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Addition of long-acting beta-agonists to inhaled corticosteroids for chronic asthma in children

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Abstract

Background—Long-acting β_2 -agonists (LABA) in combination with inhaled corticosteroids (ICS) are increasingly prescribed in asthmatic children.

Objectives—To compare the safety and benefit of adding LABA to ICS with the same or an increased dose of ICS in children with persistent asthma.

Search methods—We searched the Cochrane Airways Group Asthma Trials Register (May 2008).

Selection criteria—We included randomised controlled trials testing the combination of LABA and ICS versus the same or an increased dose of ICS for minimum of at least 28 days in children and adolescents with asthma. The main outcome was the rate of exacerbations requiring rescue oral steroids. Secondary outcomes included pulmonary function, symptoms, adverse events, and withdrawals.

Data collection and analysis—Studies were assessed independently by two review authors for methodological quality and data extraction. Confirmation was obtained from the trialists when possible.

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MNC: Protocol initiation & write-up; study assessment, characterisation & data extraction; write-up

FD: Protocol development; review development and write-up

TJL: Study assessment, data extraction; analysis; write-up

IG: Protocol development, write-up

DECLARATIONS OF INTEREST

In the past five years, Francine Ducharme received some research funding from GSK, MERCK, and Astra Zeneca and gave CME conferences supported by Merck Frost. M Ni Chroinin has received some research funding and given a CME lecture sponsored by Astra Zeneca and attended CME conferences supported by GSK. Toby Lasserson, Ilana Greenstone and previous authors: A Danish, H Magalinos, V Masse and X Zhang report no conflict of interest.

Main results—A total of 25 trials representing 31 control-intervention comparisons were included in the review randomising 5572 children. Most of the participants were inadequately controlled on current ICS dose. We assessed the addition of LABA to the same dose of ICS and to an increased dose of ICS:

- (1) The addition of LABA to ICS was compared to same dose ICS, namely 400 mcg/day of beclomethasone or less in 16 of the 24 studies. The mean age of participants was 10 years and males accounted for 64% of the study populations. The mean FEV₁ at baseline was 80% of predicted or above in 10 studies; FEV₁ 61% to 79% of predicted in eight studies; and unreported in the remaining study. Participants were inadequately controlled before randomisation in all but seven studies. Compared to ICS alone, the addition of LABA to ICS was not associated with a significant reduction in exacerbations requiring oral steroids (seven studies, RR 0.92 95% CI 0.60 to 1.40). Compared to ICS alone, there was a significantly greater improvement in FEV₁ with the addition of LABA (nine studies; 0.08 Litres, 95% CI 0.06 to 0.11) but no statistically significant group differences in symptom-free days, hospital admission, quality of life, use of reliever medication, and adverse events. Withdrawals occurred significantly less frequently with the addition of LABA.
- (2) A total of seven studies assessed the addition of LABA to ICS therapy compared with an increased dose of ICS randomising 1021 children. The mean age of participants was 8 years with 67% of males. The baseline mean FEV₁ was 80% of predicted or above in 2 of the 3 studies reporting this characteristic. All trials enrolled participants who were inadequately controlled on a baseline dose equivalent to 400 mcg/day of beclomethasone or less. There was no group significant difference in the risk of an exacerbation requiring oral steroids with the combination of LABA and ICS compared to a double dose of ICS (two studies, RR 1.5 95% CI 0.65 to 3.48). The increased risk of hospital admission with combination therapy was also not statistically significant (RR 2.21 95% CI 0.74 to 6.64). Compared to double dose ICS, use of LABA was associated with a significantly greater improvement in morning PEF (four studies; MD 7.55 L/min 95% CI: 3.57 to 11.53) and evening PEF L/min (three studies, MD 5.5 L/min; 95% CI 1.21 to 9.79), but there were insufficient data to aggregate data on FEV₁, symptoms, rescue reliever use, and quality of life. There was no statistically significant difference in the overall risk of all cause withdrawals (five studies; RR 0.71; 95% CI 0.42 to 1.20). There was no group difference in the risk of overall adverse effects detected. Short term growth was significantly greater in children treated with combination therapy compared to double dose ICS (two studies: MD 1.2 cm/year; 95% CI 0.72 to 1.7).

Authors' conclusions—In children with persistent asthma, the addition of LABA to ICS was not associated with a significant reduction in the rate of exacerbations requiring systemic steroids, but was superior for improving lung function compared to the same dose of ICS. Similarly, compared to a double dose ICS, the combination of LABA and ICS did not significantly increase the risk of exacerbations requiring oral steroids, but was associated with a significantly greater improvement in PEF and growth. The possibility of an increased risk of rescue oral steroids and hospital admission with LABA therapy needs to be further examined.

Medical Subject Headings (MeSH)

Adrenal Cortex Hormones [*administration & dosage; adverse effects]; Adrenergic beta-Agonists [*administration & dosage; adverse effects]; Albuterol [administration & dosage; analogs & derivatives]; Anti-Asthmatic Agents [*administration & dosage; adverse effects]; Asthma [drug therapy]; Beclomethasone [administration & dosage; adverse effects]; Drug Therapy, Combination; Ethanolamines [administration & dosage]

MeSH check words

Adolescent; Child; Female; Humans; Male

BACKGROUND

Inhaled corticosteroids (ICS) are the most effective treatment for long-term control of asthma in children (Adams 2005; Adams 2008a; Manning 2008). They are recommended as first line agent in management of childhood asthma in all national and international consensus statements. When ICS are insufficient to achieve control, various options may be considered, such as increasing the dose of inhaled corticosteroids (Adams 2008b), or adding a second drug such as a long-acting beta-2 agonist (LABA) or a leukotriene receptor antagonist (Ducharme 2006).

In adults with unsatisfactory control, international guidelines clearly favour the addition of LABA to low or moderate doses of inhaled steroids over other options such as increasing the dose of steroids or adding other agents. In children, however, recommendations regarding the dose of ICS to which LABA should be added differ markedly across national boundaries. The British Thoracic Society guidelines recommend the combination therapy at a low dose (200-400mcg /day beclomethasone equivalent, BTS 2007). In contrast, Canadian and Australian guidelines recommend the addition of LABA to a higher dose (800 mcg/day, Canadian Paediatric Asthma Consensus Guidelines; NAC Guidelines 2006). In the American guidelines no clear preference is given between adding LABA to a low dose ICS or increasing the dose ICS in children greater than 5 years of age with moderate asthma; in children with severe asthma, the addition of LABA is preferred option (NIH Publication 2007). Finally, the international GINA guidelines recommend the addition of LABA as an option, irrespective of the baseline dose of ICS (100-800 mcg/ day beclomethasone equivalent, GINA 2007). There is no formal recommendation for their use in the pre-school age group. The wide divergence of recommendations is likely to stem from the lack of solid evidence in children, which may be helped by a systematic review of the topic.

Data from paediatric clinical trials have been included in three previous meta-analyses assessing the effects of LABA. Bisgaard 2003 cautioned against the routine use of LABAs in children, since they did not offer protection against exacerbations and led to an increased risk of hospital admission. Other outcomes such as adverse effects, lung function and symptoms were not examined. More recent work has failed to detect a significant increase in the risk of exacerbations in children, although the direction of effect favoured placebo and the definition of this outcome was not consistent across the studies (OR 1.15 (95% CI 0.88

to 1.49; Walters 2007). In both Bisgaard 2003 and Walters 2007, the presence of ICS as background therapy varied between eligible trials. In 2005 we published a Cochrane review combining data from 24 adult and 10 paediatric trials (12 control-intervention comparisons), demonstrating that LABA and ICS led to a significant reduction in risk of exacerbations requiring oral steroids compared with ICS alone (Ni Chroinin 2005). With additional published and unpublished paediatric trials available, we believe that this separate review focused solely on children receiving co-treatment with ICS would shed more light on the role of LABA as an adjunct therapy to ICS in the management of children partially controlled on ICS alone.

OBJECTIVES

The objective of this review was to assess the safety and efficacy of adding a LABA to ICS in children and adolescents with asthma. We also wished to determine if the benefit of LABA was influenced by baseline severity of airway obstruction, the dose of ICS to which it was added or with which it was compared, the type of LABA used, the number of devices used to deliver combination therapy, and trial duration.

METHODS

Criteria for considering studies for this review

Types of studies—Only randomised controlled trials conducted in children, in whom a LABA was added to ICS were eligible.

Types of participants—Children aged two to 18 years with persistent asthma and having received daily ICS therapy for at least 28 days prior to study entry.

Types of interventions—LABA (salmeterol or formoterol) versus placebo administered daily for at least 28 days. The addition of LABA to ICS compared with:

1. the same ICS dose or
2. an increased dose of inhaled corticosteroids.

Studies where maintenance ICS therapy was interrupted for the purposes of run-in were not eligible for the review. Other co-interventions such as xanthines, anticholinergics and other antiasthmatic medications were permitted, provided that the dose remained unchanged throughout the study. Inhaled short-acting β_2 -agonists (SABA) and short courses of systemic steroids were allowed as rescue medications.

Types of outcome measures

Primary outcomes: The primary outcome was the number of asthma exacerbations of moderate intensity, that is, requiring a short course of systemic corticosteroids.

Secondary outcomes

1. Admissions to hospital
2. Pulmonary function test (morning and evening peak flow; FEV1)

3. Symptoms
4. Quality of life scores
5. Use of rescue SABA
6. Changes in measures of inflammation such as serum eosinophil cationic protein and sputum eosinophils.
7. Rates of clinical and biochemical adverse effects were examined.
8. Any adverse effect including growth, adrenal suppression, and bone mineral. A suite of related Cochrane reviews in consider serious adverse effects (Cates 2008a; Cates 2009a; Cates 2009b).

Search methods for identification of studies

As authors of previous related Cochrane reviews (Ni Chroinin 2005; Greenstone 2005) in adults and children, we had reviewed the literature until April 2004. For the present review, we updated the search to May 2008 using the following search strategies:

Electronic searches—An electronic literature search was carried out in the Cochrane Airways Group Specialised Register of asthma trials which is derived from systematic searches of bibliographic databases including the Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE, EMBASE and CINAHL and handsearching of respiratory journals and meeting abstracts. This Register also contains a variety of studies published in foreign languages. We did not exclude trials on the basis of language. The Register was searched using the following terms:

((((beta* and agonist*) and long-acting or “long-acting”) or ((beta* and adrenergic*) and long-acting or “long-acting”) or (bronchodilat* and long-acting or “long-acting”) or (salmeterol or formoterol or advair or symbicort)) and (((steroid* or glucocorticoid* or corticosteroid*) and inhal*) or (budesonide or beclomethasone or fluticasone or triamcinolone or flunisolide))).

This search was then limited with the text word terms (child* or paediat* or pediat* or adolesc* or infan* or toddler* or bab* or young* or preschool* or “pre school*” or pre-school* or newborn* or “new born*” or new-born* or neo-nat* or neonat*)

Searching other resources—Reference lists of all included studies and reviews were checked to identify potentially relevant citations.

We searched manufacturers’ and clinical trial websites ([Glaxo Smith Kline clinical trials website](#);

[AstraZeneca clinical trials website](#); [Novartis clinical trial results website](#); [Clinical Study Results](#)), to identify other published or unpublished study data.

Data collection and analysis

Selection of studies—From the title, abstract or descriptors, the review authors (MNC & TL) independently reviewed the literature searches. All studies that were not randomised controlled trials or that clearly did not fit the inclusion criteria were excluded. All other citations were reviewed independently in full text by two review authors to assess eligibility.

Data extraction and management—Data for the trials were independently extracted by two review authors (MNC & TL) in Excel spreadsheets and entered into the Cochrane Collaboration software program Review Manager. Where necessary expansions of graphic reproductions and estimations from other data presented in the paper were performed. Primary authors or sponsors were requested to confirm the methodology and data extraction and were asked to provide additional information as needed.

We recorded as a ‘User defined order’:

1. the mean daily dose of inhaled corticosteroids in trials where both the intervention and control groups used the same dose of inhaled steroid and
2. the dose difference between the two groups in studies comparing the addition of LABA to ICS with an increased dose of inhaled corticosteroid. Both values were reported in chlorofluorocarbon (CFC)-propelled beclomethasone-equivalents, where 1 µg of beclomethasone dipropionate equates to 1 µg of budesonide and 0.5 µg of fluticasone propionate (NIH Publication 2007). All doses of inhaled medications were reported as ex-valve, rather than ex-inhaler, values.

Assessment of risk of bias in included studies—We assessed the risk of bias according to five domains:

1. Allocation generation & concealment
2. Blinding
3. Handling of missing data
4. Selective reporting bias
5. Information on the proportion of the screened population that meet the eligibility criteria.

For each domain we judged the risk of bias as being low (‘Yes’), unclear (‘Unclear’), and high (‘No’), in line with recommendations from the Cochrane Handbook.

Unit of analysis issues—We excluded crossover studies from contributing data to dichotomous measurements of exacerbations since we used analyses that assume measurements are taken from independent samples.

Dealing with missing data—We contacted study investigators (or study sponsors where trials had pharmaceutical company sponsorship) directly to obtain confirmation of the methodology and to obtain data missing from the original trial report. We primarily sought data on the outcomes relating to exacerbations (oral steroid use and admission to hospital).

Assessment of heterogeneity—Homogeneity of effect sizes between pooled studies was examined with the I^2 statistic using 25% or more as a cut-off for exploring possible causes of heterogeneity (Higgins 2003). In the absence of heterogeneity, the fixed-effect model was used, otherwise the DerSimonian and Laird random-effects model (DerSimonian 1986) was applied to the summary estimates. Results of the fixed effects model have been reported unless otherwise stated in the text.

Assessment of reporting biases—Funnel plots were used to check for the indications of possible publication bias.

Data synthesis—Treatment effects for dichotomous variables were calculated as a pooled relative risk (RR) with 95% confidence intervals (CI). For continuous outcomes, such as pulmonary function tests, pooled statistics were calculated as weighted mean differences (MD) or standardized mean differences (SMD) if results were on different scales, and reported with 95% confidence intervals. When standard deviations were not presented but could be estimated from an effect estimate and either confidence intervals, standard error, or P-value, we combined the mean differences with the generic inverse variance function in Review Manager (GIV).

Equivalence was assumed if the relative risk estimate and its confidence interval were between 0.9 and 1.1. Numbers needed to treat (NNT) were derived from the pooled Risk Ratios using [Visual Rx](#).

The analysis examined two main comparisons namely the combination of LABA and ICS to:

1. A similar dose of ICS with placebo, representing step 2 of the BTS guidelines.
2. An increased dose of ICS with placebo, representing step 3 of the BTS guidelines.

When a trial tested more than two arms, additional control-intervention group comparisons were considered for this review. If the same group was used twice as a comparator in a three-arm study, the number of participants in the group used twice was halved to avoid over-representation. For event rates, the denominator was also halved in the control group. (Zimmerman 2004b; Zimmerman 2004a; Pohunek 2006a; Pohunek 2006b; SD 039 0725a; SD 039 0725b; Morice 2008a; Morice 2008b).

Subgroup analysis and investigation of heterogeneity—Subgroup analyses were planned to explore possible reasons for heterogeneity and, in the absence of heterogeneity, to identify potential effect modifiers where the magnitude of benefit may vary according to baseline characteristics. The following *a priori* defined subgroups were examined:

1. Magnitude of airway obstruction at baseline as determined by the mean percent predicted forced expiratory volume in one second (FEV_1): classified as mild (80% of predicted or more), moderate (61 to 79% of predicted) or severe (60% of predicted or less) (GINA 2007).
2. Mean dose (ex-valve) of ICS in comparison 1 when comparing LABA + ICS versus placebo + ICS and the dose difference in comparison 2 when comparing

LABA + ICS versus increased dose of ICS, both reported in CFC-propelled beclomethasone-equivalent doses ($\mu\text{g}/\text{day}$) and portrayed as the user-defined number

3. Usual versus higher than usual dose (reported as ex-valve in μg) of the LABA (salmeterol or formoterol).
4. Type of LABA (salmeterol versus formoterol).
5. Use of one or two devices to deliver the combination of ICS and LABA.
6. Trial duration comparing trials 16 weeks to those 24 weeks.

Sensitivity analysis—Sensitivity analyses were performed to assess whether the results of our primary outcome was sensitive to blinding and completeness of follow-up, publication status, and funding.

RESULTS

Description of studies

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

Results of the search

See Figure 1 for an overview of the literature search results, their assessment and inclusion of studies in the review. Updated electronic and additional handsearches from February 2004 to May 2008 retrieved 337 additional citations. We included 15 new trials, giving a total of 25 eligible trials.

Six of the trials generated an additional control-intervention comparison. Three trials (representing six control-intervention comparisons) assessed two forms of additive therapy (ICS and LABA via one inhaler or via two inhaler devices against one dose of ICS): Morice 2008a; Morice 2008b; Pohunek 2006a; Pohunek 2006b; SD 039 0725a; SD 039 0725b. Three trials (representing six control-intervention comparisons) assessed one form of ICS and LABA against two doses of ICS (SAM40012a; SAM40012b; Verberne 1998a; Verberne 1998b; Zimmerman 2004a; Zimmerman 2004b). The review therefore lists 31 control-intervention comparisons.

Included studies

The trials randomized 5,572 children. Sixteen were available as full text publications and nine were unpublished reports of trials accessed from pharmaceutical company trials registries.

The majority of studies were funded by producers of both LABA and ICS inhalers: ten were supported by GSK; nine by Astra Zeneca; one by Allen & Hanburys, a subsidiary of GSK in the United Kingdom (Russell 1995). Only two were independently supported by a charitable organization (Langton Hewer 1995; Stelmach 2007), and three failed to identify the source of funding (Heuck 2000; Teper 2005; Zimmerman 2004a; Zimmerman 2004b).

The studies were classified in to one of two comparisons according to the research question addressed. In accordance to with therapeutic management recommended by GINA 2007 and BTS 2007, patients on ICS alone were considered as receiving step 2 therapy. The comparison of the addition of LABA versus placebo to the same ICS dose, were referred to **Step 3 versus Step 2** comparison (24 control-intervention comparisons). Comparisons testing the combination of LABA and ICS to a double dose of the ICS used before randomisation are hereafter referred to a **Step 3 versus Step 3** comparison (seven control-intervention comparisons). Bisgaard 2006 examined the addition of LABA to a lower dose of ICS (BDP 100mcg) than has been advocated by international guidelines as Step 3, and was included in the Step 3/Step 3 comparison.

We describe hereafter the characteristics of the studies which contribute outcome data to one or more comparisons in the review. Full study description of each eligible study see Characteristics of included studies.

Long-acting beta β 2 agonist + inhaled corticosteroid versus same dose of inhaled corticosteroid as used prior to randomisation (Step 3/Step 2)—Twenty-four control-intervention comparisons randomising 4,625 children assessed the addition of LABA versus placebo with the same dose of ICS in the control group (Akpınarli 1999; Langton Hewer 1995; Meijer 1995; Morice 2008a; Morice 2008b; Pohunek 2006a; Pohunek 2006b; Russell 1995; SAM40012a; Malone 2005; SD 039 0714, SD 039 0718; SD 039 0719; SD 039 0725a; SD 039 0725b; SFA100314; SFA100316; Simons 1997; Stelmach 2007; Tal 2002; Teper 2005; Verberne 1998a; Zimmerman 2004b and Zimmerman 2004a).

Participants—The mean age of participants was 10 years and males accounted for 64% of the study populations. Mean FEV₁ % predicted at baseline was 80% predicted or above) in 10 control-intervention comparisons (Langton Hewer 1995; Malone 2005; Meijer 1995; Pohunek 2006a; Pohunek 2006b; SD 039 0718; SD 039 0719; Simons 1997; Teper 2005; Verberne 1998a); FEV₁ 61% to 79% of predicted) in eight control-intervention comparisons Akpınarli 1999; Russell 1995, SD 039 0714, SD 039 0725a; SD 039 0725b; Tal 2002; Zimmerman 2004b; Zimmerman 2004a) and unreported in the remaining studies. Participants were inadequately controlled before randomisation in all but five studies where they were described as well controlled (Meijer 1995; Pohunek 2006a; Pohunek 2006b; Simons 1997) or where control was unreported (SD 039 0725a; SD 039 0725b; SFA100314; SFA100316; Teper 2005).

Interventions—Salmeterol was assessed in 10, and formoterol in 14, control-intervention comparisons. All but one comparison tested the usual recommended dose of the long-acting β 2-agonist (that is, salmeterol 50 μ g twice daily, formoterol 6 or 12 μ g twice daily); in Langton Hewer 1995, salmeterol 100 bid was used. The dose of inhaled steroid (BDP equivalent) was 200mcg/d in four studies (SD 039 0718; SD 039 0725a; SD 039 0725b; Stelmach 2007); 400 mcg/day in 11 (46%) control-intervention comparisons (Morice 2008a; Morice 2008b; Pohunek 2006a; Pohunek 2006b; SAM40012a; SFA100314; SFA100316; Malone 2005; SD 039 0714; Tal 2002; Verberne 1998a) 500mcg/day was used in two studies (Meijer 1995; Teper 2005); 800mcg in SD 039 0719 and an unspecified/varied dose

in six studies (Akpınarli 1999; Langton Hewer 1995; Russell 1995; Simons 1997; Zimmerman 2004a; Zimmerman 2004b).

Twelve (50%) control-intervention comparisons assessed the combination of LABA and ICS in a single device, the remainder assessed the efficacy and safety of a LABA administered separately to ICS.

Trial duration varied from eight weeks or less in six studies (Akpınarli 1999; Simons 1997; Langton Hewer 1995; SFA100314; SFA100316; Stelmach 2007), 12-16 weeks in 14 control-intervention comparisons (Meijer 1995; Morice 2008a; Morice 2008b; Pohunek 2006a; Pohunek 2006b; Russell 1995; Malone 2005; SD 039 0714; SD 039 0718; SD 039 0725a; SD 039 0725b; Tal 2002; Zimmerman 2004b; Zimmerman 2004a), 24-26 weeks in two studies (SAM40012a; SD 039 0719) and one year in two studies (Teper 2005; Verberne 1998a).

Although co-intervention with other prophylactic medications was permitted, trial protocols stipulated that their doses should remain unchanged throughout. The proportion of patients on additional therapy was not consistently reported. Permitted drugs included systemic steroids, anticholinergics, and xanthines (Langton Hewer 1995), immunotherapy (Zimmerman 2004b; Zimmerman 2004a), unspecified agents (Russell 1995). Other preventative medication were not permitted in the other studies except for Teper 2005, where this was unspecified. Rescue medications such as inhaled short-acting β_2 -agonists and systemic steroids were permitted in all the studies.

Outcomes—The primary outcome of this review is the proportion of participants who experienced exacerbations requiring systemic steroids. This was available for eight studies. Where data were not reported, or were only described in a format we could not use directly, we requested study sponsors to provide further information. Our requests for data on exacerbations requiring rescue oral steroids for Morice 2008a; Morice 2008b; Pohunek 2006a; Pohunek 2006b; SD 039 0714; SD 039 0718; SD 039 0719; SD 039 0725a; SD 039 0725b; Stelmach 2007 have not been successful.

Hospital admission data were available for six studies. A measurement of lung function was reported in all studies. Symptoms were reported in all studies except for (SD 039 0714; Simons 1997). Data on rescue β_2 -agonist were available for all but one study (Simons 1997). Withdrawals were reported in all but three studies (Akpınarli 1999; Meijer 1995; Teper 2005). Adverse events were reported in all studies.

Long-acting beta β_2 agonist + Inhaled corticosteroid versus increased dose of inhaled corticosteroid (Step 3/Step3)—A total of seven studies assessed the addition of LABA versus placebo to ICS therapy with increased dose of ICS in the control group (Bisgaard 2006; Heuck 2000; Ortega-Cisneros 1998; SAM40012b; SAM40100; SAM104926 and Verberne 1998b). One study did not contribute data (Ortega-Cisneros 1998). The studies randomised 1048 children.

