERS: No laboratory analysis was performed ADVERSE EFFECTS: Reported WITHDRAWALS: Reported
Notes	Full-text publication Funded by Glaxo Welcome 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	Number coded inhalers supplied by pharmacy
Blinding? All outcomes	Yes	Identical placebos used
Incomplete outcome data addressed? All outcomes	Unclear	"All efficacy and safety analyses were performed on the intent-to-treat (ITT) population consisting of all subjects randomised to blinded study medication."

Free of selective reporting?	Yes	OCS-treated exacerbations available on request from GSK

O'Byrne 2001

Methods	Parallel-group, multicentre study. Four treatment groups of which 2 considered for this review, namely: BUD 200 + F12 bid and BUD 400 bid Jadad quality score: 4
Participants	Symptomatic asthmatic teenagers >= 12 years and adults % ELIGIBLE OF SCREENED POPULATION: Not reported % RUN-IN PARTICIPANTS RANDOMISED: Not reported RANDOMISED: 634 (BUD200 + F: 323; BUD400: 312) WITHDRAWALS: Not reported by subgroup AGE mean: 37 GENDER (% male): 43.6 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 5 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 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
Interventions	LABA + ICS vs INCREASED 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 100 mcg bid + formoterol 12 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: Not reported FUNCTIONAL STATUS: Asthma symptom days; nocturnal awakenings; rescue medication use; exacerbations INFLAMMATORY MARKERS: Not reported ADVERSE EFFECTS: Not reported WITHDRAWAL: Not 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 obtained User-defined number: 200

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
Incomplete outcome data addressed? All outcomes	Unclear	Intention-to-treat analysis stated, but explicit description of its composition not available
Free of selective reporting?	Yes	Primary outcome data available from study publication

O'Byrne 2005

Methods	Parallel-group, multicentre study (246 centres in 22 countries). Three treatment groups: BUD; BUD/F and BUD/F (with BUD/F also as reliever) Jadad quality score: 4
Participants	Symptomatic asthmatic adults and children % ELIGIBLE OF SCREENED POPULATION: Not reported % RUN-IN PARTICIPANTS RANDOMISED: 85 RANDOMISED: 1835 (BUD: 926; BUD/F: 909) WITHDRAWALS: BUD/F: 148; BUD: 142 AGE mean (range): 35 (4 to 79) GENDER (% male): 44 SEVERITY: Moderate BASELINE % PREDICTED FEV1 (mean): 73 BASELINE DOSE OF ICS: 615 mcg/d ASTHMA DURATION: 9 years ATOPY (%): Not reported ELIGIBILITY CRITERIA: 4 to 80 years; treatment with 400 to 1000 mcg/d ICS (200 to 500 mcg/d for participants aged 4 to 11 years) for 3 or more months; FEV1 predicted 60% to 100%; 12 or more inhalations during last 10 days of run-in (8 for participants aged 4 to 11 years) EXCLUSION CRITERIA: Participants using 10 or more inhalations on one day during run-in (7 or more for participants aged 4 to 11 years); participants experiencing an exacerbation of asthma during run-in period
Interventions	LABA + ICS versus INCREASED dose ICS OUTCOMES: TIMING 12 months RUN-IN: 14 to 18 days DOSE OF ICS DURING RUN-IN: Same as pre-study ICS dose (+ terbutaline) INTERVENTION PERIOD: 12 months TEST GROUP: Combination budesonide and formoterol (100/6 mcg) bid CONTROL GROUP: Budesonide 400 mcg bid (plus as needed terbutaline) DEVICE: Turbohaler NUMBER OF DEVICES: 1 COMPLIANCE: Self-reported compliance on 84% of days; self-reported non-compliance on 3% of days; incomplete records on 13% of days CO-TREATMENT: prn SABA
Outcomes	PULMONARY FUNCTION TEST: FEV1; am PEF; pm PEF SYMPTOM SCORES: Daytime scores; nighttime scores; % symptom-free days FUNCTIONAL STATUS: Exacerbations (treated with oral steroids, hospitalisation or ED visit)*; rescue medication use; night awakenings INFLAMMATORY MARKERS: Not reported ADVERSE EFFECTS: Reported WITHDRAWALS: Reported Primary outcome measure*
Notes	Full-text publication Source of funding Astra Zeneca Confirmation of methodology and data: Requested, obtained for adults. Data on children were requested directly from the study sponsors concurrently. The data for OCS-treated exacerbations for children were not available User defined number: 800

Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	Yes	Computer-generated randomisation scheme

Allocation concealment?	Unclear	Eligible patients were randomised in balanced blocks by allocating patient numbers in consecutive order
Blinding? All outcomes	Yes	Double-blind; identical inhaler devices used
Incomplete outcome data addressed? All outcomes	Unclear	"All analyses were performed on an intention-to-treat basis." Additional information on the composition of the ITT population was not provided
Free of selective reporting?	Yes	Data on OCS-treated exacerbations reported as composite with ED visits/hospitalisations, PEF falls and requirement for medical intervention. Separate data for OCS-treated exacerbations and hospital admission received. Data on adults were received from study sponsors directly. We requested data for children from the study sponsors concurrently but these were not available

Ortega-Cisneros 1998

Methods	Parallel-group study Jadad quality score: 1
Participants	Symptomatic asthmatic children % ELIGIBLE OF SCREENED POPULATION: Not reported % RUN-IN PARTICIPANTS RANDOMISED: Not reported RANDOMISED: 20 (BDP/Sal: 10; BDP: 10) WITHDRAWALS: Not described AGE range: 6 to 19 years GENDER (% male): Not described SEVERITY: Moderate BASELINE % PREDICTED FEV1: Not described ASTHMA DURATION: Not reported ATOPY(%): Not reported ELIGIBILITY CRITERIA: Still symptomatic despite maintenance treatment with 200 mcg bid of BDP EXCLUSION CRITERIA: Not described
Interventions	LABA + ICS vs INCREASED dose ICS OUTCOMES: reported at 8,12 weeks RUN-IN PERIOD: 2 weeks DOSE OF ICS DURING RUN-IN: BDP 200 bid DOSE OPTIMISATION PERIOD: None INTERVENTION PERIOD: 12 weeks TEST GROUP: Salmeterol 50 mcg bid + beclomethasone 200 mcg bid CONTROL GROUP: Beclomethasone 400 bid DEVICE: Not specified NUMBER OF DEVICES: 2 COMPLIANCE: Not reported CO-TREATMENT: Not specified
Outcomes	PULMONARY FUNCTION TEST: FEV1; PEF; FEF 25% to 75% SYMPTOM SCORES: Daily symptoms (no data for control group) FUNCTIONAL STATUS: Not reported INFLAMMATORY MARKERS: Not reported ADVERSE EFFECTS: Not reported WITHDRAWAL: Not reported
Notes	Abstract Funding not reported Confirmation of methodology and data extraction: 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	No	Open label
Incomplete outcome data addressed? All outcomes	Unclear	No information provided
Free of selective reporting?	Unclear	Unclear whether data on OCS-treated exacerbations were collected in the study

Pauwels 1997

Methods	Parallel-group, multicentre study (71 centres). Four treatment groups of which 2 considered here, namely: F12 + BUD 100 bid and BUD 400 + placebo bid Jadad quality score: 5
Participants	Symptomatic asthmatic adults % ELIGIBLE OF SCREENED POPULATION: Not reported % RUN-IN PARTICIPANTS RANDOMISED: 77 RANDOMISED: 424 (F12 bid + BUD 100 bid: 210; BUD 400 mcg bid: 214) WITHDRAWAL: BUD/F: 39; BUD: 37 AGE: mean (range): 42 (18 to 70) GENDER (% male): 49 ASTHMA SEVERITY: Moderate BASELINE % PREDICTED FEV1 mean: 75.6 BASELINE DOSE OF ICS (start of run-in): 820 (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 mcg/day or budesonide by MDI > 1600 mcg/day or budesonide by turbuhaler > 800 mcg/day or fluticasone > 800 mcg/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 INCREASED dose of ICS OUTCOMES reported at 1, 2, 3, 6, 9 and 12 months RUN-IN PERIOD: 4 weeks to document stability and compliance DOSE OF ICS DURING RUN-IN: BUD 800 bid DOSE OPTIMISATION PERIOD: None INTERVENTION PERIOD: 12 months TEST GROUP: (BUD/F) formoterol 12 mcg bid + budesonide 100 mcg bid CONTROL GROUP: (BUD) 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	PULMONARY FUNCTION TEST: FEV1 predicted; am PEF; pm PEF SYMPTOM SCORES: Mean daytime and nighttime symptom scores at end of study (4-point scale: averaged over 10 days) FUNCTIONAL STATUS: Rescue medication use; nocturnal awakening (number per night); severe exacerbation (requiring systemic steroids); episode free days (mean % of year) INFLAMMATORY MARKERS: Not reported ADVERSE EFFECTS: Reported WITHDRAWAL: Reported *Primary outcome: 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: 600

Risk of bias		
Item	**Authors' judgement**	**Description**
Adequate sequence generation?	Yes	Computer-generated random numbers list
Allocation concealment?	Unclear	Information not available
Blinding? All outcomes	Yes	Identical inhaler devices
Incomplete outcome data addressed? All outcomes	No	Last observation carried forward: "The analysis included all randomised 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 from study report

Pearlman 1999

Methods	Parallel-group, multicentre study (11 centres). Six treatment groups of which 2 are considered for this review, namely: FP 100 bid + SL 50 bid; FP250 bid + placebo Jadad quality score = 5
Participants	Symptomatic asthmatic adults % ELIGIBLE OF SCREENED POPULATION: Not reported % RUN-IN PARTICIPANTS RANDOMISED: Not reported RANDOMISED: 48 (FP/Sal: 25; FP: 23) WITHDRAWALS: FP/Sal: 2; FP: 2 AGE: mean (range): 32 (14 to 61) GENDER (% male): 48 SEVERITY: Moderate BASELINE % PREDICTED FEV1: 66 BASELINE DOSE OF ICS (SE): Steroid-naive for at least 30 days prior to study onset ASTHMA DURATION: >= 6 months and < 1 year: 0; >= 1 year and < 5 years: 8; >= 5 years and < 10 years: 5; >= 10 years and < 15 years: 6; >= 15 years: 29 ATOPY(%): Not recorded ELIGIBILITY CRITERIA: >= 12 years; FEV1 between 50% and 80% of predicted value for age, sex, height and race; medical history of asthma of at least 6 months requiring pharmacotherapy; >= 15% increase in FEV1 15 minutes after 2 puffs of inhaled albuterol; being treated with daily or as-needed short-acting beta-sympathomimetic bronchodilators; females had negative pregnancy tests, or be surgically sterile, or postmenopausal for at least 1 year, or using acceptable birth control for at least 1 month prior to participation EXCLUSION CRITERIA: History of life-threatening asthma; hypersensitivity reaction to sympathomimetic drugs or corticosteroids; smoking within the previous year or a history of > 10 pack-years; use of oral, inhaled, injectable, or intranasal corticosteroid therapy within the previous month; use of daily oral corticosteroid treatment within the previous 6 months; use of any other prescription or over-the-counter medication that may affect the course of asthma or interact with sympathomimetic amines; abnormal chest X-rays; clinically significant abnormal 12-lead electrocardiograms; history of significant concurrent disease CRITERIA FOR RANDOMISATION DURING RUN-IN: Completion of daily diary cards and report medication compliance; patients were not eligible for inclusion if they used 12 or more puffs of albuterol daily for more than 2 days or if they had more than 2 nighttime awakenings due to asthma requiring treatment with albuterol during the 7 days immediately preceding the randomisation period; FEV 1 had to be between 50% and 80% of the predicted value and within 15% of the FEV1 obtained at the beginning of the screening period
Interventions	LABA + ICS vs INCREASED dose ICS OUTCOMES reported at 2 and 4 weeks RUN-IN PERIOD: 2 weeks DOSE OF ICS DURING RUN-IN: Same as usual DOSE OPTIMISATION PERIOD: None INTERVENTION PERIOD: 4 weeks

	TEST GROUP: (SL50 + FP100) salmeterol 50 mg bid + fluticasone propionate 100 mg bid CONTROL GROUP: (FP 250) fluticasone propionate 250 mg bid DEVICE: Metered-dose inhaler NUMBER OF DEVICES: 2 COMPLIANCE: Evaluated CO-TREATMENT: prn SABA
Outcomes	PULMONARY FUNCTION TEST: FEV1; am PEF SYMPTOM SCORE: Score of 0 to 4 mean change from baseline FUNCTIONAL STATUS: Rescue medication use; mean change in % nights with no awakenings; episode-free days INFLAMMATORY MARKERS: Not measured ADVERSE EFFECTS: Reported WITHDRAWALS: Reported Primary outcome measure: Not reported
Notes	Full-text publication Funded by Glaxo Wellcome Confirmation of methodology and data confirmed User defined number: 600

Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	Yes	See Appendix 3
Allocation concealment?	Yes	See Appendix 3
Blinding? All outcomes	Yes	Use of identical placebo (double-dummy design)
Incomplete outcome data addressed? All outcomes	Unclear	Intention-to-treat population defined as "all randomised subjects exposed to the study drug". Handling of withdrawals not explicit
Free of selective reporting?	Yes	Exacerbations not assessed

SAM104926

Methods	Parallel-group, multicentre study
Participants	% ELIGIBLE OF SCREENED POPULATION: Not reported % RUN-IN PARTICIPANTS RANDOMISED: Not reported RANDOMISED: 321 (FP/SAL: 160; FP: 161) WITHDRAWALS: FP/SAL: 3; FP: 6 AGE mean: 8 SEVERITY: Not reported BASELINE % PREDICTED FEV1: 102 BASELINE DOSE OF ICS: Not stated ASTHMA DURATION: Not stated ATOPY (%): Not stated ELIGIBILITY CRITERIA: 4 to 1 years; diagnosis of asthma for aminimum of 6 months; airway reversibility of = 15% based either on FEV1 or PEF; treatment with medium dose ICS (beclomethasone dipropionate (BDP) equivalent 400 to 500 mcg/day for 3 months prior to Visit 1 EXCLUSION CRITERIA: Respiratory tract infection in previous 4 weeks; acute asthma exacerbation requiring emergency room treatment within the last 4 weeks/ hospitalisation within last 12 weeks; use of systemic corticosteroid within the last 12 weeks, or use of LABA, oral ß2-agonists, leukotriene antagonists or theophyllines during 4 weeks prior to screening visit; ineligible for randomisation if, during the run-in period, change in asthma medication including use of systemic corticosteroids, or respiratory tract infection or asthma exacerbation ELIGIBILITY CRITERIA DURING RUN-IN: Asthma assessed as not "well-controlled" for at least 2 of 4 weeks of run-in; FEV1 > 60% during run-in
Interventions	LABA + ICS versus INCREASED dose ICS OUTCOMES: 12 weeks RUN-IN PERIOD: 4 weeks DOSE OPTIMISATION PERIOD: N/A INTERVENTION PERIOD: 12 weeks

	TEST GROUP: Combination fluticasone and salmeterol 100/50 mcg bid CONTROL GROUP: Fluticasone 200 mcg bid INHALER DEVICE: Dry powder inhaler NUMBER OF DEVICES: 1 COMPLIANCE: Not assessed CO-TREATMENT: prn SABA
Outcomes	PULMONARY FUNCTION TEST: am PEF SYMPTOM SCORES: NA FUNCTIONAL STATUS: N achieving well-controlled asthma INFLAMMATORY MARKERS: NA ADVERSE EFFECTS: Reported WITHDRAWALS: Reported
Notes	Unpublished study Funding source: GSK Confirmation of methodology and data: obtained for methods User defined: 800

Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	Yes	See Appendix 3
Allocation concealment?	Yes	See Appendix 3
Blinding? All outcomes	Yes	Double-blind; double-dummy
Incomplete outcome data addressed? All outcomes	Unclear	No detailed information on how intention-to-treat population was composed
Free of selective reporting?	Yes	OCS-exacerbations available on request from study sponsor

SAM30013

Methods	Parallel-group, multicentre study (40 centres in Canada) Jadad quality score = 4
Participants	Symptomatic asthmatic adults % ELIGIBLE OF SCREENED POPULATION: Not reported % RUN-IN PARTICIPANTS RANDOMISED: Not reported RANDOMISED: 237 (FP/SAL: 121; FP: 116) WITHDRAWALS: FP/SAL: 4; FP: 7 AGE mean: 37 GENDER (% male): 35 SEVERITY: Moderate BASELINE % PREDICTED FEV1 (mean): Not reported BASELINE DOSE OF ICS: 100 mcg/d FP ASTHMA DURATION: Not reported ATOPY (%): Not reported ELIGIBILITY CRITERIA: >= 12 years of age; symptomatic despite low doses of ICS (<= 500 mcg/d or equivalent of BUD) for less than 4 weeks (criterion for run-in phase - participants who met the above criterion but had been on ICS for longer bypassed the run-in phase); symptomatic at end of run-in phase (on low-dose FP) EXCLUSION CRITERIA: < 60% or > 90% predicted of PEF at visit 1
Interventions	LABA + ICS versus INCREASED dose of FP OUTCOMES - TIMING 12 weeks RUN-IN: 2 weeks DOSE OF ICS DURING RUN-IN: 100 mcg/d FP INTERVENTION PERIOD: 12 weeks TEST GROUP: Combination fluticasone and salmeterol 100/50 bid CONTROL GROUP: Fluticasone 250 mcg bid DEVICE: 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: Not reported FUNCTIONAL STATUS: Not reported INFLAMMATORY MARKERS: Not reported ADVERSE EFFECTS: Reported WITHDRAWALS: Reported Primary outcome measure*
Notes	Unpublished full 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 3
Allocation concealment?	Yes	See Appendix 3
Blinding? All outcomes	Yes	Identical inhaler devices used
Incomplete outcome data addressed? All outcomes	Unclear	"The Intent-to-Treat (ITT) population was used for all analyses including demographic, efficacy, safety and health outcome endpoints. This population consisted of all subjects who entered the study and were randomised to treatment."
Free of selective reporting?	Yes	Moderate exacerbations used as proxy for steroid-treated exacerbations (see Analysis 3.1)

SAM30022

Methods	Parallel-group, multicentre study (61 centres in UK) Jadad quality score = 4
Participants	Moderately severe steroid using asthmatic adults % ELIGIBLE OF SCREENED POPULATION: Not reported % RUN-IN PARTICIPANTS RANDOMISED: Not reported RANDOMISED: 68 (FP/SAL: 35; BDP: 33) WITHDRAWALS: FP/SAL: 10; BDP: 10 AGE: mean: 44 GENDER (% male): 50 SEVERITY: Moderate BASELINE % PREDICTED FEV1 (mean): 75 BASELINE DOSE OF ICS: 400 to 500 mcg/d BDP ASTHMA DURATION: Not reported ATOPY (%): Not reported ELIGIBILITY CRITERIA: >= 12 years of age; 400-500 mcg/d BDP equivalent; >= 50% < 85% predicted PEF during run-in; relief medication on >= 2 occasions on 3 of last 7 days; >= 2 on symptom scores on 3 of last 7 days on baseline OR >= 1 on night symptoms during same period EXCLUSION CRITERIA: Not reported
Interventions	LABA + ICS versus INCREASED dose ICS OUTCOMES: TIMING 12 weeks RUN-IN: 2 weeks DOSE OF ICS DURING RUN-IN: Current ICS treatment INTERVENTION PERIOD: 12 weeks TEST GROUP: Combination fluticasone and salmeterol 100/50 mcg bid CONTROL GROUP: Beclomethasone 400 mcg bid DEVICE: FP/SAL: Evohaler; BDP: Accuhaler NUMBER OF DEVICES: 1 (double-dummy design meant that participants given 2 inhalers) COMPLIANCE: Not assessed CO-TREATMENT: prn SABA

Outcomes	PULMONARY FUNCTION TEST: am PEF*; pm PEF SYMPTOM SCORES: Percentage symptom-free days* FUNCTIONAL STATUS: Rescue medication usage; health-related quality of life (AQLQ) INFLAMMATORY MARKERS: Not reported ADVERSE EFFECTS: Reported WITHDRAWALS: Reported Primary outcome measures*
Notes	Unpublished full data set available from http://www.ctr.gsk.co.uk Source of funding: GSK Confirmation of methodology and data: Obtained for methods User defined number: 800

Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	Yes	See Appendix 3
Allocation concealment?	Yes	See Appendix 3
Blinding? All outcomes	Yes	Double-dummy design
Incomplete outcome data addressed? All outcomes	Unclear	"The intention-to-treat (ITT) sample was used for the efficacy and safety analyses. This consisted of all subjects randomised to and receiving at least one dose of study medication."
Free of selective reporting?	Yes	OCS-treated exacerbations available on request from study sponsor

SAM40012

Methods	Parallel-group, multicentre study Jadad quality score = 4
Participants	Steroid-using asthmatic children % ELIGIBLE OF SCREENED POPULATION: Not reported % RUN-IN PARTICIPANTS RANDOMISED: Not reported RANDOMISED: 367 (FP/SAL: 181; FP: 186) WITHDRAWAL: FP/SAL: 3; FP: 5 AGE mean: 7.8 years GENDER (male %): 72 ASTHMA SEVERITY: Moderate BASELINE % PREDICTED FEV1: Not reported (PEF: 88%) BASELINE DOSE OF ICS (start of run-in): Not reported ASTHMA DURATION: Not reported ATOPY(%): Not reported ELIGIBILITY CRITERIA: 4 to 11 years, inclusive; documented evidence of asthma; BDP, BUD or equivalent 400 to 500 mcg/day/FP 200 to 250 mcg/day for at least 4 weeks before Visit 1 EXCLUSION CRITERIA: Not reported Criteria for randomisation post-run-in: Symptom score >= 2 on 3 of last 7 days of run-in; mean morning PEF > 50% and < 85%; dairy card completion of 70%
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: 6 months TEST GROUP: Combination salmeterol 50/fluticasone 100 mcg bid CONTROL GROUP: Fluticasone 200 mcg bid DEVICE: Diskus NUMBER OF DEVICES: 1 COMPLIANCE: Not reported CO-TREATMENT: prn SABA

Outcomes	PULMONARY FUNCTION TEST: am PEF; pm PEF; FEV1 SYMPTOM SCORES: % Symptom-free days*; % symptom-free nights* 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: Obtained for methods, not obtained for data User defined number: 400

Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	Yes	See Appendix 3
Allocation concealment?	Yes	See Appendix 3
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. Data used in sensitivity analysis (see Analysis 3.1)

SAM40090

Methods	Parallel-group, multicentre study (79 centres in Canada) Jadad quality score = 4
Participants	Controlled moderately severe asthmatic adults % ELIGIBLE OF SCREENED POPULATION: 71 % RUN-IN PARTICIPANTS RANDOMISED: Not reported RANDOMISED: 483 (FP/SAL: 242; FP: 241) WITHDRAWALS: FP/SAL: 43; FP: 41 AGE: mean: 39 GENDER (% male): 42 SEVERITY: Moderate BASELINE % PREDICTED FEV1: Not reported BASELINE DOSE OF ICS: >= BUD 400 mcg/d or equivalent ASTHMA DURATION: Not reported ATOPY (%): Not reported ELIGIBILITY CRITERIA: 12 to 70 years of age; clinical diagnosis of persistent asthma; ability to use HFA-salbutamol as prn SABA; >= BUD 400 mcg/d or equivalent; asthma control during run-in (defined by Canadian guidelines) EXCLUSION CRITERIA: Not reported
Interventions	LABA + ICS versus INCREASED dose ICS OUTCOMES TIMING: 12 weeks RUN-IN: 2 weeks DOSE OF ICS DURING RUN-IN: FP 250 mcg bid INTERVENTION PERIOD: 12 weeks TEST GROUP: Combination fluticasone and salmeterol 100/50 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 SYMPTOM SCORES: % symptom-free days FUNCTIONAL STATUS: Rescue medication use; nocturnal awakenings INFLAMMATORY MARKERS: Not reported

	ADVERSE EFFECTS: Reported WITHDRAWALS: Reported Primary outcome measure*
Notes	Unpublished full data-set available from http://www.ctr.gsk.co.uk Source of funding: GSK Confirmation of methodology and data: Obtained for methods, not obtained for data User defined number: 1000

Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	Yes	See Appendix 3
Allocation concealment?	Yes	See Appendix 3
Blinding? All outcomes	Yes	Identical inhaler devices used
Incomplete outcome data addressed? All outcomes	Unclear	"The primary population was the Intent-to-Treat (ITT) population. The ITT population was defined as subjects who were randomised and treated with at least one dose of investigational product."
Free of selective reporting?	Yes	OCS-treated exacerbations available on request from study sponsor

SAM40100

Methods	Parallel-group, multicentre study
Participants	% ELIGIBLE OF SCREENED POPULATION: Not reported % RUN-IN PARTICIPANTS RANDOMISED: Not reported RANDOMISED: 24 (FP/SAL: 12; FP: 12) WITHDRAWALS: F/SAL: 1; FP: 1 AGE mean: 7.3 SEVERITY: Not stated BASELINE % PREDICTED FEV1: Not reported BASELINE DOSE OF ICS: Not stated ASTHMA DURATION: Not reported ATOPY (%): Not reported ELIGIBILITY CRITERIA: 4 to 8 years; history of asthma for at least 3 months; maintenance ICS dose of 200 to 800 mcg /day BDP or equivalent for at least 4 weeks; sufficiently stable to receive FP 200 mcg/day during 2-week run-in; sRAW value of = 1.3 kPa.s for entry into the screening and treatment period EXCLUSION CRITERIA: Use of systemic steroids in 4 weeks prior to study entry; required 3 or more courses of oral corticosteroids in 12 months prior to study entry; admitted to intensive care for asthma within 3 months prior to study entry ELIGIBILITY CRITERIA DURING RUN-IN: Participants who had a change in medication following an exacerbation during run-in were excluded
Interventions	LABA + ICS versus INCREASED DOSE ICS OUTCOMES: 6 weeks RUN-IN PERIOD: 2 weeks DOSE OPTIMISATION PERIOD: 2 weeks INTERVENTION PERIOD: 6 weeks TEST GROUP: Combination fluticasone and salmeterol 100/50 mcg bid via DPI CONTROL GROUP: Fluticasone 200 mcg bid via DPI NUMBER OF DEVICES: 1 COMPLIANCE: Not assessed CO-TREATMENT: prn SABA
Outcomes	PULMONARY FUNCTION TEST: FEV1 SYMPTOM SCORES: Day and nocturnal scores FUNCTIONAL STATUS: Rescue medication use INFLAMMATORY MARKERS: sRAW* ADVERSE EFFECTS: Reported WITHDRAWALS: Reported
Notes	Unpublished data sourced from http://ctr.gsk.co.uk Funding source: GSK

	Confirmation of methodology and data not obtained User defined: 400

Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	Yes	See Appendix 3
Allocation concealment?	Yes	See Appendix 3
Blinding? All outcomes	Yes	Double-blind; identical devices used
Incomplete outcome data addressed? All outcomes	Unclear	No detailed information on how intention-to-treat population was composed
Free of selective reporting?	Unclear	Unclear whether data on OCS-treated exacerbations were collected. Request for data from study sponsors has not been successful

SAM40120

Methods	Parallel-group, multicentre study (10 centres in UK) Jadad quality score = 4
Participants	Moderately severe asthmatic adults with smoking history % ELIGIBLE OF SCREENED POPULATION: Not reported % RUN-IN PARTICIPANTS RANDOMISED: Not reported RANDOMISED: 18 (FP/SAL: 8; FP: 10) WITHDRAWALS: FP/SAL: 1; FP: 2 AGE mean: 55 GENDER (% male): 56 SEVERITY: Moderate BASELINE % PREDICTED FEV1: Not reported BASELINE DOSE OF ICS: 200 to 400 mcg/d FP ASTHMA DURATION: Not reported ATOPY (%): Not reported ELIGIBILITY CRITERIA: Current/former smokers with >= 10 pack years; >= 200 mcg/d to <= 400 mcg/d FP or equivalent; PEF between 50% and 85% predicted during last 7 days of run-in OR symptom score < 2 on >= 3 of last 7 days of run-in OR night symptoms of >= 1 on >= 3 days of last 7 days of run-in EXCLUSION CRITERIA: Not reported
Interventions	LABA + ICS versus INCREASED dose of ICS OUTCOMES TIMING: 12 weeks RUN-IN: 2 weeks DOSE OF ICS DURING RUN-IN: Not clear INTERVENTION PERIOD: 12 weeks TEST GROUP: Combination fluticasone and salmeterol 100/50 mcg bid CONTROL GROUP: Fluticasone 250 mcg bid DEVICE: Evohaler NUMBER OF DEVICES: 1 COMPLIANCE: Not assessed CO-TREATMENT: prn SABA
Outcomes	PULMONARY FUNCTION TEST: am PEF* SYMPTOM SCORES: Not reported FUNCTIONAL STATUS: AQLQ INFLAMMATORY MARKERS: Not reported ADVERSE EFFECTS: Reported WITHDRAWALS: Reported Primary outcome measure*
Notes	Unpublished full data set available from http://www.ctr.gsk.co.uk Source of funding: GSK Confirmation of methodology and data: Obtained for methods, not obtained for data User defined number: 1000

Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	Yes	See Appendix 3
Allocation concealment?	Yes	See Appendix 3
Blinding? All outcomes	Yes	Identical inhaler device used
Incomplete outcome data addressed? All outcomes	Unclear	"The sample used for the analysis was the intention-to-treat sample (all subjects randomised & receiving at least one dose of study medication)."
Free of selective reporting?	Unclear	Unclear whether data on OCS-treated exacerbations were collected. Request for data from study sponsors has not been successful

SAS40013

Methods	Parallel-group trial, single centre in Netherlands Jadad quality score = 4
Participants	Moderately severe asthmatic adults % ELIGIBLE OF SCREENED POPULATION: Not reported % RUN-IN PARTICIPANTS RANDOMISED: Not reported RANDOMISED: 12 (FP/SAL: 5; FP: 7) WITHDRAWALS: 0 AGE: mean: 39 GENDER (% male): 5 SEVERITY: Moderate BASELINE % PREDICTED FEV1: Not reported BASELINE DOSE OF ICS: 500 to 1000 mcg/d FP ASTHMA DURATION: Not reported ATOPY (%): Not reported ELIGIBILITY CRITERIA: Requirement for 500 to 1000 mcg/d FP; morning PEF during run-in 50% to 85%; cumulative symptom score indicating moderate asthma; PC20 > 4 mg/ml histamine EXCLUSION CRITERIA: Dermatitis; recent lower RTI; exacerbation in last 3 months; smoking history of at least 10 pack-years
Interventions	LABA + ICS versus INCREASED dose ICS OUTCOMES TIMING: 58 weeks RUN-IN: Not specified DOSE OF ICS DURING RUN-IN: Not specified INTERVENTION PERIOD: 58 weeks TEST GROUP: Combination fluticasone and salmeterol 250/50 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: Not reported SYMPTOM SCORES: Not reported FUNCTIONAL STATUS: Exacerbations (not defined) INFLAMMATORY MARKERS: PC20* ADVERSE EFFECTS: Reported WITHDRAWALS: Reported Primary outcome measure*
Notes	Unpublished full data set from http://www.ctr.gsk.co.uk Source of funding: GSK Confirmation of methodology and data: Not obtained User defined number: 2000

Risk of bias

Item	Authors' judgement	Description

Adequate sequence generation?	Yes	See Appendix 3
Allocation concealment?	Yes	See Appendix 3
Blinding? All outcomes	Yes	Identical inhaler devices used
Incomplete outcome data addressed? All outcomes	Yes	No withdrawals occurred
Free of selective reporting?	Yes	Exacerbations described in trial report available; OCS-treated exacerbations could not be identified from the data available. Data used in sensitivity analysis (see Analysis 3.1)

SAS40026

Methods	Parallel-group, multicentre study (95 centres in North America) Jadad quality score = 4
Participants	Moderately severe asthmatic adults % ELIGIBLE OF SCREENED POPULATION: Not reported % RUN-IN PARTICIPANTS RANDOMISED: Not reported RANDOMISED: 636 (FP/SAL: 321; FP: 315) WITHDRAWALS: FP/SAL: 32; FP: 44 AGE mean: 39 GENDER (% male): 38 SEVERITY: Moderate BASELINE % PREDICTED FEV1: 80.4 BASELINE DOSE OF ICS: Not reported ASTHMA DURATION: Not reported ATOPY (%): Not reported ELIGIBILITY CRITERIA: 12 years or older - medium dose of ICS for at least 30 days prior to randomisation (dose not specified); ATS defined asthma for at least 6 months; FEV1 65% to 95% predicted; >= 12% reversibility post-SABA EXCLUSION CRITERIA: Life-threatening asthma/hospitalisation within 3 months of study entry; OCS within 30 days of screening OR 2 courses within 90 days; other concurrent respiratory disease; more than a 10 pack-year history of smoking
Interventions	LABA + ICS versus INCREASED dose ICS OUTCOMES TIMING: 12, 24 weeks (trial extension) RUN-IN: Not reported DOSE OF ICS DURING RUN-IN: Not reported INTERVENTION PERIOD: 12 weeks TEST GROUP: Combination fluticasone and salmeterol 100/50 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; FEV1 SYMPTOM SCORES: % symptom-free days FUNCTIONAL STATUS: Rescue medication usage INFLAMMATORY MARKERS: Not reported ADVERSE EFFECTS: Reported WITHDRAWALS: Due to lack of efficacy*, other reasons 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: Obtained for methods, not for data User defined number: 1000

Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	Yes	See Appendix 3

Allocation concealment?	Yes	See Appendix 3
Blinding? All outcomes	Yes	Identical inhaler devices used
Incomplete outcome data addressed? All outcomes	Unclear	"Efficacy and safety analyses were performed on the intent-to-treat (ITT) population which consisted of all subjects who were randomised to study drug regardless of enrolment date."
Free of selective reporting?	Yes	OCS-treated exacerbations available on request from GSK

SD 039 0726

Methods	Parallel-group, multicentre study (151 centres in USA). Five treatment arms of which 2 are considered here
Participants	% ELIGIBLE OF SCREENED POPULATION: 28 % RUN-IN PARTICIPANTS RANDOMISED: 63 RANDOMISED: 297 (BUD/F 200 qd: 152; BUD 400 qd: 145) WITHDRAWALS: BUD/F 200 qd: 19;BUD/F 400 qd: 28 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	OUTCOMES: 12 weeks RUN-IN PERIOD: 4 to 5 weeks DOSE OPTIMISATION PERIOD: None INTERVENTION PERIOD: 12 weeks TEST GROUP: Combination budesonide and formoterol (200/12 mcg) qd CONTROL GROUP: Budesonide 400 mcg qd NUMBER OF DEVICES: 2 (double-dummy design; LABA co-delivered with ICS in 1 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 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?	Unclear	"The efficacy analysis set (EAS), defined as all randomised subjects who took at least 1 dose of double-

All outcomes		blind treatment and who contributed at least 1 evening PEF diary entry after receiving randomised 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 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: 265 (BUD/F 132; 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 HIGHER dose ICS OUTCOMES: 52 weeks RUN-IN PERIOD: 2 weeks DOSE OPTIMISATION PERIOD: None INTERVENTION PERIOD: 52 weeks TEST GROUP: Combination budesonide and formoterol 400/12 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 www.astrazenecaclinicaltrials.com Funding source: AZ Data and methodology: Not obtained User defined: 800

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	Identical inhaler devices used
Incomplete outcome data addressed? All outcomes	Unclear	"…all randomised subjects who received at least 1 dose of randomised study drug, the post-dose analysis set, consisting of all subjects who had clinic visit safety assessments measured 1-2 hours after randomised treatment at all visits, was also used in the analysis of some safety data."

