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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 &2 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 β_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 β_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 β_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 B2 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 B₂ agonists do not seem to have any effect on overall severity of asthma, nor on inflammation (Sears 1998). Long-acting β_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 β_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 B₂ 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 β_2 agonists have been shown to reduce daytime and nighttime symptoms, improve quality of sleep, reduce requirement for shortacting B₂ 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 β_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 β_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 β_2 agonists, leukotriene receptor antagonists or theophylline. Of all add-on therapies, long-acting β_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 β_2 agonists for adults, children, toddlers and infants/ toddlers.

In adults, all but the British guidelines prefer the addition of long-acting β_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 B₂ agonists if control is unsatisfactory with 400 mcg/day of CFCbeclomethasone 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 β_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 BDPequivalent, 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 β_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 β_2 agonist. In contrast, the British (BTS 2008 (updated June 09)) guidelines recommend the addition of long-acting B₂ 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 β_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 β_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 β_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 β_2 agonist; and

3. were limited to adult trials.

However, the safety of long-acting β_2 agonists alone or in combination with inhaled corticosteroids has been challenged. There have been clear indications that the use of long-acting β_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 β_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 β_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 β_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 β_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 β_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 β_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 β_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 β_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 β_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 β_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 β_2 agonists and short courses of oral corticosteroids were permitted rescue interventions.

Types of outcome measures

<u>Primary outcomes:</u> 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 B2 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 flutisolide)).

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 I² 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).

- 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 B2 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 failsafe 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 websites, 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 β_2 **agonist, delivery device, inhaled steroid and co-treatment:** The long-acting β_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 β_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 β_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 β_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 β_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 β_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 symptomfree 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 β_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 -0.23 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.

<u>Adverse events:</u> 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 B2 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 FEV1 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 β_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 β_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.

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 β_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 B2 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 MOSE 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 oral or injectable corticosteroids within 4 weeks prior to the study; use of oral or injectable corticosteroids within 4 weeks prior to the study; use of oral or injectable corticosteroids within 4 weeks prior to the study; use of oral or injectable corticosteroids within 4 weeks prior to the study; use of oral or injectable corticosteroids within 4 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-countel medication that might affect the course of asthma or interact with sympathomimet 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 exacerbatic 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; sympto 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

Authors' judgement	Description
Yes	Computer-generated random numbers
Yes	Numbered coded inhalers supplied by pharmacy
Yes	Double-dummy design; use of identical placebo
Unclear	"Analyses were based on data from the intent-to- treat population, consisting of all patients exposed to the study drug."
Yes	Data available for meta-analysis
	Yes Yes Unclear

Bateman 2003

Methods	Parallel-group, multicentre (37 centres in 6 countries) Jadad quality score = 5 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	
Participants		
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: pm 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 obta	ained
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 % PRED FEV1 (mean): 70 BASELINE % PRED FEV1 (mean): 70 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, nedocromis sodium, ketotifen, methylxanthines, anti-cholinergica 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: pm SABA	
Outcomes	PULMONARY FUNCTION TEST: am PEF*; pm PEF; FEV1 SYMPTOM SCORES: Daytime symptoms; nightime 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 DOSE OF ICS: Mean mcg/day BDP equivalent: 800 to 1000 of BDP of 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 treate with 800 to 1000 mcg/day of BUD or BDP (or 500 FP) per day for at least 3 month prior to study EXCLUSION CRITERIA: Previous therapy with inhaled LABA, oral beta-agonist 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 symptom score >= 10 points (sums of scores from 14 days and nights); excluded if incomplet 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

	mcg bid (1 inhaler) CONTROL GROUP: (FP 500) DEVICE: Diskus NUMBER OF DEVICES: 1 COMPLIANCE: Assessed usin	weeks SALM50) fluticasone 200 mcg bid + salmeterol 50 fluticasone 500 mcg bid g diary cards ine, cholinergic drugs or leukotrienes if dose was not
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

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 % PREDICTED FEV1: 60% to 79% (estimated) BASELINE 0OSE 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 leas 1 month prior to enrolment, at a constant daily dose of 500 mg EXCLUSION CRITERIA: One - 100 mg/day of population of 100 mg/day of 100 mg/day BASELINE women; patients on B-blocker therapy or hypersensitivity of sympathomimetic amines; received a short course of oral corticosteroid in the 6

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	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 OF ICS DURING RUN-IN: BDP 500 mcg/day DOSE OF ICS DURINO PERIOD: None INTERVENTION 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 nightime 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	used)	ICS 2 and 24 weeks (only those at 12 weeks 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."

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 asthma % ELIGIBLE OF SC % RUN-IN PARTIC RANDOMISED: 43' WITHDRAWALS: 1 AGE mean: 36.9 yea GENDER (% male): SEVERITY: Modera BASELINE % PREI BASELINE % PREI BASELINE 00SE (ASTHMA DURATI ATOPY(%): Not rep SMOKERS: None ELIGIBLITY CRIT in FEV1 by 15% or g to 80% of predicted or months EXCLUSION asthma in the past 30 positive pregnancy te exacerbation CRITERIA FOR RA of predicted normal; randomisation: an av evening PEF variatic asthma; 3 or more da asthma; 3 or more da		Salm50: 221; FP250: 216) lm50: 19; F250: 30 EV1: 61	
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 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 MORE 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."

		cinteria.
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 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 f 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</li--> 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) > 159 increase in FEV1 post-SABA; 2) > 20% within-day variability in PEF assesed 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 wee 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 infectio 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* Full-text article Funding source: Not disclosed Methodology and data: TJL emailed 17 April 2008. Response from RG with detai of randomisation and data User defined: 800	
Notes		
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 ha received short course of oral corticosteroids in the 6 weeks prior to start of study or

	newly prescribed asthma ther prior to entering the study. Pi baseline. Patients who had a investigator's opinion should concurrent medical condition or renal dysfunction, thyroto: neoplastic disease, tuberculo: prescribed therapy 2 weeks p currently receiving other long who were pregnant or lactatin precautions, patients whose f patients who were receiving month, patients previously et abuse, known hypersensitivit dipropionate CRITERIA FOR RANDOM over 1 week of >= 15% (high percentage of highest value;)	short courses in the last year. Patients who had received apy or who had changed asthma therapy in the 6 weeks titents with FEV1 < 50% or predicted at the start of medical or physiological condition which in the preclude them from the study, or one or more of the s: severe cardiac disease, clinically significant hepatic kicosis, uncontrolled diabetes mellitus, history of active sis, acute respiratory infection which required rior to study, patients receiving beta-blockers, patients g-acting B2-adrenoreceptor agonists, female patients is for were not taking adequate contraceptive istory over the previous year was not documented, or had received research medication in the previous arolled in this study, patients with evidence of alcohol y to salbutamol, salmeterol or beclomethasone ISATION DURING RUN-IN: Period variation in PEF test evening PEF minus lowest morning PEF as a symptoms on >= 4 of 7 days during the second	
Interventions	baseline week 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: Nightime 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 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 nightime 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 computerise 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	
	Yes		

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	% 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 LABA + ICS vs INCREASED dose of ICS OUTCOMES: 6, 12 18 and 24 weeks	
Interventions	OUTCOMES: 6, 12 18 and 24 we RUN-IN PERIOD: 4 weeks DOSE OF ICS DURING RUN-IN DOSE OPTIMISATION PERIOD INTERVENTION PERIOD: 6 m TEST GROUP: Combination fluti one device) INCREASED DOSE: FP 500 mcg DEVICE: MDI NUMBER OF DEVICES: 1 COMPLIANCE: Not reported	eks I: FP 250 mcg bid D: None onths icasone propionate/salmeterol 250/50 mcgs bid
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."

ree of selective reporting.	Free	of selective	reporting?	Yes
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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 ASTHIMA 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 > 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 thar 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 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 diseas 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 day in each group; % symptom-free days in each group; exacerbations severe (requirin 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 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 an nightime 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)	

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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 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 symptomati 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

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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 MOSE 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

	CONTROL GROUP: (BUD8 DEVICE: Turbuhaler NUMBER OF DEVICES: 2	12 months F) budesonide 100 mcg + formoterol 12 mcg bid 800) budesonide 400 mcg + placebo bid by means of hidden counter in inhaler
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 a User-defined number: 200	nd data: Not obtained
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 FEV1 % predicted median (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	exacerbations requiring OCS OTHER: Methacholine challenge INFLAMMATORY MARKERS:	to 4 (mean/day) e medication use; nocturnal awakenings; PD 20 methacholine before and after treatment on BAL and bronchial biopsy; mast cells in BAL; in BAL; macrophages in BAL and bronchial ted
Notes	Full-text publication Funded by Glaxo Wellcome, Alfr Confirmation of methodology and User-defined number: 400	ed Foundation and the NH&MRC of Australia d data obtained
Risk of bias		
Item	Authors' judgement	Description
Adequate sequence generation?	Yes	Computer-generated numbers in balanced blocks
Allocation concealment?	Yes	Opaque consecutive numbered envelopes containing assignment
Blinding? All outcomes	Unclear	Identical inhaler devices
Incomplete outcome data addressed? All outcomes	No	Completers analysed

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

	predicted 60% or more millilitre or less within EXCLUSION CRITEF use, or use of additiona exceeding 38.0 °C, or 1 ELIGIBILITY CRITEJ card; FEV1 > 80% pred	RIA: physician-diagnosed asthma; > 6 years; FEV1 ; > 12% reversibility to SABA or a pc20 of 8 mg per
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		nd methodology: Not obtained. TJL contacted for separate een adults and children
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 i the evening."
	Unclear	"Analyses were performed on the basis of the intention-t treat principle; all available data from all patients were included in all analyses."
Incomplete outcome data addressed? All outcomes		merudeu m un unuryses.

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

	FEV1 >= of predicted and increased b agonists or historical evidence of rever (metered dose inhaler) at a constant da dipropionate or 800 mcg budesonide f EXCLUSION CRITERIA: Change in of a LABA or having received a cours the screening; problems using the Aer CRITERIA FOR RANDOMISATION the following on at least 2 of the last 7 once/night because of asthma; asthma	DMISED: 203/274 (74%) DP: 101) 2 Hean: 72 rted rs ***********************************
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)

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 % PREDICTED FEV1 mean: 65 BASELINE MODER 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 adputime 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 INTER VENTION 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 performe 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 aday, 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 % 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	

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

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 gluccoorticoids		
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 co only be seen by investigators CO-TREATMENT: pm SABA		
Outcomes	PULMONARY FUNCTION TEST: FEV1 predicted; am PEF; pm PEF SYMPTOM SCORES: Mean daytime and nighttime symptom scores at end of stud (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 pe 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 MOED 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, nijectable, or intranasal corticosteroid therapy within the previous month; use of aliy 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 digease 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 nightrime awakenings due to asthma requiring treatment with albuterol during the 7 days immediately preceding the randomisation per
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) mg bid CONTROL GROUP: (FP 250) ff DEVICE: Metered-dose inhaler NUMBER OF DEVICES: 2 COMPLIANCE: Evaluated CO-TREATMENT: prn SABA	salmeterol 50 mg bid + fluticasone propionate 100 uticasone propionate 250 mg bid
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

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 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

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 00SE 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	entions 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	

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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 % 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

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 0DSE 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)

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 MORE WITHER PROJECTION (% The State of t	
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: Re WITHDRAWALS: Repor Primary outcome measure	ted
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

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 LABA + ICS versus INCREASED DOSE ICS OUTCOMES: 6 weeks RUN-IN PERIOD: 2 weeks INTERVENTION 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 	
Interventions		
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	

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	

Confirmation of methodology and data not obtained User defined: 400

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; >= 20 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		

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 PEI 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	% RUN-IN PARTICIPANTS R RANDOMISED: 636 (FP/SAL WITHDRAWALS: FP/SAL: 32 AGE mean: 39 GENDER (% male): 38 SEVERITY: Moderate BASELINE % PREDICTED FI BASELINE MORE OF ICS: NO ASTHMA DURATION: Not re ATOPY (%): Not reported ELIGIBILITY CRITERIA: 12 days prior to randomisation (do months; FEV1 65% to 95% pre EXCLUSION CRITERIA: Life of study entry; OCS within 30 c	ELIGIBLE OF SCREENED POPULATION: Not reported UN-IN PARTICIPANTS RANDOMISED: Not reported NDOMISED: 636 (FP/SAL: 321; FP: 315) IFHDRAWALS: FP/SAL: 32; FP: 44 E mean: 39 NDER (% male): 38 //ERITY: Moderate SELINE % PREDICTED FEV1: 80.4 SELINE DOSE OF ICS: Not reported IFHMA DURATION: Not reported		
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: pm 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 MORATION: 19.7 ATOPY (%): Not reported ELIGIBILITY CRITERIA: > 16 years; documented clinical diagnosis of asthma for at least 6 months prior to screening; stable condition; maintenance asthma treatment with a low to medium dose ICS for at least 4 weeks prior to the screening; FEV1 60% to 90% predicted EXCLUSION CRITERIA: Not reported ELIGIBILITY CRITERIA: Not reported ELIGIBILITY CRITERIA: Not reported	
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 MOSE 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 treatment with a stable dose of inhaled 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?

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 % PREDICTED FEV1: 90 BASELINE MORATION: 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 receiven at least one dose of study medication and for whom the assessment data f	

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 % PREDICTED FEV1(mean): 60.5% BASELINE 00SE 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

	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 variatior 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

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 00SE 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-agonist; 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 follow therapy instructions, inability to inhale medications adequately or inability to follow therapy instructions, inability to inhale medications dequately 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	
Interventions	Intions 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: Some INTERVENTION PERIOD: 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?	Unclear	Not clear how population for primary outcome Incomplete diary card data not included in
All outcomes		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."

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 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 that 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 o 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 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: pm 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

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	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 PEI 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 assessmen of efficacy and safety."
Free of selective reporting?	No	OCS-treated exacerbations not available for meta-analysis after request

Woolcock 1996b

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: 169) WITHDRAWALS: FP/SAL: 20; BUD: 18 AGE: mean (range): 46 (44 to 47) GENDER (% male): 54 SEVERITY: Unclear BASELINE MRED 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 i the study	
BUD = budesonide ED = emergency department F = formoterol FEV1 = forced expiratory volume in Form = formoterol FP = fluticasone GSK = GlaxoSmithKline ICS = inhaled corticosteroids ITT = intention-to-treat	n one second		
LABA = long-acting &2 agonist mcg = microgram qd = four times a day RTI = respiratory tract infection SABA = short-acting &2 agonist SAL = salmeterol Salm = salmeterol			
mcg = microgram qd = four times a day RTI = respiratory tract infection SABA = short-acting ß2 agonist SAL = salmeterol	i		

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 20	000Not 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			

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 device		
Verberne 1997	No consistent co-intervention with ICS - approximately 20% were taking regular ICS at ent		
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

 $LABA = long-acting \beta 2 agonist$

LTRA = leukotriene receptor agonist

 $SAB2 = short-acting \beta 2 agonist$

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]

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	

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	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	

Comparison 2

LABA + ICS	versus higher	dose ICS	(subgroup and	l 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

trial report

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]

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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Study or subgroup	LABA + ICS n/N	Increased ICS n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
I Baseline FEV1 >= 80 % pr	redicted				
O'Byme 2001	58/323	61/312	-	11.0 %	0.92 [0.66, 1.27]
SAM104926	2/160	1/161		0.2 %	2.01 [0.18, 21.97]
Wallin 2003	1/18	2/19		0.3 %	0.53 [0.05, 5.33]
Busse 2003	6/281	3/277		0.5 %	1.97 [0.50, 7.80]
LOCCS	9/162	11/168		1.9 %	0.85 [0.36, 1.99]
Vermetten 1999	8/113	14/120		2.4 %	0.61 [0.26, 1.39]
Li 1999	3/13	0/16		0.1 %	8.50 [0.48, 151.05]
SAS40026	5/295	8/279		1.5 %	0.59 [0.20, 1.79]
SFCF4026	12/154	16/156		2.8 %	0.76 [0.37, 1.55]
Verberne 1998	10/60	7/60		1.2 %	1.43 [0.58, 3.50]
O'Byrne 2005	145/789	149/819	-	26.0 %	1.01 [0.82, 1.24]
Subtotal (95% CI)	2368	2387	•	48.0 %	0.97 [0.83, 1.13]
Total events: 259 (LABA + I	CS), 272 (Increased ICS)			
Heterogeneity: Chi ² = 7.34,		=0.0%			
Test for overall effect: Z = 0 2 Baseline FEVI 61-79 % pro	()				
Johansson 2001	4/176	7/173		1.3 %	0.56 [0.17, 1.88]
Baraniuk 1999	11/231	28/223		5.1 %	0.38 [0.19, 0.74]
SAM30022	1/34	1/33		0.2 %	0.97 [0.06, 14.88]
Bouros 1999	8/69	3/65		0.5 %	2.51 [0.70, 9.06]
Kips 2000	8/29	12/31		2.1 %	0.71 [0.34, 1.49]
Greening 1994	18/220	19/206		3.5 %	0.89 [0.48, 1.64]
Condemi 1999	21/221	31/216	-	5.6 %	0.66 [0.39, 1.12]
Kelsen 1999	26/239	40/244	•	7.0 %	0.66 [0.42, 1.05]
Murray 1999	29/260	35/254	+	6.3 %	0.81 [0.51, 1.28]
	4/246	5/238		0.9 %	0.77 [0.21, 2.85]



Risk Ratio	Weight	Risk Ratio	Increased ICS	LABA + ICS	Study or subgroup
M-H,Fixed,95% C		M-H,Fixed,95% CI	n/N	n/N	
1.05 [0.78, 1.42	10.6 %	+	60/214	62/210	Pauwels 1997
1.04 [0.53, 2.01	2.7 %	-	15/135	16/139	Van Noord 1999
0.81 [0.68, 0.95]	45.7 %	•	2032	2074	Subtotal (95% CI)
				6), 256 (Increased ICS)	Total events: 208 (LABA + IC
			%	$ff = (P = 0.28); ^2 = $	Heterogeneity: Chi ² = 13.24,
				2 (P = 0.012)	Test for overall effect: $Z = 2.5$
				ed	3 Baseline FEV1 <60% predic
0.62 [0.36, 1.05	5.7 %	-	32/243	20/246	SLGA5021
0.62 [0.36, 1.05]	5.7 %	•	243	246	Subtotal (95% CI)
				, 32 (Increased ICS)	Total events: 20 (LABA + ICS
					Heterogeneity: not applicable
				8 (P = 0.074)	Test for overall effect: $Z = 1.7$
					4 Baseline FEV1 unclear
1.33 [0.30, 5.87	0.5 %		3/241	4/242	SAM40090
1.33 [0.30, 5.87]	0.5 %	-	241	242	Subtotal (95% CI)
				3 (Increased ICS)	Total events: 4 (LABA + ICS),
					Heterogeneity: not applicable
				(P = 0.71)	Test for overall effect: $Z = 0.3$
0.88 [0.78, 0.98]	100.0 %	•	4903	4930	Total (95% CI)
				· · · · · ·	Total events: 491 (LABA + IC
					Heterogeneity: $Chi^2 = 24.51$,
				8 (P = 0.020)	Test for overall effect: $Z = 2.3$

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

Study or subgroup	LABA + ICS n/N	Increased ICS n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Baseline FEV >= 80 % pre	edicted				
Busse 2003	0/288	0/287			Not estimable
Lalloo 2003	1/230	0/237		1.2 %	3.09 [0.13, 75.49]
LOCCS	0/163	0/169			Not estimable
SAM104926	1/160	0/161	·	1.2 %	3.02 [0.12, 73.55]
SAS40026	0/321	0/315			Not estimable
Verberne 1998	1/60	0/60		1.2 %	3.00 [0.12, 72.20]
Vermetten 1999	0/113	0/120			Not estimable
Wallin 2003	0/18	0/19			Not estimable
Subtotal (95% CI)	1353	1368	-	3.5 %	3.04 [0.48, 19.15]
2 Baseline FEV1 61-79 % pre Baraniuk 1999	3/231	2/223		4.8 %	1.45 [0.24, 8.58]
Baraniuk 1999	3/231	2/223		4.8 %	1.45 [0.24, 8.58]
Bateman 2003	0/168	2/176		5.7 %	0.21 [0.01, 4.33]
Bateman 2003 Bateman 2006	0/168	2/176 0/238		5.7 %	0.21 [0.01, 4.33] 2.90 [0.12, 70.91]
Bateman 2006	1/246	0/238		1.2 %	2.90 [0.12, 70.91]
Bateman 2006 Bergmann 2004	1/246 0/180	0/238		1.2 % 3.5 %	2.90 [0.12, 70.91] 0.35 [0.01, 8.44]
Bateman 2006 Bergmann 2004 Bouros 1999	1/246 0/180 0/69	0/238 1/187 1/65		1.2 % 3.5 % 3.6 %	2.90 [0.12, 70.91] 0.35 [0.01, 8.44] 0.31 [0.01, 7.58]
Bateman 2006 Bergmann 2004 Bouros 1999 Condemi 1999	1/246 0/180 0/69 1/221	0/238 1/187 1/65 2/216		1.2 % 3.5 % 3.6 % 4.8 %	2.90 [0.12, 70.91] 0.35 [0.01, 8.44] 0.31 [0.01, 7.58] 0.49 [0.04, 5.35]
Bateman 2006 Bergmann 2004 Bouros 1999 Condemi 1999 Greening 1994	1/246 0/180 0/69 1/221 1/220	0/238 1/187 1/65 2/216 0/206		1.2 % 3.5 % 3.6 % 4.8 %	2.90 [0.12, 70.91] 0.35 [0.01, 8.44] 0.31 [0.01, 7.58] 0.49 [0.04, 5.35] 2.81 [0.12, 68.59]
Bateman 2006 Bergmann 2004 Bouros 1999 Condemi 1999 Greening 1994 Ind 2003	1/246 0/180 0/69 1/221 1/220 1/171	0/238 1/187 1/65 2/216 0/206 1/165		1.2 % 3.5 % 3.6 % 1.2 % 2.4 %	2.90 [0.12, 70.91] 0.35 [0.01, 8.44] 0.31 [0.01, 758] 0.49 [0.04, 5.35] 2.81 [0.12, 6859] 0.96 [0.06, 15.30]
Bateman 2006 Bergmann 2004 Bouros 1999 Condemi 1999 Greening 1994 Ind 2003 Jenkins 2000	1/246 0/180 0/69 1/221 1/220 1/171 1/180	0/238 1/187 1/65 2/216 0/206 1/165 1/173		1.2 % 3.5 % 3.6 % 4.8 % 1.2 % 2.4 %	2.90 [0.12, 70.91] 0.35 [0.01, 8.44] 0.31 [0.01, 7.58] 0.49 [0.04, 5.35] 2.81 [0.12, 68.59] 0.96 [0.06, 15.30] 0.96 [0.06, 15.25]
Bateman 2006 Bergmann 2004 Bouros 1999 Condemi 1999 Greening 1994 Ind 2003 Jenkins 2000 Johansson 2001	1/246 0/180 0/69 1/221 1/220 1/171 1/180 3/176	0/238 1/187 1/65 2/216 0/206 1/165 1/173 0/173		1.2 % 3.5 % 3.6 % 4.8 % 1.2 % 2.4 % 2.4 % 1.2 %	290 [0.12, 7091] 0.35 [0.01, 844] 0.31 [0.01, 758] 0.49 [0.04, 535] 2.81 [0.12, 6859] 0.96 [0.06, 1520] 0.96 [0.06, 1525] 6.88 [0.36, 13224]

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

Risk Ratio	Weight	Risk Ratio	Increased ICS	LABA + ICS	Study or subgroup
M-H,Fixed,95% CI		M-H,Fixed,95% CI	n/N	n/N	
0.33 [0.01, 8.05]	3.5 %		1/250	0/253	Murray 1999
1.28 [0.60, 2.71]	27.9 %	+	12/925	15/906	O'Byrne 2005
0.20 [0.02, 1.73]	11.6 %		5/214	1/210	Pauwels 1997
Not estimable			0/33	0/35	SAM30022
Not estimable			0/135	0/139	Van Noord 1999
1.54 [0.16, 14.62]	3.1 %		1/125	3/244	Woolcock 1996a
1.04 [0.09, 11.33]	3.1 %		1/126	2/243	Woolcock 1996b
1.00 [0.63, 1.57]	87.1 %	•	4006	4260	Subtotal (95% CI)
			0%	$If = 17 (P = 0.94); I^2 = 0.94$ I (P = 0.99)	Total events: 34 (LABA + ICS Heterogeneity: $Chi^2 = 9.03$, d Test for overall effect: $Z = 0.0$ 3 Baseline FEVI <= 60 % pre
0.98 [0.06, 15.64]	2.4 %		1/242	1/246	SLGA5021
0.98 [0.06, 15.64]	2.4 %	-	242	246	Subtotal (95% CI)
Not estimable			0/116		Heterogeneity: not applicable Test for overall effect: Z = 0.0 4 Baseline FEV1 unclear SAM30013
0.33 [0.01, 8.13]	3.5 %		1/180	0/180	SAM40012
0.33 [0.01, 8.11]	3.5 %		1/241	0/242	SAM40090
Not estimable			0/10	0/8	SAM40120
0.33 [0.03, 3.18]	7.1 %	-	547	551	Subtotal (95% CI)
0.00 [0100, 0120]			<i>p</i> = <i>r</i>	. 2 (Increased ICS) If = 1 (P = 1.00); I ² =0.	Total events: 0 (LABA + ICS), Heterogeneity: $Chi^2 = 0.00$, d Test for overall effect: $Z = 0.9$
1.02 [0.67, 1.56]	100.0 %	•	6163	6410), 35 (Increased ICS) df = 23 (P = 0.98); I ² =	Total (95% CI) Total events: 38 (LABA + ICS Heterogeneity: $Chi^2 = 11.31$, Test for overall effect: Z = 0.1

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

Study or subgroup	LABA + ICS n/N	Increased ICS n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Baseline FEV1 >= 80 % pr	redicted				
Heuck 2000	0/27	2/27		1.6 %	0.20 [0.01, 3.98]
Lalloo 2003	6/230	5/237		3.2 %	1.24 [0.38, 4.00]
Verberne 1998	0/60	1/60		1.0 %	0.33 [0.01, 8.02]
Li 1999	2/13	0/16		0.3 %	6.07 [0.32, 116.33]
Vermetten 1999	6/113	10/120	-	6.3 %	0.64 [0.24, 1.70]
Busse 2003	14/281	19/277	+	12.3 %	0.73 [0.37, 1.42]
SAS40026	13/317	23/311	•	15.0 %	0.55 [0.29, 1.07
SFCF4026	4/158	10/159	-	6.4 %	0.40 [0.13, 1.26
Wallin 2003	0/18	1/19		0.9 %	0.35 [0.02, 8.09]
Subtotal (95% CI)	1217	1226	•	47.0 %	0.65 [0.45, 0.93]
Heterogeneity: $Chi^2 = 5.28$, est for overall effect: Z = 2 Baseline FEVI 61-79 % pn	.37 (P = 0.018)	0.0%			
÷ ,	.37 (P = 0.018)	0/20			Not estimable
est for overall effect: Z = 2 Baseline FEV1 61-79 % pri	.37 (P = 0.018) edicted			3.8 %	
est for overall effect: Z = 2 Baseline FEVI 61-79 % pro Fowler 2002	.37 (P = 0.018) edicted 0/19	0/20		3.8 % 3.3 %	0.51 [0.13, 2.02
est for overall effect: Z = 2 Baseline FEVI 61-79 % pro Fowler 2002 Kelsen 1999	.37 (P = 0.018) edicted 0/19 3/239	0/20 6/244			0.51 [0.13, 2.02
est for overall effect: Z = 2 Baseline FEVI 61-79 % pri Fowler 2002 Kelsen 1999 Murray 1999	.37 (P = 0.018) edicted 0/19 3/239 5/260	0/20 6/244 5/254		3.3 %	0.51 [0.13, 2.02 0.98 [0.29, 3.33 2.95 [0.31, 28.07
est for overall effect: Z = 2 Baseline FEV1 61-79 % pro Fowler 2002 Kelsen 1999 Murray 1999 Johansson 2001	.37 (P = 0.018) edicted 0/19 3/239 5/260 3/176	0/20 6/244 5/254 1/173		3.3 % 0.7 %	0.51 [0.13, 2.02 0.98 [0.29, 3.33 2.95 [0.31, 28.07 0.94 [0.06, 14.75
iest for overall effect: Z = 2 Baseline FEVI 61-79 % pro Fowler 2002 Kelsen 1999 Murray 1999 Johansson 2001 Bouros 1999	1.37 (P = 0.018) edicted 0/19 3/239 5/260 3/176 1/69	0/20 6/244 5/254 1/173 1/65		3.3 % 0.7 % 0.7 %	0.51 [0.13, 2.02 0.98 [0.29, 3.33 2.95 [0.31, 28.07 0.94 [0.06, 14.75 0.75 [0.28, 1.96
iest for overall effect: Z = 2 Baseline FEVI 61-79 % pri Fowler 2002 Ketsen 1999 Murray 1999 Johansson 2001 Bouros 1999 Jenkins 2000	1.37 (P = 0.018) edicted 0/19 3/239 5/260 3/176 1/69 7/180	0/20 6/244 1/173 1/65 9/173		3.3 % 0.7 % 0.7 % 5.9 %	0.51 [0.13, 2.02 0.98 [0.29, 3.33 2.95 [0.31, 28.07 0.94 [0.06, 14.75 0.75 [0.28, 1.96 0.39 [0.11, 1.46
est for overall effect: Z = 2 Baseline FEVI 61-79 % pri Fowler 2002 Kelsen 1999 Murray 1999 Johansson 2001 Bouros 1999 Jenkins 2000 Bateman 2003	1.37 (P = 0.018) edicted 0/19 3/239 5/260 3/176 1/69 7/180 3/168	0/20 6/244 1/173 1/65 9/173 8/176		3.3 % 0.7 % 5.9 % 5.0 %	Not estimable 0.51 [0.13, 2.02 0.98 [0.29, 3.33 2.95 [0.31, 28.07 0.94 [0.06, 14.75 0.75 [0.28, 1.96 0.39 [0.11, 1.46 2.77 [0.12, 64.76 0.22 [0.05, 0.99
est for overall effect: Z = 2 Baseline FEVI 61-79 % pri Fowler 2002 Kelsen 1999 Johansson 2001 Bouros 1999 Jenkins 2000 Bateman 2003 Pearlman 1999	237 (P = 0.018) edicted 0/19 3/239 5/260 3/176 1/69 7/180 3/168 1/25	0/20 6/244 1/1/3 1/65 9/1/73 8/1/76 0/23		3.3 % 0.7 % 0.7 % 5.9 % 5.0 % 0.3 %	0.51 [0.13, 2.02 0.98 [0.29, 3.33 2.95 [0.31, 2.807 0.94 [0.06, 14.75 0.75 [0.28, 1.96 0.39 [0.11, 1.46 2.77 [0.12, 64.76
est for overall effect: Z = 2 Baseline FEVI 61-79 % pri Fowler 2002 Kelsen 1999 Murray 1999 Johansson 2001 Bouros 1999 Jenkins 2000 Bateman 2003 Pearlman 1999 Condemi 1999	237 (P = 0.018) edicted 3/239 5/260 3/176 1/69 7/180 3/168 1/25 2/221	0/20 6/244 5/254 1/1/3 1/65 9/1/73 8/1/76 0/23 9/216		3.3 % 0.7 % 5.9 % 5.0 % 0.3 % 5.9 %	0.51 [0.13, 2.02 0.98 [0.29, 3.33 2.95 [0.31, 2.807 0.94 [0.06, 14.75 0.75 [0.28, 1.96 0.39 [0.11, 1.46 2.77 [0.12, 64.76 0.22 [0.05, 0.99

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

Risk Rat	Weight	Risk Ratio	Increased ICS	LABA + ICS	Study or subgroup
M-H,Fixed,95% (M-H,Fixed,95% CI	n/N	n/N	
1.66 [0.69, 3.97	5.1 %	-	8/926	13/909	O'Byme 2005
4.82 [0.57, 40.86	0.7 %		1/165	5/171	Ind 2003
0.50 [0.07, 3.52	1.7 %		2/122	2/243	Woolcock 1996b
0.33 [0.01, 8.01	1.0 %		1/101	0/102	Mitchell 2003
0.34 [0.06, 1.98	2.6 %		3/123	2/244	Woolcock 1996a
0.81 [0.58, 1.12	49.8 %	•	3424	3687	Subtotal (95% CI)
			%	3 (P = 0.20)	Heterogeneity: $Chi^2 = 16.30$, c Test for overall effect: $Z = 1.28$ 3 Baseline FEV1 <= 60 % prec
0.14 [0.01, 2.71	2.3 %		3/242	0/246	SLGA5021
0.14 [0.01, 2.71	2.3 %	-	242	246 3 (Increased ICS)	Subtotal (95% CI) Total events: 0 (LABA + ICS), 1
					Heterogeneity: not applicable
				. ,	Test for overall effect: $Z = 1.30$
					4 Baseline FEV1 predicted not
Not estimab			0/196	0/202	Zhong 2005
0.33 [0.01, 8.11	1.0 %		1/241	0/242	SAM40090
0.33 [0.01, 8.11	1.0 %		437	444	Subtotal (95% CI)
				I (Increased ICS)	Total events: 0 (LABA + ICS),
					Heterogeneity: not applicable
				B (P = 0.50)	Test for overall effect: $Z = 0.68$
0.71 [0.56, 0.91	100.0 %	•	5329	5594	Total (95% CI)
					Total events: 108 (LABA + ICS
			.0%		Heterogeneity: $Chi^2 = 23.65$, c
				3 (P = 0.0055)	Test for overall effect: $Z = 2.78$

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

	LABA + ICS n/N	Increased ICS n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% C
Baseline FEV >= 80 % pre	edicted				
Lalloo 2003	15/230	22/237		2.4 %	0.70 [0.37, 1.32]
Li 1999	3/13	0/16		0.0 %	8.50 [0.48, 151.05]
Verberne 1998	5/60	4/60		0.4 %	1.25 [0.35, 4.43]
LOCCS	16/163	13/169		1.4 %	1.28 [0.63, 2.57
SAM104926	3/150	6/153		0.7 %	0.51 [0.13, 2.00]
SAS40026	32/321	44/315		4.9 %	0.71 [0.47, 1.09
SFCF4026	15/158	30/159		3.3 %	0.50 [0.28, 0.90
Busse 2003	35/281	42/277		4.6 %	0.82 [0.54, 1.25
Wallin 2003	0/18	3/19	•••••••	0.4 %	0.15 [0.01, 2.72
Subtotal (95% CI)	1394	1405	•	18.0 %	0.76 [0.61, 0.95]
	45 (P = 0.014)				
	15 (1 01011)				
2 Baseline FEVI 61-79 % pre Kelsen 1999		49/244	+	5.3 %	1.00 [0.70, 1.43]
Kelsen 1999	dicted	49/244 57/254	+	5.3 % 6.3 %	
	dicted 48/239		+		0.86 [0.61, 1.20
Kelsen 1999 Murray 1999 Fowler 2002	dicted 48/239 50/260 0/19	57/254 0/19	+	6.3 %	0.86 [0.61, 1.20 Not estimable
Murray 1999	dicted 48/239 50/260	57/254	+		1.00 [0.70, 1.43] 0.86 [0.61, 1.20] Not estimable 1.51 [0.81, 2.79] 0.63 [0.19, 2.12]
Kelsen 1999 Murray 1999 Fowler 2002 Johansson 2001	dicted 48/239 50/260 0/19 23/176	57/254 0/19 15/173	+	6.3 %	0.86 [0.61, 1.20 Not estimable 1.51 [0.81, 2.79 0.63 [0.19, 2.12
Kelsen 1999 Murray 1999 Fowler 2002 Johansson 2001 Bouros 1999	dicted 48/239 50/260 0/19 23/176 4/69	57/254 0/19 15/173 6/65	+ + 	6.3 % 1.7 % 0.7 %	0.86 [0.61, 1.20 Not estimable 1.51 [0.81, 2.79
Kelsen 1999 Murray 1999 Fowler 2002 Johansson 2001 Bouros 1999 Condemi 1999	dicted 48/239 50/260 0/19 23/176 4/69 19/221	57/254 0/19 15/173 6/65 30/216	+	6.3 % 1.7 % 0.7 % 3.3 %	0.86 [0.61, 1.20] Not estimable 1.51 [0.81, 2.79] 0.63 [0.19, 2.12] 0.62 [0.36, 1.07] 0.79 [0.42, 1.48]
Kelsen 1999 Murray 1999 Fowler 2002 Johansson 2001 Bouros 1999 Condemi 1999 Bateman 2003	dicted 48/239 50/260 0/19 23/176 4/69 19/221 15/168	57/254 0/19 15/173 6/65 30/216 20/176	+	6.3 % 1.7 % 0.7 % 3.3 % 2.1 %	0.86 [0.61, 1.20 Not estimable 1.51 [0.81, 2.79 0.63 [0.19, 2.12] 0.62 [0.36, 1.07
Kelsen 1999 Murray 1999 Fowler 2002 Johansson 2001 Bouros 1999 Condemi 1999 Bateman 2003 Baranuk 1999	dicted 48/239 50/260 0/19 23/176 4/69 19/221 15/168 16/231	57/254 0/19 15/173 6/65 30/216 20/176 13/223		6.3 % 1.7 % 0.7 % 3.3 % 2.1 % 1.4 %	0.86 (0.61, 120 Not estimable 1.51 (0.81, 279 0.63 (0.19, 2.12 0.62 (0.36, 1.07 0.79 (0.42, 1.48 1.19 (0.59, 2.41
Kelsen 1999 Murray 1999 Fowler 2002 Johansson 2001 Bouros 1999 Condemi 1999 Bateman 2003 Baransiuk 1999 Bateman 2006	dicted 48/2.39 50/2.60 0/19 2.3/1.76 4/69 19/221 15/168 16/2.31 6/246	57/254 0/19 15/173 6/65 30/216 20/176 13/223 4/238		6.3 % 0.7 % 3.3 % 2.1 % 1.4 %	0.86 (0.61, 120 Not estimable 1.51 (0.81, 279 0.63 (0.19, 2.12 0.62 (0.36, 107 0.79 (0.42, 1.48 1.19 (0.59, 2.41 1.45 (0.41, 5.08

0.1 0.2 0.5 1 2 5 10 Favours LABA + ICS Favours Higher ICS Ducharme et al.