Participants—The mean age of participants was 10 years with 77% of males. Baseline airway obstruction was reported in three of the six studies (SAM104926: 102%; Verberne 1998b: 87%; Bisgaard 2006: 75%). Heuck 2000 recruited children with mild asthma; however, the remaining trials recruited participants whose asthma was inadequately controlled asthma at the time of enrolment on inhaled steroids.

Interventions—Salmeterol and formoterol were studied in four and three studies respectively. All of the comparisons tested the usual recommended dose of the long-acting β_2 -agonist (i.e. salmeterol 50 μg twice daily, formoterol 6 or 12 μg twice daily). Intervention groups in four studies received BDP equivalent doses of 400 mcg/day (SAM40012b; SAM104926; SAM40100; Verberne 1998b). BDP at 100mcg/d was used in Bisgaard 2006 and 200mcg/day was used in Heuck 2000. The respective control groups received double the dose of inhaled steroid administered as the intervention group dose. Four studies assessed LABA and ICS as a single inhaler administration (Bisgaard 2006; SAM40012b; SAM40100; SAM104926).

Study duration was 6 weeks in SAM40100, 12-16 weeks in three studies (Bisgaard 2006; Heuck 2000; SAM104926), 24 weeks in one comparison (SAM40012b), and one year for the one (Verberne 1998b).

All studies recruited children who were taking an inhaled steroid at baseline. Rescue medications such as inhaled short-acting β_2 -agonists and systemic steroids were permitted in all the trials.

Outcomes—Data on oral steroid exacerbations were available from three studies (Heuck 2000; SAM104926; Verberne 1998b). Since Heuck 2000 was a crossover study however, we were not able to combine dichotomous data from this with the other trials. Where data were not reported, or were described for an undefined exacerbation or composite of types of exacerbations, we requested study sponsors to provide further information. Our requests for data on exacerbations requiring rescue oral steroids from study sponsors for Bisgaard 2006; SAM40012b; SAM40100 have not been successful.

Hospital admission data were available for two studies. Lung function outcomes were available for all studies. Data on symptoms, rescue β_2 -agonist use, adverse events and withdrawals were reported in all studies. Two studies provided data on growth (Bisgaard 2006, Verberne 1998b).

Excluded studies

Details of 63 studies which did not meet the eligibility criteria of our review are given in Characteristics of excluded studies (this number is drawn from all years searches to May 2008 across this review, Greenstone 2005 and Ni Chroinin 2005).

Risk of bias in included studies

An overview of judgements on domains relating to the risk of bias is provided in Figure 2. We summarise our findings below.

Verification of study details with study authors was obtained for six control-intervention comparisons (Pohunek 2006a; Pohunek 2006b; Russell 1995; Simons 1997; Verberne 1998a; Verberne 1998b). Information on the design of GSK-sponsored studies was provided in correspondence (Appendix 1).

Allocation—In 19 studies randomisation procedures were adequate in reducing the risk of group imbalances at baseline; in the remaining 12 studies this was unclear.

Blinding—Blinding of intervention was maintained with double-dummy designs, or the use of identical inhaler devices in 29 studies. Two studies had an open-label design; one study primarily designed to assess safety outcomes (SD 039 0719), the other study did not contribute any numerical outcome data (Ortega-Cisneros 1998).

Incomplete outcome data—There was a lack of information available on the definition of intention to treat principles across the studies. Our judgments of this aspect of the studies reflect uncertainty over the reliability of the stated methods.

Selective reporting—The availability of our pre-specified primary outcome, patients with exacerbations requiring rescue systemic steroids, from the reports of trials was limited. This is partly explained by different definitions of exacerbation used by investigators across the studies. Despite extensive efforts to obtain data for our primary outcome we have only a limited amount of data available for analysis. We remain uncertain as to whether data for this end-point were collected in 10 studies (Langton Hewer 1995; Meijer 1995; Ortega-Cisneros 1998; Pohunek 2006a; Pohunek 2006b; SAM104926; SAM40100; Stelmach 2007; Tal 2002; Teper 2005).

Effects of interventions

Long-acting beta β 2 agonist + inhaled corticosteroid versus same dose of inhaled corticosteroid (Step 3 versus Step 2)

Primary outcome: There was no statistically significant difference in the risk of exacerbations requiring systemic corticosteroids between treatments (seven studies; RR 0.92 95% CI 0.60 to 1.40, N = 1,088; Figure 3).

Subgroup analysis: Since the number of studies was low, together with inconsistent reporting of characteristics, the impact of the baseline severity of airway obstruction, baseline dose of ICS, type of LABA, and trial duration on the magnitude of effect could not be examined.

Sensitivity analysis: With all the studies being double-dummy or used identical inhaler devices, sensitivity analysis on the quality of blinding was not done. The removal of two studies where follow-up of randomized patients was at a high risk of bias gave a similar effect size to the primary analysis (RR 0.99 95% CI 0.53 to 1.85). Removing three studies where data were available on request, and not from full text sources, gave a pooled result of RR 0.9 (0.57 to 1.42). All studies were funded by manufacturers of the products.

Secondary outcomes

Hospital admission, serious adverse events & withdrawal: There was no statistically significant difference in exacerbations requiring admission to hospital (five studies, RR 1.65 95% CI 0.83 to 3.25, Figure 4), serious adverse events (seventeen studies, RR 1.16 95% CI 0.73, 1.85; Analysis 1.3), withdrawals due to poor asthma control (six studies, RR 0.69; 95% CI: 0.34 to 1.4; Analysis 1.5). Withdrawal due to any reason was lower with LABA compared to placebo (21 studies, RR 0.79 95% CI 0.67 to 0.93; Analysis 1.4).

Lung function: The addition of LABA to ICS provided significantly greater improvement from baseline in lung function compared to using placebo and ICS. This was true, irrespective of whether the group differences were reported for FEV₁ as change in litres (nine studies; 0.08 Litres, 95% CI 0.06 to 0.11, random-effects model; Analysis 1.8), change in % predicted (2.35% 95% CI 0.07 to 4.64; Analysis 1.9) in % predicted at endpoint (3.79%; 95% CI 1.99 to 5.60; Analysis 1.10), as change in morning peak expiratory flow (14 studies; MD 10.38 L/min, 95% CI 8.23, 12.52, random-effects model; Analysis 1.14) or evening peak expiratory flow, (11 studies, MD 9.37 L/min, 95% CI 6.96 to 11.79; Analysis 1.17). The severity of airway obstruction at baseline had no apparent effect of the magnitude of improvement in lung function when assessed using morning PEF ($P=0.647$). Duration of intervention did not affect the magnitude of improvement in FEV₁ over time (Analysis 1.11). The favourable effect of LABA was sustained from 6 to 24 weeks, which did not support the presence of tachyphylaxis. The studies contributing data to lung function endpoints recruited children with mild to moderate airway obstruction, with a range of lung function at baseline and examined the effects of both salmeterol and formoterol, given in conjunction with a range of doses of ICS.

Symptoms, rescue beta-agonist use & quality of life: The addition of LABA did not result in significant group differences for the following outcomes:

Change in mean symptom scores (four studies, SMD -0.04; 95% CI -0.16 to 0.08; Analysis 1.22).

% symptom-free days as end of treatment values (outcome 01.24; two studies, WMD 0.07; 95% CI -0.14 to 0.27; Analysis 1.27). Change in symptom-free days (three studies WMD 1.30%; 95% CI -3.12 to 5.71; Analysis 1.26).

Change in daytime use of rescue short-acting β_2 -agonists (five studies, WMD -0.07 puffs/day, 95% CI -0.14 to 0.01; Analysis 1.20).

% days without relief medication use (three studies, WMD -0.56%; 95% CI -2.84 to 1.73; Analysis 1.21).

Asthma quality of life questionnaire scores (PAQLQ; ten studies, WMD 0.03; 95% CI -0.04 to 0.11; Analysis 1.29).

There was an insufficient number of studies to combine data on other outcomes relating to the change in number of night time rescue inhalations (Analysis 1.23), change in night time

awakenings (Analysis 1.24), % nights with awakening (Analysis 1.25), % symptom-free nights (Analysis 1.28), and non-specific cardiovascular events (Analysis 1.35).

Tolerability: There was no statistically significant difference in the risk of overall adverse effects (15 studies, RR 1.04; 95% CI 0.98 to 1.10; Analysis 1.30), reaching our *a priori* defined criteria for equivalence. Specifically, there was no significant group difference in the risk of oral candidiasis (two studies; RR 3.78, 95% CI 0.63, 22.75; Analysis 1.32); tremor (two studies; RR 3.07; 95% CI 0.38, 25.05; Analysis 1.33), palpitations (two studies; RR 0.4 95% CI: 0.05 to 3.25; Analysis 1.34), and headache (14 studies, RR 1.10 95% CI 0.90 to 1.33; Analysis 1.31). The large confidence interval for specific adverse events, due to the small number of reporting trials, rules out total reassurance.

Although the effect on growth could not be aggregated because only one study documented this outcome (Verberne 1998a), there was no statistically significant group difference in the growth velocity over 52 weeks in prepubertal children (mean age 10-11 years) comparing BDP 400 mcg + Salmeterol to BDP 400 mcg alone (5.1cm versus 4.5 cm respectively). No studies reported deaths. The risk of withdrawals due to adverse effects was not significantly different between groups (18 studies, RR 0.78 95% CI 0.52 to 1.19; Analysis 1.7).

Long-acting β_2 agonist and inhaled corticosteroid versus increased dose of inhaled corticosteroids (Step 3 versus Step3)—Six studies contributed data to outcomes under this comparison (Bisgaard 2006; Heuck 2000; SAM40012b; SAM104926; SAM40100; Verberne 1998b).

Primary outcome: Despite correspondence with study sponsors to obtain data on exacerbations requiring rescue oral steroids, data was obtained from only two studies SAM104926; Verberne 1998b. There was no significant group difference in the risk of patients having an exacerbation requiring oral steroids between LABA+ICS and higher dose ICS (RR 1.5 95% CI 0.65 to 3.48, two studies, N = 441 Figure 5).

Secondary outcomes: There was no significant group difference in the risk of exacerbations requiring hospitalisation (four studies; RR 2.21 95% CI 0.74 to 6.64, Figure 6), or the risk of serious adverse events (RR 1.45 95% CI 0.63 to 3.33, Analysis 2.3). There was no statistically significant difference in the overall risk of all cause withdrawals (five studies; RR 0.71; 95% CI 0.42 to 1.20, Analysis 2.4).

The addition of LABA to ICS was led to greater improvement from baseline in the change in morning PEF (four studies; MD 7.55 L/min 95% CI: 3.57 to 11.53, Analysis 2.10), evening PEF L/min (three studies, MD 5.5 L/min; 95% CI 1.21 to 9.79, Analysis 2.11). Change from baseline in FEV1 was not statistically significant between treatment options (2 trials, MD 0.01 L, 95% CI -0.03, 0.05) (Analysis 2.7). There was insufficient data to pool other lung function data.

There were insufficient studies to aggregate other data related to symptoms including number of daytime rescue inhalations, number of nighttime awakenings, daytime symptoms, and nighttime symptoms.

There was insufficient number of trials to aggregate data on inflammatory mediators.

There was no statistically significant difference in the risk of overall adverse effects: four studies; RR 1.05 95% CI 0.90 to 1.23, Analysis 2.15, failing to meet our *a priori* criteria for equivalence. The relative risk of headache (three studies; RR 1.37 95% CI 0.98 to 1.90; Analysis 1.31), or withdrawal due to adverse effects (two studies; RR 1.44 95% CI 0.25 to 8.42, Analysis 2.5) did not reach statistically significant differences. Growth over one year was measured in two studies (Verberne 1998b; Bisgaard 2006); the findings favoured LABA-treated children by an average of (1.2 cm/year 95% CI 0.72 to 1.7, Analysis 2.17).

DISCUSSION

In school-aged children insufficiently controlled on inhaled corticosteroids (ICS), there is no statistically significant benefit of adding long-acting beta2-agonist (LABA) to ICS compared to using the same or an increased dose of ICS for preventing exacerbations requiring systemic steroids. Lung function endpoints consistently favoured the addition of LABA to ICS therapy, whether compared to the same dose or increased dose ICS. Irrespective of the intervention compared to the combination of LABA and ICS, it was not possible to identify the characteristics of patients (age, severity of airway obstruction, duration of disease) or the characteristics of the intervention (ICS dose, duration of treatment) associated with greatest benefit. The addition of LABA to ICS did not result in significantly greater improvement in symptoms or reduction in the use of rescue β_2 -agonist (SABA) compared with the same dose of ICS, and there were insufficient data to assess these outcomes comparing LABA with an increased ICS dose. With one notable exception, there was no statistically significant group differences in reported adverse events, but the wide confidence interval for most outcomes preclude reassurance. It was noteworthy that the combination of LABA and ICS lead to a greater gain in linear growth than an increased dose of ICS by 300 to 400 mcg/day. Moreover, while not statistically significant, there was also a trend towards a more than two-fold increase in the risk of exacerbations requiring systemic steroids and hospital admissions respectively, in children treated with combination therapy, compared with a double dose of ICS; the possibility of increased risks of such exacerbations on combination therapy will need to be tested in future trials.

The lack of an effect of combination therapy on exacerbations requiring systemic steroids when used as step 3 compared to same dose of ICS (step 2) is concordant with findings of Bisgaard 2003 and Walters 2007. We must interpret these findings in view of the fact that in our review most data were derived from school-aged children with normal or near normal lung function; they were predominantly treated with ICS and salmeterol delivered in separate devices, and the dose of maintenance ICS varied across the studies. One may anticipate different results in more severe patients, treated for longer, although this is not suggested by the subgroup analysis of children with moderate (RR 0.89 95% CI 0.48 to 1.64) versus mild (RR 0.87 95% CI 0.47 to 1.64) airway obstruction.

There are some aspects of our findings which contrast with estimates derived from our prior systematic review of adult trials. Indeed, when compared with a similar dose of ICS, the addition of LABA to ICS reduces by 20% the risk of adults with exacerbations requiring

systemic steroids (RR 0.80; 95% CI 0.73 to 0.89; Ni Chroinin 2005). This was accompanied by a notably greater improvement in lung function (170 mL in FEV1) and symptom-free days (+ 17%) and a modest reduction in the use of rescue SABA (−0.7 puffs/days). In this paediatric review, other than an improvement in lung function, the addition of LABA to ICS did not result in improvements in clinical outcomes. One might argue that considering the smaller lung volumes in children, the observed 80mL greater improvement in FEV1 associated with the addition of LABA to ICS in children may be of clinical importance, similar perhaps to that observed in adults. Yet, the improvement in lung function appears to contradict the lack of protection for exacerbations. This disparity may be due to a more rapid effect of LABA on lung function, more easily detectable in studies of short duration, whereas a longer period of follow-up may be required to detect an effect on exacerbations, particularly in children with normal or near normal lung function. In view of the requirement for significant reversibility with SABA for study eligibility, the observed improvement in FEV1 may also be both expected and specific to these patients, and may not be generalisable to other patients. Hence the importance of other outcomes to judge the benefit of LABA, which unfortunately were not observed in the studies. While the absence of a significant group difference in other outcomes may be due to patient characteristics (age, severity of airway obstruction, duration of asthma) or study design (ICS dose, duration of treatment, reported outcomes and power), the aggregation of the best available evidence provides little data to support the addition of LABA to ICS as a step 3 approach, let alone enables us to identify whom and at which dose this approach may be most effective.

With regard to the second comparison in our review (LABA and ICS versus a higher dose of ICS), our findings differ from those of an ongoing update of a Cochrane review of studies in adults (personal communication Ducharme et al), which demonstrates a significant reduction in the risk of patients with exacerbations requiring rescue systemic steroids.

Disappointingly, despite the identification of six studies, only two provided data for the primary outcome under this comparison. A modest improvement (<7 L/min) in morning and evening PEF, but not in FEV1, was associated with the use of LABA compared to a higher ICS dose. Insufficient reporting prevented the aggregation of other outcomes. However, the trends toward an increased risk of exacerbations requiring systemic steroids and admission and serious adverse effects with combination therapy is of concern. Is it possible that ongoing inflammation associated with the use of a lower dose of ICS or tachyphylaxis associated with the prolonged use of LABA may be associated with more severe exacerbations with combination therapy? These concerns call for urgent trials to clarify these observations. Meanwhile, the available data are also insufficient to recommend the preference of any given step 3 strategy over any other. One must weigh the greater linear growth and modest improvement in PEF against the possible but unproven increased risk of increased severity of exacerbations associated with combination therapy.

There was no group difference in adverse effects or withdrawals due to adverse effects when the combination of LABA and ICS was compared to either step 2 or step 3 strategy. Of note, side effects were scarcely reported in the short-term trials and there was a paucity of long-term studies. Moreover, while an increased dose of inhaled corticosteroids calls for the assessment of growth, adrenal function and bone mineralization in children, no trial reported data that could be aggregated on adrenal function and bone mineralization. Growth was

examined in only two studies examining the addition of LABA to 400 mcg versus 800mcg of BDP (Verberne 1998b) and to 100 mcg versus 400 mcg of Budesonide (Bisgaard 2006), a differential of 300 to 400 mcg of BDP-equivalent. The observed reduction in growth averaging 1.2 cm/year is in line with the documented decrease in linear growth associated with 400 mcg/day of BDP (Sharek 1999); the data may also indicate a dose-response relationship with inhaled steroids. Any apparent benefit of doubling the dose ICS should be weighed against the possible impact on growth compared to other therapeutic regimes, and deserves careful evaluation.

Although we have managed to identify a number of unpublished studies, we have had only limited success in obtaining usable data for our primary outcome. We successfully obtained data for exacerbations requiring rescue systemic steroids and for hospital admissions for a small number of trials from a recent meta-analysis of GSK sponsored trials (Bateman 2008). The availability of data in study reports available as downloads from pharmaceutical company trial results registries was poor. Moreover, the limited response from study authors or sponsors to our requests for providing data contributed to the lack of precision of, and possible bias in, our main outcome. At the time of writing, we are still awaiting the response to requests for data on exacerbations requiring rescue oral steroids from study sponsors for: Bisgaard 2006; SAM104926; SAM40012a; SAM40012b; SAM40100; SD 039 0714; SD 039 0718; SD 039 0719; SD 039 0725a; SD 039 0725b; Zimmerman 2004a; Zimmerman 2004b. These studies represent 52% of the children randomised.

AUTHORS' CONCLUSIONS

Implications for practice

There is insufficient evidence at present to firmly support the use of LABA as adjunct therapy to ICS as a step 3 strategy to reduce the risk of asthma exacerbations requiring steroids, as compared to using the same dose of ICS or an increase in the dose of ICS. The wide confidence intervals do not rule out a superior effect of either treatment; however the trend for an increased risk of exacerbations requiring systemic steroids, hospital admission, and serious adverse health event associated with combination therapy compared with an increased dose of ICS is of some concern, and indicates that trials are urgently required to address this issue. There is clear evidence that stepping up therapy with the addition of LABA improves lung function beyond that observed with remaining on ICS as step 2 strategy, with no apparent effect on symptoms and use of rescue β_2 -agonists. Significant improvements with LABA in morning PEF over increased dose of ICS have not been associated with improvements in other outcomes and more work is a priority in this area. The apparent reduction in growth associated with use of 400 to 800 mcg/day of BDP-equivalent raises concern if high dose BDP or BUD are considered.

Implications for research

Future trials should aim for the following characteristics:

Population

There urgently needs to be a large study in children with more severe asthma than those recruited to the trials in this review. Stratification according to age, degree of airway obstruction (i.e. baseline FEV1), and the inclusion of younger, pre-school aged children should feature in the design of such trials. It should also include those with a clinical diagnosis of asthma who do not necessarily have a positive bronchodilator response which would then be more generalisable to the general paediatric asthma population.

Interventions

Future interventions should examine combination therapy delivered using a single inhaler (combining LABA and ICS) to avoid use of LABA as monotherapy. Interventions may include head-to-head comparisons of salmeterol versus formoterol, combined with low or moderate dose inhaled steroids, as once versus twice daily regimen. The control intervention should include an increased dose of inhaled corticosteroids (step 3) and a similar dose ICS (step 2).

Design

1. Double blinding, adequate randomisation and complete reporting of withdrawals and dropouts with an explicit definition of the intention-to-treat population analysed.
2. Intervention period of 24 weeks or more to properly assess the impact on exacerbations requiring systemic corticosteroids, and those resulting in hospital admission as well as adverse health events (growth, adrenal function, bone mineralization, serious adverse health events).
3. Clear reporting of the per cent (and reasons) of non-eligibility of approached patients and of those enrolled in the run-in period are required as inadequate reporting of the selected population results in difficulty in identifying to whom the results can be generalized.
4. Complete reporting of continuous (denominators, mean change and mean standard deviation of change) and dichotomous (denominators and rate) data in the units used in this systematic review would allow aggregation of data.

Outcomes of particular importance to assess include:

1. Exacerbations requiring systemic corticosteroid;
2. Asthma-related hospital admission;
3. Compliance to either intervention both pre (for ICS) and post -randomisation (for both ICS and combination therapy). The impact of compliance to combination therapy versus placebo and ICS on the magnitude of the effect size should be examined;
4. Cost effectiveness of use of combination inhalers as compared to inhaled corticosteroids alone;

5. Long-term side effects of long-acting β_2 -agonists on serious adverse effects, and admission and of ICS (growth, adrenal function, bone mineralization);
6. Functional measures including quality of life.

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Internal sources

- St George's University of London, UK.