Free of selective reporting?	Unclear	Not clear whether OCS-treated exacerbations collected in the study

SFCF4026

Methods	Parallel-group, multicentre study (124 centres in France). Three treatment groups (FP/SAL 250/50; FP/SAL 100/50; FP250) Jadad quality score = 4
Participants	Moderately severe well-controlled asthmatic adults % ELIGIBLE OF SCREENED POPULATION: Not reported % RUN-IN PARTICIPANTS RANDOMISED: Not reported RANDOMISED: 318 (FP/SAL: 158; FP: 159) WITHDRAWALS: FP/SAL: 15; FP: 30 AGE mean: 45 GENDER (% male): 50 SEVERITY: Moderately severe BASELINE % PREDICTED FEV1: 90 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 INCREASED dose ICS OUTCOMES TIMING: 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 100/50 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: Obtained for methods, not obtained for data User defined number: 1000

Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	Yes	See Appendix 3
Allocation concealment?	Yes	See Appendix 3
Blinding? All outcomes	Yes	Identical inhaler devices used
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	OCS-treated exacerbations available on request from study sponsor

SLGA5021

Methods	Parallel-group, multicentre study Jadad quality score = 5
Participants	Symptomatic asthmatic adults on prn SABA % ELIGIBLE OF SCREENED POPULATION: Not reported % RUN-IN PARTICIPANTS RANDOMISED: Not reported RANDOMISED: 488 (FP/SAL: 246; FP: 242) WITHDRAWALS: FP/SAL: 31; FP: 35 AGE mean: 37.5 years GENDER (% male): 50.2 SEVERITY: Moderate to severe persistent asthma BASELINE % PREDICTED FEV1(mean): 60.5% BASELINE DOSE OF ICS: Not described ASTHMA DURATION: Not reported ATOPY (%): Not reported ELIGIBILITY CRITERIA: FEV1 40% to 80% predicted; FEV1 reversibility >= 15% post-SABA; if participant's FEV1 between 65% to 80% also required to: i) average > 4 puffs/d of SABA in 7 days prior to screening ii) nocturnal awakenings on 3 nights/week over 2 weeks prior to screening) asthma symptoms on half run-in days EXCLUSION CRITERIA: Current tobacco use, a hospital admission for asthma in the past 30 days, an upper or lower respiratory tract infection within 30 days; female patients who had a positive pregnancy test result or were lactating; the following medications were not allowed for the indicated times before screening: oral or parenteral corticosteroid therapy within 30 days, oral or long-acting inhaled bronchodilators within 48 hours, and cromolyn or nedocromil within 30 days
Interventions	LABA + ICS versus INCREASED dose of ICS OUTCOMES reported at 2, 4, 8, 12, 16, 20 and 24 weeks RUN-IN: 2 weeks (prn SABA) DOSE OF ICS DURING RUN-IN: 0 INTERVENTION PERIOD: 24 weeks TEST GROUP: Fluticasone 100 mcg bid plus salmeterol 50 mcg bid CONTROL GROUP: Fluticasone 250 mcg bid DEVICE: MDI NUMBER OF DEVICES: 2 COMPLIANCE: Not assessed CO-TREATMENT: prn SABA
Outcomes	PULMONARY FUNCTION TEST: am PEF*; pm PEF; FEV1 SYMPTOM SCORES: Combined symptoms FUNCTIONAL STATUS: Awakenings per night; rescue medication usage; exacerbations (OCS treatment) 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: obtained User defined number: 1000

Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	Yes	See Appendix 3
Allocation concealment?	Yes	See Appendix 3
Blinding? All outcomes	Yes	Identical inhaler devices used in double-dummy design

Incomplete outcome data addressed? All outcomes	Unclear	"All statistical analyses were performed on the intent-to-treat (ITT) population. The ITT population consisted of all subjects who had been randomised to study drug."
Free of selective reporting?	Yes	OCS-treated exacerbations available on request from GSK

Van Noord 1999

Methods	Parallel-group, multicentre study (27 centres) Jadad quality score = 4
Participants	Symptomatic asthmatic adults % ELIGIBLE OF SCREENED POPULATION: Not reported % RUN-IN PARTICIPANTS RANDOMISED: 74 RANDOMISED: 274 (FP + Sal: 139; FP: 135) WITHDRAWALS: FP + Sal: 6; FP: 9 AGE mean: 47 years GENDER (% males): 48 SEVERITY: Moderate BASELINE % PREDICTED FEV1: 72 BASELINE DOSE OF ICS: 400 to 1200 ASTHMA DURATION: Not reported ATOPY (%): Not reported ELIGIBILITY CRITERIA: Aged at least 18 years; receiving 400 to 600 mcg BDP or 800 to 1200 mcg BUD daily CRITERIA FOR RANDOMISATION DURING RUN-IN: FEV1 at least 50% of predicted value at visit 3 ; >= 10% improvement from baseline of FEV1 following inhaled salbutamol; daytime and nighttime symptom score >= 1 or diurnal variation in PEF of >= 15% or use of rescue salbutamol >= 2 times/24 hours on >= 4 days of the last 2 weeks of the run-in EXCLUSION CRITERIA: Change in asthma medication in pervious 6 weeks; use of oral steroids in previous 3 months; upper or lower tract infection needing antibiotics or admission to hospital for asthma in the previous month
Interventions	LABA + ICS versus INCREASED dose of ICS OUTCOMES: Reported at 1,4 and 12 weeks RUN-IN PERIOD: 4 weeks DOSE OF ICS DURING RUN-IN: If pre-trial dose 400 to 600 run-in dose was FP 100 bid. If pre-trial dose ICS 800 to 1200 run-in dose was FP 250 bid DOSE OPTIMISATION PERIOD: None INTERVENTION PERIOD: 12 weeks TEST GROUP: (Salm 50 + FP100) salmeterol 50 mg bid + fluticasone propionate 100 mg bid or high-dose (Salm 50 + FP250) salmeterol 50 mg bid + fluticasone propionate 250 mg bid CONTROL GROUP: (FP200) fluticasone propionate 200 mg bid or (FP500) fluticasone propionate 500 mg bid DEVICE: Diskhaler NUMBER OF DEVICES: 2 COMPLIANCE: Not reported CO-TREATMENT: prn SABA; stable dose of methylxanthines or anticholinergics
Outcomes	PULMONARY FUNCTIONTEST: am PEF; pm PEF; diurnal variation in PEF; FEV1 SYMPTOM SCORES: score of 0 to 4 FUNCTIONAL STATUS: Rescue medication use; nocturnal awakenings; severe exacerbation (requiring systemic steroids) INFLAMMATORY MARKERS: Not described ADVERSE EFFECTS: Reported WITHDRAWALS: Described *Primary outcome: daily records of PEF, symptom scores and clinic lung function
Notes	Full-text publication Funded by Glaxo Wellcome Confirmation of methodology and data: not obtained User-defined number: 400 or 1000 (reported as 700)
Risk of bias	

Item	Authors' judgement	Description
Adequate sequence generation?	Unclear	Described as randomised. Patients were stratified prior to randomisation according to the baseline dose of ICS. Those with a pre-trial dose of 400 to 600 mcg/day received FP 100 bid (low-dose group) and those on a pre-trial dose of 800 to 1200 mcg/day received FP 250 bid (high-dose group). The statistical analyses were only performed on both groups combined i.e. comparison of doubling existing dose of FP or addition of salmeterol 50 bid
Allocation concealment?	Unclear	Information not available
Blinding? All outcomes	Yes	Identical inhalers used in double-dummy design
Incomplete outcome data addressed? All outcomes	Unclear	No information reported
Free of selective reporting?	Yes	OCS-treated exacerbations available for meta-analysis

Verberne 1998

Methods	Parallel-group, multicentre study (9 centres). Three groups of which 2 are considered in this review Jadad quality score = 5
Participants	Asthmatic children % ELIGIBLE OF SCREENED POPULATION: Not reported % RUN-IN PARTICIPANTS RANDOMISED: Not reported RANDOMISED: 120 (BDP400 + Sal: 60; BDP800: 60) WITHDRAWALS: BDP400 + Sal: 5; BDP800: 6 AGE mean: 11.1 years GENDER (% male): 63 SEVERITY: Mild BASELINE % PREDICTED FEV1: 87.5 BASELINE DOSE OF ICS: 497 mcg ASTHMA DURATION means: 8.5 years ATOPY (%): 90 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 desensitisation 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 versus INCREASED dose ICS OUTCOMES: Reported at 6, 12, 18, 24, 30, 36, 42, 48 and 54 RUN-IN PERIOD: 6 weeks DOSE OF ICS DURING RUN-IN: BDP 200 bid DOSE OPTIMISATION PERIOD: None INTERVENTION PERIOD: 54 weeks TEST GROUP: (Salm50 + BDP200) salmeterol 50 mcg bid + beclomethasone dipropionate 200 mcg bid

	CONTROL GROUP: (BDP400 + placebo) beclomethasone dipropionate 400 mcg/day + 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; % children reporting no symptoms FUNCTIONAL STATUS: Rescue medication use; exacerbation (requiring systemic 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 Glaxo Wellcome Confirmation of methodology and data obtained up to 24 weeks 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	Double-blind; identical placebo used
Incomplete outcome data addressed? All outcomes	Unclear	Not clear how population for primary outcome Incomplete diary card data not included in analysis: "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-wk assessment."
Free of selective reporting?	Unclear	OCS-treated exacerbation data available

Vermetten 1999

Methods	Parallel-group Jadad quality score = 3
Participants	Well-controlled asthmatic adults % ELIGIBLE OF SCREENED POPULATION: Not reported % RUN-IN PARTICIPANTS RANDOMISED: 57 RANDOMISED: 233 (BDP + Sal: 113; BDP: 120) WITHDRAWALS: 31; not described by group AGE mean: 42 GENDER (% male): 45 SEVERITY: Mild BASELINE MORNING % PREDICTED PEF: 84 BASELINE DOSE OF ICS: 360 ASTHMA DURATION: Not described ATOPY(%): Not described ELIGIBILITY CRITERIA: > 18 to 66 years old; BDP 200 to 400/day for more than 6 weeks; no recent exacerbation; no additional anti-asthmatic Rx CRITERIA FOR RANDOMISATION DURING RUN-IN: Baseline PEF at the randomisation visit had to be at least 60% predicted; ability to inhale medication correctly, proper PEF technique and complete daily records; reversibility of 15% of the baseline value was required on one of the visits

	EXCLUSION CRITERIA: Exacerbation requiring new medication
Interventions	LABA + ICS versus INCREASED dose of ICS OUTCOMES: 7 and 12 weeks RUN-IN PERIOD: 2 weeks DOSE OF ICS DURING RUN-IN: BDP 100 or 200 bid DOSE OPTIMISATION PERIOD: None INTERVENTION PERIOD: 12 weeks TEST GROUP: (BDP200 + Sal 50 bid) beclomethasone 200 mcg bid + salmeterol 50 mcg bid CONTROL GROUP: (BDP400) beclomethasone 400 mcg bid DEVICE: Diskhaler (dry powder inhaler) NUMBER OF DEVICES: 2 COMPLIANCE: Not reported CO-TREATMENT: prn SABA
Outcomes	PULMONARY FUNCTION TEST: % of run-in am and pm PEF; diurnal variation in PEF SYMPTOM SCORES: Score of 0 to 3 (averaged over 1 to 2 weeks) FUNCTIONAL STATUS: Rescue medication use; Hyland quality of life INFLAMMATORY MARKERS: Not reported ADVERSE EFFECTS: Reported WITHDRAWALS: Reported but not described *Primary outcome: Not specified
Notes	Full-text publication Funded by Glaxo Wellcome 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	See Appendix 3
Blinding? All outcomes	Yes	Double-dummy design
Incomplete outcome data addressed? All outcomes	No	Patients who were withdrawn during the treatment period were evaluated up to the day of withdrawal
Free of selective reporting?	Yes	OCS-treated exacerbations available for meta-analysis

Wallin 2003

Methods	Parallel-group, multicentre study. Three treatment groups of which 2 are considered here Jadad quality score = 3
Participants	Symptomatic asthmatic adults % ELIGIBLE OF SCREENED POPULATION: Not reported % RUN-IN PARTICIPANTS RANDOMISED: Not reported RANDOMISED: 37 (FP + Sal: 18; FP: 19) WITHDRAWALS: FP + Sal: 0; FP: 3 AGE mean: 41.5 GENDER (% male): 55.5 SEVERITY: Not stated BASELINE FEV1 % PRED: 86 BASELINE DOSE OF ICS BDP equivalent (range): 600 to 1200 ASTHMA DURATION months: 189 ATOPY (%): 59 ELIGIBILITY CRITERIA: Free of respiratory tract infection for 4 weeks before study CRITERIA FOR RANDOMISATION DURINGRUN-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 INCREASED dose of ICS OUTCOMES before and after 12 weeks treatment RUN-IN PERIOD: 2 to 4 weeks DOSE OF ICS DURING RUN-IN (mean): 805 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: Fluticasone propionate 500 mcg bid DEVICE: Diskhaler (dry powder inhaler) NUMBER OF DEVICES: 2 COMPLIANCE: Not reported CO-TREATMENT: prn SABA
Outcomes	PULMONARY FUNCTION TEST: am PEF predicted; pm PEF predicted; FEV1 SYMPTOM SCORES: None 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 Primary outcome measure: Not reported
Notes	Full-text publication Funded by Glaxo Wellcome Confirmation of methodology and data not obtained User-defined number: 1200

Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	Yes	See Appendix 3
Allocation concealment?	Yes	See Appendix 3
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

Woolcock 1996a

Methods	Parallel-group, multicentre study (72 centres in 14 countries). Three groups of which 2 are considered here Jadad quality score = 5
Participants	Symptomatic asthmatic adults % ELIGIBLE OF SCREENED POPULATION: Not reported % RUN-IN PARTICIPANTS RANDOMISED: 75 RANDOMISED: 495 (BDP 1000: 251; BDP 500 + Salm 100: 244) WITHDRAWALS: BDP 1000: 35; BDP500 + Salm 100: 29 AGE: mean (range): 44 (17 to 75) GENDER (% male): 52.5 SEVERITY: Moderate BASELINE % PREDICTED FEV1 mean: 73 BASELINE DOSE OF ICS : BDP 800 to 1000 or equivalent ASTHMA DURATION: Not described ATOPY (%): Not described

	ELIGIBILITY CRITERIA: Male and female patients at least 17 years; receiving 400 to 500 mcg bid of BDP or equivalent CRITERIA FOR RANDOMISATION FOLLOWING RUN-IN: FEV1 or mean PEF over the 7 days prior to randomisation > 50% predicted; 15% improvement in baseline FEV1 following inhaled salbutamol; either a total daytime symptom score >= 2, diurnal variation in PEF > 15% or use of rescue salbutamol >= 4 times/24 hours on 4 of the 7 days immediately prior to randomisation EXCLUSION CRITERIA: Change in asthma medication; hospitalisation for asthma or upper respiratory tract infection requiring antibiotics or a lower respiratory tract infection in the previous month; maintenance oral or parenteral corticosteroids
Interventions	LABA + ICS versus INCREASED dose of ICS OUTCOMES: Reported at 4,8,16 and 24 weeks RUN-IN PERIOD #1: 1 week for patients receiving beclomethasone 500 mcg bid; 4 weeks for patients receiving beclomethasone 400 mcg bid or other steroid equivalent RUN-IN PERIOD #2: 1 week (baseline period) DOSE OF ICS DURING RUN-IN: BDP 500 bid TREATMENTGROUP: (Salm 100 + BDP 500) salmeterol 100 mcg bid + beclomethasone 500 mcg bid CONTROL GROUP: (BDP 1000) beclomethasone 1000 mcg bid DEVICE: Metered dose inhaler NUMBER OF DEVICES: 2 COMPLIANCE: Not reported CO-TREATMENT: prn SABA. Usual doses of methylxanthines - sodium cromoglycate and inhaled anticholinergics
Outcomes	PULMONARY FUNCTION TEST: am PEF predicted; pm PEF predicted; FEV1; bronchial hyper-responsiveness (PD20) SYMPTOM SCORES: Score of 0 to 5 FUNCTIONAL STATUS: Symptom-free days; % nights with no awakenings; % rescue-free days; exacerbations (defined as any worsening of asthma symptoms requiring a change in prescribed therapy other than an increase in rescue medication); number of patients requiring hospitalisation INFLAMMATORY MARKERS: Not described ADVERSE EFFECTS: Described WITHDRAWALS: Described Primary outcome measure: Not reported
Notes	Full-text publication Funded by Glaxo Research and Development Confirmation of methodology and data confirmed User-defined number: 1000

Risk of bias

Item	**Authors' judgement**	**Description**
Adequate sequence generation?	Yes	Computer-generated random numbers. See Appendix 3
Allocation concealment?	Yes	Numbered coded solutions supplied by pharmacy. See Appendix 3
Blinding? All outcomes	Yes	Identical placebo devices
Incomplete outcome data addressed? All outcomes	Unclear	"The Intent-to-Treat (ITT) Population consisted of all subjects randomised to treatment and was used for the assessment of efficacy and safety."
Free of selective reporting?	No	OCS-treated exacerbations not available for meta-analysis after request

Woolcock 1996b

Methods	See Woolcock 1996a
Participants	See Woolcock 1996a, except for RANDOMISED: 494 (BDP500 + Salm 50: 243; BDP 1000: 251) WITHDRAWALS: BDP500 + Salm 50: 25; BDP 1000: 35)

	AGE: mean (range): 43 (17 to 79) GENDER (% male): 52.5 SEVERITY: Moderate BASELINE % PREDICTED FEV1 mean: 73.5
Interventions	LABA ICS versus INCREASED dose of ICS See Woolcock 1996a, except for: TEST GROUP: (Salm 50 + BDP 500) salmeterol 50 mcg bid + beclomethasone 500 mcg bid
Outcomes	See Woolcock 1996a
Notes	Full-text publication Funded by Glaxo Research and Development Confirmation of methodology and data confirmed User-defined number: 1000

Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	Yes	See Appendix 3
Allocation concealment?	Yes	See Appendix 3
Blinding? All outcomes	Yes	See Woolcock 1996a
Incomplete outcome data addressed? All outcomes	Unclear	See Woolcock 1996a
Free of selective reporting?	No	See Woolcock 1996a

Zhong 2005

Methods	Parallel-group, multicentre study (21 centres in China) Jadad quality score = 2
Participants	Symptomatic asthmatic adults % ELIGIBLE OF SCREENED POPULATION: Not reported % RUN-IN PARTICIPANTS RANDOMISED: Not reported RANDOMISED: 398 (FP/SAL: 202; BUD: 169) WITHDRAWALS: FP/SAL: 20; BUD: 18 AGE: mean (range): 46 (44 to 47) GENDER (% male): 54 SEVERITY: Unclear BASELINE % PRED FEV1: Not reported BASELINE DOSE OF ICS: Not reported ASTHMA DURATION: Not reported ATOPY (%): Not reported ELIGIBILITY CRITERIA: 18 to 70 years; symptom score > 2 on 4 of last 7 days of run-in; documented reversibility to SABA-FEV1 40% to 85% predicted EXCLUSION CRITERIA: Not reported
Interventions	LABA + ICS versus INCREASED dose ICS OUTCOMES TIMING: 6 weeks RUN-IN: 2 weeks DOSE OF ICS DURING RUN-IN: Not specified (routine ICS and prn SABA for duration of run-in) INTERVENTION PERIOD: 6 weeks TEST GROUP: Combination fluticasone and salmeterol 100/50 mcg bid CONTROL GROUP: Budesonide 400 mcg bid DEVICE: FP/SAL: Accuhaler; BUD: Turbuhaler 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: Not reported INFLAMMATORY MARKERS: Not reported

	ADVERSE EFFECTS: Reported WITHDRAWALS: Reported by treatment group 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: Obtained for methods, not obtained for data User defined number: 800

Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	Yes	See Appendix 3
Allocation concealment?	Yes	See Appendix 3
Blinding? All outcomes	No	Open label study
Incomplete outcome data addressed? All outcomes	Unclear	"The Intent-to-Treat (ITT) population for analysis included all the subjects who were randomised and received at least one dose of study medication, and who had no post-treatment efficacy data recorded (ITT). This population was used for statistical analysis and summaries of efficacy data."
Free of selective reporting?	Unclear	Not clear whether OCS-treated exacerbations collected in the study

ATS = American Thoracic Society

BDP = beclomethasone

bid = twice a day

BUD = budesonide

ED = emergency department

F = formoterol

FEV1 = forced expiratory volume in one second

Form = formoterol

FP = fluticasone

GSK = GlaxoSmithKline

ICS = inhaled corticosteroids

ITT = intention-to-treat

LABA = long-acting ß2 agonist

mcg = microgram

qd = four times a day

RTI = respiratory tract infection

SABA = short-acting ß2 agonist

SAL = salmeterol

Salm = salmeterol

SL = salmeterol

URTI = upper respiratory tract infection

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
AkpinarLi 1999	LABA added to same dose of ICS
Ankerst 2003	Cross-over study of inadequate duration
Anonymous 1999	Wrong type of beta-agonist
Anonymous a 2003	Control intervention not ICS alone
Anonymous b 2003	Review article
Anonymous c 2003	Description of SMART trial
Arvidsson 1991	Control intervention not inhaled glucocorticoids alone
Aubier 1999	The treatment and intervention groups compared the same classes of medications either in combination or with different delivery devices
Aziz 1998	Inadequate duration
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
Baki 1998	No consistent intervention with ICS
Balachandran 2001	Review article
Balzano 2002	Review article
Bateman 1998	Intervention and control groups compared the same medications either in combination or with different delivery devices
Bateman 2001	Both the treatment and intervention groups compared ICS and LAB2 agonists, using different propellants (FP/SAL delivered as HFA MDI, FP as CFC Diskus)
Baumgarten 2002	Non-randomised before and after study
Beckett 2003	Mixed population at baseline
Beeh 2002	Not randomised
Behling 1999	Inadequate duration
Bennett 2002	Review article
Bensch 2002	ICS in control groups not increased
Berggren 2001	Intervention not regular but prn inhaled long-acting beta2-agonists
Berlinski 2001	Assessment of different inhaler devices
Bernstein 2002	Not randomised
Bessmertny 2002	Intervention not LAB2 agonists
Bijl-Hofland 2001	No consistent co -treatment with ICS
Bjermer 2000	Control intervention not inhaled glucocorticoids alone but montelukast
Boonsawat 2003	Outcome measures not asthma control
Booth 1993	No consistent co-intervention with ICS
Boulet 1998	No prior ICS exposure

Study	Reason for exclusion
Boyd 1995	Addition of LABA to ICS compared to same dose ICS
Brambilla 1994	Control intevention not ICS but rather slow-release oral beta2-agonist
Braunstein 2002	Review article
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
Brogden 1991	Not randomised
Buchvald 2003	No group receiving ICS alone
Buhl 2003a	Addition of LABA to ICS compared to same dose ICS
Buhl 2003b	No regular LABA
Buhl 2003c	Addition of LABA to ICS compared to same dose ICS
Busse 1999	Control intervention not inhaled glucocorticoids alone
Byrnes 2000	Control intervention not inhaled glucocorticoids alone
Calhoun 2001	Control intervention is not ICS (but rather anti-leukotrienes)
Calverley 2002	Not asthma
Castle 1993	Not randomised
Cazzola 2000	Not asthma
Chalmers 1999	Inadequate duration
Chan 2001	I ntervention not regular inhaled long -acting beta2- agonist
Chapman 1999	Tx and Intervention compared LAB2 and ICS but in combined vs concurrent devices
Cheer 2003	Review article
Chuchalin 2002	Addition of LABA to ICS compared to same dose ICS
Chuchalin 2008	Steroid naive patients
Cloosterman 2001	No consistent co-intervention with ICS Control intervention is not ICS alone (but rather regular short-acting beta2-agonist)
Condemi 2001	Control intervention not ICS alone (but rather another LAB2)
Creticos 1999	Addition of LABA to ICS compared to same dose ICS
Crompton 1999	Control intervention not ICS alone but oral bambuterol
Currie 2003a	Inadequate duration
Currie 2003b	Co -intervention with non -permitted treatment
Currie 2003c	Assessment of anti-leukotriene agent in asthma
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
D'Urzo 2001	Addition of LABA to ICS compared to same dose ICS
Dahl 1989	Intervention not i nhaled LAB2
Dahl 1991	No consistent co-treatment with ICS
Dal Negro 2001a	Not randomised
Dal Negro 2001b	The treatment and intervention groups compared the same medications either in combination or with different delivery devices

Study	Reason for exclusion
Dal Negro 2002	Not randomised
Davis 2001	Not randomised
Dekhuijzen 2002	Review article on anti-leukotriene agent
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)
Dente 2001	Not randomised
Di Franco 1999	Addition of LABA to ICS compared to same dose ICS
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
Dorinsky 2001	Not randomised
Dorinsky 2002	ICS given at same dose in both groups
Durham 1999	Review article
Ek 2000	Healthy volunteers
Eliraz 2001a	Inadequate duration
Eliraz 2001b	LABA compared with different inhaler devices
Eliraz 2002	Not randomised
Ericsson 2001	Not randomised
Everden 2002	The treatment and intervention groups compared the same medications either in combination or with different delivery devices
Faurschou 1994	Duration < 30 days
Faurschou 1996	Control intervention not ICS alone (but regular SAB2)
Fish 2001	Control intervention is not ICS (but rather anti-leukotrienes)
Fitzgerald 1999	Addition of LABA to ICS compared to same dose ICS
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
Fuglsang 1995	Duration < 30 days
Garcia-Marcos 2003	Review article
Gardiner 1994	Addition of LABA to ICS compared to same dose ICS
Gessner 2003	Before and after study
Giannini 1996	Inadequate duration
Giannini 1998	Inadequate duration
Giannini 1999	Duration < 30 days
Giannini 2000	Duration < 30 days
Giannini 2001	Inadequate duration
Giannini 2002	No consistent intervention with inhaled glucocorticoids in all subjects
Gizycki 2000	No consistent intervention with inhaled glucocorticoids in all subjects
GOAL	Assessment of combination therapy against same dose ICS
Gold 2001	Control intervention not inhaled glucocorticoids alone

Study	Reason for exclusion
Grootendorst 2001	Before and after study
Grutters 1999	Addition of LABA to ICS compared to same dose ICS
Gustafsson 1994	Tx and intervention compared ICS + LAB2 combination therapy using 2 different devices
Hacki 2001	Review article
Hasani 2003	No consistent intervention with inhaled glucocorticoids in all subjects
Heyneman 2002	Review article
Hultquist 2000	Addition of LABA to ICS compared to same dose ICS
Ind 2002	No ICS alone
Isabelle 2001	Not randomised
Jarvis 1999	Review article
Jeffery 2002	Control intervention not inhaled glucocortocoids alone
Jenkins 2002a	The treatment and intervention groups compared the same medications either in combination or with different delivery devices
Jenkins 2002b	The treatment and intervention groups compared the same medications either in combination or with different delivery devices
Johansson 1999	Same dose ICS given to both treatment groups
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)
Kalra 1996	Duration < 30 days
Kardos 2001	Tx and intervention compared ICS + LAB2 in a fixed versus flexible schedule
Kavuru 2000	Addition of LABA to ICS compared to same dose ICS
Keating 2002	Review article
Keith 2001	Combination versus combination
Kemp 1984	Comparison of beta-agonist with theophylline
Kemp 1998	Addition of LABA to ICS compared to same dose ICS
Ketchell 2002	Duration of intervention < 30 days
Kidney 1995	No consistent intervention with inhaled glucocorticoids in all subjects
Kirby 2000	Subjects not asthmatics
Knobil 2000	Control intervention not inhaled glucocorticoids alone
Knorr 2001	Intervention is not LAB2 (but rather an anti-leukotriene agent: montelukast)
Kopp 2002	Review article
Kraft 2003	No consistent co-treatment with ICS
Kuna 2002	Review article
LaForce 1994	Not randomised
Lai 1995	Control intervention was not ICS alone but regular short-acting beta2-agonist instead of placebo Duration of intervention < 30 day: the treatment period was only 2 weeks long Co-intervention with non-permitted drugs: oral steroids
Lange 2001	Inadequate duration
Langton Hewer 1995	Addition of LABA to ICS compared to same dose ICS
Lazarus 2001	No consistent co-intervention with ICS - intervention is monotherapy with LAB2

Study	Reason for exclusion
Leblanc 1996	Addition of LABA to ICS compared to same dose ICS
Lemanske 2001	Complicated protocol. No data provided for comparison groups of interest
Lenney 1995	Not randomised
LHSRG 2000	Subjects have COPD
Lindqvist 2001	No consistent co- treatment with ICS
Lipworth 1998	Inadequate duration
Lipworth 1999a	Not randomised
Lipworth 1999b	Inadequate duration
Lipworth 2000 a	Inadequate duration
Lipworth 2000 b	Inadequate duration
Lipworth 2002	Correspondence
Lockey 1999	No consistent co-intervention with inhaled corticosteroids
Lowhagen 2002	Intervention not regular inhaled long-acting beta2-agonists
Lucioni 2002	Economic evaluation
Lötvall 2002	Comparison of the onset of different combination therapies
Magadle 2001	Duration < 30 days
Malmqvist-Granlund 2000	Not randomised
Malolepszy 2002	Control intervention not ICS (but oral theophylline)
McCarthy 2000	Control intervention not inhaled glucocorticoids alone
McCarthy 2002	Not randomised
Mcivor 1998	No consistent co-treatment with a stable dose of ICS (tapering)
Meier 1997	Open cohort study
Meijer 1995	Addition of LABA to ICS compared to same dose ICS
Michel 2000	Duration < 30 days
Midgren 1992	Control intervention not ICS alone
Miraglia del Giudice	No prior ICS exposure
Molimard 2001	Addition of LABA to ICS compared to same dose ICS
Murray 1998	No consistent intervention with inhaled glucocorticoids in all subjects
Nagel 2002	Duplicate
Nathan 1998	Comparison of salmeterol and beclomethasone
Nathan 2001	Same dose of ICS given to both groups
Nelson 1999	Not randomised
Nelson 2000	No prior ICS exposure
Nelson 2001	Control intervention ICS alone (but LTRA - zafirlukast)
Nelson 2003	Addition of LABA to ICS compared to same dose ICS
Newnham 1995	No consistent co-treatment with ICS
Nielsen 1999	Not randomised
Nightingale 2002	Treatment and intervention groups compared the same medications either in combination or with different delivery devices
Norhaya 1999	Addition of LABA to ICS compared to same dose ICS

Study	Reason for exclusion
Nsouli 2001	Control intervention not inhaled glucocorticoids alone
O'Brian 2001	Duration of intervention < 30 days
O'Connor 2002	Retrospective study
Orsida 2001	Control population did not have asthma
Palmer 1992	Control intervention is not ICS alone: both treatment groups received long-acting beta2-agonists but in different doses
Palmqvist 2001	Both the treament and control groups compared ICS and LAB2 with different drugs and inhaler devices
Paterson 1999	Treatment and intervention groups compared the same medications either in combination or with different delivery devices
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 Control intervention was not ICS but short-acting beta2-agonist
Pearlman 1994	No consistent co-treatment with ICS 26%
Pearlman 2001	Not randomised
Pearlman 2002	Control intervention is not ICS alone (but anti-leukotriene montelukast as maintenance)
Perez 2000	Overview of antileukotriene agent
Peters 2000	Control intervention is not ICS alone (but oral steroids, SAB2 and anticholinergics- in hospital setting)
Pifferi 2002	Before and after study
Pinnas 1998	No consistent intervention with inhaled glucocorticoids in all subjects
Pizzichini 1996	Duration < 30 days
Pljaskic-Kamenov 2000	Cannot determine prior ICS exposure
Pohl 2006	Adjustable dosing regimens
Pohunek 2006	Similar dose ICS
Price 2002	Addition of LABA to ICS compared to same dose ICS
Pujet 1995	Intervention is not LAB2 (but theophylline)
Pyke 2001	Comparison of LABA and ICS in separate versus combination devices
Rance 2002	Unable to determine eligibility from abstract details
Remington 2002	Review article
Rickard 1999	Outcomes measures did not reflect asthma control
Rickard 2001	Control intervention not inhaled glucocorticoids alone
Rijssenbeek-Nouwens	Intervention is not LAB2 (but anti-allergic casing)
Ringbaek 1996	Control intervention not ICS alone but oral SAB2 as maintenance
Ringdal 1997	Not randomised
Ringdal 2002	Comparison of combination ICS and LABA against separately administered ICS and LABA
Robert 2002	Control group did not receive increase in ICS dose
Rocca-Serra 2002	Intervention not regular long -acting beta2 -agonist
Rosenhall 2002	Treatment and intervention groups compared the same medications either in combination or with different delivery devices
Rosenhall 2003	Treatment and intervention groups compared the same medications either in combination or with different delivery devices
Rosenthal 1999	No consistent co-intervention with ICS

Study	Reason for exclusion
Roth 2002	In vitro study
Russell 1995	Addition of LABA to ICS compared to same dose ICS
Saari 2002	Before and after study
SAM40034	Steroid naive patients
SAM40036	Steroid naive patients
SAS30015	Comparison between combination HFA and CFC BDP
Schreurs 1996	No consistent co-intervention with ICS - 90% used regular ICS at entry
Seares 2003	Not randomised
Serrier 2003	Treatment and intervention groups compared the same medications either in combination or with different delivery devices
Shapiro 2000	Addition of LABA to ICS compared to same dose ICS
Shapiro 2001	Intervention is not LAB2
Sheth 2002	Control intervention not inhaled glucocorticoids alone
Sienra-Monge 2001	The treatment and intervention groups compared the same medications either in combination or with different delivery devices
Simons 1997 a	Addition of LABA to ICS compared to same dose ICS
Simons 1997 b	No consistent co-intervention with inhaled corticosteroids. Treatment groups compared ICS to longacting beta2-agonist alone
Sorkness 2007	Steroid naive patients
Sovani 2008	Comparison of combination therapy with best practice
Staehr 1995	Control intervention not ICS (but SAB2 maintenance)
Stanford 2002	Outcomes measures did not reflect asthma control
Stelmach 2002a	No co-intervention with ICS
Stelmach 2002b	No co-intervention with ICS
Stempel 2002	Non-randomised economic analysis
Stoloff 2002	Not randomised
Strand 2003	Sreroid naive patients
Tal 2003	Addition of LABA to ICS compared to same dose ICS
Tan 1997	Outcomes measures did not reflect asthma control
Tattersfield 2001	Intervention is not daily LAB2 (but rather on-demand LAB2)
Thomson 2003	Assessment of anti-leukotriene agents
Tonelli 2001	No consistent intervention with inhaled glucocorticoids in all subjects
Trautmann 2001	Not randomised
Turner 1998	No consistent co-intervention with ICS
Ullman 1990	Duration < 30 days
Vagaggini 1999	Asthma patients with different severities compared
Van Asperen 2002	Position statament on use of ICS
Van den Berg 2000	No consistent co-intervention with LAB2-both groups received LAB2 but compared delivery devices
Van der Molen 1997a	Addition of LABA to ICS compared to same dose ICS
Van der Woude 2001	The treatment and intervention groups compared the same medications either in combination or with different delivery devices

Study	Reason for exclusion
Van Noord 2001	Both the treament and control groups compared ICS and LAB2 with different inhaler devices
Verberne 1997	No consistent co-intervention with ICS - approximately 20% were taking regular ICS at entry
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	Outcome measures did not reflect asthma control
Von Berg 1989	Duration < 30 days
Wallaert 1999	Control intervention not ICS alone (but another LAB2)
Wallin 1990	Control intervention not ICS alone (but regular SAB2)
Wallin 2002	Comparison of ICS with LABA
Warner 2001	Review article of anti-leukotriene agents
Weersink 1997	Addition of LABA to ICS compared to same dose ICS
Weinstein 1998	No consistent co-intervention with ICS - only 57% were on ICS
Weinstein 2001	Not randomised
Wempe 1992	No consistent co-treatment with ICS
Wilcke 1998	Duration < 30 days
Wilding 1997	Not randomised
Wilson 2001a	Control intervention is not ICS alone (but rather ICS with an anti-leukotriene agent - montelukast)
Wilson 2001b	Not randomised
Wong 1992	Duration < 30 days
Woolcock 1995	Not randomised
Wooltorton 2003	Correspondence
Yancey 1997	Comparison of LABA with theophylline
Yates 1995	Duration < 30 days. No co-treatment with ICS.
Yates 1996	Duration < 30 days
Youngchaiyud 1995	Intervention not LAB2 (but theophylline)
Yurdakul 2002	Control intervention not regular inhaled long -acting beta2 -agonists alone
Zarkovic 1998	No consistent co-intervention with ICS Control intervention is placebo
Zetterstrom 2001	Addition of LABA to ICS compared to same dose ICS
Zhong 2002	Concomitant delivery versus combined delivery of ICS and LABA
Zimmerman 2004	Addition of LABA to ICS compared to same dose ICS

BDP = beclomethasone

COPD = chronic obstructive pulmonary disease

FEV1 = forced expiratory volume in one second

FP = fluticasone

ICS = inhaled corticosteroids

LABA = long-acting ß2 agonist

LTRA = leukotriene receptor agonist

SAB2 = short-acting ß2 agonist

SAL = salmeterol

DATA AND ANALYSES

Comparison 1

LABA + ICS versus higher dose ICS

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 # patients with exacerbations requiring oral steroids	25	9833	Risk Ratio (M-H, Fixed, 95% CI)	0.88 [0.78, 0.98]
1.1 Baseline FEV1 >= 80 % predicted	11	4755	Risk Ratio (M-H, Fixed, 95% CI)	0.97 [0.83, 1.13]
1.2 Baseline FEV1 61-79 % predicted	12	4106	Risk Ratio (M-H, Fixed, 95% CI)	0.81 [0.68, 0.95]
1.3 Baseline FEV1 <60% predicted	1	489	Risk Ratio (M-H, Fixed, 95% CI)	0.62 [0.36, 1.05]
1.4 Baseline FEV1 unclear	1	483	Risk Ratio (M-H, Fixed, 95% CI)	1.33 [0.30, 5.87]
2 # patients with exacerbations requiring hospitalisation	33	12573	Risk Ratio (M-H, Fixed, 95% CI)	1.02 [0.67, 1.56]
2.1 Baseline FEV1 >= 80 % predicted	8	2721	Risk Ratio (M-H, Fixed, 95% CI)	3.04 [0.48, 19.15]
2.2 Baseline FEV1 61-79 % predicted	20	8266	Risk Ratio (M-H, Fixed, 95% CI)	1.00 [0.63, 1.57]
2.3 Baseline FEV1 <= 60 % predicted	1	488	Risk Ratio (M-H, Fixed, 95% CI)	0.98 [0.06, 15.64]
2.4 Baseline FEV1 unclear	4	1098	Risk Ratio (M-H, Fixed, 95% CI)	0.33 [0.03, 3.18]
3 # withdrawals due to poor asthma control or exacerbation	29	10923	Risk Ratio (M-H, Fixed, 95% CI)	0.71 [0.56, 0.91]
3.1 Baseline FEV1 >= 80 % predicted	9	2443	Risk Ratio (M-H, Fixed, 95% CI)	0.65 [0.45, 0.93]
3.2 Baseline FEV1 61-79 % predicted	17	7111	Risk Ratio (M-H, Fixed, 95% CI)	0.81 [0.58, 1.12]
3.3 Baseline FEV1 <= 60 % predicted	1	488	Risk Ratio (M-H, Fixed, 95% CI)	0.14 [0.01, 2.71]
3.4 Baseline FEV1 predicted not reported	2	881	Risk Ratio (M-H, Fixed, 95% CI)	0.33 [0.01, 8.11]
4 Total # withdrawals	39	13654	Risk Ratio (M-H, Fixed, 95% CI)	0.92 [0.84, 1.00]
4.1 Baseline FEV1 >= 80 % predicted	9	2799	Risk Ratio (M-H, Fixed, 95% CI)	0.76 [0.61, 0.95]
4.2 Baseline FEV1 61-79 % predicted	23	8851	Risk Ratio (M-H, Fixed, 95% CI)	0.95 [0.86, 1.05]
4.3 Baseline FEV1 <= 60 % predicted	1	488	Risk Ratio (M-H, Fixed, 95% CI)	0.87 [0.56, 1.37]
4.4 Baseline FEV1 predicted not reported	6	1516	Risk Ratio (M-H, Fixed, 95% CI)	0.99 [0.73, 1.34]
5 # withdrawals due to adverse events	30	10017	Risk Ratio (M-H, Fixed, 95% CI)	0.99 [0.78, 1.26]
5.1 Baseline FEV1 >= 80 % predicted	9	2799	Risk Ratio (M-H, Fixed, 95% CI)	0.92 [0.48, 1.76]

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Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
5.2 Baseline FEV1 61-79 % predicted	18	6095	Risk Ratio (M-H, Fixed, 95% CI)	0.95 [0.72, 1.25]
5.3 Baseline FEV1 <= 60 % predicted	1	488	Risk Ratio (M-H, Fixed, 95% CI)	1.18 [0.37, 3.82]
5.4 Baseline FEV1 predicted not reported	2	635	Risk Ratio (M-H, Fixed, 95% CI)	2.35 [0.68, 8.08]
6 FEV1 at endpoint	11	2841	L (Fixed, 95% CI)	0.08 [0.03, 0.13]
6.1 Baseline FEV1 >= 80 % predicted	0	0	L (Fixed, 95% CI)	Not estimable
6.2 Baseline FEV1 61-79 % predicted	10	2841	L (Fixed, 95% CI)	0.09 [0.03, 0.14]
6.3 Baseline FEV1 <= 60 % predicted	0	0	L (Fixed, 95% CI)	Not estimable
6.4 Baseline FEV1 not reported	1	0	L (Fixed, 95% CI)	−0.14 [−0.50, 0.22]
7 FEV1 (predicted) at endpoint	7		Mean Difference (Fixed, 95% CI)	1.78 [0.39, 3.18]
7.1 Baseline FEV1 >= 80 % predicted	2		Mean Difference (Fixed, 95% CI)	4.46 [1.38, 7.53]
7.2 Baseline FEV1 61-79 % predicted	5		Mean Difference (Fixed, 95% CI)	1.10 [−0.46, 2.66]
8 Change in FEV1 at endpoint	22	8888	L (Fixed, 95% CI)	0.08 [0.06, 0.09]
8.1 Baseline FEV1 >= 80 % predicted	4	1798	L (Fixed, 95% CI)	0.07 [0.05, 0.10]
8.2 Baseline FEV1 61-79 % predicted	14	5874	L (Fixed, 95% CI)	0.09 [0.06, 0.11]
8.3 Baseline FEV1 <= 60 % predicted	1	478	L (Fixed, 95% CI)	0.01 [−0.07, 0.09]
8.4 Baseline FEV1 not reported	3	738	L (Fixed, 95% CI)	0.05 [−0.00, 0.11]
9 Change in FEV1 stratifying on treatment period	19		L (Fixed, 95% CI)	0.09 [0.08, 0.11]
9.1 At 6 +/− 2 weeks	5		L (Fixed, 95% CI)	0.09 [0.05, 0.13]
9.2 At 12 +/− 4 weeks	10		L (Fixed, 95% CI)	0.10 [0.08, 0.12]
9.3 At 24 +/− 4 weeks	8		L (Fixed, 95% CI)	0.09 [0.06, 0.12]
9.4 At 52 +/− 4 weeks	2		L (Fixed, 95% CI)	0.07 [0.03, 0.12]
10 Change in FEV1 (predicted) at endpoint	2		% (Fixed, 95% CI)	0.35 [−0.18, 0.87]
10.1 Baseline FEV1 >= 80 % predicted	1		% (Fixed, 95% CI)	0.28 [−0.25, 0.81]
10.2 Baseline FEV1 61-79 % predicted	1		% (Fixed, 95% CI)	3.9 [−0.01, 7.81]
11 Morning PEF at endpoint	14	2938	L/min (Random, 95% CI)	23.31 [18.09, 28.52]
11.1 Baseline FEV1 >= 80 % predicted	2	77	L/min (Random, 95% CI)	26.43 [−11.11, 63.97]
11.2 Baseline FEV1 61-79 % predicted	12	2861	L/min (Random, 95% CI)	23.86 [17.94, 29.77]
11.3 Baseline FEV1 <=60% predicted	0	0	L/min (Random, 95% CI)	Not estimable