Risk Ratio M-H,Fixed,95% C	Weight	Risk Ratio M-H,Fixed,95% Cl	Increased ICS n/N	LABA + ICS n/N	Study or subgroup
1.07 [0.71, 1.61	4.0 %		37/214	39/210	Pauwels 1997
1.06 [0.86, 1.31]	15.4 %	+	142/926	148/909	O'Byrne 2005
1.46 [0.53, 3.98	0.7 %		6/135	9/139	Van Noord 1999
0.65 [0.38, 1.11	3.1 %		28/145	19/152	SD 039 0726
0.81 [0.48, 1.37]	2.8 %		26/133	21/132	SD 039 0728
1.18 [0.70, 1.99]	2.5 %		22/165	27/171	Ind 2003
0.58 [0.24, 1.41]	1.3 %		12/101	7/102	Mitchell 2003
0.72 [0.41, 1.27]	2.6 %		18/126	25/243	Woolcock 1996b
0.87 [0.50, 1.53]	2.5 %		17/125	29/244	Wookock 1996a
0.75 [0.38, 1.49]	1.9 %		18/177	13/170	Bergmann 2004
0.94 [0.45, 1.97]	1.1 %		10/33	10/35	SAM30022
0.95 [0.86, 1.05]	70.1 %	•	4290	4561	Subtotal (95% CI) Total events: 630 (LABA + 10
				4 (P = 0.35) dicted	Heterogeneity: Chi ² = 14.93, Test for overall effect: Z = 0.9 3 Baseline FEV1 <= 60 % pre
0.87 [0.56, 1.37]	3.9 %		35/242	31/246	SLGA5021
				0 (P = 0.55)	Total events: 31 (LABA + ICS Heterogeneity: not applicable Test for overall effect: Z = 0.6 4 Baseline FEV1 predicted no
0.61 [0.15, 2.53]	0.5 %		5/180	3/176	SAM40012
1.08 [0.59, 1.98]	2.0 %		18/196	20/202	Zhong 2005
1.04 [0.71, 1.54]	4.5 %		41/241	43/242	SAM140090
0.55 [0.16, 1.82]	0.8 %		7/116	4/121	SAM30013
2.50 [0.27, 22.86	0.1 %		1/10	2/8	SAM40120
1.00 [0.07, 14.21]	0.1 %		1/12	1/12	SAM40100
0.99 [0.73, 1.34]	8.0 %	-	755	$ff = 5 (P = 0.82); I^2 = 0.0$	Subtotal (95% CI) Total events: 73 (LABA + ICS Heterogeneity: Chi ² = 2.19, o Test for overall effect: Z = 0.0
0.92 [0.84, 1.00]	100.0 %	•	6692	6962 S), 898 (Increased ICS) df = 37 (P = 0.78); I ² =	Test for overall effect: $Z = 0.0$ Total (95% CI) Total events: 858 (LABA + IC Heterogeneity: Chi ² = 30.08, Test for overall effect: $Z = 1.5$

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

Study or subgroup	LABA + ICS n/N	Increased ICS n/N	Risk Ratio M-H,Fixed,95% Cl	Weight	Risk Ratio M-H.Fixed,95% C
aseline FEV I >= 80 % pred					
Lalloo 2003	3/230	3/2.37		2.4 %	1.03 [0.21, 5.05
Li 1999	2/13	0/16		0.4 %	6.07 [0.32, 116.33
Verberne 1998	2/60	1/60		0.8 %	2.00 [0.19, 21.47
LOCCS	1/163	1/169		0.8 %	1.04 [0.07, 16.44
5AM104926	0/150	1/153		1.2 %	0.34 [0.01, 8.28
SAS40026	3/321	2/315		1.6 %	1.47 [0.25, 8.75
SFCF4026	3/158	6/159		4.8 %	0.50 [0.13, 1.98]
Wallin 2003	0/18	1/19		1.2 %	0.35 [0.02, 8.09
Busse 2003	1/281	2/277		1.6 %	0.49 [0.04, 5.40]
btotal (95% CI) al events: 15 (LABA + ICS) terogeneity: Chi ² = 4.02, df	$f = 8 (P = 0.86); I^2 = 0$	1405	-	14.7 %	0.92 [0.48, 1.76
al events: 15 (LABA + ICS) terogeneity: $Chi^2 = 4.02$, dt t for overall effect: $Z = 0.22$), 17 (Increased ICS) f = 8 (P = 0.86); I ² =0 7 (P = 0.79)		-	14.7 %	0.92 [0.48, 1.76]
al events: 15 (LABA + ICS) terogeneity: $Chi^2 = 4.02$, dl t for overall effect: $Z = 0.2$ aseline FEV1 61-79 % pred), 17 (Increased ICS) f = 8 (P = 0.86); I ² =0 7 (P = 0.79)		-	14.7 %	
al events: 15 (LABA + ICS) terogeneity: $Chi^2 = 4.02$, dt t for overall effect: $Z = 0.23$ aseline FEV1 61-79 % pred Johansson 2001), 17 (Increased ICS) f = 8 (P = 0.86); I ² =(7 (P = 0.79) licted I/176	1/173		0.8 %	0.98 [0.06, 15.59
al events: 15 (LABA + ICS) terogeneity: Chi ² = 4.02, dl t. for overall effect: Z = 0.2; aseline FEV1 61-79 % pred lohansson 2001 Kelsen 1999), I7 (Increased ICS) f = 8 (P = 0.86); I ² = (7 (P = 0.79) licted I/176 I6/239	1/173 16/244	•	0.8 %	0.98 [0.06, 15.59 1.02 [0.52, 1.99
al events: 15 (LABA + ICS) terogeneity: $Chi^2 = 4.02$, dt t for overall effect: $Z = 0.23$ aseline FEV1 61-79 % pred Johansson 2001), 17 (Increased ICS) f = 8 (P = 0.86); I ² =(7 (P = 0.79) licted I/176	1/173	•	0.8 %	0.92 [0.48, 1.76] 0.98 [0.06, 15.59 1.02 [0.52, 1.99 1.95 [0.60, 6.41 Not estimable
al events: 15 (LABA + ICS) terogeneity: Chi ² = 4.02, dt t for overall effect: Z = 0.2 aseline FEV1 61-79 % pred lohansson 2001 Kelsen 1999 Murray 1999), 17 (Increased ICS) f = 8 (P = 0.86); I ² = (7 (P = 0.79) licted 1/176 16/239 8/260	1/173 16/244 4/254	•	0.8 % 12.7 % 3.2 %	0.98 [0.06, 15.59 1.02 [0.52, 1.99 1.95 [0.60, 6.41 Not estimable
al events: 15 (LABA + ICS) terogeneity: Chi ² = 4.02, di t for overall effect: Z = 0.21 aseline FCV1 61-79 % pred lohansson 2001 Kelsen 1999 Murray 1999 Fowler 2002), 17 (Increased ICS) f = 8 (P = 0.86); I ² = (7 (P = 0.79) licted 1/176 16/239 8/260 0/19	10% 1/173 16/244 4/254 0/20	•	0.8 %	0.98 [0.06, 15.59 1.02 [0.52, 1.99
al events: 15 (LABA + ICS) terogeneity: Chi ² = 4.02, dl tfor overall effect: Z = 0.21 aseline FEV1 61-79 % pred ohamsson 2001 Kelsen 1999 Murray 1999 Fowler 2002 Baraniuk 1999), 17 (Increased ICS) f = 8 (P = 0.86); I ² =(7 (P = 0.79) licted 1/176 16/239 8/260 0/19 9/231	10% 1/173 16/244 4/254 0/20 3/223		0.8 % 12.7 % 3.2 % 2.4 %	0.98 [0.06, 15.59 1.02 [0.52, 1.99 1.95 [0.60, 6.41 Not estimable 2.90 [0.79, 10.56
al events: 15 (LABA + ICS) terrogeneity: Chi ² = 4.02, dt f or overall effect: Z = 0.2 assenie FEV 16 1/79 % pred johansson 2001 Kelsen 1999 Murray 1999 Fowler 2002 Baraniuk: 1999 enklins 2000	1, 17 (Increased ICS)	1/173 16/244 4/254 0/20 3/223 4/173	•	0.8 % 12.7 % 3.2 % 2.4 % 3.3 %	0.98 [0.06, 15.59 1.02 [0.52, 1.99 1.95 [0.60, 6.41 Not estimabl 2.90 [0.79, 10.56 0.72 [0.16, 3.17

Favours LABA+ICS Favours Higher ICS

Risk Ra	Weight	Risk Ratio	Increased ICS	LABA + ICS	Study or subgroup
M-H,Fixed,95%		M-H,Fixed,95% CI	n/N	n/N	
0.76 [0.27, 2.1	6.3 %	-	8/214	6/210	Pauwels 1997
0.19 [0.01, 4.0	2.0 %		2/238	0/246	Bateman 2006
0.09 [0.00, 1.6	4.4 %	·	5/216	0/221	Condemi 1999
0.11 [0.01, 2.0	3.6 %		4/129	0/130	Van Noord 1999
3.90 [0.44, 34.4	0.8 %		1/153	4/157	D5896C00001
1.34 [0.48, 3.7	4.8 %		6/133	8/132	SD 039 0728
1.04 [0.31, 3.5	3.9 %		5/187	5/180	Bergmann 2004
1.13 [0.39, 3.2	4.9 %	-	6/165	7/171	Ind 2003
0.50 [0.09, 2.6	3.2 %		4/101	2/102	Mitchell 2003
0.95 [0.72, 1.2	78.5 %	•	3028	3067	Subtotal (95% CI)
1.18 [0.37, 3.8	4.0 %	-	5/242	6/246	SLGA5021
				edicted	3 Baseline FEV I <= 60 % pre
1.18 [0.37, 3.82	4.0 %	+	242	246	Subtotal (95% CI)
					Total events: 6 (LABA + ICS),
					Heterogeneity: not applicable Test for overall effect: Z = 0.2
					4 Baseline FEV1 predicted not
1.94 [0.49, 7.6	2.4 %		3/196	6/202	Zhong 2005
4.80 [0.23, 98.8	0.4 %		0/116	2/121	SAM30013
2.35 [0.68, 8.03	2.8 %	-	312	323	Subtotal (95% CI)
				, 3 (Increased ICS)	Total events: 8 (LABA + ICS),
			6	$if = 1 (P = 0.59); I^2 = 0.0$	Heterogeneity: Chi ² = 0.29, d
					Test for overall effect: $Z = 1.3$
0.99 [0.78, 1.20	100.0 %	•	4987	5030	Total (95% CI)
0.77 [0.76, 1.26]					Total events: 121 (LABA + IC
			17%	dt = 27 (P = 0.84); P = 0.84	Heterogeneity: Chi ² = 19.75,
					Test for overall effect: $Z = 0.0$

Favours LABA+ICS Favours Higher ICS

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

Baseline FEVI >= 80 % predic Subtotal (95% CI) Heterogeneity: not applicable fest for overall effect: not applica 2 Baseline FEVI 61-79 % predict	ted O					
leterogeneity: not applicable fest for overall effect: not applica	0					
fest for overall effect: not applica		0				Not estimable
2. Daseline FEVT 61-77 76 predict						
Fowler 2002	19	20	0.2 (0.4898)		0.3 %	0.20 [-0.76, 1.16]
Murray 1999	210	197	0.14 (0.0765)	-	12.9 %	0.14 [-0.01, 0.29]
Johansson 2001	156	161	-0.04 (0.0918)	-	9.0 %	-0.04 [-0.22, 0.14]
Kelsen 1999	190	195	0.17 (0.0765)		12.9 %	0.17 [0.02, 0.32]
Bouros 1999	69	65	0.2 (0.1786)		2.4 %	0.20 [-0.15, 0.55]
Greening 1994	148	141	0.04 (0.0969)	-	8.0 %	0.04 [-0.15, 0.23]
Jenkins 2000	158	147	0.09 (0.0561)	•	24.0 %	0.09 [-0.02, 0.20]
Condemi 1999	194	176	0.14 (0.0765)	•	12.9 %	0.14 [-0.01, 0.29]
Van Noord 1999	130	129	-0.01 (0.102)		7.3 %	-0.01 [-0.21, 0.19]
Ind 2003	171	165	0 (0.0969)	+	8.0 %	0.0 [-0.19, 0.19]
Subtotal (95% CI)	1445	1396		•	97.8 %	0.09 [0.03, 0.14]
Heterogeneity: Chi ² = 6.45, df =	9 (P = 0.69);	$ ^2 = 0.0\%$				
Test for overall effect: $Z = 3.09$ (
3 Baseline FEV1 <= 60 % predic						
Subtotal (95% CI)	0	0				Not estimable
Heterogeneity: not applicable						
Fest for overall effect: not applica Baseline FEV1 not reported	able					
SAM40100	0	0	-0.14 (0.1837)		2.2 %	-0.14 [-0.50, 0.22]
Subtotal (95% CI)	0	0		-	2.2 %	-0.14 [-0.50, 0.22]
leterogeneity: not applicable						
Test for overall effect: $Z = 0.76$ (P = 0.45)					
Total (95% CI)	1445	1396		•	100.0 %	0.08 [0.03, 0.13]
Heterogeneity: Chi ² = 7.93, df =	= 10 (P = 0.64)	$ ^2 = 0.0\%$				
Test for overall effect: $Z = 2.94$ (
Test for subgroup differences: Ch	$mi^2 = 1.48, df =$	= I (P = 0.22), I ² =	=32%			

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

Study or subgroup	Mean Difference (SE)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI	
I Baseline FEVI >= 80 % pre	dicted				
Li 1999	10 (5.8571)		1.5 %	10.00 [-1.48, 21.48]	
LOCCS	4.03 (1.6276)		19.0 %	4.03 [0.84, 7.22]	
Subtotal (95% CI)		+	20.5 %	4.46 [1.38, 7.53]	
Heterogeneity: $Chi^2 = 0.96$, d	If = 1 (P = 0.33); I ² =0.0%				
Test for overall effect: $Z = 2.8$	4 (P = 0.0045)				
2 Baseline FEV1 61-79 % prec	ficted				
Bergmann 2004	3 (2.6888)		7.0 %	3.00 [-2.27, 8.27]	
Jenkins 2000	2 (1.275)		31.0 %	2.00 [-0.50, 4.50]	
Johansson 2001	0 (1.53)	+	21.5 %	0.0 [-3.00, 3.00]	
Kips 2000	4.03 (6.801)		1.1 %	4.03 [-9.30, 17.36]	
Pauwels 1997	0 (1.6276)	+	19.0 %	0.0 [-3.19, 3.19]	
Subtotal (95% CI)		•	79.5 %	1.10 [-0.46, 2.66]	
Heterogeneity: Chi ² = 2.16, d	$f = 4 (P = 0.71); I^2 = 0.0\%$				
Test for overall effect: Z = 1.3	8 (P = 0.17)				
Total (95% CI)		•	100.0 %	1.78 [0.39, 3.18]	
Heterogeneity: Chi ² = 6.78, d	$f = 6 (P = 0.34); I^2 = I I\%$				
Test for overall effect: $Z = 2.5$	2 (P = 0.012)				
Test for subgroup differences:	Chi ² = 3.65, df = 1 (P = 0.06), l ² =73%				
		-20 -10 0 10 20			

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

IV.Fixed.95% C	Weight	L IV.Fixed,95% CI	L (SE)	Increased ICS N	LABA + ICS N	Study or subgroup
IV,FIXEU,75% C		IV,FIXEU,75% CI		IN		Baseline FEV >= 80 % (
0.10 [0.06, 0.14	17.7 %	-	0.1 (0.017858)	277	281	Busse 2003
0.0 [-0.05, 0.05	10.7 %	+	0 (0.023)	153	150	SAM104926
0.09 [0.05, 0.13	13.6 %	-	0.09 (0.0204)	311	316	SAS40026
0.21 [-0.02, 0.44	0.4 %		0.21 (0.1173)	154	156	SFCF4026
0.07 [0.05, 0.10]	42.4 %			895	903	Subtotal (95% CI)
0107 [0105] 0120]						Heterogeneity: $Chi^2 = 14.4$
				È.	6.29 (P < 0.00001	Test for overall effect: Z =
					redicted	2 Baseline FEVI 61-79 % p
0.10 [0.01, 0.19	2.7 %		0.1 (0.0459)	210	215	Baraniuk 1999
0.15 [0.08, 0.22	4.4 %	+	0.15 (0.0357)	233	238	Bateman 2006
0.11 [0.00, 0.22	1.8 %		0.11 (0.0561)	177	170	Bergmann 2004
0.10 [0.00, 0.20	2.2 %		0.1 (0.051)	176	194	Condemi 1999
0.06 [0.01, 0.11	8.7 %	-	0.06 (0.0255)	151	152	D5896C00001
-0.12 [-0.21, -0.03	2.5 %		-0.12 (0.047449)	39	39	Green 2006
0.09 [0.01, 0.17	3.4 %	+	0.09 (0.0408)	195	190	Kelsen 1999
0.14 [0.04, 0.24	2.2 %		0.14 (0.051)	197	210	Murray 1999
0.06 [-0.01, 0.13	4.6 %		0.06 (0.035)	925	906	O'Byrne 2005
0.29 [0.03, 0.55	0.3 %		0.29 (0.1327)	23	25	Pearlman 1999
0.14 [0.07, 0.21	4.4 %	+	0.14 (0.0357)	144	152	SD 039 0726
0.08 [0.02, 0.14	6.0 %	•	0.08 (0.0306)	132	129	SD 039 0728
0.10 [0.00, 0.20	2.2 %		0.1 (0.051)	108	215	Woolcock 1996a
0.11 [0.01, 0.21	2.2 %	-+-	0.11 (0.051)	109	220	Woolcock 1996b
0.09 [0.06, 0.11	47.6 %	·				Subtotal (95% CI) Heterogeneity: Chi ² = 30.1
				1		Test for overall effect: Z = 3 Baseline FEV1 <= 60 % p
0.01 [-0.07, 0.09	3.4 %	1	0.01 (0.0408)	238	predicted 240	3 Baseline FEVT <= 60 % p SLGA5021
	51170			250	210	

l	Weight	L	L (SE)	ncreased ICS	LABA + ICS	Study or subgroup
IV,Fixed,95% C		IV,Fixed,95% CI		N	N	
0.01 [-0.07, 0.09]	3.4 %	+		238	240	Subtotal (95% CI)
					ole	Heterogeneity: not applical
					0.25 (P = 0.81)	Test for overall effect: $Z =$
					ed	4 Baseline FEV1 not report
0.17 [0.05, 0.29	1.4 %		0.17 (0.063)	59	56	Joshi 2005
0.01 [-0.10, 0.12	1.8 %	-	0.01 (0.0561)	116	121	SAM30013
0.03 [-0.05, 0.11	3.4 %	+	0.03 (0.0408)	187	199	Zhong 2005
0.05 [0.00, 0.11]	6.6 %	•		362	376	Subtotal (95% CI)
				=54%	, df = 2 (P = 0.11);	Heterogeneity: Chi ² = 4.35
					1.87 (P = 0.061)	Test for overall effect; Z =
0.08 [0.06, 0.09]	100.0 %	•		4314	4574	Total (95% CI)
				14); I ² =60%	1, df = 21 (P = 0.0	Heterogeneity: Chi ² = 53.0
					10.09 (P < 0.00001	Test for overall effect: $Z =$
			7%	$(P = 0.25), I^2 = 2$	es: Chi ² = 4.12, df =	Test for subgroup difference

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

-

IV,Fixed,95%	Weight	L IV,Fixed,95% CI	L (SE)	Study or subgroup
				1 At 6 +/- 2 weeks
0.09 [0.01, 0.17	3.0 %		0.09 (0.0408)	Baraniuk 1999
0.09 [0.01, 0.17	3.0 %		0.09 (0.0408)	Conderni 1999
0.12 [0.04, 0.20	3.0 %		0.12 (0.0408)	Kelsen 1999
0.29 [0.03, 0.55	0.3 %		0.29 (0.1327)	Pearlman 1999
0.03 [-0.05, 0.11	3.0 %		0.03 (0.0408)	Zhong 2005
0.09 [0.05, 0.13	12.4 %	•		Subtotal (95% CI) Heterogeneity: Chi ² = 4.96, c Test for overall effect: Z = 4.3 2 At 12 +/- 4 weeks
0.10 [0.01, 0.19	2.4 %		0.1 (0.0459)	Baraniuk 1999
0.11 [0.00, 0.22	1.6 %		0.11 (0.0561)	Bergmann 2004
0.10 [0.07, 0.13	21.6 %	-	0.1 (0.0153)	Busse 2003
0.11 [0.03, 0.19	3.0 %		0.11 (0.0408)	Condemi 1999
0.06 [0.01, 0.11	7.8 %		0.06 (0.0255)	D5896C00001
0.17 [0.05, 0.29	1.3 %		0.17 (0.063)	Joshi 2005
0.14 [0.06, 0.22	3.0 %	\longrightarrow	0.14 (0.0408)	Kelsen 1999
0.01 [-0.10, 0.12	1.6 %		0.01 (0.0561)	SAM30013
0.09 [0.05, 0.13	12.1 %	-	0.09 (0.0204)	SAS40026
0.14 [0.07, 0.21	4.0 %		0.14 (0.0357)	SD 039 0726
0.10 [0.08, 0.12	58.4 %	•	· /	Subtotal (95% CI) Heterogeneity: Chi ² = 8.73, c Test for overall effect: Z = 10 3 At 24 +/- 4 weeks
0.10 [0.00, 0.20	1.9 %		0.1 (0.051)	Condemi 1999
0.09 [0.01, 0.17	3.0 %		0.09 (0.0408)	Kelsen 1999
	1.9 %	\longrightarrow	0.14 (0.051)	Murray 1999

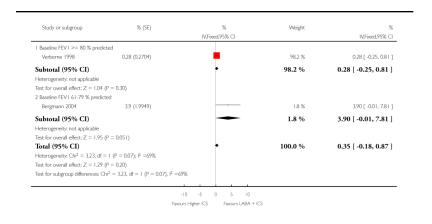
Study or subgroup	L (SE)	L	Weight	L
		IV,Fixed,95% CI		IV,Fixed,95% CI
SAS40026	0.09 (0.0306)		5.4 %	0.09 [0.03, 0.15]
SFCF4026	0.21 (0.1173)		0.4 %	0.21 [-0.02, 0.44]
SLGA5021	0.01 (0.0408)		3.0 %	0.01 [-0.07, 0.09]
Woolcock 1996a	0.1 (0.051)		1.9 %	0.10 [0.00, 0.20]
Woolcock 1996b	0.11 (0.051)		1.9 %	0.11[0.01,0.21]
Subtotal (95% CI)		•	19.6 %	0.09 [0.06, 0.12]
Heterogeneity: Chi ² = 6.08, dt	= 7 (P = 0.53); ² = 0.0%			
Test for overall effect: Z = 5.5.	B (P < 0.00001)			
4 At 52 +/- 4 weeks				
O'Byme 2005	0.06 (0.035)		4.1 %	0.06 [-0.01, 0.13]
SD 039 0728	0.08 (0.0306)		5.4 %	0.08 [0.02, 0.14]
Subtotal (95% CI)		•	9.5 %	0.07 [0.03, 0.12]
Heterogeneity: $Chi^2 = 0.19$, df	= I (P = 0.67); I ² =0.0%			
Test for overall effect: $Z = 3.10$) (P = 0.0020)			
Total (95% CI)		•	100.0 %	0.09 [0.08, 0.11]
Heterogeneity: Chi ² = 21.17, o	$f = 24 (P = 0.63); I^2 = 0.0\%$			
Test for overall effect: $Z = 12.9$	92 (P < 0.00001)			
Test for subgroup differences:	$Chi^2 = 1.22$, $df = 3$ (P = 0.75), $l^2 =$	=0.0%		
		-0.2 -0.1 0 0.1 0.2		
	F.	avours Higher ICS Favours LABA + ICS	5	

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

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

Study or subgroup	Treatment N	Control N	L/min (SE)	L/min IV,Random,95% CI	Weight	L/min IV,Random,95% CI
Baseline FEV1 >= 80 % pr	redicted					
Heuck 2000	24	24	20.7 (22.8418)		1.3 %	20.70 [-24.07, 65.47]
Li 1999	13	16	40 (35.148)		0.6 %	40.00 [-28.89, 108.89]
Subtotal (95% CI)	37	40		-	1.9 %	26.43 [-11.11, 63.97]
Heterogeneity: Tau ² = 0.0; 0		I (P = 0.65);	1 ² =0.0%			
est for overall effect: $Z = I$						
Baseline FEV1 61-79 % pn Bouros 1999	edicted 69	65	39 (17.4337)		2.3 %	39.00 [4.83, 73.17]
Fowler 2002	19	20	32 (7.398)	-	11.6 %	32.00 [17.50, 46.50]
Greening 1994	140	127	36 (13.9031)		3.5 %	36.00 [8.75, 63.25]
Jenkins 2000	173	165	26 (5.2857)	-	20.5 %	26.00 [15.64, 36.36]
	175	173		_	25.5 %	
Johansson 2001			11 (4.6)			11.00 [1.98, 20.02]
Kelsen 1999	188	192	29.6 (10.5357)		6.0 %	29.60 [8.95, 50.25]
Kips 2000	20	22	24 (34.74)		0.6 %	24.00 [-44.09, 92.09]
Mitchell 2003	100	101	27.65 (7.3724)	-	11.6 %	27.65 [13.20, 42.10]
Murray 1999	207	193	27 (9.898)	-	6.8 %	27.00 [7.60, 46.40]
Pauwels 1997	205	206	29 (10.8662)		5.7 %	29.00 [7.70, 50.30]
Pearlman 1999	20	21	13 (27.5867)		0.9 %	13.00 [-41.07, 67.07]
Van Noord 1999	130	129	2 (15.0357)	_	3.0 %	2.00 [-27.47, 31.47]
Subtotal (95% CI)	1447	1414		•	98.1 %	23.86 [17.94, 29.77]
leterogeneity: Tau ² = 19.70); Chi ² = 13.65,	df = (P = (0.25); I ² =19%			
est for overall effect: $Z = 7$		1)				
Baseline FEV1 <=60% pre Subtotal (95% CI)	dicted	0				Not estimable
leterogeneity: not applicabl	-	0				1101 6511111010
est for overall effect: not ap						
lotal (95% CI)	1484	1454	20112 (0)	•	100.0 %	23.31 [18.09, 28.52]
Heterogeneity: Tau ² = 6.54; Test for overall effect: Z = 8			.30); 1* =6%			

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

Study or subgroup	LABA + ICS	Increased ICS N	L/min (SE)	L/min	Weight	L/mi
D E EDU - 00.00	N	N		IV,Random,95% CI		IV,Random,95% C
Baseline FEV1 >= 80 % Busse 2003	predicted 281	277	18.2 (5)		3.5 %	18.20 [8.40, 28.00
Lalloo 2003	230	237	9.2 (2.9235)	-	4.9 %	9.20 [3.47, 14.93
SAM104926	0	0	7.6 (3.0051)	+	4.8 %	7.60 [1.71, 13.49
SA540026	316	311	17.9 (5.2194)	-	3.4 %	17.90 [7.67, 28.13
SFCF4026	156	154	15.56 (3.8673)	-+-	4.2 %	15.56 [7.98, 23.14
			. ,			
Verberne 1998	60	60	8.35 (6.0255)		2.9 %	8.35 [-3.46, 20.16
Vermetten 1999	113	119	11.96 (5.051)		3.5 %	11.96 [2.06, 21.86
Subtotal (95% CI) Heterogeneity: Tau ² = 2.7	1156	1158		•	27.1 %	11.74 [8.47, 15.00
Baseline FEV1 61-79 %						
est for overall effect: Z = Baseline FEV1 61-79 %						
Baraniuk 1999	228	223	10.97 (7.3112)		2.4 %	10.97 [-3.36, 25.30
Bateman 2003	168	176	19.7 (4.3776)	-	3.9 %	19.70 [11.12, 28.28
Bateman 2006	246	238	12.9 (2.6531)	•	5.0 %	12.90 [7.70, 18.10
Bergmann 2004	170	177	16 (7.6071)		2.2 %	16.00 [1.09, 30.91
Condemi 1999	194	172	21 (6.2296)		2.8 %	21.00 [8.79, 33.21
Green 2006	39	39	1.2 (6.377551)	-	2.8 %	1.20 [-11.30, 13.70
Greening 1994	137	126	21 (6.801)		2.6 %	21.00 [7.67, 34.33
Ind 2003	171	165	26.5 (4.2653)		4.0 %	26.50 [18.14, 34.86
Johansson 2001	176	173	10 (4.5714)		3.8 %	10.00 [1.04, 18.96
Kelsen 1999	188	192	26.1 (5.3112)		3.3 %	26.10 [15.69, 36.51
Murray 1999	207	193	17 (5.6582)		3.1 %	17.00 [5.91, 28.09
O'Byrne 2005	906	925	7 (2.124)	-	5.4 %	7.00 [2.84, 11.16
		22	32 (13.6224)		0.9 %	32.00 [5.30, 58.70
Pearlman 1999	25	22	3Z (13.0ZZ*)			

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

Weight	L/min	L/min (SE)	Increased ICS	LABA + ICS	Study or subgroup
2.2 %		26 (7.7908)	144	152	SD 039 0726
3.9 %		27.99 (4.3622)	132	130	SD 039 0728
4.2 %	+	30 (3.83)	248	2.39	Woolcock 1996b
53.7 %	•		3378	3410	Subtotal (95% CI)
		I); I ² =75%	= 16 (P<0.0000	19; Chi² = 62.76, d	Heterogeneity: Tau ² = 63.4
					Test for overall effect: $Z = 1$
				redicted	3 Baseline FEV1 <=60% pr
3.6 %		13.7 (4.8827)	238	240	SLGA5021
3.6 %	•		238	240	Subtotal (95% CI)
				ble	Heterogeneity: not applicat
					Test for overall effect: $Z = 3$
				ted	4 Baseline FEV1 not report
0.9 %		40 (14.2824)	59	56	Joshi 2005
1.9 %		13.7 (8.6276)	116	121	SAM30013
4.0 %	-	5.9 (4.1734)	180	176	SAM40012
5.8 %	•	17.4 (1.3597)	235	234	SAM40090
3.1 %		22.52 (5.75)	187	199	Zhong 2005
15.6 %	•		777	786	Subtotal (95% CI)
		2 =63%	= 4 (P = 0.03); H)4; Chi² = 10.77, d	Heterogeneity: $Tau^2 = 36.0$
				4.40 (P = 0.00001	Test for overall effect: $Z = -$
100.0 %	•		5551	5592	Total (95% CI)
		I); I ² =67%			0 ,
				11.33 (P < 0.0000	Test for overall effect: $Z =$
	22% 39% 42% 53.7% 3.6% 3.6% 0.9% 1.9% 4.0% 5.8% 3.1%	NBandom,95% CI 22 % + 39 % + 42 % • 53.7 % + 3.6 % + 3.6 % + 0.9 % + 1.9 % + 4.0 % • 58 % + 3.1 % • 15.6 %	MBandom 95% Cl 22 % 26 (7.7908) 22 % 27.99 (43622) 3.9 % 30 (383) 42 % • 53.7 % • 1); P = 75% • 53.7 % 137 (48827) 3.6 % 40 (142824) 0.9 % 9.8 % 137 (86276) 1.9 % 5.9 (41.734) 17.4 (1.3597) 5.8 % 3.1 % 22.52 (5.75) 3.1 % • 15.6 % •	N MRandom 95% CI 144 26 (7.7908) 2.2 % 132 27.99 (4.3622) 3.9 % 248 30 (1.83) 4.2 % 3378 • 53.7 % f= 16 (P<0.00001); P = 75%	N N MRandom 95% CI 152 144 26 (7.7908) 2.2 % 130 132 27.99 (43622) 3.9 % 239 248 30 (3.83) 4.2 % 3410 3378 • 53.7 % 9; Ch ² = 6276, df = 16 (P<000001); P = 75%

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

Study or subgroup	LABA + ICS		Higher ICS		Mean Difference	Weight	Mear Difference
	N	Mean(SD)	N	Mean(SD)	IV,Random,95% CI		IV,Random,95% C
I Baseline FEVI >=80% p	redicted						
Vermetten 1999	113	90.58 (16.07)	119	89.1 (16.33)	+	20.3 %	1.48 [-2.69, 5.65
LOCCS	161	99 (12.62)	168	96.2 (11.57)	+	37.1 %	2.80 [0.18, 5.42
Woolcock 1996b	243	93.48 (15.28)	126	85.65 (25.82)	•	15.8 %	7.83 [2.93, 12.73
Woolcock 1996a	244	90.87 (20.31)	125	85.65 (25.82)	-	14.4 %	5.22 [0.03, 10.41
Subtotal (95% CI)	761		538		•	87.6 %	3.86 [1.37, 6.35]
Heterogeneity: Tau ² = 2.2	5; Chi ² = 4.59, (df = 3 (P = 0.20)	i ² =35%				
Test for overall effect: Z =	3.04 (P = 0.002	24)					
2 Baseline FEV1 61-79% o	f predicted						
Bergmann 2004	170	84 (27)	177	83 (27)	+	12.4 %	1.00 [-4.68, 6.68
Subtotal (95% CI)	170		177		+	12.4 %	1.00 [-4.68, 6.68
Heterogeneity: not applica	ble						
Test for overall effect: Z =	0.34 (P = 0.73)						
Total (95% CI)	931		715		•	100.0 %	3.45 [1.28, 5.63]
Heterogeneity: Tau ² = 1.5	4; Chi ² = 5.31, (df = 4 (P = 0.26)	1 ² =25%				
Test for overall effect: $Z =$	3.11 (P = 0.00)	9)					
				-10	0 -50 0 50 I Higher ICS Favours LAE	00	