External sources

- No sources of support supplied

CHARACTERISTICS OF STUDIES

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

Akpinarli 1999

Methods	Parallel group, multicentre study.
Participants	<p>Symptomatic asthmatic children % ELIGIBLE OF SCREENED POPULATION: Not reported % RUN-IN PARTICIPANTS RANDOMISED: Not reported RANDOMISED: 32 (ICS + F12 (BID): 16; ICS: 16) WITHDRAWALS: Not described AGE mean (range) or mean (SD): 6 to 14 years GENDER:(% male): 47% SEVERITY: not reported BASELINE % PRED. FEV1: Not described BASELINE DOSE OF ICS: 400-800mcg ASTHMA DURATION: not described ATOPY (%): 68 ELIGIBILITY CRITERIA: Met ATS criteria for asthma; $\geq 15\%$ increase in FEV1 within the previous year EXCLUSION CRITERIA: Asthma exacerbation or respiratory infection in < month ELIGIBILITY CRITERIA DURING RUN IN: Only patients requiring salbutamol more than once a week were randomised</p>
Interventions	<p>LABA + ICS vs SAME dose of ICS OUTCOMES reported at 6 weeks RUN IN PERIOD: 2 weeks with ICS 400-800 mcg/day to document symptoms and beta2-use DOSE OPTIMISATION PERIOD: NONE INTERVENTION PERIOD: 6 weeks TEST GROUP: (ICS + F12) ICS 400-800 mcg/day + formoterol 12 mcg BID CONTROL GROUP: (ICS) ICS (400-800 mcg/day) + placebo BID DEVICE: MDI + large volume spacer (Volumatic) NUMBER OF DEVICES: 2 COMPLIANCE: assessed by weighing canisters CO-TREATMENT: prn SABA</p>

Outcomes	PULMONARY FUNCTION TEST: FEV1 predicted; am PEFR; pm PEF; PEF variability (%); PC 20 SYMPTOM SCORES: score of 0 to 3 (max 9); nighttime symptom score; symptom-free days or nights FUNCTIONAL STATUS: Rescue medication use; exacerbation requiring systemic steroids; exacerbations requiring admission INFLAMMATORY MARKERS: not described ADVERSE EFFECTS: described WITHDRAWALS: not described primary outcome measure not reported
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Notes	Full-text publication Funded by Astra Zeneca Author contacted and unable to confirm methodology or data User-defined number: 600 (mean ICS dose in LAB2 group in mcg/day of BDP-equivalent: 400 - 800)
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<i>Risk of bias</i>		
Item	Authors' judgement	Description
Adequate sequence generation?	Unclear	Described as randomised; no other information presented
Allocation concealment?	Unclear	Information not available
Blinding? All outcomes	Yes	Double-blind; identical placebo used
Incomplete outcome data addressed? All outcomes	Unclear	No information available on the statistical handling of missing data
Free of selective reporting?	Yes	Data on OCS-treated exacerbations available
Free of other bias?	Unclear	No data provided on % participants meeting eligibility criteria from screening or run-in populations

Bisgaard 2006

Methods	Parallel group, multicentre study
Participants	Steroid-using asthmatic children %ELIGIBLE OF SCREENED POPULATION: Not reported %RUN-IN PARTICIPANTS RANDOMISED: Not reported RANDOMISED: 223 (Bud/F: 117; Bud: 106) WITHDRAWAL: Not reported AGE mean (range): 8 years (4-11) GENDER (% male): 68 ASTHMA SEVERITY: Moderate BASELINE % PRED. FEV1 mean: 76 BASELINE DOSE OF ICS (start of run in): 200-500mcg per day ASTHMA DURATION: Not reported ATOPY(%): Not reported ELIGIBILITY CRITERIA: ICS 200-500mcg BDP equivalent (≥ 3 months prior to run-in); FEV1 60-100% predicted normal; ≥ 1 severe exacerbation ≤ 12 months prior to run-in EXCLUSION CRITERIA: Not reported CRITERIA FOR RANDOMISATION DURING RUN-IN: 8 puffs over last 10 days of run-in
Interventions	LABA + ICS versus INCREASED dose of ICS OUTCOMES: Reported at 12 months RUN IN PERIOD: 2 weeks to document stability DOSE OF ICS DURING RUN IN: Not clear DOSE OPTIMISATION PERIOD: None reported INTERVENTION PERIOD: 12 months TEST GROUP: Combination Formoterol 4.5/Budesonide 80mcg qd CONTROL GROUP: Budesonide 320mcg qd DEVICE: Turbuhaler NUMBER OF DEVICES: 1 COMPLIANCE: Not reported

CO-TREATMENT: prn SABA		
Outcomes	PULMONARY FUNCTION TEST: Recorded but not reported SYMPTOM SCORES: Recorded but not reported FUNCTIONAL STATUS: Night awakenings; rescue medication use; exacerbations* (hospitalisation/need for OCS or other medication, increase in ICS, PEF $\geq$ 70% baseline on two consecutive days) INFLAMMATORY MARKERS: Not reported ADVERSE EFFECTS: Reported WITHDRAWAL: Not reported *primary outcome	
Notes	Full text article Additional data downloaded from AZ website (www.astrazenecaclinicaltrials.com) Funded by AstraZeneca User defined: 320	
<i>Risk of bias</i>		
Item	Authors' judgement	Description
Adequate sequence generation?	Yes	Computer generated randomisation scheme
Allocation concealment?	Unclear	Eligible patients were randomized 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. Request for separate data on OCS-treated exacerbations from study sponsors has not been successful
Free of other bias?	Unclear	No data provided on % participants meeting eligibility criteria from screening or run-in populations

Heuck 2000

Methods	Crossover study; single centre (outpatient referral centre).
Participants	Asthmatic Children %ELIGIBLE OF SCREENED POPULATION: Not reported %RUN IN PARTICIPANTS RANDOMISED: Not reported RANDOMISED: 27 WITHDRAWALS: 2 patients were withdrawn during treatment with budesonide alone 1 withdrawal - unclear which period MEAN AGE (RANGE): 9.6 (6.1-13.5) GENDER (% male): 52 SEVERITY: Mild to moderate BASELINE FEV1: Not reported BASELINE PEF L/min (range): 280 l/min BASELINE DOSE OF ICS: Mean (range) - BUD 200 bid or equivalent ASTHMA DURATION (range in years): 4.5 (1.4-9.5) ATOPY (%): Not reported ELIGIBILITY CRITERIA: Treatment with inhaled budesonide 200 ?g twice daily (or equipotent doses of other ICS) for one month before study entry; children were prepubertal 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 + ICS Budesonide 200 bid DEVICE: Turbuhaler (ICS) and Aerolizer (formoterol) NUMBER OF DEVICES: 2 COMPLIANCE: Turbuhalers weighed and number of formoterol capsules counted CO-TREATMENT: prn SABA
Outcomes	PULMONARY FUNCTION TEST: FEV1; am PEF; pm PEF SYMPTOM SCORE: Daytime and night time score (score of 0 to 4) FUNCTIONAL STATUS Exacerbations; rescue medication use; lower leg growth; serum and urinary markers of type I and III collagen turnover INFLAMMATORY MARKERS: Inflammatory markers in serum ADVERSE EFFECTS: Reported WITHDRAWALS: Reported Primary outcome measure: Not reported
Notes	Full text publication Source of funding not stated Confirmation of methodology and data not obtained User-defined number: 200 (400-200)

Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	Yes	'Treatment order was allocated by a computerised randomisation scheme prepared in balanced blocks.'
Allocation concealment?	Unclear	Information on concealment of allocation not provided
Blinding? All outcomes	Yes	Double-blind; double dummy
Incomplete outcome data addressed? All outcomes	Unclear	No information available
Free of selective reporting?	Yes	Data on OCS-treated exacerbations available
Free of other bias?	Unclear	No data provided on % participants meeting eligibility criteria from screening or run-in populations

Langton Hewer 1995

Methods	Parallel group, single centre study
Participants	Symptomatic children %ELIGIBLE OF SCREENED POPULATION: Not reported % RUN IN PARTICIPANTS RANDOMISED: Not reported NUMBER RECRUITED NOT RANDOMISED: Not stated RANDOMISED: 23 (usual ICS + Sal 100 bid: 11; usual ICS: 12) WITHDRAWALS: Usual ICS + S: 0; usual ICS: 2 AGE median (range) years: 15 (12-17) GENDER:(% male): 70 SEVERITY: Severe BASELINE % PRED. FEV1: 82 BASELINE DOSE OF ICS (start of run in): 400 ASTHMA DURATION: 13 years ATOPY (%): 100% ELIGIBILITY CRITERIA: Severe asthma (not defined but severe enough to be attending residential school for asthma and persistent symptoms) EXCLUSION CRITERIA: Already on LABA; CRITERIA FOR RANDOMISATION DURING RUN-IN: None specified
Interventions	LABA + ICS versus SAME DOSE (usual dose) of ICS OUTCOMES reported at 8 & 10 weeks RUN IN PERIOD: 2 weeks DOSE OF ICS DURING RUN IN: Same as during study DOSE OPTIMISATION PERIOD: None INTERVENTION PERIOD: 8 weeks

TEST GROUP: (Usual ICS+S): Salmeterol 100mcg bid
 CONTROL GROUP: Usual ICS and placebo bid
 DEVICE: diskhaler
 NUMBER OF DEVICES: 2
 COMPLIANCE: Supervised in school taking medication by investigators
 CO-TREATMENT oral steroids, methylxanthines & anticholinergics taken by 20% participants

Outcomes	PULMONARY FUNCTION TEST: FEV1; am PEF; pm PEF SYMPTOM SCORES: Morning and evening symptom scores FUNCTIONAL STATUS: Rescue B2-agonist; symptom-free days/nights; exacerbation (requiring systemic steroids); quality of life score INFLAMMATORY MARKERS: none ADVERSE EFFECTS: described WITHDRAWALS: described Primary outcome measure not reported	
Notes	Full-text publication Funded by Charity Confirmation of methodology and data pending User-defined number: not reported	
<i>Risk of bias</i>		
Item	Authors' judgement	Description
Adequate sequence generation?	Unclear	Described as randomised; no other information presented
Allocation concealment?	Unclear	Information not available
Blinding? All outcomes	Yes	Identical placebo
Incomplete outcome data addressed? All outcomes	Unclear	Data analysis described as intention to treat; methods applied not elaborated
Free of selective reporting?	Yes	Data on OCS-treated exacerbations available
Free of other bias?	Unclear	No data provided on % participants meeting eligibility criteria from screening or run-in populations (niche population sampled for residential school for children with particularly difficult to treat asthma)

Malone 2005

Methods	Parallel group, multicentre (66 centres in North America)
Participants	Steroid-using asthmatic children %ELIGIBLE OF SCREENED POPULATION: Not reported %RUN-IN PARTICIPANTS RANDOMISED: 48 RANDOMISED: 203 (FP/SAL: 101; FP: 102) WITHDRAWAL: FP/SAL: 19; FP: 16 AGE mean: 8 years GENDER (male%): 64 ASTHMA SEVERITY: Mild-moderate BASELINE % PRED. FEV1 mean: 80 BASELINE DOSE OF ICS (start of run in): 166mcg (FP stratum) ASTHMA DURATION: Not reported ATOPY(%): Not reported ELIGIBILITY CRITERIA: 4-11 years; ATS defined asthma for at least 2 months; ICS therapy (BDP equivalent 252-336mcg/d) for 1 month prior to entry; participants aged 6-11 required to have FEV1% predicted; participants aged 4-5 required to have am PEF 50-95% predicted; $\geq 12\%$ response to beta-agonist at screening visit or within one year of screening visit EXCLUSION CRITERIA: History of life-threatening asthma; hospitalisation with asthma twice or more in previous year; significant concurrent disease; oral or parenteral use of steroids in month prior to study entry CRITERIA FOR RANDOMISATION DURING RUN-IN: am FEV1 50-95% predicted; daytime asthma (score at least 1)/use of SABA on 3+ days of last 7 days of run-in; 70% or greater diary card entry

Interventions	LABA + ICS versus SAME dose of ICS OUTCOMES: Reported at 3 months RUN IN PERIOD: 2 weeks DOSE OF ICS DURING RUN IN: Usual maintenance dose INTERVENTION PERIOD: 3 months TEST GROUP: Combination Salmeterol 50/Fluticasone 100mcg bid CONTROL GROUP: Fluticasone 100mcg bid DEVICE: Diskus NUMBER OF DEVICES: 1 COMPLIANCE: Not reported CO-TREATMENT: prn SABA
Outcomes	PULMONARY FUNCTION TEST: FEV1; Clinic PEF; am PEF; pm PEF SYMPTOM SCORES: Symptom scores; symptom-free days FUNCTIONAL STATUS: OCS-treated exacerbations; hospitalisations; Use of reliever medication; SABA-free days INFLAMMATORY MARKERS: Not reported ADVERSE EFFECTS: Reported WITHDRAWAL: Stated * primary outcome: not identified (safety study)
Notes	Full-text publication Funded by GSK User-defined number: 400 Confirmation of data and methodology obtained

<i>Risk of bias</i>		
Item	Authors' judgement	Description
Adequate sequence generation?	Yes	See Appendix 1
Allocation concealment?	Yes	See Appendix 1
Blinding? All outcomes	Yes	Double-blind; identical inhaler devices
Incomplete outcome data addressed? All outcomes	No	'For patients who withdrew from the study prematurely, all available data up to the time of discontinuation were included in the intent-to-treat population.'
Free of selective reporting?	Yes	Data on OCS treated exacerbations and hospital admission available on request
Free of other bias?	Yes	48% of screening population eligible for randomisation

Meijer 1995

Methods	Parallel group, single centre study
Participants	Asymptomatic asthmatic children %ELIGIBLE OF SCREENED POPULATION: Not reported %RUN-IN PARTICIPANTS RANDOMISED: Not reported RANDOMISED: 40 (Sal 50 mcg BID + ICS: 20; ICS + Placebo: 20) WITHDRAWALS: Sal50 mcg BID + ICS: 0; ICS + Placebo: 1 (5%) AGE: mean (SD): 11.4 (2.6) GENDER (%male): 58 SEVERITY: Mild BASELINE % PRED. FEV1: 94 BASELINE DOSE OF ICS: Twice daily 200 or 400 mcg beclomethasone dipropionate rotadisk ASTHMA DURATION: 8.4 years ATOPY (%): 100 ELIGIBILITY CRITERIA: None reported EXCLUSION CRITERIA: None reported CRITERIA FOR RANDOMISATION DURING RUN IN: N/A
Interventions	LABA + ICS versus SAME dose of ICS

OUTCOMES: reported at 1, 8, 16 weeks
 RUN IN PERIOD: None
 DOSE OPTIMISATION PERIOD: None
 INTERVENTION PERIOD: 16 weeks
 TEST GROUP: Salmeterol 50 mcg BID + BDP 250 mcg BID
 CONTROL GROUP: BDP 250 mcg BID + placebo
 DEVICE: dry powder inhaler (diskhaler)
 NUMBER OF DEVICES: 2
 COMPLIANCE: Returned powder disks counted
 CO-TREATMENT: prn SABA

Outcomes	PULMONARY FUNCTION TEST: FEV1 predicted; PC20 doubling doses (DD); circadian variation (day-night differences in FEV1) SYMPTOM SCORES: Only individual symptoms reported (yes/no) FUNCTIONAL STATUS: Rescue medication use INFLAMMATORY MARKERS: Not reported ADVERSE EFFECTS: Not reported WITHDRAWALS: Reported Primary outcome not specified
Notes	Full-text publication Funded by Glaxo User-defined number: 500 Confirmation of data and methodology not obtained

Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	Unclear	Described as randomised; no other information presented
Allocation concealment?	Unclear	Information not available
Blinding? All outcomes	Yes	Double-blind; double dummy
Incomplete outcome data addressed? All outcomes	Unclear	Not enough information presented to determine this
Free of selective reporting?	Unclear	Unclear whether data on OCS-treated exacerbations were collected in the study
Free of other bias?	Unclear	No data presented on % screening population eligible for randomisation

Morice 2008a

Methods	Parallel group, multicentre study (53 centres in South America, Europe, Hong Kong and Taiwan)
Participants	% ELIGIBLE OF SCREENED POPULATION: Not reported % RUN-IN PARTICIPANTS RANDOMISED: 77 RANDOMISED: 622 (BUD: 207; BUD/F (dpi): 203; BUD/F (mdi): 212) WITHDRAWALS: BUD: 14 BUD/F (dpi): 11; BUD/F (mdi): 14 AGE: mean (range): 9 (6-11 years) GENDER (% male): 66 SEVERITY: Not specified BASELINE % PRED. FEV1: 89 BASELINE DOSE OF ICS: (start of run-in): 470mcg ASTHMA DURATION: Not reported ATOPY (%): Not reported ELIGIBILITY CRITERIA: Age 6-11 years; diagnosis of asthma for at least 6 months; PEF >50% of predicted normal; history daily ICS use (stable dose of 375-1000 mcg 30 days prior to enrolment); clinically important exercise-induced bronchoconstriction for 3 months before enrolment; ability to use DPI, pMDI & peak flow meter EXCLUSION CRITERIA: Not reported CRITERIA FOR RANDOMISATION DURING RUN-IN: Symptom score 1-4; mean morning PEF 50-85% post-SABA

Interventions	<p>OUTCOMES: 12 weeks RUN-IN PERIOD: 2 weeks DOSE OF ICS DURING RUN-IN: 470 DOSE OPTIMISATION PERIOD: Not reported INTERVENTION PERIOD: 12 weeks TEST GROUP: Combination formoterol and budesonide (160/9mcg) BID via dry powder inhaler + placebo metered dose inhaler CONTROL GROUP: Budesonide 100mcg BID DEVICE: BUD/F mdi and Budesonide: MDI; BUD/F dpi: DPI NUMBER OF DEVICES: 2 COMPLIANCE: Not reported CO-TREATMENT: prn SABA</p>
Outcomes	<p>PULMONARY FUNCTION TEST: Am PEF*; pm PEF; FEV1 SYMPTOM SCORES: Day/night scores FUNCTIONAL STATUS: Paediatric AQLQ INFLAMMATORY MARKERS: NA ADVERSE EFFECTS: Stated WITHDRAWALS: Stated Primary outcome measure*</p>
Notes	<p>Full text publication AZ funded User defined: 200 Confirmation of data and methodology not obtained</p>

<i>Risk of bias</i>		
Item	Authors' judgement	Description
Adequate sequence generation?	Yes	Computer-generated schedule
Allocation concealment?	Unclear	Information not provided
Blinding? All outcomes	Yes	Double-blind; double dummy
Incomplete outcome data addressed? All outcomes	Unclear	'...all randomised patients with post-randomisation data.'
Free of selective reporting?	No	Data on OCS-treated exacerbations were not reported in the trial publication. Study sponsors have indicated that the data from this study are not available
Free of other bias?	Yes	77% of screening population eligible for randomisation

Morice 2008b

Methods	See Morice 2008a	
Participants	See Morice 2008a	
Interventions	See Morice 2008a, except for: TEST GROUP: Combination formoterol and budesonide (160/9mcg) BID via metered dose inhaler + placebo dry powder inhaler	
Outcomes	See Morice 2008a	
Notes	See Morice 2008a	
<i>Risk of bias</i>		
Item	Authors' judgement	Description
Adequate sequence generation?	Yes	See Morice 2008a
Allocation concealment?	Unclear	See Morice 2008a

Blinding? All outcomes	Yes	See Morice 2008a
Incomplete outcome data addressed? All outcomes	Unclear	See Morice 2008a
Free of selective reporting?	No	See Morice 2008a
Free of other bias?	Yes	See Morice 2008a

Ortega-Cisneros 1998

Methods	Parallel-group, single centre
Participants	Symptomatic Asthmatic children %ELIGIBLE OF SCREENED POPULATION: Not reported %RUN IN PARTICIPANTS RANDOMISED: Not reported RANDOMISED: S50 + BDP: 10; BDP: 10 WITHDRAWALS: Not described AGE (range): 6 to 19 years GENDER (%male): Not described SEVERITY: Moderate BASELINE % PRED. FEV1 mean (SD): 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 versus INCREASED dose ICS RUN-IN PERIOD: 2 weeks OUTCOMES: Reported at 8,12 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 200mcg 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 25-75% SYMPTOM SCORES: Symptoms FUNCTIONAL STATUS: Not reported INFLAMMATORY MARKERS: Not reported ADVERSE EFFECTS: Not reported WITHDRAWAL: Not reported
Notes	Abstract Funding not reported Confirmation of methodology and data extraction: not obtained User-defined order: 400

Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	Unclear	Described as randomised; no other information presented
Allocation concealment?	Unclear	Information not provided
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
Free of other bias?	Unclear	No information provided

Pohunek 2006a

Methods	Parallel group, multicentre study (80 centres in Europe). Three treatment groups
Participants	<p>Steroid-using asthmatic children</p> <p>%ELIGIBLE OF SCREENED POPULATION: Not reported</p> <p>%RUN-IN PARTICIPANTS RANDOMISED: 77</p> <p>RANDOMISED: 429 (BUD/F: 216; BUD: 213)</p> <p>WITHDRAWAL: BUD/F: 14 BUD: 13</p> <p>AGE mean (range) 8 (4-11)</p> <p>GENDER (male%): 67</p> <p>ASTHMA SEVERITY: Mild-moderate</p> <p>BASELINE % PRED. FEV1 mean: 92%</p> <p>BASELINE DOSE OF ICS (start of run in): 454 mcg/d</p> <p>ASTHMA DURATION: 3</p> <p>ATOPY(%): Not reported</p> <p>ELIGIBILITY CRITERIA: 4-11 years; diagnosis of asthma (ATS) for a minimum period of 6 months; pre-SABA PEF $\geq$ 50% predicted; ICS treatment for at least 12 weeks before entry into the study, at a constant dose of 375?1000 mcg/d during the 30 days prior to enrolment; History an average of $\geq$1 clinically important exercise induced bronchoconstriction per week during the 12 weeks months leading up to the study; ability to use Turbuhaler device & peak flow metre</p> <p>EXCLUSION CRITERIA: Oral, parenteral or rectal corticosteroids within 30 days; respiratory infection affecting asthma control within 30 days; any significant coexisting disease/disorder; known/suspected hypersensitivity to study medication or inhaled lactose; inhaled anticholinergics, beta-blockers (including eye drops), xanthines & other anti-asthma agents not permitted during the study</p> <p>POST-RUN IN: Total asthma-symptom score of at least one on a minimum of four of last 7 days of the run-in period; during last 7 days of the run-in, patients had to have a mean morning PEF of 50-85% of the post-SABA PEF</p>
Interventions	<p>LABA + ICS versus SAME dose ICS</p> <p>OUTCOMES: 12 weeks</p> <p>RUN IN PERIOD: 10-14 days</p> <p>DOSE OF ICS DURING RUN IN: Usual dose of ICS</p> <p>INTERVENTION PERIOD: 12 weeks</p> <p>TEST GROUP: Combination Budesonide/Formoterol 200/6mcg bid</p> <p>CONTROL GROUP: Budesonide 200mcg bid</p> <p>DEVICE: Turbuhaler</p> <p>NUMBER OF DEVICES: 2 (double dummy)</p> <p>COMPLIANCE: Not reported</p> <p>CO-TREATMENT: prn SABA</p>
Outcomes	<p>PULMONARY FUNCTION TEST: Am PEF; pm PEF; FEV1</p> <p>SYMPTOM SCORES: Not reported</p> <p>FUNCTIONAL STATUS: Not reported</p> <p>INFLAMMATORY MARKERS: Not reported</p> <p>ADVERSE EFFECTS: Reported</p> <p>WITHDRAWAL: Not reported</p> <p>primary outcome: not reported</p>
Notes	<p>Full-text publication</p> <p>Funded by AstraZeneca</p> <p>Confirmation of methodology and data: Not obtained</p> <p>User-defined order: 400</p>

Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	Yes	Schedule generated using a computer program (AstraZeneca, UK)
Allocation concealment?	Yes	Person not involved in the study team generated the randomisation schedule

Blinding? All outcomes	Yes	Double-blind; double dummy
Incomplete outcome data addressed? All outcomes	Unclear	'Intent to treat analysis was performed using data from all randomized patients.' No additional data were provided on the composition of the ITT population
Free of selective reporting?	Unclear	Unclear whether OCS-treated exacerbations were collected in the study. Correspondence with trialist has failed to clarify this
Free of other bias?	Yes	78% screening population eligible for randomisation

Pohunek 2006b

Methods	See Pohunek 2006a	
Participants	See Pohunek 2006a, except for RANDOMISED: 414 (F + BUD: 201; Bud: 213)	
Interventions	See Pohunek 2006a, except for TEST GROUP: Separate Formoterol 6 and Budesonide 200mcg bid NUMBER OF DEVICES: 2	
Outcomes	See Pohunek 2006a	
Notes	See Pohunek 2006a	
<i>Risk of bias</i>		
Item	Authors' judgement	Description
Adequate sequence generation?	Yes	See Pohunek 2006a
Allocation concealment?	Yes	See Pohunek 2006a
Blinding? All outcomes	Yes	See Pohunek 2006a
Incomplete outcome data addressed? All outcomes	Unclear	See Pohunek 2006a
Free of selective reporting?	Unclear	See Pohunek 2006a
Free of other bias?	Yes	See Pohunek 2006a