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Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
12 Change in morning or clinic PEF at endpoint	30	11143	L/min (Random, 95% CI)	16.30 [13.48, 19.11]
12.1 Baseline FEV1 >= 80 % predicted	7	2314	L/min (Random, 95% CI)	11.74 [8.47, 15.00]
12.2 Baseline FEV1 61-79 % predicted	17	6788	L/min (Random, 95% CI)	18.64 [13.93, 23.34]
12.3 Baseline FEV1 <=60% pedicted	1	478	L/min (Random, 95% CI)	13.70 [4.13, 23.27]
12.4 Baseline FEV1 not reported	5	1563	L/min (Random, 95% CI)	16.30 [9.03, 23.56]
13 Morning PEF (% predicted) at endpoint	5	1646	Mean Difference (IV, Random, 95% CI)	3.45 [1.28, 5.63]
13.1 Baseline FEV1 >=80% predicted	4	1299	Mean Difference (IV, Random, 95% CI)	3.86 [1.37, 6.35]
13.2 Baseline FEV1 61-79% of predicted	1	347	Mean Difference (IV, Random, 95% CI)	1.0 [−4.68, 6.68]
14 Evening PEF at endpoint	4		L/min (Fixed, 95% CI)	16.79 [10.72, 22.85]
14.1 Baseline FEV1 >=80% predicted	1		L/min (Fixed, 95% CI)	4.0 [−37.59, 45.59]
14.2 Baseline FEV1 61-79% of predicted	3		L/min (Fixed, 95% CI)	17.07 [10.93, 23.20]
14.3 Baseline FEV1 <= 60 % predicted	0		L/min (Fixed, 95% CI)	Not estimable
15 Change in morning PEF (predicted)	0		% (Random, 95% CI)	Not estimable
15.1 Baseline FEV1 >= 80 % predicted	0		% (Random, 95% CI)	Not estimable
15.2 Baseline FEV1 61-79 % predicted	0		% (Random, 95% CI)	Not estimable
15.3 Baseline FEV1 <=60% predicted	0		% (Random, 95% CI)	Not estimable
15.4 Baseline FEV1 not reported	0		% (Random, 95% CI)	Not estimable
16 Change in evening PEF at endpoint	22	8544	L/min (Random, 95% CI)	13.70 [10.28, 17.12]
16.1 Baseline FEV1 >=80% predicted	6	2737	L/min (Random, 95% CI)	12.01 [7.99, 16.02]
16.2 Baseline FEV1 61-79% of predicted	11	4332	L/min (Random, 95% CI)	15.05 [8.98, 21.12]
16.3 Baseline FEV1 <=60% predicted	1	478	L/min (Random, 95% CI)	14.5 [5.47, 23.53]
16.4 Baseline FEV1 not reported	4	997	L/min (Random, 95% CI)	11.31 [3.85, 18.78]
17 Change in evening PEF predicted	0		% (Random, 95% CI)	Totals not selected
17.1 Baseline FEV1 >=80% predicted	0		% (Random, 95% CI)	Not estimable
17.2 Baseline FEV1 61-79% of predicted	0		% (Random, 95% CI)	Not estimable
17.3 Baseline FEV1 not reported	0		% (Random, 95% CI)	Not estimable

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
18 PEF variability at endpoint	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
18.1 Baseline FEV1 61-79 % predicted	1		Mean Difference (IV, Fixed, 95% CI)	Not estimable
19 Change in PEF variability at endpoint	7	2353	Mean Difference (IV, Fixed, 95% CI)	−4.55 [−6.32, −2.78]
19.1 Baseline FEV1 >= 80 % predicted	1	232	Mean Difference (IV, Fixed, 95% CI)	−5.4 [−7.83, −2.97]
19.2 Baseline FEV1 61-79 % predicted	4	1245	Mean Difference (IV, Fixed, 95% CI)	−4.66 [−7.95, −1.36]
19.3 Baseline FEV1 <= 60 % predicted	2	876	Mean Difference (IV, Fixed, 95% CI)	−1.90 [−6.05, 2.26]
20 Change in daytime symptom score at endpoint	5	1965	Std. Mean Difference (IV, Fixed, 95% CI)	−0.26 [−0.35, −0.17]
20.1 Baseline FEV1 >= 80 % predicted	1	225	Std. Mean Difference (IV, Fixed, 95% CI)	−0.14 [−0.40, 0.13]
20.2 Baseline FEV1 61-79 % predicted	4	1740	Std. Mean Difference (IV, Fixed, 95% CI)	−0.27 [−0.37, −0.18]
20.3 Baseline FEV1 <= 60 % predicted	0	0	Std. Mean Difference (IV, Fixed, 95% CI)	Not estimable
21 Change in overall (24 hrs) symptom score at endpoint	6	2279	Std. Mean Difference (IV, Random, 95% CI)	−0.23 [−0.37, −0.08]
21.1 Baseline FEV1 >= 80 % predicted	1	558	Std. Mean Difference (IV, Random, 95% CI)	−0.12 [−0.29, 0.05]
21.2 Baseline FEV1 61-79 % predicted	4	1243	Std. Mean Difference (IV, Random, 95% CI)	−0.27 [−0.52, −0.03]
21.3 Baseline FEV1 % <= 60%	1	478	Std. Mean Difference (IV, Random, 95% CI)	−0.26 [−0.44, −0.08]
22 Change in % symptom-free days at endpoint	12	6039	% (Random, 95% CI)	9.18 [6.02, 12.33]
22.1 Baseline FEV1 >=80% predicted	3	1646	% (Random, 95% CI)	5.67 [2.87, 8.46]
22.2 Baseline FEV1 61-79% of predicted	8	3925	% (Random, 95% CI)	12.32 [8.44, 16.21]
22.3 Baseline FEV1 <=60% predicted	0	0	% (Random, 95% CI)	Not estimable
22.4 Baseline FEV1 % predicted not reported	1	468	% (Random, 95% CI)	1.9 [−1.18, 4.98]
23 % symptom-free days at endpoint	8	3901	Mean Difference (IV, Random, 95% CI)	5.81 [−1.14, 12.76]
23.1 Baseline FEV1 >= 80 % predicted	2	555	Mean Difference (IV, Random, 95% CI)	−2.38 [−6.92, 2.17]
23.2 Baseline FEV1 61-79 % predicted	5	2960	Mean Difference (IV, Random, 95% CI)	6.58 [−1.73, 14.90]
23.3 Baseline FEV1 % predicted not reported	1	386	Mean Difference (IV, Random, 95% CI)	18.80 [9.64, 27.96]
24 Daytime symptom score at endpoint	5	2465	Std. Mean Difference (IV, Random, 95% CI)	−0.28 [−0.67, 0.11]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
24.1 Baseline FEV1 >= 80 % predicted	1	48	Std. Mean Difference (IV, Random, 95% CI)	0.12 [−0.45, 0.69]
24.2 Baseline FEV1 61-79 % predicted	4	2417	Std. Mean Difference (IV, Random, 95% CI)	−0.38 [−0.84, 0.07]
25 Nighttime symptom score at endpoint	3	2082	Std. Mean Difference (IV, Fixed, 95% CI)	−0.24 [−0.49, 0.01]
25.1 Baseline FEV1 >= 80% predicted	1	48	Std. Mean Difference (IV, Fixed, 95% CI)	−0.16 [−0.73, 0.41]
25.2 Baseline FEV1 61-79 % predicted	2	2034	Std. Mean Difference (IV, Fixed, 95% CI)	−0.26 [−0.54, 0.02]
26 Change in nighttime symptom score at endpoint	2	710	Mean Difference (IV, Fixed, 95% CI)	−0.01 [−0.04, 0.01]
26.1 Baseline FEV1 61-79 % predicted	1	484	Mean Difference (IV, Fixed, 95% CI)	−0.01 [−0.04, 0.02]
26.2 Baseline FEV1 >= 80 % predicted	1	226	Mean Difference (IV, Fixed, 95% CI)	−0.08 [−0.19, 0.03]
27 % symptom-free nights at endpoint	2	580	Mean Difference (IV, Fixed, 95% CI)	−2.10 [−7.98, 3.79]
27.1 Baseline FEV1 >= 80 % predicted	1	231	Mean Difference (IV, Fixed, 95% CI)	1.60 [−8.49, 11.69]
27.2 Baseline FEV1 61-79 % predicted	1	349	Mean Difference (IV, Fixed, 95% CI)	−4.0 [−11.24, 3.24]
28 Change in night time awakenings (number of nights) at endpoint	7	3172	Std. Mean Difference (IV, Fixed, 95% CI)	−0.03 [−0.10, 0.04]
28.1 Baseline FEV1 >= 80 % predicted	1	558	Std. Mean Difference (IV, Fixed, 95% CI)	0.03 [−0.13, 0.20]
28.2 Baseline FEV1 61-79 % predicted	4	167	Std. Mean Difference (IV, Fixed, 95% CI)	−0.07 [−0.16, 0.03]
28.3 Baseline FEV1 <= 60 % predicted	1	478	Std. Mean Difference (IV, Fixed, 95% CI)	0.03 [−0.15, 0.20]
28.4 Baseline FEV1 % predicted not reported	1	469	Std. Mean Difference (IV, Fixed, 95% CI)	Not estimable
29 % nighttime awakenings at endpoint	2	2175	Mean Difference (IV, Fixed, 95% CI)	−0.40 [−0.55, −0.25]
29.1 Baseline FEV1 61-79% predicted	2	2175	Mean Difference (IV, Fixed, 95% CI)	−0.40 [−0.55, −0.25]
30 % nights with no awakenings at endpoint	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
30.1 Baseline FEV1 61-79 % predicted	1		Mean Difference (IV, Fixed, 95% CI)	Not estimable
31 Change in % nights with no awakenings at endpoint	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
31.1 Baseline FEV1 61-79 % predicted	1		Mean Difference (IV, Fixed, 95% CI)	Not estimable
32 Change in # daytime rescue inhalations at endpoint	5	3455	Mean Difference (IV, Random, 95% CI)	−0.48 [−0.77, −0.20]
32.1 Baseline FEV1 >= 80 % predicted	0	0	Mean Difference (IV, Random, 95% CI)	Not estimable

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
32.2 Baseline FEV1 61-79 % predicted	5	3455	Mean Difference (IV, Random, 95% CI)	−0.48 [−0.77, −0.20]
32.3 Baseline FEV1 <= 60 % predicted	0	0	Mean Difference (IV, Random, 95% CI)	Not estimable
33 Change in # nighttime rescue inhalations at endpoint	4	2980	Std. Mean Difference (IV, Random, 95% CI)	−0.13 [−0.21, −0.05]
33.1 Baseline FEV1 61-79 % predicted	4	2980	Std. Mean Difference (IV, Random, 95% CI)	−0.13 [−0.21, −0.05]
33.2 Baseline FEV1 <= 60 % predicted	0	0	Std. Mean Difference (IV, Random, 95% CI)	Not estimable
34 Absolute (or %) change in # rescue inhalations (per 24 hrs) at endpoint	12	4631	Std. Mean Difference (IV, Random, 95% CI)	−0.20 [−0.29, −0.11]
34.1 Baseline FEV1 >= 80% predicted	4	1870	Std. Mean Difference (IV, Random, 95% CI)	−0.14 [−0.23, −0.05]
34.2 Baseline FEV1 61-79 % predicted	6	1815	Std. Mean Difference (IV, Random, 95% CI)	−0.26 [−0.35, −0.17]
34.3 Baseline FEV1 <= 60 % predicted	1	478	Std. Mean Difference (IV, Random, 95% CI)	−0.42 [−0.60, −0.24]
34.4 Baseline FEV1 not reported	1	468	Std. Mean Difference (IV, Random, 95% CI)	0.12 [−0.07, 0.30]
35 # daytime rescue inhalations (puffs/day) at endpoint	5	544	Mean Difference (IV, Random, 95% CI)	−0.44 [−0.94, 0.06]
35.1 Baseline FEV1 >= 80 % predicted	2	278	Mean Difference (IV, Random, 95% CI)	−0.15 [−0.38, 0.07]
35.2 Baseline FEV1 61-79 % predicted	2	242	Mean Difference (IV, Random, 95% CI)	−1.44 [−1.96, −0.93]
35.3 Baseline FEV1 not reported	1	24	Mean Difference (IV, Random, 95% CI)	0.04 [−0.28, 0.36]
36 # nighttime rescue inhalations at endpoint (puffs/day)	4	941	Mean Difference (IV, Random, 95% CI)	−0.09 [−0.23, 0.04]
36.1 Baseline FEV1 >=80% predicted	2	714	Mean Difference (IV, Random, 95% CI)	−0.04 [−0.10, 0.01]
36.2 Baseline FEV1 61-79 % predicted	1	203	Mean Difference (IV, Random, 95% CI)	−0.74 [−1.13, −0.35]
36.3 Baseline FEV1 not reported	1	24	Mean Difference (IV, Random, 95% CI)	Not estimable
37 % overall rescue-free days at endpoint	3		Mean Difference (IV, Random, 95% CI)	Subtotals only
37.1 Baseline FEV1 61-79 % predicted	3	2516	Mean Difference (IV, Random, 95% CI)	5.14 [−2.79, 13.08]
38 Change in % symptom-free days at endpoint	1		% (Random, 95% CI)	−0.24 [−1.20, 0.72]
38.1 Baseline FEV1 >= 80% predicted	0		% (Random, 95% CI)	Not estimable
38.2 Baseline FEV1 61% to 79% of predicted	1		% (Random, 95% CI)	−0.24 [−1.20, 0.72]
38.3 Baseline FEV1 <= 60% predicted	0		% (Random, 95% CI)	Not estimable

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
38.4 Baseline FEV1 % predicted not reported	0		% (Random, 95% CI)	Not estimable
39 Change in mean % rescue-free days at endpoint	3	1332	Mean Difference (IV, Fixed, 95% CI)	11.48 [7.98, 14.98]
39.1 Baseline FEV1 >= 80 % predicted	1	558	Mean Difference (IV, Fixed, 95% CI)	5.40 [−0.14, 10.94]
39.2 Baseline FEV1 61% to 79% predicted	2	774	Mean Difference (IV, Fixed, 95% CI)	15.50 [10.99, 20.02]
40 Change in asthma control days at endpoint (%)	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
40.1 Baseline FEV1 >= 80 % predicted	1		Mean Difference (IV, Fixed, 95% CI)	Not estimable
41 Change in quality of life (AQLQ score) at endpoint	4	341	Mean Difference (IV, Fixed, 95% CI)	0.10 [−0.06, 0.26]
41.1 Baseline FEV1 61% to 79 % predicted	3	323	Mean Difference (IV, Fixed, 95% CI)	0.10 [−0.06, 0.26]
41.2 Baseline FEV1 not reported	1	18	Mean Difference (IV, Fixed, 95% CI)	0.18 [−0.72, 1.08]
42 Change in Hyland QOL at endpoint	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
42.1 Baseline FEV1 >= 80 % predicted	1		Mean Difference (IV, Fixed, 95% CI)	Not estimable
43 # Achieving good asthma control	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
43.1 Baseline FEV1 >= 80 % predicted	0		Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
43.2 Baseline FEV1 61% to 79 % predicted	1		Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
43.3 Baseline FEV1 <= 60 % predicted	0		Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
44 % asthma control days at endpoint	2		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
44.1 Baseline FEV1 61% to 79 % predicted	2		Mean Difference (IV, Fixed, 95% CI)	Not estimable
45 Serum ECP(microg /L)	2	87	Mean Difference (IV, Fixed, 95% CI)	0.62 [−2.45, 3.70]
45.1 Baseline FEV1 >= 80% predicted	1	48	Mean Difference (IV, Fixed, 95% CI)	−0.70 [−4.51, 3.11]
45.2 Baseline FEV1 61% to 79 % predicted	1	39	Mean Difference (IV, Fixed, 95% CI)	3.10 [−2.11, 8.31]
46 Plasma cortisol (nmol/L) 8am at 8 weeks	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
46.1 Baseline FEV1 61% to 79 % predicted	1		Mean Difference (IV, Fixed, 95% CI)	Not estimable
47 Tidal exhaled NO(ppb)	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
47.1 Baseline FEV1 61% to 79 % predicted	1		Mean Difference (IV, Fixed, 95% CI)	Not estimable

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
48 PD20 @ 8 weeks	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
48.1 Baseline FEV1 61% to 79 % predicted	1		Mean Difference (IV, Fixed, 95% CI)	Not estimable
49 PC20	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
49.1 Baseline FEV1 not reported	1		Mean Difference (IV, Fixed, 95% CI)	Not estimable
50 Change in mean urine Cortisol/ Creatinine ratio	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
50.1 Baseline FEV1 61% to 79 % predicted	1		Mean Difference (IV, Fixed, 95% CI)	Not estimable
51 Change in PC20	0		Doubl'g doses (Fixed, 95% CI)	Totals not selected
51.1 Baseline FEV1 >= 80 % predicted	0		Doubl'g doses (Fixed, 95% CI)	Not estimable
51.2 Baseline FEV1 61% to 79 % predicted	0		Doubl'g doses (Fixed, 95% CI)	Not estimable
51.3 Baseline FEV1 <= 60 % predicted	0		Doubl'g doses (Fixed, 95% CI)	Not estimable
51.4 Baseline FEV1 not reported	0		Doubl'g doses (Fixed, 95% CI)	Not estimable
52 Serious adverse events	35	13640	Risk Ratio (M-H, Fixed, 95% CI)	1.12 [0.91, 1.37]
52.1 Baseline FEV1 >= 80 % predicted	6	2345	Risk Ratio (M-H, Fixed, 95% CI)	0.82 [0.50, 1.34]
52.2 Baseline FEV1 61% to 79% predicted	18	7978	Risk Ratio (M-H, Fixed, 95% CI)	1.23 [0.97, 1.56]
52.3 Baseline FEV1 <= 60 % predicted	1	488	Risk Ratio (M-H, Fixed, 95% CI)	1.38 [0.44, 4.28]
52.4 Baseline FEV1 not reported	10	2829	Risk Ratio (M-H, Fixed, 95% CI)	0.77 [0.35, 1.72]
53 # patients with tremor	11	5562	Risk Ratio (M-H, Fixed, 95% CI)	1.84 [1.20, 2.82]
53.1 Baseline FEV1 >= 80 % predicted	1	233	Risk Ratio (M-H, Fixed, 95% CI)	0.15 [0.01, 2.90]
53.2 Baseline FEV1 61% to 79 % predicted	9	4841	Risk Ratio (M-H, Fixed, 95% CI)	2.03 [1.29, 3.19]
53.3 Baseline FEV1 <= 60% predicted	1	488	Risk Ratio (M-H, Fixed, 95% CI)	1.97 [0.18, 21.56]
54 # patients with oral thrush	14	7727	Risk Ratio (M-H, Random, 95% CI)	0.58 [0.40, 0.86]
54.1 Baseline FEV1 >= 80 % predicted	3	1427	Risk Ratio (M-H, Random, 95% CI)	0.38 [0.14, 1.05]
54.2 Baseline FEV1 61-79 % predicted	9	5329	Risk Ratio (M-H, Random, 95% CI)	0.74 [0.44, 1.24]
54.3 Baseline FEV1 <= 60 % predicted	1	488	Risk Ratio (M-H, Random, 95% CI)	0.33 [0.13, 0.81]
54.4 Baseline FEV1 predicted not reported	1	483	Risk Ratio (M-H, Random, 95% CI)	0.50 [0.05, 5.45]
55 Total # adverse events	30	11483	Risk Ratio (M-H, Random, 95% CI)	0.99 [0.95, 1.03]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
55.1 Baseline FEV1 >= 80 % predicted	7	2634	Risk Ratio (M-H, Random, 95% CI)	0.99 [0.90, 1.09]
55.2 Baseline FEV1 61-79 % predicted	17	7326	Risk Ratio (M-H, Random, 95% CI)	0.99 [0.93, 1.05]
55.3 Baseline FEV1<=60 % predicted	1	488	Risk Ratio (M-H, Random, 95% CI)	1.03 [0.95, 1.11]
55.4 Baseline FEV1 predicted not reported	5	1035	Risk Ratio (M-H, Random, 95% CI)	0.94 [0.83, 1.07]
56 # patients with adverse cardiovascular events	9	3439	Risk Ratio (M-H, Random, 95% CI)	0.99 [0.49, 2.01]
56.1 Baseline FEV1 >= 80 % predicted	1	233	Risk Ratio (M-H, Random, 95% CI)	0.27 [0.03, 2.34]
56.2 Baseline FEV1 61% to 79 % predicted	7	2718	Risk Ratio (M-H, Random, 95% CI)	1.04 [0.47, 2.29]
56.3 Baseline FEV1 <= 60% predicted	1	488	Risk Ratio (M-H, Random, 95% CI)	2.95 [0.31, 28.17]
57 # patients with headache	25	10824	Risk Ratio (M-H, Fixed, 95% CI)	1.02 [0.92, 1.12]
57.1 Baseline FEV1 >= 80 % predicted	6	2179	Risk Ratio (M-H, Fixed, 95% CI)	1.11 [0.96, 1.28]
57.2 Baseline FEV1 61% to 79 % predicted	15	7070	Risk Ratio (M-H, Fixed, 95% CI)	0.94 [0.82, 1.07]
57.3 Baseline FEV1 <= 60 % predicted	1	488	Risk Ratio (M-H, Fixed, 95% CI)	1.23 [0.70, 2.15]
57.4 Baseline FEV1 predicted not reported	3	1087	Risk Ratio (M-H, Fixed, 95% CI)	1.26 [0.70, 2.26]
58 # patients with hoarseness	9	4963	Risk Ratio (M-H, Fixed, 95% CI)	0.95 [0.79, 1.14]
58.1 Baseline FEV1 >/= 80% predicted	2	646	Risk Ratio (M-H, Fixed, 95% CI)	1.00 [0.82, 1.22]
58.2 Baseline FEV1 61% to 79 % predicted	4	2957	Risk Ratio (M-H, Fixed, 95% CI)	0.86 [0.54, 1.36]
58.3 Baseline FEV1 <= 60% predicted	1	488	Risk Ratio (M-H, Fixed, 95% CI)	0.98 [0.43, 2.23]
58.4 Baseline FEV1 predicted not reported	2	872	Risk Ratio (M-H, Fixed, 95% CI)	0.62 [0.16, 2.37]
59 # patients with tachycardia or palpitations	15	7284	Risk Ratio (M-H, Fixed, 95% CI)	1.20 [0.78, 1.84]
59.1 Baseline FEV1 >= 80 % predicted	1	233	Risk Ratio (M-H, Fixed, 95% CI)	0.15 [0.01, 2.90]
59.2 Baseline FEV1 61% to 79 % predicted	11	5691	Risk Ratio (M-H, Fixed, 95% CI)	1.11 [0.61, 2.02]
59.3 Baseline FEV1 <= 60 % predicted	1	488	Risk Ratio (M-H, Fixed, 95% CI)	6.89 [0.36, 132.62]
59.4 Baseline FEV1 predicted not reported	2	872	Risk Ratio (M-H, Fixed, 95% CI)	1.39 [0.70, 2.74]
60 Growth (paediatric data)	1		cm (Random, 95% CI)	Totals not selected

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Comparison 2

LABA + ICS versus higher dose ICS (subgroup and sensitivity analyses)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 # patients with exacerbations requiring oral steroids: children versus adults	25		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
1.1 Children	3	480	Risk Ratio (M-H, Fixed, 95% CI)	1.24 [0.58, 2.66]
1.2 Adults	23	9349	Risk Ratio (M-H, Fixed, 95% CI)	0.87 [0.78, 0.97]
2 # patients with exacerbations requiring oral steroids: ICS dose associated with LABA	25		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
2.1 ICS dose <=400 mcg/day or equivalent in LABA group	22	9388	Risk Ratio (M-H, Fixed, 95% CI)	0.86 [0.77, 0.97]
2.2 ICS dose 400-1000 mcg/day of BDP-equivalent in LABA group	3	445	Risk Ratio (M-H, Fixed, 95% CI)	1.21 [0.69, 2.12]
3 # patients with exacerbations requiring oral steroids: ICS dose difference between LABA and higher ICS groups	25		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
3.1 ICS dose difference of <= 400 mcg/day of BDP-equivalent	10	3081	Risk Ratio (M-H, Fixed, 95% CI)	0.84 [0.69, 1.03]
3.2 ICS dose difference of >= 500 mcg/day of BDP-equivalent	15	6752	Risk Ratio (M-H, Fixed, 95% CI)	0.89 [0.78, 1.02]
4 # patients with exacerbations requiring oral steroids: formoterol versus salmeterol	25		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
4.1 Formoterol	5	2861	Risk Ratio (M-H, Fixed, 95% CI)	1.00 [0.87, 1.16]
4.2 Salmeterol	20	6972	Risk Ratio (M-H, Fixed, 95% CI)	0.75 [0.63, 0.89]
5 # patients with exacerbations requiring oral steroids: 1 versus 2 devices to deliver LABA + ICS	25		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
5.1 One device (combination therapy)	11	5573	Risk Ratio (M-H, Fixed, 95% CI)	0.92 [0.77, 1.09]
5.2 Two devices (concomitant terapy)	14	4260	Risk Ratio (M-H, Fixed, 95% CI)	0.85 [0.73, 0.98]
6 # patients with exacerbations requiring oral steroids: duration of trial	24	9350	Risk Ratio (M-H, Fixed, 95% CI)	0.87 [0.78, 0.98]
6.1 <= 24 weeks	19	6503	Risk Ratio (M-H, Fixed, 95% CI)	0.74 [0.63, 0.89]
6.2 > 24 weeks	5	2847	Risk Ratio (M-H, Fixed, 95% CI)	1.00 [0.86, 1.15]
7 # patients with exacerbations requiring oral steroids: publication status of data	25		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
7.1 Data available from study report	9	2242	Risk Ratio (M-H, Fixed, 95% CI)	0.95 [0.78, 1.17]
7.2 Data available from correspondence or study sponsor trial report	16	7591	Risk Ratio (M-H, Fixed, 95% CI)	0.85 [0.74, 0.97]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
8 # patients with exacerbations requiring oral steroids: funding status	25		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
8.1 Manufacturer sponsorship	25	9833	Risk Ratio (M-H, Fixed, 95% CI)	0.88 [0.78, 0.98]
8.2 Non-manufacturer sponsorship	0	0	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
9 # patients with exacerbations requiring oral steroids: sensitivity analysis by allocation sequence generation	23	9229	Risk Ratio (M-H, Fixed, 95% CI)	0.87 [0.78, 0.98]
10 # patients with exacerbations requiring oral steroids: sensitivity analysis by allocation concealment	22	7527	Risk Ratio (M-H, Fixed, 95% CI)	0.78 [0.67, 0.91]
11 # patients with exacerbations requiring oral steroids: sensitivity analysis by blinding	23	9670	Risk Ratio (M-H, Fixed, 95% CI)	0.86 [0.77, 0.96]
12 # patients with exacerbations requiring hospitalisation: children versus adults	33		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
12.1 Adults	29	11215	Risk Ratio (M-H, Fixed, 95% CI)	0.87 [0.54, 1.38]
12.2 Children and adults	1	332	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
12.3 Children	4	1026	Risk Ratio (M-H, Fixed, 95% CI)	2.21 [0.74, 6.64]

Comparison 3

WMD archive

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 FEV1 (L) at endpoint	12	4688	Mean Difference (IV, Random, 95% CI)	0.08 [0.03, 0.14]
2 FEV1 (% predicted) at endpoint	5		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
3 Change in FEV1 (L) at endpoint	19		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
4 Change in FEV1 (L) stratifying on treatment period	10		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
4.1 At 6 +/− 2 weeks	4	1346	Mean Difference (IV, Fixed, 95% CI)	0.11 [0.06, 0.15]
4.2 At 12 +/− 4 weeks	8	3484	Mean Difference (IV, Fixed, 95% CI)	0.09 [0.07, 0.11]
4.3 At 24 +/− 4 weeks	4	1463	Mean Difference (IV, Fixed, 95% CI)	0.10 [0.06, 0.14]
4.4 New Subgroup	0	0	Mean Difference (IV, Fixed, 95% CI)	Not estimable
5 Morning PEF (L/min) at endpoint	14		Mean Difference (IV, Random, 95% CI)	Totals not selected
6 Evening PEF (L/min) at endpoint	3	425	Mean Difference (IV, Fixed, 95% CI)	20.18 [12.75, 27.62]

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Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
6.1 Baseline FEV1 >= 80% predicted	1	48	Mean Difference (IV, Fixed, 95% CI)	4.0 [−37.59, 45.59]
6.2 Baseline FEV1 61% to 79 % predicted	2	377	Mean Difference (IV, Fixed, 95% CI)	20.72 [13.16, 28.27]
7 Change in morning or clinic PEF (L/min) at endpoint	28	10784	Mean Difference (IV, Random, 95% CI)	16.25 [13.59, 18.90]
8 Change in evening PEF (L/min) at endpoint	18		Mean Difference (IV, Random, 95% CI)	Totals not selected
9 Change in FEV1 (% predicted) at endpoint	2	467	Mean Difference (IV, Random, 95% CI)	1.55 [−1.84, 4.94]
9.1 Baseline FEV1 >= 80 % predicted	1	120	Mean Difference (IV, Random, 95% CI)	0.28 [−0.25, 0.81]
9.2 Baseline FEV1 61% to 79 % predicted	1	347	Mean Difference (IV, Random, 95% CI)	3.90 [−0.01, 7.81]
10 Change in % symptom-free days at endpoint	11	4470	Mean Difference (IV, Random, 95% CI)	9.66 [6.04, 13.29]
11 # patients with exacerbations requiring oral steroids	25	9833	Risk Ratio (M-H, Fixed, 95% CI)	0.88 [0.78, 0.98]

Analysis 1.1. Comparison 1 LABA + ICS versus higher dose ICS, Outcome 1 # patients with exacerbations requiring oral steroids

Review: Addition of long-acting beta2-agonists to inhaled steroids versus higher dose inhaled steroids in adults and children with persistent asthma

Comparison: 1 LABA + ICS versus higher dose ICS

Outcome: 1 # patients with exacerbations requiring oral steroids

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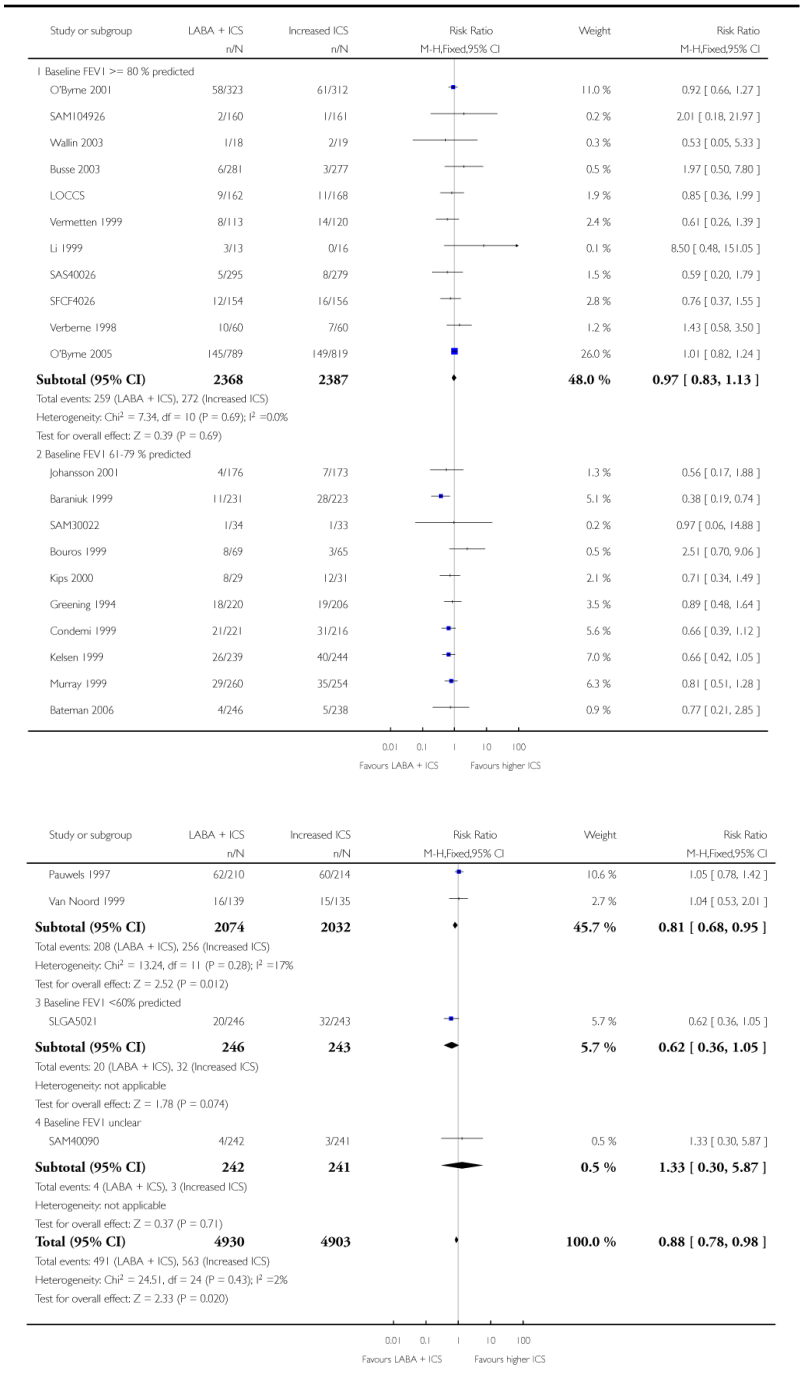
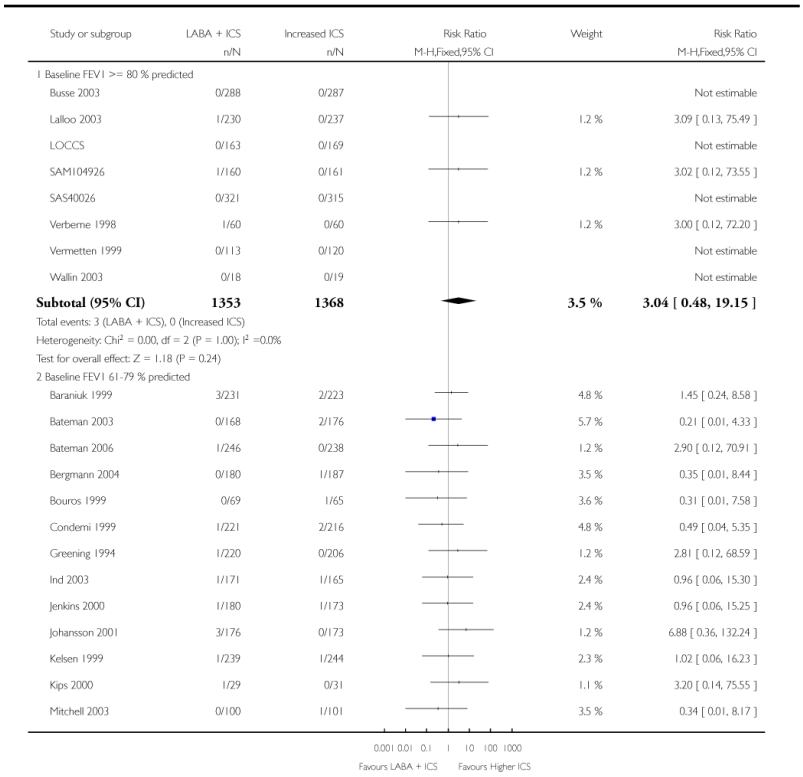


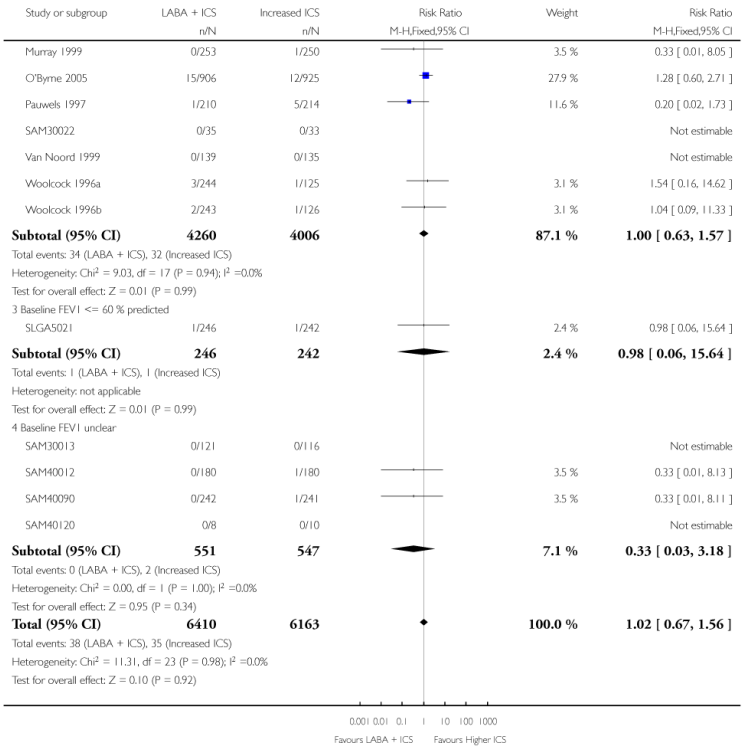
Analysis 1.2. Comparison 1 LABA + ICS versus higher dose ICS, Outcome 2 # patients with exacerbations requiring hospitalisation

Review: Addition of long-acting beta2-agonists to inhaled steroids versus higher dose inhaled steroids in adults and children with persistent asthma

Comparison: 1 LABA + ICS versus higher dose ICS

Outcome: 2 # patients with exacerbations requiring hospitalisation





Analysis 1.3. Comparison 1 LABA + ICS versus higher dose ICS, Outcome 3 # withdrawals due to poor asthma control or exacerbation