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

L/mir IV,Fixed,95% C	Weight	L/min IV,Fixed,95% Cl	L/min (SE)	Study or subgroup
			licted	I Baseline FEV I >=80% pred
4.00 [-37.59, 45.59	2.1 %	+	4 (21.2194)	Heuck 2000
4.00 [-37.59, 45.59	2.1 %	•		Subtotal (95% CI)
• • • • • • •				Heterogeneity: not applicable
				Test for overall effect: $Z = 0.1$
			redicted	2 Baseline FEV I 61-79% of pr
10.00 [-0.51, 20.51	33.3 %	•	10 (5.36)	Johansson 2001
28.00 [13.51, 42.49	17.5 %	· · · ·	28 (7.3929)	Fowler 2002
18.00 [9.15, 26.85	47.0 %	•	18 (4.5153)	Jenkins 2000
17.07 [10.93, 23.20	97.9 %			Subtotal (95% CI)
			df = 2 (P = 0.14); $I^2 = 50\%$	Heterogeneity: Chi ² = 3.97, d
			45 (P < 0.00001)	Test for overall effect: Z = 5.4
			edicted	3 Baseline FEV I <= 60 % pre
Not estimable				Subtotal (95% CI)
			1	Heterogeneity: not applicable
			plicable	Test for overall effect: not app
16.79 [10.72, 22.85	100.0 %			Total (95% CI)
			$df = 3 (P = 0.23); I^2 = 31\%$	Heterogeneity: Chi ² = 4.34, d
			42 (P < 0.00001)	Test for overall effect: $Z = 5.4$
		=0.0%	: $Chi^2 = 0.37$, $df = 1$ (P = 0.54), $I^2 =$	Test for subgroup differences:

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

Study or subgroup	LABA + ICS	Increased ICS	L/min (SE)	L/min	Weight	L/mir
	N	N		IV,Random,95% CI		IV,Random,95% C
I Baseline FEVI >=80% p	redicted					
Busse 2003	281	281	15.9 (5.2092)		4.2 %	15.90 [5.69, 26.11
Lalloo 2003	230	237	9.5 (2.801)	•	5.8 %	9.50 [4.01, 14.99
SAM104926	150	153	5.4 (3.04)	-	5.6 %	5.40 [-0.56, 11.36
SAM40090	234	235	17.6 (2.9694)	•	5.7 %	17.60 [11.78, 23.42]
SAS40026	317	309	14.7 (5.4847)		4.1 %	14.70 [3.95, 25.45
SFCF4026	156	154	12.13 (3.3929)	•	5.4 %	12.13 [5.48, 18.78
Subtotal (95% CI)	1368	1369		•	30.8 %	12.01 [7.99, 16.02]
Heterogeneity: Tau ² = 11. Test for overall effect: Z = 2 Baseline FEV1 61-79% o	5.86 (P < 0.0000)	. ,				
Baraniuk 1999	228	223	5.83 (6.7143)		3.4 %	5.83 [-7.33, 18.99
Bateman 2003	168	176	17.2 (4.3214)	+	4.8 %	17.20 [8.73, 25.67
Bateman 2006	246	238	13.8 (2.4745)	-	6.0 %	13.80 [8.95, 18.65
Bergmann 2004	170	177	17 (7.4286)		3.0 %	17.00 [2.44, 31.56
Condemi 1999	221	216	-4.2 (2.6327)	-	5.9 %	-4.20 [-9.36, 0.96
Greening 1994	135	126	19 (6.4643)		3.5 %	19.00 [6.33, 31.67
Ind 2003	171	165	22.1 (5.6888)		3.9 %	22.10 [10.95, 33.25
Kelsen 1999	184	191	22.7 (4.9694)	-	4.4 %	22.70 [12.96, 32.44
Murray 1999	260	254	12.8 (3.1327)	•	5.6 %	12.80 [6.66, 18.94
SD 039 0726	152	144	17.98 (3.7092)	+	5.2 %	17.98 [10.71, 25.25
Woolcock 1996b	239	248	24 (3.32)	+	5.5 %	24.00 [17.49, 30.51
Subtotal (95% CI)	2174	2158		•	51.2 %	15.05 [8.98, 21.12]
Heterogeneity: Tau ² = 83.			1); I ² =85%			
Test for overall effect: $Z =$)				
3 Baseline FEV1 <=60% p SLGA5021	redicted 240	238	14.5 (4.6071)	-+-	4.6 %	14.50 [5.47, 23.53

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

Study or subgroup	LABA + ICS	Increased ICS	L/min (SE)	L/min	Weight	L/min
	N	N		IV,Random,95% CI		IV,Random,95% CI
Subtotal (95% CI)	240	238		•	4.6 %	14.50 [5.47, 23.53]
Heterogeneity: not applicat	ole					
Test for overall effect: $Z =$	3.15 (P = 0.0016)					
4 Baseline FEV1 not report	ed					
SAM30013	121	116	17.5 (8.2041)		2.7 %	17.50 [1.42, 33.58]
SAM40012	176	180	4.4 (4.3112)		4.8 %	4.40 [-4.05, 12.85]
SAM40120	8	10	23 (11.7449)		1.7 %	23.00 [-0.02, 46.02]
Zhong 2005	199	187	13.5 (5.4031)		4.1 %	13.50 [2.91, 24.09]
Subtotal (95% CI)	504	493		•	13.3 %	11.31 [3.85, 18.78]
Heterogeneity: Tau ² = 16.4	13; Chi ² = 4.16, df	= 3 (P = 0.24); I ²	=28%			
Test for overall effect: $Z =$	2.97 (P = 0.0030)					
Total (95% CI)	4286	4258		•	100.0 %	13.70 [10.28, 17.12]
Heterogeneity: $Tau^2 = 44.6$	il; Chi ² = 80.35, d	f = 21 (P<0.0000)); I ² =74%			
Test for overall effect: Z =	7.86 (P < 0.0000))				
			-10	00 -50 0 50 10	10	
			Favour	s Higher ICS Favours LAB/	A + ICS	

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

Study or subgroup	LABA + ICS		Increased ICS	M (77)		Mean ference	Mea Difference
	N	Mean(SD)	N	Mean(SD)	IV,Fix	ed,95% Cl	IV,Fixed,95% C
I Baseline FEVI 61-79	% predicted						
Jenkins 2000	173	6 (3.81)	165	8 (3.85)	+		-2.00 [-2.82, -1.18
					-10 -5	0 5 I	0
				Favo	ours LABA + ICS	Favours High	ner ICS

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

Study or subgroup	LABA + ICS N	Mean(SD)	Increased ICS N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
Baseline FEV >= 80 %	predicted						
Vermetten 1999	113	-3.2 (11.1)	119	2.2 (7.3)	-	53.0 %	-5.40 [-7.83, -2.97]
Subtotal (95% CI) Heterogeneity: not applic	able		119		•	53.0 %	-5.40 [-7.83, -2.97]
Test for overall effect: Z =		0013)					
2 Baseline FEV1 61-79 %	predicted						
Kelsen 1999	183	-10.3 (33.82)	190	-5.1 (37.22)		6.0 %	-5.20 [-12.41, 2.01]
Murray 1999	206	-9 (28.71)	192	-5 (27.71)		10.2 %	-4.00 [-9.54, 1.54]
Condemi 1999	221	-8.5 (26.8)	206	-4.3 (27.3)		11.9 %	-4.20 [-9.34, 0.94]
Pearlman 1999	25	-10.5 (38.5)	22	6.3 (34.24)		0.7 %	-16.80 [-37.60, 4.00]
Subtotal (95% CI)	635		610		+	28.8 %	-4.66 [-7.95, -1.36]
Heterogeneity: Chi ² = 1.	42, df = 3 (P = 0	0.70); I ² =0.0%					
Test for overall effect: Z =	= 2.77 (P = 0.00	57)					
3 Baseline FEV I <= 60 %	5 predicted						
Mitchell 2003	206	-9 (28.71)	192	-5 (27.71)		10.2 %	-4.00 [-9.54, 1.54]
SLGA5021	240	-7.2 (30.98)	238	-8 (38.57)		8.0 %	0.80 [-5.47, 7.07]
Subtotal (95% CI)	446		430		-	18.2 %	-1.90 [-6.05, 2.26]
Heterogeneity: Chi ² = 1.	26, df = 1 (P = 0	0.26); I ² =21%					
Test for overall effect: Z =	= 0.89 (P = 0.37)					
Total (95% CI)	1194		1159		•	100.0 %	-4.55 [-6.32, -2.78]
Heterogeneity: Chi ² = 4.	72, df = 6 (P = 0	0.58); I ² =0.0%					
Test for overall effect: Z =	= 5.04 (P < 0.00	001)					
Test for subgroup differer	nces: $Chi^2 = 2.04$	df = 2 (P = 0.)	36), I ² =2%				
				-20	-10 0 10	20	
				-20	-10 0 10	20	

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

Comparison: 1 LABA + ICS versus higher dose ICS

Outcome: 20 Change in daytime symptom score at endpoint

Mear Difference IV,Fixed,95% C	Weight	Std. Mean Difference IV,Fixed,95% Cl	Mean(SD)	Increased ICS N	Mean(SD)	LABA + ICS N	Study or subgroup
						predicted	Baseline FEV >= 80 %
-0.14 [-0.40, 0.13	11.5 %		-0.1 (0.35)	116	-0.15 (0.38)	109	Vermetten 1999
-0.14 [-0.40, 0.13]	11.5 %	-		116		109	Subtotal (95% CI)
						ble	Heterogeneity: not applica
						1.02 (P = 0.31)	Test for overall effect: Z =
						predicted	2 Baseline FEVI 61-79 % p
-0.17 [-0.38, 0.03	19.3 %		-0.3 (0.69)	191	-0.42 (0.68)	185	Kelsen 1999
-0.44 [-0.62, -0.27	25.8 %		-0.19 (0.48)	254	-0.44 (0.64)	260	Murray 1999
-0.19 [-0.37, -0.01	24.8 %		0.14 (0.31)	238	0.08 (0.31)	246	Bateman 2006
-0.24 [-0.45, -0.04	18.6 %		-0.35 (0.79)	173	-0.53 (0.69)	193	Conderni 1999
-0.27 [-0.37, -0.18]	88.5 %	•		856		884	Subtotal (95% CI)
					15); I ² =43%	7, df = 3 (P = 0	Heterogeneity: Chi ² = 5.2
					01)	5.64 (P < 0.000	Test for overall effect: $Z =$
							3 Baseline FEVI <= 60 %
Not estimable				0		0	Subtotal (95% CI)
							Heterogeneity: not applica
							Test for overall effect: not a
-0.26 [-0.35, -0.17]	100.0 %	•		972		993	Total (95% CI)
							Heterogeneity: $Chi^2 = 6.11$
							Test for overall effect: Z =
				34), I ² =0.0%	df = 1 (P = 0.3)	:es: Chi² = 0.91,	Test for subgroup difference

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

1 Baseline FEV 1 >= 80 % predicted Bases 2003 281 0.2 (0.67) 20.5 % 0.12 [-0.29 , 0.05 Subtotal (95% CI) 281 277 0.12 [-0.29 , 0.05 Heterogeneity: not applicable 20.5 % -0.12 [-0.29 , 0.05 Easteine FEV 16 /7.9 % predicted 20.5 % -0.12 [-0.29 , 0.05 Murray 1999 206 -0.54 (0.72) 193 -0.27 (0.7) Baraniuk 1999 228 -0.44 (0.76) 223 -0.46 (0.76) Peartman 1999 25 -0.81 (1) 21 -0.3 (0.46) Bergrann 2004 170 -1.5 (1.4) 177 -1 (1.5) Subtotal (95% CI) 629 614 60.0 % -0.27 [-0.52 , -0.03 Heterogeneity: Tat ² = 0.04; (0.76) 238 -0.27 (0.62) 19.5 % -0.26 [-0.44 , -0.08 Subtotal (95% CI) 240 238 -0.29 (0.62) 19.5 % -0.26 [-0.44 , -0.08 Heterogeneity: not applicable 23.00 (0.62) 238 -0.26 [-0.44 , -0.08 19.5 % -0.26 [-0.44 , -0.08 Subtotal (95% CI) 240 238 -0.27 (0.62) 19.5 % -0	Study or subgroup	ABA + ICS N	Mean(SD)	Increased ICS	Mean(SD)	Std. Mean Difference IV.Random,95% CI	Weight	Std Mear Difference IV.Random,95% C
Buse 2003 281 -0.2 (0.67) 277 -0.12 (0.67) 20.5 % -0.12 [-0.29 , 0.05 Subtocal (95% CI) 281 277 -0.12 (-0.29 , 0.05 20.5 % -0.12 [-0.29 , 0.05 Heterogenetry: not applicable Text or overall effect: Z = 1.41 ($p = 0.16$) 2 20.5 % -0.12 [-0.29 , 0.05 Baraniuk 1999 206 -0.54 (0.72) 193 -0.27 (0.7) 18.4 % -0.38 [-0.58 , 0.18 Baraniuk 1999 228 -0.44 (0.76) 223 -0.46 (0.76) 19.2 % 0.03 [-0.16 , 0.21 Peartman 1999 25 -0.81 (1) 21 -0.3 (0.46) 49.% -0.61 [-1.21 , -0.02 Bergmann 2004 170 -1.5 (1.4) 177 -1 (1.5) 17.5 % -0.31 [-0.52 , -0.03 Heterogenety: Tax ² -0.45 (0.62) 238 -0.29 (0.62) 19.5 % -0.26 [-0.44 , -0.08 Subtocal (95% CI) 240 -0.45 (0.62) 238 19.5 % -0.26 [-0.44 , -0.08 Heterogenety: not applicable 21.20 (-0.45 (0.62) 238 19.5 % -0.26 [-0.44 , -0.08 Heterogenety: not applica			(JC)		(JD)	Ny, Naridon (7576 Cr		14,141001(7578 C
Subtract (95% C1) 281 277 A field (1) <li< td=""><td></td><td></td><td></td><td></td><td></td><td></td><td>205.01</td><td></td></li<>							205.01	
Heterogeneity: not applicable Test for overall effect: $Z = 1.41$ ($P = 0.16$) 2 Backine FEV 16 16.7% predicted Murray 1999 206 -0.54 (0.72) 193 -0.27 (0.7) I8.4% -0.38 [-0.58, -0.18 Baraniuk 1999 228 -0.44 (0.76) 223 -0.46 (0.76) 19.2% 0.03 [-0.16, 0.21 Peartman 1999 25 -0.8 (1) 21 -0.3 (0.46) 49% -0.61 [-1.21, -0.02 Bergmann 2004 170 -1.5 (1.4) 177 -1 (1.5) 17.5% -0.34 [-0.56, -0.13 Subtotal (95% CL) 629 614 60.0% -0.27 [-0.52, -0.03 Heterogeneity: Tau ² = 0.04; Ch ² = 1.229, df = 3 ($P = 0.01$); $P = 76\%$ Subtotal (95% CL) 240 -0.45 (0.62) 238 -0.29 (0.62) 19.5% -0.26 [-0.44, -0.08 Heterogeneity: not applicable Test for overall effect: $Z = 2.30$ ($P = 0.0050$) Total (95% CL) 1150 1129 100.0% -0.23 [-0.37, -0.08	Busse 2003	281	-0.2 (0.67)	2//	-0.12 (0.67)	1	20.5 %	-0.12 [-0.29, 0.05]
Test for overall effect: $Z = 1.41$ ($P = 0.16$) 2 Baseline FEV 1 61-79 % predicted Murray 1999 206 0.54 (0.72) 193 0.27 (0.7) 184.% 0.38 [-0.58, 0.18 Baraniuk 1999 228 0.44 (0.76) 223 0.46 (0.76) 19.2 % 0.03 [-0.16, 0.21 Pearlman 1999 25 0.08 (1) 21 0.3 (0.46) 9% 0.61 [-1.21, 0.02 Bergman 2004 170 -1.5 (1.4) 177 -1 (1.5) 175 0.5 Subtocal (95% CL) 629 614 60.614 Heterogeneity: Tat ² = 0.04; Chi ² = 1.29, df = 3 ($P = 0.01$); $P = 76\%$ Test for overall effect: $Z = 2.17$ ($P = 0.030$) 3 Baseline FEV1 % <= 60% Subtocal (95% CL) 240 238 9.029 (0.62) 155 0.26 [-0.44, -0.08 Heterogeneity: not applicable Test for overall effect: $Z = 2.08$ ($P = 0.0050$) Total (95% CL) 150 1129 9 100.0 % -0.23 [-0.37, -0.08	Subtotal (95% CI)	281		277		•	20.5 %	-0.12 [-0.29, 0.05]
2 Baseline FEV1 61-79 % predicted Murrary 1999 26 -0.54 (0.72) 193 -0.27 (0.7) 184 % -0.38 [-0.58, -0.18 Baraniuk 1999 228 -0.44 (0.76) 223 -0.46 (0.76) 19.2 % 0.33 [-0.16, 0.21 Peartman 1999 25 -0.8 (1) 21 -0.3 (0.46) 49 % -0.61 [-1.21, -0.02 Bergmann 2004 170 -1.5 (1.4) 177 -1 (1.5) 175 % -0.34 [-0.56, -0.13 Subtoxal (95% CI) 629 614 614 60.0 % -0.27 [-0.52, -0.03 Heterogeneity: not applicable Text for overall effect: $Z = 2.07$ ($P = 0.00$); $P = 76\%$ Subtoxal (95% CI) 240 -0.45 (0.62) 238 -0.29 (0.62) 19.5 % -0.26 [-0.44, -0.08 Heterogeneity: not applicable Text for overall effect: $Z = 2.30$ ($P = 0.005$) Total (95% CI) 1150 1129 • 100.0 % -0.23 [-0.37, -0.08	Heterogeneity: not applicable	2						
$\begin{array}{c c c c c c c c c c c c c c c c c c c $	Test for overall effect: $Z = 1$.	41 (P = 0.16)						
Baraniuk 1999 Z28 -0.44 (0.76) Z23 -0.46 (0.76) 19.2 % 0.03 [-0.16, 0.21] Pearlman 1999 Z5 -0.8 (1) Z1 -0.3 (0.46) 49 % -0.61 [-1.21, -0.02] Bergmann 2004 170 -1.5 (1.4) 177 -1 (1.5) 17.5 % -0.34 [-0.56, -0.13] Subtoat (95% CI) 629 614 60.0 % -0.27 [-0.52, -0.03] Heterogeneity: Tat ² = 0.04; Ch ² = 1/2.29, df = 3 (P = 0.01); P = 76% 7.8 % 60.0 % -0.27 [-0.52, -0.03] Subtoat (95% CI) 240 -0.45 (0.62) 238 9.5 % -0.26 [-0.44, -0.08] Subtoat (95% CI) 240 238 19.5 % -0.26 [-0.44, -0.08] Heterogeneity: not applicable Text for overall effect: Z = 2.30 (P = 0.0050) 1129 100.0 % -0.23 [-0.37, -0.08] Heterogeneity: Tat ² = 0.02; Ch ² = 1.381, df = 5 (P = 0.02); P = 64% 1129 100.0 % -0.23 [-0.37, -0.08]	2 Baseline FEVI 61-79 % pre	edicted						
Pearlman 1999 25 -0.8 (1) 21 -0.3 (0.46) 49 % -0.61 [-1.21, -0.02 Bergmann 2004 170 -1.5 (1.4) 177 -1 (1.5) 175 % -0.34 [-0.56, -0.13 Subtoral (95% CI) 629 614 60.0 % -0.27 [-0.52, -0.03 Heterogeneity: Tait = 0.04: Chi² = 12.29, df = 3 (° = 0.01); i² = 76% 3 sakine FEV (% <= 60%	Murray 1999	206	-0.54 (0.72)	193	-0.27 (0.7)	•	18.4 %	-0.38 [-0.58, -0.18]
Bergmann 2004 1.70 -1.5 (1.4) 1.77 -1.6 (1.5) Subtoal (95% CI) 629 614 60.0 % -0.27 [-0.52, -0.03 Heterogeneity: Tar? = 0.04; Chi² = 12.29, df = 3 (P = 0.01); P = 76% 60.0 % -0.27 [-0.52, -0.03 Text for overall effect: $Z = 2.17$ (P = 0.030) 3 Baseline FV1 % <= 60%	Baraniuk 1999	228	-0.44 (0.76)	223	-0.46 (0.76)	+	19.2 %	0.03 [-0.16, 0.21
Subtotal (95% CI) 629 614 60.0 % -0.27 [-0.52, -0.03 Heterogeneity: Tau ² = 0.04; Ch ² = 12.29, df = 3 (P = 0.01); P = 76% 60.0 % -0.27 [-0.52, -0.03 Text for overall effect: $Z = 2.17$ (P = 0.030) 3 Baseline FV1 % <= 60%	Pearlman 1999	25	-0.8 (1)	21	-0.3 (0.46)		4.9 %	-0.61 [-1.21, -0.02
Heterogeneity: Tau ² = 0.04; Ch ² = 12.29, df = 3 (P = 0.01); l ² = 76% Text for overall effect: $Z = 2.17$ (P = 0.030) 3 Baseline FEV1 % <= 60%	Bergmann 2004	170	-1.5 (1.4)	177	-1 (1.5)	-	17.5 %	-0.34 [-0.56, -0.13]
Test for overall effect: $Z = 2.17$ ($P = 0.030$) 3 Baseline FV1 % <= 60% SLGS0521 240 -0.45 (0.62) 238 -0.29 (0.62) 19.5 % -0.26 [-0.44, -0.08 Subtoati (95% CI) 240 238 19.5 % -0.26 [-0.44, -0.08 Heterogeneity: not applicable Test for overall effect: $Z = 2.80$ ($P = 0.0050$) Total (95% CI) 1150 1129 100.0 % -0.23 [-0.37, -0.08 Heterogeneity: Tau ² = 0.02; Ch ² = 1381, df = 5 ($P = 0.02$); $P = 64\%$	Subtotal (95% CI)	629		614		•	60.0 %	-0.27 [-0.52, -0.03]
$ \begin{array}{c ccccccccccccccccccccccccccccccccccc$	Heterogeneity: Tau ² = 0.04;	Chi ² = 12.29,	df = 3 (P = 0.0); I ² =76%				
SLGA5021 240 -0.45 (0.62) 238 -0.29 (0.62) 19.5 % -0.26 [-0.44, -0.08 Subtotal (95% CI) 240 238 19.5 % -0.26 [-0.44, -0.08 Heterogeneity: not applicable Test for overall effect: Z = 280 (P = 0.0050) Total (95% CI) 1150 1129 Heterogeneity: Tau ² = 0.02; Ch ² = 13.81, df = 5 (P = 0.02); P = 64% 100.0 % -0.23 [-0.37, -0.08	Test for overall effect: $Z = 2$.	I7 (P = 0.030))					
Subtract (95% CI) 240 238 • 19.5 % -0.26 [-0.44, -0.08 Heterogeneity: not applicable Text for overall effect Z = 2.30 (P = 0.0050) Total (95% CI) 1150 1129 • Heterogeneity: Tau ² = 0.02; Ch ² = 1.381, df = 5 (P = 0.02); P ² = 64% • • • •	3 Baseline FEV I % <= 60%							
$eq:linear_line$	SLGA5021	240	-0.45 (0.62)	238	-0.29 (0.62)	-	19.5 %	-0.26 [-0.44, -0.08]
Test for overall effect: Z = 2.80 (P = 0.0050) Total (95% CI) 1150 1129 + 100.0 % -0.23 [-0.37, -0.08 Heterogeneity: Tau ² = 0.02; Ch ² = 1.3.81, df = 5 (P = 0.02); H = 64%				238		•	19.5 %	-0.26 [-0.44, -0.08]
Total (95% CI) 1150 1129 100.0 % -0.23 [-0.37, -0.08 Heterogeneity: Tau ² = 0.02; Ch ² = 13.81, df = 5 (P = 0.02); H ² = 64% 100.0 % -0.23 [-0.37, -0.08			- - 					
Heterogeneity: Tau ² = 0.02; Chi ² = 13.81, df = 5 (P = 0.02); l ² = 64%			(0)	1129		•	100.0 %	-0.23 [-0.37, -0.08]
Test for overall effect: $Z = 3.11$ (P = 0.0019)	,		df = 5 (P = 0.0)				10010 /0	0120 (010/, 0100)
	0 /							
			~					
-4 -2 0 2 4					.4	-7 D 7	4	

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

Study or subgroup	LABA + ICS N	Increased ICS N	% (SE)	% IV,Random,95% CI	Weight	9 IV,Random,95% C
Baseline FEV I >=80% pr	edicted					
Busse 2003	281	277	6 (2.6888)	•	9.6 %	6.00 [0.73, 11.27
Lalloo 2003	230	237	6 (2.2959)	•	10.3 %	6.00 [1.50, 10.50
SAS40026	313	308	5 (2.4745)	-	10.0 %	5.00 [0.15, 9.85
Subtotal (95% CI)	824	822		•	29.9 %	5.67 [2.87, 8.46]
-leterogeneity: Tau ² = 0.0;	Chi ² = 0.11, df =	2 (P = 0.95); I ² =0	.0%			
Test for overall effect: $Z = $	3.97 (P = 0.00007	1)				
Baseline FEVI 61-79% of	predicted					
Baraniuk 1999	228	223	6.6 (3.829)	•	7.5 %	6.60 [-0.90, 14.10
Bergmann 2004	170	177	11 (4.1888)	-	6.9 %	11.00 [2.79, 19.21
Condemi 1999	193	173	15.6 (4.2245)	+	6.9 %	15.60 [7.32, 23.88
Kelsen 1999	239	244	11.1 (2.5663)	•	9.8 %	11.10 [6.07, 16.13
Murray 1999	206	193	20 (4.2449)	+	6.8 %	20.00 [11.68, 28.32
O'Byme 2005	906	925	6.5 (1.972)	-	10.9 %	6.50 [2.63, 10.37
Pearlman 1999	25	23	22 (11.4031)		1.7 %	22.00 [-0.35, 44.35
SD 039 0728	0	0	17.6 (3.6122)	•	7.9 %	17.60 [10.52, 24.68
Subtotal (95% CI)	1967	1958		•	58.5 %	12.32 [8.44, 16.21
Heterogeneity: Tau ² = 16.3	I; Chi ² = 16.47, c	$If = 7 (P = 0.02); I^2$	=57%			
fest for overall effect: $Z =$)				
8 Baseline FEV1 <=60% pr						
Subtotal (95% CI)	0	0				Not estimable
Heterogeneity: not applicate fest for overall effect: not a						
Baseline FEV I % predicte						
SAM40090	234	234	1.9 (1.5714)		11.6 %	1.90 [-1.18, 4.98
Subtotal (95% CI)	234	234		•	11.6 %	1.90 [-1.18, 4.98
leterogeneity: not applicat	ke					
lest for overall effect: Z =	I.21 (P = 0.23)					
Total (95% CI)	3025	3014		•	100.0 %	9.18 [6.02, 12.33
Heterogeneity: Tau ² = 19.8			15); I ² =72%			
Test for overall effect: $Z = $	5.70 (P < 0.00001)				
			-10	0 -50 0 50 11	00	

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

Study or subgroup	LABA + ICS		Increased ICS		Mean Difference	Weight	Mean Difference
	Ν	Mean(SD)	Ν	Mean(SD)	IV,Random,95% CI		IV,Random,95% CI
Baseline FEV >= 80 %	predicted						
Vermetten 1999	111	66.4 (38.9)	119	66.2 (36)	-	4. %	0.20 [-9.51, 9.91]
LOCCS	160	82.7 (24.92)	165	85.8 (22.28)	-	17.5 %	-3.10 [-8.24, 2.04]
Subtotal (95% CI)	271		284		•	31.6 %	-2.38 [-6.92, 2.17]
Heterogeneity: Tau ² = 0.0;	$Chi^2 = 0.35$, d	f = 1 (P = 0.56)	; I ² =0.0%				
Test for overall effect: $Z =$	1.02 (P = 0.31)					
2 Baseline FEV1 61-79 % p	redicted						
Kelsen 1999	185	42.2 (43.52)	191	27.2 (38.7)	•	15.2 %	15.00 [6.67, 23.33]
Johansson 2001	176	53 (38)	173	55 (38)	+	15.4 %	-2.00 [-9.97, 5.97]
Bateman 2003	168	60.4 (39.53)	176	55.5 (40.46)	•	15.1 %	4.90 [-3.55, 13.35]
Kips 2000	29	41.3 (37.7)	31	30.4 (34.4)		8.3 %	10.90 [-7.40, 29.20]
O'Byrne 2005	906	53 (0)	925	46 (0)			Not estimable
Subtotal (95% CI)	1464		1496		•	53.9 %	6.58 [-1.73, 14.90]
Heterogeneity: Tau ² = 44.3	71; Chi ² = 8.69	, df = 3 (P = 0.	03); I ² =65%				
Test for overall effect: Z =	1.55 (P = 0.12)					
3 Baseline FEV1 % predicte	d not reporte	đ					
Zhong 2005	199	63.2 (45)	187	44.4 (46.75)	+	14.5 %	18.80 [9.64, 27.96]
Subtotal (95% CI)	199		187		•	14.5 %	18.80 [9.64, 27.96]
Heterogeneity: not applical	ole						
Test for overall effect: $Z =$		0058)					
Total (95% CI)	1934		1967		•	100.0 %	5.81 [-1.14, 12.76]
Heterogeneity: Tau ² = 64.8			0.00013); I ² =789	6			
Test for overall effect: Z =	1.64 (P = 0.10))					
				-100) -50 0 50 I	00	
				Favours	Higher ICS Favours LAB	BA + ICS	

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

Heterogeneity: $Tau^2 = 0.1$ Test for overall effect: Z =		df = 3 (P = 0.004); I ² =78%				
Total (95% CI)	1219		1246		•	100.0 %	-0.28 [-0.67, 0.11
Test for overall effect: Z =							
Heterogeneity: $Tau^2 = 0.1$		df = 2 (P = 0.003)				, , , 0	5155 1 5101, 010/
Subtotal (95% CI)	1195		1222		+	79.8 %	-0.38 [-0.84, 0.07
Mitchell 2003	102	0.49 (0.71)	101	0.99 (0.76)	-	29.7 %	-0.68 [-0.96, -0.39
O'Byme 2005	906	0.5 (0)	925	0.59 (0)			Not estimabl
Bateman 2003	168	0.76 (1.24)	176	0.85 (1.24)	1	31.9 %	-0.07 [-0.28, 0.14
Fowler 2002	19	0.7 (0.67)	20	I (0.68)		18.2 %	-0.44 [-1.07, 0.20
2 Baseline FEV1 61-79 %							
Test for overall effect: Z =	0.42 (P = 0.68)						
Heterogeneity: not applica	able						
Subtotal (95% CI)	24		24		+	20.2 %	0.12 [-0.45, 0.69
I Baseline FEVI >= 80 % Heuck 2000	predicted 24	0.24 (0.49)	24	0.18 (0.49)	-	20.2 %	0.12 [-0.45, 0.69
		(idan(ob)		(loan(bb)	ing calcomp site of		110 60 60 70 70 70 70
study or subgroup	LABA + ICS	IF Mean(SD)	creased ICS	Mean(SD)	IV.Random.95% CI	vveight	IV.Random,95% C
Study or subgroup	LABA + ICS		creased ICS		Mean Difference	Weight	M Differe

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

Study or subgroup	LABA + ICS		Increased ICS		Std. Mean Difference	Weight	Std. Mean Difference
	N	Mean(SD)	N	Mean(SD)	IV,Fixed,95% CI		IV,Fixed,95% CI
I Baseline FEVI >= 80% p	predicted						
Heuck 2000	24	0.1 (0.19)	24	0.15 (0.39)		19.2 %	-0.16 [-0.73, 0.41]
Subtotal (95% CI)	24		24			19.2 %	-0.16 [-0.73, 0.41]
Heterogeneity: not applical	ble						
Test for overall effect: Z =	0.55 (P = 0.58)						
2 Baseline FEVI 61-79 % p	predicted						
O'Byme 2005	906	0.36 (0)	925	0.46 (0)			Not estimable
Mitchell 2003	102	0.34 (0.65)	101	0.5 (0.57)		80.8 %	-0.26 [-0.54, 0.02]
Subtotal (95% CI)	1008		1026		-	80.8 %	-0.26 [-0.54, 0.02]
Heterogeneity: not applical	ble						
Test for overall effect: Z =	1.85 (P = 0.064)					
Total (95% CI)	1032		1050		-	100.0 %	-0.24 [-0.49, 0.01]
Heterogeneity: Chi ² = 0.10	0, $df = 1$ (P = 0.	76); I ² =0.0%					
Test for overall effect: Z =	1.90 (P = 0.057)					
Test for subgroup difference	es: Chi ² = 0.10,	df = 1 (P = 0.7)	6), I ² =0.0%				
				-1	-0.5 0 0.5	1	
				Encurr	.ABA+ICS Favours Hi	abar ICS	

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

IV,Fixed,95% CI	IV,Fixed,95% CI	IV.Fixed.9					Study or subgroup
			Mean(SD)	N	Mean(SD)	N	
						predicted	Baseline FEV1 61-79 % p
94.0 % -0.01 [-0.04, 0.02]	94.0 %		0.06 (0.15)	238	0.05 (0.16)	246	Bateman 2006
94.0 % -0.01 [-0.04, 0.02]	• 94.0 %	•		238		246	Subtotal (95% CI)
						ible	leterogeneity: not applical
						0.71 (P = 0.48)	Test for overall effect: Z =
						predicted	2 Baseline FEV I >= 80 % j
6.0 % -0.08 [-0.19, 0.03]	- 6.0 %	-	-0.15 (0.44)	117	-0.23 (0.4)	109	Vermetten 1999
6.0 % -0.08 [-0.19, 0.03]		+		117		109	Subtotal (95% CI)
						ible	Heterogeneity: not applical
						1.43 (P = 0.15)	Test for overall effect: $Z =$
100.0 % -0.01 [-0.04, 0.01]	100.0 %	1		355		355	Total (95% CI)
					22); I ² =32%	8, $df = 1$ (P = 0.	Heterogeneity: Chi ² = 1.48
						1.04 (P = 0.30)	Test for overall effect: $Z =$
				22), I ² =32%	df = 1 (P = 0.2)	ces: Chi ² = 1.48,	Test for subgroup difference

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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Mean Difference	Weight	Mean Difference		Increased ICS		ABA + ICS	Study or subgroup L
IV,Fixed,95% CI		IV,Fixed,95% CI	Mean(SD)	N	Mean(SD)	N	
						edicted	I Baseline FEVI >= 80 % pr
1.60 [-8.49, 11.69]	34.0 %	+	58.2 (37.9)	119	59.8 (40.2)	112	Vermetten 1999
1.60 [-8.49, 11.69]	34.0 %	+		119		112	Subtotal (95% CI)
						e	Heterogeneity: not applicable
						31 (P = 0.76)	Test for overall effect: $Z = 0$.
						dicted	2 Baseline FEVI 61-79 % pre
-4.00 [-11.24, 3.24]	66.0 %	-	72 (33)	173	68 (36)	176	Johansson 2001
-4.00 [-11.24, 3.24]	66.0 %	•		173		176	Subtotal (95% CI)
						e	Heterogeneity: not applicable
						08 (P = 0.28)	Test for overall effect: $Z = I$.
-2.10 [-7.98, 3.79]	100.0 %	•		292		288	Total (95% CI)
					38); I ² =0.0%	df = 1 (P = 0.	Heterogeneity: Chi ² = 0.78,
						70 (P = 0.49)	Test for overall effect: $Z = 0$.
				38), I ² =0.0%	df = I (P = 0.	s: Chi ² = 0.78,	Test for subgroup differences