Russell 1995

Methods	Parallel-group, multicentre study (78 centres)
Participants	Symptomatic Asthmatic Children %ELIGIBLE OF SCREENED POPULATION: Not reported %RUN-IN PARTICIPANTS RANDOMISED: Not reported RANDOMISED: 208 (Salm50 + ICS: 99; Placebo + ICS: 109) WITHDRAWALS: Salm50 + ICS: 22%; Placebo + ICS: 16.8% AGE: mean (SD): 10.2 (2.7) GENDER: (% male): 60 SEVERITY: Moderate BASELINE MEAN % PRED. FEV1: 78 BASELINE DOSE OF ICS: 750 mcg ASTHMA DURATION (%): <1 year: 3; 1 to 5 years: 20; >5 years: 77 ATOPY(%): 77 ELIGIBILITY CRITERIA DURING RUN-IN: Morning PEF-PP(percent predicted) <=90 on 4 or more days of the last 10 days of the baseline period; either recorded symptoms on at least 7 of 14 days of the baseline period for which they used at least

	one salbutamol blister per episode; recorded a diurnal variation in PEF of $\geq 15\%$ on at least 7 occasions during baseline period EXCLUSION CRITERIA: Received a course of oral corticosteroids; change in prophylactic therapy during the previous 2 weeks
Interventions	LABA + ICS vs SAME dose of ICS OUTCOMES: Reported at 4, 8 and 12 weeks RUN IN PERIOD: 2 weeks DOSE OF ICS DURING RUN-IN: Continued on usual ICS of at least 400mcg/day BDP DOSE OPTIMISATION PERIOD: None INTERVENTION PERIOD: 12 weeks TEST GROUP: (Salm 50 + ICS) Salmeterol 50 mg bid + ICS 400-2400 mg/day (average: 750 mcg/day) CONTROL GROUP: (Placebo+ICS) Placebo + ICS 400-2400 mg/day (average 750 mcg/day) DEVICE: Diskhaler NUMBER OF DEVICES: 2 COMPLIANCE: Evaluated using patient kept record booklets CO-TREATMENT: Salbutamol as needed and any other prophylactic asthma medication via diskhaler
Outcomes	PULMONARY FUNCTION TEST: am PEF percent predicted*; pm PEF percent predicted SYMPTOM SCORES: Symptoms were recorded daily as either being present or absent, wheeze or cough during day or night FUNCTIONAL STATUS: Proportion symptom-free days; proportion symptom-free nights; rescue medication use INFLAMMATORY MARKERS: Not described ADVERSE EFFECTS: Described WITHDRAWALS: Described primary outcome measure*
Notes	Full-text publication Funded by Allen & Hanburys Confirmation of methodology and data obtained. User-defined number: 750 (750 mcg/day)

Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	Yes	Computer generated random numbers
Allocation concealment?	Yes	Numbered coded envelopes supplied by Pharmacy
Blinding? All outcomes	Yes	Double-blind; identical placebo
Incomplete outcome data addressed? All outcomes	No	'Total population used, this comprised all subjects who received at least one puff of medication and recorded at least one day of valid diary or clinic data during the treatment period. Where a subject withdrew before completion of the study, data recorded after this withdrawal data was excluded.'
Free of selective reporting?	Yes	OCS-treated exacerbation data available
Free of other bias?	Unclear	Information on % screening population eligible not available

SAM104926

Methods	Parallel group, multicentre study
Participants	% ELIGIBLE OF SCREENED POPULATION: Not reported % RUN-IN PARTICIPANTS RANDOMISED: Not reported RANDOMISED: 321 (FP/SAL: 160; FP: 161) WITHDRAWALS: FP/SAL: 3; FP: 6 AGE mean (range) or mean (SD): 8 (2)

	<p>SEVERITY: Not reported BASELINE % PRED. FEV1: 102 BASELINE DOSE OF ICS: Not stated ASTHMA DURATION: Not stated ATOPY (%): Not stated ELIGIBILITY CRITERIA: 4-11 years; diagnosis of asthma for a minimum of 6 months; airway reversibility of $\geq 15\%$ based either on FEV1 or PEF; treatment with medium dose ICS (beclomethasone dipropionate (BDP) equivalent 400-500 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 β_2-agonists, leukotriene antagonists or theophyllines during 4 weeks prior to screening visit; e 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</p>
Interventions	<p>ICS and LABA versus INCREASED dose ICS OUTCOMES: 12 weeks RUN IN PERIOD: 4 weeks DOSE OPTIMISATION PERIOD: NA INTERVENTION PERIOD: 12 weeks TEST GROUP: Combination fluticasone and salmeterol 100/50 mcg BID, via DPI CONTROL GROUP: Fluticasone 200mcg BID, via DPI NUMBER OF DEVICES: 1 COMPLIANCE: Not assessed CO-TREATMENT: prn SABA</p>
Outcomes	<p>PULMONARY FUNCTION TEST: Am PEF SYMPTOM SCORES: NA FUNCTIONAL STATUS: N achieving well controlled asthma INFLAMMATORY MARKERS: NA ADVERSE EFFECTS: Reported WITHDRAWALS: Reported</p>
Notes	<p>Unpublished study Funding source: GSK Confirmation of methodology and data not obtained. User defined: 800</p>

Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	Yes	See Appendix 1
Allocation concealment?	Yes	See Appendix 1
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?	Unclear	Unclear whether data on OCS-treated exacerbations were collected. Request for data from study sponsors has not been successful. Data on hospital admission available from published meta-analysis
Free of other bias?	Unclear	Information on % screening population eligible not reported

SAM40012a

Methods	Parallel group, multicentre study in Europe and Middle East.
Participants	<p>Steroid-using asthmatic children %ELIGIBLE OF SCREENED POPULATION: Not reported</p>

%RUN-IN PARTICIPANTS RANDOMISED: Not reported
 RANDOMISED: 362 (FP/SAL: 181; FP: 181)
 WITHDRAWAL: FP/SAL: 3; FP: 10
 AGE mean: 8 years
 GENDER (male%): 68
 ASTHMA SEVERITY: Moderate
 BASELINE % PRED. FEV1 mean: Not reported
 BASELINE DOSE OF ICS (start of run in): Not reported
 ASTHMA DURATION: Not reported
 ATOPY(%): Not reported
 ELIGIBILITY CRITERIA: 4-500mcg BDP equivalent; documented history of asthma
 EXCLUSION CRITERIA: Not reported
 ELIGIBILITY CRITERIA DURING RUN-IN: Symptom score ≥ 2 on three of last seven days of run-in

Interventions	LABA + ICS versus SAME dose of ICS OUTCOMES: Reported at 6 months RUN IN PERIOD: 2 weeks DOSE OF ICS DURING RUN IN: Not clear DOSE OPTIMISATION PERIOD: None reported INTERVENTION PERIOD: 6 months TEST GROUP: Combination Salmeterol 50/Fluticasone 100mcg bid CONTROL GROUP: Fluticasone 100mcg bid DEVICE: Diskus NUMBER OF DEVICES: 1 COMPLIANCE: Not reported CO-TREATMENT: pm SABA
Outcomes	OUTCOMES: Reported at 6 months PULMONARY FUNCTION TEST: am PEF; pm PEF; FEV1 SYMPTOM SCORES: Symptom-free days FUNCTIONAL STATUS: Use of reliever medication; exacerbations (undefined) INFLAMMATORY MARKERS: Not reported ADVERSE EFFECTS: Reported WITHDRAWAL: Reported *primary outcome
Notes	Full unpublished data set available from http://www.ctr.gsk.co.uk Source of funding: GSK Confirmation of methodology and data: Not obtained User defined number: 400

Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	Yes	See Appendix 1
Allocation concealment?	Yes	See Appendix 1
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?	Unclear	Exacerbations described in trial report available; OCS-treated exacerbations could not be identified from the data available
Free of other bias?	Unclear	Information not available

SAM40012b

Methods	See SAM40012a
Participants	See SAM40012a, except for RANDOMISED: FP/SAL: 181; FP: 186 WITHDRAWAL: FP/SAL: 3; FP: 5

Interventions	See SAM40012a	
Outcomes	See SAM40012a	
Notes	See SAM40012a	
<i>Risk of bias</i>		
Item	Authors' judgement	Description
Adequate sequence generation?	Yes	See Appendix 1
Allocation concealment?	Yes	See Appendix 1
Blinding? All outcomes	Yes	See SAM40012a
Incomplete outcome data addressed? All outcomes	Unclear	See SAM40012a
Free of selective reporting?	Unclear	See SAM40012a
Free of other bias?	Unclear	See SAM40012a

SAM40100

Methods	Parallel group, multicentre study
Participants	<p>% 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 % PRED. FEV1: Not reported. BASELINE DOSE OF ICS: Not stated. ASTHMA DURATION: Not reported ATOPY (%): Not reported ELIGIBILITY CRITERIA: 4-8 years; history of asthma for at least 3 months; maintenance ICS dose of 200-800mcg/day BDP or equivalent for at least 4 weeks; sufficiently stable to receive FP 200mcg/day during 2-week run-in; sRAW value of ≤ 1.3kPa.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</p>
Interventions	<p>LABA+ICS versus INCREASED DOSE ICS OUTCOMES: 6 weeks RUN IN PERIOD: 2 weeks DOSE OPTIMISATION PERIOD: 2 weeks INTERVENTION PERIOD: 6 weeks TEST GROUP: Combination fluticasone and salmeterol 100/50mcg BID via DPI CONTROL GROUP: Fluticasone 200mcg BID via DPI NUMBER OF DEVICES: 1 COMPLIANCE: Not assessed CO-TREATMENT: prn SABA</p>
Outcomes	<p>PULMONARY FUNCTION TEST: FEV1 SYMPTOM SCORES: Day and nocturnal scores FUNCTIONAL STATUS: Rescue medication use INFLAMMATORY MARKERS: sRAW* ADVERSE EFFECTS: Reported WITHDRAWALS: Reported</p>
Notes	<p>Unpublished data sourced from http://ctr.gsk.co.uk Funding source: GSK Confirmation of methodology and data not obtained. User defined: 400</p>
<i>Risk of bias</i>	

Item	Authors' judgement	Description
Adequate sequence generation?	Yes	See Appendix 1
Allocation concealment?	Yes	See Appendix 1
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
Free of other bias?	Unclear	Information on % screening/run-in population eligible not reported

SD 039 0714

Methods	Parallel group, multicentre study
Participants	<p>Steroid-using symptomatic asthmatic adolescents</p> <p>%ELIGIBLE OF SCREENED POPULATION Not reported</p> <p>%RUN-IN PARTICIPANTS RANDOMISED: 60%</p> <p>RANDOMISED: 271 (F6/Bud 200mcg bid: 136; Bud 200mcg bid: 135)</p> <p>WITHDRAWAL: F6/Bud 200mcg bid: 25; Bud 200mcg bid: 27</p> <p>AGE: mean (range): 14 (11-17)</p> <p>GENDER (male%): 42</p> <p>ASTHMA SEVERITY: Moderate</p> <p>BASELINE % PRED. FEV1 mean: 75</p> <p>BASELINE DOSE OF ICS (start of run in): Not reported</p> <p>ASTHMA DURATION: Not reported</p> <p>ATOPY(%): Not reported</p> <p>ELIGIBILITY CRITERIA: ICS 375-1000mcg BDP equivalent; FEV1 40-90% predicted normal; $\geq 12\%$ improvement following inhalation of 1mg of terbutaline</p> <p>EXCLUSION CRITERIA: Not reported</p> <p>CRITERIA FOR RANDOMISATION DURING RUN-IN: Symptomatic</p>
Interventions	<p>LABA + ICS versus SAME dose of ICS</p> <p>OUTCOMES: Reported at 1, 2 and 3 months</p> <p>RUN IN PERIOD: 2 weeks to document stability</p> <p>DOSE OF ICS DURING RUN IN: Not clear</p> <p>DOSE OPTIMISATION PERIOD: None reported</p> <p>INTERVENTION PERIOD: 3 months</p> <p>TEST GROUP: Combination budesonide and formoterol 200/6 mcg bid</p> <p>CONTROL GROUP: Budesonide 200 mcg bid</p> <p>DEVICE:-Turbuhaler</p> <p>NUMBER OF DEVICES: 1</p> <p>COMPLIANCE: Not reported</p> <p>CO-TREATMENT: prn SABA</p>
Outcomes	<p>PULMONARY FUNCTION TEST: FEV1; am PEF*; pm PEF</p> <p>SYMPTOM SCORES: Recorded but not reported</p> <p>FUNCTIONAL STATUS: Rescue medication use (recorded but not reported); nocturnal awakening (recorded but not reported); episode free days (recorded but not reported)</p> <p>INFLAMMATORY MARKERS: Not reported</p> <p>ADVERSE EFFECTS: Reported</p> <p>WITHDRAWAL: Reported</p> <p>* primary outcome</p>
Notes	<p>Unpublished data downloaded from AZ website (www.astrazenecaclinicaltrials.com)</p> <p>Funded by AstraZeneca</p> <p>Confirmation of data and methodology: Obtained</p> <p>User defined: 400</p>

Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	Unclear	Information not available
Allocation concealment?	Unclear	Information not available
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?	Unclear	OCS-treated exacerbations were not reported in the study publication. Data request has been made to study sponsors for this information
Free of other bias?	Yes	59% run-in population eligible

SD 039 0718

Methods	Parallel group; multicentre study (52 centres in USA)
Participants	% ELIGIBLE OF SCREENED POPULATION: Not reported % RUN-IN PARTICIPANTS RANDOMISED 60 RANDOMISED: 273 (BUD/F: 128; BUD: 145) WITHDRAWALS: BUD/F: 36; BUD: 51 AGE mean (range) or mean (SD): 10.4 (2.6) SEVERITY: Not stated BASELINE % PRED. FEV1: 82 BASELINE DOSE OF ICS: 235mcg/d ASTHMA DURATION: 7 years ATOPY (%): Not stated ELIGIBILITY CRITERIA: 6-15 years; low to medium dose of ICS; FEV1 predicted >50%; reversibility criteria age dependent: >12 years 14% and 0.2L; <12 years: 12% EXCLUSION CRITERIA: Not reported. ELIGIBILITY CRITERIA DURING RUN IN: Symptoms and lung function not otherwise described
Interventions	LABA+ICS versus SAME DOSE ICS OUTCOMES: 12 weeks RUN IN PERIOD: 1-2 weeks DOSE OPTIMISATION PERIOD: Not applicable INTERVENTION PERIOD: 12 weeks TEST GROUP: Combination budesonide/formoterol (100/9 mcg) BID via metered dose inhaler CONTROL GROUP: Budesonide 100mcg BID via metered dose inhaler NUMBER OF DEVICES: 1 COMPLIANCE: Not assessed CO-TREATMENT: prn SABA
Outcomes	PULMONARY FUNCTION TEST: Am PEF; pm PEF; FEV1 SYMPTOM SCORES: NA FUNCTIONAL STATUS: NA INFLAMMATORY MARKERS: NA ADVERSE EFFECTS: Stated WITHDRAWALS: Stated
Notes	Unpublished data from AZ clinical trials website Funded by AstraZeneca Confirmation of data and methodology: Obtained User defined: 200

Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	Unclear	Described as randomised; no other information presented

Allocation concealment?	Unclear	Information not available
Blinding? All outcomes	Yes	Double-blind; double dummy
Incomplete outcome data addressed? All outcomes	Unclear	'The efficacy analysis set (EAS) was defined as all randomized subjects who took at least 1 dose of study medication and contributed at least 1 PEF value to the primary end-point.' No information given on whether EAS population included last observation
Free of selective reporting?	Unclear	OCS-treated exacerbations were not reported in the study publication. Data request has been made to study sponsors for this information
Free of other bias?	Yes	59% screening population eligible

SD 039 0719

Methods	Parallel group, multicentre study.
Participants	% ELIGIBLE OF SCREENED POPULATION: Not stated % RUN-IN PARTICIPANTS RANDOMISED: 74 RANDOMISED: 186 (BUD/F: 123; BUD: 63) WITHDRAWALS: BUD/F: 13; BUD: 10 AGE mean (range) or mean (SD): 9 (1.7) SEVERITY: Not stated BASELINE % PRED. FEV1: 84% BASELINE DOSE OF ICS: 307 ASTHMA DURATION: 6 years ATOPY (%): Not stated ELIGIBILITY CRITERIA: 6-12 years; inhaled steroid-dependent asthma; FEV1 >50% of predicted; history of PEF or FEV1 reversibility 12%; subjects without history of reversibility must have demonstrated FEV1 reversibility as above at any time before Visit 2 EXCLUSION CRITERIA: Not reported ELIGIBILITY CRITERIA DURING RUN IN: Not reported
Interventions	LABA and ICS versus SAME dose ICS OUTCOMES: 26 weeks RUN IN PERIOD: 1 week DOSE OPTIMISATION PERIOD: NA INTERVENTION PERIOD: 26 weeks TEST GROUP: Combination budesonide and formoterol 160/4.5 mcg per actuation, 2 puffs BID via MDI CONTROL GROUP: Budesonide 160mcg per actuation, 2 puffs BID via MDI NUMBER OF DEVICES: 1 COMPLIANCE: Not assessed CO-TREATMENT: prn SABA
Outcomes	PULMONARY FUNCTION TEST: FEV1; am PEF SYMPTOM SCORES: NA FUNCTIONAL STATUS: Paediatric AQLQ INFLAMMATORY MARKERS: NA ADVERSE EFFECTS: Adverse events* WITHDRAWALS: Stated per treatment group *Primary outcome
Notes	Downloaded from AZ clinical trials website (accessed 4 th January 2008) Funded by Astra Zeneca Confirmation of data: Provided by AZ in April 2008 User-defined number: 640

Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	Unclear	Described as randomised; no other information presented

Allocation concealment?	Unclear	Information not available
Blinding? All outcomes	No	Open label
Incomplete outcome data addressed? All outcomes	Unclear	'The safety analysis set was defined as all randomized subjects who took at least 1 dose of study medication.' No information given on whether safety population included last observation
Free of selective reporting?	No	OCS-treated exacerbations were not reported in the study publication. Data request has been made to study sponsors for this information
Free of other bias?	Yes	74% screening population eligible for randomisation

SD 039 0725a

Methods	Parallel group, multicentre study
Participants	% ELIGIBLE OF SCREENED POPULATION: 35 % RUN-IN PARTICIPANTS RANDOMISED: 79 RANDOMISED: 521 (BUD/F BID: 184; BUD/F QD: 168; BUD: 169) WITHDRAWALS: BUD/F BID: 21; BUD/F QD: 37; BUD: 33 AGE mean (range) or mean (SD): 10.3 (2.5) SEVERITY: Not stated BASELINE % PRED. FEV1: 78.3 (8.56) BASELINE DOSE OF ICS: 245.3 ASTHMA DURATION: 6.8 ATOPY (%): Not reported ELIGIBILITY CRITERIA: 6-15 years; diagnosis of asthma for at least 6 months; maintenance inhaled corticosteroids treatment for at least 4 weeks prior to screening; FEV1 predicted 60-90% predicted; reversibility of FEV1 of 12% or more and >0.20 L from baseline; children >11 years were required to demonstrate reversibility of >12% only EXCLUSION CRITERIA: Not stated. ELIGIBILITY CRITERIA DURING RUN IN Stable asthma symptoms
Interventions	LABA and ICS versus SAME DOSE ICS OUTCOMES: 12 weeks RUN IN PERIOD: 4-5 weeks DOSE OPTIMISATION PERIOD: Not reported INTERVENTION PERIOD: 12 weeks TEST GROUP: Combination budesonide and formoterol 80/9mcg BID via MDI CONTROL GROUP: Budesonide 160mcg QD via MDI NUMBER OF DEVICES: 1 COMPLIANCE: Not assessed CO-TREATMENT: prn SABA
Outcomes	PULMONARY FUNCTION TEST: FEV1; Am PEF; Pm PEF* SYMPTOM SCORES: Day & nocturnal symptoms FUNCTIONAL STATUS: AQLQ INFLAMMATORY MARKERS: Not reported ADVERSE EFFECTS: Reported WITHDRAWALS: Reported by treatment group
Notes	Funding source: AZ Confirmation of methodology and data obtained from AZ in April 2008 Unpublished data downloaded from: http://www.astrazenecaclinicaltrials.com User defined: 160

Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	Unclear	Described as randomised; no other information presented. Age-based strata to ensure balance in ages between groups (6-11 years & 12-15 years)

Allocation concealment?	Unclear	Information not available
Blinding? All outcomes	Yes	Double-blind; double dummy
Incomplete outcome data addressed? All outcomes	Unclear	Efficacy analysis does not explicitly describe whether missing data imputed or drawn from follow-up: 'all randomized subjects who took at least 1 dose of double-blind treatment, and who contributed at least 1 evening PEF diary entry after receiving double-blind medication, was used in the primary analysis.'
Free of selective reporting?	No	OCS-treated exacerbations were not reported in the study publication. Data request has been made to study sponsors for this information
Free of other bias?	Yes	37% screening population eligible for randomisation

SD 039 0725b

Methods	See SD 039 0725b
Participants	See SD 039 0725b
Interventions	See SD 039 0725b TEST GROUP: Combination budesonide and formoterol 160/9mcg QD via MDI
Outcomes	See SD 039 0725b
Notes	See SD 039 0725b

Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	Unclear	Information not available
Allocation concealment?	Unclear	Information not available
Blinding? All outcomes	Yes	Double-blind; double dummy
Incomplete outcome data addressed? All outcomes	Unclear	Efficacy analysis does not explicitly describe whether missing data imputed or drawn from follow-up: 'all randomized subjects who took at least 1 dose of double-blind treatment, and who contributed at least 1 evening PEF diary entry after receiving double-blind medication, were used in the primary analysis.'
Free of selective reporting?	No	OCS-treated exacerbations were not reported in the study publication. Data request has been made to study sponsors for this information
Free of other bias?	Yes	37% screening population eligible for randomisation

SFA100314

Methods	Parallel group, multicentre study (51 centres in USA)
Participants	% ELIGIBLE OF SCREENED POPULATION: Not reported % RUN-IN PARTICIPANTS RANDOMISED: Not reported RANDOMISED: 248 (FP/SAL: 124; FP: 124) WITHDRAWALS: FP/SAL: 13/124; FP: 22/124 AGE mean (range) or mean (SD): 11 SEVERITY: Not reported

BASELINE % PRED. FEV1: Not reported
 BASELINE DOSE OF ICS: 100 mcg/day
 ASTHMA DURATION: Not reported
 ATOPY (%): Not reported
 ELIGIBILITY CRITERIA: Diagnosed with persistent asthma for 3 months or longer; experience worsened asthma symptoms during physical activity; using or used an inhaled steroid for the last 4 weeks or longer (such as Aerobid, Azmacort, Flovent, Pulmicort, QVAR, or Vanceril)
 EXCLUSION CRITERIA: Use of systemic steroids as either liquids, pills, or injections to treat asthma within the last 3 months; intermittent, seasonal, or exercise induced asthma, and not persistent asthma; admitted to a hospital within the last 6 months due to asthma symptoms; poorly controlled medical conditions that may make study participation unsafe or inappropriate in the opinion of the study physician (such as cystic fibrosis, congenital heart disease, insulin dependent diabetes, glaucoma, drug allergies, etc.)
 ELIGIBILITY CRITERIA DURING RUN IN : Not reported

Interventions	PROTOCOL: LABA+ICS versus SAME dose ICS OUTCOMES: 4 weeks RUN IN PERIOD: 7-14 days DOSE OPTIMISATION PERIOD: Not reported INTERVENTION PERIOD: 4 weeks TEST GROUP: Combination fluticasone and salmeterol 100/50mcg bid CONTROL GROUP: Fluticasone 100mcg bid NUMBER OF DEVICES: 1 COMPLIANCE: Not assessed CO-TREATMENT: prn SABA
Outcomes	PULMONARY FUNCTION TEST: FEV1 AUC; SYMPTOM SCORES: Not reported FUNCTIONAL STATUS: exacerbations requiring rescue oral steroids INFLAMMATORY MARKERS: Not reported ADVERSE EFFECTS: Reported WITHDRAWALS: Reported
Notes	Funding source: GSK Confirmation of methodology and data obtained from GSK in August 2008 Unpublished data downloaded from: www.ctr.gsk.co.uk User defined: 400

Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	Yes	See Appendix 1
Allocation concealment?	Yes	See Appendix 1
Blinding? All outcomes	Yes	Identical in haler devices used
Incomplete outcome data addressed? All outcomes	Unclear	The ITT population consisted of all subjects who were randomized to study drug.'
Free of selective reporting?	Yes	OCS-treated exacerbation data available from GSK on request
Free of other bias?	Unclear	N of screening population not reported

SFA100316

Methods	Parallel group, multicentre study (49 centres in USA)
Participants	% ELIGIBLE OF SCREENED POPULATION: Not reported % RUN-IN PARTICIPANTS RANDOMISED: Not reported RANDOMISED: 231 (FP/SAL: 113; FP: 118) WITHDRAWALS: FP/SAL: 7/113; FP 10/118 AGE mean (range) or mean (SD): 11.6 SEVERITY: Not reported BASELINE % PRED. FEV1: Not reported