Review: Addition of long-acting beta2-agonists to inhaled steroids versus higher dose inhaled steroids in adults and children with persistent asthma

Comparison: 1 LABA + ICS versus higher dose ICS

Outcome: 3 # withdrawals due to poor asthma control or exacerbation

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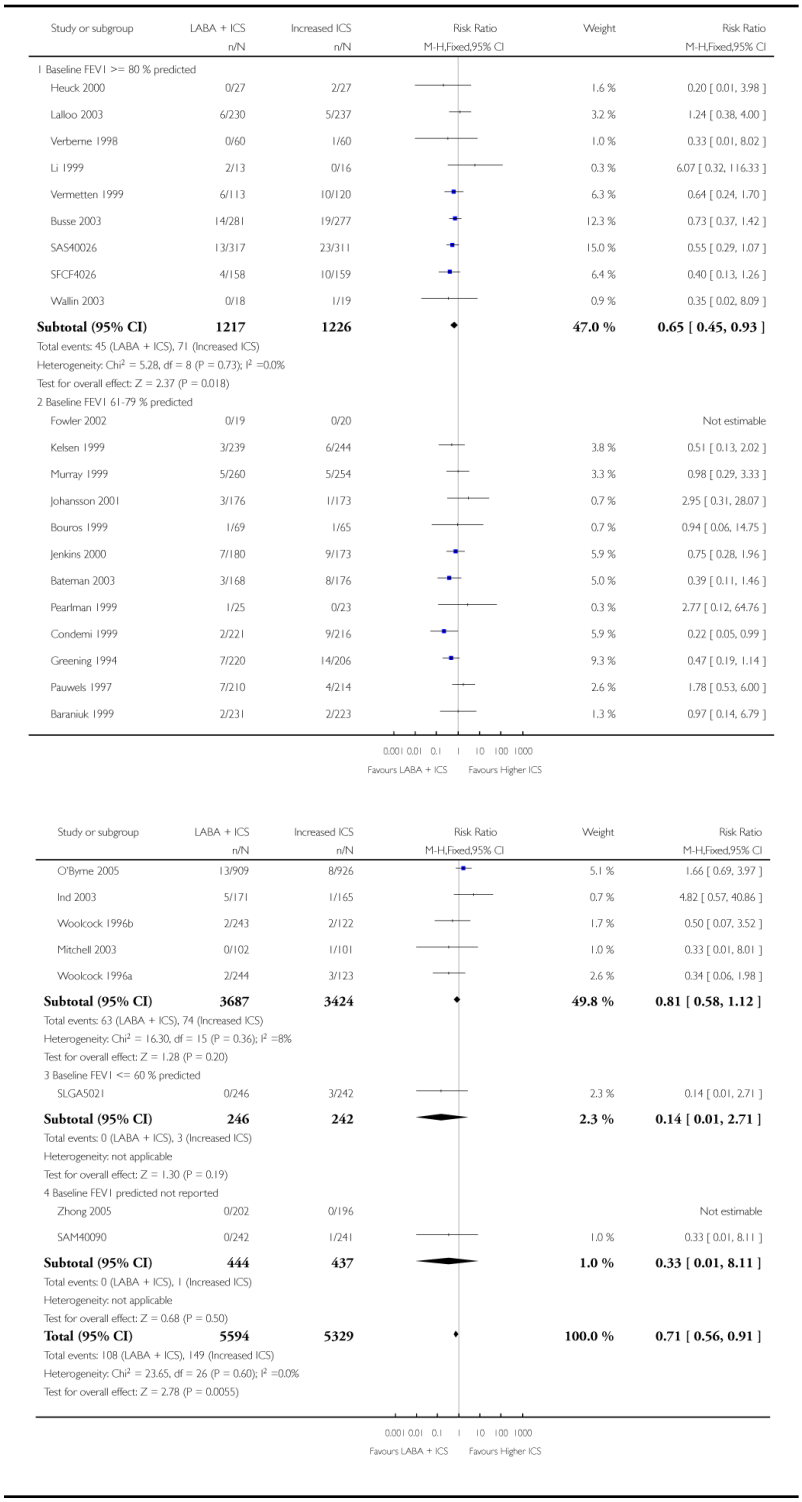

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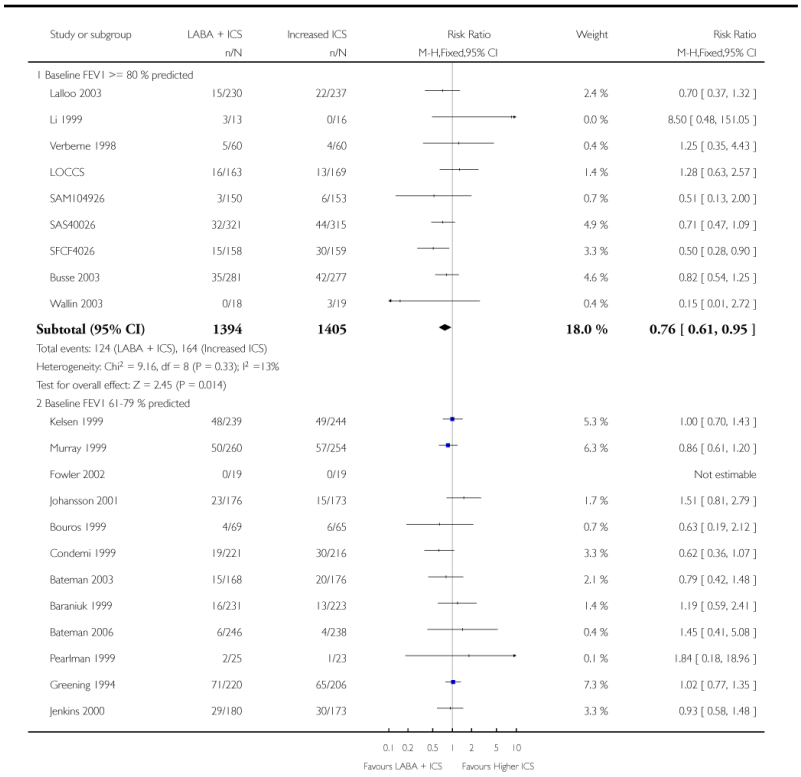
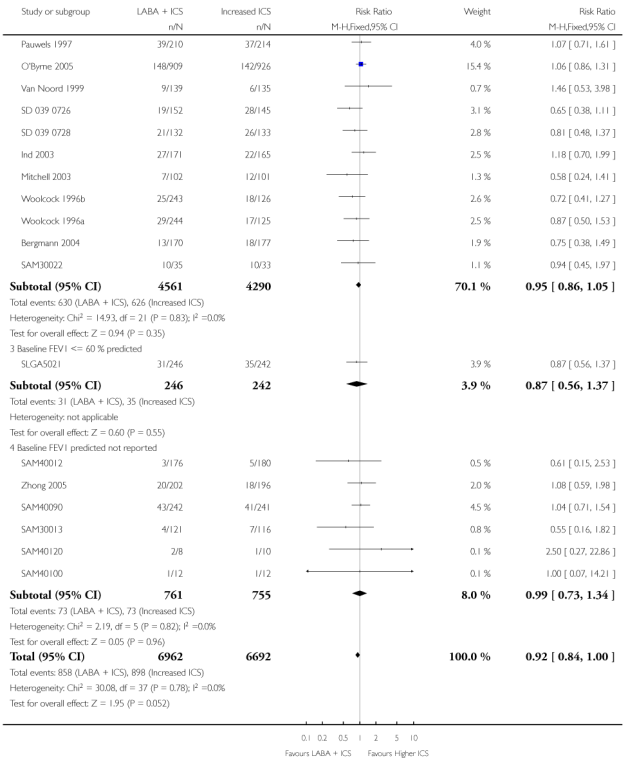
Analysis 1.4. Comparison 1 LABA + ICS versus higher dose ICS, Outcome 4 Total # withdrawals

Review: Addition of long-acting beta2-agonists to inhaled steroids versus higher dose inhaled steroids in adults and children with persistent asthma

Comparison: 1 LABA + ICS versus higher dose ICS

Outcome: 4 Total # withdrawals





Analysis 1.5. Comparison 1 LABA + ICS versus higher dose ICS, Outcome 5 # withdrawals due to adverse events

Review: Addition of long-acting beta2-agonists to inhaled steroids versus higher dose inhaled steroids in adults and children with persistent asthma

Comparison: 1 LABA + ICS versus higher dose ICS

Outcome: 5 # withdrawals due to adverse events

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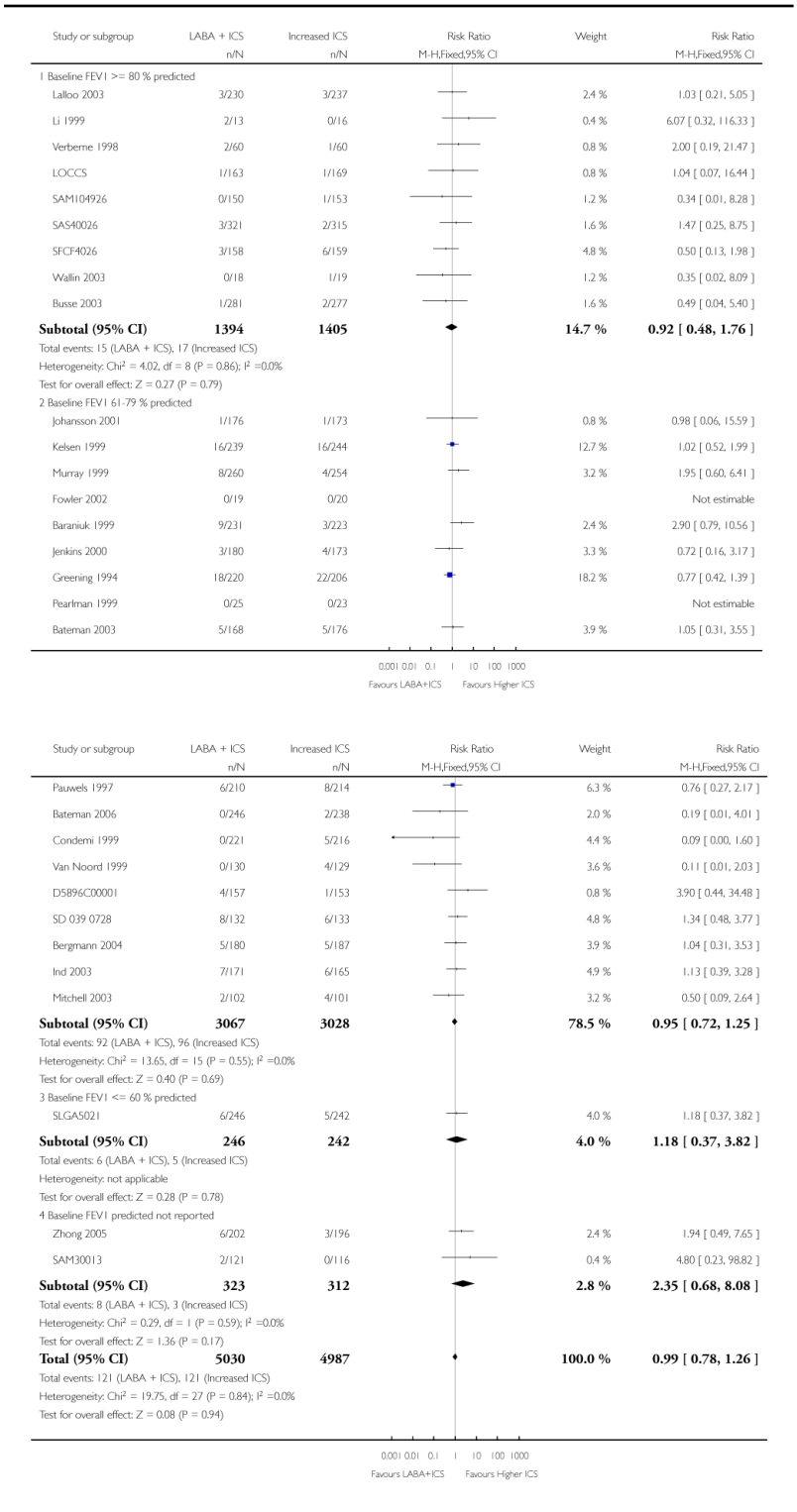

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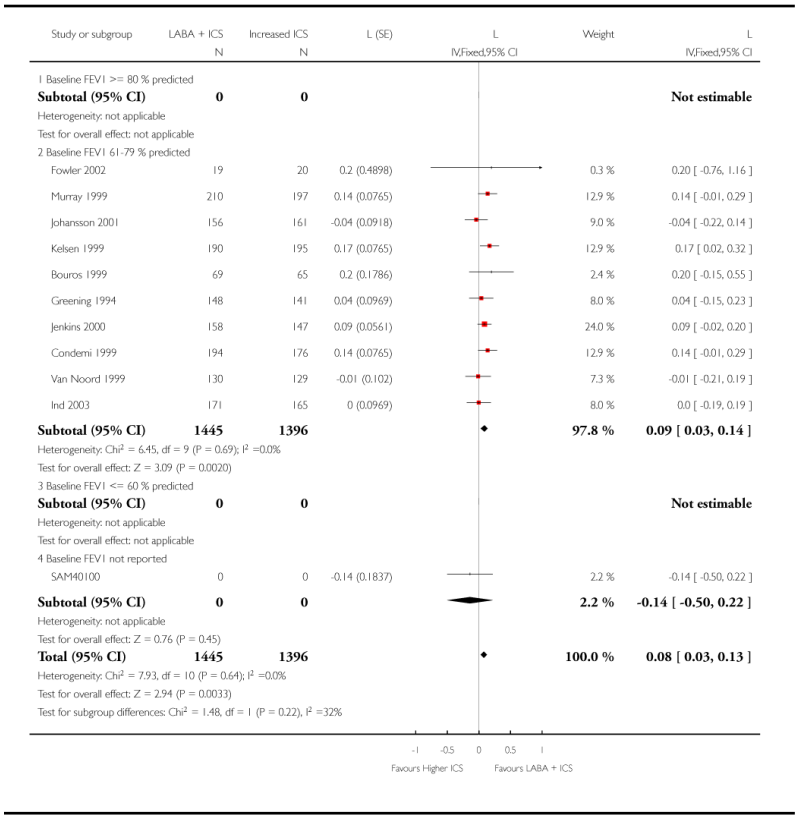
Analysis 1.6. Comparison 1 LABA + ICS versus higher dose ICS, Outcome 6 FEV1 at endpoint

Review: Addition of long-acting beta2-agonists to inhaled steroids versus higher dose inhaled steroids in adults and children with persistent asthma

Comparison: 1 LABA + ICS versus higher dose ICS

Outcome: 6 FEV1 at endpoint

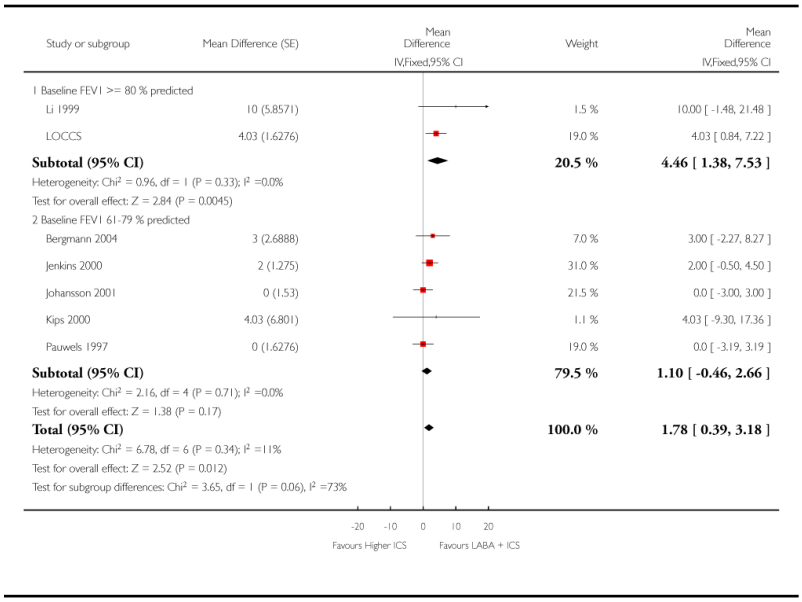


Analysis 1.7. Comparison 1 LABA + ICS versus higher dose ICS, Outcome 7 FEV1 (predicted) at endpoint

Review: Addition of long-acting beta2-agonists to inhaled steroids versus higher dose inhaled steroids in adults and children with persistent asthma

Comparison: 1 LABA + ICS versus higher dose ICS

Outcome: 7 FEV1 (predicted) at endpoint



Analysis 1.8. Comparison 1 LABA + ICS versus higher dose ICS, Outcome 8 Change in FEV1 at endpoint

Review: Addition of long-acting beta2-agonists to inhaled steroids versus higher dose inhaled steroids in adults and children with persistent asthma

Comparison: 1 LABA + ICS versus higher dose ICS

Outcome: 8 Change in FEV1 at endpoint

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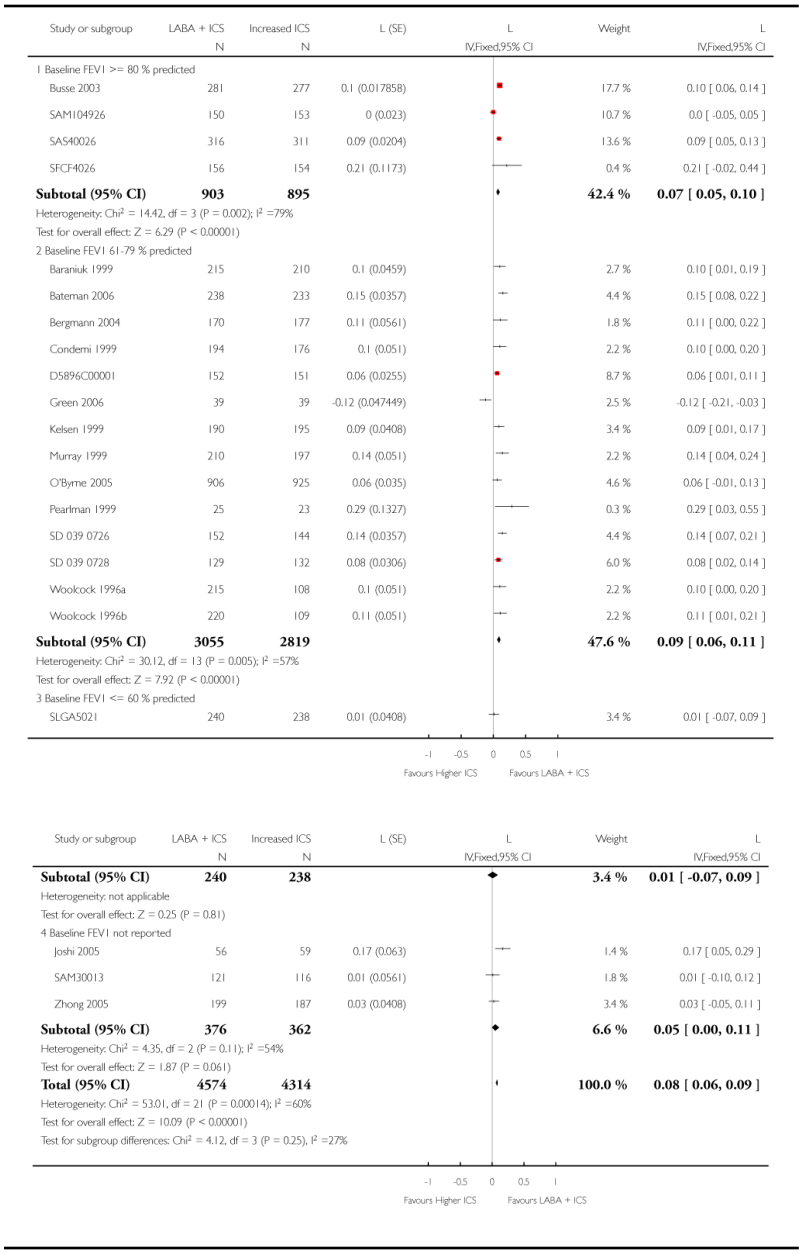
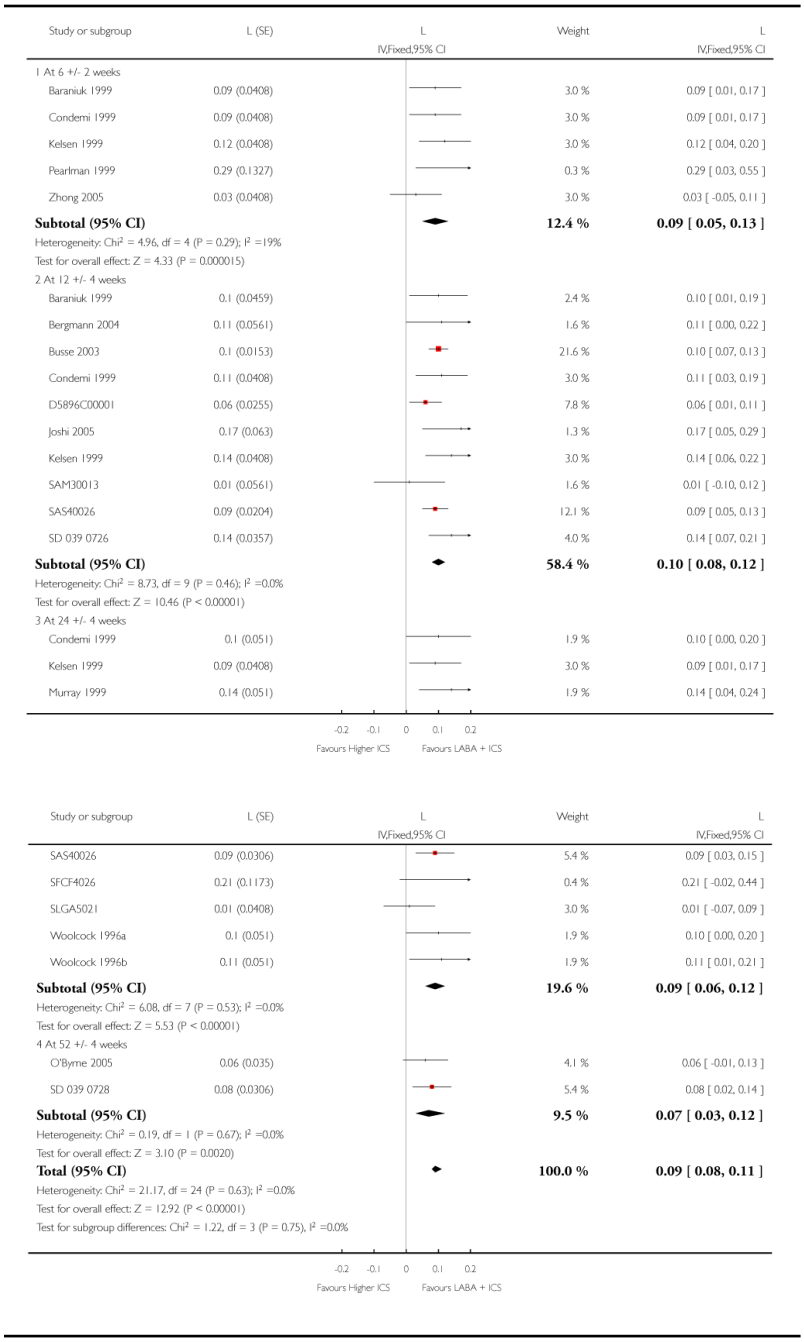


Analysis 1.9. Comparison 1 LABA + ICS versus higher dose ICS, Outcome 9 Change in FEV1 stratifying on treatment period

Review: Addition of long-acting beta2-agonists to inhaled steroids versus higher dose inhaled steroids in adults and children with persistent asthma

Comparison: 1 LABA + ICS versus higher dose ICS

Outcome: 9 Change in FEV1 stratifying on treatment period



Analysis 1.10. Comparison 1 LABA + ICS versus higher dose ICS, Outcome 10 Change in FEV1 (predicted) at endpoint

Review: Addition of long-acting beta2-agonists to inhaled steroids versus higher dose inhaled steroids in adults and children with persistent asthma

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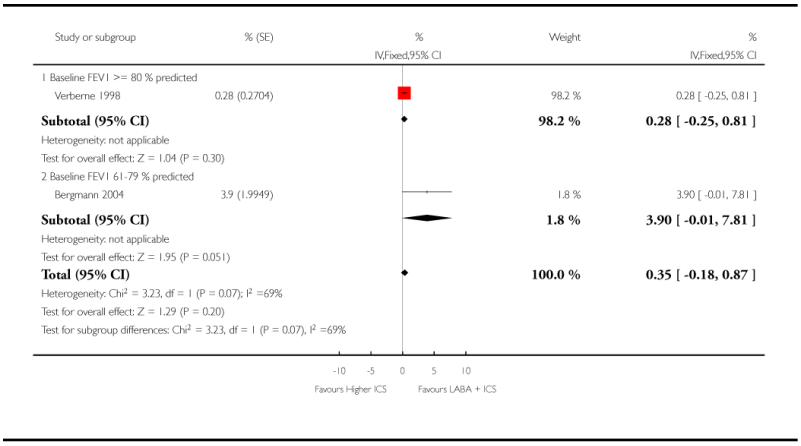
Comparison: 1 LABA + ICS versus higher dose ICS

Outcome: 10 Change in FEV1 (predicted) at endpoint



Analysis 1.11. Comparison 1 LABA + ICS versus higher dose ICS, Outcome 11 Morning PEF at endpoint

Review: Addition of long-acting beta2-agonists to inhaled steroids versus higher dose inhaled steroids in adults and children with persistent asthma

Comparison: 1 LABA + ICS versus higher dose ICS

Outcome: 11 Morning PEF at endpoint

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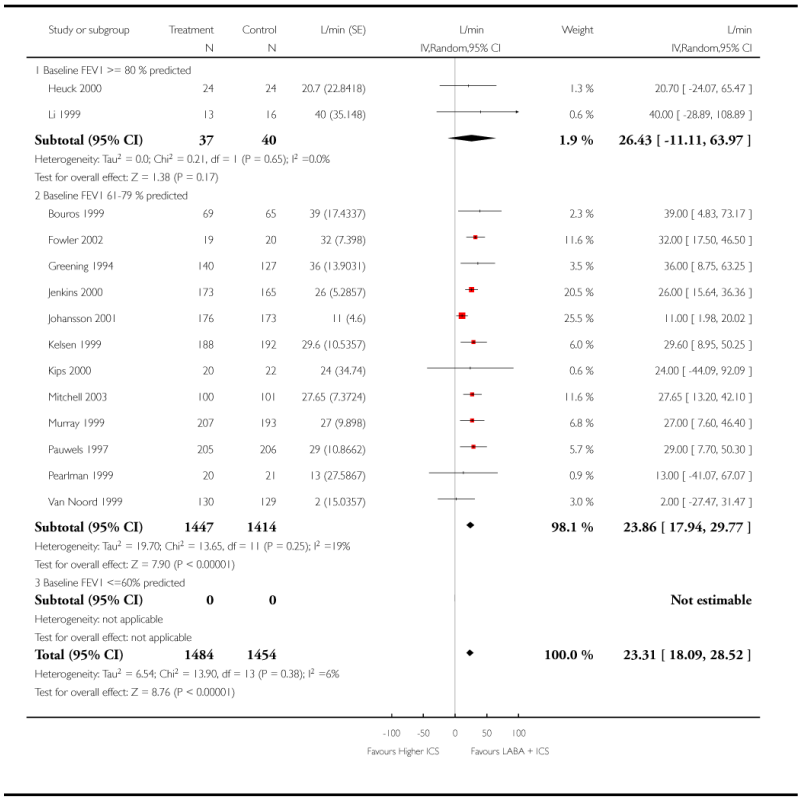

Analysis 1.12. Comparison 1 LABA + ICS versus higher dose ICS, Outcome 12 Change in morning or clinic PEF at endpoint

Review: Addition of long-acting beta2-agonists to inhaled steroids versus higher dose inhaled steroids in adults and children with persistent asthma

Comparison: 1 LABA + ICS versus higher dose ICS

Outcome: 12 Change in morning or clinic PEF at endpoint

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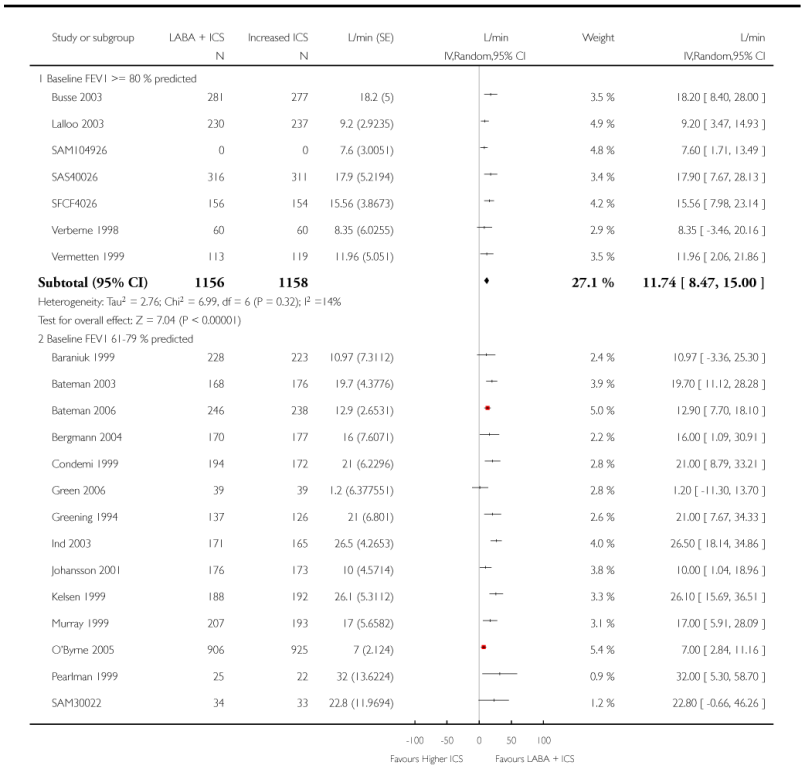

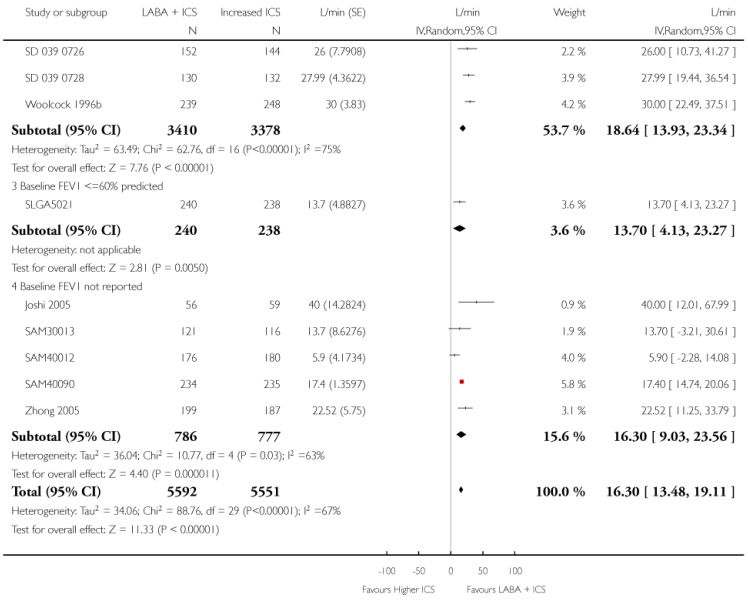

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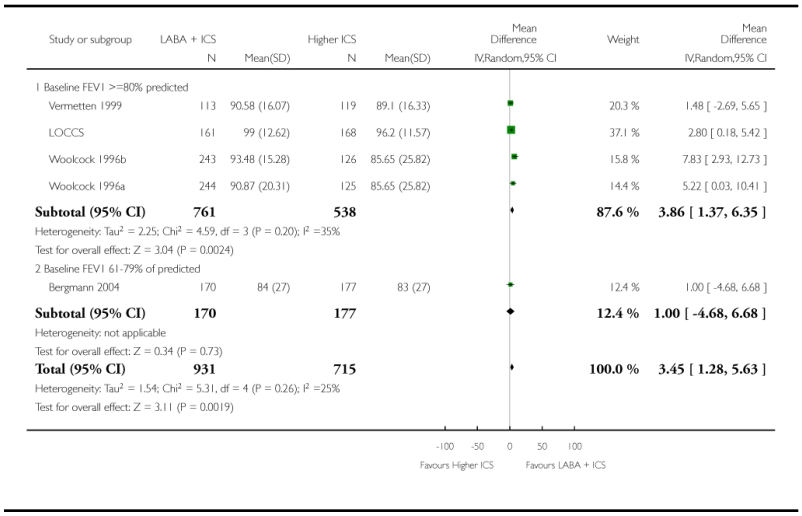
Analysis 1.13. Comparison 1 LABA + ICS versus higher dose ICS, Outcome 13 Morning PEF (% predicted) at endpoint

Review: Addition of long-acting beta2-agonists to inhaled steroids versus higher dose inhaled steroids in adults and children with persistent asthma

Comparison: 1 LABA + ICS versus higher dose ICS

Outcome: 13 Morning PEF (% predicted) at endpoint

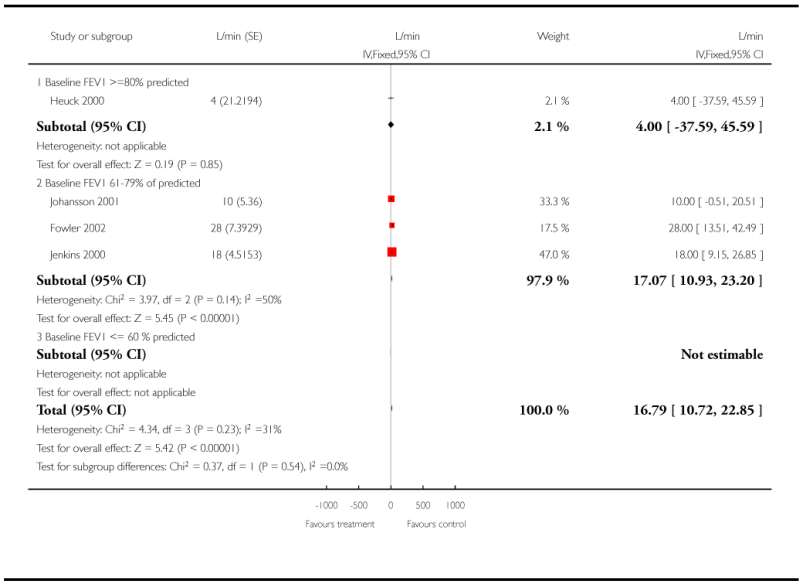


Analysis 1.14. Comparison 1 LABA + ICS versus higher dose ICS, Outcome 14 Evening PEF at endpoint

Review: Addition of long-acting beta2-agonists to inhaled steroids versus higher dose inhaled steroids in adults and children with persistent asthma

Comparison: 1 LABA + ICS versus higher dose ICS

Outcome: 14 Evening PEF at endpoint



Analysis 1.16. Comparison 1 LABA + ICS versus higher dose ICS, Outcome 16 Change in evening PEF at endpoint

Review: Addition of long-acting beta2-agonists to inhaled steroids versus higher dose inhaled steroids in adults and children with persistent asthma

Comparison: 1 LABA + ICS versus higher dose ICS

Outcome: 16 Change in evening PEF at endpoint

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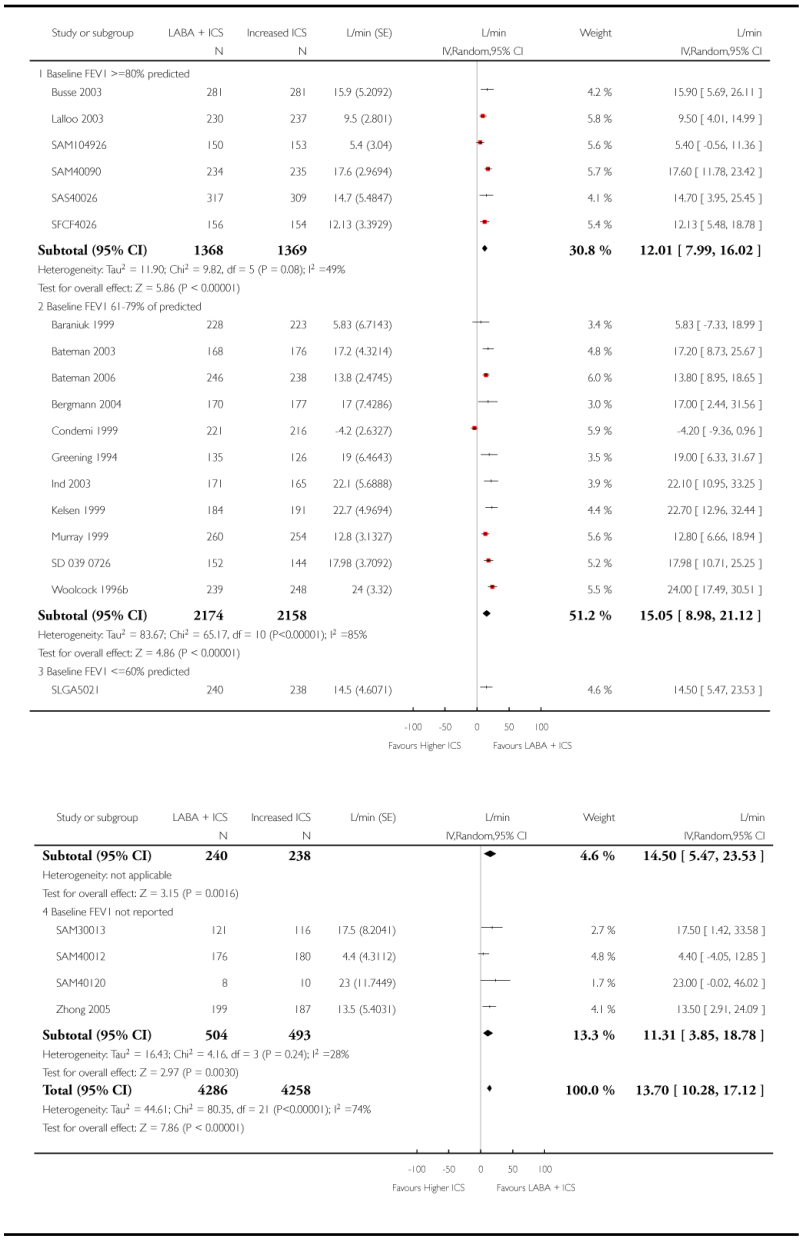

Analysis 1.18. Comparison 1 LABA + ICS versus higher dose ICS, Outcome 18 PEF variability at endpoint

Review: Addition of long-acting beta2-agonists to inhaled steroids versus higher dose inhaled steroids in adults and children with persistent asthma