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

Study or subgroup L	ABA + ICS		Increased ICS		Std. Mean Difference	Weight	Std. Mean Difference
	N	Mean(SD)	N	Mean(SD)	IV,Fixed,95% CI		IV,Fixed,95% CI
I Baseline FEVI >= 80 % pre	edicted						
Busse 2003	281	-0.29 (1.51)	277	-0.34 (1.66)	-	17.6 %	0.03 [-0.13, 0.20]
Subtotal (95% CI)	281		277		+	17.6 %	0.03 [-0.13, 0.20]
Heterogeneity: not applicable							
Test for overall effect: $Z = 0.3$	87 (P = 0.71)						
2 Baseline FEV1 61-79 % pred	dicted						
Murray 1999	207	-0.28 (0.58)	193	-0.29 (0.56)	-	12.6 %	0.02 [-0.18, 0.21]
Kelsen 1999	189	-0.27 (0.55)	192	-0.25 (0.55)	-	12.0 %	-0.04 [-0.24, 0.16]
Condemi 1999	221	-0.21 (0.45)	216	-0.11 (0.29)		13.7 %	-0.26 [-0.45, -0.07]
Baraniuk 1999	226	-0.31 (0.6)	223	-0.32 (0.6)		14.2 %	0.02 [-0.17, 0.20]
Subtotal (95% CI)	843		824		•	52.5 %	-0.07 [-0.16, 0.03]
Heterogeneity: Chi ² = 5.75, c	f = 3 (P = 0.1)	12); 1 ² =48%					
Test for overall effect: Z = 1.3	89 (P = 0.16)						
3 Baseline FEV1 <= 60 % pre	dicted						
SLGA5021	240	-0.16 (0.31)	238	-0.17 (0.46)		15.1 %	0.03 [-0.15, 0.20]
Subtotal (95% CI)	240		238		+	15.1 %	0.03 [-0.15, 0.20]
Heterogeneity: not applicable							
Test for overall effect: $Z = 0.2$	28 (P = 0.78)						
4 Baseline FEV1 % predicted	not reported						
SAM40090	235	0.02 (0.2)	234	0.02 (0.2)	-	14.8 %	0.0 [-0.18, 0.18]
Subtotal (95% CI)	235		234		+	14.8 %	0.0 [-0.18, 0.18]
Heterogeneity: not applicable							
Test for overall effect: $Z = 0.0$) (P = 1.0)						
Total (95% CI)	1599		1573		•	100.0 %	-0.03 [-0.10, 0.04]
Heterogeneity: Chi ² = 7.35, c	`	29); I ² =18%					
Test for overall effect: $Z = 0.7$							
Test for subgroup differences:	Chi ² = 1.60,	df = 3 (P = 0.	66), I ² =0.0%				
				-1	-0.5 0 0.5	1	

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

Mear Difference	Weight	Mean Difference			Higher ICS		LABA + ICS	Study or subgroup
IV,Fixed,95% C		Fixed,95% CI		Mean(SD)	N	Mean(SD)	N	
							6 predicted	I Baseline FEVI 61-799
-1.70 [-5.77, 2.37	0.1 %	·		9.6 (19.5)	176	7.9 (19.05)	168	Bateman 2003
-0.40 [-0.55, -0.25]	99.9 %			8.6 (1.63)	925	8.2 (1.63)	906	O'Byrne 2005
-0.40 [-0.55, -0.25]	100.0 %	•			1101			Total (95% CI) Heterogeneity: Chi ² = Test for overall effect: 2
						cable	rences: Not appl	Test for subgroup differ
	10	0 5	-10					
	igher ICS	Favours h	urs LABA	Favou				

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

Study or subgroup	LABA + ICS		Increased ICS		Mean Difference	Mea Difference
	N	Mean(SD)	N	Mean(SD)	IV,Fixed,95% CI	IV,Fixed,95% C
Baseline FEV1 61-79	% predicted					
Kelsen 1999	189	88.4 (24.75)	192	85.4 (26.33)		3.00 [-2.13, 8.13
						-
					-10 -5 0 5 1	U

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

Study or subgroup	LABA + ICS		Increased ICS		Dif	Mean ference	Mea Differenc
	Ν	Mean(SD)	Ν	Mean(SD)	IV,Fixe	ed,95% Cl	IV,Fixed,95% (
I Baseline FEVI 61-79	% predicted						
O'Byme 2005	906	12 (0)	925	12 (0)			Not estimabl
					-10 -5	0 5 10	
				Fa	avours Higher ICS	Favours LABA +	ICS

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

1ean ence	Me Differen	Weight	Mean Difference		Increased ICS		LABA + ICS	Study or subgroup
% CI	IV,Random,95%		IV,Random,95% CI	Mean(SD)	N	Mean(SD)	N	
							5 predicted	Baseline FEV >= 80 %
ble	Not estimab				0		0	Subtotal (95% CI)
							able	Heterogeneity: not applic
							t applicable	Test for overall effect: not
							predicted	2 Baseline FEV1 61-79 %
.95]	-1.46 [-1.97, -0.9	14.8 %	-	-0.87 (2.78)	193	-2.33 (2.44)	206	Murray 1999
.28]	-0.83 [-1.38, -0.2	13.7 %		-1.37 (2.76)	191	-2.2 (2.72)	185	Kelsen 1999
.01]	-0.07 [-0.13, -0.0	28.5 %	-	0.09 (0.31)	238	0.02 (0.31)	246	Bateman 2006
.04]	-0.53 [-1.02, -0.0	15.6 %		-1.53 (2.37)	173	-2.06 (2.36)	192	Condemi 1999
.07]	-0.19 [-0.31, -0.0	27.3 %	-	-0.66 (1.36)	925	-0.85 (1.36)	906	O'Byrne 2005
20]	-0.48 [-0.77, -0.20	100.0 %	•		1720		1735	Subtotal (95% CI)
					0001); I ² =90%	df = 4 (P<0.00	07; Chi ² = 39.38,	Heterogeneity: $Tau^2 = 0$.
						181)	= 3.35 (P = 0.000	Test for overall effect: Z =
							5 predicted	3 Baseline FEV1 <= 60 %
ble	Not estimab				0		0	Subtotal (95% CI)
							able	Heterogeneity: not applic
							t applicable	Test for overall effect: not
20]	-0.48 [-0.77, -0.20	100.0 %	•		1720		1735	Total (95% CI)
					0001); I ² =90%	df = 4 (P<0.00	07; Chi ² = 39.38,	Heterogeneity: $Tau^2 = 0.$
						81)	= 3.35 (P = 0.000	Test for overall effect: Z =
						181)	= 3.35 (P = 0.000	t for overall effect; Z. :
		4		-4				
			-2 0 2 LABA+ICS Favours Hi					

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

Study or subgroup	LABA + ICS		Increased ICS		Std. Mean Difference	Weight	Std. Mean Difference
	Ν	Mean(SD)	N	Mean(SD)	IV,Random,95% CI		IV,Random,95% CI
I Baseline FEVI 61-79 %	predicted						
Murray 1999	207	-0.51 (0.86)	193	-0.4 (.)		16.2 %	-0.11 [-0.31, 0.09]
Kelsen 1999	189	-0.5 (1.1)	192	-0.51 (1.25)	-	15.5 %	0.01 [-0.19, 0.21]
Condemi 1999	194	-0.6 (1.11)	174	-0.33 (0.92)		14.9 %	-0.26 [-0.47, -0.06]
O'Byrne 2005	906	-0.36 (0.5)	925	-0.29 (0.5)	-	53.5 %	-0.14 [-0.23, -0.05]
Subtotal (95% CI)	1496		1484		•	100.0 %	-0.13 [-0.21, -0.05]
Heterogeneity: $Tau^2 = 0.0$	00; Chi ² = 3.51,	df = 3 (P = 0.3	2); I ² =15%				
Test for overall effect: Z =	= 3.06 (P = 0.00)	22)					
2 Baseline FEV I <= 60 %	predicted						
Subtotal (95% CI)	0		0				Not estimable
Heterogeneity: not applic	able						
Test for overall effect: not	applicable						
Total (95% CI)	1496		1484		•	100.0 %	-0.13 [-0.21, -0.05]
Heterogeneity: $Tau^2 = 0.0$	00; Chi ² = 3.51,	df = 3 (P = 0.3	2); I ² =15%				
Test for overall effect: Z =	3.06 (P = 0.00)	22)					
				-1	-0.5 0 0.5	1	
				Environne I	ABA + ICS Favours Hig	har ICS	

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

Study or subgroup	LABA + ICS N	Mean(SD)	Increased ICS N	Mean(SD)	Mean Difference IV,Random,95% CI	Weight	Mean Difference IV,Random,95% CI
Baseline FEV >= 80%	predicted						
Busse 2003	281	-0.3 (1.17)	277	-0.18(1)		10.1 %	-0.11 [-0.28, 0.06]
Lalloo 2003	230	-0.33 (1.1)	237	-0.1 (1.1)		9.5 %	-0.21 [-0.39, -0.03]
SAS40026	312	-0.31 (1.06)	309	-0.23 (1.23)		10.5 %	-0.07 [-0.23, 0.09]
Vermetten 1999	109	-0.57 (1.07)	115	-0.31 (1.06)		6.7 %	-0.24 [-0.51, 0.02]
Subtotal (95% CI) Heterogeneity: $Tau^2 = 0.0$ Test for overall effect: Z =			938); I ² =0.0%		•	36.9 %	-0.14 [-0.23, -0.05]
2 Baseline FEV1 61-79 % i							
Baraniuk 1999	228	-2.91 (3.02)	223	-2.39 (3.14)		9.4 %	-0.17 [-0.35, 0.02]
Bateman 2003	168	-0.31 (0.77)	176	-0.13 (0.8)		8.4 %	-0.23 [-0.44, -0.02]
Bergmann 2004	170	-1.6 (1.9)	177	-1 (2.2)		8.4 %	-0.29 [-0.50, -0.08]
Condemi 1999	193	-0.58 (0.56)	174	-0.38 (0.53)		8.6 %	-0.37 [-0.57, -0.16]
Pearlman 1999	24	-1.5 (2.45)	22	-1.4 (1.88)		2.1 %	-0.04 [-0.62, 0.53]
SD 039 0728	130	-0.7 (1.8)	130	-0.2 (1.3)		7.3 %	-0.32 [-0.56, -0.07]
Subtotal (95% CI) Heterogeneity: Tau ² = 0.0 Test for overall effect: Z = 3 Baseline FEVI <= 60 %	5.53 (P < 0.000 predicted	101)			•		-0.26 [-0.35, -0.17]
SLGA5021	240	-2.33 (3.1)	238	-1.3 (1.54)		9.5 %	-0.42 [-0.60, -0.24]
Subtotal (95% CI) Heterogeneity: not applica Test for overall effect: Z = 4 Baseline FEV1 not repor SAM40090	4.54 (P < 0.000	01) 0.03 (0.26)	238	0 (0.26)	•	9.5 %	-0.42 [-0.60, -0.24] 0.12 [-0.07, 0.30]
Subtotal (95% CI)	234		234		-	9.5 %	0.12 [-0.07, 0.30]
Heterogeneity: not applica Test for overall effect: Z = Total (95% CI) Heterogeneity: Tau ² = 0.0	1.25 (P = 0.21) 2319		2312 0.01); l ² =57%		•	100.0 %	-0.20 [-0.29, -0.11]
Test for overall effect; Z =	4.28 (P = 0.000	1019)			-0.5 0 0.5		

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

Mean Difference	Weight	Mean Difference		Increased ICS		LABA + ICS	Study or subgroup
IV,Random,95% Cl	_	IV,Random,95% CI	Mean(SD)	Ν	Mean(SD)	Ν	
						predicted	Baseline FEV >= 80 %
-0.21 [-0.64, 0.22]	22.8 %	-	0.46 (1.02)	24	0.25 (0.34)	24	Heuck 2000
-0.13 [-0.39, 0.13]	25.4 %	-	0.61 (1.09)	119	0.48 (0.95)	111	Vermetten 1999
-0.15 [-0.38, 0.07]	48.2 %	•		143		135	Subtotal (95% CI)
				I ² =0.0%	= I (P = 0.76)); $Chi^2 = 0.10$, df	Heterogeneity: $Tau^2 = 0.0$;
						= 1.32 (P = 0.19)	Test for overall effect: Z =
						predicted	2 Baseline FEV1 61-79 % p
-0.90 [-2.60, 0.80]	6.6 %		3.5 (2.7)	20	2.6 (2.7)	19	Fowler 2002
-1.50 [-2.04, -0.96]	20.6 %	-	2.43 (2.43)	101	0.93 (1.38)	102	Mitchell 2003
-1.44 [-1.96, -0.93]	27.2 %	•		121		121	Subtotal (95% CI)
				12 =0.0%	= I (P = 0.5 I)); $Chi^2 = 0.44$, df	Heterogeneity: Tau ² = 0.0;
					01)	5.46 (P < 0.000	Test for overall effect: Z =
						rted	3 Baseline FEV1 not report
0.04 [-0.28, 0.36]	24.6 %	+	0.26 (0.27)	12	0.3 (0.5)	12	SAM40100
0.04 [-0.28, 0.36]	24.6 %	+		12		12	Subtotal (95% CI)
						able	Heterogeneity: not applical
						0.24 (P = 0.81)	Test for overall effect: Z =
-0.44 [-0.94, 0.06]	100.0 %	+		276		268	Total (95% CI)
				0006); I ² =84%	df = 4 (P = 0.0	24; Chi ² = 24.76,	Heterogeneity: $Tau^2 = 0.24$
)	1.73 (P = 0.084	Test for overall effect: Z =

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)

Study or subgroup	LABA + ICS		Increased ICS		Mean Difference	Weight	Mean Difference
	Ν	Mean(SD)	Ν	Mean(SD)	IV,Random,95% CI		IV,Random,95% CI
I Baseline FEVI >=80% pr	edicted						
Vermetten 1999	111	0.3 (0.63)	119	0.37 (0.66)		23.7 %	-0.07 [-0.24, 0.10]
Bateman 2006	246	0.03 (0.31)	238	0.07 (0.31)	-	35.9 %	-0.04 [-0.10, 0.02]
Subtotal (95% CI)	357		357		•	59.6 %	-0.04 [-0.10, 0.01]
Heterogeneity: Tau ² = 0.0;	$Chi^2 = 0.11$, df	= I (P = 0.74	; I ² =0.0%				
Test for overall effect: Z =	I.6I (P = 0.II)						
2 Baseline FEV1 61-79 % p	redicted						
Mitchell 2003	102	0.69 (1.27)	101	1.43 (1.56) *	-	8.7 %	-0.74 [-1.13, -0.35]
Subtotal (95% CI)	102		101	-	-	8.7 %	-0.74 [-1.13, -0.35]
Heterogeneity: not applicat	ole						
Test for overall effect: $Z = 2$	3.70 (P = 0.000	121)					
3 Baseline FEV1 not report	ed						
SAM40100	12	0.05 (0.06)	12	0.05 (0.16)	+	31.7 %	0.0 [-0.10, 0.10]
Subtotal (95% CI)	12		12		+	31.7 %	0.0 [-0.10, 0.10]
Heterogeneity: not applicat	ble						
Test for overall effect: $Z = 0$	0.0 (P = 1.0)						
Total (95% CI)	471		470		•	100.0 %	-0.09 [-0.23, 0.04]
Heterogeneity: Tau ² = 0.01	; Chi ² = 13.05,	df = 3 (P = 0.	005); I ² =77%				
Test for overall effect: $Z =$	I.42 (P = 0.15)						
				-1	-0.5 0 0.5	1	
				Favours L	ABA + ICS Favours Hig	her ICS	

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

Study or subgroup	LABA + ICS	Ir	creased ICS		Mean Difference	Weight	Mean Difference
	Ν	Mean(SD)	N	Mean(SD)	IV,Random,95% CI		IV,Random,95% CI
I Baseline FEV1 61-79 %	predicted						
Johansson 2001	176	64 (37)	173	63 (38)	+	48.8 %	1.00 [-6.87, 8.87]
Bateman 2003	168	75.5 (34.61)	168	66.4 (35.42)	-	51.2 %	9.10 [1.61, 16.59]
O'Byrne 2005	906	54 (0)	925	45 (0)			Not estimable
Subtotal (95% CI) Heterogeneity: Tau ² = 17	1250 44; Chi ² = 2.14	, df = 1 (P = 0.14);	1266 2 =53%		•	100.0 %	5.14 [-2.79, 13.08]
Test for overall effect: Z =	= 1.27 (P = 0.20))					
				-10	D -50 0 50 I	00	
				Favours	Higher ICS Favours LAB	A + ICS	

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

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ots	

%	Weight	%	% (SE)	Study or subgroup
IV,Random,95% CI		IV,Random,95% CI		
			ed	I Baseline FEVI >= 80% predic
Not estimable				Subtotal (95% CI)
				Heterogeneity: not applicable
			able	Test for overall effect: not applie
			predicted	2 Baseline FEV1 61% to 79% of
-0.24 [-1.20, 0.72]	100.0 %	· -	-0.24 (0.489796)	Green 2006
-0.24 [-1.20, 0.72]	100.0 %			Subtotal (95% CI)
				Heterogeneity: not applicable
			(P = 0.62)	Test for overall effect: Z = 0.49
			ed	3 Baseline FEV I <= 60% predic
Not estimable				Subtotal (95% CI)
				Heterogeneity: not applicable
			able	Test for overall effect: not applie
			reported	4 Baseline FEV1 % predicted no
Not estimable				Subtotal (95% CI)
				Heterogeneity: not applicable
			able	Test for overall effect: not applie
-0.24 [-1.20, 0.72]	100.0 %			Total (95% CI)
				Heterogeneity: not applicable
			P = 0.62	Test for overall effect: $Z = 0.49$

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

Study or subgroup LA	BA + ICS	h	ncreased ICS		Mean Difference	Weight	Mean Difference
	N	Mean(SD)	N	Mean(SD)	IV,Fixed,95% CI		IV,Fixed,95% CI
I Baseline FEVI >= 80 % pre	dicted						
Busse 2003	281	14.7 (33.53)	277	9.3 (33.29)	-	39.9 %	5.40 [-0.14, 10.94]
Subtotal (95% CI)	281		277		•	39.9 %	5.40 [-0.14, 10.94]
Heterogeneity: not applicable							
Test for overall effect: Z = 1.9	I (P = 0.05	6)					
2 Baseline FEV1 61% to 79% p	predicted						
Murray 1999	260	31 (37)	254	14.9 (30)	-	36.2 %	16.10 [10.28, 21.92]
SD 039 0728	130	22.2 (32.1)	130	7.6 (26.5)	+	23.9 %	14.60 [7.44, 21.76]
Subtotal (95% CI)	390		384		•	60.1 %	15.50 [10.99, 20.02]
Heterogeneity: Chi ² = 0.10, d	f = 1 (P = 0	0.75); I ² =0.0%					
Test for overall effect: $Z = 6.7$	3 (P < 0.00	001)					
Total (95% CI)	671		661		•	100.0 %	11.48 [7.98, 14.98]
Heterogeneity: Chi ² = 7.77, d	f = 2 (P = 0	0.02); I ² =74%					
Test for overall effect: $Z = 6.4$	3 (P < 0.00	001)					
Test for subgroup differences:	Chi ² = 7.67	df = 1 (P = 0.01)), l ² =87%				
				-100	-50 0 50	100	
				Favours H	igher ICS Favours LA		

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 (%)

Study or subgroup	LABA + ICS		Increased ICS		Mean Difference	Mean Difference
	N	Mean(SD)	N	Mean(SD)	IV,Fixed,95% CI	IV,Fixed,95% CI
I Baseline FEVI >= 80) % predicted					
Lalloo 2003	230	17 (27.4)	237	10 (27.4)	-+-	7.00 [2.03, 11.97]
					-100 -50 0 50	100
				Fav	ours Higher ICS Favours LA	BA + ICS

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

Study or subgroup	LABA + ICS N	Mean(SD)	Increased ICS N	Mean(SD)	Mean Difference IV,Fixed,95% Cl	Weight	Mean Difference IV,Fixed,95% CI
Baseline FEVI 61% to 7	9 % predicted						
Fowler 2002	19	0.09 (0.76)	20	-0.34 (0.73)		11.6 %	0.43 [-0.04, 0.90]
Pauwels 1997	112	0.06 (0.68)	105	-0.01 (0.73)	-	72.0 %	0.07 [-0.12, 0.26]
SAM30022	34	0.66 (1.17)	33	0.7 (0.57)		13.2 %	-0.04 [-0.48, 0.40]
Subtotal (95% CI)	165		158		+	96.8 %	0.10 [-0.06, 0.26]
Test for overall effect: Z = 2 Baseline FEV1 not repor SAM40120	()	0.37 (1.01)	10	0.19 (0.91)		· 3.2 %	0.18 [-0.72, 1.08]
Subtotal (95% CI) Heterogeneity: not applica	8 able	0.37 (1.01)	10	0.19 (0.91)			0.18 [-0.72, 1.08]
Test for overall effect: Z =			168			100.0.0/	0.101.000.0001
Total (95% CI) Heterogeneity: Chi ² = 2.4 Test for overall effect: Z = Test for subgroup differen	1.24 (P = 0.22)					100.0 %	0.10 [-0.06, 0.26]
					-0.5 0 0.5		

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

Study or subgroup	LABA + ICS		Increased ICS		Mean Difference	Mean Difference
N		Mean(SD)	Ν	Mean(SD)	IV,Fixed,95% CI	IV,Fixed,95% C
I Baseline FEVI >= 80) % predicted					
Vermetten 1999	104	-2.74 (4.74)	102	-1.13 (4.5)		-1.61 [-2.87, -0.35]
					-10 -5 0 5	10
				Favour	s LABA + ICS Favours	s Higher ICS

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

Study or subgroup	LABA + ICS n/N	Increased ICS n/N	Risk Ratio M-H,Fixed,95% Cl	Risk Ratio M-H,Fixed,95% C
I Baseline FEVI >= 80 % p	predicted			
2 Baseline FEV1 61% to 79	% predicted			
Bateman 2006	188/245	164/237	+	1.11 [0.99, 1.24
3 Baseline FEV1 <= 60 % p	predicted			
			0.1 0.2 0.5 1 2 5 10	
			Favours Higher ICS Favours LABA + ICS	

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

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Outcome: 44 % asthma control days at endpoint

Study or subgroup	LABA + ICS		Increased ICS		Diff	Mean ference	Mea Differenc
	Ν	Mean(SD)		Mean(SD)	IV,Fixe	ed,95% CI	IV,Fixed,95% C
Baseline FEVI 61% t	to 79 % predicted						
Bateman 2003	168	57.8 (42.2)	176	52.4 (42.58)			5.40 [-3.56, 14.36
O'Byrne 2005	906	44 (0)	925	37 (0)			Not estimable
					-10 -5	0 5 10	
				Fav	ours LABA + ICS	Favours LABA	+ ICS

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)

Study or subgroup	LABA + ICS	Inc	reased ICS		Mean Difference	Weight	Mean Difference
	N	Mean(SD)	Ν	Mean(SD)	IV,Fixed,95% CI		IV,Fixed,95% CI
I Baseline FEVI >= 80% p	redicted						
Heuck 2000	24	9 (5.39)	24	9.7 (7.84)	-	65.2 %	-0.70 [-4.51, 3.11]
Subtotal (95% CI)	24		24		-	65.2 %	-0.70 [-4.51, 3.11]
Heterogeneity: not applicat	ble						
Test for overall effect: Z =	0.36 (P = 0.72)						
2 Baseline FEV1 61% to 79	% predicted						
Fowler 2002	19	20.8 (8.78)	20	17.7 (7.76)		34.8 %	3.10 [-2.11, 8.31
Subtotal (95% CI)	19		20			34.8 %	3.10 [-2.11, 8.31]
Heterogeneity: not applicat	ble						
Test for overall effect: $Z =$	I.I7 (P = 0.24)						
Total (95% CI)	43		44		-	100.0 %	0.62 [-2.45, 3.70]
Heterogeneity: Chi ² = 1.33	$B_{r}, df = 1 (P = 0.1)$	25); I ² =25%					
Test for overall effect: $Z = 0$	0.40 (P = 0.69)						
Test for subgroup difference	es: Chi² = 1.33,	df = 1 (P = 0.25),	2 =25%				
				-10	-5 0 5	10	
				Favours LA	BA + ICS Favours Hi	igher ICS	

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

Study or subgroup	LABA + ICS N	Mean(SD)	Increased ICS	Mean(SD)	Mean Difference W.Fixed.95% CI	Mear Difference IV.Fixed.95% C
I Baseline FEVI 61% Fowler 2002		412 (00.07)	20	202 (05.02)	_	20.001 41.10 01.10
Fowler 2002	19	413 (98.97)	20	393 (95.83)		20.00 [-41.19, 81.19]
						1000
					Favours Higher ICS Favours	ABA + ICS

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)

Study or subgroup	LABA + ICS		Increased ICS			Dif	Mea ferenc			Mei Differen
	Ν	Mean(SD)	Ν	Mean(SD)		IV,Fix	ed,959	6 CI		IV,Fixed,95%
I Baseline FEVI 61% t	o 79 % predicted									
Fowler 2002	19	6.7 (1.83)	20	5.4 (2.34)			+			1.30 [-0.01, 2.6
					-10	-5	0	5	10	
				Fav	ours LABA	+ ICS	E	avours	Higher IC	ŝ

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

Study or subgroup LABA + ICS			Increased ICS		Mean Difference	Mea Difference
	Ν	Mean(SD)	N	Mean(SD)	IV,Fixed,95% CI	IV,Fixed,95% (
I Baseline FEVI 61% to	79 % predicted					
Fowler 2002	19	149.9 (91.4)	20	71.2 (43.47)	-	78.70 [33.40, 124.00
					-1000 -500 0 500 100	20.
					-1000 -500 0 500 100 ins LABA + ICS Favours High	

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

Study or subgroup	LABA + ICS		Increased ICS		Diff	Mean erence	Mear Difference
	Ν	Mean(SD)	Ν	Mean(SD)	IV,Fixe	ed,95% CI	IV,Fixed,95% C
I Baseline FEVI not re	eported						
SAS40013	5	1.79 (0)	7	1.79 (0)			Not estimable
					-10 -5	0 5 10	
				Fa	avours Higher ICS	Favours LABA +	ICS

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

Study or subgroup	LABA + ICS		Increased ICS			Mean erence	Mear Difference
	N	Mean(SD)	N	Mean(SD)	IV,Fixe	:d,95% Cl	IV,Fixed,95% C
I Baseline FEVI 61%1	to 79 % predicted						
Mitchell 2003	102	3.48 (38.2)	101	-13.38 (29.91)			16.86 [7.43, 26.29
		51.10 (5511)		10100 (2010-1)			
					-100 -50	0 50 10	10
					Favours Higher ICS	Favours LAB	

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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n/N				
	n/N	M-H,Fixed,95% CI		M-H,Fixed,95% (
i				
1/281	3/277		1.8 %	0.33 [0.03, 3.14
5/230	2/237		1.2 %	2.58 [0.50, 13.14
4/163	6/169		3.5 %	0.69 [0.20, 2.40
12/323	19/312		11.4 %	0.61 [0.30, 1.24
3/60	3/60		1.8 %	1.00 [0.21, 4.76
2/113	0/120		0.3 %	5.31 [0.26, 109.35
1170	1175	•	19.9 %	0.82 [0.50, 1.34
(Increased ICS)				
$(P = 0.44); I^2 = 0.$.0%			
	1/281 5/230 4/163 12/323 3/60 2/113 1170 Increased ICS)	1/281 3/277 5/230 2/237 4/163 6/169 1/2/323 19/312 3/60 3/60 2/113 0/120 1170 1175	1/281 3/277 5/230 2/237 4/163 6/169 1/2/323 19/312 3/60 3/60 2/113 0/120 1170 1175	1/281 3/277 1.8 % 5/230 2/237 1.2 % 4/163 6/169 3.5 % 1/2/323 19/312 11.4 % 3/60 3/60 1.8 % 2/113 0/120 0.3 % 1170 1175 19.9 %

Favours LABA + ICS Favours higher ICS

Study or subgroup	LABA + KCS	Increased ICS	Risk Ratio	Weight	Risk Rati
	n/N	n/N	M-H,Fixed,95% CI		M-HuFixed,95% (
Test for overall effect: Z = 0.1 2 Baseline FEV1 61% to 79%					
2 Baseline FEVT 6176 to 7976 Bateman 2003	0/168	3/176	·	2.0 %	0.15 [0.01, 2.87
Bateman 2006	4/246	1/238	· · · · · ·	0.6 %	3.87 [0.44, 34.37
Bergmann 2004	2/179	2/186		1.2 %	1.04 { 0.15, 7.30
Bouros 1999	1/69	1/65		0.6 %	
					0.94 [0.06, 14.75
Condemi 1999	1/221	1/216		0.6 %	0.98 [0.06, 15.53
Greening 1994	7/220	3/206		1.8 %	2.18 [0.57, 8.34
Ind 2003	9/171	5/160		3.0 %	1.68 [0.58, 4.92
Jenkins 2000	6/180	6/173		3.6 %	0.96 [0.32, 2.92
Johansson 2001	3/176	0/173		0.3 %	6.88 [0.36, 132.24
Kelsen 1999	5/239	12/244		7.0 %	0.43 [0.15, 1.19
Mitchell 2003	1/102	1/101		0.6 %	0.99 [0.06, 15.62
Murray 1999	7/260	7/254		4.2 %	0.98 [0.35, 2.75
O'Byme 2005	60/906	47/925	-	27.4 %	1.30 [0.90, 1.89
Pauwels 1997	10/210	12/214	-	7.0 %	0.85 [0.38, 1.92
SD 039 0726	0/152	1/145	· · · · · · · · · · · · · · · · · · ·	0.9 %	0.32 [0.01, 7.75
SD 039 0728	12/132	5/133		2.9 %	2.42 [0.88, 6.67
Wookock 1996a	16/244	3/125		2.3 %	2.73 [0.81, 9.20
Wookock 1996b	6/243	4/126		3.1 %	0.78 [0.22, 2.71
Subtotal (95% CI)	4118	3860		69.2 %	1.23 [0.97, 1.56
Total events: 150 (LABA + K Heterogeneity: Chi ² = 15.40, Test for overall effect: Z = L 3 Baseline FEV1 <= 60 % pro	df = 17 (P = 0.57); I^2 59 (P = 0.090) edicted	=0.0%			
SLGA5021	7/246	5/242		3.0 %	1.38 [0.44, 4.28
Subtotal (95% CI) Total events: 7 (LABA + ICS) Heterogeneity: not applicable Test for overall effect: Z = 0.1 4 Baseline FEV1 not reporter	55 (P = 0.58)	242		3.0 %	1.38 [0.44, 4.28
4 Baseline FEVT not reporter SAM104926	1/150	1/153		0.6 %	1.02 [0.06, 16.16
SAM30013	1/121	1/116		0.6 %	0.96 [0.06, 15.15
SAM30022	1/35	1/33		0.6 %	0.94 [0.06, 14.47
SAM40012	2/181	4/186		2.3 %	0.51 [0.10, 2.77
SPECTOOLE.	2/101	4100		2.3 /0	0.51 [0.10, 2.77

0.6 %	M-H,Fixed,95% Cl	n/N	n/N	
0.6 %		1/241	1/242	0
			112.12	SAM40090
		0/10	0/8	SAM40120
		0/7	0/5	SAS40013
1.8 %		3/315	3/321	SAS40026
0.9 %	•	1/159	0/157	SFCF4026
0.6 %		1/189	1/200	Zhong 2005
8.0 %	-	1409	1420	Subtotal (95% CI)
), 13 (Increased ICS)	otal events: 10 (LABA + ICS)
		5	$f = 7 (P = 1.00); I^2 = 0.09$	leterogeneity: Chi ² = 0.71, d
			4 (P = 0.53)	est for overall effect: Z = 0.6
100.0 %	•	6686	6954	Total (95% CI)
			S), 165 (Increased ICS)	otal events: 194 (LABA + IC
		0%	df = 32 (P = 0.84); $l^2 = 0$	leterogeneity: Chi ² = 24.02,
			5 (P = 0.29)	est for overall effect: Z = 1.0
0.9 % 0.6 % 3.0 %			3/315 1/159 1/189 1409 6686 100	3/32 I 3/315 0/157 I/159 1/200 I/189 1/420 1409 € k 13 (noreased ICS) f = 7 (P = 1.00); P = 0.0% 4 (P = 0.53) 5954 6686 € 100 5), 165 (Increased ICS) df = 32 (P = 0.84); P = 0.0%

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

Study or subgroup	LABA + ICS n/N	Increased ICS n/N	Risk Ratio M-H.Fixed,95% Cl	Weight	Risk Ratio M-H,Fixed,95% C
Baseline FEV1 >= 80 % pre	dicted				
Vermetten 1999	0/113	3/120		10.1 %	0.15 [0.01, 2.90]
ubtotal (95% CI)	113	120	-	10.1 %	0.15 [0.01, 2.90]
otal events: 0 (LABA + ICS),	3 (Increased ICS)				
leterogeneity: not applicable					
est for overall effect: Z = 1.2 Baseline FEV1 61% to 79 %					
Kelsen 1999	2/239	1/244		3.0 %	2.04 [0.19, 22.37
Pauwels 1997	2/210	0/214		1.5 %	5.09 [0.25, 105.49
Baraniuk 1999	2/231	1/223		3.0 %	1.93 [0.18, 21.14
Pearlman 1999	1/25	0/23	.	1.6 %	2.77 [0.12, 64.76
Condemi 1999	3/221	0/216		1.5 %	6.84 [0.36, 131.68
Greening 1994	13/220	4/206		12.3 %	3.04 [1.01, 9.18
O'Byrne 2005	18/906	19/925	+	56.1 %	0.97 [0.51, 1.83
Woolcock 1996b	6/243	1/126		3.9 %	3.11 [0.38, 25.56
Woolcock 1996a	19/244	1/125		3.9 %	9.73 [1.32, 71.87]
ubtotal (95% CI)	2539	2302	•	86.9 %	2.03 [1.29, 3.19]
eterogeneity: Chi ² = 9.27, d leterogeneity: Chi ² = 9.27, d lest for overall effect: Z = 3.0 Baseline FEV1 <= 60% prec SLGA5021	f = 8 (P = 0.32); I ² = 7 (P = 0.0021)	1/742		20.94	1071010 2157
				3.0 %	1.97 [0.18, 21.56]
Subtotal (95% CI) Sotal events: 2 (LABA + ICS), Heterogeneity: not applicable set for overall effect: Z = 0.5		242	-	3.0 %	1.97 [0.18, 21.56]
fotal (95% CI)	2898	2664	•	100.0 %	1.84 [1.20, 2.82]
otal events: 68 (LABA + ICS					
leterogeneity: Chi ² = 11.62,		=14%			
est for overall effect: $Z = 2.7$	9 (P = 0.0053)				
			2.001.0.01.0.1 1 10 100 1000		