	<p>BASELINE DOSE OF ICS: FP 100mcg ASTHMA DURATION: Not reported ATOPY (%): Not reported ELIGIBILITY CRITERIA: Diagnosed with persistent asthma for 3 months or longer; experience worsened asthma symptoms during physical activity; using or used an inhaled steroid for the last 4 weeks or longer (such as Aerobid, Azmacort, Flovent, Pulmicort, QVAR, or Vanceril) EXCLUSION CRITERIA: Use of systemic steroids as either liquids, pills, or injections to treat asthma within the last 3 months; intermittent, seasonal, or exercise induced asthma, and not persistent asthma; admitted to a hospital within the last 6 months due to asthma symptoms; poorly controlled medical conditions that may make study participation unsafe or inappropriate in the opinion of the study physician (such as cystic fibrosis, congenital heart disease, insulin dependent diabetes, glaucoma, drug allergies, etc.) ELIGIBILITY CRITERIA DURING RUN IN: Not reported</p>
Interventions	<p>PROTOCOL: LABA+ICS versus SAME dose ICS OUTCOMES: 4 weeks RUN IN PERIOD: 7-14 days DOSE OPTIMISATION PERIOD: Not reported INTERVENTION PERIOD: 4 weeks TEST GROUP: Combination fluticasone and salmeterol 100/50mcg bid CONTROL GROUP: Fluticasone 100mcg bid NUMBER OF DEVICES: 1 COMPLIANCE: Not assessed CO-TREATMENT: prn SABA</p>
Outcomes	<p>PULMONARY FUNCTION TEST: FEV1 AUC. SYMPTOM SCORES: Not reported FUNCTIONAL STATUS: exacerbations requiring rescue oral steroids INFLAMMATORY MARKERS: Not reported ADVERSE EFFECTS: Reported WITHDRAWALS: Reported</p>
Notes	<p>Funding source: GSK Confirmation of methodology and data obtained from GSK in August 2008 Unpublished data downloaded from: www.ctr.gsk.co.uk User defined: 400</p>

Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	Yes	See Appendix 1
Allocation concealment?	Yes	See Appendix 1
Blinding? All outcomes	Yes	Identical in haler devices used
Incomplete outcome data addressed? All outcomes	Unclear	Intention to treat population; no further details on analytical model used
Free of selective reporting?	Yes	OCS-treated exacerbation data available from GSK on request
Free of other bias?	Unclear	N of screening population not reported

Simons 1997

Methods	Crossover, single centre study
Participants	<p>Asymptomatic Children %ELIGIBLE OF SCREENED POPULATION: Not reported %RUN-IN PARTICIPANTS RANDOMISED: Not reported RANDOMISED: 16 WITHDRAWALS: 2 (13%) AGE mean (range): 13.1 (12-16 yrs) GENDER (% male): 44 SEVERITY: Not described</p>

	<p>BASELINE % PRED. FEV1: 93.4 BASELINE DOSE OF ICS: 100-200 mcg BDP BID ASTHMA DURATION: 5.9 +/- 3.4 yrs ATOPY (%): 100 ELIGIBILITY CRITERIA: 12 to 18 years old; well-controlled chronic asthma; diagnosed according to American Thoracic Society criteria; able to perform treadmill running tests; do pulmonary function tests satisfactorily; use a Nebulizer Chronolog correctly EXCLUSION CRITERIA: Any significant medical conditions other than mild asthma, allergic rhinitis, or eczema; respiratory tract infection, or an acute asthma exacerbation within the previous month; prednisone treatment, and emergency department visit or hospitalization within 3 months; life-threatening asthma episode or an adverse reaction to any B2-adrenergic agonist, or used salmeterol previously CRITERIA FOR RANDOMISATION DURING RUN-IN: N/A</p>
Interventions	<p>LABA + ICS vs SAME dose of ICS OUTCOMES measured at: day 1 and 28 RUN IN PERIOD: Not specified DOSE OF ICS DURING RUN-IN: Not reported DOSE OPTIMISATION PERIOD: None INTERVENTION PERIOD: 28 days WASH OUT PERIOD: 14 days TEST GROUP: Salmeterol 50 mcg once daily + BDP 100-200 mcg BID CONTROL GROUP: BDP 100-200 mcg BID + placebo DEVICE: Metered-dose inhaler and Nebulizer Chronolog device NUMBER OF DEVICES: 2 COMPLIANCE: Medication usage recorded in patient diary. A device inserted into MDI recorded date, hour and minute of each inhalation CO-TREATMENT: prn SABA (200 ug up to three times daily) except that albuterol was not permitted 8 hours before each exercise test. If subjects had allergic rhinitis, they were permitted to use pseudoephedrine (Sudafed) one to three times daily as needed, except on the days when exercise tests were scheduled</p>
Outcomes	<p>PULMONARY FUNCTION TEST: Exercise challenge (max % fall in FEV1 from pre-exercise baseline) SYMPTOM SCORES: Symptoms FUNCTIONAL STATUS: Rescue medication use; exacerbations requiring systemic steroids INFLAMMATORY MARKERS: Not reported ADVERSE EFFECTS: Reported WITHDRAWALS: Described Primary outcome: Not specified</p>
Notes	<p>Full-text publication Funded by GSK Confirmation of data and methodology obtained User defined number: 300 (1/2 with BDP 100 bid; 1/2 with BDP 200 bid)</p>

Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	Yes	Computer generated random numbers
Allocation concealment?	Unclear	Information not available
Blinding? All outcomes	Yes	Double-blind; double dummy
Incomplete outcome data addressed? All outcomes	Yes	All participants completed the study
Free of selective reporting?	Yes	Data on OCS-treated exacerbations available
Free of other bias?	Unclear	Information on % screening population eligible not available

Stelmach 2007

Methods	Parallel group single centre study in Poland
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Participants	% ELIGIBLE OF SCREENED POPULATION: 97 % RUN-IN PARTICIPANTS RANDOMISED: Not reported RANDOMISED: 58 (BUD/F: 29; BUD: 29) WITHDRAWALS: 0 AGE mean (range) or mean (SD): 10 years SEVERITY: Moderate BASELINE % PRED. FEV1: 94% BASELINE DOSE OF ICS: 400mcg/d BDP equivalent ASTHMA DURATION: 4 years ATOPY (%): 100 ELIGIBILITY CRITERIA: 6-18 years; history of asthma requiring treatment with ICS EXCLUSION CRITERIA: Upper RTI in previous 3 weeks; sinus disease requiring antibiotics within 4 weeks; oral steroids within 4 weeks of study entry; immunotherapy ELIGIBILITY CRITERIA DURING RUN IN: Not reported
Interventions	ICS and LABA versus SAME DOSE ICS OUTCOMES: 8 weeks RUN IN PERIOD: 4 weeks DOSE OPTIMISATION PERIOD: INTERVENTION PERIOD: 8 weeks TEST GROUP: Budesonide 200mcg + formoterol 9mcg via turbuhaler CONTROL GROUP: Budesonide 200mcg daily via turbuhaler NUMBER OF DEVICES: 2 COMPLIANCE: Not assessed CO-TREATMENT: prn SABA
Outcomes	PULMONARY FUNCTION TEST: FEV1 predicted; FEF25-75; SRaw SYMPTOM SCORES: Not reported FUNCTIONAL STATUS: Not reported INFLAMMATORY MARKERS: Not reported ADVERSE EFFECTS: Not reported WITHDRAWALS: Reported
Notes	Full-text article Funded by grant from Lodz University, Poland Confirmation of data and methodology: Not obtained User defined: 200

Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	Yes	Computer-generated randomisation schedule
Allocation concealment?	Unclear	Information not available
Blinding? All outcomes	Yes	Double-blind; double dummy
Incomplete outcome data addressed? All outcomes	Yes	All completed
Free of selective reporting?	Unclear	Unclear whether data on OCS-treated exacerbations were collected. Request for this information from study investigator has not been successful
Free of other bias?	Yes	97% screening population eligible for study

Tal 2002

Methods	Parallel study, multicentre study (48 centers in 7 countries)
Participants	Asymptomatic children %ELIGIBLE OF SCREENED POPULATION: Not reported %RUN-IN PARTICIPANTS RANDOMISED: Not reported RANDOMISED: 286 (F+BDP: 148; BDP: 138) WITHDRAWALS: F/BDP: 9; BDP: 9

AGE: mean (range): 11(4-17)
 GENDER: (%male): 62
 SEVERITY: Mild
 BASELINE % PRED. FEV1: 75
 BASELINE DOSE OF ICS: 548
 ASTHMA DURATION: 6.8 years
 ATOPY (%): Not reported
 ELIGIBILITY CRITERIA: 4-17rs old; asthma diagnosed minimum 6 months;
 FEV1 40-90%predicted and >15% reversibility in FEV1 within 15 minutes of
 bronchodilator; constant dose ICS for prior 6 weeks (>400mcg budesonide
 turbuhaler, >600mcg Budes-onide via MDI, >375 mcg fluticasone propionate or >
 600mcg CFC beclomethasone dipropionate)
 EXCLUSION CRITERIA: Unstable asthma (defined as use of oral, parenteral or
 rectal corticosteroids within 30 days of study commencement); respiratory tract
 infection within previous 4 weeks; if they had known hypersensitivity to study
 medications or inhaled lactose; use of inhaled ICS other than study medication not
 allowed
 CRITERIA FOR RANDOMISATION DURING RUN-IN: No other additional
 criteria

Interventions	LABA + ICS vs SAME dose of ICS OUTCOMES measured at: 4,8 and 12 weeks RUN IN PERIOD: 2-4 weeks DOSE OF ICS DURING RUN-IN: BUD 200 bid DOSE OPTIMISATION PERIOD: None INTERVENTION PERIOD: 12 weeks TEST GROUP: Formoterol 12 mcg bid + BDP 200 mcg BID CONTROL GROUP: BDP 200 mcg bid and placebo DEVICE: Turbuhaler NUMBER OF DEVICES: 2 COMPLIANCE: Not reported CO-TREATMENT: prn SABA. If subjects had allergic rhinitis, they were permitted to use nasal corticosteroids; treatment with other asthma medication not permitted
Outcomes	PULMONARY FUNCTION TEST: Am PEF*; pm PEF; FEV1 predicted SYMPTOM SCORES: Daily and nocturnal on 4 point scale FUNCTIONAL STATUS: Rescue medication use; night time awakening; symptom-free days INFLAMMATORY MARKERS: Not reported ADVERSE EFFECTS: Reported WITHDRAWALS: Described Primary outcome*
Notes	Full-text publication Source of Funding Astra Zeneca Confirmation of data and methodology obtained User defined number: 400

Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	Yes	Computer generated random numbers
Allocation concealment?	Yes	'Individual treatment code envelopes were provided for each subject.'
Blinding? All outcomes	Yes	Double-blind; double dummy
Incomplete outcome data addressed? All outcomes	Unclear	Explicit description of how ITT population was composed was not presented: 'An intention-to-treat analysis was used with all available data.'
Free of selective reporting?	Unclear	Unclear whether data on OCS-treated exacerbations were collected in the study. Correspondence with study investigators has not clarified this
Free of other bias?	Unclear	No information available on % screening/run-in populations eligible for the study

Teper 2005

Methods	Parallel group, single centre study	
Participants	Mild-moderate asthmatic children %ELIGIBLE OF SCREENED POPULATION: Not reported %RUN-IN PARTICIPANTS RANDOMISED: Not reported RANDOMISED: 82 (FP/SAL: 43; FP: 39) WITHDRAWAL: Not reported AGE mean: 10 years GENDER (male%): 59 ASTHMA SEVERITY: Mild to moderate BASELINE % PRED. FEV1: 95 BASELINE DOSE OF ICS (start of run in): Not reported ASTHMA DURATION: Not reported ATOPY(%): Not reported ELIGIBILITY CRITERIA: ATS diagnosed mild or moderate asthma; age 6-14 years participants; FEV1 >70 % predicted; methacholine PC20 <2mcg/ml EXCLUSION CRITERIA: Not reported CRITERIA FOR RANDOMISATION DURING RUN-IN: Not reported	
Interventions	LABA + ICS versus SAME dose ICS OUTCOMES: 12 months RUN IN PERIOD: Unclear DOSE OF ICS DURING RUN IN: Not reported DOSE OPTIMISATION PERIOD: None reported INTERVENTION PERIOD: 12 months TEST GROUP: Combination fluticasone and salmeterol 125/25 bid CONTROL GROUP: Fluticasone 125mcg bid DEVICE: MDI (+ aerochamber) NUMBER OF DEVICES: 1 COMPLIANCE: Not reported CO-TREATMENT: prn SABA	
Outcomes	PULMONARY FUNCTION TEST: FEV1 % predicted SYMPTOM SCORES: % symptom-free days; % symptom-free nights FUNCTIONAL STATUS: % SABA-free days INFLAMMATORY MARKERS: PC20 ADVERSE EFFECTS: Reported WITHDRAWAL: Not reported Primary outcome: not clear	
Notes	Unpublished conference abstract Source of Funding: Not reported Confirmation of data and methodology: Not obtained User defined number: 500	
Risk of bias		
Item	Authors' judgement	Description
Adequate sequence generation?	Unclear	Described as randomised; no other information available
Allocation concealment?	Unclear	Information not available
Blinding? All outcomes	Unclear	Double-blind; means by which assignment to treatment group is masked is not available
Incomplete outcome data addressed? All outcomes	Unclear	No information provided on ITT population
Free of selective reporting?	Unclear	Unclear whether data on OCS-treated exacerbations were collected
Free of other bias?	Unclear	No information available on % screening/ run-in populations eligible for the study

Verberne 1998a

Methods	Parallel group, multicentre study (9 centres). Three groups of which two are considered in this review
Participants	<p>Asthmatic Children</p> <p>%ELIGIBLE OF SCREENED POPULATION: Not reported</p> <p>%RUN-IN PARTICIPANTS</p> <p>RANDOMISED: Not reported</p> <p>RANDOMISED: 117 (BDP400 + Salm: 60; BDP400: 57)</p> <p>WITHDRAWALS: BDP400 + Salm: 5; BDP400: 4</p> <p>AGE: mean (SD): 11 (2.6) years</p> <p>GENDER (% male): 65</p> <p>SEVERITY: Mild</p> <p>BASELINE % PRED.FEV1: 88</p> <p>BASELINE DOSE OF ICS (SD): 489 (153)</p> <p>ASTHMA DURATION mean (SD): 8.1 (3.2)</p> <p>ATOPY(%): 88</p> <p>ELIGIBILITY CRITERIA: FEV1 between 55 and 90% predicted or a FEV1/FVC ratio of 50 to 75%; $\geq 10\%$ 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;</p> <p>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 two weeks; were allergic to B-agonists; were pregnant or lactating, or females of childbearing age who in the opinion of the supervising physician were not taking adequate contraceptive precautions; an ongoing hyposensitising programme; inability to follow therapy instructions, inability to inhale medications adequately or inability to use peak flow meter. During study: non-compliance with respect to study medication, completing the diary cards, clinic visits; withdrawal at own or investigators discretion; total number of course of oral corticosteroids more than allowed in study</p> <p>CRITERIA FOR RANDOMISATION DURING RUN IN: No additional criteria</p>
Interventions	<p>LABA + ICS vs SAME dose ICS</p> <p>OUTCOMES: Reported at 6,12,18,24, 30,36,42,48 and 54 weeks</p> <p>RUN IN PERIOD: 6 weeks</p> <p>DOSE OF ICS DURING RUN IN: BDP 200 bid</p> <p>INTERVENTION PERIOD: 54 weeks</p> <p>DOSE OPTIMISATION PERIOD: None</p> <p>TEST GROUP: (Salm50 + BDP200) Salmeterol 50 mcg bid and Beclomethasone 200 mcg bid</p> <p>CONTROL GROUP: (BDP 200 + placebo) Beclomethasone 200 mcg bid + placebo</p> <p>DEVICE: Rotadisks in combination with a diskhaler</p> <p>NUMBER OF DEVICES: 2</p> <p>COMPLIANCE: Not reported</p> <p>CO-TREATMENT: pm SABA</p>
Outcomes	<p>PULMONARY FUNCTION TEST: FEV1; am PEF; pm PEF; FVC</p> <p>SYMPTOM SCORES: Asthma symptoms like wheezing, dyspnea, exercise induced asthma and cough were scored in the morning and evening using a scale from 1 to 3</p> <p>FUNCTIONAL STATUS: Rescue medication use; exacerbation (requiring systemic steroids); height, body weight, heart rate, systolic and diastolic blood pressure were measured</p> <p>INFLAMMATORY MARKERS: Total IgE</p> <p>ADVERSE EFFECTS: Reported</p> <p>WITHDRAWALS: Reported</p> <p>*primary outcome: airway calibre measured as FEV1 and airway responsiveness to methacholine</p>
Notes	<p>Full-text publication</p> <p>Funded by GSK</p> <p>Confirmation of methodology and data obtained</p> <p>User-defined number: 400</p>
Risk of bias	
Item	Authors' judgement
	Description

Adequate sequence generation?	Yes	Computer generated random numbers
Allocation concealment?	Yes	Telephone notification of assignment by coordinating centre
Blinding? All outcomes	Yes	Double-blind; identical placebo used
Incomplete outcome data addressed? All outcomes	Unclear	Not clear how population for primary outcome. Incomplete diary card data not included in analysis: 'Where patients failed to complete their daily record cards for more than 7 d in any 14-d period such assessments were not included in the analysis. Otherwise, when there were missing days in the record, pro rata adjustment was made to give a 2-wk assessment.'
Free of selective reporting?	Yes	OCS-treated exacerbation data available
Free of other bias?	Unclear	No information available on % screening/run-in populations eligible for the study

Verberne 1998b

Methods	See Verberne 1998a
Participants	As for Verberne 1998a, except for RANDOMISED: 120 (BDP400 + Salm: 60; BDP800: 60) WITHDRAWALS: BDP400 + Salm: 5; BDP800: 6
Interventions	LABA + ICS vs INCREASED dose ICS OUTCOMES: reported at 6,12,18,24, 30,36,42,48 and 54 RUN IN PERIOD: 6 weeks DOSE OF ICS DURING RUN-IN: BDP 200 bid DOSE OPTIMISATION PERIOD: None INTERVENTION PERIOD: 54 weeks TEST GROUP: (Salm50 + BDP200): Salmeterol 50 mcg bid + beclomethasone dipropionate 200 mcg bid CONTROL GROUP: (BDP400 + placebo): Beclomethasone dipropionate 400 mcg/day + placebo DEVICE: Rotadisks in combination with a diskhaler NUMBER OF DEVICES: 2 COMPLIANCE: Not reported CO-TREATMENT: prn SABA
Outcomes	PULMONARY FUNCTION TEST: FEV1; am PEF; pm PEF; FVC SYMPTOM SCORES: Asthma symptoms like wheezing, dyspnea, exercise induced asthma and cough were scored in the morning and evening using a scale from 1 to 3 FUNCTIONAL STATUS: Rescue medication use; exacerbation (requiring 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 GSK Confirmation of methodology and data obtained User-defined number: 400

Risk of bias

Item	Authors' judgement	Description
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Adequate sequence generation?	Yes	See Verberne 1998a
Allocation concealment?	Yes	See Verberne 1998a
Blinding? All outcomes	Yes	See Verberne 1998a
Incomplete outcome data addressed? All outcomes	Unclear	See Verberne 1998a
Free of selective reporting?	Yes	See Verberne 1998a
Free of other bias?	Unclear	See Verberne 1998a

Zimmerman 2004a

Methods	Parallel-group, multicentre study (27 centres in Canada). Three treatment arms comparing LABA/ICS with 2 doses of LABA and ICS alone. Two groups will be considered here and since the same control group is being used for both comparisons half the control group will be applied to each
Participants	Children aged ≥ 6 -11 years %ELIGIBLE OF SCREENED POPULATION: Not reported % RUN-IN PARTICIPANTS RANDOMISED: 68 RANDOMISED: 196 (F + usual ICS bid: 95; usual ICS: 101) WITHDRAWALS: F + usual ICS: 7; usual ICS: 16 Mean AGE years(range): 9 (6 to 11) GENDER: (%male): 63 SEVERITY: Moderate BASELINE FEV1 (% Pred): 77.4 BASELINE DOSE OF ICS: 445 ASTHMA DURATION (years): 5.7 ATOPY (%): Not reported ELIGIBILITY CRITERIA: Aged ≥ 12 years; clinical diagnosis of asthma according to ATS criteria for at least 12 months; treated with ICS for at least 3 month prior to entry; FEV1 between 50-90 % predicted normal; $\geq 15\%$ reversibility after bronchodilator; asthma symptoms suggestive that additional therapy might be needed; able to use peak flow meter and turbuhaler, answer questions form the Pediatric Asthma Quality of Life Questionnaire and parent or guardian had to complete a daily diary card EXCLUSION CRITERIA: Systemic corticosteroids or anti-leukotrienes within 30 days of study entry, astemizole within 120 days, sodium cromoglycate or ketotifen within 7 days, salmeterol or formoterol within 72 hours or xanthines or antihistamines within 48 hours; nasal corticosteroids and immunotherapy permitted provided dose had been constant for at least 30 days and 90 days respectively prior to study entry; smoking history RANDOMISATION CRITERIA FOLLOWING RUN-IN: Post-bronchodilator reversibility of at least 12 % of the pre-bronchodilator value or at least 9% of predicted normal or diurnal variability or at least 15% on any 5 of the last 10 days of run-in; 75/24% compliance with prescribed dose as assessed by diary card; symptoms during the last 10 days of run-in (defined as having one or more of the following: four or more inhalations of rescue medication; daytime symptoms on 4 or more days, or night time awakening on 1 or more nights)
Interventions	LABA + ICS versus usual dose of ICS OUTCOMES: Measured at trial entry and after 4,8 and 12 week intervals RUN-IN PERIOD: 2 weeks DOSE OF ICS DURING RUN-IN: Usual ICS DOSE OPTIMISATION PERIOD: None INTERVENTION PERIOD: 12 weeks TEST GROUP: Usual dose ICS + Formoterol 12 mcgs bid CONTROL GROUP: Usual dose ICS + placebo bid DEVICE: Turbuhaler NUMBER OF DEVICES: 2 COMPLIANCE: Measured during run-in CO-TREATMENT: prn SABA
Outcomes	PULMONARY FUNCTION TEST: am PEF*; pm PEF; FEV1 (Note: Mean value during treatment for 12 weeks reported rather than value at endpoint) SYMPTOM SCORES: Total asthma symptom score

FUNCTIONAL STATUS: Rescue medication use; Pediatric asthma quality of life score
 INFLAMMATORY MARKERS: Not described
 ADVERSE EFFECTS: Described
 WITHDRAWALS: Described
 Primary outcome measure*

Notes	Full-text publication Supported by: not stated Confirmation of methodology and data extraction not obtained User defined number (mean ICS dose in LABA group in mcg/day of BDP-equivalent): 444
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Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	Unclear	Described as randomised; no other information presented
Allocation concealment?	Unclear	Information not available
Blinding? All outcomes	Yes	Double-blind; double dummy
Incomplete outcome data addressed? All outcomes	Unclear	Intention to treat population presented in the study publication, but handling of missing data not described
Free of selective reporting?	Yes	Exacerbations described as those requiring OCS-treatment and those requiring increased inhaled steroid. Separate OCS-treated exacerbation data could not be extracted
Free of other bias?	Yes	68% of screening population randomised

Zimmerman 2004b

Methods	See Zimmerman 2004a
Participants	See Zimmerman 2004a, except for RANDOMISED: 196 (F + Usual ICS: 95; usual ICS: 101) WITHDRAWALS: F + usual ICS: 7; usual ICS: 16
Interventions	As for Zimmerman 2004a, except for: TEST GROUP: Usual dose ICS + Formoterol 6 mcgs bid
Outcomes	See Zimmerman 2004a
Notes	See Zimmerman 2004a

Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	Unclear	See Zimmerman 2004a
Allocation concealment?	Unclear	See Zimmerman 2004a
Blinding? All outcomes	Yes	See Zimmerman 2004a
Incomplete outcome data addressed? All outcomes	Unclear	See Zimmerman 2004a
Free of selective reporting?	Yes	See Zimmerman 2004a
Free of other bias?	Yes	See Zimmerman 2004a