Comparison: 1 LABA + ICS versus higher dose ICS

Outcome: 18 PEF variability at endpoint

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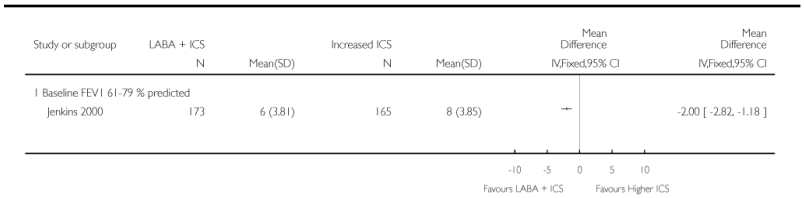
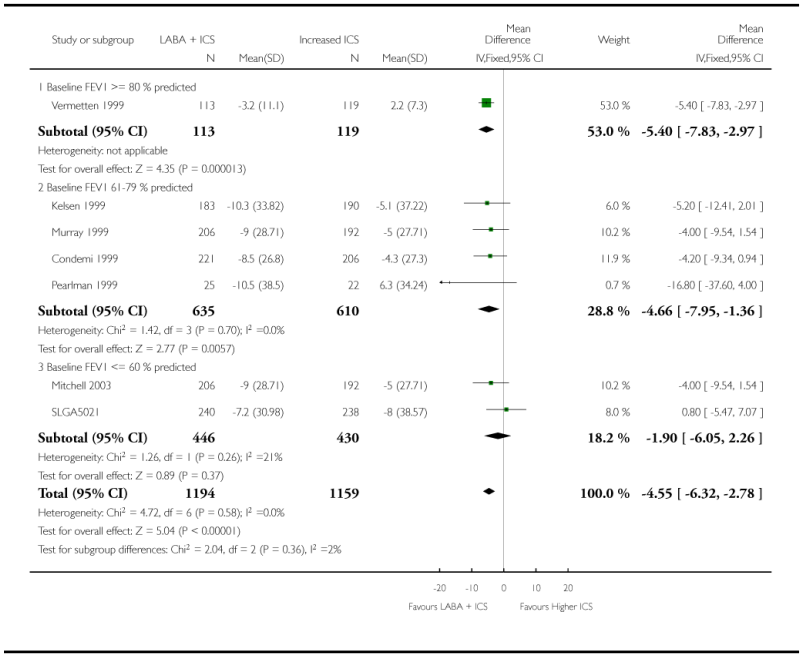


Analysis 1.19. Comparison 1 LABA + ICS versus higher dose ICS, Outcome 19 Change in PEF variability at endpoint

Review: Addition of long-acting beta2-agonists to inhaled steroids versus higher dose inhaled steroids in adults and children with persistent asthma

Comparison: 1 LABA + ICS versus higher dose ICS

Outcome: 19 Change in PEF variability at endpoint



Analysis 1.20. Comparison 1 LABA + ICS versus higher dose ICS, Outcome 20 Change in daytime symptom score at endpoint

Review: Addition of long-acting beta2-agonists to inhaled steroids versus higher dose inhaled steroids in adults and children with persistent asthma

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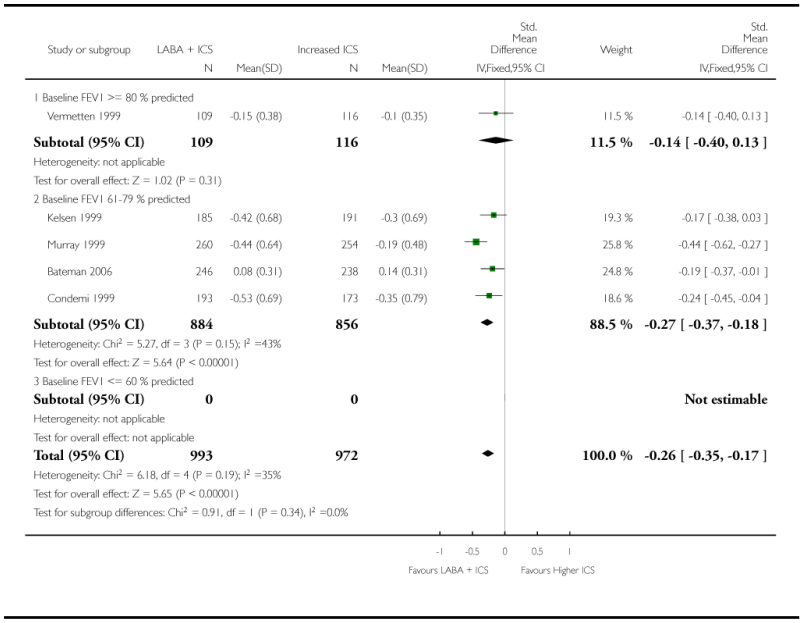
Comparison: 1 LABA + ICS versus higher dose ICS

Outcome: 20 Change in daytime symptom score at endpoint



Analysis 1.21. Comparison 1 LABA + ICS versus higher dose ICS, Outcome 21 Change in overall (24 hrs) symptom score at endpoint

Review: Addition of long-acting beta2-agonists to inhaled steroids versus higher dose inhaled steroids in adults and children with persistent asthma

Comparison: 1 LABA + ICS versus higher dose ICS

Outcome: 21 Change in overall (24 hrs) symptom score at endpoint

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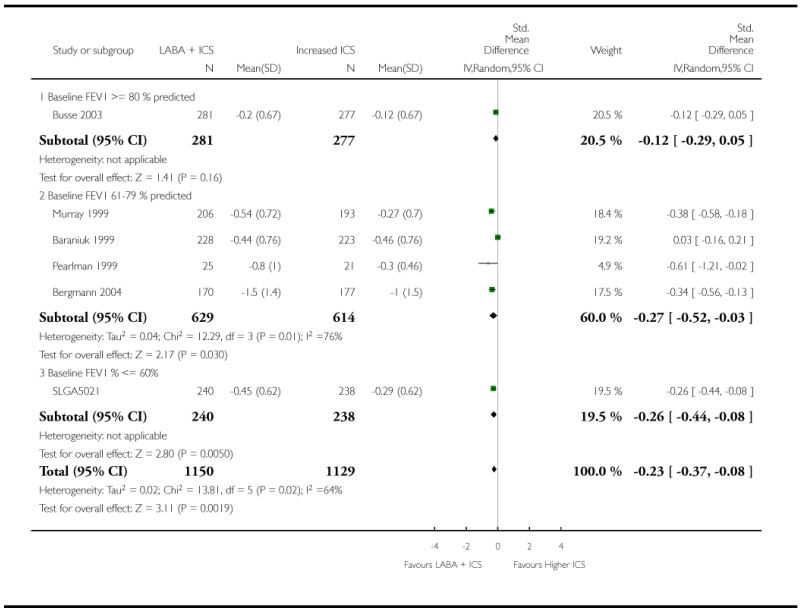

Analysis 1.22. Comparison 1 LABA + ICS versus higher dose ICS, Outcome 22 Change in % symptom-free days at endpoint

Review: Addition of long-acting beta2-agonists to inhaled steroids versus higher dose inhaled steroids in adults and children with persistent asthma

Comparison: 1 LABA + ICS versus higher dose ICS

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

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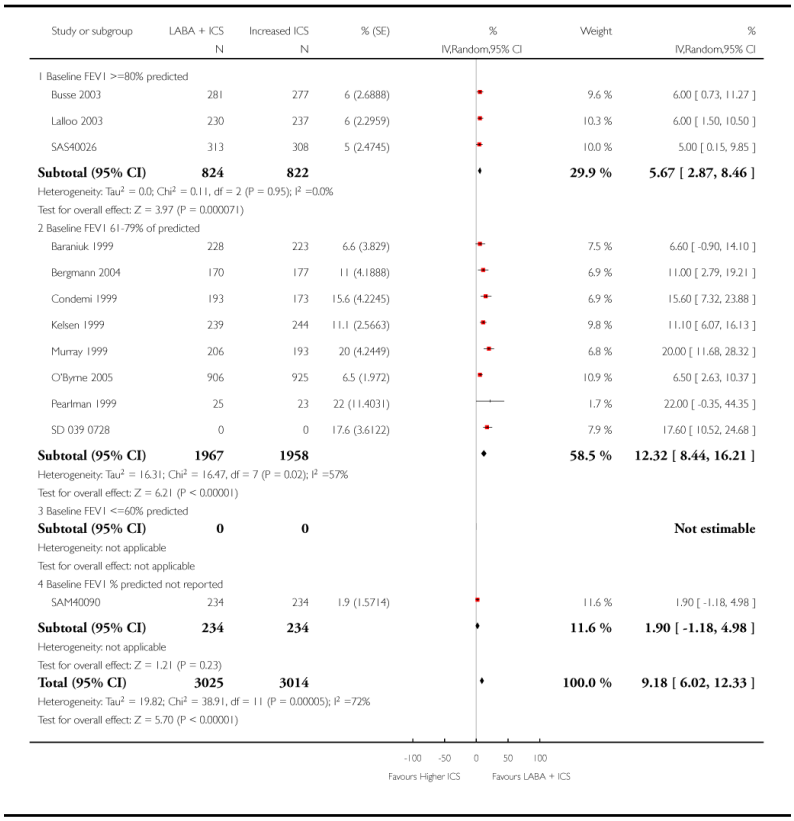

Analysis 1.23. Comparison 1 LABA + ICS versus higher dose ICS, Outcome 23 % symptom-free days at endpoint

Review: Addition of long-acting beta2-agonists to inhaled steroids versus higher dose inhaled steroids in adults and children with persistent asthma

Comparison: 1 LABA + ICS versus higher dose ICS

Outcome: 23 % symptom-free days at endpoint

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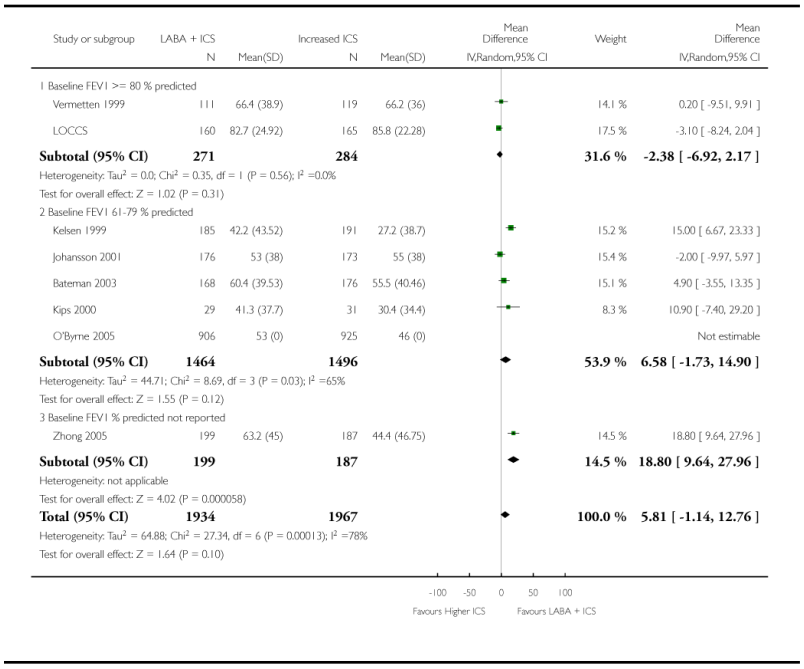

Analysis 1.24. Comparison 1 LABA + ICS versus higher dose ICS, Outcome 24 Daytime symptom score at endpoint

Review: Addition of long-acting beta2-agonists to inhaled steroids versus higher dose inhaled steroids in adults and children with persistent asthma

Comparison: 1 LABA + ICS versus higher dose ICS

Outcome: 24 Daytime symptom score at endpoint

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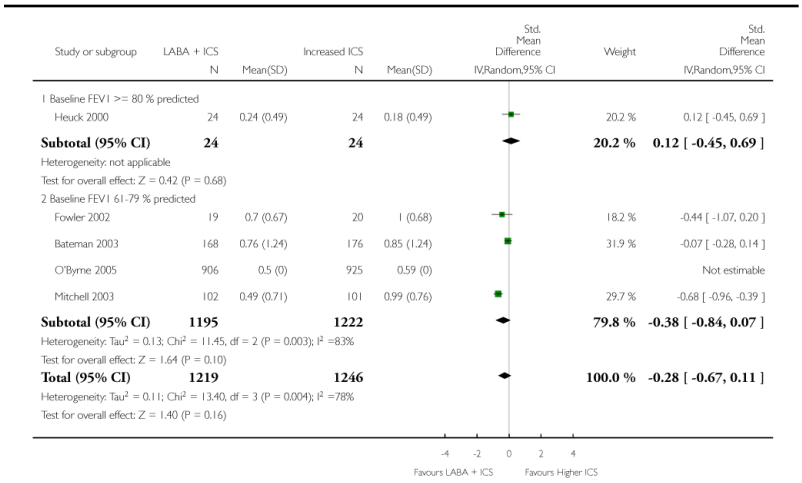
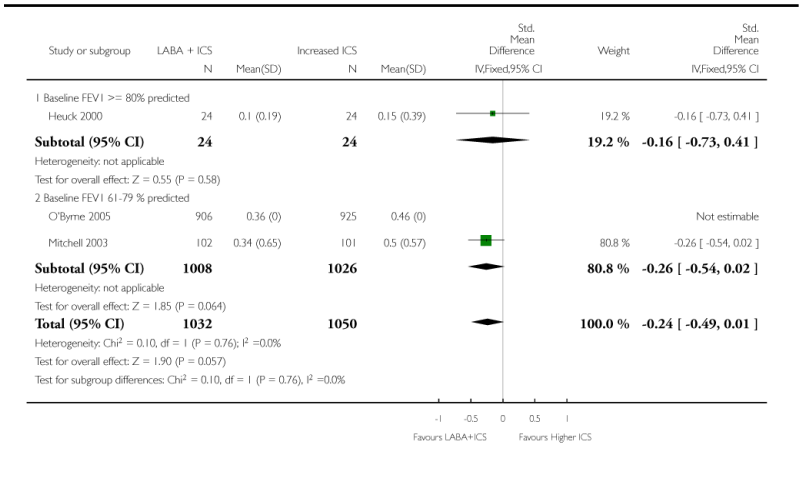


Analysis 1.25. Comparison 1 LABA + ICS versus higher dose ICS, Outcome 25 Nighttime symptom score at endpoint

Review: Addition of long-acting beta2-agonists to inhaled steroids versus higher dose inhaled steroids in adults and children with persistent asthma

Comparison: 1 LABA + ICS versus higher dose ICS

Outcome: 25 Nighttime symptom score at endpoint



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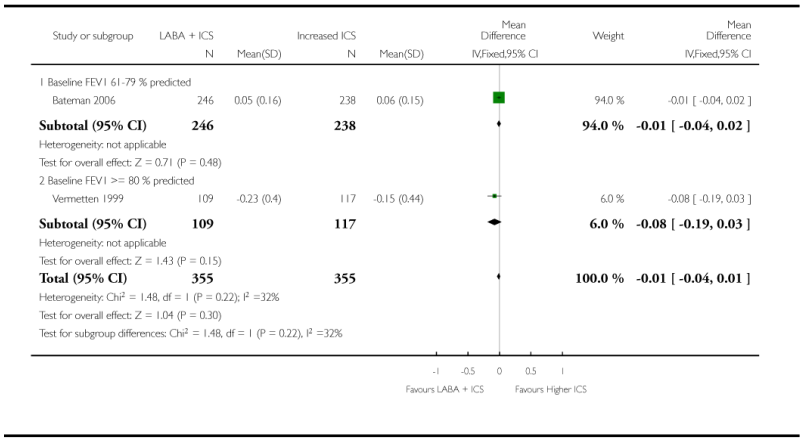
Analysis 1.26. Comparison 1 LABA + ICS versus higher dose ICS, Outcome 26 Change in nighttime symptom score at endpoint

Review: Addition of long-acting beta2-agonists to inhaled steroids versus higher dose inhaled steroids in adults and children with persistent asthma

Comparison: 1 LABA + ICS versus higher dose ICS

Outcome: 26 Change in nighttime symptom score at endpoint



Analysis 1.27. Comparison 1 LABA + ICS versus higher dose ICS, Outcome 27 % symptom-free nights at endpoint

Review: Addition of long-acting beta2-agonists to inhaled steroids versus higher dose inhaled steroids in adults and children with persistent asthma

Comparison: 1 LABA + ICS versus higher dose ICS

Outcome: 27 % symptom-free nights at endpoint

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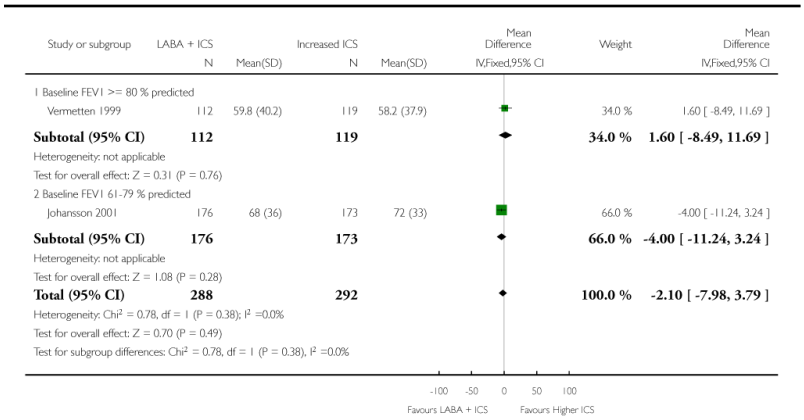

Analysis 1.28. Comparison 1 LABA + ICS versus higher dose ICS, Outcome 28 Change in night time awakenings (number of nights) at endpoint

Review: Addition of long-acting beta2-agonists to inhaled steroids versus higher dose inhaled steroids in adults and children with persistent asthma

Comparison: 1 LABA + ICS versus higher dose ICS

Outcome: 28 Change in night time awakenings (number of nights) at endpoint

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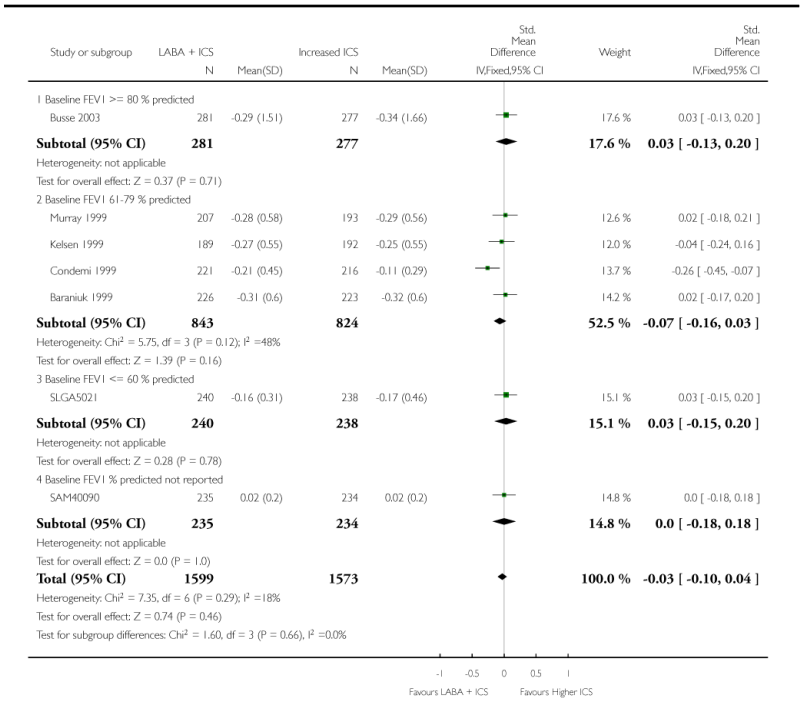
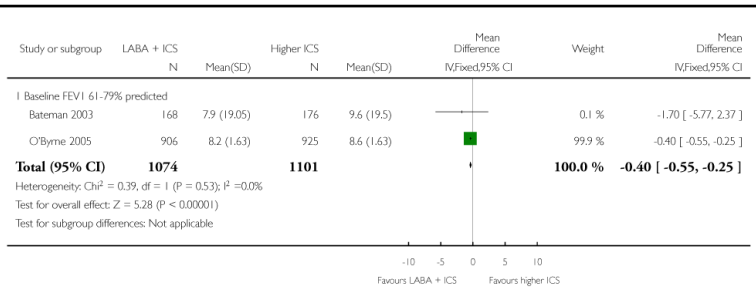


Analysis 1.29. Comparison 1 LABA + ICS versus higher dose ICS, Outcome 29 % nighttime awakenings at endpoint

Review: Addition of long-acting beta2-agonists to inhaled steroids versus higher dose inhaled steroids in adults and children with persistent asthma

Comparison: 1 LABA + ICS versus higher dose ICS

Outcome: 29 % nighttime awakenings at endpoint



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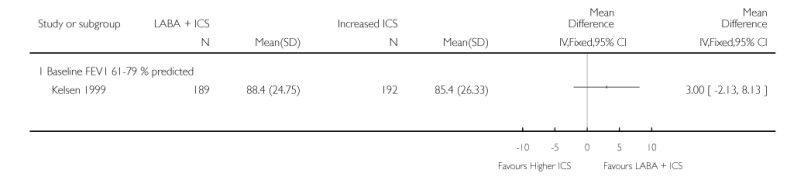
Analysis 1.30. Comparison 1 LABA + ICS versus higher dose ICS, Outcome 30 % nights with no awakenings at endpoint

Review: Addition of long-acting beta2-agonists to inhaled steroids versus higher dose inhaled steroids in adults and children with persistent asthma

Comparison: 1 LABA + ICS versus higher dose ICS

Outcome: 30 % nights with no awakenings at endpoint

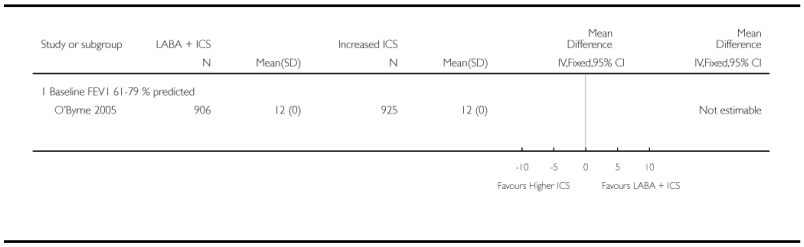


Analysis 1.31. Comparison 1 LABA + ICS versus higher dose ICS, Outcome 31 Change in % nights with no awakenings at endpoint

Review: Addition of long-acting beta2-agonists to inhaled steroids versus higher dose inhaled steroids in adults and children with persistent asthma

Comparison: 1 LABA + ICS versus higher dose ICS

Outcome: 31 Change in % nights with no awakenings at endpoint

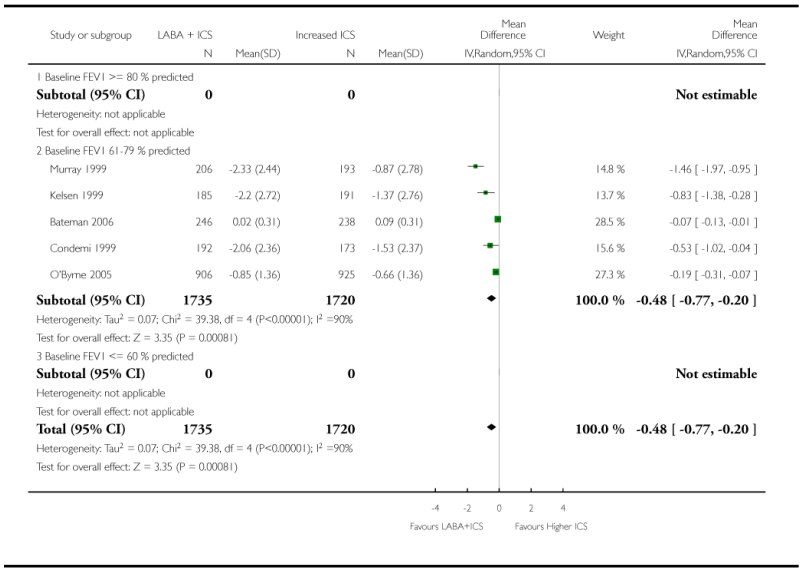


Analysis 1.32. Comparison 1 LABA + ICS versus higher dose ICS, Outcome 32 Change in # daytime rescue inhalations at endpoint

Review: Addition of long-acting beta2-agonists to inhaled steroids versus higher dose inhaled steroids in adults and children with persistent asthma

Comparison: 1 LABA + ICS versus higher dose ICS

Outcome: 32 Change in # daytime rescue inhalations at endpoint

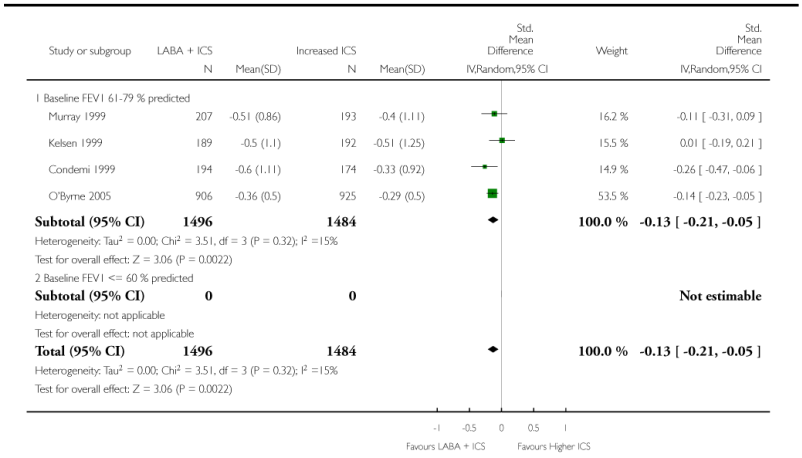


Analysis 1.33. Comparison 1 LABA + ICS versus higher dose ICS, Outcome 33 Change in # nighttime rescue inhalations at endpoint

Review: Addition of long-acting beta2-agonists to inhaled steroids versus higher dose inhaled steroids in adults and children with persistent asthma

Comparison: 1 LABA + ICS versus higher dose ICS

Outcome: 33 Change in # nighttime rescue inhalations at endpoint



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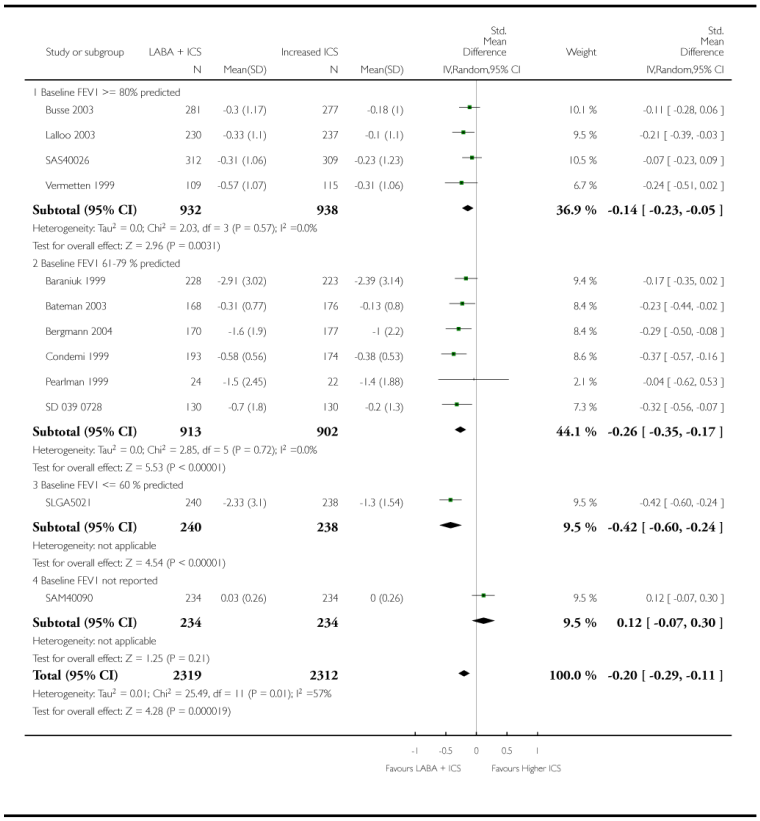
Analysis 1.34. Comparison 1 LABA + ICS versus higher dose ICS, Outcome 34 Absolute (or %) change in # rescue inhalations (per 24 hrs) at endpoint

Review: Addition of long-acting beta2-agonists to inhaled steroids versus higher dose inhaled steroids in adults and children with persistent asthma

Comparison: 1 LABA + ICS versus higher dose ICS

Outcome: 34 Absolute (or %) change in # rescue inhalations (per 24 hrs) at endpoint

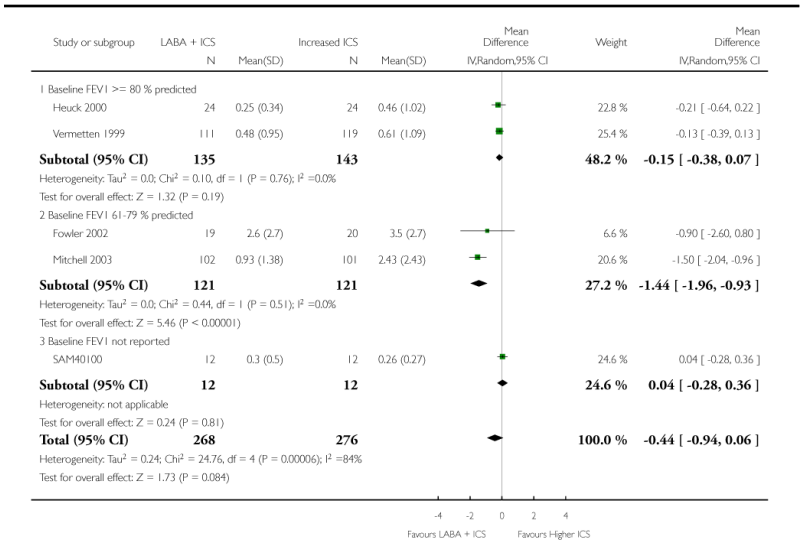


Analysis 1.35. Comparison 1 LABA + ICS versus higher dose ICS, Outcome 35 # daytime rescue inhalations (puffs/day) at endpoint

Review: Addition of long-acting beta2-agonists to inhaled steroids versus higher dose inhaled steroids in adults and children with persistent asthma

Comparison: 1 LABA + ICS versus higher dose ICS

Outcome: 35 # daytime rescue inhalations (puffs/day) at endpoint

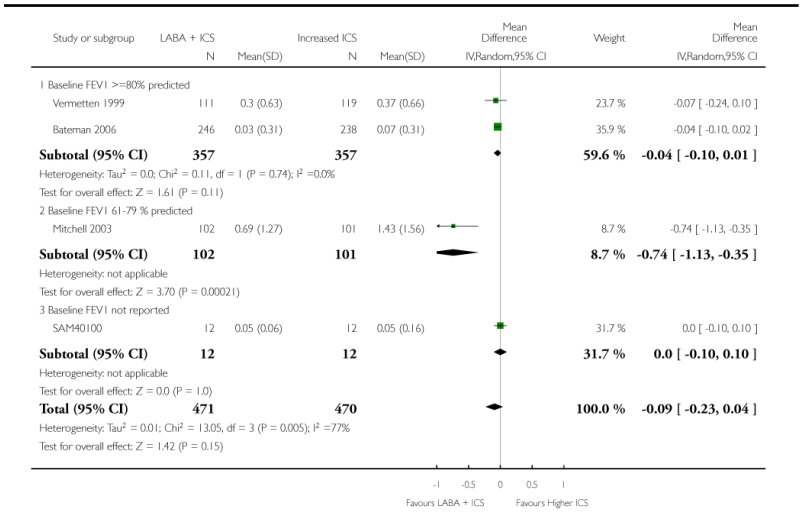


Analysis 1.36. Comparison 1 LABA + ICS versus higher dose ICS, Outcome 36 # nighttime rescue inhalations at endpoint (puffs/day)

Review: Addition of long-acting beta2-agonists to inhaled steroids versus higher dose inhaled steroids in adults and children with persistent asthma

Comparison: 1 LABA + ICS versus higher dose ICS

Outcome: 36 # nighttime rescue inhalations at endpoint (puffs/day)



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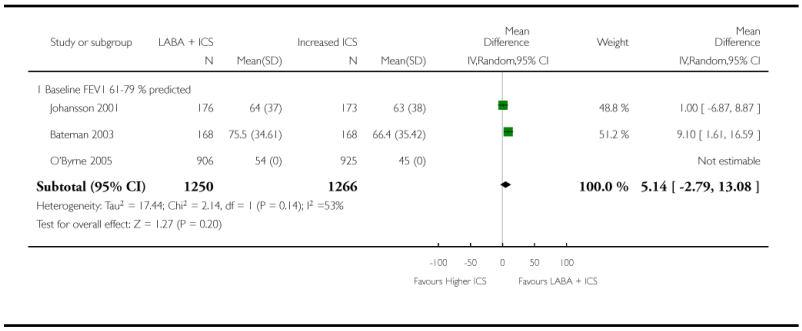
Analysis 1.37. Comparison 1 LABA + ICS versus higher dose ICS, Outcome 37 % overall rescue-free days at endpoint

Review: Addition of long-acting beta2-agonists to inhaled steroids versus higher dose inhaled steroids in adults and children with persistent asthma

Comparison: 1 LABA + ICS versus higher dose ICS

Outcome: 37 % overall rescue-free days at endpoint

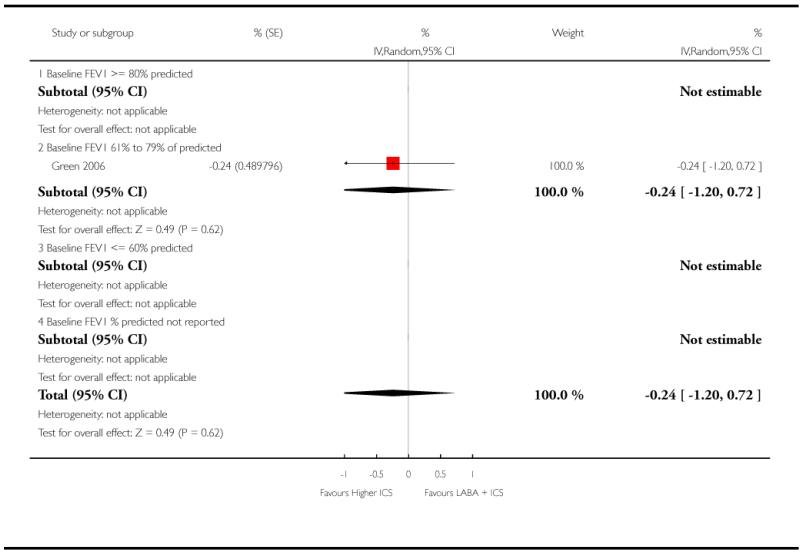


Analysis 1.38. Comparison 1 LABA + ICS versus higher dose ICS, Outcome 38 Change in % symptom-free days at endpoint

Review: Addition of long-acting beta2-agonists to inhaled steroids versus higher dose inhaled steroids in adults and children with persistent asthma

Comparison: 1 LABA + ICS versus higher dose ICS

Outcome: 38 Change in % symptom-free days at endpoint

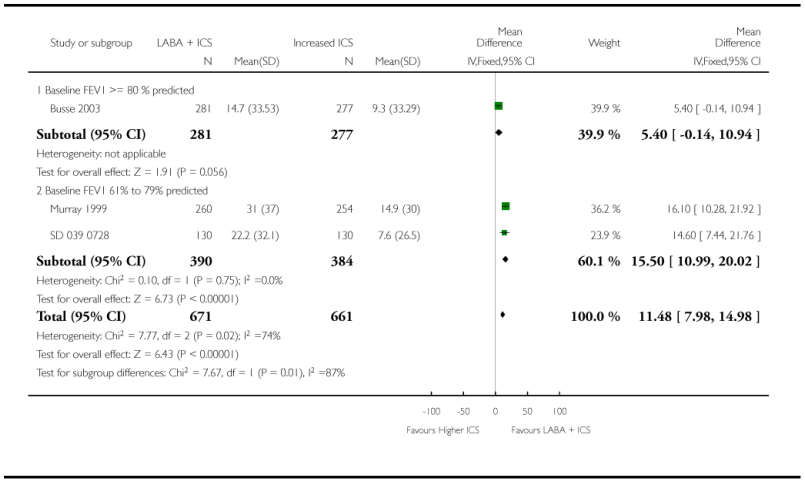


Analysis 1.39. Comparison 1 LABA + ICS versus higher dose ICS, Outcome 39 Change in mean % rescue-free days at endpoint

Review: Addition of long-acting beta2-agonists to inhaled steroids versus higher dose inhaled steroids in adults and children with persistent asthma

Comparison: 1 LABA + ICS versus higher dose ICS

Outcome: 39 Change in mean % rescue-free days at endpoint



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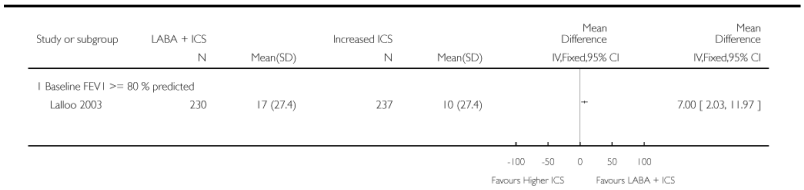
Analysis 1.40. Comparison 1 LABA + ICS versus higher dose ICS, Outcome 40 Change in asthma control days at endpoint (%)

Review: Addition of long-acting beta2-agonists to inhaled steroids versus higher dose inhaled steroids in adults and children with persistent asthma

Comparison: 1 LABA + ICS versus higher dose ICS

Outcome: 40 Change in asthma control days at endpoint (%)

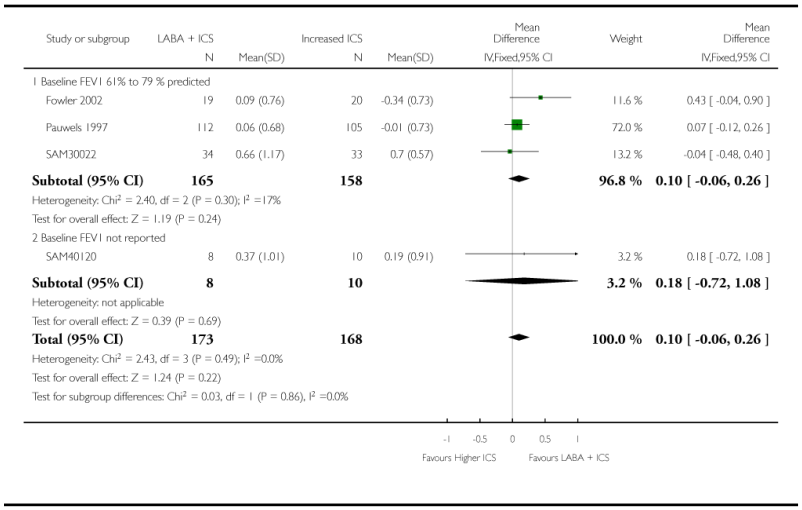


Analysis 1.41. Comparison 1 LABA + ICS versus higher dose ICS, Outcome 41 Change in quality of life (AQLQ score) at endpoint

Review: Addition of long-acting beta2-agonists to inhaled steroids versus higher dose inhaled steroids in adults and children with persistent asthma