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

Study or subgroup	LABA + ICS	Increased ICS	Risk Ratio M-	Weight	Risk Ratio M-
	n/N	n/N	H,Random,95% Cl		H,Random,95 Cl
I Baseline FEVI >= 80 % pr					
Vermetten 1999	0/113	0/120			Not estimable
Busse 2003	2/281	5/277		5.4 %	0.39 [0.08, 2.02]
SAS40026	3/321	8/315		8.1 %	0.37 [0.10, 1.37]
Subtotal (95% CI)	715	712	+	13.6 %	0.38 [0.14, 1.05]
Total events: 5 (LABA + ICS					
Heterogeneity: $Tau^2 = 0.0$; C Test for overall effect: $Z = 1$.		0.95); 1² =0.0%			
2 Baseline FEV1 61-79 % pre					
Murray 1999	9/260	14/254	-	18.8 %	0.63 [0.28, 1.42]
Kelsen 1999	1/239	2/244		2.6 %	0.51 [0.05, 5.59]
Jenkins 2000	5/180	1/173		3.2 %	4.81 [0.57, 40.72]
Greening 1994	4/220	5/206		8.3 %	0.75 [0.20, 2.75]
Bateman 2006	5/246	3/238		7.1 %	1.61 [0.39, 6.67]
Baraniuk 1999	5/231	4/223	_	8.3 %	1.21 [0.33, 4.44]
Condemi 1999	1/221	11/216		3.5 %	0.09 [0.01, 0.68]
O'Byme 2005	6/906	10/925		13.2 %	0.61 [0.22, 1.68]
Bergmann 2004	1/170	3/177		2.9 %	0.35 [0.04, 3.30]
Subtotal (95% CI) Total events: 37 (LABA + IC	2673	2656	•	68.0 %	0.74 [0.44, 1.24]
3 Baseline FEV I <= 60 % pr SLGA5021	6/246	18/242 242	-	15.9 %	0.33 [0.13, 0.81]
Subtotal (95% CI) Total events: 6 (LABA + ICS Heterogeneity: not applicabl Test for overall effect: Z = 2 4 Baseline FEV1 predicted ni	e .41 (P = 0.016)	242		15.9 %	0.33 [0.13, 0.81]
SAM40090	1/242	2/241		2.6 %	0.50 [0.05, 5.45]
			0.01 0.1 1 10 100 Favours LABA + ICS Favours Higher ICS	i	
Study or subgroup	LABA + ICS	Increased ICS	Risk Ratio M-	Weight	Risk Ratio M-
	n/N	n/N	H,Random,95% Cl		H,Random,9 Cl
Subtotal (95% CI)	242	241	-	2.6 %	0.50 [0.05, 5.45]
otal events: I (LABA + ICS) leterogeneity: not applicable					
feterogeneity: not applicable fest for overall effect: Z = 0.5					
Total (95% CI)	3876	3851	•	100.0 %	0.58 [0.40, 0.86]
fotal events: 49 (LABA + ICS					
Heterogeneity: Tau ² = 0.04; (iest for overall effect: $Z = 2.5$		P = 0.38); I ² =7%			

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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Study or subgroup	LABA + ICS	Increased ICS	Risk Ratio M-	Weight	Risk Ratio M-
	n/N	n/N	H,Random,95% CI		H,Random,95% Cl
I Baseline FEVI >= 80 % pr	edicted				
Busse 2003	141/281	155/277		4.6 %	0.90 [0.77, 1.05]
Lalloo 2003	90/230	94/237		2.6 %	0.99 [0.79, 1.24]
SAM104926	87/150	86/153		3.3 %	1.03 [0.85, 1.25]
SAS40026	172/321	170/315	-	5.1 %	0.99 [0.86, 1.15]
SFCF4026	45/158	43/159		1.2 %	1.05 [0.74, 1.50]
Verberne 1998	59/60	52/60		7.5 %	1.13 [1.02, 1.26]
Vermetten 1999	61/113	77/120		2.8 %	0.84 [0.68, 1.04]
Subtotal (95% CI)	1313	1321	•	27.2 %	0.99 [0.90, 1.09]
Total events: 655 (LABA + 10	CS), 677 (Increased ICS)			

0.5 0.7 Favours LABA + ICS 1.5 2 Favours higher ICS

Study or subgroup	LABA + ICS	Increased ICS	Risk Ratio M-	Weight	Risk Ratio
	n/N	n/N	H,Random,95% Cl		H,Random, C
Heterogeneity: $Tau^2 = 0.01$;	Chi ² = 11.73, df = 6 (F	° = 0.07); I ² =49%			
Test for overall effect: $Z = 0$.					
2 Baseline FEV1 61-79 % pre					
Baraniuk 1999	33/231	30/223		0.7 %	1.06 [0.67, 1.68
Bateman 2006	57/246	61/238		15%	0.90 [0.66, 1.24
Bergmann 2004	45/170	43/177		1.1 %	1.09 [0.76, 1.56
Bouros 1999	7/69	27/65	•	0.3 %	0.24 [0.11, 0.52
Condemi 1999	190/221	186/216	+	9.9 %	1.00 [0.93, 1.08
D5896C00001	77/157	84/153		2.9 %	0.89 [0.72, 1.11
Greening 1994	195/220	178/206	-	10.2 %	1.03 [0.95, 1.10
Jenkins 2000	25/180	31/173	· · · · · ·	0.7 %	0.78 [0.48, 1.26
Kelsen 1999	26/239	34/244	· · · · · ·	0.7 %	0.78 [0.48, 1.26
Mitchell 2003	69/102	71/101		3.6 %	0.96 [0.80, 1.16
Murray 1999	28/253	31/260		0.7 %	0.93 [0.57, 1.50
O'Byme 2005	24/909	24/926		0.5 %	1.02 [0.58, 1.78
Pearlman 1999	4/25	0/23	· · · ·	0.0 %	8.31 [0.47, 146.32
SD 039 0726	84/152	76/145		2.9 %	1.05 [0.85, 1.30
SD 039 0728	111/132	118/133	-	8.2 %	0.95 [0.86, 1.04
Wookock 1996a	179/244	86/125		5.3 %	1.07 [0.93, 1.23
Wookock 1996b	176/243	86/125		5.3 %	1.05 [0.91, 1.21
Subtotal (95% CI)	3793	3533	•	54.5 %	0.99 [0.93, 1.05
Total events: 1330 (LABA +	ICS), 1166 (Increased I				
Heterogeneity: $Tau^2 = 0.00;$	Chi ² = 23.78, df = 16 ($P = 0.09$; $I^2 = 33\%$			
Test for overall effect: $Z = 0$.	44 (P = 0.66)				
3 Baseline FEV1<=60 % pres					
SLGA5021	213/246	204/242	1	10.1 %	1.03 [0.95, 1.11
Subtotal (95% CI)	246	242	+	10.1 %	1.03 [0.95, 1.11
Total events: 213 (LABA + IO)			
Heterogeneity: not applicable					
Test for overall effect: $Z = 0$.					
4 Baseline FEV1 predicted no					
SAM30013	74/121	73/116		3.2 %	0.97 [0.80, 1.19
SAM40012	99/181	112/186		3.9 %	0.91 [0.76, 1.08
SAM40100	9/12	6/12		0.4 %	1.50 [0.78, 2.88
SAM40120	1/8	3/10	• • • • •	0.0 %	0.42 [0.05, 3.28
	<u> </u>				A

Study or subgroup	LABA + ICS	Increased ICS	Risk Ratio M- H.Random,95%	Weight	Risk Ratio M- H.Random,959
	n/N	n/N	CI		CI
Zhong 2005	31/200	34/189		0.8 %	0.86 [0.55, 1.34]
Subtotal (95% CI)	522	513	+	8.3 %	0.94 [0.83, 1.07]
Total events: 214 (LABA + IC	CS), 228 (Increased ICS)			
Heterogeneity: Tau ² = 0.0; C	hi ² = 3.00, df = 4 (P =	0.56); I ² =0.0%			
Test for overall effect: $Z = 0.9$	93 (P = 0.35)				
Total (95% CI)	5874	5609	•	100.0 %	0.99 [0.95, 1.03]
Total events: 2412 (LABA +	ICS), 2275 (Increased I	CS)			
Heterogeneity: Tau ² = 0.00;	Chi ² = 40.55, df = 29 (P = 0.08); I ² =28%			
Test for overall effect: $Z = 0.2$	37 (P = 0.71)				
			0.5 0.7 1 1.5 2		
		Faur	ours LABA + ICS Favours highe	r 1/75	

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

Study or subgroup	LABA + ICS	Increased ICS	Risk Ratio M- H.Random,95%	Weight	Risk Ratio M- H,Random,95
	n/N	n/N	Cl		CI
I Baseline FEV I >= 80 % pre Vermetten 1999	dicted 1/113	4/120		8.9 %	0.27 [0.03, 2.34]
Subtotal (95% CI)	113	120		8.9 %	0.27 [0.03, 2.34]
Total events: 1 (LABA + ICS), Heterogeneity: not applicable Test for overall effect: Z = 1.1 2 Baseline FEV1 61% to 79 %	9 (P = 0.23)				
Kelsen 1999	6/239	11/244	-	27.3 %	0.56 [0.21, 1.48]
Murray 1999	2/253	0/2.50		4.9 %	4.94 [0.24, 102.40]
Pearlman 1999	1/25	0/23		4.6 %	2.77 [0.12, 64.76]
		Favou	0.01 0.1 1 10 100 rrs LABA + ICS Favours Higher	ICS	
Study or subgroup	LABA + ICS	Increased ICS	Risk Ratio	Weight	Risk Ratio
	n/N	n/N	M- H,Random,95% CI		M- H,Random,955 Cl
Baraniuk 1999	7/231	1/223		9.5 %	6.76 [0.84, 54.48]
Conderni 1999	4/221	7/216		21.3 %	0.56 [0.17, 1.88]
Greening 1994	1/220	2/206		7.5 %	0.47 [0.04, 5.12]
Bergmann 2004	2/180	1/187	- -	7.6 %	2.08 [0.19, 22.71]
Subtotal (95% CI)	1369	1349	+	82.8 %	1.04 [0.47, 2.29]
Total events: 23 (LABA + ICS Heterogeneity: Tau ² = 0.25; 0 Test for overall effect: Z = 0.1 3 Baseline FEV1 <= 60% pres SLGA5021	$Chi^2 = 7.78$, df = 6 (P 0 (P = 0.92)	= 0.25); I ² =2.3% I/242		8.3 %	2.95 [0.31, 28.17]
Subtotal (95% CI) Total events: 3 (LABA + ICS).	246 I (Increased ICS)	242	-	8.3 %	2.95 [0.31, 28.17]
Heterogeneity: not applicable Test for overall effect: Z = 0.9 Total (95% CI) Total events: 27 (LABA + ICS Heterogeneity: Tau ² = 0.22; C Test for overall effect: Z = 0.0	1728), 27 (Increased ICS) Chi ² = 9.99, df = 8 (P	1711 = 0.27); I ² =20%	•	100.0 %	0.99 [0.49, 2.01]

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

Study or subgroup	LABA + ICS n/N	Increased ICS n/N	Risk Ratio M-H,Fixed,95% Cl	Weight	Risk Rati M-H,Fixed,95% (
I Baseline FEVI >= 80 % pri	edicted				
Busse 2003	14/281	9/277		1.6 %	1.53 [0.67, 3.48
LOCCS	110/161	120/168	•	21.3 %	0.96 [0.83, 1.10
SAM104926	27/150	23/153		4.1 %	1.20 [0.72, 1.99
SA540026	17/321	12/315		2.2 %	1.39 [0.68, 2.86
Verberne 1998	25/60	16/60		2.9 %	1.56 [0.93, 2.62
Vermetten 1999	14/113	12/120		2.1 %	1.24 [0.60, 2.56
Subtotal (95% CI)	1086	1093	•	34.3 %	1.11 [0.96, 1.28
Test for overall effect: Z = 1. 2 Baseline FEV1 61% to 79 %	predicted				
Baraniuk 1999	15/231	20/223		3.7 %	0.72 [0.38, 1.38
Bergmann 2004	1/180	4/187		0.7 %	0.26 [0.03, 2.30
Condemi 1999	27/221	26/216	-	4.8 %	1.01 [0.61, 1.68
D5896C00001	12/157	13/153		2.4 %	0.90 [0.42, 1.91
Greening 1994	118/220	114/206	•	21.4 %	0.97 [0.81, 1.15
Ind 2003	8/171	8/165		1.5 %	0.96 [0.37, 2.51
Jenkins 2000	16/180	13/173		2.4 %	1.18 [0.59, 2.39
Johansson 2001	7/176	2/173		0.4 %	3.44 [0.72, 16.33
Kelsen 1999	20/239	17/244		3.1 %	1.20 [0.65, 2.24
Murray 1999	3/260	2/254		0.4 %	1.47 [0.25, 8.70
O'Byrne 2005	35/906	42/925	+	7.5 %	0.85 [0.55, 1.32
Pauwels 1997	1/210	0/214		0.1 %	3.06 [0.13, 74.62
Pearlman 1999	0/25	0/23			Not estimab
Woolcock 1996a	38/244	21/125	+	5.0 %	0.93 [0.57, 1.51
Woolcock 1996b	26/243	22/126	-	5.3 %	0.61 [0.36, 1.04



group LAE	A + ICS	Increased ICS	Risk Ratio	Weight	Risk Ri
	n/N	n/N	M-H,Fixed,95% CI		M-H,Fixed,95% C
5% CI)	3663	3407		58.6 %	0.94 [0.82, 1.07
7 (LABA + ICS), 304 (Increased ICS)			
Chi ² = 9.38, df = 13 (F	P = 0.74); I ² =	0.0%			
effect: $Z = 0.94$ (P = 0	.35)				
<= 60 % predicted					
	25/246	20/242		3.7 %	1.23 [0.70, 2.15
5% CI)	246	242	+	3.7 %	1.23 [0.70, 2.15
(LABA + ICS), 20 (Inc	reased ICS)				
not applicable					
effect: $Z = 0.72$ (P = 0	.47)				
predicted not reporte	ed .				
	8/121	8/116		1.5 %	0.96 [0.37, 2.47
	4/ 8	10/186		1.8 %	1.44 [0.66, 3.16
	2/242	1/241		0.2 %	1.99 [0.18, 21.82
5% CI)	544	543	+	3.5 %	1.26 [0.70, 2.26
(LABA + ICS), 19 (Inc	reased ICS)				
Chi ² = 0.57, df = 2 (P	= 0.75); I ² =0	.0%			
effect: $Z = 0.78$ (P = 0	.43)				
CI)	5539	5285		100.0 %	1.02 [0.92, 1.12
13 (LABA + ICS), 535 (Increased ICS)			
Chi ² = 18.03, df = 23	(P = 0.76); I ²	=0.0%			
effect: $Z = 0.37$ (P = 0	.71)				
			rs LABA + ICS Favours Higher	-	

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

Study or subgroup	LABA + ICS n/N	Increased ICS n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Baseline FEV >/= 80% pred	icted				
LOCCS	87/161	93/168	+	62.2 %	0.98 [0.80, 1.19]
SFCF4026	2/158	0/159		0.3 %	5.03 [0.24, 103.97]
Subtotal (95% CI)	319	327	+	62.5 %	1.00 [0.82, 1.22]
Total events: 89 (LABA + ICS),	93 (Increased ICS)				
Heterogeneity: Chi ² = 1.15, df	$= (P = 0.28); ^2 = $	3%			
Test for overall effect: $Z = 0.02$					
2 Baseline FEV1 61% to 79 % p					
Jenkins 2000	6/180	9/173		6.3 %	0.64 [0.23, 1.76]
Conderni 1999	9/221	12/216		8.3 %	0.73 [0.32, 1.70]
O'Byme 2005	13/906	12/925		8.1 %	1.11 [0.51, 2.41]
	5/171	5/165		3.5 %	0.96 [0.28, 3.27]
Ind 2003	01111				
Subtotal (95% CI) Total events: 33 (LABA + ICS), Heterogeneity: Chi ² = 0.90, df Test for overall effect: Z = 0.66	1478 38 (Increased ICS) = 3 (P = 0.83); I ² =0. (P = 0.51)	1479	-	26.1 %	0.86 [0.54, 1.36]
Subtotal (95% CI) Total events: 33 (LABA + ICS), Heterogeneity: $Chi^2 = 0.90$, df Test for overall effect: Z = 0.66 3 Baseline FEV1 <= 60% predi	1478 38 (Increased ICS) = 3 (P = 0.83); I ² =0. (P = 0.51) cted	.0%	-		
Subtotal (95% CI) Total events: 33 (LABA + ICS), Heterogeneity: Chi ² = 0.90, df Test for overall effect: Z = 0.66 3 Baseline FEV1 <= 60% predi SLGA5021	1478 38 (Increased ICS) = 3 (P = 0.83); I ² = 0. (P = 0.51) cted I 1/246	11/242	-	7.6 %	0.98 [0.43, 2.23]
Subtotal (95% CI) Total events: 33 (LABA + ICS), Heterogeneity: Chi ² = 0.90, df Test for overall effect: Z = 0.66 3 Baseline FEV1 <= 60% predi SLGA5021 Subtotal (95% CI)	1478 38 (Increased ICS) = 3 (P = 0.83); I ² = 0. (P = 0.51) cted 11/246 246	.0%	•		
Subtotal (95% CI) Total events: 33 (LABA + ICS), Heterogeneity: Chi ² = 0.90, df Test for overall effect Z = 0.66 3 Baseline FVI <= 60% predi SLGA5021 Subtotal (95% CI) Total events: 11 (LABA + ICS),	1478 38 (Increased ICS) = 3 (P = 0.83); I ² = 0. (P = 0.51) cted 11/246 246	11/242	-	7.6 %	0.98 [0.43, 2.23]
Subtotal (95% CI) Total events: 33 (LABA + ICS), Heterogeneity: Chi ² = 0.90, df Test for overall effect. Z = 0.66 3 Baseline FEV I <= 60% predi SLGA5021 Subtotal (95% CI) Total events: I1 (LABA + ICS), Heterogeneity: not applicable	1478 38 (Increased ICS) = 3 (P = 0.83); I ² = 0. (P = 0.51) cted 11/246 246 11 (Increased ICS)	11/242	•	7.6 %	0.98 [0.43, 2.23]
Subtotal (95% CI) Total events: 33 (LABA + ICS), Heterogeneity: Chi ² = 0.90, df Test for overall effect Z = 0.66 3 Baseline FVI <= 60% predi SLGA5021 Subtotal (95% CI) Total events: 11 (LABA + ICS),	1478 38 (Increased ICS) = 3 (P = 0.83); I ² = 0. (P = 0.51) cted 11/246 246 11 (Increased ICS) (P = 0.97)	11/242	•	7.6 %	0.98 [0.43, 2.23]
Suboral (95% CI) Total events: 33 (LABA + ICS), Heterogeneity: Ch ² = 0.90, df Test for overall effect: Z = 0.66 Successful (95% CI) Suboral (95% CI) Total events: 11 (LABA + ICS), Total events: 11 (LABA + ICS) Total events: 11 (LABA + ICS), Total events: 11 (LABA + ICS), To	1478 38 (Increased ICS) = 3 (P = 0.83); I ² = 0. (P = 0.51) cted 11/246 246 11 (Increased ICS) (P = 0.97)	11/242	-	7.6 %	0.98 [0.43, 2.23]
Subtotal (95% CI) Total events: 33 (LABA + ICS), Total events: 33 (LABA + ICS), Test for overall effect: Z = 0.66 3 Baseline FIVI <= 60% predi \$LGA5021 Subtotal (95% CI) Total events: 11 (LABA + ICS), Heterogeneity: not applicable Test for overall effect: Z = 0.04 Haseline FIV1 predicted not	1478 38 (Increased ICS) = 3 (P = 0.83); I ² = 0. (P = 0.51) cted 11/246 246 11 (Increased ICS) (P = 0.97) reported	0% 11/242 242	•	7.6 % 7.6 %	098 [0.43, 2.23] 0.98 [0.43, 2.23]
Subtotal (95% CI) Total events: 33 (LABA + ICS), Total events: 33 (LABA + ICS), Test for overall effect: Z = 0.66 38 aseline FEVI <= 60% predi SLGA021 Subtotal (95% CI) folal events: 11 (LABA + ICS), Heterogeneity: not applicable Test for overall effect: Z = 0.04 Heseline FEVI predicted not Zhong 2005	1478 38 (Increased ICS) = 3 (P = 0.83); P = 0 (P = 0.51) (Cell = 0.51) 11/246 246 11 (Increased ICS) (P = 0.97) reported 3/200	0% 11/242 242 1/189	-	7.6 % 7.6 % 0.7 %	0.98 [0.43, 2.23] 0.98 [0.43, 2.23] 2.84 [0.30, 27.02]
Subtotal (95% CI) Total events: 33 (LABA + ICS), Heterogeneity: Ch ² = 0.90, off Electro-event effect: Z = 0.66 38 aseline FEVI <= 60% predi SLGA5021 Subtotal events: 11 (LABA + ICS), Heterogeneity: not applicable Test for overall effect: Z = 0.04 Baseline FEVI provall effect: Z = 0.04 Baseline FEVI provall effect: Z = 0.04 Baseline FEVI provall effect. Z = 0.04 Subtotal events: 11 (LABA + ICS), For a subtotal events: 11 (LABA +	1478 38 (Increased ICS) = 3 (P = 0.83); P = 0 (P = 0.51) 11/246 246 11 (Increased ICS) (P = 0.97) reported 3/200 0/242 442	0% 11/242 242 1/189 4/241	-	7.6 % 7.6 % 0.7 % 3.1 %	0.98 [0.43, 2.23] 0.98 [0.43, 2.23] 2.84 [0.30, 27.02] 0.11 [0.01, 2.04]
Subtotal (95% CI) Total events: 33 (LABA + ICS), Heterogeneity. Ch ² = 0.90, of I End for overall effect: Z = 0.66 Saseline FEVI <= 60% predit SLGA5021 Subtotal (95% CI) Total events: II (LABA + ICS), Total events: II (LABA + ICS), Saseline FEVI predicated not Zhong 2005 SAM40090 Subtotal (95% CI)	1478 38 (Increased ICS) = 3 (P = 0.83); P = 0 (P = 0.51) cted 11 (Increased ICS) (P = 0.97) reported 3/200 0/242 442 5 (Increased ICS)	11/242 242 1/189 4/241 430	-	7.6 % 7.6 % 0.7 % 3.1 %	0.98 [0.43, 2.23] 0.98 [0.43, 2.23] 2.84 [0.30, 27.02] 0.11 [0.01, 2.04]
Subtotal (95% CI) Total events: 33 (LABA + ICS), Total events: 33 (LABA + ICS), Heterogeneity: Ch ² = 0.90, df Iter for overall effect: Z = 0.66 3 Baseline FEVI <= 60% predit	1478 38 (Increased ICS) = 3 (P = 0.83); P = 0 (P = 0.51) ted 11/246 246 11 (Increased ICS) (P = 0.97) reported 3/200 0/242 442 5 (Increased ICS) 0/242 1 (P = 0.08); P = 6 (P = 0.48); P =	11/242 242 1/189 4/241 430		7.6 % 7.6 % 0.7 % 3.1 % 3.8 %	0.98 [0.43, 2.23] 0.98 [0.43, 2.23] 2.84 [0.30, 27.02] 0.11 [0.01, 2.04] 0.62 [0.16, 2.37]
Subtotal (95% CI) Total events: 33 (LABA + ICS). Total events: 33 (LABA + ICS). Test for overall effect: Z = 0.66 3 Baseline FEVI <= 60% predi 5 LGA5021 Subtotal (95% CI) Total events: 11 (LABA + ICS). Test for overall effect: Z = 0.04 4 Baseline FEVI predicted not Zhong 2005 SAH0030 Subtotal (95% CI) Total events: 31 (LABA + ICS). Total events: 41 (LABA + ICS). To	$\begin{array}{c} 1478\\ 36 \ (\text{Increased ICS})\\ = 3 \ (P = 0.83); \ P = 0 \ (P = 0.51) \ \text{cted}\\ 11246\\ 246\\ 111 \ (\text{Increased ICS})\\ (P = 0.97)\\ \text{reported}\\ 3/200\\ 0/242\\ 442\\ 5 \ (\text{Increased ICS})\\ = 1 \ (P = 0.08); \ P = 6\\ (P = 0.48)\\ P = 0.48\\ 11246\\ 3/200\\ 0/242\\ 442\\ 5 \ (\text{Increased ICS})\\ = 1 \ (P = 0.08); \ P = 6\\ (P = 0.48)\\ P = 0.48\\ 1226\\ $	0% 11/242 242 1/189 4/241 430 8% 2478	-	7.6 % 7.6 % 0.7 % 3.1 %	0.98 [0.43, 2.23] 0.98 [0.43, 2.23] 2.84 [0.30, 27.02] 0.11 [0.01, 2.04]
Subtotal (95% CI) Total events: 33 (LABA + ICS), Total events: 33 (LABA + ICS), Heterogeneity: Ch ² = 0.90, df Ise for overall effect: Z = 0.66 Baseline FEVI <= 60% predi	1478 38 (Increased ICS) = 3 ($P = 0.83$); $P = 0$ ($P = 0.51$) cted 11 (Increased ICS) ($P = 0.97$) reported 3/200 0/242 442 5 (Increased ICS) = 1 ($P = 0.08$); $P = 6$ ($P = 0.08$); $P = 6$ ($P = 0.08$); $P = 4$ 2485), 147 (Increased ICS)	0% 11/242 242 1/189 4/241 430 8% 2478	•	7.6 % 7.6 % 0.7 % 3.1 % 3.8 %	0.98 [0.43, 2.23] 0.98 [0.43, 2.23] 2.84 [0.30, 27.02] 0.11 [0.01, 2.04] 0.62 [0.16, 2.37]
Subtotal (95% CI) Total events: 33 (LABA + ICS). Total events: 33 (LABA + ICS). Test for overall effect: Z = 0.66 3 Baseline FEVI <= 60% predi 5 LGA5021 Subtotal (95% CI) Total events: 11 (LABA + ICS). Test for overall effect: Z = 0.04 4 Baseline FEVI predicted not Zhong 2005 SAH0030 Subtotal (95% CI) Total events: 31 (LABA + ICS). Total events: 41 (LABA + ICS). To	1478 38 (Increased ICS) = 3 ($P = 0.83$); $P = 0$. ($P = 0.51$) ted 11/246 11 (Increased ICS) ($P = 0.77$) reported 3/200 0/242 442 5 (Increased ICS) = 1 ($P = 0.08$); $P = 6$ ($P = 0.48$) = 2485 2485 2485 2485 2485 2485 2485 2485	0% 11/242 242 1/189 4/241 430 8% 2478	•	7.6 % 7.6 % 0.7 % 3.1 % 3.8 %	0.98 [0.43, 2.23] 0.98 [0.43, 2.23] 2.84 [0.30, 27.02] 0.11 [0.01, 2.04] 0.62 [0.16, 2.37]

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

Study or subgroup	LABA + ICS n/N	Increased ICS n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Baseline FEV1 >= 80 % pr	edicted				
Vermetten 1999	0/113	3/120		8.9 %	0.15 [0.01, 2.90]
Subtotal (95% CI)	113	120		8.9 %	0.15 [0.01, 2.90]
fotal events: 0 (LABA + ICS					
-leterogeneity: not applicable fest for overall effect: Z = 1.					
Baseline FEVI 61% to 79 9					
Murray 1999	1/253	0/250		1.3 %	2.96 [0.12, 72.43]
Kelsen 1999	2/239	3/244		7.8 %	0.68 [0.11, 4.04]
Condemi 1999	0/221	3/216		9.3 %	0.14 [0.01, 2.69]
Pauwels 1997	0/210	0/214			Not estimable
Pearlman 1999	1/25	0/23		1.4 %	2.77 [0.12, 64.76]
Baraniuk 1999	5/231	1/223		2.7 %	4.83 [0.57, 40.99]
			_		
Greening 1994	2/220	4/206	-	10.9 %	0.47 [0.09, 2.53]
O'Byrne 2005	4/906	3/925		7.8 %	1.36 [0.31, 6.07]
Woolcock 1996a	5/244	1/125		3.5 %	2.56 [0.30, 21.69]
Woolcock 1996b	4/243	1/126		3.5 %	2.07 [0.23, 18.36]
Woolcock 1996D					
Woolcock 1996b Bergmann 2004	0/170	2/177		6.5 %	0.21 [0.01, 4.31]
Bergmann 2004 Subtotal (95% CI) fotal events: 24 (LABA + IC Heterogeneity: Chi ² = 7.83, fest for overall effect: Z = 0.	2962 S), 18 (Increased ICS) df = 9 (P = 0.55); I ² = 33 (P = 0.74)	2729	•	65 % 54.6 %	
Bergmann 2004 Subtotal (95% CI) fotal events: 24 (LABA + IC Heterogeneity: Chi ² = 7.83, fest for overall effect: Z = 0. 8 Baseline FEV I <= 60 % pr	2962 5), 18 (Increased ICS) df = 9 (P = 0.55); I ² = 33 (P = 0.74) edicted	2729	•	54.6 %	1.11 [0.61, 2.02]
Bergmann 2004 Subtotal (95% CI) fotal events: 24 (LABA + IC Heterogeneity: Chi ² = 7.83, fest for overall effect: Z = 0.	2962 S), 18 (Increased ICS) df = 9 (P = 0.55); I ² = 33 (P = 0.74)	2729			6.89 [0.36, 132.62]
Bergmann 2004 Subtotal (95% CI) Total events: 24 (LABA + IC) eterogeneity: Ch ² = 7.83, Test for overall effect: Z = 0. 8 Baseline FEV I <= 60 % pr SLGA5021	2962 S), 18 (Increased ICS) df = 9 (P = 0.55); I ² =1 33 (P = 0.74) edicted 3/246	2729 0.0% 0/242 242		54.6 %	6.89 [0.36, 132.62]
Bergmann 2004 Subtotal (95% CI) Total events: 24 (LABA + IC) eterogeneity: Ch ² = 7.83, Test for overall effect: Z = 0. 8 Baseline FEV I <= 60 % pr SLGA5021	2962 S), 18 (Increased ICS) df = 9 (P = 0.55); I ² =1 33 (P = 0.74) edicted 3/246	2729 0.0% 0/242 242		54.6 % 1.3 % 1.3 %	6.89 [0.36, 132.62]
Bergmann 2004 Subtotal (95% CI) Total events: 24 (LABA + IC) eterogeneity: Ch ² = 7.83, Test for overall effect: Z = 0. 8 Baseline FEV I <= 60 % pr SLGA5021	2962 S), 18 (Increased ICS) df = 9 (P = 0.55); I ² =1 33 (P = 0.74) edicted 3/246	2729 0.0% 0/242 242	001 0.01 0.1 1 10 100 1000 rs LABA + ICS Favours Higher IC	54.6 % 1.3 % 1.3 %	6.89 [0.36, 132.62
Bergmann 2004 Subtotal (95% CI) Total events: 24 (LABA + IC) eterogeneity: Ch ² = 7.83, Test for overall effect: Z = 0. 8 Baseline FEV I <= 60 % pr SLGA5021	2962 S), 18 (Increased ICS) df = 9 (P = 0.55); I ² =1 33 (P = 0.74) edicted 3/246	2729 0.0% 0/242 242		54.6 % 1.3 % 1.3 %	6.89 [0.36, 132.62]
Bergmann 2004 Subtoxal (95% CI) fotal events 24 (LABA + IC Heterogeneity: Chi ² = 783, fest for overal effect: Z = 0. Baseline FEV ($< 60 \%$ pr SLGA5021 Subtoxal (95% CI)	2962 5), 18 (Increased ICS) df = 9 (P = 0.55); P =1 33 (P = 0.74) edicted 3/246 246	2729 0.0% 0/242 242 Face	irs LABA + ICS Favours Higher IC	54.6 % 1.3 % 1.3 %	1.11 [0.61, 2.02] 6.89 [0.36, 132.62] 6.89 [0.36, 132.62]
Bergmann 2004 Subtotal (95% CI) Total events: 24 (LABA + IC) eterogeneity: Ch ² = 7.83, Test for overall effect: Z = 0. 8 Baseline FEV I <= 60 % pr SLGA5021	2962 5), 18 (horeased ICS) df = 9 (P = 0.55; k ² = 3) (P = 0.74) edicted 3/246 246 LABA + ICS	2729 0.0% 0/242 242 0 Face Increased ICS	irs LABA + ICS Favours Higher IC Risk Ratio	54.6 % 1.3 % 1.3 %	1.11 [0.61, 2.02] 689 [0.36, 132.62 6.89 [0.36, 132.62] Risk Rat
Bergmann 2004 Subtocal (95% CI) Total events: 24 (LABA + ICC teterogeneity: CIn ² = 78.3, 8 asseline FEV I <= 60 % pr SLGA5021 Subtocal (95% CI) Study or subgroup	2962 S), 18 (horeased ICS) df = 9 (P = 0.55); I ² = 33 (P = 0.74) edicted 3/246 246 LABA + ICS n/N	2729 0.0% 0/242 242 Face	irs LABA + ICS Favours Higher IC	54.6 % 1.3 % 1.3 %	1.11 [0.61, 2.02] 6.89 [0.36, 132.62] 6.89 [0.36, 132.62] Resk Rat
Bergmann 2004 Subtoxal (95% CI) fotal events 24 (LABA + IC Heterogeneity, Chi ² = 783, fest for overal effect: Z = 0. Baseline FEV ($< 60 \%$ pr SLGA5021 Subtoxal (95% CI)	2962 5), 18 (Increased ICS) df = 9 (P = 0.55; I ² = 33 (P = 0.74) edicted 246 LABA + ICS n/N . 0 (Increased ICS)	2729 0.0% 0/242 242 0 Face Increased ICS	irs LABA + ICS Favours Higher IC Risk Ratio	54.6 % 1.3 % 1.3 %	1.11 [0.61, 2.02] 6.89 [0.36, 132.62] 6.89 [0.36, 132.62] Resk Rat
Bergmann 2004 Subtocal (95% CI) fotal events: 24 (JABA + ICC teterogeneity: CIN ² = 783, 8 Baseline FEVI <= 60 % pr SLGA5021 Study or subgroup potal events: 3 (JABA + ICS) tetrogeneity: not applicable stor overall effect Z = 1.2	2962 5), 18 (Increased ICS) df = 9 (P = 0.55; H = 1 33 (P = 0.74) edicted 37246 246 LABA + ICS n/N 0 (Increased ICS) 38 (P = 0.20)	2729 0.0% 0/242 242 0 Face Increased ICS	irs LABA + ICS Favours Higher IC Risk Ratio	54.6 % 1.3 % 1.3 %	1.11 [0.61, 2.02] 6.89 [0.36, 132.62] 6.89 [0.36, 132.62] Resk Rat
Bergmann 2004 Subtocal (95% CI) fotal events: 24 (LABA + IC) feterogeneity: Chi ² = 7.83, fest for overal effect; Z = 0. Baseline FEV I <= 60 % pr SLGA5021 Study or subgroup tal events: 3 (LABA + ICS) terorgeneity: not applicable terorgeneity: not applicable Baseline FEV I predicted no	2962 5), 18 (Increased ICS) df = 9 (P = 0.55; I ² = 1 33 (P = 0.74) edicted 2246 246 LABA + ICS NN , 0 (Increased ICS) 18 (P = 0.20) t reported	2729 0/242 242 Increased ICS n/N	irs LABA + ICS Favours Higher IC Risk Ratio	54.6 % 1.3 % 1.3 %	 1.11 [0.61, 2.02] 6.89 [0.36, 132.62] 6.89 [0.36, 132.62] Risk Rat M+t-Freed,95% (
Bergmann 2004 Subtocal (95% CI) Total events: 24 (LABA + IC) Total events: 24 (LABA + IC) Sestion FU <= 60 % pr SLGA5021 Subtocal (95% CI) Study or subgroup tal events: 3 (LABA + ICS) terrogeneity: not applicable terrogeneity: not appli	2962 5), 18 (Increased ICS) df = 9 (P = 0.55; I ² = 1 33 (P = 0.74) edicted 2246 246 LABA + ICS n/N . 0 (Increased ICS) 18 (P = 0.20) treported 17/200	2729 0.0% 0/242 242 0 Faces Increased ICS n/N	irs LABA + ICS Favours Higher IC Risk Ratio	54.6 % 1.3 % 1.3 % s Weight	 1.11 [0.61, 2.02] 6.89 [0.36, 132.62] 6.89 [0.36, 132.62] Risk Rat M+H-Field 95% (1.34 [0.66, 2.73
Bergmann 2004 Subtocal (95% CI) Total events: 24 (LABA + IC) Total events: 24 (LABA + IC) Estimation (1974 - 28.3) Estimation (1974 - 28.3) Subtocal events: 24 - 20.5 Study or subgroup tal events: 3 (LABA + ICS) tetrogrammal effect: 2 = 1.2 Baseline FEV I predicted no Zhong 2005 SAM40090	2962 5), 18 (Increased ICS) df = 9 (P = 0.55; I ² = 1 33 (P = 0.74) edicted 2246 LABA + ICS n/N . 0 (Increased ICS) 88 (P = 0.20) treported 17/200 2/242	2729 0/242 242 0 Faes Increased ICS n/N 12/189 1/241	irs LABA + ICS Favours Higher IC Risk Ratio	54.6 % 1.3 % 1.3 % 5 S Weight 32.5 % 2.6 %	 1.11 [0.61, 2.02] 6.89 [0.36, 132.62] 6.89 [0.36, 132.62] Resk Rat M+H-Fixed 95%. 1.34 [0.66, 2.73 1.99 [0.18, 21.82
Bergmann 2004 Subtocal (95% CI) fotal events: 24 (LABA + IC) Electrogeneity: Chi ² = 783, Electro overall effect: Z = 0. 8 asaeline FEVI <= 60 % pr SLGA5021 Study or subgroup Study or subgroup tal events: 3 (LABA + ICS) teterogeneity: not applicable est for overall effect: Z = 1. Baseline FEVI predicted no Zhong 2005 SAMM0090 ubtotal (95% CI)	2962 5), 18 (Increased ICS) df = 9 (P = 0.55; F = 3 3/246 246 246 LABA + ICS n/N . 0 (Increased ICS) 8 (P = 0.20) t reported 17/200 2/242 442	2729 0.0% 0/242 242 0 Faces Increased ICS n/N	irs LABA + ICS Favours Higher IC Risk Ratio	54.6 % 1.3 % 1.3 % s Weight	1.11 [0.61, 2.02] 6.89 [0.36, 132.62] 6.89 [0.36, 132.62] Risk Rat M-H.Fixed.95% (1.34 [0.66, 2.73 1.99 [0.18, 21.82
Bergmann 2004 Subtocal (95% CI) Total events: 24 (LABA + ICC teterogeneity: CIN ² = 783, Statist for overall effect: Z = 0, 8 asseline FEV1 <= 60 % pr SLGA5021 Study or subgroup tal events: 3 (LABA + ICS) Baseline FEV1 predicted no Zhong 2005 SAM40090 ubtocal (95% CI) tal events: 19 (LABA + ICS)	2962 5), 18 (Increased ICS) df = 9 (P = 0.55; H = 3 37/46 246 LABA + ICS n/N 0 (Increased ICS) 18 (P = 0.20) treported 17/200 2/242 442	2729 0.0% 0/242 242 0 Face Increased ICS n/N 12/189 1/241 430	irs LABA + ICS Favours Higher IC Risk Ratio	54.6 % 1.3 % 1.3 % 5 S Weight 32.5 % 2.6 %	 1.11 [0.61, 2.02] 6.89 [0.36, 132.62] 6.89 [0.36, 132.62] Resk Rat M+H-Fixed 95%. 1.34 [0.66, 2.73 1.99 [0.18, 21.82
Bergmann 2004 Subtocal (95% CI) fotal events: 24 (LABA + IC) Electrogeneity: Chi ² = 783, Electro overall effect: Z = 0. 8 asaeline FEVI <= 60 % pr SLGA5021 Study or subgroup Study or subgroup tal events: 3 (LABA + ICS) teterogeneity: not applicable est for overall effect: Z = 1. Baseline FEVI predicted no Zhong 2005 SAMM0090 ubtotal (95% CI)	2962 5), 18 (Increased ICS) df = 9 (P = 0.55; P = 1 33 (P = 0.74) edicted 2246 246 LABA + ICS n/N , 0 (Increased ICS) 5 8 (P = 0.20) t reported 177200 2/242 5), 13 (Increased ICS) 442 5), 13 (Increased ICS) 441 442 442	2729 0.0% 0/242 242 0 Face Increased ICS n/N 12/189 1/241 430	irs LABA + ICS Favours Higher IC Risk Ratio	54.6 % 1.3 % 1.3 % 5 S Weight 32.5 % 2.6 %	 1.11 [0.61, 2.02] 6.89 [0.36, 132.62] 6.89 [0.36, 132.62] Resk Rat M+H-Fixed 95%. 1.34 [0.66, 2.73 1.99 [0.18, 21.82
Bergmann 2004 Subtocal (95% CI) fotal events: 24 (LABA + IC) fotal events: 24 (LABA + IC) fotal events: 24 (LABA + IC) 8 Isseline FEV1 < 60 % pr SLGA5021 Subtocal (95% CI) Study or subgroup tal events: 3 (LABA + ICS) Baseline FEV1 predicted no Zhong 2005 SAM40090 ubtocal (95% CI) tal events: 19 (LABA + ICS) SAM40090	2962 5), 18 (horeased ICS) df = 9 (P = 0.55; I ² = 3 3) (P = 0.74) edicted 3/246 246 LABA + ICS n/N 0 (horeased ICS) if = 1 (P = 0.76; I ² = 4 4/2 5), 13 (horeased ICS) if = 1 (P = 0.76; I ² = 4 5), 13 (horeased ICS) if = 1 (P = 0.76; I ² = 4 5), 13 (horeased ICS) if = 1 (P = 0.76; I ² = 4 5), 13 (horeased ICS) if = 1 (P = 0.76; I ² = 4 5), 13 (horeased ICS) if = 1 (P = 0.76; I ² = 4 5), 13 (horeased ICS) if = 1 (P = 0.76; I ² = 4 5), 13 (horeased ICS) if = 1 (P = 0.76; I ² = 4 5), 13 (horeased ICS) if = 1 (P = 0.76; I ² = 4 5), 13 (horeased ICS) if = 1 (P = 0.76; I ² = 4 5), 14 (P = 0.76; I ² = 4 (horeased ICS) (horeased ICS) (horeased ICS) (horea	2729 0.0% 0/242 242 0 Face Increased ICS n/N 12/189 1/241 430	irs LABA + ICS Favours Higher IC Risk Ratio	54.6 % 1.3 % 1.3 % 5 S Weight 32.5 % 2.6 %	021 [001, 43]] 1.11 [0.61, 2.02] 6.89 [0.36, 132.62] 6.89 [0.36, 132.62] Risk Rat M-H.Fixed.95% (1.34 [0.66, 2.73 1.99 [0.18, 21.82 1.39 [0.70, 2.74 1.20 [0.78, 1.84