LABA: Long-acting beta agonist (salmeterol or formoterol);

Sal: Salmeterol;

F: Formoterol;

ICS: Inhaled corticosteroid;

BUD: Budesonide;

FP: Fluticasone;

BID: twice per day;

QD: once per day

Characteristics of excluded studies [ordered by study ID]

Study	Reason for exclusion
Aldington 2006	Inadequate duration
Aubier 1999	Study conducted in adults
Bergmann 2004	Not exclusively children
Borker 2005	No LABA alone
Boulet 2003	Adult study
Bousquet 2005	No LABA alone
Bracamonte 2005	Comparison of devices
Bruce 2005	Review article
Bruggenjurgen 2005	Not exclusively paediatric
Buchvald 2002	No ICS alone
Buhl 2004	Adjustable dosing in adults
Caffey 2005	No LABA alone
Chopra 2005	No ICS alone
Chuchalin 2005	No ICS alone
Cowan 2004	Not RCT
Daviskas 2005	No ICS alone
Delaronde 2005	No assessment of asthma control
Dubus 2003	No LABA
Emeryk 2003	Comparison of devices
Everden 2004	Not placebo-controlled
Fardon 2005	No LABA
Grady 1995	Not exclusively children
Holgate 2004	Study of Xolair
Holt 2005	Not exclusively children
Ilowite 2004	Adult study
Jenkins 2005	Adult study
Karaman 2007	No prior ICS exposure
Lara-Perez 2005	No ICS alone
Levy 2005	Co-treatment with ICS in only 3/4 of participants. Study primarily interested in efficacy of formoterol on top of usual therapy. ICS dosing not standardised
LOCCS	Adult study
Matthys 2004	Open study
Miraglia 2007	No prior exposure to ICS

Mitchell 2005	Not LABA
Mitra 2003	No concurrent ICS
Morice 2005	Not exclusively children
Morice 2005a	Not exclusively children
Murray 2004	Not exclusively children
Nathan 2005	Not exclusively children
Nelson 2006	Not exclusively children
Nguyen 2005	Not RCT
O'Byrne 2001	Adolescents and adults
Pearlman 2004	Study in adults
Peroni 2005	No ICS alone
Pijnenburg 2005	No LABA
Prieto 2005	Not exclusively children
Renzi 2005	Not exclusively children
SAM30002	Not exclusively children
SAM40101	Inadequate duration
SAS30021	Steroid naive children
Schauer 2003	No ICS alone
Scicchitano 2004a	Study in adults
Selroos 2004	No LABA
SFCF3001	Different devices
SFCF3002	Different devices
Sienra-Monge 2004	Not RCT
Sorkness 2007	Mixed population at baseline
Stelmach 2008	Steroids were stopped for 4 weeks prior to study visit
Storms 2004	Study in adults
van den Toorn 2005	No ICS alone
Vogelmeier 2005	No ICS alone
Von Berg 2003	No concurrent ICS.
Weiler 2005	Study in adults
You-Ning 2005	Study in adults; no ICS alone

EIB: Exercise-induced bronchoconstriction; LABA: long-acting beta-agonist

DATA AND ANALYSES

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

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 # patients with exacerbations requiring systemic steroids	8	1084	Risk Ratio (M-H, Fixed, 95% CI)	0.92 [0.60, 1.40]
1.1 Mean baseline FEV1 $\geq$ 80% of predicted	4	375	Risk Ratio (M-H, Fixed, 95% CI)	0.87 [0.47, 1.64]
1.2 Mean baseline FEV1 61-79% of predicted	2	230	Risk Ratio (M-H, Fixed, 95% CI)	0.89 [0.48, 1.64]
1.3 Mean baseline FEV1 not reported	2	479	Risk Ratio (M-H, Fixed, 95% CI)	1.54 [0.26, 9.09]
2 # patients with exacerbations requiring hospitalisation	6	1266	Risk Ratio (M-H, Fixed, 95% CI)	1.65 [0.83, 3.25]
2.1 Mean baseline FEV1 $\geq$ 80% of predicted	2	139	Risk Ratio (M-H, Fixed, 95% CI)	0.99 [0.18, 5.39]
2.2 Mean baseline FEV1 61-79% of predicted	3	772	Risk Ratio (M-H, Fixed, 95% CI)	1.81 [0.86, 3.82]
2.3 Mean baseline FEV1 not reported	1	355	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
3 Serious adverse events	17	4165	Risk Ratio (M-H, Fixed, 95% CI)	1.16 [0.73, 1.85]
3.1 Mean baseline FEV1 $\geq$ 80% of predicted	9	2041	Risk Ratio (M-H, Fixed, 95% CI)	0.87 [0.42, 1.80]
3.2 Mean baseline FEV1 61-79% of predicted	5	1283	Risk Ratio (M-H, Fixed, 95% CI)	1.39 [0.74, 2.59]
3.3 Mean baseline FEV1 not reported	3	841	Risk Ratio (M-H, Fixed, 95% CI)	2.0 [0.18, 21.86]
4 Total # withdrawals	21	4295	Risk Ratio (M-H, Fixed, 95% CI)	0.79 [0.67, 0.93]
4.1 Mean baseline FEV1 $\geq$ 80% of predicted	11	2126	Risk Ratio (M-H, Fixed, 95% CI)	0.80 [0.63, 1.02]
4.2 Mean baseline FEV1 61-79% of predicted	6	1315	Risk Ratio (M-H, Fixed, 95% CI)	0.88 [0.68, 1.15]
4.3 Mean baseline FEV1 not reported	4	854	Risk Ratio (M-H, Fixed, 95% CI)	0.56 [0.35, 0.91]
5 # withdrawals due to poor asthma control or exacerbation	9	1615	Risk Ratio (M-H, Fixed, 95% CI)	0.79 [0.42, 1.48]
5.1 Mean baseline FEV1 $\geq$ 80% of predicted	3	342	Risk Ratio (M-H, Fixed, 95% CI)	0.54 [0.15, 1.92]
5.2 Mean baseline FEV1 61-79% of predicted	4	794	Risk Ratio (M-H, Fixed, 95% CI)	0.78 [0.34, 1.81]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
5.3 Mean baseline FEV1 not reported	2	479	Risk Ratio (M-H, Fixed, 95% CI)	1.36 [0.31, 5.98]
6 # withdrawals due to serious non-respiratory event	2		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
6.1 Mean baseline FEV1 61-79% of predicted	2		Risk Ratio (M-H, Random, 95% CI)	Not estimable
7 # withdrawals due to adverse events	19	4419	Risk Ratio (M-H, Fixed, 95% CI)	0.78 [0.52, 1.19]
7.1 Mean baseline FEV1 >=80% of predicted	9	2052	Risk Ratio (M-H, Fixed, 95% CI)	0.62 [0.34, 1.13]
7.2 Mean baseline FEV1 61-79% of predicted	7	1585	Risk Ratio (M-H, Fixed, 95% CI)	1.40 [0.68, 2.87]
7.3 Mean baseline FEV1 not reported	3	782	Risk Ratio (M-H, Fixed, 95% CI)	0.37 [0.11, 1.25]
8 Change in FEV1 at endpoint stratifying on baseline FEV1	9	1235	Litres (Random, 95% CI)	0.08 [0.06, 0.11]
8.1 Mean Baseline FEV1 >= 80% of predicted	5	808	Litres (Random, 95% CI)	0.09 [0.04, 0.15]
8.2 Mean Baseline FEV1 61-79% of predicted	4	427	Litres (Random, 95% CI)	0.08 [0.05, 0.11]
8.3 Mean Baseline FEV1 not reported	0	0	Litres (Random, 95% CI)	Not estimable
9 Change in FEV1 at endpoint (% predicted) stratifying on baseline FEV1	5	476	Mean Difference (IV, Fixed, 95% CI)	2.35 [0.07, 4.64]
9.1 Mean baseline FEV1 >= 80 % predicted	2	156	Mean Difference (IV, Fixed, 95% CI)	3.20 [0.07, 6.33]
9.2 Mean Baseline FEV1 61-79% of predicted	2	238	Mean Difference (IV, Fixed, 95% CI)	3.35 [-1.50, 8.20]
9.3 Mean Baseline FEV1 not reported	1	82	Mean Difference (IV, Fixed, 95% CI)	-0.40 [-5.03, 4.23]
10 FEV1 predicted at endpoint stratifying on baseline FEV1	4	634	% (Random, 95% CI)	3.56 [1.83, 5.28]
10.1 Mean Baseline FEV1 >= 80% of predicted	1	58	% (Random, 95% CI)	1.1 [-4.74, 6.94]
10.2 Mean Baseline FEV1 61-79% of predicted	3	576	% (Random, 95% CI)	3.79 [1.99, 5.60]
10.3 Mean Baseline FEV1 not reported	0	0	% (Random, 95% CI)	Not estimable
11 Change in FEV1 (L or % pred) stratifying on trial duration	11		Std. Mean Difference (Fixed, 95% CI)	Subtotals only

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
11.1 Change in FEV1 (L) or (% predicted) at 6 +/- 2 weeks of treatment	1		Std. Mean Difference (Fixed, 95% CI)	0.31 [-0.31, 0.93]
11.2 Change in FEV1 (L) or (% predicted) at 12 +/- 4 weeks of treatment	10		Std. Mean Difference (Fixed, 95% CI)	0.32 [0.23, 0.42]
11.3 Change in FEV1 (L) or (% predicted) at 24 +/- 4 weeks of treatment	2		Std. Mean Difference (Fixed, 95% CI)	0.36 [0.13, 0.60]
11.4 Change in FEV1 (L) or (% predicted) at 52 +/- 4 weeks of treatment	0		Std. Mean Difference (Fixed, 95% CI)	Not estimable
12 End of treatment FEV1 (L)	3	901	Mean Difference (IV, Fixed, 95% CI)	-0.54 [-0.61, -0.47]
12.1 Mean Baseline FEV1 >= 80% of predicted	2	615	Mean Difference (IV, Fixed, 95% CI)	-0.54 [-0.61, -0.47]
12.2 Mean baseline FEV1 61-79% of predicted	1	286	Mean Difference (IV, Fixed, 95% CI)	Not estimable
13 Change in PEF variability at endpoint	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
13.1 Mean baseline FEV1 61-79% of predicted	1		Mean Difference (IV, Fixed, 95% CI)	Not estimable
14 Change in morning PEF at endpoint	14	2934	L/min (Fixed, 95% CI)	10.38 [8.23, 12.52]
14.1 Mean Baseline FEV1 >= 80% of predicted	8	1870	L/min (Fixed, 95% CI)	11.23 [8.31, 14.15]
14.2 Mean Baseline FEV1 61-79% of predicted	5	713	L/min (Fixed, 95% CI)	9.99 [6.58, 13.41]
14.3 Mean Baseline FEV1 not reported	1	351	L/min (Fixed, 95% CI)	5.7 [-2.62, 14.02]
15 Morning PEF at endpoint	3	459	L/min (Fixed, 95% CI)	8.64 [2.53, 14.75]
15.1 Mean Baseline FEV1 >= 80% of predicted	0	0	L/min (Fixed, 95% CI)	Not estimable
15.2 Mean Baseline FEV1 61-79% of predicted	3	459	L/min (Fixed, 95% CI)	8.64 [2.53, 14.75]
16 Change in morning PEF (% predicted)	1		% (Fixed, 95% CI)	Totals not selected
16.1 Mean Baseline FEV1 >= 80% of predicted	0		% (Fixed, 95% CI)	Not estimable
16.2 Mean Baseline FEV1 61-79% of predicted	1		% (Fixed, 95% CI)	Not estimable
16.3 Mean Baseline FEV1 not reported	0		% (Fixed, 95% CI)	Not estimable

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
17 Change in evening PEF at endpoint	11	2636	L/min (Fixed, 95% CI)	9.37 [6.96, 11.79]
17.1 Mean Baseline FEV1 >= 80% of predicted	7	1480	L/min (Fixed, 95% CI)	9.38 [6.29, 12.47]
17.2 Mean Baseline FEV1 61-79% of predicted	3	805	L/min (Fixed, 95% CI)	10.46 [6.15, 14.78]
17.3 Mean Baseline FEV1 not reported	1	351	L/min (Fixed, 95% CI)	5.0 [-3.58, 13.58]
18 Change in evening PEF (% predicted)	1		% (Fixed, 95% CI)	Totals not selected
18.1 Mean Baseline FEV1 >= 80% of predicted	0		% (Fixed, 95% CI)	Not estimable
18.2 Mean Baseline FEV1 61-79% of predicted	1		% (Fixed, 95% CI)	Not estimable
18.3 Mean Baseline FEV1 not reported	0		% (Fixed, 95% CI)	Not estimable
19 Change in clinic PEF (L/min)	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
19.1 Mean baseline FEV1 not reported	1		Mean Difference (IV, Fixed, 95% CI)	Not estimable
20 Change in # daytime rescue inhalations (puffs per day) at endpoint	5	1278	Mean Difference (IV, Random, 95% CI)	-0.07 [-0.14, 0.01]
20.1 Mean baseline FEV1 61-79% of predicted	5	1278	Mean Difference (IV, Random, 95% CI)	-0.07 [-0.14, 0.01]
20.2 Mean Baseline FEV1 not reported	0	0	Mean Difference (IV, Random, 95% CI)	Not estimable
21 % days without bronchodilator usage	3	712	Mean Difference (IV, Fixed, 95% CI)	-0.56 [-2.84, 1.73]
21.1 Mean baseline FEV1 >= 80 % predicted	2	630	Mean Difference (IV, Fixed, 95% CI)	0.01 [-3.45, 3.47]
21.2 Mean baseline FEV1 not reported	1	82	Mean Difference (IV, Fixed, 95% CI)	-1.0 [-4.04, 2.04]
22 Mean change in asthma symptom score	4	1119	Std. Mean Difference (IV, Fixed, 95% CI)	-0.04 [-0.16, 0.08]
22.1 Mean baseline FEV1 >=80% of predicted	4	1119	Std. Mean Difference (IV, Fixed, 95% CI)	-0.04 [-0.16, 0.08]
23 Change in # nighttime rescue inhalations at endpoint	1		Mean Difference (IV, Random, 95% CI)	Totals not selected
23.1 Mean baseline FEV1 61-79% of predicted	1		Mean Difference (IV, Random, 95% CI)	Not estimable
24 Change in night time awakening (number of nights) at endpoint	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
24.1 Mean baseline FEV1 61-79% of predicted	1		Mean Difference (IV, Fixed, 95% CI)	Not estimable

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
25 % nights with awakening	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
25.1 Mean Baseline FEV1 $\geq$ 80% of predicted			Mean Difference (IV, Fixed, 95% CI)	Not estimable
25.2 Mean baseline FEV1 61-79% of predicted	1		Mean Difference (IV, Fixed, 95% CI)	Not estimable
26 Change in % symptom-free days at endpoint	3	833	Mean Difference (IV, Random, 95% CI)	1.30 [-3.12, 5.71]
26.1 Mean baseline FEV1 $\geq$ 80% of predicted	3	833	Mean Difference (IV, Random, 95% CI)	1.30 [-3.12, 5.71]
26.2 Mean baseline FEV1 61-79% of predicted	0	0	Mean Difference (IV, Random, 95% CI)	Not estimable
27 % symptom-free days	3	392	Std. Mean Difference (IV, Random, 95% CI)	0.07 [-0.14, 0.27]
27.1 Mean baseline FEV1 61-79% of predicted	1	286	Std. Mean Difference (IV, Random, 95% CI)	0.12 [-0.11, 0.35]
27.2 Mean baseline FEV1 $\geq$ 80% of predicted	0	0	Std. Mean Difference (IV, Random, 95% CI)	Not estimable
27.3 Unclear baseline FEV1	2	106	Std. Mean Difference (IV, Random, 95% CI)	-0.12 [-0.56, 0.31]
28 % symptom-free nights at 52 +/- 4 weeks	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
28.1 Mean Baseline FEV1 not reported	1		Mean Difference (IV, Fixed, 95% CI)	Not estimable
29 Quality of life (P-AQLQ)	10	2333	Mean Difference (IV, Fixed, 95% CI)	0.03 [-0.04, 0.11]
29.1 Mean baseline FEV1 61-79% of predicted	4	747	Mean Difference (IV, Fixed, 95% CI)	-0.12 [-0.28, 0.03]
29.2 Mean baseline FEV1 $\geq$ 80% of predicted	6	1586	Mean Difference (IV, Fixed, 95% CI)	0.07 [-0.01, 0.16]
29.3 Unclear baseline FEV1	0	0	Mean Difference (IV, Fixed, 95% CI)	Not estimable
30 Total # adverse events	15	3284	Risk Ratio (M-H, Fixed, 95% CI)	1.04 [0.98, 1.10]
30.1 Mean baseline FEV1 $\geq$ 80% of predicted	7	1424	Risk Ratio (M-H, Fixed, 95% CI)	1.09 [1.01, 1.19]
30.2 Mean baseline FEV1 61-79% of predicted	4	995	Risk Ratio (M-H, Fixed, 95% CI)	1.02 [0.93, 1.12]
30.3 Mean baseline FEV1 not reported	4	865	Risk Ratio (M-H, Fixed, 95% CI)	0.94 [0.80, 1.09]
31 # patients with headache	14	2966	Risk Ratio (M-H, Fixed, 95% CI)	1.10 [0.90, 1.33]
31.1 Mean baseline FEV1 $\geq$ 80% of predicted	4	779	Risk Ratio (M-H, Fixed, 95% CI)	1.02 [0.78, 1.33]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
31.2 Mean baseline FEV1 61-79% of predicted	7	1346	Risk Ratio (M-H, Fixed, 95% CI)	1.18 [0.85, 1.65]
31.3 Mean baseline FEV1 not reported	3	841	Risk Ratio (M-H, Fixed, 95% CI)	1.15 [0.65, 2.04]
32 # patients with oral thrush	5	1155	Risk Ratio (M-H, Fixed, 95% CI)	3.78 [0.63, 22.75]
32.1 Mean baseline FEV1 61-79% of predicted	1	206	Risk Ratio (M-H, Fixed, 95% CI)	3.24 [0.13, 78.62]
32.2 FEV1 $\geq$ 80% predicted	4	949	Risk Ratio (M-H, Fixed, 95% CI)	4.04 [0.46, 35.52]
32.3 Mean baseline FEV1 not reported	0	0	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
33 # patients with tremor	6	1467	Risk Ratio (M-H, Fixed, 95% CI)	3.07 [0.38, 25.05]
33.1 Mean baseline FEV1 $\geq$ 80% of predicted	3	959	Risk Ratio (M-H, Fixed, 95% CI)	5.30 [0.26, 109.66]
33.2 Mean baseline FEV1 61-79% of predicted	3	508	Risk Ratio (M-H, Fixed, 95% CI)	1.46 [0.06, 35.18]
33.3 Mean baseline FEV1 not reported	0	0	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
34 # patients with tachycardia or palpitations	5	1052	Risk Ratio (M-H, Fixed, 95% CI)	0.40 [0.05, 3.25]
34.1 Mean baseline FEV1 $\geq$ 80% of predicted	2	545	Risk Ratio (M-H, Fixed, 95% CI)	0.33 [0.01, 8.02]
34.2 Mean baseline FEV1 61-79% of predicted	3	507	Risk Ratio (M-H, Fixed, 95% CI)	0.49 [0.03, 7.61]
34.3 Mean baseline FEV1 not reported	0	0	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
35 # patients with adverse cardiovascular events	2	148	Risk Ratio (M-H, Fixed, 95% CI)	0.31 [0.01, 7.49]
35.1 Mean baseline FEV1 $\geq$ 80% of predicted	1	116	Risk Ratio (M-H, Fixed, 95% CI)	0.31 [0.01, 7.49]
35.2 Mean baseline FEV1 61-79% of predicted	1	32	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
36 Change in % PC 20 at endpoint	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
36.1 Mean baseline FEV1 $\geq$ 80% of predicted	1		Mean Difference (IV, Fixed, 95% CI)	Not estimable
37 Change in height (cm) as SD scores at 24 $\pm$ 4 weeks	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
37.1 Mean baseline FEV1 $\geq$ 80% of predicted	1		Mean Difference (IV, Fixed, 95% CI)	Not estimable

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
38 Change in height at one year	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected

Comparison 2
Long-acting beta2 agonist + ICS versus placebo +
higher dose of ICS

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 # patients with exacerbations requiring oral steroids	2	441	Risk Ratio (M-H, Fixed, 95% CI)	1.50 [0.65, 3.48]
1.1 Baseline FEV1 $\geq$ 80 % predicted	2	441	Risk Ratio (M-H, Fixed, 95% CI)	1.50 [0.65, 3.48]
1.2 Baseline FEV1 61-79 % predicted	0	0	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
2 # patients with exacerbations requiring hospitalisation	4	1026	Risk Ratio (M-H, Fixed, 95% CI)	2.21 [0.74, 6.64]
2.1 Baseline FEV1 $\geq$ 80 % predicted	2	441	Risk Ratio (M-H, Fixed, 95% CI)	3.01 [0.32, 28.65]
2.2 Baseline FEV1 61-79 % predicted	1	225	Risk Ratio (M-H, Fixed, 95% CI)	3.17 [0.67, 14.95]
2.3 Mean baseline FEV1 not reported	1	360	Risk Ratio (M-H, Fixed, 95% CI)	0.33 [0.01, 8.13]
3 Serious adverse events	5	1037	Risk Ratio (M-H, Random, 95% CI)	1.45 [0.63, 3.33]
3.1 Baseline FEV1 $\geq$ 80 % predicted	2	423	Risk Ratio (M-H, Random, 95% CI)	1.00 [0.26, 3.91]
3.2 Baseline FEV1 61-79 % predicted	1	223	Risk Ratio (M-H, Random, 95% CI)	2.90 [1.10, 7.64]
3.3 Mean baseline FEV1 not reported	2	391	Risk Ratio (M-H, Random, 95% CI)	0.51 [0.10, 2.77]
4 Total # withdrawals	5	1026	Risk Ratio (M-H, Fixed, 95% CI)	0.71 [0.42, 1.20]
4.1 Baseline FEV1 $\geq$ 80 % predicted	1	120	Risk Ratio (M-H, Fixed, 95% CI)	1.25 [0.35, 4.43]
4.2 Baseline FEV1 61-79 % predicted	1	223	Risk Ratio (M-H, Fixed, 95% CI)	0.65 [0.30, 1.39]
4.3 Mean baseline FEV1 not reported	3	683	Risk Ratio (M-H, Fixed, 95% CI)	0.59 [0.24, 1.49]
5 # withdrawals due to adverse events	2	343	Risk Ratio (M-H, Fixed, 95% CI)	1.44 [0.25, 8.42]
5.1 Baseline FEV1 $\geq$ 80 % predicted	1	120	Risk Ratio (M-H, Fixed, 95% CI)	2.0 [0.19, 21.47]
5.2 Baseline FEV1 61-79 % predicted	1	223	Risk Ratio (M-H, Fixed, 95% CI)	0.91 [0.06, 14.30]
5.3 Baseline FEV1 $\leq$ 60 % predicted	0	0	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
5.4 Mean baseline FEV1 not reported	0	0	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
6 # withdrawals due to poor asthma control or exacerbation	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
6.1 Baseline FEV1 >= 80 % predicted	1		Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
6.2 Baseline FEV1 61-79 % predicted	0		Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
6.3 Baseline FEV1 <= 60 % predicted	0		Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
7 Change in FEV1 at endpoint	2	526	Mean Difference (Fixed, 95% CI)	0.01 [-0.03, 0.05]
7.1 Baseline FEV1 >= 80 % predicted	1	303	Mean Difference (Fixed, 95% CI)	Not estimable
7.2 Baseline FEV1 61-79 % predicted	1	223	Mean Difference (Fixed, 95% CI)	0.04 [-0.06, 0.14]
8 FEV1 at endpoint	1		Mean Difference (IV, Random, 95% CI)	Totals not selected
8.1 Baseline FEV1 >= 80 % predicted	0		Mean Difference (IV, Random, 95% CI)	Not estimable
8.2 Baseline FEV1 61-79 % predicted	0		Mean Difference (IV, Random, 95% CI)	Not estimable
8.3 Mean Baseline FEV1 not reported	1		Mean Difference (IV, Random, 95% CI)	Not estimable
9 Change in FEV1 predicted at endpoint	1		% (Random, 95% CI)	Totals not selected
9.1 Baseline FEV1 >= 80 % predicted	1		% (Random, 95% CI)	Not estimable
9.2 Baseline FEV1 61-79 % predicted	0		% (Random, 95% CI)	Not estimable
10 Change in morning PEF (L/min) at endpoint	4	1002	Mean Difference (IV, Random, 95% CI)	7.55 [3.57, 11.53]
10.1 Baseline FEV1 >= 80 % predicted	2	423	Mean Difference (IV, Random, 95% CI)	7.75 [2.48, 13.02]
10.2 Baseline FEV1 61-79 % predicted	1	223	Mean Difference (IV, Random, 95% CI)	9.0 [-0.07, 18.07]
10.3 Mean Baseline FEV1 not reported	1	356	Mean Difference (IV, Random, 95% CI)	5.90 [-2.28, 14.08]
11 Change in pm PEF		882	Mean Difference (Fixed, 95% CI)	5.50 [1.21, 9.79]
11.1 Baseline FEV1 predicted >=80%	1	303	Mean Difference (Fixed, 95% CI)	5.4 [-0.56, 11.36]
11.2 Baseline FEV1 61-79 % predicted	1	223	Mean Difference (Fixed, 95% CI)	7.0 [-2.07, 16.07]
11.3 Mean Baseline FEV1 not reported	1	356	Mean Difference (Fixed, 95% CI)	4.4 [-4.05, 12.85]
12 Change in clinic PEF (L/min)	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
12.1 Mean Baseline FEV1 not reported	1		Mean Difference (IV, Fixed, 95% CI)	Not estimable
13 # daytime rescue inhalations at endpoint	1		puffs/d (Fixed, 95% CI)	Totals not selected
13.1 Baseline FEV1 61-79% predicted	1		puffs/d (Fixed, 95% CI)	Not estimable