Comparison: 1 LABA + ICS versus higher dose ICS

Outcome: 41 Change in quality of life (AQLQ score) at endpoint

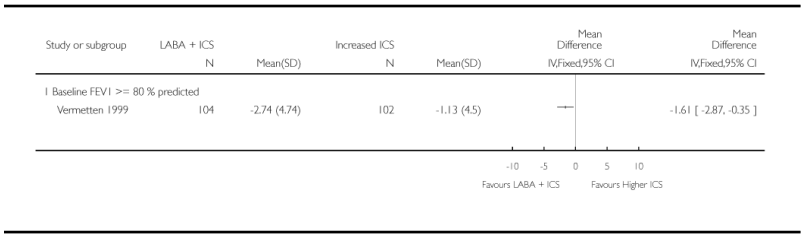


Analysis 1.42. Comparison 1 LABA + ICS versus higher dose ICS, Outcome 42 Change in Hyland QOL at endpoint

Review: Addition of long-acting beta2-agonists to inhaled steroids versus higher dose inhaled steroids in adults and children with persistent asthma

Comparison: 1 LABA + ICS versus higher dose ICS

Outcome: 42 Change in Hyland QOL at endpoint

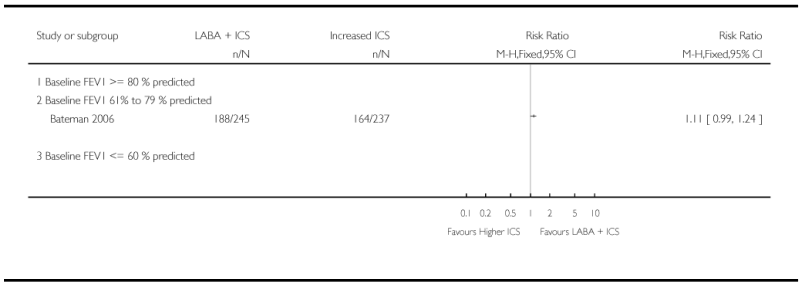


Analysis 1.43. Comparison 1 LABA + ICS versus higher dose ICS, Outcome 43 # Achieving good asthma control

Review: Addition of long-acting beta2-agonists to inhaled steroids versus higher dose inhaled steroids in adults and children with persistent asthma

Comparison: 1 LABA + ICS versus higher dose ICS

Outcome: 43 # Achieving good asthma control

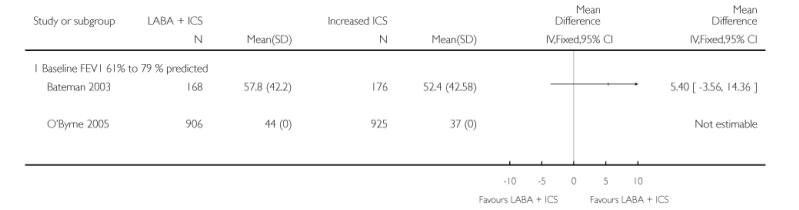


Analysis 1.44. Comparison 1 LABA + ICS versus higher dose ICS, Outcome 44 % asthma control days at endpoint

Review: Addition of long-acting beta2-agonists to inhaled steroids versus higher dose inhaled steroids in adults and children with persistent asthma

Comparison: 1 LABA + ICS versus higher dose ICS

Outcome: 44 % asthma control days at endpoint

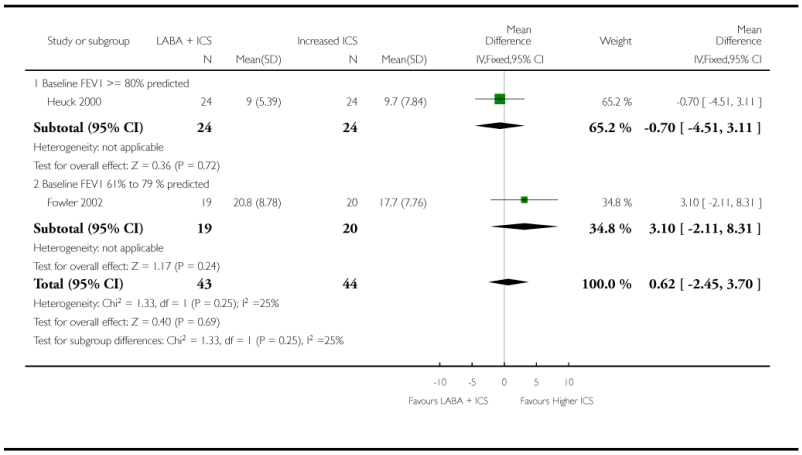


Analysis 1.45. Comparison 1 LABA + ICS versus higher dose ICS, Outcome 45 Serum ECP(microg /L)

Review: Addition of long-acting beta2-agonists to inhaled steroids versus higher dose inhaled steroids in adults and children with persistent asthma

Comparison: 1 LABA + ICS versus higher dose ICS

Outcome: 45 Serum ECP(microg /L)



Analysis 1.46. Comparison 1 LABA + ICS versus higher dose ICS, Outcome 46 Plasma cortisol (nmol/L) 8am at 8 weeks

Review: Addition of long-acting beta2-agonists to inhaled steroids versus higher dose inhaled steroids in adults and children with persistent asthma

Comparison: 1 LABA + ICS versus higher dose ICS

Outcome: 46 Plasma cortisol (nmol/L) 8am at 8 weeks

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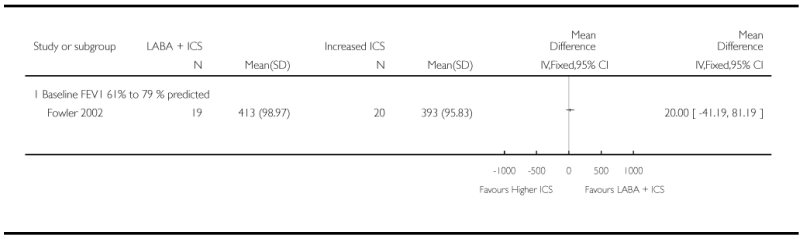
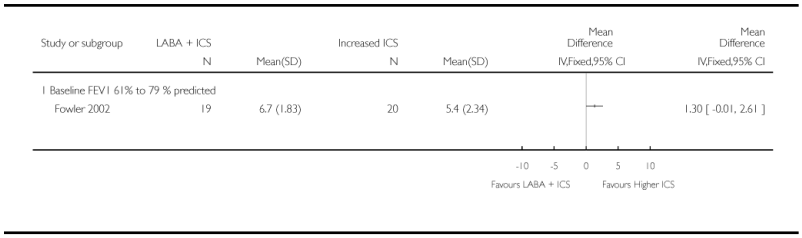


Analysis 1.47. Comparison 1 LABA + ICS versus higher dose ICS, Outcome 47 Tidal exhaled NO(ppb)

Review: Addition of long-acting beta2-agonists to inhaled steroids versus higher dose inhaled steroids in adults and children with persistent asthma

Comparison: 1 LABA + ICS versus higher dose ICS

Outcome: 47 Tidal exhaled NO(ppb)

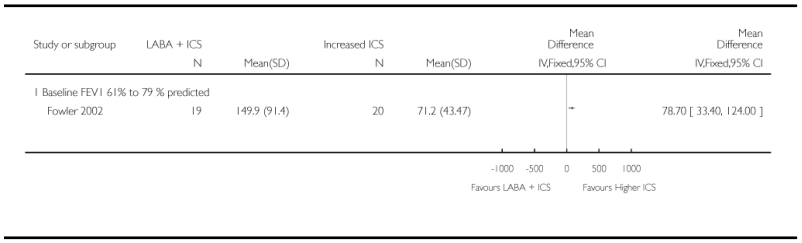


Analysis 1.48. Comparison 1 LABA + ICS versus higher dose ICS, Outcome 48 PD20 @ 8 weeks

Review: Addition of long-acting beta2-agonists to inhaled steroids versus higher dose inhaled steroids in adults and children with persistent asthma

Comparison: 1 LABA + ICS versus higher dose ICS

Outcome: 48 PD20 @ 8 weeks



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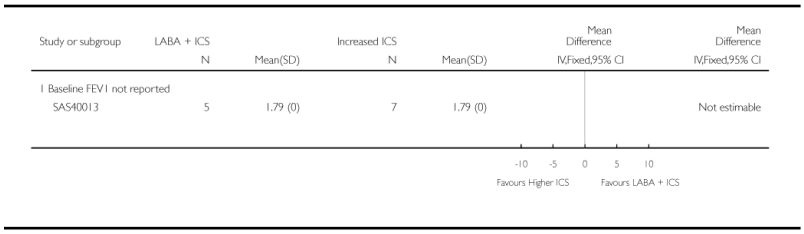
Analysis 1.49. Comparison 1 LABA + ICS versus higher dose ICS, Outcome 49 PC20

Review: Addition of long-acting beta2-agonists to inhaled steroids versus higher dose inhaled steroids in adults and children with persistent asthma

Comparison: 1 LABA + ICS versus higher dose ICS

Outcome: 49 PC20

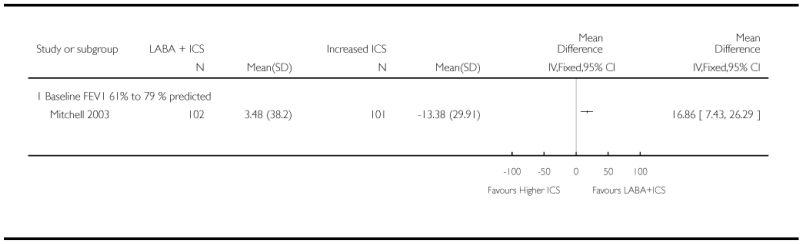


Analysis 1.50. Comparison 1 LABA + ICS versus higher dose ICS, Outcome 50 Change in mean urine Cortisol/Creatinine ratio

Review: Addition of long-acting beta2-agonists to inhaled steroids versus higher dose inhaled steroids in adults and children with persistent asthma

Comparison: 1 LABA + ICS versus higher dose ICS

Outcome: 50 Change in mean urine Cortisol/Creatinine ratio

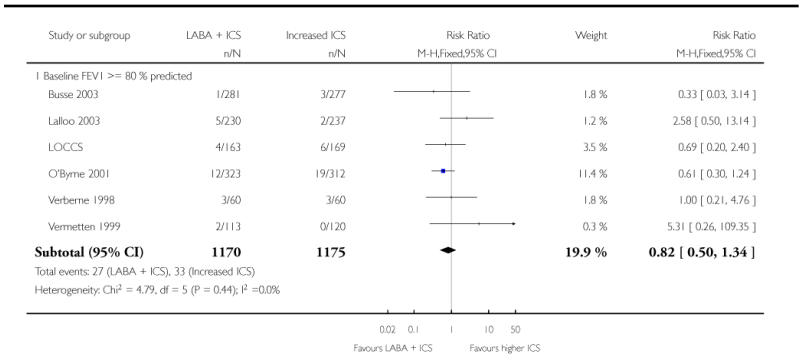


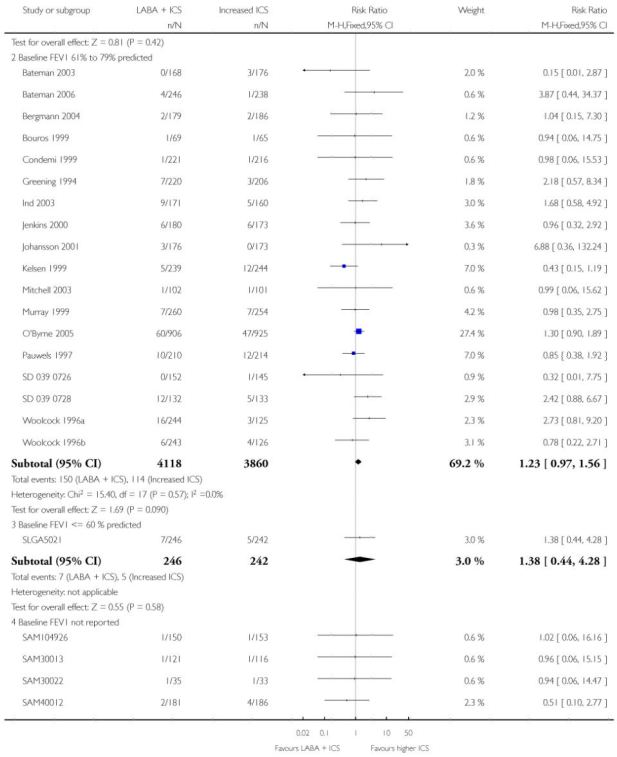
Analysis 1.52. Comparison 1 LABA + ICS versus higher dose ICS, Outcome 52 Serious adverse events

Review: Addition of long-acting beta2-agonists to inhaled steroids versus higher dose inhaled steroids in adults and children with persistent asthma

Comparison: 1 LABA + ICS versus higher dose ICS

Outcome: 52 Serious adverse events





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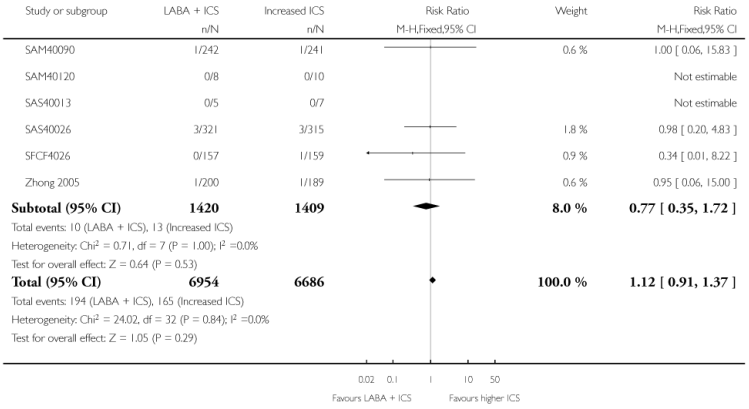

Analysis 1.53. Comparison 1 LABA + ICS versus higher dose ICS, Outcome 53 # patients with tremor

Review: Addition of long-acting beta2-agonists to inhaled steroids versus higher dose inhaled steroids in adults and children with persistent asthma

Comparison: 1 LABA + ICS versus higher dose ICS

Outcome: 53 # patients with tremor

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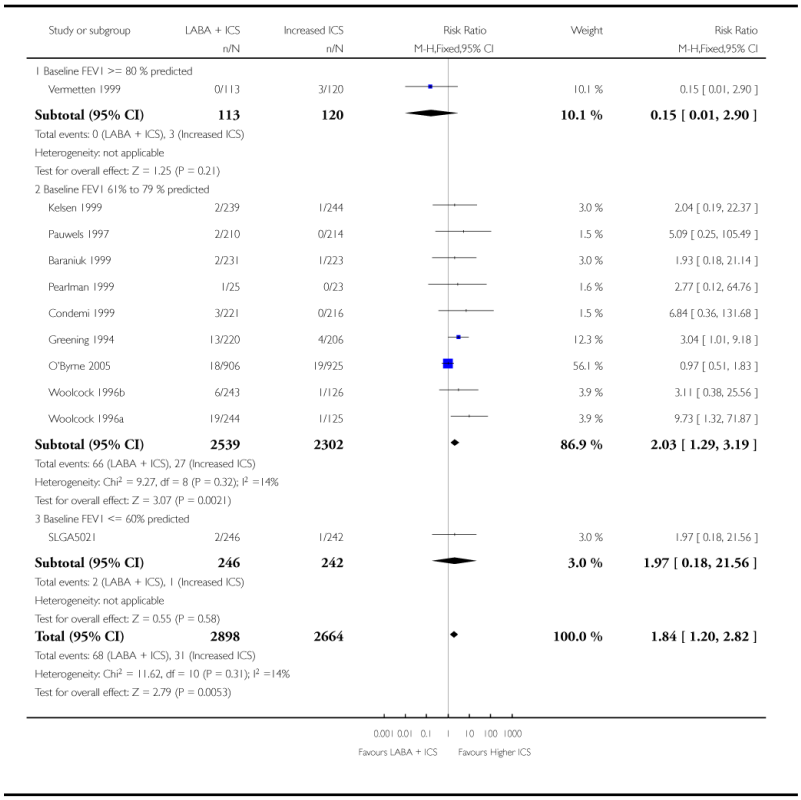

Analysis 1.54. Comparison 1 LABA + ICS versus higher dose ICS, Outcome 54 # patients with oral thrush

Review: Addition of long-acting beta2-agonists to inhaled steroids versus higher dose inhaled steroids in adults and children with persistent asthma

Comparison: 1 LABA + ICS versus higher dose ICS

Outcome: 54 # patients with oral thrush

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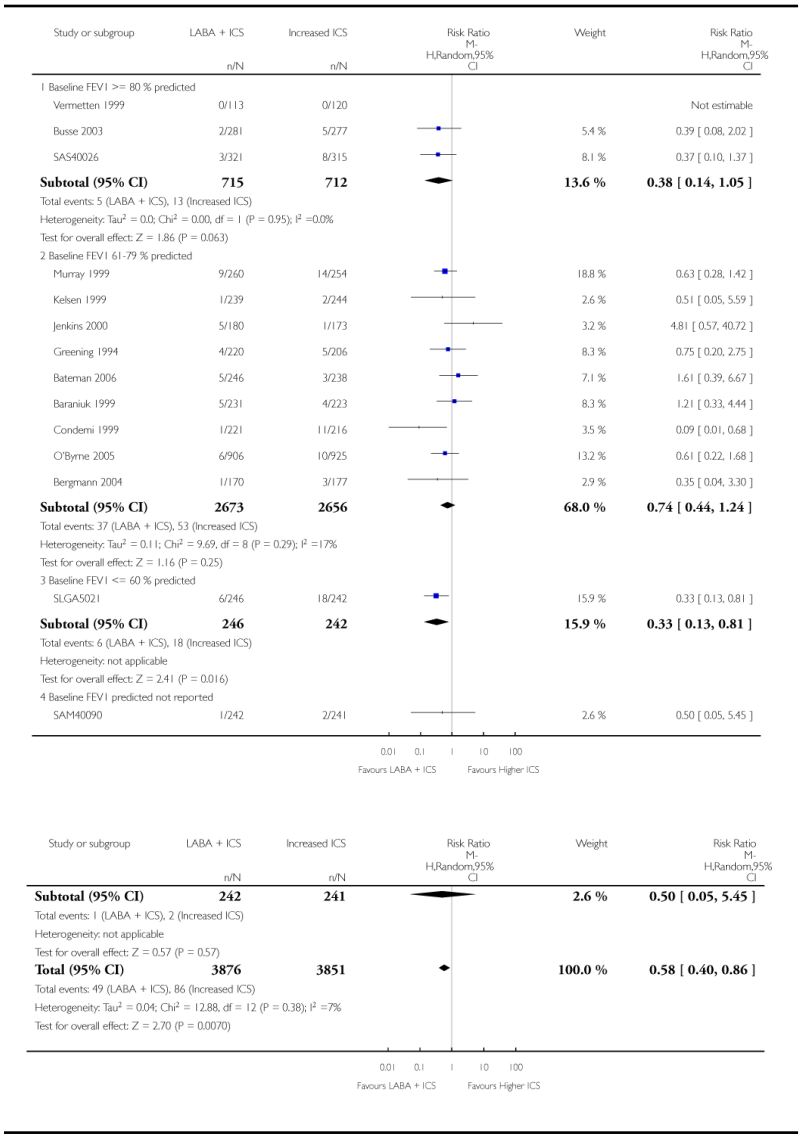

Analysis 1.55. Comparison 1 LABA + ICS versus higher dose ICS, Outcome 55 Total # adverse events

Review: Addition of long-acting beta2-agonists to inhaled steroids versus higher dose inhaled steroids in adults and children with persistent asthma

Comparison: 1 LABA + ICS versus higher dose ICS

Outcome: 55 Total # adverse events

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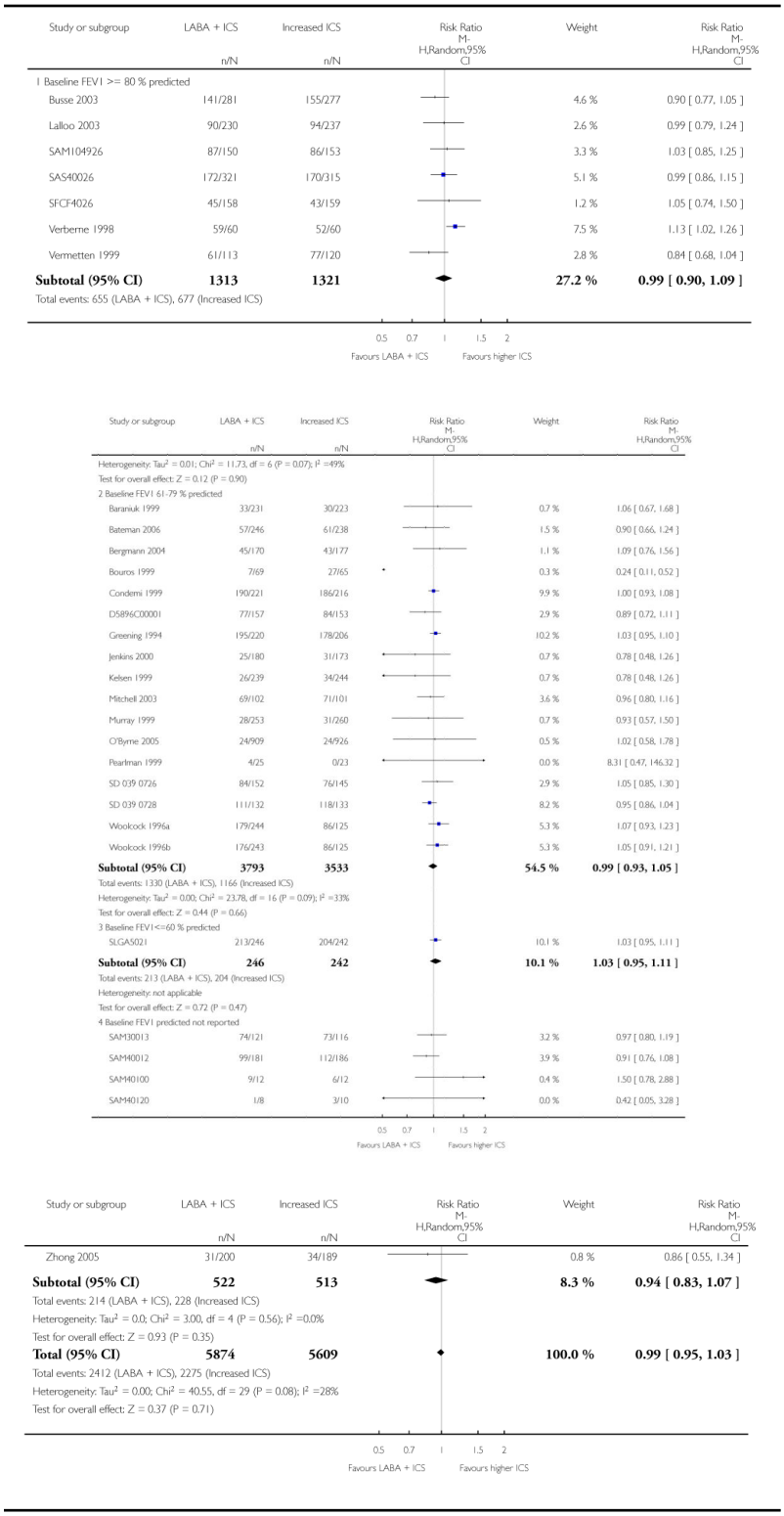

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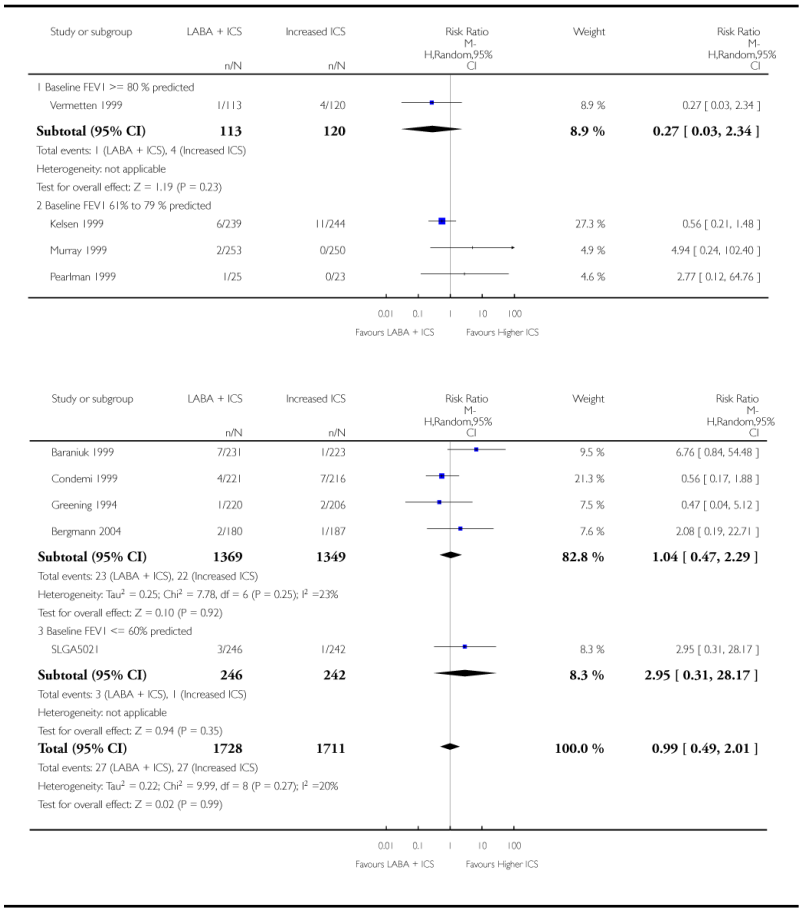
Analysis 1.56. Comparison 1 LABA + ICS versus higher dose ICS, Outcome 56 # patients with adverse cardiovascular events

Review: Addition of long-acting beta2-agonists to inhaled steroids versus higher dose inhaled steroids in adults and children with persistent asthma

Comparison: 1 LABA + ICS versus higher dose ICS

Outcome: 56 # patients with adverse cardiovascular events

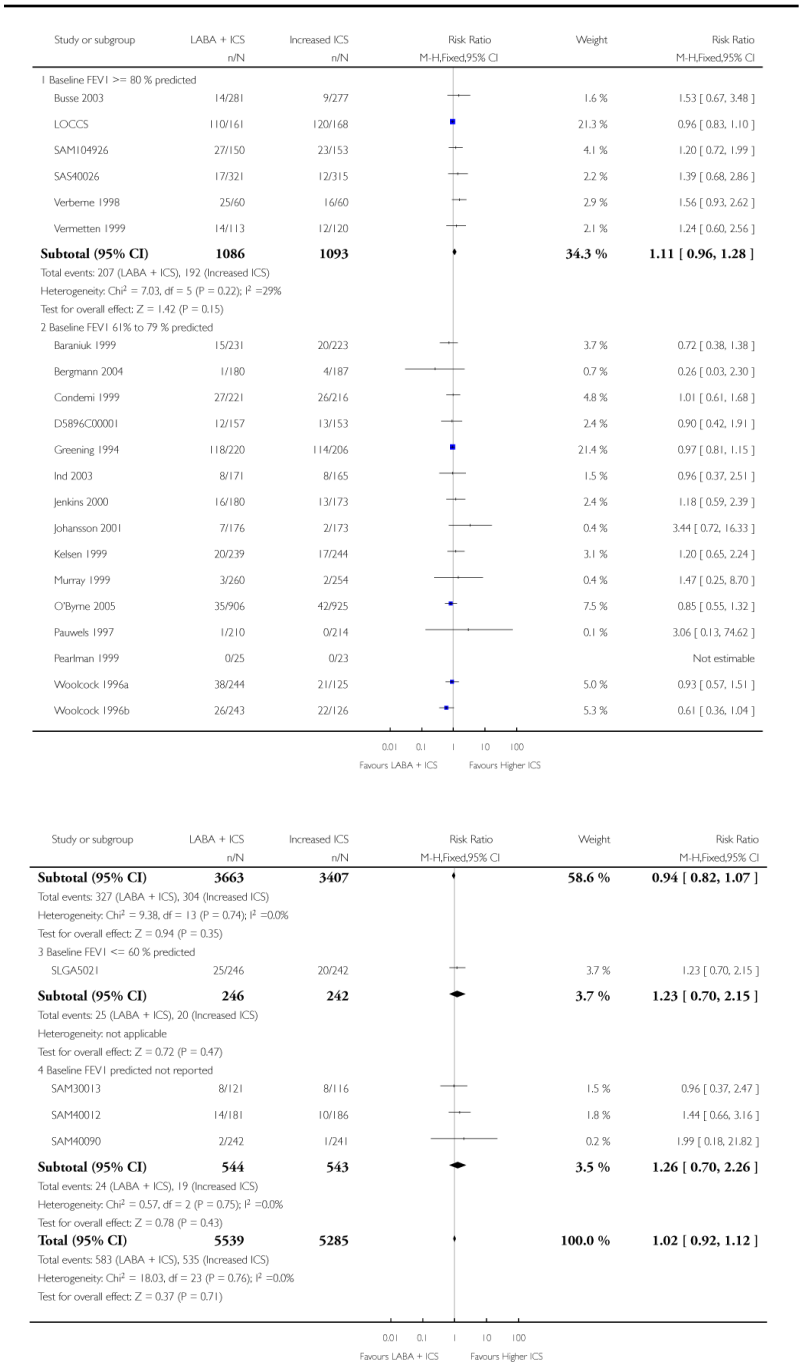


Analysis 1.57. Comparison 1 LABA + ICS versus higher dose ICS, Outcome 57 # patients with headache

Review: Addition of long-acting beta2-agonists to inhaled steroids versus higher dose inhaled steroids in adults and children with persistent asthma

Comparison: 1 LABA + ICS versus higher dose ICS

Outcome: 57 # patients with headache



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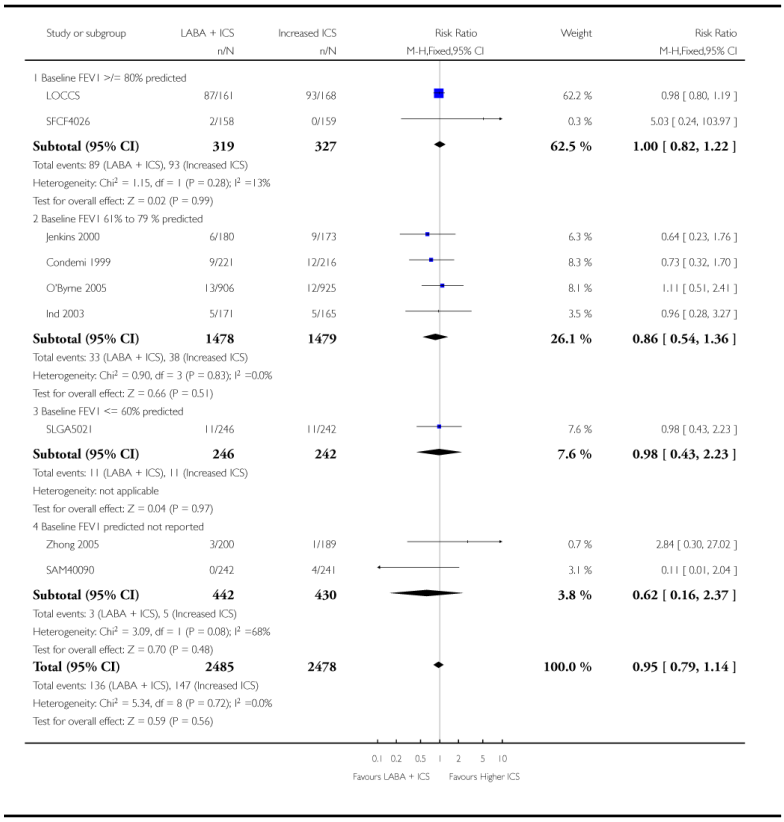
Analysis 1.58. Comparison 1 LABA + ICS versus higher dose ICS, Outcome 58 # patients with hoarseness

Review: Addition of long-acting beta2-agonists to inhaled steroids versus higher dose inhaled steroids in adults and children with persistent asthma

Comparison: 1 LABA + ICS versus higher dose ICS

Outcome: 58 # patients with hoarseness

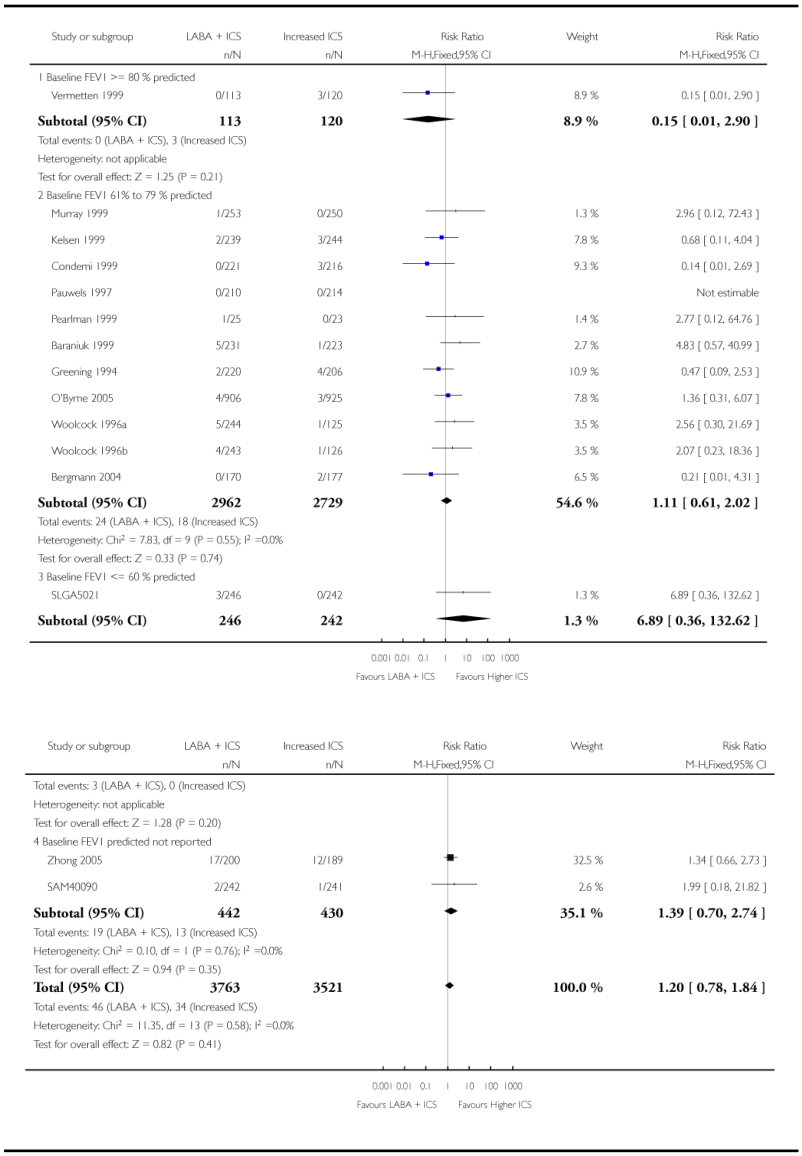


Analysis 1.59. Comparison 1 LABA + ICS versus higher dose ICS, Outcome 59 # patients with tachycardia or palpitations

Review: Addition of long-acting beta2-agonists to inhaled steroids versus higher dose inhaled steroids in adults and children with persistent asthma

Comparison: 1 LABA + ICS versus higher dose ICS

Outcome: 59 # patients with tachycardia or palpitations



Analysis 1.60. Comparison 1 LABA + ICS versus higher dose ICS, Outcome 60 Growth (paediatric data)

Review: Addition of long-acting beta2-agonists to inhaled steroids versus higher dose inhaled steroids in adults and children with persistent asthma

Comparison: 1 LABA + ICS versus higher dose ICS

Outcome: 60 Growth (paediatric data)

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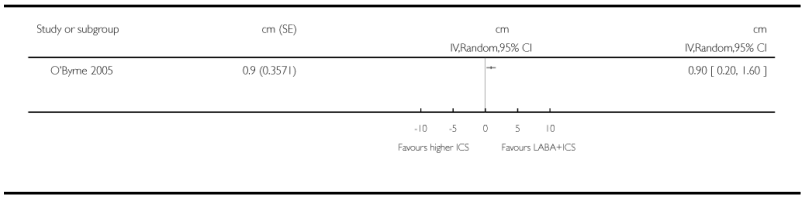
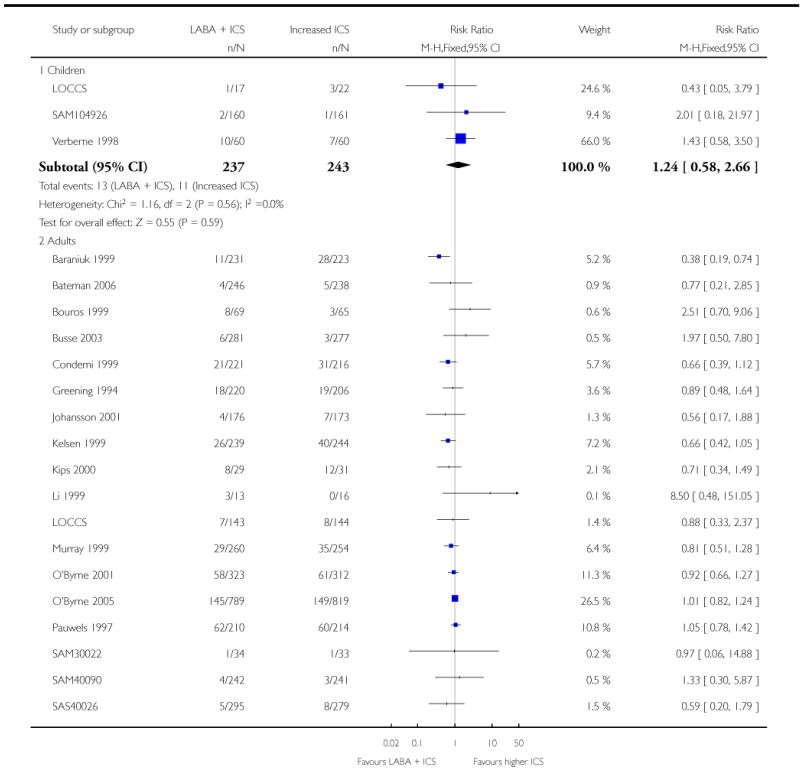


Analysis 2.1. Comparison 2 LABA + ICS versus higher dose ICS (subgroup and sensitivity analyses), Outcome 1 # patients with exacerbations requiring oral steroids: children versus adults

Review: Addition of long-acting beta2-agonists to inhaled steroids versus higher dose inhaled steroids in adults and children with persistent asthma

Comparison: 2 LABA + ICS versus higher dose ICS (subgroup and sensitivity analyses)

Outcome: 1 # patients with exacerbations requiring oral steroids: children versus adults