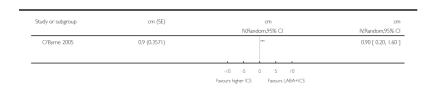
Analysis 1.60. Comparison 1 LABA + ICS versus higher dose ICS, Outcome 60 Growth (paediatric data)

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

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)



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

	Risk Rat M-H,Fixed,95%	Weight	Risk Ratio M-H,Fixed,95% CI	Increased ICS n/N	LABA + ICS n/N	Study or subgroup
Î						I Children
)	0.43 [0.05, 3.79	24.6 %		3/22	1/17	LOCCS
7	2.01 [0.18, 21.97	9.4 %	- _	1/161	2/160	SAM104926
)	1.43 [0.58, 3.50	66.0 %	-	7/60	10/60	Verberne 1998
;	1.24 [0.58, 2.66	100.0 %	+	243	237	Subtotal (95% CI)
				0%	$df = 2 (P = 0.56); I^2 = 0.56$	Total events: 13 (LABA + IC: Heterogeneity: Chi ² = 1.16, Test for overall effect: $Z = 0$. 2 Adults
1	0.38 [0.19, 0.74	5.2 %	-	28/223	11/231	Baraniuk 1999
5	0.77 [0.21, 2.85	0.9 %		5/238	4/246	Bateman 2006
ć	2.51 [0.70, 9.06	0.6 %		3/65	8/69	Bouros 1999
	1.97 [0.50, 7.80	0.5 %		3/277	6/281	Busse 2003
2	0.66 [0.39, 1.12	5.7 %	-	31/216	21/221	Condemi 1999
1	0.89 [0.48, 1.64	3.6 %	_	19/206	18/220	Greening 1994
3	0.56 [0.17, 1.88	1.3 %		7/173	4/176	Johansson 2001
5	0.66 [0.42, 1.05	7.2 %	-	40/244	26/239	Kelsen 1999
,	0.71 [0.34, 1.49	2.1 %		12/31	8/29	Kips 2000
5	8.50 [0.48, 151.05	0.1 %		0/16	3/13	Li 1999
7	0.88 [0.33, 2.37	1.4 %		8/144	7/143	LOCCS
3	0.81 [0.51, 1.28	6.4 %	-	35/254	29/260	Murray 1999
7	0.92 [0.66, 1.27	11.3 %	+	61/312	58/323	O'Byrne 2001
1	1.01 [0.82, 1.24	26.5 %	•	149/819	145/789	O'Byme 2005
2	1.05 [0.78, 1.42	10.8 %	+	60/214	62/210	Pauwels 1997
3	0.97 [0.06, 14.88	0.2 %		1/33	1/34	SAM30022
7	1.33 [0.30, 5.87	0.5 %	_ 	3/241	4/242	SAM40090
)	0.59 [0.20, 1.79	1.5 %		8/279	5/295	SAS40026

Study or subgroup	LABA + ICS	Increased ICS	Risk Ratio	Weight	Risk Ratio
	n/N	n/N	M-H,Fixed,95% CI		M-H,Fixed,95% CI
SFCF4026	12/154	16/156		2.9 %	0.76 [0.37, 1.55]
SLGA5021	20/246	32/243	•	5.8 %	0.62 [0.36, 1.05]
Van Noord 1999	16/139	15/135	+	2.8 %	1.04 [0.53, 2.01]
Vermetten 1999	8/113	14/120		2.5 %	0.61 [0.26, 1.39]
Wallin 2003	1/18	2/19		0.4 %	0.53 [0.05, 5.33]
Subtotal (95% CI)	4691	4658	•	100.0 %	0.87 [0.78, 0.97]
Total events: 477 (LABA + IC	CS), 552 (Increased ICS)			
Heterogeneity: Chi ² = 22.93,	df = 22 (P = 0.41); I ²	=4%			
Test for overall effect: Z = 2.4	47 (P = 0.014)				
			0.02 0.1 1 10 50		
		Favour	rs LABA + ICS Favours higher	ICS	

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

M-H,Fixed,95% C
6 0.92 [0.66, 1.27
۵.92 [0.66, I.27
L
6 0.66 [0.42, 1.05
6 0.81 [0.51, 1.28
8.50 [0.48, 151.05
6 1.43 [0.58, 3.50
6 0.61 [0.26, 1.39
6 0.38 [0.19, 0.74
9

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Study or subgroup	LABA + ICS n/N	Increased ICS n/N	Risk Ratio M-H,Fixed,95% Cl	Weight	Risk Ratio M-H,Fixed,95% C
Kips 2000	8/29	12/31	-+-	2.1 %	0.71 [0.34, 1.49
Greening 1994	18/220	19/206		3.6 %	0.89 [0.48, 1.64
Condemi 1999	21/221	31/216	-	5.8 %	0.66 [0.39, 1.12
Pauwels 1997	62/210	60/214	+	11.0 %	1.05 [0.78, 1.42
O'Byrne 2005	145/789	149/819	•	27.0 %	1.01 [0.82, 1.24
Busse 2003	6/281	3/277		0.6 %	1.97 [0.50, 7.80
LOCCS	9/162	11/168		2.0 %	0.85 [0.36, 1.99
SAS40026	5/295	8/279		1.5 %	0.59 [0.20, 1.79
SLGA5021	20/246	32/243	-	5.9 %	0.62 [0.36, 1.05
Bateman 2006	4/246	5/238		0.9 %	0.77 [0.21, 2.85
Johansson 200 I	4/176	7/173		1.3 %	0.56 [0.17, 1.88
SAM104926	2/160	1/161		0.2 %	2.01 [0.18, 21.97
SAM30022	1/34	1/33		0.2 %	0.97 [0.06, 14.88
SAM40090	4/242	3/241		0.6 %	1.33 [0.30, 5.87
SFCF4026	12/154	16/156		2.9 %	0.76 [0.37, 1.55
Subtotal (95% CI) Fotal events: 466 (LABA + IC Heterogeneity: Chi ² = 21.53, Fest for overall effect: Z = 2.5	df = 21 (P = 0.43); l ² 3 (P = 0.011)	=2%	·	100.0 %	0.86 [0.77, 0.97
2 ICS dose 400-1000 mcg/da Bouros 1999	y of BDP-equivalent in 8/69	LABA group 3/65		15.3 %	2.51 [0.70, 9.06
Van Noord 1999	16/139	15/135	_	75.1 %	1.04 [0.53, 2.01
Wallin 2003	1/18	2/19		9.6 %	0.53 [0.05, 5.33
Subtotal (95% CI) Fotal events: 25 (LABA + ICS Heterogeneity: Chi ² = 1.95, c Fest for overall effect: Z = 0.6	226 5), 20 (Increased ICS) ff = 2 (P = 0.38); I ² =0	219	•	100.0 %	1.21 [0.69, 2.12

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

Study or subgroup	LABA + ICS	Increased ICS n/N	Risk Ratio M-H.Fixed.95% Cl	Weight	Risk Ratio M-H.Fixed,95% C
I ICS dose difference of <=					
Johansson 2001	4/176	7/173		4.0 %	0.56 [0.17, 1.88
Kelsen 1999	26/239	40/244	-	22.2 %	0.66 [0.42, 1.05
Li 1999	3/13	0/16		0.3 %	8.50 [0.48, 151.05
LOCCS	9/162	11/168	-	6.1 %	0.85 [0.36, 1.99
Murray 1999	29/260	35/254	+	19.9 %	0.81 [0.51, 1.28
O'Byrne 2001	58/323	61/312	+	34.9 %	0.92 [0.66, 1.27
SAM104926	2/160	1/161		0.6 %	2.01 [0.18, 21.97
SAM30022	1/34	1/33		0.6 %	0.97 [0.06, 14.88
Verberne 1998	10/60	7/60		3.9 %	1.43 [0.58, 3.50
Vermetten 1999	8/113	14/120	-	7.6 %	0.61 [0.26, 1.39
Subtotal (95% CI)	1540	1541	•	100.0 %	0.84 [0.69, 1.03
2 ICS dose difference of >= Baraniuk 1999	500 mcg/day of BDP-e 11/231	quivalent 28/223	-	7.4 %	0.38[0.19.0.74
Test for overall effect: $Z = 1$. 2 ICS dose difference of >=		quivalent			
					0.38 [0.19, 0.74
Bateman 2006	4/246	5/238		1.3 %	0.77 [0.21, 2.85
Bouros 1999	8/69	3/65		0.8 %	2.51 [0.70, 9.06
Busse 2003	6/281	3/277		0.8 %	1.97 [0.50, 7.80
Condemi 1999	21/221	31/216	-	8.2 %	0.66 [0.39, 1.12
Greening 1994	18/220	19/206	+	5.1 %	0.89 [0.48, 1.64
Kips 2000	8/29	12/31		3.0 %	0.71 [0.34, 1.49
O'Byrne 2005	145/789	149/819	· · · ·	38.0 %	1.01 [0.82, 1.24
Pauwels 1997	62/210	60/214	+	15.5 %	1.05 [0.78, 1.42
SAM40090	4/242	3/241	_ 	0.8 %	1.33 [0.30, 5.87
		Fa	0.01 0.1 1 10 100 vours LABA + ICS Favours higher I	cs	
Study or subgroup	LABA + ICS	Increased ICS	Risk Ratio		Risk Ra

Study or subgroup	LABA + ICS	Increased ICS	Risk Ratio	Weight	Risk Ratio
	n/N	n/N	M-H,Fixed,95% CI		M-H,Fixed,95% CI
SAS40026	5/295	8/279		2.1 %	0.59 [0.20, 1.79]
SFCF4026	12/154	16/156		4.1 %	0.76 [0.37, 1.55]
SLGA5021	20/246	32/243	-	8.4 %	0.62 [0.36, 1.05]
Van Noord 1999	16/139	15/135	+	4.0 %	1.04 [0.53, 2.01]
Wallin 2003	1/18	2/19		0.5 %	0.53 [0.05, 5.33]
Subtotal (95% CI)	3390	3362	•	100.0 %	0.89 [0.78, 1.02]
Total events: 341 (LABA + IC	CS), 386 (Increased ICS)			
Heterogeneity: Chi ² = 17.47,	df = 14 (P = 0.23); 12	=20%			
Test for overall effect: $Z = 1.6$	69 (P = 0.091)				
			0.01 0.1 1 10 100		
		Fav	ours LABA + ICS Favours higher	ICS	

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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Kips 2000 O'Byrne 2001	8/29 58/323	12/31 61/312		4.1 %	0.71 [0.34, 1.49] 0.92 [0.66, 1.27]
O'Byrne 2001 O'Byrne 2005	145/789	61/312	1	51.8 %	1.01 [0.82, 1.24]
Pauwels 1997	62/210	60/214	+	21.0 %	1.05 [0.78, 1.42]
Subtotal (95% CI)	1420	1441	•	100.0 %	1.00 [0.87, 1.16]



Study or subgroup	LABA + ICS	Increased ICS	Risk Ratio	Weight	Risk Rati
	n/N	n/N	M-H,Fixed,95% CI		M-H,Fixed,95%
Heterogeneity: $Chi^2 = 3.18$, o		1.0%			
Test for overall effect: Z = 0.0 2 Salmeterol)4 (P = 0.97)				
Baraniuk 1999	11/231	28/223	-	10.2 %	0.38 [0.19, 0.74
Bateman 2006	4/246	5/238		1.8 %	0.77 [0.21, 2.8
Busse 2003	6/281	3/277		1.1 %	1.97 [0.50, 7.80
Condemi 1999	21/221	31/216	-	11.2 %	0.66 [0.39, 1.12
Greening 1994	18/220	19/206	+	7.0 %	0.89 [0.48, 1.64
Johansson 2001	4/176	7/173		2.5 %	0.56 [0.17, 1.88
Kelsen 1999	26/239	40/244	-	14.1 %	0.66 [0.42, 1.0
Li 1999	3/13	0/16		0.2 %	8.50 [0.48, 151.0
LOCCS	9/162	11/168		3.9 %	0.85 [0.36, 1.9
Murray 1999	29/260	35/254	+	12.6 %	0.81 [0.51, 1.2
SAM104926	2/160	1/161	·	0.4 %	2.01 [0.18, 21.9
SAM30022	1/34	1/33		0.4 %	0.97 [0.06, 14.8
SAM40090	4/242	3/241	```	1.1 %	1.33 [0.30, 5.8
SAS40026	5/295	8/279		2.9 %	0.59 [0.20, 1.7
SFCF4026	12/154	16/156	-	5.7 %	0.76 [0.37, 1.5
SLGA5021	20/246	32/243	-	11.5 %	0.62 [0.36, 1.0
Van Noord 1999	16/139	15/135	-	5.4 %	1.04 [0.53, 2.0
Verberne 1998	10/60	7/60		2.5 %	1.43 [0.58, 3.5
Vermetten 1999	8/113	14/120		4.9 %	0.61 [0.26, 1.3
Wallin 2003	1/18	2/19		0.7 %	0.53 [0.05, 5.3
Subtotal (95% CI)	3510	3462	•	100.0 %	0.75 [0.63, 0.89
Total events: 210 (LABA + IC Heterogeneity: Chi ² = 14.94, Test for overall effect: $Z = 3.2$	df = 19 (P = 0.73); l^2				

Favours LABA + ICS Favours higher ICS

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

	LABA + ICS n/N	Increased ICS n/N	Risk Ratio M-H,Fixed,95% Cl	Weight	Risk Rat M-H,Fixed,95%
One device (combination	therapy)				
Bateman 2006	4/246	5/238		2.2 %	0.77 [0.21, 2.89
Busse 2003	6/281	3/277		1.3 %	1.97 [0.50, 7.80
Johansson 2001	4/176	7/173		3.0 %	0.56 [0.17, 1.88
LOCCS	9/162	11/168		4.6 %	0.85 [0.36, 1.9
O'Byrne 2005	145/789	149/819	•	62.6 %	1.01 [0.82, 1.24
SAM104926	2/160	1/161		0.4 %	2.01 [0.18, 21.9
SAM30022	1/34	1/33		0.4 %	0.97 [0.06, 14.8
SAM40090	4/242	3/241		1.3 %	1.33 [0.30, 5.8
SAS40026	5/295	8/279		3.5 %	0.59 [0.20, 1.7
SFCF4026	12/154	16/156	-	6.8 %	0.76 [0.37, 1.5
SLGA5021	20/246	32/243	-	13.8 %	0.62 [0.36, 1.0
ubtotal (95% CI)	2785	2788	•	100.0 %	0.92 [0.77, 1.09
Baraniuk 1999	11/231	28/223	-	8.7 %	0381019.07
Two devices (concomitant Baraniuk 1999		28/223	-	8.7 %	0.38 [0.19, 0.7
D 1000					0.50 [0.177 0.7
Bouros 1999	8/69	3/65		0.9 %	
Bouros 1999 Condemi 1999	8/69 21/221	3/65 31/216	•		2.51 [0.70, 9.0
			•	0.9 %	2.51 [0.70, 9.0 0.66 [0.39, 1.1
Condemi 1999	21/221	31/216		0.9 % 9.5 %	2.51 [0.70, 9.0 0.66 [0.39, 1.1 0.89 [0.48, 1.6
Condemi 1999 Greening 1994	21/221	31/216	+ + +	0.9 % 9.5 % 6.0 %	2.51 [0.70, 9.0 0.66 [0.39, 1.1 0.89 [0.48, 1.6 0.66 [0.42, 1.0
Condemi 1999 Greening 1994 Kelsen 1999	21/221 18/220 26/239	31/216 19/206 40/244		0.9 % 9.5 % 6.0 % 12.0 %	2.51 [0.70, 9.0 0.66 [0.39, 1.1 0.89 [0.48, 1.6 0.66 [0.42, 1.0 0.71 [0.34, 1.4
Condemi 1999 Greening 1994 Kelsen 1999 Kips 2000	21/221 18/220 26/239 8/29	31/216 19/206 40/244 12/31		0.9 % 9.5 % 6.0 % 12.0 % 3.5 %	2.51 [0.70, 9.0 0.66 [0.39, 1.1 0.89 [0.48, 1.6 0.66 [0.42, 1.0 0.71 [0.34, 1.4 8.50 [0.48, 151.0
Condemi 1999 Greening 1994 Kelsen 1999 Kips 2000 Li 1999	21/221 18/220 26/239 8/29 3/13	31/216 19/206 40/244 12/31 0/16	- - - - -	0.9 % 9.5 % 6.0 % 3.5 % 0.1 %	2.51 [0.70, 9.0 0.66 [0.39, 1.1 0.89 [0.48, 1.6 0.66 [0.42, 1.0 0.71 [0.34, 1.4 8.50 [0.48, 151.0 0.81 [0.51, 1.2
Condemi 1999 Greening 1994 Kelsen 1999 Kips 2000 Li 1999 Murray 1999	21/221 18/220 26/239 8/29 3/13 29/260	31/216 19/206 40/244 12/31 0/16 35/254		0.9 % 9.5 % 6.0 % 3.5 % 0.1 % 10.8 %	2.51 [0.70, 9.0 0.66 [0.39, 1.1 0.89 [0.48, 1.6 0.66 [0.42, 1.0 0.71 [0.34, 1.4 8.50 [0.48, 151.0 0.81 [0.51, 1.2 0.92 [0.66, 1.2
Condemi 1999 Greening 1994 Kelsen 1999 Kips 2000 Li 1999 Murray 1999 C/Byrne 2001	21/221 18/220 26/239 8/29 3/13 29/260 58/323	31/216 19/206 40/244 12/31 0/16 35/254 61/312		0.9 % 9.5 % 12.0 % 3.5 % 0.1 % 10.8 %	2.51 [0.70, 9.0 0.66 [0.39, 1.1 0.89 [0.48, 1.6 0.66 [0.42, 1.0 0.71 [0.34, 1.4 8.50 [0.48, 151.0 0.81 [0.51, 1.2 0.92 [0.66, 1.2
Condemi 1999 Greening 1994 Kelsen 1999 Kips 2000 Li 1999 Murray 1999 C/Byrne 2001	21/221 18/220 26/239 8/29 3/13 29/260 58/323	31/216 19/206 40/244 12/31 0/16 35/254 61/312 60/214	0.01 0.1 1 10 100 acours LABA + ICS Facuus higher K	0.9 % 9.5 % 6.0 % 12.0 % 3.5 % 0.1 % 10.8 % 18.9 % 18.1 %	2.51 [0.70, 9.0 0.66 [0.39, 1.1 0.89 [0.48, 1.6 0.66 [0.42, 1.0 0.71 [0.34, 1.4 8.50 [0.48, 151.0 0.81 [0.51, 1.2 0.92 [0.66, 1.2
Condemi 1999 Greening 1994 Kelsen 1999 Kips 2000 Li 1999 Murray 1999 C/Byrne 2001	21/221 18/220 26/239 8/29 3/13 29/260 58/323	31/216 19/206 40/244 12/31 0/16 35/254 61/312 60/214		0.9 % 9.5 % 6.0 % 12.0 % 3.5 % 0.1 % 10.8 % 18.9 % 18.1 %	2.51 [0.70, 9.0 0.66 [0.39, 1.1 0.89 [0.48, 1.6 0.66 [0.42, 1.0 0.71 [0.34, 1.4 8.50 [0.48, 151.0 0.81 [0.51, 1.2 0.92 [0.66, 1.2 1.05 [0.78, 1.4]
Condemi 1999 Greening 1994 Kelsen 1999 Kips 2000 Li 1999 Murray 1999 C/Byrne 2001	21/221 18/220 26/239 8/29 3/13 29/260 58/323	31/216 19/206 40/244 12/31 0/16 35/254 61/312 60/214		0.9 % 9.5 % 6.0 % 12.0 % 3.5 % 0.1 % 10.8 % 18.9 % 18.1 %	2.51 [0.70, 9.0 0.66 [0.39, 1.1 0.89 [0.48, 1.6 0.66 [0.42, 1.0 0.71 [0.34, 1.4 8.50 [0.48, 151.0 0.81 [0.51, 1.2 0.92 [0.66, 1.2

Study or subgroup	LABA + ICS	Increased ICS	Risk Ratio	Weight	Risk Ratio
	n/N	n/N	M-H,Fixed,95% CI		M-H,Fixed,95% CI
Van Noord 1999	16/139	15/135	-	4.6 %	1.04 [0.53, 2.01]
Verberne 1998	10/60	7/60		2.1 %	1.43 [0.58, 3.50]
Vermetten 1999	8/113	14/120		4.1 %	0.61 [0.26, 1.39]
Wallin 2003	1/18	2/19		0.6 %	0.53 [0.05, 5.33]
Subtotal (95% CI)	2145	2115	•	100.0 %	0.85 [0.73, 0.98]
Total events: 279 (LABA + IC	CS), 327 (Increased ICS)				
Heterogeneity: Chi ² = 17.62,	$df = 13 (P = 0.17); I^2 =$	26%			
Test for overall effect: $Z = 2.2$	24 (P = 0.025)				
			0.01 0.1 1 10 100		
		Favo	urs LABA + ICS Favours higher I	CS	

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

Study or subgroup	LABA + ICS	Increased ICS	Risk Ratio	Weight	Risk Rat
	n/N	n/N	M-H,Fixed,95% CI		M-H,Fixed,95% (
<= 24 weeks			_		
Baraniuk 1999	11/231	28/223	-	5.1 %	0.38 [0.19, 0.74
Bateman 2006	4/246	5/238		0.9 %	0.77 [0.21, 2.85
Bouros 1999	8/69	3/65		0.6 %	2.51 [0.70, 9.06
Busse 2003	6/281	3/277		0.5 %	1.97 [0.50, 7.80
Condemi 1999	21/221	31/216	-	5.6 %	0.66 [0.39, 1.12
Greening 1994	18/220	19/206		3.5 %	0.89 [0.48, 1.64
Johansson 2001	4/176	7/173		1.3 %	0.56 [0.17, 1.88
Kelsen 1999	26/239	40/244	-	7.1 %	0.66 [0.42, 1.05
		(
		Favour	rs LABA + ICS Favours higher I	cs	
Study or subgroup	LABA + ICS n/N	Increased ICS n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% C
Li 1999	3/13	0/16		0.1 %	8.50 [0.48, 151.05
LOCCS	9/162	11/168		1.9 %	0.85 [0.36, 1.99
Murray 1999	29/260	35/254	+	6.3 %	0.81 [0.51, 1.28
SAM104926	2/160	1/161		0.2 %	2.01 [0.18, 21.97
SAM30022	1/34	1/33		0.2 %	0.97 [0.06, 14.88
SAS40026	5/295	8/279		1.5 %	0.59 [0.20, 1.79
SFCF4026	12/154	16/156		2.8 %	0.76 [0.37, 1.55
SLGA5021					
	20/246	32/243		5.8 %	0.62 [0.36, 1.05
Van Noord 1999	16/139	15/135		2.7 %	1.04 [0.53, 2.01
Vermetten 1999	8/113	14/120		2.4 %	0.61 [0.26, 1.39
Wallin 2003	1/18	2/19		0.3 %	0.53 [0.05, 5.33
Subtotal (95% CI)	3277	3226	•	48.8 %	0.74 [0.63, 0.89]
Total events: 204 (LABA + IC Heterogeneity: Chi ² = 15.79,					
Test for overall effect: $Z = 3.3$	4 (P = 0.00082)				
2 > 24 weeks Kips 2000	8/29	12/31		2.1 %	0.71 [0.34, 1.49
O'Byrne 2001					
	58/323	61/312	1	11.1%	0.92 [0.66, 1.27
O'Byrne 2005	145/789	149/819	I	26.1 %	1.01 [0.82, 1.24
Pauwels 1997	62/210	60/214	Ī	10.6 %	1.05 [0.78, 1.42
Verberne 1998	10/60	7/60	_	1.3 %	1.43 [0.58, 3.50
Subtotal (95% CI) Total events: 283 (LABA + IC	1411	1436	ł	51.2 %	1.00 [0.86, 1.15
Heterogeneity: Chi ² = 1.80, d					
Test for overall effect: $Z = 0.0$	4 (P = 0.97)				
Total (95% CI)	4688	4662	•	100.0 %	0.87 [0.78, 0.98]
Total events: 487 (LABA + IC Heterogeneity: Chi ² = 24.23,					
Test for overall effect: $Z = 2.3$					

Favours LABA + ICS Favours higher ICS

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

M-H,Fixed,95% C	Weight	Risk Ratio M-H,Fixed,95% Cl	Increased ICS n/N	LABA + ICS	Study or subgroup
111,000,000 0		111,000,000 G	1014		I Data available from study
2.51 [0.70, 9.06	1.9 %		3/65	8/69	Bouros 1999
0.66 [0.39, 1.12	19.6 %	-	31/216	21/221	Condemi 1999
0.89 [0.48, 1.64]	12.3 %	-	19/206	18/220	Greening 1994
0.71 [0.34, 1.49]	7.2 %	-	12/31	8/29	Kips 2000
0.85 [0.36, 1.99]	6.7 %	-	11/168	9/162	LOCCS
1.05 [0.78, 1.42]	37.1 %	+	60/214	62/210	Pauwels 1997
1.04 [0.53, 2.01]	9.5 %	-	15/135	16/139	Van Noord 1999
1.43 [0.58, 3.50]	4.4 %		7/60	10/60	Verberne 1998
0.53 [0.05, 5.33]	1.2 %		2/19	1/18	Wallin 2003
0.95 [0.78, 1.17]	100.0 %	•	1114	1128	Subtotal (95% CI)
0381019.074	71%			pondence or study spor	
	7.1 %	-	28/223	11/231	Baraniuk 1999
0.77 [0.21, 2.85	1.3 %		28/223 5/238	11/231 4/246	Baraniuk 1999 Bateman 2006
0.77 [0.21, 2.85			28/223	11/231	Baraniuk 1999
0.38 [0.19, 0.74] 0.77 [0.21, 2.85] 1.97 [0.50, 7.80] 0.56 [0.17, 1.88]	1.3 %		28/223 5/238	11/231 4/246	Baraniuk 1999 Bateman 2006
0.77 [0.21, 2.85]	1.3 % 0.8 %	• 	28/223 5/238 3/277	11/231 4/246 6/281	Baraniuk 1999 Bateman 2006 Busse 2003
0.77 [0.21, 2.85 1.97 [0.50, 7.80 0.56 [0.17, 1.88 0.66 [0.42, 1.05	1.3 % 0.8 % 1.8 %	• 	28/223 5/238 3/277 7/173	4/246 6/281 4/176	Baraniuk 1999 Bateman 2006 Busse 2003 Johansson 2001
0.77 [0.21, 2.85 1.97 [0.50, 7.80 0.56 [0.17, 1.88	1.3 % 0.8 % 1.8 % 9.8 %	+ 	28/223 5/238 3/277 7/173 40/244	11/231 4/246 6/281 4/176 26/239	Baraniuk 1999 Bateman 2006 Busse 2003 Johansson 2001 Kelsen 1999
0.77 [0.21, 2.85 1.97 [0.50, 7.80 0.56 [0.17, 1.88 0.66 [0.42, 1.05 8.50 [0.48, 151.05	1.3 % 0.8 % 1.8 % 9.8 % 0.1 %	+ + 	28/223 5/238 3/277 7/173 40/244 0/16	11/231 4/246 6/281 4/176 26/239 3/13	Baraniuk 1999 Bateman 2006 Busse 2003 Johansson 2001 Kelsen 1999 Li 1999
0.77 [0.21, 2.85 1.97 [0.50, 7.80 0.56 [0.17, 1.88 0.66 [0.42, 1.05 8.50 [0.48, 151.05 0.81 [0.51, 1.28	1.3 % 0.8 % 1.8 % 9.8 % 0.1 % 8.8 %	+ + + 	28/223 5/238 3/277 7/173 4/0/244 0/16 35/254	11/231 4/246 6/281 4/176 26/239 3/13 29/260	Baraniuk 1999 Bateman 2006 Busse 2003 Johansson 2001 Kelsen 1999 Li 1999 Murray 1999
0.77 [0.21, 285 1.97 [0.50, 780 0.56 [0.17, 1.88 0.66 [0.42, 105 8.50 [0.48, 151.55 0.81 [0.51, 1.28] 0.92 [0.66, 1.27	1.3 % 0.8 % 1.8 % 9.8 % 0.1 % 8.8 % 15.4 %		28/223 5/238 3/277 7/173 4/0/244 0/16 35/254 61/312	11/231 4/246 6/281 4/176 2.6/239 3/13 29/260 58/323	Baraniuk 1999 Bateman 2006 Busse 2003 Johansson 2001 Kelsen 1999 Li 1999 Murray 1999 O'Byrne 2001
0.77 [0.21, 285] 1.97 [0.50, 780] 0.56 [0.17, 1.88] 0.66 [0.42, 1.05] 8.50 [0.48, 151.05] 0.81 [0.51, 1.28] 0.92 [0.66, 1.27] 1.01 [0.82, 1.24]	1.3 % 0.8 % 1.8 % 9.8 % 0.1 % 8.8 % 15.4 % 36.3 %		28/223 5/238 3/277 7/173 40/244 0/16 35/254 6//312 149/819	117231 4/246 6/281 4/176 26/239 3/13 29/260 58/323 145/789	Baraniuk 1999 Bateman 2006 Busse 2003 Johansson 2001 Kelsen 1999 Li 1999 Murray 1999 O'Byrne 2001 O'Byrne 2005