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
14 Number of nighttime awakenings	1		Awakenings/yr (Fixed, 95% CI)	Totals not selected
14.1 Baseline FEV1 61-79% predicted	1		Awakenings/yr (Fixed, 95% CI)	Not estimable
15 Total # adverse events		814	Risk Ratio (M-H, Random, 95% CI)	1.05 [0.90, 1.23]
15.1 Baseline FEV1 >= 80 % predicted	1	120	Risk Ratio (M-H, Random, 95% CI)	1.13 [1.02, 1.26]
15.2 Baseline FEV1 61-79 % predicted	0	0	Risk Ratio (M-H, Random, 95% CI)	Not estimable
15.3 Mean baseline FEV1 not reported	3	694	Risk Ratio (M-H, Random, 95% CI)	0.99 [0.84, 1.16]
16 # patients with headache	3	790	Risk Ratio (M-H, Fixed, 95% CI)	1.37 [0.98, 1.90]
16.1 Baseline FEV1 >= 80 % predicted	1	120	Risk Ratio (M-H, Fixed, 95% CI)	1.56 [0.93, 2.62]
16.2 Baseline FEV1 61-79 % predicted	0	0	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
16.3 Mean baseline FEV1 not reported	2	670	Risk Ratio (M-H, Fixed, 95% CI)	1.27 [0.83, 1.95]
17 Linear growth	2		Mean Difference (Fixed, 95% CI)	1.21 [0.72, 1.70]
18 # nighttime rescue inhalations (puffs per day; mean over study period)	1		Mean Difference (IV, Random, 95% CI)	Totals not selected
18.1 Mean baseline FEV1 61-79% of predicted	0		Mean Difference (IV, Random, 95% CI)	Not estimable
18.2 Mean Baseline FEV1 not reported	1		Mean Difference (IV, Random, 95% CI)	Not estimable
19 # daytime rescue inhalations (puffs per day; mean over study period)	1		Mean Difference (IV, Random, 95% CI)	Totals not selected
19.1 Mean baseline FEV1 61-79% of predicted	0		Mean Difference (IV, Random, 95% CI)	Not estimable
19.2 Mean Baseline FEV1 not reported	1		Mean Difference (IV, Random, 95% CI)	Not estimable
20 Deaths	2	459	Risk Difference (M-H, Fixed, 95% CI)	Not estimable
20.1 Baseline FEV1 >= 80 % predicted	0	0	Risk Difference (M-H, Fixed, 95% CI)	Not estimable
20.2 Baseline FEV1 61-79 % predicted	0	0	Risk Difference (M-H, Fixed, 95% CI)	Not estimable
20.3 Mean baseline FEV1 not reported	2	459	Risk Difference (M-H, Fixed, 95% CI)	Not estimable
21 Daytime asthma symptom score (mean over study period)	1		Std. Mean Difference (IV, Fixed, 95% CI)	Totals not selected
21.1 Mean baseline FEV1 >= 80% of predicted	0		Std. Mean Difference (IV, Fixed, 95% CI)	Not estimable
21.2 Mean Baseline FEV1 not reported	1		Std. Mean Difference (IV, Fixed, 95% CI)	Not estimable

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
22 Nighttime asthma symptom score (mean over study period)	1		Std. Mean Difference (IV, Fixed, 95% CI)	Totals not selected
22.1 Mean baseline FEV1 $\geq$ 80% of predicted	0		Std. Mean Difference (IV, Fixed, 95% CI)	Not estimable
2.2 Mean Baseline FEV1 not reported	1		Std. Mean Difference (IV, Fixed, 95% CI)	Not estimable

Comparison 3
Subgroup analyses (comparison 01: LABA+ICS versus SAME DOSE ICS)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 # patients with exacerbations requiring oral steroids by FEV1 % predicted at baseline	8	1084	Risk Ratio (M-H, Fixed, 95% CI)	0.92 [0.60, 1.40]
1.1 Mean baseline FEV1 $\geq$ 80% of predicted	4	375	Risk Ratio (M-H, Fixed, 95% CI)	0.87 [0.47, 1.64]
1.2 Mean baseline FEV1 61-79% of predicted	2	230	Risk Ratio (M-H, Fixed, 95% CI)	0.89 [0.48, 1.64]
1.3 Mean baseline FEV1 not reported	2	479	Risk Ratio (M-H, Fixed, 95% CI)	1.54 [0.26, 9.09]
2 # patients with exacerbations requiring oral steroids by whether funded by producers of LABA	8	1084	Risk Ratio (M-H, Fixed, 95% CI)	0.92 [0.60, 1.40]
2.1 Charity Funded	1	23	Risk Ratio (M-H, Fixed, 95% CI)	1.09 [0.28, 4.32]
2.2 Funded by manufacturers of LABA	7	1061	Risk Ratio (M-H, Fixed, 95% CI)	0.90 [0.58, 1.41]
3 # patients with exacerbations requiring oral steroids by dose of ICS in both groups	8	1084	Risk Ratio (M-H, Fixed, 95% CI)	0.92 [0.60, 1.40]
3.1 Low dose of ICS ($\leq$ 400 mcg/day of BDP-eq)	5	831	Risk Ratio (M-H, Fixed, 95% CI)	0.91 [0.48, 1.76]
3.2 Moderate dose of ICS (401-800 mcg/day of BDP-eq)	2	230	Risk Ratio (M-H, Fixed, 95% CI)	0.89 [0.48, 1.64]
3.3 High dose of ICS ($>$ 800 mcg/day of BDP-eq)	0	0	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
3.4 Unspecified dose of ICS or range of dose only mentioned	1	23	Risk Ratio (M-H, Fixed, 95% CI)	1.09 [0.28, 4.32]
4 # patients with exacerbations requiring oral steroids by combination inhaler or separate inhaler for LABA	8	1084	Risk Ratio (M-H, Fixed, 95% CI)	0.92 [0.60, 1.40]
4.1 Combination inhaler	3	682	Risk Ratio (M-H, Fixed, 95% CI)	1.02 [0.30, 3.47]
4.2 Separate inhaler	5	402	Risk Ratio (M-H, Fixed, 95% CI)	0.90 [0.57, 1.42]
4.3 Not reported	0	0	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
5 # patients with exacerbations requiring oral steroids by whether LABA dose is usual or higher than usual	8	1084	Risk Ratio (M-H, Fixed, 95% CI)	0.92 [0.60, 1.40]
5.1 LABA at usual dose	7	1061	Risk Ratio (M-H, Fixed, 95% CI)	0.90 [0.58, 1.41]
5.2 LABA at higher than usual dose	1	23	Risk Ratio (M-H, Fixed, 95% CI)	1.09 [0.28, 4.32]
6 # patients with exacerbations requiring oral steroids by type of LABA	8	1084	Risk Ratio (M-H, Fixed, 95% CI)	0.92 [0.60, 1.40]
6.1 Formoterol	1	32	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
6.2 Salmeterol	7	1052	Risk Ratio (M-H, Fixed, 95% CI)	0.92 [0.60, 1.40]
7 # patients with exacerbations requiring oral steroids by trial duration	8	1084	Risk Ratio (M-H, Fixed, 95% CI)	0.92 [0.60, 1.40]
7.1 <16weeks	7	967	Risk Ratio (M-H, Fixed, 95% CI)	0.90 [0.55, 1.49]
7.2 >=24 weeks	1	117	Risk Ratio (M-H, Fixed, 95% CI)	0.95 [0.43, 2.11]
8 Change in FEV1 at endpoint (L or % predicted) stratifying by type of LABA used	11		Std. Mean Difference (Fixed, 95% CI)	Subtotals only
8.1 Formoterol	6		Std. Mean Difference (Fixed, 95% CI)	0.34 [0.23, 0.45]
8.2 Salmeterol	5		Std. Mean Difference (Fixed, 95% CI)	0.30 [0.12, 0.48]

Comparison 4

Subgroup analyses (comparison 02: 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 by FEV1 % predicted at baseline	1	120	Risk Ratio (M-H, Fixed, 95% CI)	1.43 [0.58, 3.50]
1.1 Baseline FEV1 >= 80 % predicted	1	120	Risk Ratio (M-H, Fixed, 95% CI)	1.43 [0.58, 3.50]
1.2 Baseline FEV1 61-79 % predicted	0	0	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
2 # patients with exacerbations requiring oral steroids by whether funded by producers of LABA	1	120	Risk Ratio (M-H, Fixed, 95% CI)	1.43 [0.58, 3.50]
2.1 Charity Funded	0	0	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
2.2 Funded by manufacturers of LABA	1	120	Risk Ratio (M-H, Fixed, 95% CI)	1.43 [0.58, 3.50]
3 # patients with exacerbations requiring oral steroids by dose of ICS in control groups	1	120	Risk Ratio (M-H, Fixed, 95% CI)	1.43 [0.58, 3.50]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
3.1 Low dose of ICS ($\leq$ 400 mcg/day of BDP-eq)	1	120	Risk Ratio (M-H, Fixed, 95% CI)	1.43 [0.58, 3.50]
3.2 Moderate dose of ICS (401-800 mcg/day of BDP-eq)	0	0	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
3.3 High dose of ICS ($>$ 800 mcg/day of BDP-eq)	0	0	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
3.4 Unspecified dose of ICS or range of dose only mentioned	0	0	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
4 # patients with exacerbations requiring oral steroids by combination inhaler or separate inhaler for LABA	1	120	Risk Ratio (M-H, Fixed, 95% CI)	1.43 [0.58, 3.50]
4.1 Combination inhaler	0	0	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
4.2 Separate inhaler	1	120	Risk Ratio (M-H, Fixed, 95% CI)	1.43 [0.58, 3.50]
4.3 Not reported	0	0	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
5 # patients with exacerbations requiring oral steroids by whether LABA dose is usual or higher than usual	1	120	Risk Ratio (M-H, Fixed, 95% CI)	1.43 [0.58, 3.50]
5.1 LABA at usual dose	1	120	Risk Ratio (M-H, Fixed, 95% CI)	1.43 [0.58, 3.50]
5.2 LABA at higher than usual dose	0	0	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
6 # patients with exacerbations requiring oral steroids by type of LABA	1	120	Risk Ratio (M-H, Fixed, 95% CI)	1.43 [0.58, 3.50]
6.1 Formoterol	0	0	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
6.2 Salmeterol	1	120	Risk Ratio (M-H, Fixed, 95% CI)	1.43 [0.58, 3.50]
7 # patients with exacerbations requiring oral steroids by trial duration	1	120	Risk Ratio (M-H, Fixed, 95% CI)	1.43 [0.58, 3.50]
7.1 $<$ 16 weeks	0	0	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
7.2 $\geq$ 24 weeks	1	120	Risk Ratio (M-H, Fixed, 95% CI)	1.43 [0.58, 3.50]

Comparison 5 WMD archive

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Change in FEV1 (% predicted) at endpoint	4		Mean Difference (IV, Random, 95% CI)	Totals not selected
1.1 Baseline FEV1 $\geq$ 80 % predicted	2		Mean Difference (IV, Random, 95% CI)	Not estimable
1.2 Baseline FEV1 61-79 % predicted	2		Mean Difference (IV, Random, 95% CI)	Not estimable

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
2 Change in height at 1 year	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
3 Change in am PEF	5		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
4 Change in FEV1 (L or % pred)stratifying on trial duration	4		Std. Mean Difference (IV, Random, 95% CI)	Totals not selected
4.1 Change in FEV1 (L or (% predicted) at 6 +/- 2 weeks of treatment	1		Std. Mean Difference (IV, Random, 95% CI)	Not estimable
4.2 Change in FEV1 (L or (% predicted) at 12 +/- 4 weeks of treatment	4		Std. Mean Difference (IV, Random, 95% CI)	Not estimable
4.3 Change in FEV1 (L or (% predicted) at 24 +/- 4 weeks of treatment	1		Std. Mean Difference (IV, Random, 95% CI)	Not estimable
4.4 Change in FEV1 (L or (% predicted) at 52 +/- 4 weeks of treatment	0		Std. Mean Difference (IV, Random, 95% CI)	Not estimable
5 am PEF	3		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
6 Pm PEF	2		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
7 Change in pm PEF	2		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
8 Change in FEV1 (L) versus baseline	3		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
9 Change in evening PEF (L/min) at endpoint	2		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
9.1 Baseline FEV1 >= 80 % predicted	0		Mean Difference (IV, Fixed, 95% CI)	Not estimable
9.2 Baseline FEV1 61-79 % predicted	1		Mean Difference (IV, Fixed, 95% CI)	Not estimable
9.3 Mean Baseline FEV1 not reported	1		Mean Difference (IV, Fixed, 95% CI)	Not estimable

Analysis 1.1

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

Review: Addition of long-acting beta-agonists to inhaled corticosteroids for chronic asthma in children

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

Outcome: 1 # patients with exacerbations requiring systemic steroids

Analysis 1.2

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

Review: Addition of long-acting beta-agonists to inhaled corticosteroids for chronic asthma in children

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

Outcome: 2 # patients with exacerbations requiring hospitalisation

Analysis 1.3

Comparison 1 Long-acting beta2 versus placebo: both groups receiving similar dose ICS, Outcome 3 Serious adverse events

Review: Addition of long-acting beta-agonists to inhaled corticosteroids for chronic asthma in children

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

Outcome: 3 Serious adverse events

Analysis 1.4

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

Review: Addition of long-acting beta-agonists to inhaled corticosteroids for chronic asthma in children

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

Outcome: 4 Total # withdrawals

Analysis 1.5

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

Review: Addition of long-acting beta-agonists to inhaled corticosteroids for chronic asthma in children

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

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

Analysis 1.6
Comparison 1 Long-acting beta2 versus placebo: both
groups receiving similar dose ICS, Outcome 6 #
withdrawals due to serious non-respiratory event

Review: Addition of long-acting beta-agonists to inhaled corticosteroids for chronic asthma in children

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

Outcome: 6 # withdrawals due to serious non-respiratory event

Analysis 1.7
Comparison 1 Long-acting beta2 versus placebo: both
groups receiving similar dose ICS, Outcome 7 #
withdrawals due to adverse events

Review: Addition of long-acting beta-agonists to inhaled corticosteroids for chronic asthma in children

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

Outcome: 7 # withdrawals due to adverse events

Analysis 1.8

Comparison 1 Long-acting beta2 versus placebo: both groups receiving similar dose ICS, Outcome 8 Change in FEV1 at endpoint stratifying on baseline FEV1

Review: Addition of long-acting beta-agonists to inhaled corticosteroids for chronic asthma in children

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

Outcome: 8 Change in FEV1 at endpoint stratifying on baseline FEV1

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

Review: Addition of long-acting beta-agonists to inhaled corticosteroids for chronic asthma in children

Comparison: 1 Long-acting beta2 versus placebo: both groups receiving similar dose ICS
 Outcome: 9 Change in FEV1 at endpoint (% predicted) stratifying on baseline FEV1

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

Review: Addition of long-acting beta-agonists to inhaled corticosteroids for chronic asthma in children

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

Outcome: 10 FEV1 predicted at endpoint stratifying on baseline FEV1

Analysis 1.11
Comparison 1 Long-acting beta2 versus placebo: both
groups receiving similar dose ICS, Outcome 11 Change
in FEV1 (L or % pred) stratifying on trial duration

Review: Addition of long-acting beta-agonists to inhaled corticosteroids for chronic asthma in children

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

Outcome: 11 Change in FEV1 (L or % pred) stratifying on trial duration

Analysis 1.12

Comparison 1 Long-acting beta2 versus placebo: both groups receiving similar dose ICS, Outcome 12 End of treatment FEV1 (L)

Review: Addition of long-acting beta-agonists to inhaled corticosteroids for chronic asthma in children

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

Outcome: 12 End of treatment FEV1 (L)

Analysis 1.13

Comparison 1 Long-acting beta2 versus placebo: both groups receiving similar dose ICS, Outcome 13 Change in PEF variability at endpoint

Review: Addition of long-acting beta-agonists to inhaled corticosteroids for chronic asthma in children

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

Outcome: 13 Change in PEF variability at endpoint

Analysis 1.14

Comparison 1 Long-acting beta2 versus placebo: both groups receiving similar dose ICS, Outcome 14 Change in morning PEF at endpoint

Review: Addition of long-acting beta-agonists to inhaled corticosteroids for chronic asthma in children

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

Outcome: 14 Change in morning PEF at endpoint

Analysis 1.15

Comparison 1 Long-acting beta2 versus placebo: both groups receiving similar dose ICS, Outcome 15 Morning PEF at endpoint

Review: Addition of long-acting beta-agonists to inhaled corticosteroids for chronic asthma in children

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

Outcome: 15 Morning PEF at endpoint

Analysis 1.16

Comparison 1 Long-acting beta2 versus placebo: both groups receiving similar dose ICS, Outcome 16 Change in morning PEF (% predicted)

Review: Addition of long-acting beta-agonists to inhaled corticosteroids for chronic asthma in children

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

Outcome: 16 Change in morning PEF (% predicted)

Analysis 1.17

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

Review: Addition of long-acting beta-agonists to inhaled corticosteroids for chronic asthma in children

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

Outcome: 17 Change in evening PEF at endpoint

Analysis 1.18
Comparison 1 Long-acting beta2 versus placebo: both
groups receiving similar dose ICS, Outcome 18 Change
in evening PEF (% predicted)

Review: Addition of long-acting beta-agonists to inhaled corticosteroids for chronic asthma in children

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

Outcome: 18 Change in evening PEF (% predicted)

Analysis 1.19
Comparison 1 Long-acting beta2 versus placebo: both
groups receiving similar dose ICS, Outcome 19 Change
in clinic PEF (L/min)

Review: Addition of long-acting beta-agonists to inhaled corticosteroids for chronic asthma in children

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

Outcome: 19 Change in clinic PEF (L/min)

Analysis 1.20
Comparison 1 Long-acting beta2 versus placebo: both
groups receiving similar dose ICS, Outcome 20 Change
in # daytime rescue inhalations (puffs per day) at
endpoint

Review: Addition of long-acting beta-agonists to inhaled corticosteroids for chronic asthma in children

Comparison: 1 Long-acting beta2 versus placebo: both groups receiving similar dose ICS
 Outcome: 20 Change in # daytime rescue inhalations (puffs per day) at endpoint

Analysis 1.21

Comparison 1 Long-acting beta2 versus placebo: both groups receiving similar dose ICS, Outcome 21 % days without bronchodilator usage

Review: Addition of long-acting beta-agonists to inhaled corticosteroids for chronic asthma in children

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

Outcome: 21 % days without bronchodilator usage

Analysis 1.22

Comparison 1 Long-acting beta2 versus placebo: both groups receiving similar dose ICS, Outcome 22 Mean change in asthma symptom score

Review: Addition of long-acting beta-agonists to inhaled corticosteroids for chronic asthma in children

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

Outcome: 22 Mean change in asthma symptom score

Analysis 1.23**Comparison 1 Long-acting beta2 versus placebo: both groups receiving similar dose ICS, Outcome 23 Change in # nighttime rescue inhalations at endpoint**

Review: Addition of long-acting beta-agonists to inhaled corticosteroids for chronic asthma in children

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

Outcome: 23 Change in # nighttime rescue inhalations at endpoint

Analysis 1.24**Comparison 1 Long-acting beta2 versus placebo: both groups receiving similar dose ICS, Outcome 24 Change in night time awakening (number of nights) at endpoint**

Review: Addition of long-acting beta-agonists to inhaled corticosteroids for chronic asthma in children

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

Outcome: 24 Change in night time awakening (number of nights) at endpoint

Analysis 1.25

Comparison 1 Long-acting beta2 versus placebo: both groups receiving similar dose ICS, Outcome 25 % nights with awakening

Review: Addition of long-acting beta-agonists to inhaled corticosteroids for chronic asthma in children

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

Outcome: 25 % nights with awakening

Analysis 1.26

Comparison 1 Long-acting beta2 versus placebo: both groups receiving similar dose ICS, Outcome 26 Change in % symptom-free days at endpoint

Review: Addition of long-acting beta-agonists to inhaled corticosteroids for chronic asthma in children

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

Outcome: 26 Change in % symptom-free days at endpoint

Analysis 1.27

Comparison 1 Long-acting beta2 versus placebo: both groups receiving similar dose ICS, Outcome 27 % symptom-free days

Review: Addition of long-acting beta-agonists to inhaled corticosteroids for chronic asthma in children

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

Outcome: 27 % symptom-free days

Analysis 1.28

Comparison 1 Long-acting beta2 versus placebo: both groups receiving similar dose ICS, Outcome 28 % symptom-free nights at 52 +/- 4 weeks

Review: Addition of long-acting beta-agonists to inhaled corticosteroids for chronic asthma in children

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

Outcome: 28 % symptom-free nights at 52 +/- 4 weeks

Analysis 1.29

Comparison 1 Long-acting beta2 versus placebo: both groups receiving similar dose ICS, Outcome 29 Quality of life (P-AQLQ)

Review: Addition of long-acting beta-agonists to inhaled corticosteroids for chronic asthma in children

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

Outcome: 29 Quality of life (P-AQLQ)

Analysis 1.30

Comparison 1 Long-acting beta2 versus placebo: both groups receiving similar dose ICS, Outcome 30 Total # adverse events

Review: Addition of long-acting beta-agonists to inhaled corticosteroids for chronic asthma in children

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

Outcome: 30 Total # adverse events

Analysis 1.31
Comparison 1 Long-acting beta2 versus placebo: both
groups receiving similar dose ICS, Outcome 31 #
patients with headache

Review: Addition of long-acting beta-agonists to inhaled corticosteroids for chronic asthma in children

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

Outcome: 31 # patients with headache

Analysis 1.32

Comparison 1 Long-acting beta2 versus placebo: both groups receiving similar dose ICS, Outcome 32 # patients with oral thrush