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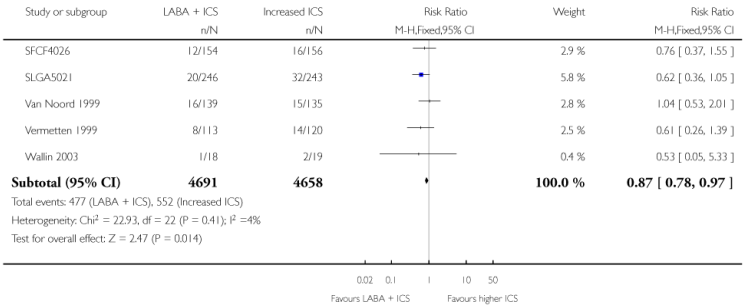
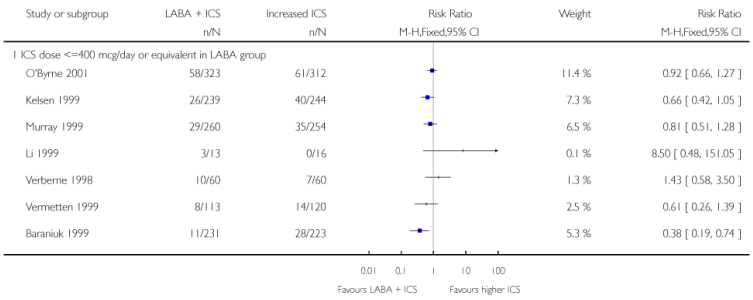


Analysis 2.2. Comparison 2 LABA + ICS versus higher dose ICS (subgroup and sensitivity analyses), Outcome 2 # patients with exacerbations requiring oral steroids: ICS dose associated with LABA

Review: Addition of long-acting beta2-agonists to inhaled steroids versus higher dose inhaled steroids in adults and children with persistent asthma

Comparison: 2 LABA + ICS versus higher dose ICS (subgroup and sensitivity analyses)

Outcome: 2 # patients with exacerbations requiring oral steroids: ICS dose associated with LABA



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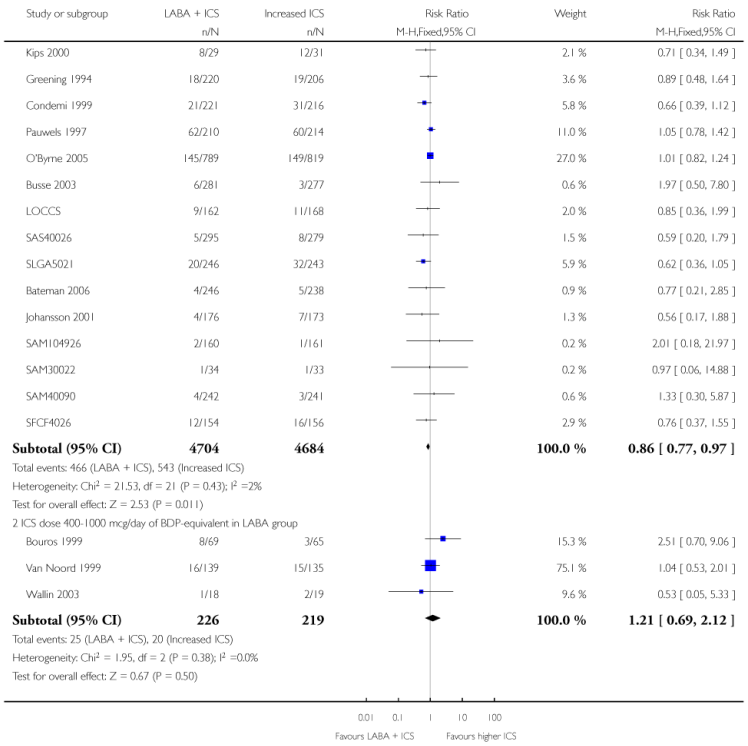

Analysis 2.3. Comparison 2 LABA + ICS versus higher dose ICS (subgroup and sensitivity analyses), Outcome 3 # patients with exacerbations requiring oral steroids: ICS dose difference between LABA and higher ICS groups

Review: Addition of long-acting beta2-agonists to inhaled steroids versus higher dose inhaled steroids in adults and children with persistent asthma

Comparison: 2 LABA + ICS versus higher dose ICS (subgroup and sensitivity analyses)

Outcome: 3 # patients with exacerbations requiring oral steroids: ICS dose difference between LABA and higher ICS groups

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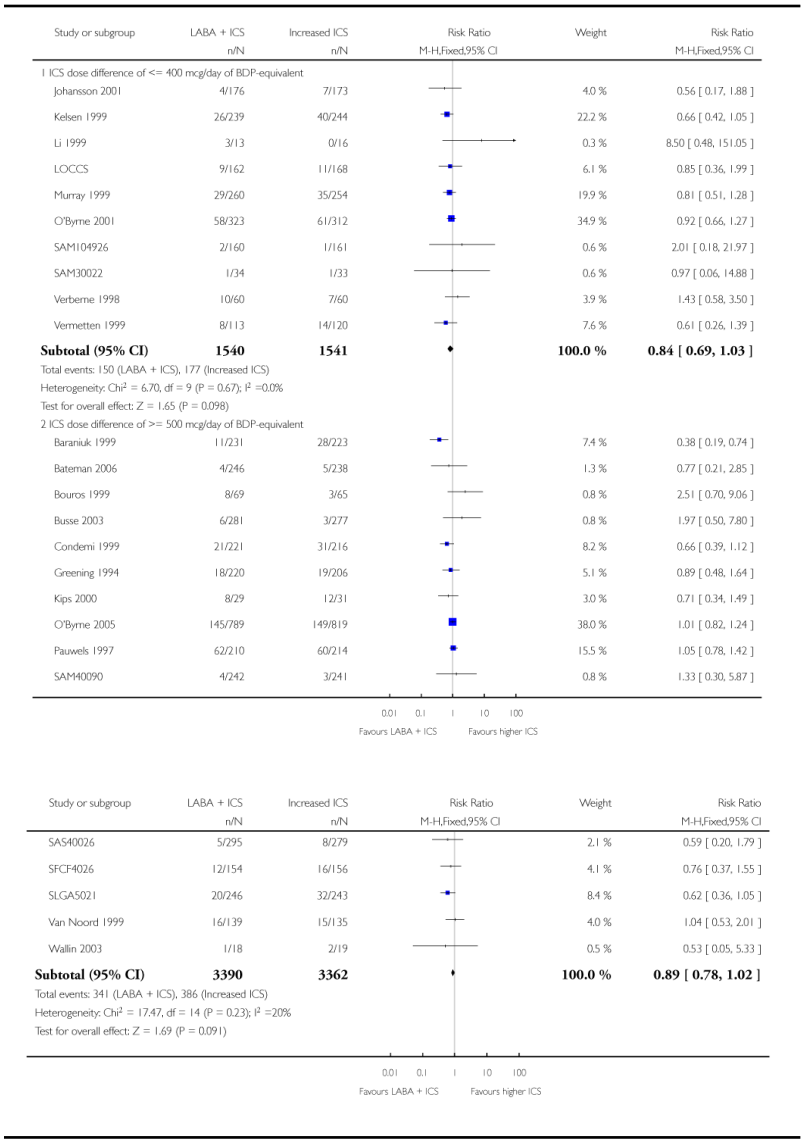

Analysis 2.4. Comparison 2 LABA + ICS versus higher dose ICS (subgroup and sensitivity analyses), Outcome 4 # patients with exacerbations requiring oral steroids: formoterol versus salmeterol

Review: Addition of long-acting beta2-agonists to inhaled steroids versus higher dose inhaled steroids in adults and children with persistent asthma

Comparison: 2 LABA + ICS versus higher dose ICS (subgroup and sensitivity analyses)

Outcome: 4 # patients with exacerbations requiring oral steroids: formoterol versus salmeterol

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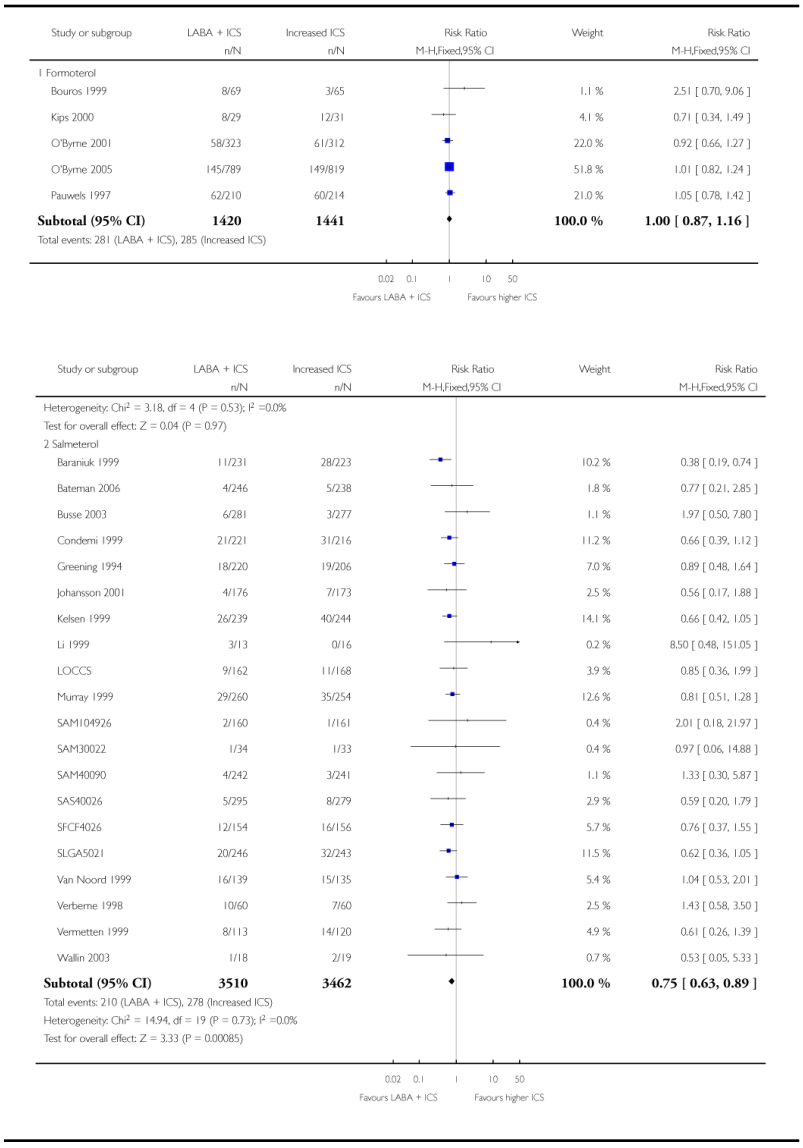

Analysis 2.5. Comparison 2 LABA + ICS versus higher dose ICS (subgroup and sensitivity analyses), Outcome 5 # patients with exacerbations requiring oral steroids: 1 versus 2 devices to deliver LABA + ICS

Review: Addition of long-acting beta2-agonists to inhaled steroids versus higher dose inhaled steroids in adults and children with persistent asthma

Comparison: 2 LABA + ICS versus higher dose ICS (subgroup and sensitivity analyses)

Outcome: 5 # patients with exacerbations requiring oral steroids: 1 versus 2 devices to deliver LABA + ICS

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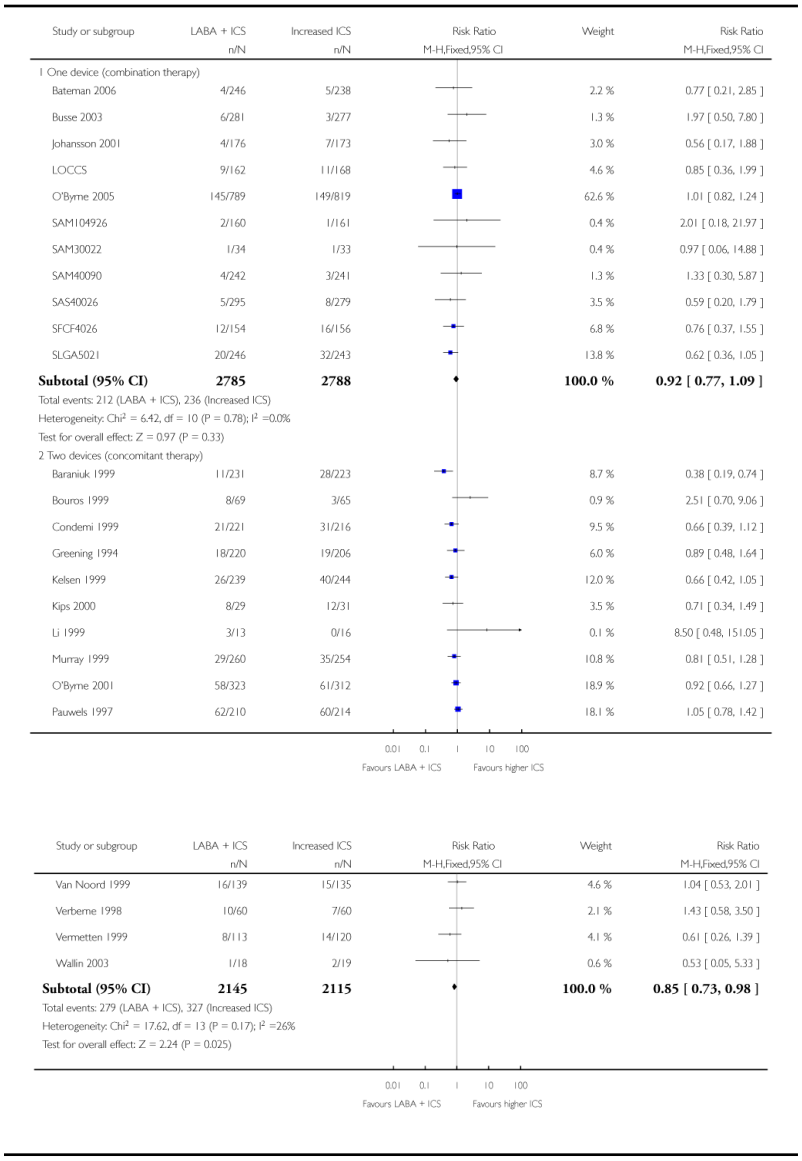

Analysis 2.6. Comparison 2 LABA + ICS versus higher dose ICS (subgroup and sensitivity analyses), Outcome 6 # patients with exacerbations requiring oral steroids: duration of trial

Review: Addition of long-acting beta2-agonists to inhaled steroids versus higher dose inhaled steroids in adults and children with persistent asthma

Comparison: 2 LABA + ICS versus higher dose ICS (subgroup and sensitivity analyses)

Outcome: 6 # patients with exacerbations requiring oral steroids: duration of trial

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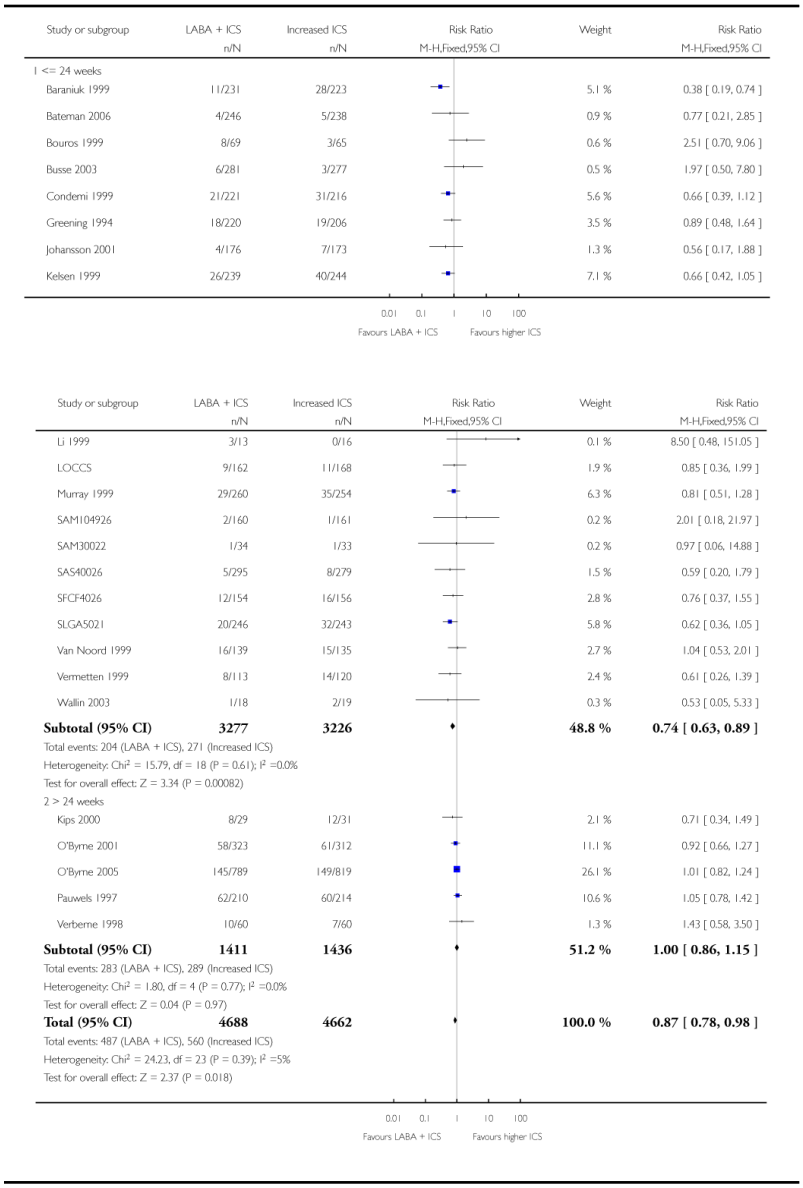

Analysis 2.7. Comparison 2 LABA + ICS versus higher dose ICS (subgroup and sensitivity analyses), Outcome 7 # patients with exacerbations requiring oral steroids: publication status of data

Review: Addition of long-acting beta2-agonists to inhaled steroids versus higher dose inhaled steroids in adults and children with persistent asthma

Comparison: 2 LABA + ICS versus higher dose ICS (subgroup and sensitivity analyses)

Outcome: 7 # patients with exacerbations requiring oral steroids: publication status of data

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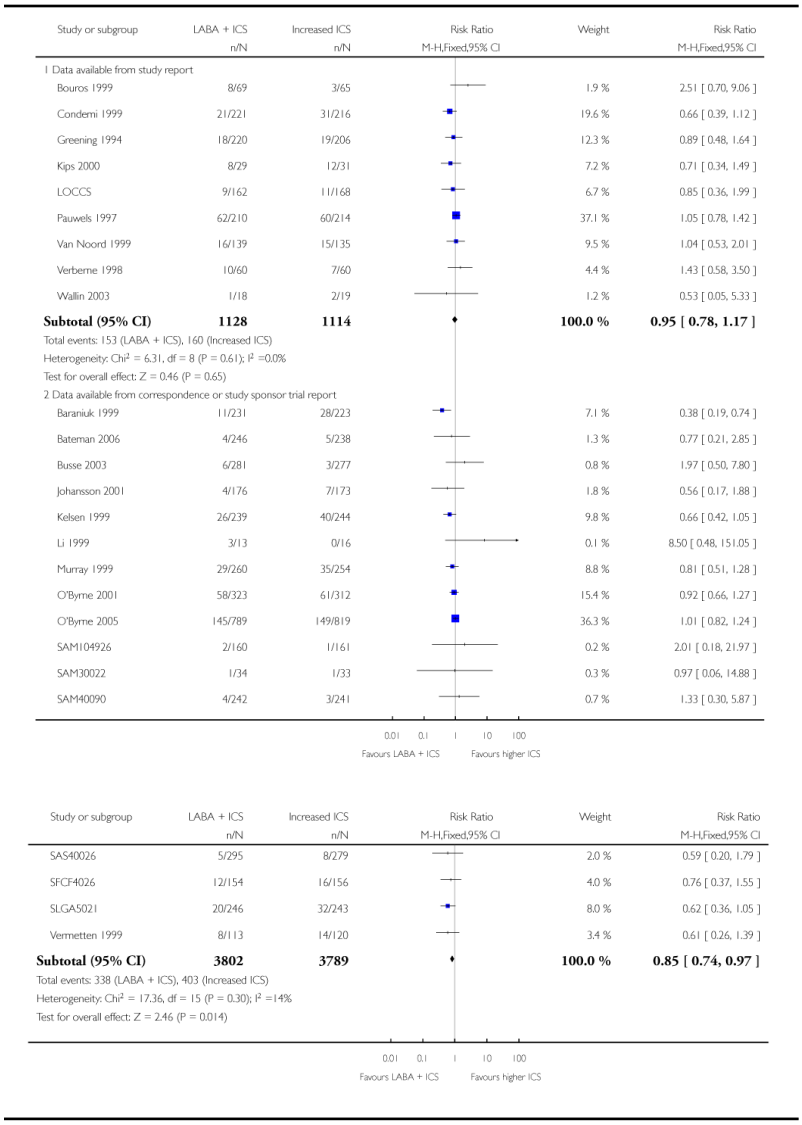
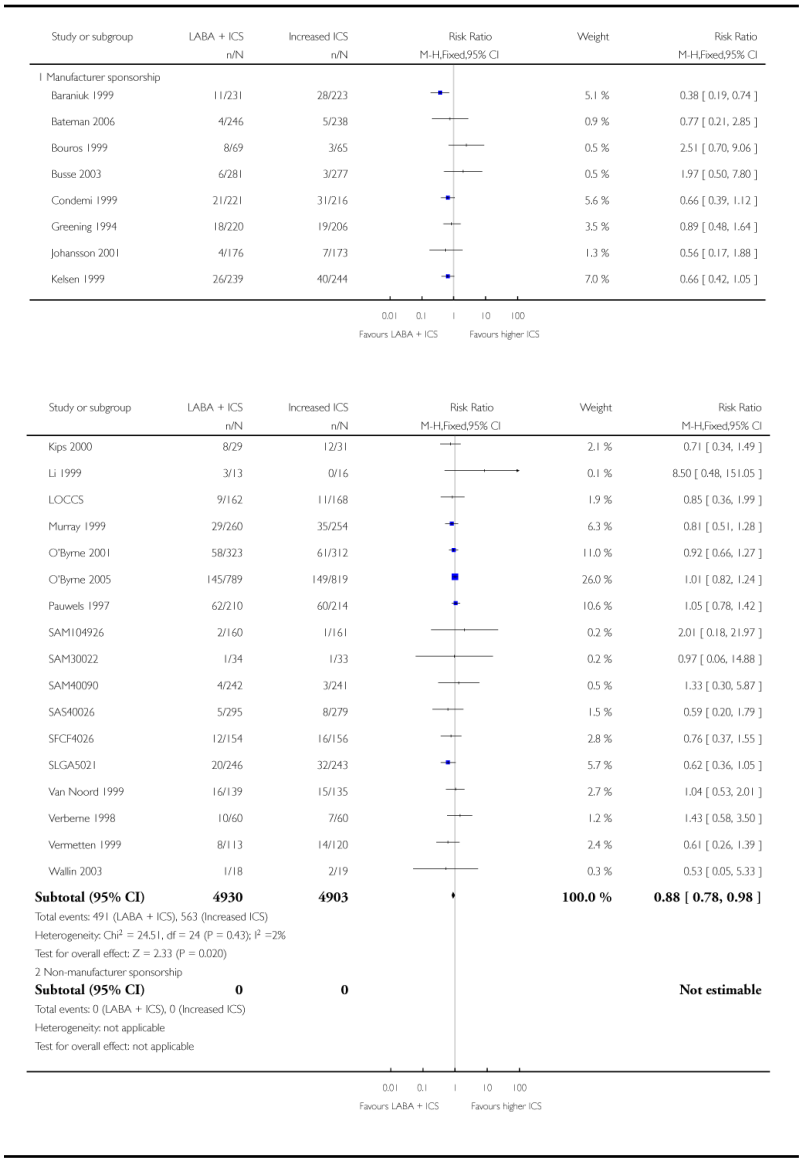


Analysis 2.8. Comparison 2 LABA + ICS versus higher dose ICS (subgroup and sensitivity analyses), Outcome 8 # patients with exacerbations requiring oral steroids: funding status

Review: Addition of long-acting beta2-agonists to inhaled steroids versus higher dose inhaled steroids in adults and children with persistent asthma

Comparison: 2 LABA + ICS versus higher dose ICS (subgroup and sensitivity analyses)

Outcome: 8 # patients with exacerbations requiring oral steroids: funding status



Analysis 2.9. Comparison 2 LABA + ICS versus higher dose ICS (subgroup and sensitivity analyses), Outcome 9 # patients with exacerbations requiring oral steroids: sensitivity analysis by allocation sequence generation

Review: Addition of long-acting beta2-agonists to inhaled steroids versus higher dose inhaled steroids in adults and children with persistent asthma

Comparison: 2 LABA + ICS versus higher dose ICS (subgroup and sensitivity analyses)

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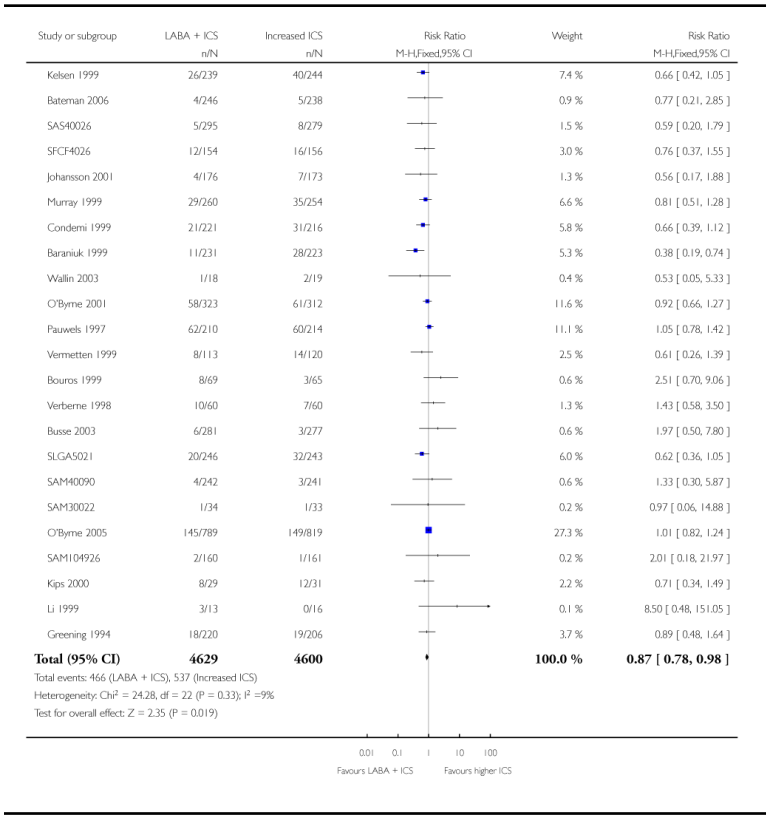
Outcome: 9 # patients with exacerbations requiring oral steroids: sensitivity analysis by allocation sequence generation



Analysis 2.10. Comparison 2 LABA + ICS versus higher dose ICS (subgroup and sensitivity analyses), Outcome 10 # patients with exacerbations requiring oral steroids: sensitivity analysis by allocation concealment

Review: Addition of long-acting beta2-agonists to inhaled steroids versus higher dose inhaled steroids in adults and children with persistent asthma

Comparison: 2 LABA + ICS versus higher dose ICS (subgroup and sensitivity analyses)

Outcome: 10 # patients with exacerbations requiring oral steroids: sensitivity analysis by allocation concealment

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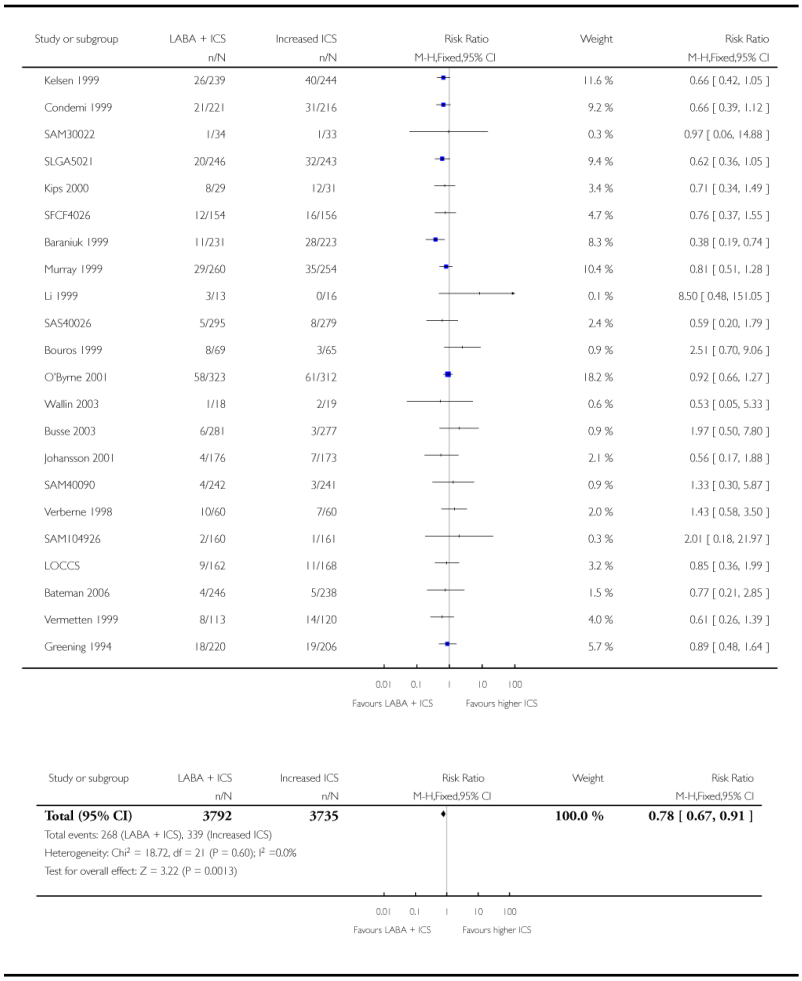
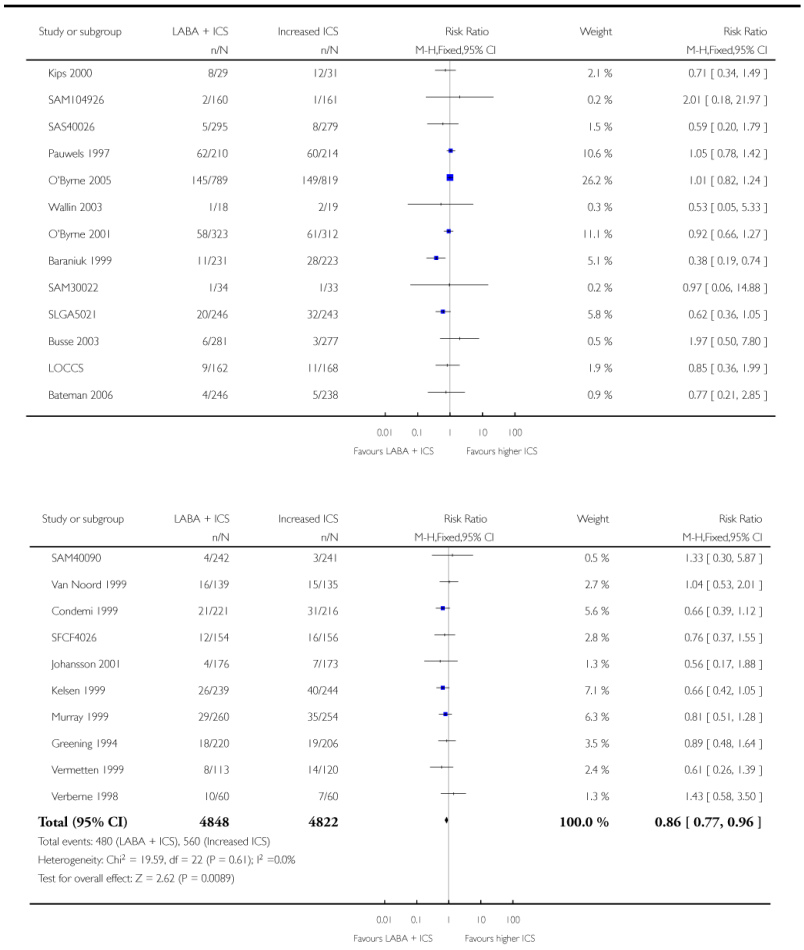


Analysis 2.11. Comparison 2 LABA + ICS versus higher dose ICS (subgroup and sensitivity analyses), Outcome 11 # patients with exacerbations requiring oral steroids: sensitivity analysis by blinding

Review: Addition of long-acting beta2-agonists to inhaled steroids versus higher dose inhaled steroids in adults and children with persistent asthma

Comparison: 2 LABA + ICS versus higher dose ICS (subgroup and sensitivity analyses)

Outcome: 11 # patients with exacerbations requiring oral steroids: sensitivity analysis by blinding



Analysis 2.12. Comparison 2 LABA + ICS versus higher dose ICS (subgroup and sensitivity analyses), Outcome 12 # patients with exacerbations requiring hospitalisation: children versus adults

Review: Addition of long-acting beta2-agonists to inhaled steroids versus higher dose inhaled steroids in adults and children with persistent asthma

Comparison: 2 LABA + ICS versus higher dose ICS (subgroup and sensitivity analyses)

Outcome: 12 # patients with exacerbations requiring hospitalisation: children versus adults

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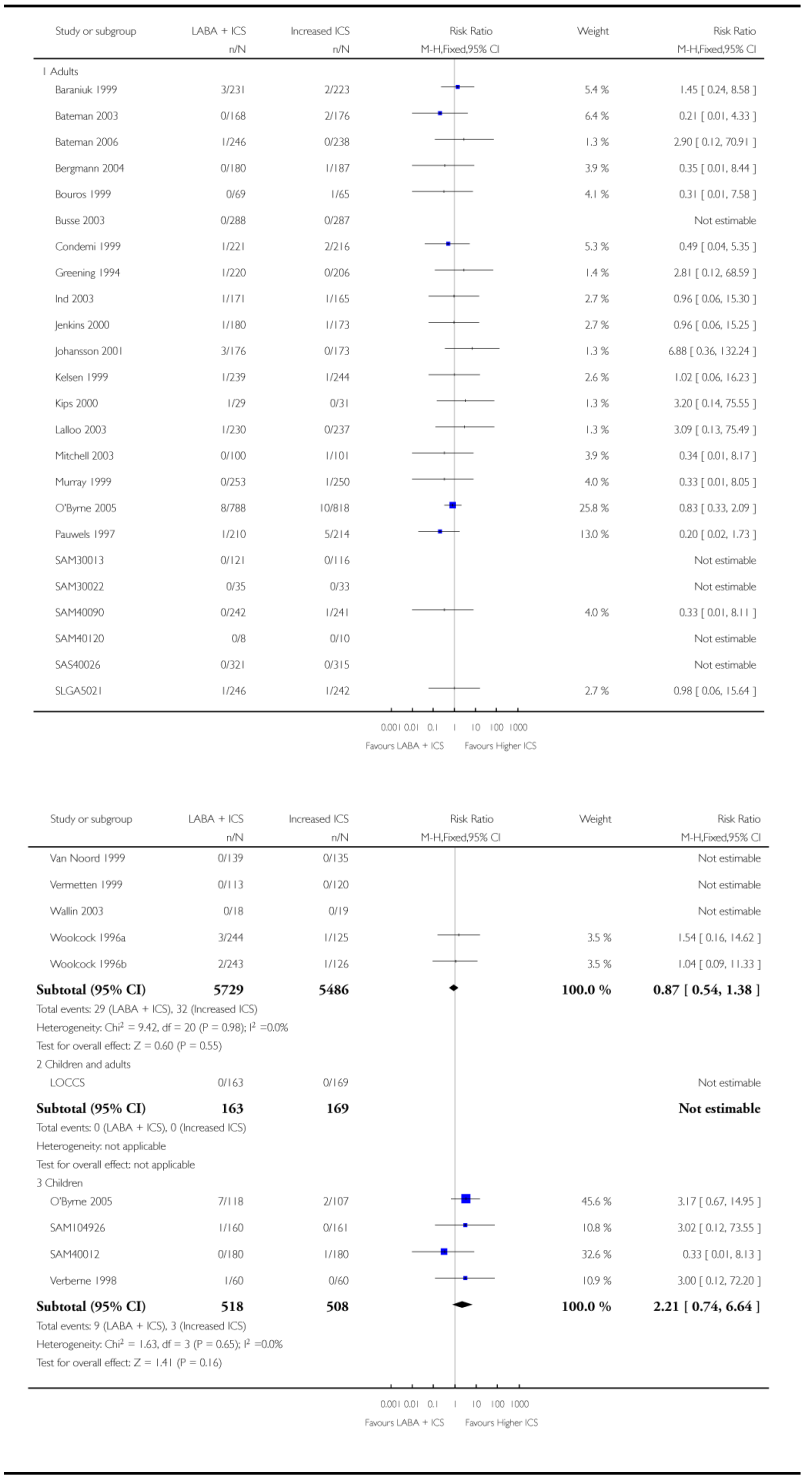

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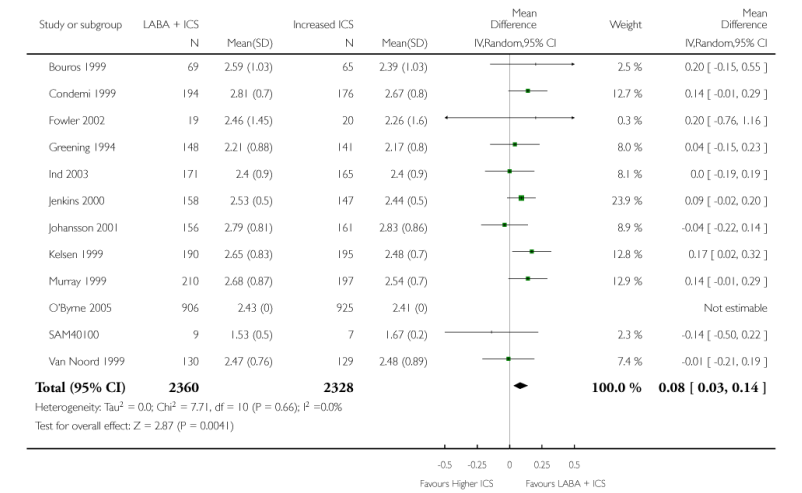
Analysis 3.1. Comparison 3 WMD archive, Outcome 1 FEV1 (L) at endpoint

Review: Addition of long-acting beta2-agonists to inhaled steroids versus higher dose inhaled steroids in adults and children with persistent asthma

Comparison: 3 WMD archive

Outcome: 1 FEV1 (L) at endpoint

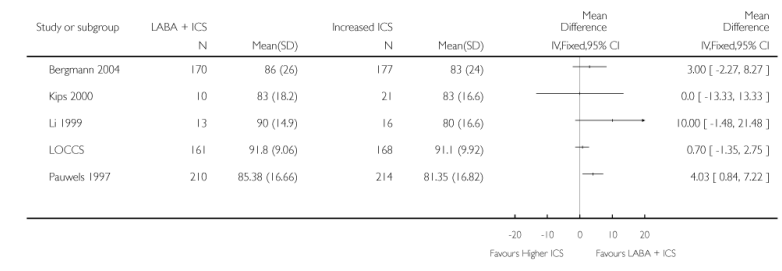


Analysis 3.2. Comparison 3 WMD archive, Outcome 2 FEV1 (% predicted) at endpoint

Review: Addition of long-acting beta2-agonists to inhaled steroids versus higher dose inhaled steroids in adults and children with persistent asthma