Study or subgroup	LABA + ICS	Increased ICS	Risk Ratio	Weight	Risk Ratio
	n/N	n/N	M-H,Fixed,95% CI		M-H,Fixed,95% CI
SAS40026	5/295	8/279		2.0 %	0.59 [0.20, 1.79]
SFCF4026	12/154	16/156		4.0 %	0.76 [0.37, 1.55]
SLGA5021	20/246	32/243	-	8.0 %	0.62 [0.36, 1.05]
Vermetten 1999	8/113	14/120	-+	3.4 %	0.61 [0.26, 1.39]
Foundation (55% CI) Total events: 338 (LABA + IC Heterogeneity: $Chi^2 = 17.36$, Test for overall effect: $Z = 2.4$	$df = 15 (P = 0.30); I^2 = I$	3789 4%		100.0 %	0.85 [0.74, 0.97]
			0.01 0.1 1 10 100 rs LABA + ICS Favours higher I		

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

Study or subgroup	LABA + ICS	Increased ICS	Risk Ratio	Weight	Risk Ratio
	n/N	n/N	M-H,Fixed,95% CI		M-H,Fixed,95% C
I Manufacturer sponsorship					
Baraniuk 1999	11/231	28/223	-	5.1 %	0.38 [0.19, 0.74]
Bateman 2006	4/246	5/238		0.9 %	0.77 [0.21, 2.85
Bouros 1999	8/69	3/65		0.5 %	2.51 [0.70, 9.06
Busse 2003	6/281	3/277		0.5 %	1.97 [0.50, 7.80]
Condemi 1999	21/221	31/216	-	5.6 %	0.66 [0.39, 1.12]
Greening 1994	18/220	19/206		3.5 %	0.89 [0.48, 1.64]
Johansson 2001	4/176	7/173		1.3 %	0.56 [0.17, 1.88
Kelsen 1999	26/239	40/244	-	7.0 %	0.66 [0.42, 1.05



Study or subgroup	LABA + ICS n/N	Increased ICS n/N	Risk Ratio M-H,Fixed,95% Cl	Weight	Risk Ratio M-H,Fixed,95% Cl
Kips 2000	8/29	12/31	-+-	2.1 %	0.71 [0.34, 1.49
Li 1999	3/13	0/16		0.1 %	8.50 [0.48, 151.05
LOCCS	9/162	11/168		1.9 %	0.85 [0.36, 1.99]
Murray 1999	29/260	35/254	+	6.3 %	0.81 [0.51, 1.28
O'Byrne 2001	58/323	61/312	+	11.0 %	0.92 [0.66, 1.27
O'Byme 2005	145/789	149/819		26.0 %	1.01 [0.82, 1.24]
Pauwels 1997	62/210	60/214	+	10.6 %	1.05 [0.78, 1.42
SAM104926	2/160	1/161		0.2 %	2.01 [0.18, 21.97
SAM30022	1/34	1/33		0.2 %	0.97 [0.06, 14.88
SAM40090	4/242	3/241		0.5 %	1.33 [0.30, 5.87
SA540026	5/295	8/279		1.5 %	0.59 [0.20, 1.79
SFCF4026	12/154	16/156		2.8 %	0.76 [0.37, 1.55
SLGA5021	20/246	32/243	-	5.7 %	0.62 [0.36, 1.05
Van Noord 1999	16/139	15/135	+	2.7 %	1.04 [0.53, 2.01
Verberne 1998	10/60	7/60		1.2 %	1.43 [0.58, 3.50
Vermetten 1999	8/113	14/120		2.4 %	0.61 [0.26, 1.39
Wallin 2003	1/18	2/19		0.3 %	0.53 [0.05, 5.33
Subtotal (95% CI)	4930	4903		100.0 %	0.88 [0.78, 0.98
Total events: 491 (LABA + ICS Heterogeneity: $Chi^2 = 24.51$, d Test for overall effect: $Z = 2.33$), 563 (Increased ICS If = 24 (P = 0.43); I ² (P = 0.020))		100.0 %	0.00 [0./ 0, 0.90
2 Non-manufacturer sponsorsh Subtotal (95% CI) Total events: 0 (LABA + ICS), (Heterogeneity: not applicable Test for overall effect: not appli	0 0 (Increased ICS)	0			Not estimabl

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)

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

Study or subgroup	LABA + ICS n/N	Increased ICS n/N	Risk Ratio M-H.Fixed.95% CI	Weight	Risk Ratio M-H,Fixed,95% Cl
Kelsen 1999	26/239	40/244	-	7.4 %	0.66 [0.42, 1.05]
Bateman 2006	4/246	5/238		0.9 %	0.77 [0.21, 2.85]
SAS40026	5/295	8/279		1.5 %	0.59 [0.20, 1.79]
SFCF4026	12/154	16/156		3.0 %	0.76 [0.37, 1.55]
Johansson 2001	4/176	7/173		1.3 %	0.56 [0.17, 1.88]
Murray 1999	29/260	35/254	+	6.6 %	0.81 [0.51, 1.28]
Condemi 1999	21/221	31/216	-	5.8 %	0.66 [0.39, 1.12]
Baraniuk 1999	11/231	28/223	-	5.3 %	0.38 [0.19, 0.74]
Wallin 2003	1/18	2/19		0.4 %	0.53 [0.05, 5.33]
O'Byrne 2001	58/323	61/312	+	11.6 %	0.92 [0.66, 1.27]
Pauwels 1997	62/210	60/214	+	11.1 %	1.05 [0.78, 1.42]
Vermetten 1999	8/113	14/120		2.5 %	0.61 [0.26, 1.39]
Bouros 1999	8/69	3/65	<u> </u>	0.6 %	2.51 [0.70, 9.06]
Verberne 1998	10/60	7/60		1.3 %	1.43 [0.58, 3.50]
Busse 2003	6/281	3/277		0.6 %	1.97 [0.50, 7.80]
SLGA5021	20/246	32/243	-	6.0 %	0.62 [0.36, 1.05]
SAM40090	4/242	3/241		0.6 %	1.33 [0.30, 5.87]
SAM30022	1/34	1/33		0.2 %	0.97 [0.06, 14.88
O'Byrne 2005	145/789	149/819	+	27.3 %	1.01 [0.82, 1.24]
SAM104926	2/160	1/161		0.2 %	2.01 [0.18, 21.97
Kips 2000	8/29	12/31		2.2 %	0.71 [0.34, 1.49]
Li 1999	3/13	0/16		0.1 %	8.50 [0.48, 151.05
Greening 1994	18/220	19/206		3.7 %	0.89 [0.48, 1.64
Total (95% CI) Total events: 466 (LABA - Heterogeneity: Chi ² = 24 Test for overall effect: Z =	.28, df = 22 (P = 0.33);		•	100.0 %	0.87 [0.78, 0.98]

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

tudy or subgroup	LABA + ICS n/N	Increased ICS n/N	Risk Ratio M-H,Fixed,95% Cl	Weight	Risk Ra M-H,Fixed,95%
Kelsen 1999	26/239	40/244		11.6 %	0.66 [0.42, 1.0
Condemi 1999	21/221	31/216	-	9.2 %	0.66 [0.39, 1.1
SAM30022	1/34	1/33		0.3 %	0.97 [0.06, 14.8
SLGA5021	20/246	32/243	-	9.4 %	0.62 [0.36, 1.0
Kips 2000	8/29	12/31		3.4 %	0.71 [0.34, 1.4
SFCF4026	12/154	16/156		4.7 %	0.76 [0.37, 1.5
Baraniuk 1999	11/231	28/223		8.3 %	0.38 [0.19, 0.7
Murray 1999	29/260	35/254	+	10.4 %	0.81 [0.51, 1.2
Li 1999	3/13	0/16		0.1 %	8.50 [0.48, 151.0
SAS40026	5/295	8/279		2.4 %	0.59 [0.20, 1.7
Bouros 1999	8/69	3/65		0.9 %	2.51 [0.70, 9.0
O'Byrne 2001	58/323	61/312	-	18.2 %	0.92 [0.66, 1.2
Wallin 2003	1/18	2/19		0.6 %	0.53 [0.05, 5.3
Busse 2003	6/281	3/277		0.9 %	1.97 [0.50, 7.8
ohansson 2001	4/176	7/173		2.1 %	0.56 [0.17, 1.8
SAM40090	4/242	3/241		0.9 %	1.33 [0.30, 5.8
Verberne 1998	10/60	7/60		2.0 %	1.43 [0.58, 3.5
SAM104926	2/160	1/161		0.3 %	2.01 [0.18, 21.9
LOCCS	9/162	11/168		3.2 %	0.85 [0.36, 1.9
Bateman 2006	4/246	5/238		1.5 %	0.77 [0.21, 2.8
Vermetten 1999	8/113	14/120		4.0 %	0.61 [0.26, 1.3
Greening 1994	18/220	19/206	+	5.7 %	0.89 [0.48, 1.6
			0.01 0.1 I 10 100 rs LABA + ICS Favours higher		
Study or subgroup	LABA + ICS n/N	Increased ICS n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Total (95% CI)	3792	3735	•	100.0 %	0.78 [0.67, 0.91]
Total events: 268 (LABA Heterogeneity: Chi ² = 1 Test for overall effect: Z	8.72, df = 21 (P = 0.60)				

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

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

Risk Rati M-H,Fixed,95% (Weight	Risk Ratio M-H,Fixed,95% Cl	Increased ICS n/N	LABA + ICS n/N	Study or subgroup
0.71 [0.34, 1.49	2.1 %		12/31	8/29	Kips 2000
2.01 [0.18, 21.97	0.2 %		1/161	2/160	SAM104926
0.59 [0.20, 1.79	1.5 %		8/279	5/295	SAS40026
1.05 [0.78, 1.42	10.6 %	+	60/214	62/210	Pauwels 1997
1.01 [0.82, 1.24	26.2 %	•	149/819	145/789	O'Byme 2005
0.53 [0.05, 5.33	0.3 %		2/19	1/18	Wallin 2003
0.92 [0.66, 1.27	11.1 %	+	61/312	58/323	O'Byrne 2001
0.38 [0.19, 0.74	5.1 %	-	28/223	11/231	Baraniuk 1999
0.97 [0.06, 14.88	0.2 %		1/33	1/34	SAM30022
0.62 [0.36, 1.05	5.8 %	-	32/243	20/246	SLGA5021
1.97 [0.50, 7.80	0.5 %		3/277	6/281	Busse 2003
0.85 [0.36, 1.99	1.9 %	-	11/168	9/162	LOCCS
0.77 [0.21, 2.85	0.9 %		5/238	4/246	Bateman 2006

Risk Rat M-H,Fixed,95% (Weight	Risk Ratio M-H,Fixed,95% Cl	reased ICS n/N	LABA + ICS n/N	Study or subgroup
1.33 [0.30, 5.87	0.5 %		3/241	4/242	SAM40090
1.04 [0.53, 2.01	2.7 %	-	15/135	16/139	Van Noord 1999
0.66 [0.39, 1.12	5.6 %		31/216	21/221	Condemi 1999
0.76 [0.37, 1.55	2.8 %		16/156	12/154	SFCF4026
0.56 [0.17, 1.88	1.3 %		7/173	4/176	Johansson 2001
0.66 [0.42, 1.05	7.1 %	-	40/244	26/239	Kelsen 1999
0.81 [0.51, 1.28	6.3 %	+	35/254	29/260	Murray 1999
0.89 [0.48, 1.64	3.5 %		19/206	18/220	Greening 1994
0.61 [0.26, 1.39	2.4 %		14/120	8/113	Vermetten 1999
1.43 [0.58, 3.50	1.3 %		7/60	10/60	Verberne 1998
0.86 [0.77, 0.96	100.0 %		4822	9, df = 22 (P = 0.61); l ² =	Total (95% CI) Total events: 480 (LABA + Heterogeneity: Chi ² = 19. Test for overall effect: Z =

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

Study or subgroup	LABA + ICS n/N	Increased ICS n/N	Risk Ratio M-H,Fixed,95% Cl	Weight	Risk Ratio M-H,Fixed,95% C
I Adults					
Baraniuk 1999	3/231	2/223		5.4 %	1.45 [0.24, 8.58]
Bateman 2003	0/168	2/176		6.4 %	0.21 [0.01, 4.33]
Bateman 2006	1/246	0/238		1.3 %	2.90 [0.12, 70.91]
Bergmann 2004	0/180	1/187		3.9 %	0.35 [0.01, 8.44]
Bouros 1999	0/69	1/65		4.1 %	0.31 [0.01, 7.58]
Busse 2003	0/288	0/287			Not estimable
Condemi 1999	1/221	2/216		5.3 %	0.49 [0.04, 5.35]
Greening 1994	1/220	0/206		1.4 %	2.81 [0.12, 68.59]
Ind 2003	1/171	1/165		2.7 %	0.96 [0.06, 15.30]
Jenkins 2000	1/180	1/173		2.7 %	0.96 [0.06, 15.25]
Johansson 2001	3/176	0/173	+	1.3 %	6.88 [0.36, 132.24]
Kelsen 1999	1/239	1/244		2.6 %	1.02 [0.06, 16.23]
Kips 2000	1/29	0/31	 •	1.3 %	3.20 [0.14, 75.55]
Lalloo 2003	1/230	0/237		1.3 %	3.09 [0.13, 75.49]
Mitchell 2003	0/100	1/101		3.9 %	0.34 [0.01, 8.17]
Murray 1999	0/253	1/250		4.0 %	0.33 [0.01, 8.05]
O'Byrne 2005	8/788	10/818	+	25.8 %	0.83 [0.33, 2.09]
Pauwels 1997	1/210	5/214		13.0 %	0.20 [0.02, 1.73]
SAM30013	0/121	0/116			Not estimable
SAM30022	0/35	0/33			Not estimable
SAM40090	0/242	1/241		4.0 %	0.33 [0.01, 8.11]
SAM40120	0/8	0/10			Not estimable
SAS40026	0/321	0/315			Not estimable
SLGA5021	1/246	1/242		2.7 %	0.98 [0.06, 15.64]

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

up LABA	+ ICS	Increased ICS	Risk Ratio	Weight	Risk Ratio
	n/N	n/N	M-H,Fixed,95% CI		M-H,Fixed,95% C
9	0/139	0/135			Not estimable
)	0/113	0/120			Not estimable
	0/18	0/19			Not estimable
a	3/244	1/125		3.5 %	1.54 [0.16, 14.62
b	2/243	1/126		3.5 %	1.04 [0.09, 11.33
CI)	5729	5486	+	100.0 %	0.87 [0.54, 1.38]
ABA + ICS), 32 (Increa	ased ICS)				
² = 9.42, df = 20 (P =	: 0.98); I ² =(0.0%			
ct: Z = 0.60 (P = 0.55	5)				
lts					
	0/163	0/169			Not estimable
OCI)	163	169			Not estimable
BA + ICS), 0 (Increase	ed ICS)				
applicable					
ct: not applicable					
	7/118	2/107		45.6 %	3.17 [0.67, 14.95
	1/160	0/161		10.8 %	3.02 [0.12, 73.55
	0/180	1/180		32.6 %	0.33 [0.01, 8.13
	1/60	0/60		10.9 %	3.00 [0.12, 72.20
CI)	518	508	•	100.0 %	2.21 [0.74, 6.64
BA + ICS), 3 (Increase	ed ICS)				
² = 1.63, df = 3 (P =	0.65); l ² =0.	0%			
ct: Z = 1.41 (P = 0.16	5)				

Favours LABA + ICS Favours Higher ICS

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

or subgroup LABA	+ ICS N	Mean(SD)	Increased ICS N	Mean(SD)	Mean Difference IV,Random,95% CI	Weight	Mear Difference IV,Random,95% C
uros 1999	69	2.59 (1.03)	65	2.39 (1.03)		2.5 %	0.20 [-0.15, 0.55
ndemi 1999	194	2.81 (0.7)	176	2.67 (0.8)		12.7 %	0.14 [-0.01, 0.29
vler 2002	19	2.46 (1.45)	20	2.26 (1.6)	••	0.3 %	0.20 [-0.76, 1.16
eening 1994	148	2.21 (0.88)	141	2.17 (0.8)		8.0 %	0.04 [-0.15, 0.23
2003	171	2.4 (0.9)	165	2.4 (0.9)		8.1 %	0.0 [-0.19, 0.19
kins 2000	158	2.53 (0.5)	147	2.44 (0.5)		23.9 %	0.09 [-0.02, 0.20
ansson 2001	156	2.79 (0.81)	161	2.83 (0.86)		8.9 %	-0.04 [-0.22, 0.14
sen 1999	190	2.65 (0.83)	195	2.48 (0.7)		12.8 %	0.17 [0.02, 0.32
may 1999	210	2.68 (0.87)	197	2.54 (0.7)		12.9 %	0.14 [-0.01, 0.29
3yme 2005	906	2.43 (0)	925	2.41 (0)			Not estimabl
M40100	9	1.53 (0.5)	7	1.67 (0.2)		2.3 %	-0.14 [-0.50, 0.22
Noord 1999	130	2.47 (0.76)	129	2.48 (0.89)		7.4 %	-0.01 [-0.21, 0.19
(95% CI)	2360		2328		*	100.0 %	0.08 [0.03, 0.14
ogeneity: Tau ² = 0.0; Ch or overall effect: Z = 2.83			66); l ² =0.0%				
i overali ellecti z. – z.o.	(1 - 0.0	((11)					

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

Study or subgroup	LABA + ICS		Increased ICS		Mean Difference	Mea Differenc
	N	Mean(SD)	N	Mean(SD)	IV,Fixed,95% CI	IV,Fixed,95% (
Bergmann 2004	170	86 (26)	177	83 (24)		3.00 [-2.27, 8.27
Kips 2000	10	83 (18.2)	21	83 (16.6)		0.0 [-13.33, 13.33
Li 1999	13	90 (14.9)	16	80 (16.6)		10.00 [-1.48, 21.48
LOCCS	161	91.8 (9.06)	168	91.1 (9.92)		0.70 [-1.35, 2.75
Pauwels 1997	210	85.38 (16.66)	214	81.35 (16.82)		4.03 [0.84, 7.22
					-20 -10 0 10 20	
				Fax	vours Higher ICS Favours LABA	+ ICS

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

Study or subgroup	LABA + ICS		Increased ICS		Mean Difference	Mea Differenc
	N	Mean(SD)	N	Mean(SD)	IV,Fixed,95% CI	IV,Fixed,95% (
Baraniuk 1999	215	0.58 (0.49)	210	0.48 (0.44)	-+-	0.10 [0.01, 0.19
Bateman 2006	238	-0.02 (0.33)	233	-0.17 (0.41)	-+-	0.15 [0.08, 0.22
Bergmann 2004	170	0.33 (0.56)	177	0.22 (0.52)		0.11 [0.00, 0.22
Busse 2003	281	0.07 (0.17)	277	-0.03 (0.17)	+	0.10 [0.07, 0.13
Condemi 1999	194	0.43 (0.56)	176	0.33 (0.4)		0.10 [0.00, 0.20
D5896C00001	152	-0.12 (0.2)	151	-0.18 (0.21)	+	0.06 [0.01, 0.11
Kelsen 1999	190	0.35 (0.41)	195	0.26 (0.42)	-+-	0.09 [0.01, 0.17
Murray 1999	210	0.36 (0.58)	197	0.22 (0.42)		0.14 [0.04, 0.24
O'Byrne 2005	906	0.32 (0)	925	0.27 (0)		Not estimab
Pearlman 1999	25	0.59 (0.5)	23	0.3 (0.43)	_ _	0.29 [0.03, 0.55
SAM30013	121	0.17 (0.45)	116	0.16 (0.44)	+	0.01 [-0.10, 0.12
SAS40026	316	0.06 (0.18)	311	-0.03 (0.35)	+	0.09 [0.05, 0.13
SD 039 0726	152	-0.06 (0.3)	144	-0.2 (0.3)	-	0.14 [0.07, 0.21
SD 039 0728	129	0.16 (0.2)	132	0.08 (0.28)	+	0.08 [0.02, 0.14
SFCF4026	156	-0.05 (1.05)	154	-0.26 (1.05)		0.21 [-0.02, 0.44
SLGA5021	240	0.36 (0.46)	238	0.35 (0.46)	+	0.01 [-0.07, 0.09
Woolcock 1996a	215	0.1 (0.45)	108	0 (0.45)		0.10 [0.00, 0.20
Wookock 1996b	220	0.11 (0.45)	109	0 (0.45)		0.11 [0.01, 0.21
Zhong 2005	199	0.31 (0.4)	187	0.28 (0.42)		0.03 [-0.05, 0.11
					-1 -0.5 0 0.5 1	
				Favou	rs Higher ICS Favours LAB	A + ICS

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

Study or subgroup	LABA + ICS N	Mean(SD)	Increased ICS N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mea Differenc IV,Fixed,95% (
I At 6 +/- 2 weeks							
Kelsen 1999	226	0.33 (0.45)	227	0.21 (0.45)	-	32.3 %	0.12 [0.04, 0.20
Pearlman 1999	25	0.59 (0.5)	23	0.3 (0.43)		3.2 %	0.29 [0.03, 0.55
Conderni 1999	208	0.33 (0.43)	194	0.24 (0.42)	-	32.1 %	0.09 [0.01, 0.17
Baraniuk 1999	224	0.52 (0.45)	219	0.43 (0.44)	-	32.3 %	0.09 [0.01, 0.17
Subtotal (95% CI)	683		663		•	100.0 %	0.11 [0.06, 0.15
Heterogeneity: $Chi^2 = 2.2$ Test for overall effect: $Z =$							
2 At 12 +/- 4 weeks Kelsen 1999	203	0.37 (0.43)	215	0.23 (0.44)		5.7 %	0.14 [0.06, 0.22
Baraniuk 1999	215	0.58 (0.49)	210	0.48 (0.44)		5.1 %	0.10 [0.01, 0.19
Condemi 1999	206	0.38 (0.43)	188	0.10 (0.11)		5.8 %	0.11 [0.03, 0.19
SLGA5021	208		238			5.9 %	0.01 [-0.07, 0.09
		0.36 (0.46)		0.35 (0.46)	T.		
Bergmann 2004	170	0.33 (0.56)	177	0.22 (0.52)	-	3.1 %	0.11 [0.00, 0.22
SAM30013	121	0.17 (0.45)	116	0.16 (0.44)	-	3.1 %	0.01 [-0.10, 0.12
SAS40026	316	0.06 (0.18)	311	-0.03 (0.35)	-	21.0 %	0.09 [0.05, 0.13
Busse 2003	281	0.07 (0.17)	277	-0.03 (0.17)	-	50.3 %	0.10 [0.07, 0.13
Subtotal (95% CI) Heterogeneity: $Chi^2 = 7.7$ Test for overall effect: Z =			1732		•	100.0 %	0.09 [0.07, 0.11
3 At 24 +/- 4 weeks		01)					
Kelsen 1999	190	0.35 (0.41)	195	0.26 (0.42)	•	21.4 %	0.09 [0.01, 0.17
Murray 1999	210	0.36 (0.58)	197	0.22 (0.42)	-	15.4 %	0.14 [0.04, 0.24
Condemi 1999	194	0.43 (0.56)	176	0.33 (0.4)	-	15.2 %	0.10 [0.00, 0.20
SA540026	159	0.08 (0.25)	142	-0.01 (0.24)	-	48.0 %	0.09 [0.03, 0.15
Subtotal (95% CI) Heterogeneity: $Chi^2 = 0.8$ Test for overall effect: Z =			710		•	100.0 %	0.10 [0.06, 0.14
				-1	-0.5 0 0.5		
				Favours	Higher ICS Favours LAI	BA + ICS	
Study or subgroup	LABA + ICS		Increased ICS		Mean Difference	Weight	Mea Differenc
stady or subgroup	N	Mean(SD)	N	Mean(SD)	IV,Fixed,95% CI	**eight	IV,Fixed,95% C
4 New Subgroup Subtotal (95% CI) Heterogeneity: not applica			0				Not estimable
Test for overall effect: not Test for subgroup differen		df = 2 (P = 0.8	7), l ² =0.0%				

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

Me Differer	Mean erence	Diff		Increased ICS		LABA + ICS	Study or subgroup
IV,Random,95%	om,95% CI		Mean(SD)	N	Mean(SD)	N	
39.00 [4.83, 73.1			378 (87.9)	65	417 (113)	69	Bouros 1999
32.00 [17.50, 46.5			402 (22.82)	20	434 (23.35)	19	Fowler 2002
36.00 [8.75, 63.2			345 (113)	127	381 (114)	140	Greening 1994
20.70 [-23.77, 65.1		_	282.5 (78.6)	24	303.2 (78.6)	24	Heuck 2000
26.00 [15.64, 36.3	-		380 (48.9)	165	406 (48.2)	173	Jenkins 2000
29.60 [8.95, 50.2			409.8 (103.92)	192	439.4 (101.46)	188	Kelsen 1999
24.00 [-44.09, 92.0	·		405 (106)	22	429 (118)	20	Kips 2000
40.00 [-28.89, 108.8		_	456 (99.2)	16	496 (89.8)	13	Li 1999
27.80 [-4.67, 60.2			361.9 (107.5)	101	389.7 (126.5)	100	Mitchell 2003
27.00 [7.60, 46.4			413 (97.25)	193	440 (100.71)	207	Murray 1999
Not estima			339 (0)	925	346 (0)	906	O'Byme 2005
29.00 [7.71, 50.2			383 (106)	206	412 (114)	205	Pauwels 1997
)	0 50 100	-100 -50					
+ ICS	Favours LABA	ours Higher ICS	Fa				
Mea Different	Mean erence			Increased ICS		LABA + ICS	Study or subgroup
IV,Random,95%	om,95% CI	IV,Rande	Mean(SD)	Ν	Mean(SD)	Ν	,
13.00 [-41.07, 67.07	·		444 (82.49)	21	457 (93.49)	20	Pearlman 1999
2.00 [-27.47, 31.47			384 (120)	129	386 (122)	130	Van Noord 1999
	50 100	-100 -50 (
+ ICS	Favours LABA	ours Higher ICS	Fa				

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

Study or subgroup L/	ABA + ICS		ncreased ICS		Mean Difference	Weight	Mean Difference
	Ν	Mean(SD)	Ν	Mean(SD)	IV,Fixed,95% C	-	IV,Fixed,95% CI
I Baseline FEVI >= 80% pre	dicted						
Heuck 2000	24	290 (73.5)	24	286 (73.5)		3.2 %	4.00 [-37.59, 45.59]
Subtotal (95% CI)	24		24		-	3.2 %	4.00 [-37.59, 45.59]
Heterogeneity: not applicable							
Test for overall effect: $Z = 0$.	9 (P = 0.85)					
2 Baseline FEV1 61% to 79 %	predicted						
Fowler 2002	19	436 (22.82)	20	408 (23.35)	-	26.3 %	28.00 [13.51, 42.49]
Jenkins 2000	173	416 (41.3)	165	398 (41.7)	-	70.5 %	18.00 [9.15, 26.85]
Subtotal (95% CI)	192		185		•	96.8 %	20.72 [13.16, 28.27]
Heterogeneity: Chi ² = 1.33, o	f = I (P = 0)	0.25); I ² =25%					
Test for overall effect: $Z = 5.3$	88 (P < 0.00	(100					
Total (95% CI)	216		209		•	100.0 %	20.18 [12.75, 27.62]
Heterogeneity: Chi ² = 1.93, o	if = 2 (P = 0	0.38); I ² =0.0%					
Test for overall effect: $Z = 5.3$	82 (P < 0.00	(100					
Test for subgroup differences	$Chi^2 = 0.60$), $df = 1$ (P = 0.4	\$), I ² =0.0%				
				-100	-50 0 50	100	
				Favours H	igher ICS Eavou	rs LABA + ICS	

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

Mei Differen IV,Random,95%	Weight	Mean Difference IV,Random,95% CI	Mean(SD)	Increased ICS N	Mean(SD)	LABA + ICS N	Study or subgroup
10.97 [-3.36, 25.30	2.5 %		46.96 (71.08)	223	57.93 (83.8)	228	Baraniuk 1999
19.70 [11.12, 28.28	4.6 %		7.7 (40.57)	176	27.4 (40.57)	168	Bateman 2003
12.90 [7.70, 18.10	6.6 %	-	-13.2 (29)	238	-0.3 (29.33)	246	Bateman 2006
16.00 [1.09, 30.91	2.3 %		36 (65)	177	52 (76)	170	Bergmann 2004
18.20 [8.40, 28.00	4.0 %		18.5 (55.92)	277	36.7 (62.02)	281	Busse 2003
21.00 [8.79, 33.21	3.1 %		31.3 (60.3)	172	52.3 (58.5)	194	Conderni 1999
21.00 [7.67, 34.33	2.7 %		7 (57)	126	28 (53)	137	Greening 1994
26.50 [18.14, 34.86	4.7 %		21.2 (28.9)	165	47.7 (47.4)	171	Ind 2003
10.00 [1.04, 18.96	4.4 %	-+-	33 (42.7)	173	43 (42.7)	176	Johansson 2001
26.10 [15.69, 36.5	3.7 %		20.9 (49.99)	192	47 (53.47)	188	Kelsen 1999
9.20 [3.47, 14.9]	6.2 %	•	7.3 (31.61)	237	16.5 (31.61)	230	Lalloo 2003
17.00 [5.91, 28.09	3.5 %	+	27 (55.57)	193	44 (57.55)	207	Murray 1999
Not estimat			0 (0)	925	0 (0)	906	O'Byrne 2005
32.00 [5.30, 58.70	0.9 %		25 (41.28)	22	57 (52)	25	Pearlman 1999
7.60 [1.71, 13.49	6.1 %	-	19.3 (26.22)	153	26.9 (26.09)	150	SAM104926
13.70 [-3.21, 30.6	1.9 %		30.7 (65.7)	116	44.4 (67.1)	121	SAM30013
22.80 [-0.66, 46.26	1.1 %		22.2 (50.2)	33	45 (47.7)	34	SAM30022
5.90 [-2.28, 14.08	4.8 %	-+-	39.2 (38.9)	180	45.1 (39.8)	176	SAM40012
17.40 [11.77, 23.0]	6.3 %	•	1.9 (31.21)	235	19.3 (30.97)	234	SAM40090
Not estimat			9 (0)	10	35.8 (0)	8	SAM40120
17.90 [7.67, 28.13	3.8 %		19.5 (63.28)	311	37.4 (67.44)	316	SAS40026
26.00 [10.73, 41.27	2.2 %		-32 (67)	144	-6 (67)	152	SD 039 0726
27.99 [19.44, 36.54	4.6 %	-	5.61 (35.5)	132	33.6 (35.1)	130	SD 039 0728

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

Study or subgroup	LABA + ICS		Increased ICS		Mean Difference	Weight	Mean Difference
	N	Mean(SD)	N	Mean(SD)	IV,Random,95% CI		IV,Random,95% CI
SFCF4026	156	I (33.47)	154	-14.56 (34.62)	+	5.1 %	15.56 [7.98, 23.14]
SLGA5021	240	43.7 (61.97)	238	30 (43.2)		4.1 %	13.70 [4.13, 23.27]
Verberne 1998	60	30.92 (33)	60	22.57 (33)	+	3.2 %	8.35 [-3.46, 20.16]
Vermetten 1999	113	31.3 (40.67)	119	19.34 (35.98)		4.0 %	11.96 [2.06, 21.86]
Zhong 2005	199	52.4 (59)	187	29.88 (54)	-+-	3.4 %	22.52 [11.25, 33.79]
Total (95% CI)	5416		5368		•	100.0 %	16.25 [13.59, 18.90]
Heterogeneity: Tau ² =	= 20.78; Chi ² =	49.03, df = 25 (P	= 0.003); 2 =4	19%			
Test for overall effect:	Z = 12.00 (P <	0.00001)					
Test for overall effect:	Z = 12.00 (P <	0.00001)					
				-	00 -50 0 50 I	00	
				Enun	rs Higher KCS Equours LAI	201 + 45	

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

Study or subgroup	LABA + ICS		Increased ICS		Mean Difference	Mear Difference
	N	Mean(SD)	N	Mean(SD)	IV,Random,95% CI	IV,Random,95% C
Lalloo 2003	230	13.7 (30.24)	237	4.2 (30.24)	-+-	9.50 [4.01, 14.99
Busse 2003	281	36.8 (62.02)	281	20.9 (61.5)		15.90 [5.69, 26.11
Greening 1994	135	15 (49)	126	-4 (55)		19.00 [6.33, 31.67
Bateman 2003	168	24 (39.66)	176	6.8 (40.46)	-	17.20 [8.73, 25.67
Bergmann 2004	170	46 (73)	177	29 (65)		17.00 [2.44, 31.56
Condemi 1999	221	-8.5 (27)	216	-4.3 (28)	-	-4.20 [-9.36, 0.96
Murray 1999	260	27.4 (35.5)	254	14.6 (35)	+	12.80 [6.71, 18.89
Ind 2003	171	31.6 (57.6)	165	9.5 (46.2)		22.10 [10.95, 33.25

Favours Higher ICS Favours LABA + ICS

Study or subgroup	LABA + ICS		Increased ICS		Mean Difference	Mean Difference
	N	Mean(SD)	N	Mean(SD)	IV,Random,95%	G CI IV,Random,95% CI
Kelsen 1999	184	37.5 (51.55)	191	14.8 (44.22)	-+-	22.70 [12.96, 32.44]
Baraniuk 1999	228	43.93 (76.56)	223	38.1 (65.71)		5.83 [-7.33, 18.99]
SAM30013	121	41.8 (63.8)	116	24.3 (62.5)		17.50 [1.42, 33.58]
Zhong 2005	199	45.6 (54)	187	32.1 (52.18)		13.50 [2.91, 24.09]
SAM40090	234	19.2 (32.28)	235	1.6 (32.04)	+	17.60 [11.78, 23.42]
SAM40012	176	43.2 (41.13)	180	38.8 (40.2)	-	4.40 [-4.05, 12.85]
SFCF4026	156	-4.2 (29.85)	154	-16.33 (29.91)	+	12.13 [5.48, 18.78]
SLGA5021	240	36.3 (54.22)	238	21.8 (46.28)		14.50 [5.47, 23.53]
SAM40120	8	15 (28)	10	-8 (20)		23.00 [-0.02, 46.02]
SD 039 0726	152	-13.9 (28.8)	144	-31.88 (34.6)	+	17.98 [10.71, 25.25]
					-100 -50 0 5	0 100
					Favours Higher ICS Favo	urs LABA + ICS

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

Study or subgroup	LABA + ICS	In	creased ICS		Mean Difference	Weight	Mear Difference
	N	Mean(SD)	N	Mean(SD)	IV,Random,95% CI		IV,Random,95% C
Baseline FEV >= 80 %	predicted						
Verberne 1998	60	4.36 (1.51)	60	4.08 (1.47)		64.9 %	0.28 [-0.25, 0.81
Subtotal (95% CI)	60		60		•	64.9 %	0.28 [-0.25, 0.81]
Heterogeneity: not applica	ble						
Test for overall effect: Z =	1.03 (P = 0.30)						
2 Baseline FEV1 61% to 79	% predicted						
Bergmann 2004	170	12.3 (20)	177	8.4 (17)		35.1 %	3.90 [-0.01, 7.81
Subtotal (95% CI)	170		177		-	35.1 %	3.90 [-0.01, 7.81]
Heterogeneity: not applica	ble						
Test for overall effect: Z =	1.95 (P = 0.051)					
Total (95% CI)	230		237		-	100.0 %	1.55 [-1.84, 4.94]
Heterogeneity: Tau ² = 4.5	2; Chi ² = 3.23, d	$f = 1 (P = 0.07); I^2$	=69%				
Test for overall effect: Z =	0.90 (P = 0.37)						
				-10	-5 0 5 1	10	
				Eavours	Higher ICS Favours LAB		

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

Study or subgroup	LABA + ICS		Increased ICS		Mean Difference	Weight	Mean Difference
	N	Mean(SD)	N	Mean(SD)	IV,Random,95% CI		IV,Random,95% CI
Busse 2003	281	11.8 (33.53)	277	5.8 (29.96)	-	10.6 %	6.00 [0.73, 11.27]
Lalloo 2003	230	16 (24.8)	237	10 (24.8)	-	11.3 %	6.00 [1.50, 10.50]
SAM40090	234	4.1 (17)	234	2.2 (17)	-	12.5 %	1.90 [-1.18, 4.98]
SAS40026	313	11.1 (30.08)	308	6.1 (31.59)	-	11.0 %	5.00 [0.15, 9.85]
Murray 1999	206	34 (43.06)	193	14 (41.68)	•	8.0 %	20.00 [11.68, 28.32]
Baraniuk 1999	228	29.2 (43.79)	223	22.6 (38.83)	-	8.5 %	6.60 [-1.03, 14.23]
Condemi 1999	193	30.83 (40.1)	173	15.23 (40.6)	•	8.0 %	15.60 [7.32, 23.88]
Pearlman 1999	25	34 (45)	23	12 (33.57)		2.2 %	22.00 [-0.35, 44.35]
Kelsen 1999	239	23.6 (31)	244	12.5 (25)	•	10.8 %	11.10 [6.07, 16.13]
Bergmann 2004	170	49 (38)	177	38 (40)	•	8.0 %	11.00 [2.79, 19.21]
SD 039 0728	130	23.5 (33.5)	132	5.9 (24.1)	•	9.0 %	17.60 [10.52, 24.68]
Total (95% CI) Heterogeneity: Tau ² =			2221 = 0.00003); ² =7	74%	•	100.0 %	9.66 [6.04, 13.29]
Test for overall effect:	Z = 5.23 (P < 0	.00001)					
				-10	0 -50 0 50 I	00	
				Eavours	Higher ICS Favours LAB	A + ICS	

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

Comparison: 3 WMD archive

Outcome: 11 # patients with exacerbations requiring oral steroids

Study or subgroup	tudy or subgroup LABA + ICS Increased ICS Risk Ratio n/N n/N M-H,Fixed,95% CI		Weight	Risk Ratio		
Baraniuk 1999	n/N	n/N 28/223	M-H,Fba	ed,95% CI	5.1 %	M-H,Fixed,95% CI 0.38 [0.19, 0.74]
Bateman 2006	4/246	5/238			0.9 %	
Bateman 2006 Bouros 1999	8/69	3/65			0.5 %	0.77 [0.21, 2.85]
Busse 2003	6/07	3/277			0.5 %	2.51 [0.70, 9.06]
Condemi 1999	21/221	31/216	-			
				_	5.6 %	0.66 [0.39, 1.12]
Greening 1994	18/220	19/206			3.5 %	0.89 [0.48, 1.64]
Johansson 2001	4/176	7/173			1.3 %	0.56 [0.17, 1.88]
Kelsen 1999	26/239	40/244	-		7.0 %	0.66 [0.42, 1.05]
Kips 2000	8/29	12/31		_	2.1 %	0.71 [0.34, 1.49]
Li 1999	3/13	0/16	_	•	0.1 %	8.50 [0.48, 151.05]
LOCCS	9/162	11/168		_	1.9 %	0.85 [0.36, 1.99]
Murray 1999	29/260	35/254	-	-	6.3 %	0.81 [0.51, 1.28]
O'Byrne 2001	58/323	61/312	-	-	11.0 %	0.92 [0.66, 1.27]
O'Byme 2005	145/789	149/819	-		26.0 %	1.01 [0.82, 1.24]
Pauwels 1997	62/210	60/214		•	10.6 %	1.05 [0.78, 1.42]
SAM104926	2/160	1/161			0.2 %	2.01 [0.18, 21.97]
SAM30022	1/34	1/33			0.2 %	0.97 [0.06, 14.88]
SAM40090	4/242	3/241			0.5 %	1.33 [0.30, 5.87]
SAS40026	5/295	8/279		_	1.5 %	0.59 [0.20, 1.79]
SFCF4026	12/154	16/156		-	2.8 %	0.76 [0.37, 1.55]
SLGA5021	20/246	32/243			5.7 %	0.62 [0.36, 1.05]
Van Noord 1999	16/139	15/135	-	-	2.7 %	1.04 [0.53, 2.01]
Verberne 1998	10/60	7/60	_	-	1.2 %	1.43 [0.58, 3.50]
Vermetten 1999	8/113	14/120		-	2.4 %	0.61 [0.26, 1.39]
Wallin 2003	1/18	2/19			0.3 %	0.53 [0.05, 5.33]
			0.01 0.1 1	10 100		
			Favours LABA + ICS	Favours higher ICS		
Study or subgroup	LABA + ICS	Increased ICS	R	lisk Ratio	Weight	Risk Rat
	n/N	n/N	M-H,Fix	ed,95% Cl		M-H,Fixed,95% (
Total (95% CI) Total events: 491 (LABA + Heterogeneity: Chi ² = 24. Test for overall effect: Z =	61, df = 24 (P = 0.43);		•		100.0 %	0.88 [0.78, 0.98

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

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

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:

- 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.