Comparison: 3 WMD archive

Outcome: 2 FEV1 (% predicted) at endpoint

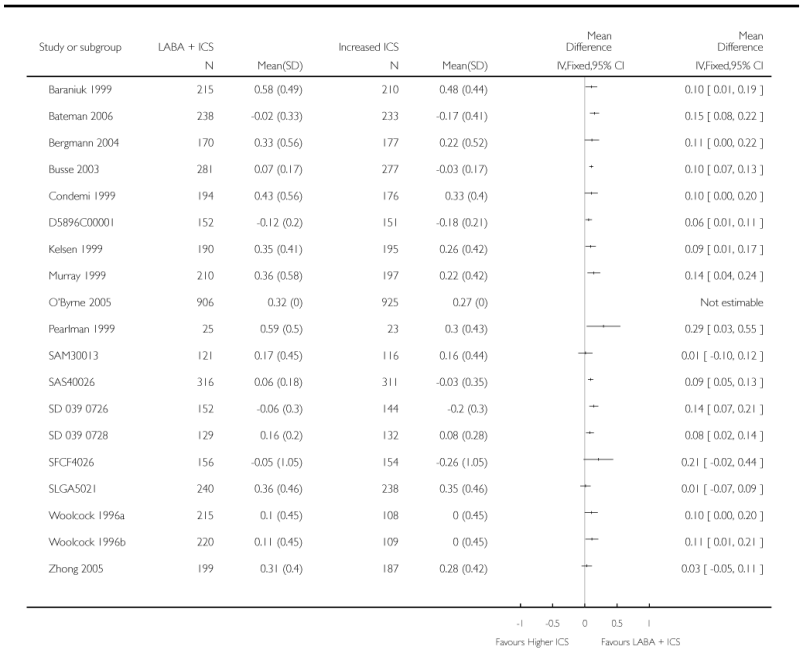


Analysis 3.3. Comparison 3 WMD archive, Outcome 3 Change in FEV1 (L) at endpoint

Review: Addition of long-acting beta2-agonists to inhaled steroids versus higher dose inhaled steroids in adults and children with persistent asthma

Comparison: 3 WMD archive

Outcome: 3 Change in FEV1 (L) at endpoint

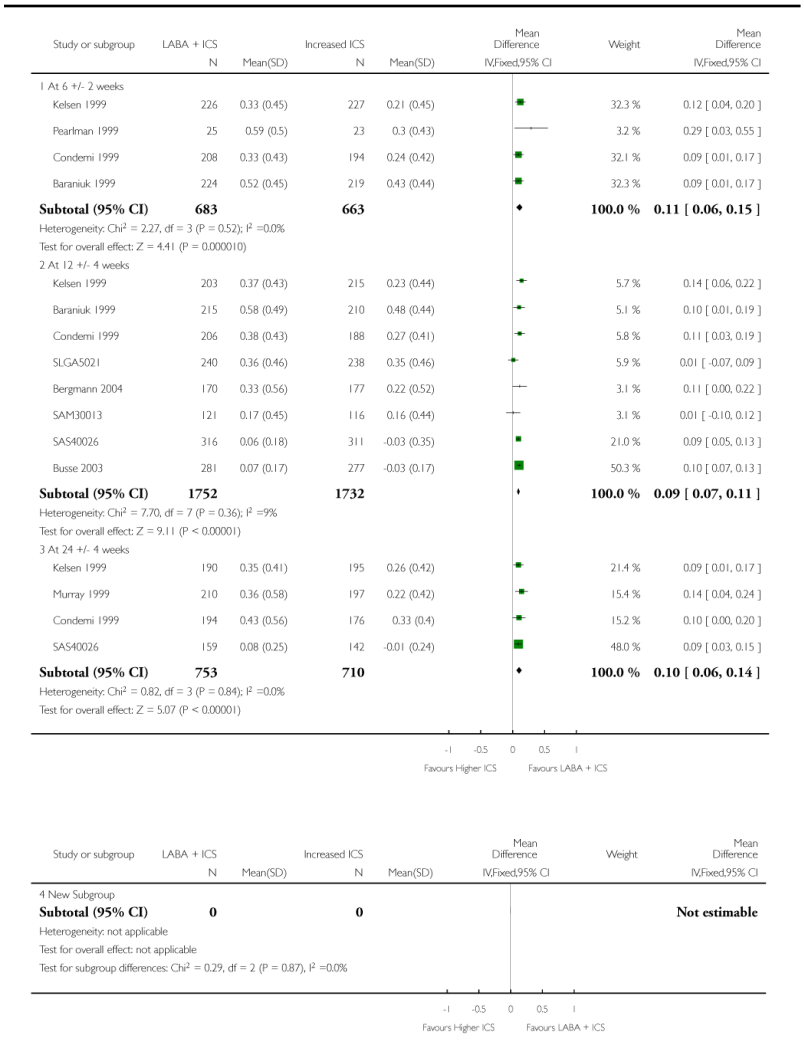


Analysis 3.4. Comparison 3 WMD archive, Outcome 4 Change in FEV1 (L) stratifying on treatment period

Review: Addition of long-acting beta2-agonists to inhaled steroids versus higher dose inhaled steroids in adults and children with persistent asthma

Comparison: 3 WMD archive

Outcome: 4 Change in FEV1 (L) stratifying on treatment period



Analysis 3.5. Comparison 3 WMD archive, Outcome 5 Morning PEF (L/min) at endpoint

Review: Addition of long-acting beta2-agonists to inhaled steroids versus higher dose inhaled steroids in adults and children with persistent asthma

Comparison: 3 WMD archive

Outcome: 5 Morning PEF (L/min) at endpoint

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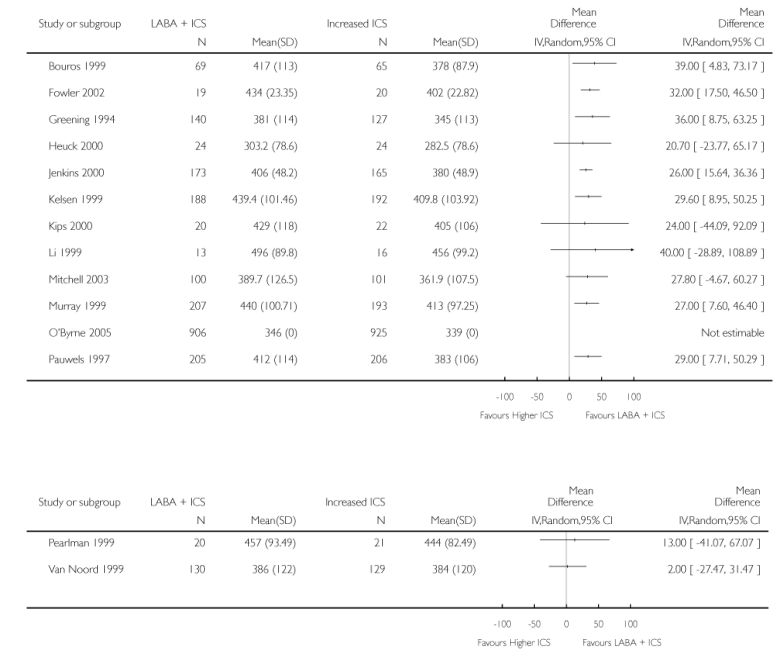

Analysis 3.6. Comparison 3 WMD archive, Outcome 6 Evening PEF (L/min) at endpoint

Review: Addition of long-acting beta2-agonists to inhaled steroids versus higher dose inhaled steroids in adults and children with persistent asthma

Comparison: 3 WMD archive

Outcome: 6 Evening PEF (L/min) at endpoint

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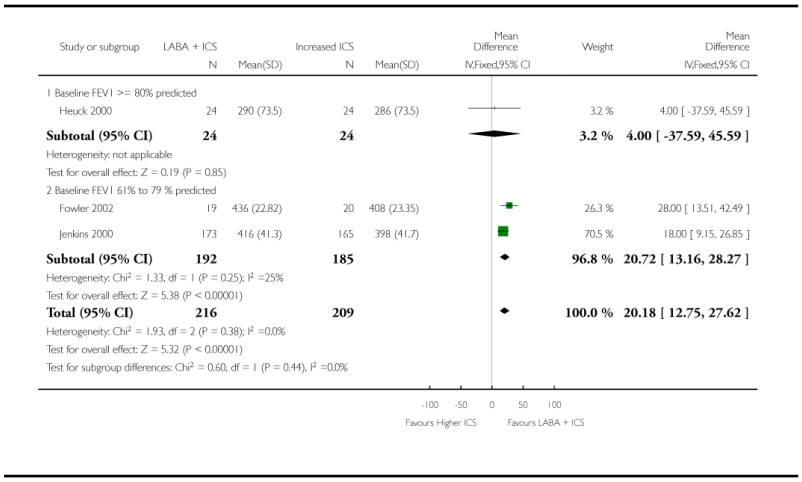

Analysis 3.7. Comparison 3 WMD archive, Outcome 7 Change in morning or clinic PEF (L/min) at endpoint

Review: Addition of long-acting beta2-agonists to inhaled steroids versus higher dose inhaled steroids in adults and children with persistent asthma

Comparison: 3 WMD archive

Outcome: 7 Change in morning or clinic PEF (L/min) at endpoint

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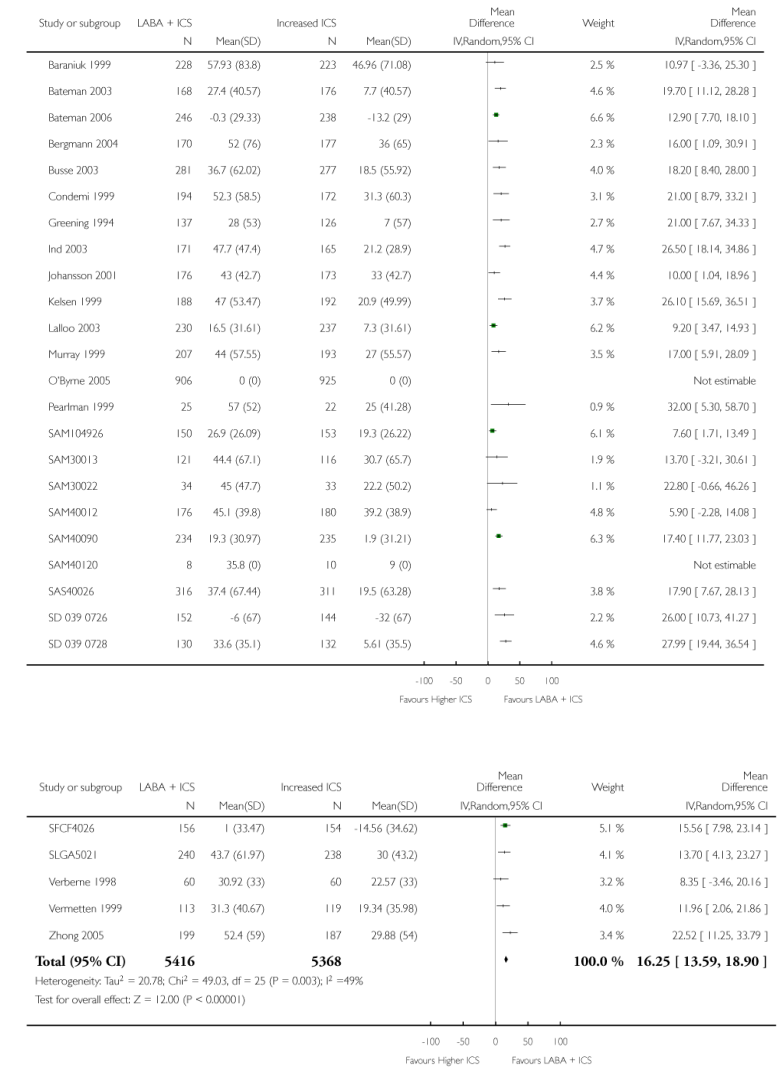

Analysis 3.8. Comparison 3 WMD archive, Outcome 8 Change in evening PEF (L/min) at endpoint

Review: Addition of long-acting beta2-agonists to inhaled steroids versus higher dose inhaled steroids in adults and children with persistent asthma

Comparison: 3 WMD archive

Outcome: 8 Change in evening PEF (L/min) at endpoint

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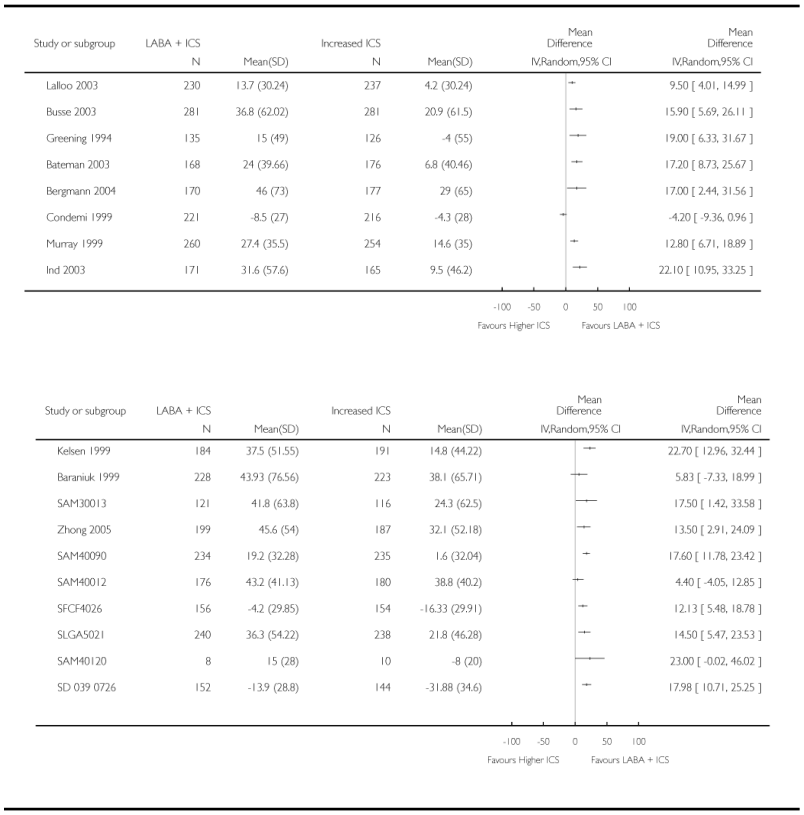

Analysis 3.9. Comparison 3 WMD archive, Outcome 9 Change in FEV1 (% predicted) at endpoint

Review: Addition of long-acting beta2-agonists to inhaled steroids versus higher dose inhaled steroids in adults and children with persistent asthma

Comparison: 3 WMD archive

Outcome: 9 Change in FEV1 (% predicted) at endpoint

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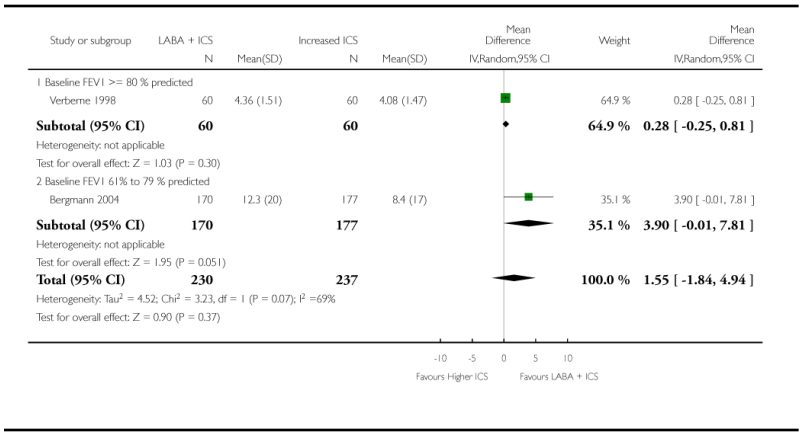
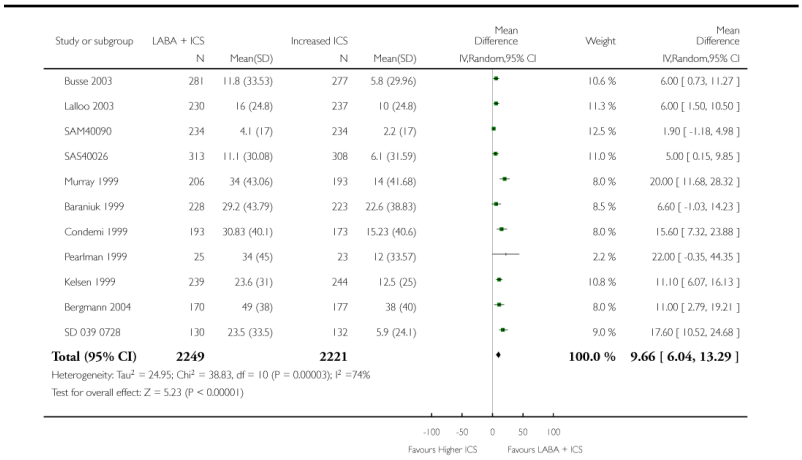


Analysis 3.10. Comparison 3 WMD archive, Outcome 10 Change in % symptom-free days at endpoint

Review: Addition of long-acting beta2-agonists to inhaled steroids versus higher dose inhaled steroids in adults and children with persistent asthma

Comparison: 3 WMD archive

Outcome: 10 Change in % symptom-free days at endpoint



Analysis 3.11. Comparison 3 WMD archive, Outcome 11 # patients with exacerbations requiring oral steroids

Review: Addition of long-acting beta2-agonists to inhaled steroids versus higher dose inhaled steroids in adults and children with persistent asthma

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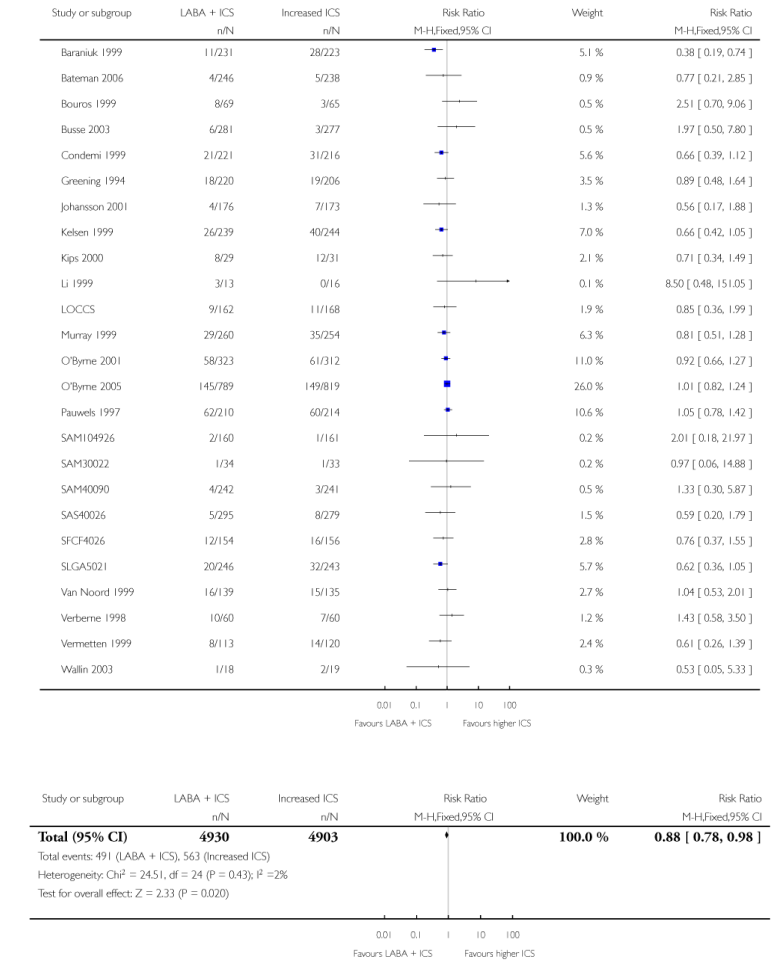
Comparison: 3 WMD archive

Outcome: 11 # patients with exacerbations requiring oral steroids



Appendix 1. 2009 update: new studies included

Bateman 2006; D5896C00001; Green 2006; Joshi 2005; LOCCS; O'Byrne 2005; SAM30013; SAM30022; SAM40012; SAM40090;SAM40120; SAS40013; SAS40026; SD 039 0726; SD 039 0728; SFCF4026; SLGA5021; Zhong 2005.

Appendix 2. Assessment of study quality

Assessment of methodological quality

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Studies to be included underwent quality assessment, performed independently by two reviewers (IRG or MNC and FMD), 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 1996 and summarised as follows:

1. Was the study described as randomised (1 = yes; 0 = no)?
2. Was the study described as double-blind (1 = yes; 0 = no)?
3. Was there a description of withdrawals and dropouts(1 = yes; 0 = no)?
4. Was the method of randomisation well described and appropriate (1 = yes; 0 = no)?
5. Was the method of double blinding well described and appropriate (1 = yes; 0 = no)?
6. Deduct one point if methods for randomisation or blinding were inappropriate.

Appendix 3. GSK randomisation procedures

The procedures for randomising GSK sponsored studies has 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 through RandAll, and is restricted so that only those reviewing the data are unblinded to treatment group allocation.

HISTORY

Protocol first published: Issue 1, 2000

Review first published: Issue 4, 2005

Date	Event	Description
21 April 2008	Amended	Converted to new review format.

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

We have adopted a risk of bias assessment rather than using Jadad scores as a basis for judging the degree to which the design of the eligible studies protects against bias.

WHAT'S NEW

Last assessed as up-to-date: 25 June 2008.

Date	Event	Description
26 June 2008	New citation required and conclusions have changed	18 new studies included in the review (see Appendix 1). We obtained unpublished and published data on exacerbations requiring steroids and hospitalisation; lung function (am PEF; pm PEF; FEV1); symptoms; rescue medication use and adverse events We applied the Cochrane Collaboration 'Risk of bias' tool to the studies included in the review. Generic inverse variance has also been used to calculate effect estimates for continuous data where only mean differences and 95% confidence intervals or standard errors were available in the original trial reports The addition of evidence from the new studies and the incorporation of unpublished data from the original studies tightened the confidence interval around the pooled estimate of the primary outcome. The previous effect estimate was borderline non-statistically significant (risk ratio 0.88, P = 0.08). The estimate became statistically significant with the new data (risk ratio 0.88, P = 0.02)
2 May 2008	New search has been performed	Literature searches re-run.

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* *Indicates the major publication for the study*

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PLAIN LANGUAGE SUMMARY

The addition of long-acting beta2-agonists to inhaled steroids compared to higher doses of inhaled steroids alone as maintenance treatment for chronic asthma

When asthma is inadequately controlled with inhaled corticosteroids, either adding medication such as long-acting beta2-agonists (LABAs) or increasing the dose of inhaled corticosteroids is recommended. The purpose of this review was to establish the benefits and safety of adding long-acting beta2-agonists or increasing the dose of inhaled corticosteroids in patients with asthma that is inadequately controlled on their current dose of inhaled corticosteroids. This review analysed data from identified randomised controlled trials comparing the addition of long-acting beta2-agonists to inhaled corticosteroids versus increasing to a higher dose of inhaled corticosteroids in asthmatic children and adults.

Based on the identified trials:

1. There is a modest advantage in adding long-acting beta2-agonists to inhaled corticosteroids, compared with increasing the dose of inhaled corticosteroids, in preventing exacerbations but many patients (more than 70) need to be treated for one to have an exacerbation prevented. The results apply particularly to adults, as no group differences were observed in children. Reduction in symptoms and use of rescue beta2-agonists as well as improvement in lung function tests also slightly favour the combination of long-acting beta2-agonists to inhaled corticosteroids over a higher corticosteroid dose.
2. Apart from an increased rate of tremor and less oral thrush, there is no apparent difference in the risk of side effects or rates of withdrawal from treatment because of side effects between the treatment options, but the long-term side effects of inhaled corticosteroids were seldom monitored. However, the trends towards an increased risk of moderate and severe exacerbations in children receiving combination therapy raises concern about this therapy, particularly in view of the modest improvement shown.

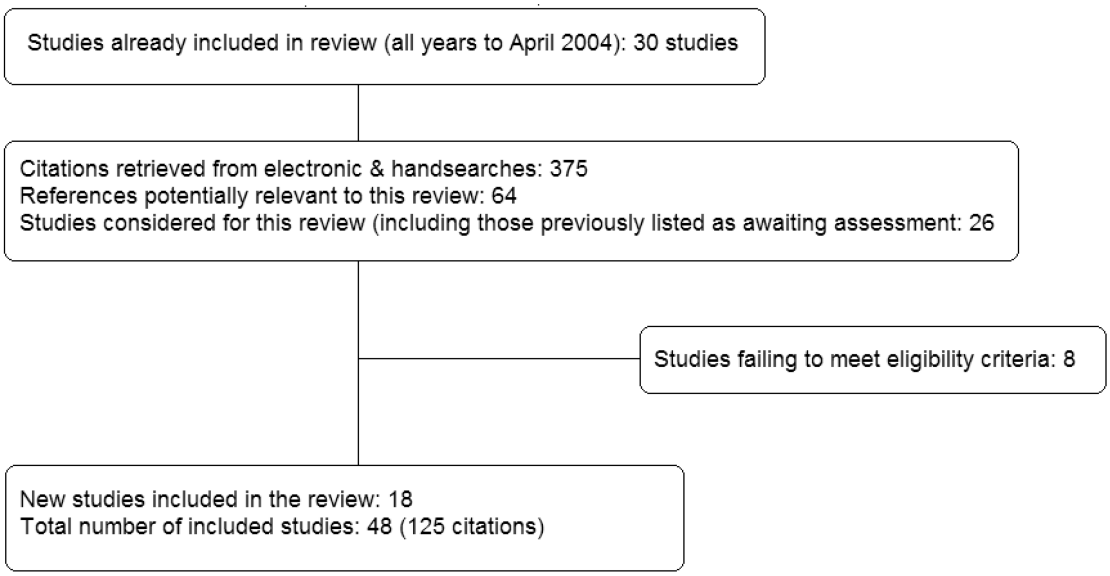

Figure 1.
Literature flow diagram for June 2008 update of the review.

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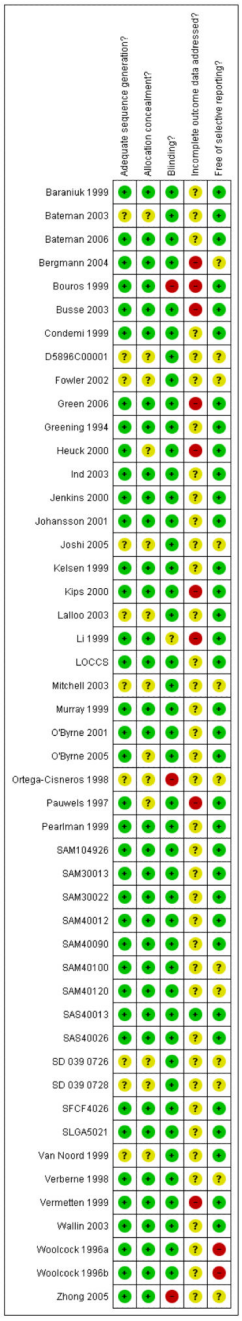

Figure 2.

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

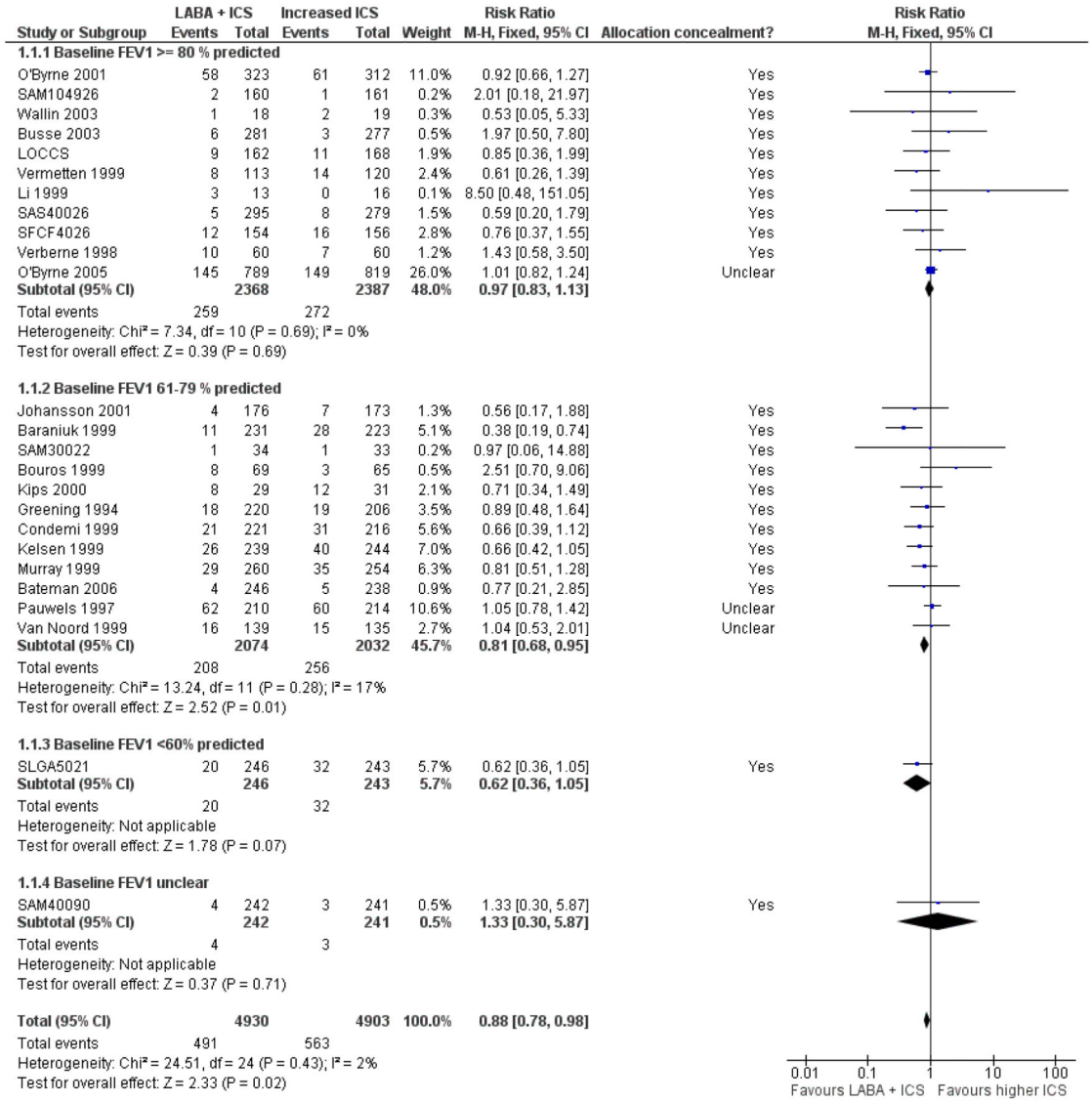

Figure 3.

Forest plot of comparison: 1 LABA + ICS versus higher dose ICS, outcome: 1.1 # patients with exacerbations requiring oral steroids.

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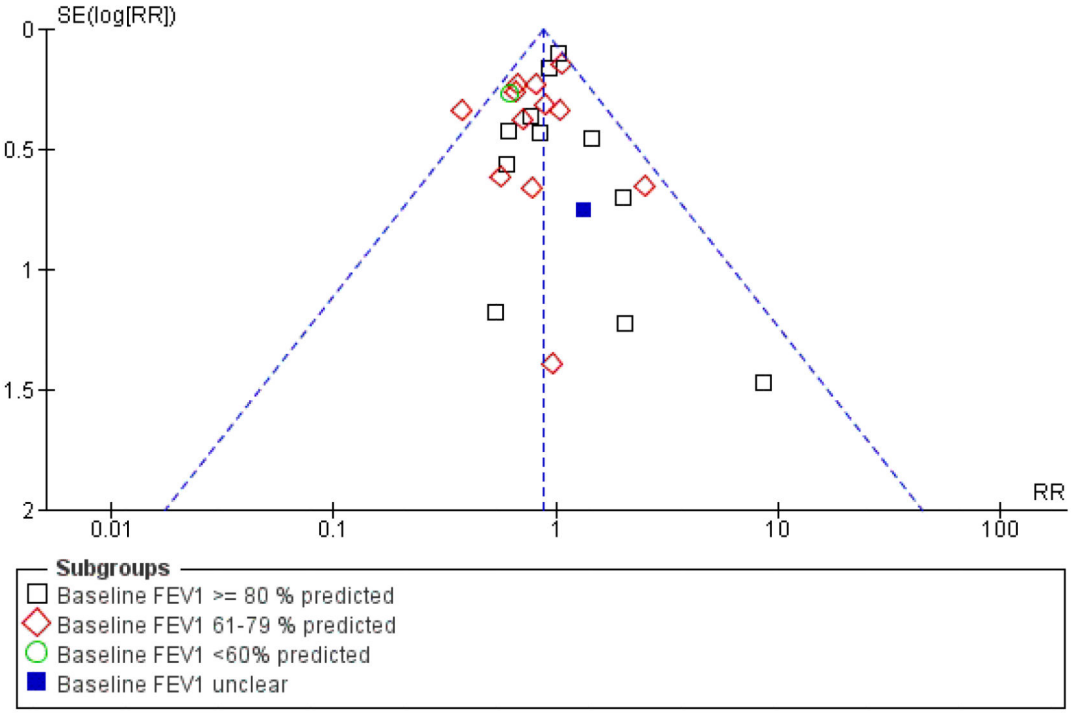

Figure 4.

Funnel plot of comparison: 1 LABA + ICS versus higher dose ICS, outcome: 1.1 # patients with exacerbations requiring oral steroids.

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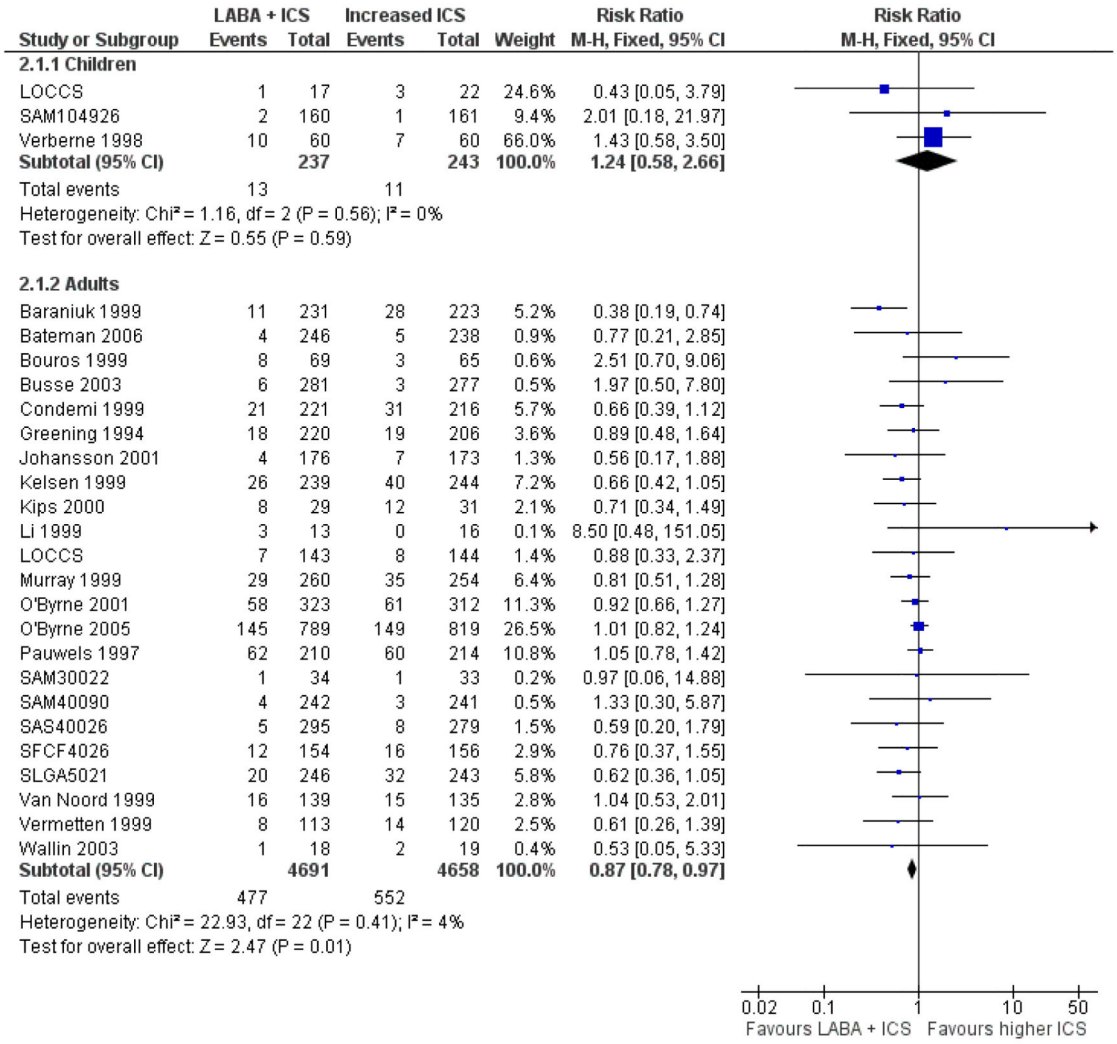

Figure 5.

Forest plot of comparison: 2 LABA + ICS versus higher dose ICS (subgroup and sensitivity analyses), outcome: 2.4 # patients requiring oral steroids: children versus adults.

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Table 1

Search history

Years	Detail
All years to April 2004	Citations identified: 593
	Excluded: 551 for the following reasons
	1 Duplicate references (N = 209)
	2 Not a randomised controlled trial (N = 68) or ongoing trial (N = 14)
	3 Subjects were not asthmatics (N = 4)
	4 No consistent intervention with inhaled corticosteroids in all subjects (N = 41)
	5 Intervention was not regular inhaled long-acting ß2 agonists (N = 19)
	6 Control intervention was not inhaled corticosteroids alone (N = 64)
	7 Duration of intervention < 30 days (N = 45)
	8 Outcomes 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 non-permitted agent (n = 1)
	11 Examination of the combination of long acting beta 2-agonist and inhaled corticosteroid to the same dose of inhaled corticosteroid alone (N = 49)
	Due to the large number of citations considered, the reasons for exclusion are provided only for published randomised controlled trials

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Table 2

Risk status

Study	Control group rate	Risk quartile
Li 1999	0.00	Low
SAM104926	0.01	Low
Busse 2003	0.01	Low
SAM40090	0.01	Low
Bateman 2006	0.02	Low
SAS40026	0.03	Low
SAM30022	0.03	Low
Johansson 2001	0.04	Low/medium
Bouros 1999	0.05	Low/medium
LOCCS	0.07	Low/medium
Greening 1994	0.09	Low/medium
SFCF4026	0.09	Low/medium
Wallin 2003	0.11	Low/medium
Van Noord 1999	0.11	Medium/high
Verberne 1998	0.12	Medium/high
Vermetten 1999	0.12	Medium/high
Baraniuk 1999	0.13	Medium/high
SLGA5021	0.13	Medium/high
Murray 1999	0.14	Medium/high
Condemi 1999	0.14	High
Kelsen 1999	0.16	High
O'Byrne 2005	0.18	High
O'Byrne 2001	0.20	High
Pauwels 1997	0.28	High
Kips 2000	0.39	High