Studies already included in review (all years to April 2004): 30 studies

Citations retrieved from electronic & handsearches: 375 References potentially relevant to this review: 64 Studies considered for this review (including those previously listed as awaiting assessment: 26

Studies failing to meet eligibility criteria: 8

New studies included in the review: 18 Total number of included studies: 48 (125 citations)

Figure 1.

Literature flow diagram for June 2008 update of the review.

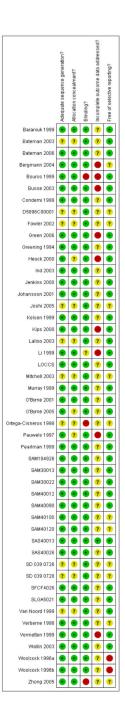


Figure 2.

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

1.1 Baseline FEV1 >= 60 % predicted Obyme 2001 68 333 61 312 11 01 0.3% 2010 16, 21 97 Yes Wes Saturation 1990 118 119 219 0.3% 139 140 219 0.3% 141 150 0.3% 1510 05, 533 Yes Yes		LABA +		Increase			Risk Ratio		Risk Ratio
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							0.92 [0.66, 1.27]		-
Jusse 2003 6 2 Pt 3 2 77 0.5% 1 47 0.60 7.80 Yes demotion 1999 8 113 14 120 2.4% 0.61 0.85 0.81 9.93 Yes demotion 1999 3 13 0 16 0.1% 8.50 [0.26, 1.30] Yes SAS40026 5 295 8 273 1.5% 0.59 (0.20, 1.73) Yes Grademan 12 154 16 156 2.8% 0.59 (0.20, 1.73) Yes Federation 1998 10 60 7 60 1.2% 1.43 (0.63, 3.50) Yes Federation 2005 145 7.89 predicted 1.01 0.02, 1.24 Unclear Unclear federogeneity, Ch ²⁺ 7.34, df=10 (P = 0.69), P = 0.68 71 0.35 0.397 0.66 0.71, 1.88 Yes staramuk 1999 11 221 223 51% 0.38 0.149 Yes descents PV1 61-79 % predicted 1.03 0.26 0.5% 2.51	SAM104926	2	160		161	0.2%	2.01 [0.18, 21.97]	Yes	
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errometen 1999 8 113 14 120 2.4% 0.61 0.26 1.39 Yes i1999 3 13 0 16 0.1% 8.50 0.43 1.05 Yes iAS40026 5 295 8 2.79 1.5% 0.59 0.20 1.79 Yes iAS40026 12 154 16 155 2.8% 0.76 0.37 1.55 Yes iAbdotal (95%) (C) 2.368 2.287 4.80% 0.97 (0.83, 1.13) Unclear iberogeneity, ChP 7.38 2.287 4.80% 0.97 (0.63, 1.13) Unclear iberogeneity, ChP 7.38 7.33 0.36 (0.17, 1.88) Yes Intervest 2.99 2.99 2.97 1.34 1.33 0.2% 0.97 (0.61, 4.88) Yes Intervest 2.92 1.34 1.33 0.2% 0.97 1.03, 1.48 Yes Intervest Intervest Intervest 1.33 1.33 0.36 0.14, 1.48 Yes Intervest Intervest Intervest Inte	3usse 2003	6	281	3	277	0.5%	1.97 [0.50, 7.80]	Yes	
$ \begin{array}{cccccccccccccccccccccccccccccccccccc$.0CCS	9	162	11	168	1.9%	0.85 [0.36, 1.99]	Yes	
Aps240026 5 295 8 279 1.5% 0.58 [0.20, 1.76] Yes FFCF4026 12 154 16 156 2.9% 0.76 [0.37, 1.56] Yes FFCF4026 12 154 16 156 2.9% 0.76 [0.37, 1.56] Yes FFCF4026 12 154 16 156 2.9% 0.76 [0.37, 1.56] Yes FFCF4026 12 3266 2.387 48.0% 0.97 [0.83, 1.13] Unclear Ictal events 2.59 2.236 1.33 0.98 [0.17, 1.88] Yes Febrome 1976 7.4 1.33 0.2% 0.97 [0.06, 14.88] Yes isotro overall effect 2.0 1.3 0.3% 0.97 [0.06, 14.88] Yes isotro strops 8.6 0.5 0.55 (0.17, 1.80) Yes	/ermetten 1999	8	113	14	120	2.4%	0.61 [0.26, 1.39]	Yes	
$ \begin{array}{cccccccccccccccccccccccccccccccccccc$	_i 1999	3	13	0	16	0.1%	8.50 [0.48, 151.05]	Yes	
Terbene 1998 10 60 7 60 12% 143 [0.63, 3.50] Yes Dyme 2005 145 789 149 819 26.0% 1.01 [0.82, 1.24] Unclear tabitotal (95% CI) 2368 2387 48.0% 0.97 [0.83, 1.13] Unclear Total events 259 272 telerogeneity; Chi" = 7.34, dir = 10 ($P = 0.80$) 1.12 Baseline FLVI 61.79 % predicted tohansson 2001 4 176 7 173 1.3% 0.56 [0.17, 1.88] Yes telerogeneity; Chi" = 12, 24, dir = 11 ($P = 0.80$) 1.2 Baseline FLVI 61.79 % predicted tohansson 2001 4 176 7 173 1.3% 0.56 [0.17, 1.88] Yes telerogeneity; Chi" = 24, 25 22 5.1% 0.38 [0.18, 0.74] Yes telerogeneity; Chi" = 24, 21 31 21% 0.71 [0.34, 1.48] Yes telerogeneity; Chi" = 24, 21 31 21% 0.71 [0.34, 1.48] Yes telerogeneity; Chi" = 24, 21 31 21% 0.71 [0.34, 1.44] Yes telerogeneity; Chi" = 24, 21 31 216 5.6% 0.66 [0.39, 1.12] Yes telerogeneity; Chi" = 24, 21 31 216 5.6% 0.66 [0.39, 1.12] Yes telerogeneity; Chi" = 24, 21 31 216 5.6% 0.66 [0.39, 1.12] Yes telerogeneity; Chi" = 24, 21 0.52 256 telerogeneity; Chi" = 132, 41 = 11 ($P = 0.20$); $P = 17\%$ telerogeneity; Chi" = 132, 41 = 11 ($P = 0.20$); $P = 17\%$ telerogeneity; Chi" = 132, 41 = 11 ($P = 0.20$); $P = 17\%$ telerogeneity; Chi" = 132, 41 = 11 ($P = 0.20$); $P = 17\%$ telerogeneity; Chi" = 132, 41 = 11 ($P = 0.20$); $P = 17\%$ telerogeneity; Chi" = 24, 52 ($P = 0.01$) 1.3 Baseline FEVI 400% predicted SLOA5021 20 246 32 243 5.7% 0.62 [0.36, 1.05] Yes telerogeneity; Chi" = 24, 51 , dir = 24 ($P = 0.07$) 1.4 Baseline FEVI ander AM40000 4 242 241 0.5% 1.33 [0.30, 5.87] Yes telerogeneity; Chi" = 24, 51 , dir = 24 ($P = 0.07$) 1.4 Baseline FEVI ander AM40000 4 242 241 0.5% 1.33 [0.30, 5.87] Yes telerogeneity; Not applicable telerogeneity; Not applicable tele	AS40026	5	295	8	279	1.5%	0.59 [0.20, 1.79]	Yes	
Disyme 2005 145 789 149 219 26.0% 1.01 $[0.2, 1.24]$ Unclear initiation (95% CI) 236 2397 48.0% 0.97 $[0.83, 1.13]$ of all events 259 272 detergenently. Chf ² = 7.34, df = 10 ($P = 0.69$); $P = 0\%$ detergenently. Chf ² = 7.34, df = 10 ($P = 0.69$); $P = 0\%$ detergenently. Chf ² = 7.34, df = 10 ($P = 0.69$); $P = 0\%$ detergenently. Chf ² = 7.34, df = 10 ($P = 0.69$); $P = 0\%$ detergenently. Chf ² = 7.34, df = 10 ($P = 0.69$); $P = 0\%$ detergenently. Chf ² = 7.34, df = 10 ($P = 0.69$); $P = 0\%$ detergenently. Chf ² = 7.34, df = 10 ($P = 0.69$); $P = 0\%$ detergenently. Chf ² = 7.34, df = 10 ($P = 0.26$); $P = 0.69$ detergenently. Chf ² = 7.34, df = 11 ($P = 0.26$); $P = 17\%$ detergenently. Chf ² = 1.78 ($P = 0.07$) 1.1 Baseline FEV1 60% predicted JLOASD 4 242 3 241 0.5% 1.33 [0.30, 5.87] vibilot all (95% CI) 246 322 243 5.7% 0.62 [0.36, 1.05] ves detergenently. Chf ² = 13.24, df = 11 ($P = 0.26$); $P = 17\%$ detergenently. Chf ² = 13.24, df = 11 ($P = 0.26$); $P = 17\%$ detergenently. Chf ² = 13.24, df = 11 ($P = 0.26$); $P = 17\%$ detergenently. Chf ² = 13.24, df = 11 ($P = 0.26$); $P = 17\%$ detergenently. Chf ² = 13.24, df = 11 ($P = 0.26$); $P = 17\%$ detergenently. Chf ² = 13.24, df = 11 ($P = 0.26$); $P = 17\%$ detergenently. Chf ² = 13.24, df = 11 ($P = 0.26$); $P = 17\%$ detergenently. Chf ² = 13.24, df = 11 ($P = 0.26$); $P = 17\%$ detergenently. Chf ² = 13.24, df = 11 ($P = 0.26$); $P = 17\%$ detergenently. Chf ² = 13.24, df = 11 ($P = 0.26$); $P = 17\%$ detergenently. Chf ² = 1.78 ($P = 0.07$) 1.1 Baseline FEV1 inclear ValueData (95% CI) 246 32 243 5.7% 0.62 [0.36, 1.05] Ves vibitotial (95% CI) 246 32 241 0.5\% 1.33 [0.30, 5.87] Ves vibitotial (95% CI) 442 3 241 0.5\% 1.33 [0.30, 5.87] Ves vibitotial fibret Z = 0.37 ($P = 0.71$) detergenently. Chf ² = 2451, df = 24 ($P = 0.43$); $P = 2\%$ vibitotial fibret Z = 0.426 0.00\%	SFCF4026	12	154	16	156	2.8%	0.76 [0.37, 1.55]	Yes	
$\begin{aligned} & \text{PSyme 2005} & 145 \ 789 \ 149 \ 819 \ 26.0\% \ 1.01 \ [0.82, 1.24] \\ & \text{Unclear} \end{aligned}$	/erberne 1998	10	60	7	60	1.2%	1.43 [0.58, 3.50]	Yes	
Subicidal (95% CI) 2368 2387 48.0% 0.97 [0.83, 1.13] Total events 259 272 Teterogeneity: ChT = 7.34, df = 10 (P = 0.69); T = 0% Test for overall effect Z = 0.39 (P = 0.69); T = 0% Test for overall effect Z = 0.39 (P = 0.69); T = 0% Test for overall effect Z = 0.39 (P = 0.69); T = 0% Samanuk 1999 11 231 28 223 5.1% 0.36 [0.17, 1.88]; Yes Test for overall effect Z = 0.39 (P = 0.48); AM30022 1 34 1 33 0.2% 0.97 [0.06, 14.88]; Yes Test for overall effect Z = 0.29; T = 0.5%, 2.51 (0.70, 9.06); Yes Test for overall effect Z = 0.29; X = 0.5%, 0.25 [0.17, 1.89]; Yes Test for overall effect Z = 0.29; X = 0.00; X = 0	D'Byrne 2005	145	789	149	819	26.0%		Unclear	+
Heterogeneity: ChiP = 7.34, df = 10 (P = 0.69); P = 0% Fest for vorerall effect $Z = 0.39$ (P = 0.69) 1.1.2 Baseline FEV1 61.79 % predicted Johansson 2001 4 176 7 173 1.3% 0.56 [0.17, 1.88] Yes SAM30022 1 34 1 73 0.2% 0.97 [0.06, 14.88] Yes SAM30022 1 34 1 73 0.2% 0.97 [0.06, 14.88] Yes Samanuk 1999 8 09 3 65 0.5% 2.51 [0.70, 9.06] Yes Samanuk 1999 8 09 3 65 0.5% 2.51 [0.70, 9.06] Yes Specing 1994 18 220 19 206 3.5% 0.89 [0.49, 1.64] Yes Sources 1999 26 239 40 244 7.0% 0.66 [0.39, 1.12] Yes Saterman 2006 4 246 5 238 0.0% 0.66 [0.42, 1.05] Yes Saterman 2006 4 246 5 238 0.0% 0.07 [0.21, 2.85] Yes Saterman 2006 4 246 5 238 0.0% 0.07 [0.21, 2.85] Yes Saterman 2006 4 246 5 238 0.0% 0.07 [0.21, 2.85] Yes Saterman 2006 4 246 5 238 0.0% 0.07 [0.21, 2.85] Yes Saterman 2006 4 246 5 238 0.0% 0.06 [0.78, 1.42] Unclear Saterman 2006 4 246 5 238 0.0% 0.06 [0.78, 1.42] Unclear Saterman 2006 4 246 5 238 0.0% 0.07 [0.21, 2.85] Yes Saterman 2006 4 246 5 2.38 0.0% 0.68 [0.78, 1.42] Unclear Saterman 2006 4 246 5 2.38 0.0% 0.06 [0.78, 1.42] Unclear Saterman 2006 4 246 5 2.38 0.0% 0.06 [0.78, 1.42] Unclear Saterman 2006 4 246 5 2.43 5.7% 0.62 [0.36, 1.05] Yes Saterman 2006 4 242 243 5.7% 0.62 [0.36, 1.05] Yes Saterman 2006 4 242 243 5.7% 0.62 [0.36, 1.05] Yes Saterman 2007 244 243 5.7% 0.62 [0.36, 1.05] Yes Saterman 2008 4 242 241 0.5% 1.33 [0.30, 5.87] Yes Saterman 200 34 242 241 0.5% 1.33 [0.30, 5.87] Yes Saterman 200 34 242 241 0.5% 1.33 [0.30, 5.87] Yes Saterman 200 34 242 241 0.5% 1.33 [0.30, 5.87] Yes Saterman 2007 4 242 241 0.5% 1.33 [0.30, 5.87] Yes Saterman 2007 4 242 241 0.5% 1.33 [0.30, 5.87] Yes Saterman 2007 4 242 241 0.5% 1.33 [0.30, 5.87] Yes Saterman 2007 4 242 241 0.5% 1.33 [0.30, 5.87] Yes Saterman 2007 4 242 241 0.5% 1.33 [0.30, 5.87] Yes Saterman 2007 4 242 241 0.5% 1.33 [0.30, 5.87] Yes Saterman 2007 4 242 241 0.5% 1.33 [0.30, 5.87] Yes Saterman 2007 4 242 241 0.5% 1.33 [0.30, 5.87] Yes Saterman 2007 4 242 241 0.5% 1.33 [0.30, 5.87] Yes Saterman 2007 4 242 241 0.5% 1.33 [Subtotal (95% CI)		2368		2387	48.0%			•
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	Greening 1994	18	220	19	206	3.5%	0.89 [0.48, 1.64]	Yes	
Murray 1999 29 260 35 254 6.3% $0.81[0.51, 1.28]$ Yes Bateman 2006 4 246 5 238 0.9% $0.77[0.21, 2.85]$ Yes Pauwels 1997 62 210 60 214 10.6% $1.05[0.78, 1.42]$ Unclear Van Noord 1999 16 133 15 1.35 2.7% $1.04[0.53, 2.01]$ Unclear Subtotal (95% CI) 2074 2032 45.7% $0.81[0.68, 0.95]$ Unclear Itereogeneity: Ch ^P = 12.324, df = 11 (P = 0.28); I ^P = 17% Test for overall effect: Z = 2.52 (P = 0.01) Ves Image: Character of the ch	Condemi 1999	21	221	31	216	5.6%	0.66 [0.39, 1.12]	Yes	
Bateman 2006 4 246 5 238 0.9% 0.77 [0.21, 2.85] Yes Pauwels 1997 62 210 60 214 10.6% 1.05 [0.78, 1.42] Unclear Van Noord 1999 16 139 15 135 2.7% 1.04 [0.53, 2.01] Unclear Van Noord 1999 16 139 2074 2022 45.7% 0.81 [0.68, 0.95] Total events 208 256 Heterogeneity: Chi ² = 13.24, df = 11 ($P = 0.28$); $P = 17\%$ Test for overall effect: $Z = 2.52$ ($P = 0.01$) 1.1.3 Baseline FEV1 <60% predicted SLGA6021 20 246 32 243 5.7% 0.62 [0.36, 1.05] Total events 20 32 Heterogeneity: Not applicable Test for overall effect: $Z = 1.78$ ($P = 0.07$) 1.1.4 Baseline FEV1 unclear SAM40090 4 242 3 241 0.5% 1.33 [0.30, 5.87] Total events 4 3 Heterogeneity: Not applicable Test for overall effect: $Z = 0.37$ ($P = 0.71$) 1.1.4 Baseline FEV1 unclear SAM40090 4 242 3 241 0.5% 1.33 [0.30, 5.87] Total events 4 3 Heterogeneity: Not applicable Test for overall effect: $Z = 0.37$ ($P = 0.71$) 1.1.4 Baseline FEV1 unclear SAM40090 4 242 7 3 241 0.5% 1.33 [0.30, 5.87] Total events 4 3 Heterogeneity: Not applicable Test for overall effect: $Z = 0.37$ ($P = 0.71$) 1.1.4 Gaseline FEV1 unclear SAM40090 4 242 9 241 0.5% 1.33 [0.30, 5.87] Total events 4 3 Heterogeneity: Chi ² = 24.51, df = 24 ($P = 0.43$); $P = 2\%$ Total events 491 563 Heterogeneity: Chi ² = 24.51, df = 24 ($P = 0.03$); $P = 2\%$ 1.0.1 1 10	Kelsen 1999	26	239	40	244	7.0%	0.66 [0.42, 1.05]	Yes	
Pauwels 1997 62 210 60 214 10.6% 1.05 $[0.79, 1.42]$ Unclear Van Noord 1999 16 139 15 135 2.7% 1.04 $[0.53, 2.01]$ Unclear Subtotal (95% CI) 2074 2032 45.7% 0.81 $[0.68, 0.95]$ Total events 208 256 Heterogeneity: Ch ² = 13.24, df = 11 (P = 0.28); P = 17% Test for overall effect: $Z = 2.52$ (P = 0.01) 1.1.3 Baseline FEV1 <60% predicted SLOA5021 20 246 32 243 5.7% 0.62 $[0.36, 1.05]$ Subtotal (95% CI) 246 243 5.7% 0.62 $[0.36, 1.05]$ Total events 20 32 Heterogeneity: Not applicable Test for overall effect: $Z = 1.78$ (P = 0.07) 1.1.4 Baseline FEV1 unclear SAM40090 4 242 3 241 0.5% 1.33 $[0.30, 5.87]$ Total events 4 3 Heterogeneity: Not applicable Test for overall effect: $Z = 0.37$ (P = 0.71) Total events 491 563 Heterogeneity: Ch ² = 24.51, df = 24 (P = 0.43); P = 2% Total events 491 563 Heterogeneity: Ch ² = 24.51, df = 24 (P = 0.43); P = 2% Total events 491 563 Heterogeneity: Ch ² = 24.51, df = 24 (P = 0.43); P = 2% Total events 491 563 Heterogeneity: Ch ² = 24.51, df = 24 (P = 0.43); P = 2% Total events 491 563 Heterogeneity: Ch ² = 24.51, df = 24 (P = 0.43); P = 2% Total events 491 563 Heterogeneity: Ch ² = 24.51, df = 24 (P = 0.43); P = 2% Total events 491 563 Heterogeneity: Ch ² = 24.51, df = 24 (P = 0.43); P = 2% Total events 491 563 Heterogeneity: Ch ² = 24.51, df = 24 (P = 0.43); P = 2% Total events 491 563 Heterogeneity: Ch ² = 24.51, df = 24 (P = 0.43); P = 2% Total events 491 563 Heterogeneity: Ch ² = 24.51, df = 24 (P = 0.43); P = 2% Total events 491 563 Heterogeneity: Ch ² = 24.51, df = 24 (P = 0.43); P = 2% Total events 491 563 Heterogeneity: Ch ² = 24.51, df = 24 (P = 0.43); P = 2% Total events 491 563 Heterogeneity: Ch ² = 24.51, df = 24 (P = 0.43); P = 2% Total events 491 563 Heterogeneity: Ch ² = 24.51, df = 24 (P = 0.43); P = 2% Total events 491 563 Heterogeneity: Ch ² = 24.51, df = 24 (P = 0.43); P = 2% Total events 491 563 Heterogeneity: Ch ² = 24.51, df = 24 (P = 0.43); P = 2% Total events 491 563 Heterogeneity: Ch ²	Murray 1999	29	260	35	254	6.3%	0.81 [0.51, 1.28]	Yes	
Van Noord 1999 16 139 15 135 2.7% $1.04[0.53, 2.01]$ Unclear Subtotal (95% CI) 2074 2032 45.7% $0.81[0.68, 0.95]$ Total events 208 256 Heterogeneity: Chi ² = 13.24, df = 11 (P = 0.28); P = 17% Test for overall effect: $Z = 2.52$ (P = 0.01) 1.1.3 Baseline FEV1 <60% predicted SLOA5021 20 246 32 243 5.7% $0.62[0.36, 1.05]$ Yes Subtotal (95% CI) 246 243 5.7% $0.62[0.36, 1.05]$ Yes Heterogeneity: Not applicable Test for overall effect: $Z = 1.78$ (P = 0.07) 1.1.4 Baseline FEV1 unclear SAM40090 4 242 3 241 0.5% 1.33 [0.30, 5.87] Subtotal (95% CI) 242 241 0.5% 1.33 [0.30, 5.87] Total events 4 3 Heterogeneity: Not applicable Test for overall effect: $Z = 0.37$ (P = 0.71) Total events 491 563 Heterogeneity: Chi ² = 24.51, df = 24 (P = 0.43); P = 2% Total events 491 563 Heterogeneity: Chi ² = 24.51, df = 24 (P = 0.43); P = 2% Total events 491 563	Bateman 2006	4	246	5	238	0.9%	0.77 [0.21, 2.85]	Yes	
Subtotal (95% CI) 2074 2032 45.7% 0.81 [0.68, 0.95] Total events 208 256 Heterogeneity: Chi ² = 13.24, df = 11 ($P = 0.28$); $P = 17\%$ Test for overall effect: Z = 2.52 ($P = 0.01$) 1.1.3 Baseline FEV1 <60% predicted SLGA5021 20 246 32 243 5.7% 0.62 [0.36, 1.05] Subtotal (95% CI) 246 243 5.7% 0.62 [0.36, 1.05] Total events 20 32 Heterogeneity: Not applicable Test for overall effect: Z = 1.78 ($P = 0.07$) 1.1.4 Baseline FEV1 unclear SAM40090 4 242 3 241 0.5% 1.33 [0.30, 5.87] Subtotal (95% CI) 242 241 0.5% 1.33 [0.30, 5.87] Total events 4 3 Heterogeneity: Not applicable Test for overall effect: Z = 0.37 ($P = 0.71$) Total events 491 563 Heterogeneity: Chi ² = 24.51, df = 24 ($P = 0.43$); $P = 2\%$ Total events 491 563 Heterogeneity: Chi ² = 24.51, df = 24 ($P = 0.43$); $P = 2\%$ Total events 401 0.1 10	Pauwels 1997	62	210	60	214	10.6%	1.05 [0.78, 1.42]	Unclear	+
Total events 208 256 Heterogeneity: $Chi^2 = 13.24$, $df = 11$ ($P = 0.28$); $P = 17\%$ Test for overall effect: $Z = 2.52$ ($P = 0.01$) 1.1.3 Baseline FEV1 <60% predicted SLGA5021 20 246 32 243 5.7% 0.62 [0.36, 1.05] Subtotal (95% CI) 246 243 5.7% 0.62 [0.36, 1.05] Total events 20 32 Heterogeneity: Not applicable Test for overall effect: $Z = 1.78$ ($P = 0.07$) 1.1.4 Baseline FEV1 unclear SAM40090 4 242 3 241 0.5% 1.33 [0.30, 5.87] Subtotal (95% CI) 242 241 0.5% 1.33 [0.30, 5.87] Total events 4 3 Heterogeneity: Not applicable Test for overall effect: $Z = 0.37$ ($P = 0.71$) Total events 491 563 Heterogeneity: $Chi^2 = 24.51$, $df = 24$ ($P = 0.43$); $P = 2\%$ Total events 491 563	van Noord 1999	16	139	15	135	2.7%	1.04 [0.53, 2.01]	Unclear	
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Test for overall effect: $Z = 2.52$ (P = 0.01) 1.1.3 Baseline FEV1 <60% predicted SLGA5021 20 246 32 243 5.7% 0.62 [0.36, 1.05] Yes Subtotal (95% CI) 246 243 5.7% 0.62 [0.36, 1.05] Yes Heterogeneity: Not applicable Test for overall effect: $Z = 1.78$ (P = 0.07) 1.1.4 Baseline FEV1 unclear SAM40090 4 242 3 241 0.5% 1.33 [0.30, 5.87] Yes Subtotal (95% CI) 242 241 0.5% 1.33 [0.30, 5.87] Yes Subtotal (95% CI) 242 241 0.5% 1.33 [0.30, 5.87] Yes Total events 4 3 Heterogeneity: Not applicable Test for overall effect: $Z = 0.37$ (P = 0.71) Total events 491 563 Heterogeneity: Chi ² = 24.51, df = 24 (P = 0.43); I ² = 2% Total events 491 563 Heterogeneity: Chi ² = 24.51, df = 24 (P = 0.43); I ² = 2%	Total events	208		256					
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Test for overall effect: Z = 1.78 (P = 0.07) 1.1.4 Baseline FEV1 unclear Subtotal (95% CI) 242 241 0.5% 1.33 [0.30, 5.87] Yes Subtotal (95% CI) 242 241 0.5% 1.33 [0.30, 5.87] Yes Total events 4 3 Heterogeneity: Not applicable Test for overall effect: Z = 0.37 (P = 0.71) Total events 491 563 Heterogeneity: Chi ² = 24.51, df = 24 (P = 0.43); I ² = 2% 0.01 0.1 Total events 491 563 Heterogeneity: Chi ² = 24.51, df = 24 (P = 0.43); I ² = 2% 0.01 0.1				32					
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East for overall effect 7 = 2.32 (B = 0.02) U.U1 U.1 1 10									
					= 2%				
	fest for overall effect:	Z = 2.33 (F	P = 0.0	2)					Favours LABA + ICS Favours higher IC
									. alone provide a deviding for the

Figure 3.

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

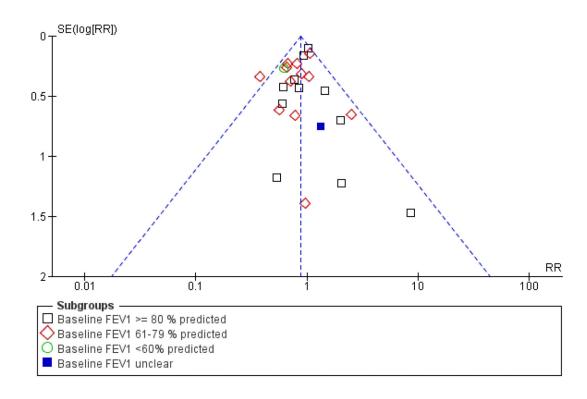


Figure 4.

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

	LABA +	ICS	Increase	dICS		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% Cl	M-H, Fixed, 95% Cl
2.1.1 Children							
LOCCS	1	17	3	22	24.6%	0.43 [0.05, 3.79]	
SAM104926	2	160	1	161	9.4%	2.01 [0.18, 21.97]	
Verberne 1998	10	60	7	60	66.0%	1.43 [0.58, 3.50]	
Subtotal (95% CI)		237		243	100.0%	1.24 [0.58, 2.66]	
Total events	13		11				
Heterogeneity: Chi ² =	1.16, df=	2 (P =	0.56); I ^z = 0)%			
Test for overall effect:	Z = 0.55 (P = 0.5	9)				
2.1.2 Adults							
	4.4	224	20	222	E 001	0.001040.074	
Baraniuk 1999	11	231	28	223	5.2%	0.38 [0.19, 0.74]	
Bateman 2006	4	246	5	238	0.9%	0.77 [0.21, 2.85]	
Bouros 1999	8	69	3	65	0.6%	2.51 [0.70, 9.06]	
Busse 2003	6	281	3	277	0.5%	1.97 [0.50, 7.80]	
Condemi 1999	21	221	31	216	5.7%	0.66 [0.39, 1.12]	
Greening 1994	18	220	19	206	3.6%	0.89 [0.48, 1.64]	
Johansson 2001	4	176	7	173	1.3%	0.56 [0.17, 1.88]	
Kelsen 1999	26	239	40	244	7.2%	0.66 [0.42, 1.05]	
Kips 2000	8	29	12	31	2.1%	0.71 [0.34, 1.49]	
Li 1999	3	13	0	16		8.50 [0.48, 151.05]	
LOCCS	7	143	8	144	1.4%	0.88 [0.33, 2.37]	
Murray 1999	29	260	35	254	6.4%	0.81 [0.51, 1.28]	
O'Byrne 2001	58	323	61	312	11.3%	0.92 [0.66, 1.27]	-
O'Byrne 2005	145	789	149	819	26.5%	1.01 [0.82, 1.24]	†
Pauwels 1997	62	210	60	214	10.8%	1.05 [0.78, 1.42]	+
SAM30022	1	34	1	33	0.2%	0.97 [0.06, 14.88]	
SAM40090	4	242	3	241	0.5%	1.33 [0.30, 5.87]	
SAS40026	5	295	8	279	1.5%	0.59 [0.20, 1.79]	
SFCF4026	12	154	16	156	2.9%	0.76 [0.37, 1.55]	
SLGA5021	20	246	32	243	5.8%	0.62 [0.36, 1.05]	
Van Noord 1999	16	139	15	135	2.8%	1.04 [0.53, 2.01]	
Vermetten 1999	8	113	14	120	2.5%	0.61 [0.26, 1.39]	
Wallin 2003	1	18	2	19	0.4%	0.53 [0.05, 5.33]	
Subtotal (95% CI)		4691		4658	100.0%	0.87 [0.78, 0.97]	•
Total events	477		552				
Heterogeneity: Chi ² =				= 4%			
Test for overall effect:	Z= 2.47 (P = 0.0	1)				
							0.02 0.1 1 10 50

0.02 0.1 1 10 50 Favours LABA + ICS Favours higher ICS

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.

Table 1

Search history

Years	Detail	
All years to April 2004	Citations i	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 $\beta 2$ 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 trials	large number of citations considered, the reasons for exclusion are provided only for published randomised controlled

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