Review: Addition of long-acting beta-agonists to inhaled corticosteroids for chronic asthma in children

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

Outcome: 32 # patients with oral thrush

Analysis 1.33

Comparison 1 Long-acting beta2 versus placebo: both groups receiving similar dose ICS, Outcome 33 # patients with tremor

Review: Addition of long-acting beta-agonists to inhaled corticosteroids for chronic asthma in children

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

Outcome: 33 # patients with tremor

Analysis 1.34
Comparison 1 Long-acting beta2 versus placebo: both
groups receiving similar dose ICS, Outcome 34 #
patients with tachycardia or palpitations

Review: Addition of long-acting beta-agonists to inhaled corticosteroids for chronic asthma in children

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

Outcome: 34 # patients with tachycardia or palpitations

Analysis 1.35

Comparison 1 Long-acting beta2 versus placebo: both groups receiving similar dose ICS, Outcome 35 # patients with adverse cardiovascular events

Review: Addition of long-acting beta-agonists to inhaled corticosteroids for chronic asthma in children

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

Outcome: 35 # patients with adverse cardiovascular events

Analysis 1.36

Comparison 1 Long-acting beta2 versus placebo: both groups receiving similar dose ICS, Outcome 36 Change in % PC 20 at endpoint

Review: Addition of long-acting beta-agonists to inhaled corticosteroids for chronic asthma in children

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

Outcome: 36 Change in % PC 20 at endpoint

Analysis 1.37
Comparison 1 Long-acting beta2 versus placebo: both groups receiving similar dose ICS, Outcome 37 Change in height (cm) as SD scores at 24 +/- 4 weeks

Review: Addition of long-acting beta-agonists to inhaled corticosteroids for chronic asthma in children

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

Outcome: 37 Change in height (cm) as SD scores at 24 +/- 4 weeks

Analysis 1.38
Comparison 1 Long-acting beta2 versus placebo: both groups receiving similar dose ICS, Outcome 38 Change in height at one year

Review: Addition of long-acting beta-agonists to inhaled corticosteroids for chronic asthma in children

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

Outcome: 38 Change in height at one year

Analysis 2.1

Comparison 2 Long-acting beta2 agonist + ICS versus placebo + higher dose of ICS, Outcome 1 # patients with exacerbations requiring oral steroids

Review: Addition of long-acting beta-agonists to inhaled corticosteroids for chronic asthma in children

Comparison: 2 Long-acting beta2 agonist + ICS versus placebo + higher dose of ICS

Outcome: 1 # patients with exacerbations requiring oral steroids

Analysis 2.2

Comparison 2 Long-acting beta2 agonist + ICS versus placebo + higher dose of ICS, Outcome 2 # patients with exacerbations requiring hospitalisation

Review: Addition of long-acting beta-agonists to inhaled corticosteroids for chronic asthma in children

Comparison: 2 Long-acting beta2 agonist + ICS versus placebo + higher dose of ICS

Outcome: 2 # patients with exacerbations requiring hospitalisation

Analysis 2.3

Comparison 2 Long-acting beta2 agonist + ICS versus placebo + higher dose of ICS, Outcome 3 Serious adverse events

Review: Addition of long-acting beta-agonists to inhaled corticosteroids for chronic asthma in children

Comparison: 2 Long-acting beta2 agonist + ICS versus placebo + higher dose of ICS

Outcome: 3 Serious adverse events

Analysis 2.4

Comparison 2 Long-acting beta2 agonist + ICS versus placebo + higher dose of ICS, Outcome 4 Total # withdrawals

Review: Addition of long-acting beta-agonists to inhaled corticosteroids for chronic asthma in children

Comparison: 2 Long-acting beta2 agonist + ICS versus placebo + higher dose of ICS

Outcome: 4 Total # withdrawals

Analysis 2.5

Comparison 2 Long-acting beta2 agonist + ICS versus placebo + higher dose of ICS, Outcome 5 # withdrawals due to adverse events

Review: Addition of long-acting beta-agonists to inhaled corticosteroids for chronic asthma in children

Comparison: 2 Long-acting beta2 agonist + ICS versus placebo + higher dose of ICS

Outcome: 5 # withdrawals due to adverse events

Analysis 2.6

Comparison 2 Long-acting beta2 agonist + ICS versus placebo + higher dose of ICS, Outcome 6 # withdrawals due to poor asthma control or exacerbation

Review: Addition of long-acting beta-agonists to inhaled corticosteroids for chronic asthma in children

Comparison: 2 Long-acting beta2 agonist + ICS versus placebo + higher dose of ICS

Outcome: 6 # withdrawals due to poor asthma control or exacerbation

Analysis 2.7

Comparison 2 Long-acting beta2 agonist + ICS versus placebo + higher dose of ICS, Outcome 7 Change in FEV1 at endpoint

Review: Addition of long-acting beta-agonists to inhaled corticosteroids for chronic asthma in children

Comparison: 2 Long-acting beta2 agonist + ICS versus placebo + higher dose of ICS

Outcome: 7 Change in FEV1 at endpoint

Analysis 2.8

Comparison 2 Long-acting beta2 agonist + ICS versus placebo + higher dose of ICS, Outcome 8 FEV1 at endpoint

Review: Addition of long-acting beta-agonists to inhaled corticosteroids for chronic asthma in children

Comparison: 2 Long-acting beta2 agonist + ICS versus placebo + higher dose of ICS

Outcome: 8 FEV1 at endpoint

Analysis 2.9

Comparison 2 Long-acting beta2 agonist + ICS versus placebo + higher dose of ICS, Outcome 9 Change in FEV1 predicted at endpoint

Review: Addition of long-acting beta-agonists to inhaled corticosteroids for chronic asthma in children

Comparison: 2 Long-acting beta2 agonist + ICS versus placebo + higher dose of ICS

Outcome: 9 Change in FEV1 predicted at endpoint

Analysis 2.10

Comparison 2 Long-acting beta2 agonist + ICS versus placebo + higher dose of ICS, Outcome 10 Change in morning PEF (L/min) at endpoint

Review: Addition of long-acting beta-agonists to inhaled corticosteroids for chronic asthma in children

Comparison: 2 Long-acting beta2 agonist + ICS versus placebo + higher dose of ICS

Outcome: 10 Change in morning PEF (L/min) at endpoint

Analysis 2.11

Comparison 2 Long-acting beta2 agonist + ICS versus placebo + higher dose of ICS, Outcome 11 Change in pm PEF

Review: Addition of long-acting beta-agonists to inhaled corticosteroids for chronic asthma in children

Comparison: 2 Long-acting beta2 agonist + ICS versus placebo + higher dose of ICS

Outcome: 11 Change in pm PEF

Analysis 2.12

Comparison 2 Long-acting beta2 agonist + ICS versus placebo + higher dose of ICS, Outcome 12 Change in clinic PEF (L/min)

Review: Addition of long-acting beta-agonists to inhaled corticosteroids for chronic asthma in children

Comparison: 2 Long-acting beta2 agonist + ICS versus placebo + higher dose of ICS

Outcome: 12 Change in clinic PEF (L/min)

Analysis 2.13
Comparison 2 Long-acting beta2 agonist + ICS versus placebo + higher dose of ICS, Outcome 13 # daytime rescue inhalations at endpoint

Review: Addition of long-acting beta-agonists to inhaled corticosteroids for chronic asthma in children

Comparison: 2 Long-acting beta2 agonist + ICS versus placebo + higher dose of ICS

Outcome: 13 # daytime rescue inhalations at endpoint

Analysis 2.14
Comparison 2 Long-acting beta2 agonist + ICS versus placebo + higher dose of ICS, Outcome 14 Number of nighttime awakenings

Review: Addition of long-acting beta-agonists to inhaled corticosteroids for chronic asthma in children

Comparison: 2 Long-acting beta2 agonist + ICS versus placebo + higher dose of ICS

Outcome: 14 Number of nighttime awakenings

Analysis 2.15

Comparison 2 Long-acting beta2 agonist + ICS versus placebo + higher dose of ICS, Outcome 15 Total # adverse events

Review: Addition of long-acting beta-agonists to inhaled corticosteroids for chronic asthma in children

Comparison: 2 Long-acting beta2 agonist + ICS versus placebo + higher dose of ICS

Outcome: 15 Total # adverse events

Analysis 2.16

Comparison 2 Long-acting beta2 agonist + ICS versus placebo + higher dose of ICS, Outcome 16 # patients with headache

Review: Addition of long-acting beta-agonists to inhaled corticosteroids for chronic asthma in children

Comparison: 2 Long-acting beta2 agonist + ICS versus placebo + higher dose of ICS

Outcome: 16 # patients with headache

Analysis 2.17

Comparison 2 Long-acting beta2 agonist + ICS versus placebo + higher dose of ICS, Outcome 17 Linear growth

Review: Addition of long-acting beta-agonists to inhaled corticosteroids for chronic asthma in children

Comparison: 2 Long-acting beta2 agonist + ICS versus placebo + higher dose of ICS

Outcome: 17 Linear growth

Analysis 2.18

Comparison 2 Long-acting beta2 agonist + ICS versus placebo + higher dose of ICS, Outcome 18 # nighttime rescue inhalations (puffs per day; mean over study period)

Review: Addition of long-acting beta-agonists to inhaled corticosteroids for chronic asthma in children

Comparison: 2 Long-acting beta2 agonist + ICS versus placebo + higher dose of ICS

Outcome: 18 # nighttime rescue inhalations (puffs per day; mean over study period)

Analysis 2.19

Comparison 2 Long-acting beta2 agonist + ICS versus placebo + higher dose of ICS, Outcome 19 # daytime rescue inhalations (puffs per day; mean over study period)

Review: Addition of long-acting beta-agonists to inhaled corticosteroids for chronic asthma in children

Comparison: 2 Long-acting beta2 agonist + ICS versus placebo + higher dose of ICS

Outcome: 19 # daytime rescue inhalations (puffs per day; mean over study period)

Analysis 2.20

Comparison 2 Long-acting beta2 agonist + ICS versus placebo + higher dose of ICS, Outcome 20 Deaths

Review: Addition of long-acting beta-agonists to inhaled corticosteroids for chronic asthma in children

Comparison: 2 Long-acting beta2 agonist + ICS versus placebo + higher dose of ICS

Outcome: 20 Deaths

Analysis 2.21

Comparison 2 Long-acting beta2 agonist + ICS versus placebo + higher dose of ICS, Outcome 21 Daytime asthma symptom score (mean over study period)

Review: Addition of long-acting beta-agonists to inhaled corticosteroids for chronic asthma in children

Comparison: 2 Long-acting beta2 agonist + ICS versus placebo + higher dose of ICS

Outcome: 21 Daytime asthma symptom score (mean over study period)

Analysis 2.22
Comparison 2 Long-acting beta2 agonist + ICS versus placebo + higher dose of ICS, Outcome 22 Nighttime asthma symptom score (mean over study period)

Review: Addition of long-acting beta-agonists to inhaled corticosteroids for chronic asthma in children

Comparison: 2 Long-acting beta2 agonist + ICS versus placebo + higher dose of ICS

Outcome: 22 Nighttime asthma symptom score (mean over study period)

Analysis 3.1
Comparison 3 Subgroup analyses (comparison 01:
LABA+ICS versus SAME DOSE ICS), Outcome 1 #
patients with exacerbations requiring oral steroids by
FEV1 % predicted at baseline

Review: Addition of long-acting beta-agonists to inhaled corticosteroids for chronic asthma in children

Comparison: 3 Subgroup analyses (comparison 01: LABA+ICS versus SAME DOSE ICS)

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

Analysis 3.2
Comparison 3 Subgroup analyses (comparison 01:
LABA+ICS versus SAME DOSE ICS),Outcome 2 #
patients with exacerbations requiring oral steroids by
whether funded by producers of LABA

Review: Addition of long-acting beta-agonists to inhaled corticosteroids for chronic asthma in children

Comparison: 3 Subgroup analyses (comparison 01: LABA+ICS versus SAME DOSE ICS)

Outcome: 2 # patients with exacerbations requiring oral steroids by whether funded by producers of LABA

Analysis 3.3
Comparison 3 Subgroup analyses (comparison 01:
LABA+ICS versus SAME DOSE ICS), Outcome 3 #
patients with exacerbations requiring oral steroids by
dose of ICS in both groups

Review: Addition of long-acting beta-agonists to inhaled corticosteroids for chronic asthma in children

Comparison: 3 Subgroup analyses (comparison 01: LABA+ICS versus SAME DOSE ICS)

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

Analysis 3.4

Comparison 3 Subgroup analyses (comparison 01: LABA+ICS versus SAME DOSE ICS), Outcome 4 # patients with exacerbations requiring oral steroids by combination inhaler or separate inhaler for LABA

Review: Addition of long-acting beta-agonists to inhaled corticosteroids for chronic asthma in children

Comparison: 3 Subgroup analyses (comparison 01: LABA+ICS versus SAME DOSE ICS)

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

Analysis 3.5
Comparison 3 Subgroup analyses (comparison 01:
LABA+ICS versus SAME DOSE ICS), Outcome 5 #
patients with exacerbations requiring oral steroids by
whether LABA dose is usual or higher than usual

Review: Addition of long-acting beta-agonists to inhaled corticosteroids for chronic asthma in children

Comparison: 3 Subgroup analyses (comparison 01: LABA+ICS versus SAME DOSE ICS)

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

Analysis 3.6
Comparison 3 Subgroup analyses (comparison 01: LABA+ICS versus SAME DOSE ICS), Outcome 6 # patients with exacerbations requiring oral steroids by type of LABA

Review: Addition of long-acting beta-agonists to inhaled corticosteroids for chronic asthma in children

Comparison: 3 Subgroup analyses (comparison 01: LABA+ICS versus SAME DOSE ICS)

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

Analysis 3.7
Comparison 3 Subgroup analyses (comparison 01: LABA+ICS versus SAME DOSE ICS), Outcome 7 # patients with exacerbations requiring oral steroids by trial duration

Review: Addition of long-acting beta-agonists to inhaled corticosteroids for chronic asthma in children

Comparison: 3 Subgroup analyses (comparison 01: LABA+ICS versus SAME DOSE ICS)

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

Analysis 3.8
Comparison 3 Subgroup analyses (comparison 01: LABA+ICS versus SAME DOSE ICS), Outcome 8
Change in FEV1 at endpoint (L or % predicted)
stratifying by type of LABA used

Review: Addition of long-acting beta-agonists to inhaled corticosteroids for chronic asthma in children

Comparison: 3 Subgroup analyses (comparison 01: LABA+ICS versus SAME DOSE ICS)

Outcome: 8 Change in FEV1 at endpoint (L or % predicted) stratifying by type of LABA used

Analysis 4.1
Comparison 4 Subgroup analyses (comparison 02: LABA+ICS versus HIGHER DOSE ICS), Outcome 1 # patients with exacerbations requiring oral steroids by FEV1 % predicted at baseline

Review: Addition of long-acting beta-agonists to inhaled corticosteroids for chronic asthma in children

Comparison: 4 Subgroup analyses (comparison 02: LABA+ICS versus HIGHER DOSE ICS)

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

Analysis 4.2
Comparison 4 Subgroup analyses (comparison 02: LABA+ICS versus HIGHER DOSE ICS), Outcome 2 # patients with exacerbations requiring oral steroids by whether funded by producers of LABA

Review: Addition of long-acting beta-agonists to inhaled corticosteroids for chronic asthma in children

Comparison: 4 Subgroup analyses (comparison 02: LABA+ICS versus HIGHER DOSE ICS)

Outcome: 2 # patients with exacerbations requiring oral steroids by whether funded by producers of LABA

Analysis 4.3
Comparison 4 Subgroup analyses (comparison 02: LABA+ICS versus HIGHER DOSE ICS), Outcome 3 # patients with exacerbations requiring oral steroids by dose of ICS in control groups

Review: Addition of long-acting beta-agonists to inhaled corticosteroids for chronic asthma in children

Comparison: 4 Subgroup analyses (comparison 02: LABA+ICS versus HIGHER DOSE ICS)

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

Analysis 4.4
Comparison 4 Subgroup analyses (comparison 02: LABA+ICS versus HIGHER DOSE ICS), Outcome 4 # patients with exacerbations requiring oral steroids by combination inhaler or separate inhaler for LABA

Review: Addition of long-acting beta-agonists to inhaled corticosteroids for chronic asthma in children

Comparison: 4 Subgroup analyses (comparison 02: LABA+ICS versus HIGHER DOSE ICS)

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

Analysis 4.5
Comparison 4 Subgroup analyses (comparison 02: LABA+ICS versus HIGHER DOSE ICS), Outcome 5 # patients with exacerbations requiring oral steroids by whether LABA dose is usual or higher than usual

Review: Addition of long-acting beta-agonists to inhaled corticosteroids for chronic asthma in children

Comparison: 4 Subgroup analyses (comparison 02: LABA+ICS versus HIGHER DOSE ICS)

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

Analysis 4.6
Comparison 4 Subgroup analyses (comparison 02:
LABA+ICS versus HIGHER DOSE ICS), Outcome 6 #
patients with exacerbations requiring oral steroids by
type of LABA

Review: Addition of long-acting beta-agonists to inhaled corticosteroids for chronic asthma in children

Comparison: 4 Subgroup analyses (comparison 02: LABA+ICS versus HIGHER DOSE ICS)

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

Analysis 4.7

Comparison 4 Subgroup analyses (comparison 02: LABA+ICS versus HIGHER DOSE ICS), Outcome 7 # patients with exacerbations requiring oral steroids by trial duration

Review: Addition of long-acting beta-agonists to inhaled corticosteroids for chronic asthma in children

Comparison: 4 Subgroup analyses (comparison 02: LABA+ICS versus HIGHER DOSE ICS)

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

Analysis 5.1

Comparison 5 WMD archive, Outcome 1 Change in FEV1 (% predicted) at endpoint

Review: Addition of long-acting beta-agonists to inhaled corticosteroids for chronic asthma in children

Comparison: 5 WMD archive

Outcome: 1 Change in FEV1 (% predicted) at endpoint

Analysis 5.2

Comparison 5 WMD archive, Outcome 2 Change in height at 1 year

Review: Addition of long-acting beta-agonists to inhaled corticosteroids for chronic asthma in children

Comparison: 5 WMD archive

Outcome: 2 Change in height at 1 year

Analysis 5.3

Comparison 5 WMD archive, Outcome 3 Change in am PEF

Review: Addition of long-acting beta-agonists to inhaled corticosteroids for chronic asthma in children

Comparison: 5 WMD archive

Outcome: 3 Change in am PEF

Analysis 5.4

Comparison 5 WMD archive, Outcome 4 Change in FEV1 (L or % pred)stratifying on trial duration

Review: Addition of long-acting beta-agonists to inhaled corticosteroids for chronic asthma in children

Comparison: 5 WMD archive

Outcome: 4 Change in FEV1 (L or % pred)stratifying on trial duration

Analysis 5.5

Comparison 5 WMD archive, Outcome 5 am PEF

Review: Addition of long-acting beta-agonists to inhaled corticosteroids for chronic asthma in children

Comparison: 5 WMD archive

Outcome: 5 am PEF

Analysis 5.6

Comparison 5 WMD archive, Outcome 6 Pm PEF

Review: Addition of long-acting beta-agonists to inhaled corticosteroids for chronic asthma in children

Comparison: 5 WMD archive

Outcome: 6 Pm PEF

Analysis 5.7

Comparison 5 WMD archive, Outcome 7 Change in pm PEF

Review: Addition of long-acting beta-agonists to inhaled corticosteroids for chronic asthma in children

Comparison: 5 WMD archive

Outcome: 7 Change in pm PEF

Analysis 5.8

Comparison 5 WMD archive, Outcome 8 Change in FEV1 (L) versus baseline

Review: Addition of long-acting beta-agonists to inhaled corticosteroids for chronic asthma in children

Comparison: 5 WMD archive

Outcome: 8 Change in FEV1 (L) versus baseline

Analysis 5.9

Comparison 5 WMD archive, Outcome 9 Change in evening PEF (L/min) at endpoint

Review: Addition of long-acting beta-agonists to inhaled corticosteroids for chronic asthma in children

Comparison: 5 WMD archive

Outcome: 9 Change in evening PEF (L/min) at endpoint

Appendix 1. Randomisation procedures for GSK sponsored studies

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 are restricted so that only those reviewing the data are unblinded to treatment group allocation.

WHAT'S NEW

Last assessed as up-to-date: 8 December 2008.

Date	Event	Description
8 December 2009	Amended	We have revised the reporting of correspondence in relation to missing data. The correspondence regarding the data from Bisgaard 2006 was made directly with the sponsors, not with Hans Bisgaard. The sponsors were unable to provide data on children with exacerbations requiring oral corticosteroids from this study.

HISTORY

Review first published: Issue 3, 2009

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

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

The principal difference between the protocol for the set of reviews relating to long-acting beta-agonists and inhaled steroids and this review is the risk of bias assessment. This has been developed by methodologists and statisticians and aims to provide a transparent mechanism for reporting the design of clinical trials, and the extent to which review authors judge them to be at risk of bias.

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**Indicates the major publication for the study*

PLAIN LANGUAGE SUMMARY

Addition of long-acting beta-agonists to inhaled corticosteroids for chronic asthma in children

Most consensus statements recommend the use of long-acting β_2 -agonists (LABA) as adjunct therapy to inhaled corticosteroids for poorly controlled asthma. The purpose of this review was to identify the benefits and safety profile of adding long-acting β_2 -agonists to inhaled corticosteroids in asthmatic children. Based on the identified paediatric randomised trials, the addition of long-acting β_2 -agonists did not significantly reduce the risk of asthma exacerbations requiring rescue systemic steroids, but improved lung function compared to ongoing treatment with a similar dose of inhaled corticosteroids. There was no evidence of increased serious side effects or withdrawals with the addition of long-acting β_2 -agonists. Compared to doubling the dose of inhaled corticosteroids, the combination of LABA and inhaled steroids did not lead to a significant reduction in the rate of moderate exacerbations or hospital admissions, but it improved lung function and lead to greater growth.

Figure 1.
Flow diagram of literature search results for review: Addition of long-acting beta-agonists to inhaled corticosteroids for chronic asthma in children

	Adequate sequence generation?	Allocation concealment?	Blinding?	Incomplete outcome data addressed?	Free of selective reporting?	Free of other bias?
Akpinarli 1999	?	?	+	?	+	?
Bisgaard 2006	+	?	+	?	+	?
Heuck 2000	+	?	+	?	+	?
Langton Hewer 1995	?	?	+	?	+	?
Malone 2005	+	+	+	+	+	+
Meijer 1995	?	?	+	?	?	?
Morice 2008a	+	?	+	?	+	+
Morice 2008b	+	?	+	?	+	+
Ortega-Cisneros 1998	?	?	+	?	?	?
Pohunek 2006a	+	+	+	?	?	+
Pohunek 2006b	+	+	+	?	?	+
Russell 1995	+	+	+	+	+	?
SAM104926	+	+	+	?	?	?
SAM40012a	+	+	+	?	?	?
SAM40012b	+	+	+	?	?	?
SAM40100	+	+	+	?	?	?
SD 039 0714	?	?	+	?	?	+
SD 039 0718	?	?	+	?	?	+
SD 039 0719	?	?	+	?	+	+
SD 039 0725a	?	?	+	?	+	+
SD 039 0725b	?	?	+	?	+	+
SFA100314	+	+	+	?	+	?
SFA100316	+	+	+	?	+	?
Simons 1997	+	?	+	+	+	?
Stelmach 2007	+	?	+	?	?	+
Tal 2002	+	+	+	?	?	?
Teper 2005	?	?	?	?	?	?
Verberne 1998a	+	+	+	?	+	?
Verberne 1998b	+	+	+	?	+	?
Zimmerman 2004a	?	?	+	?	+	+
Zimmerman 2004b	?	?	+	?	+	+

Figure 2.

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

Figure 3.

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

Figure 4.

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

Figure 5.

Forest plot of comparison: 2 Long-acting beta2 agonist + ICS versus placebo + higher dose of ICS, outcome: 2.1 # patients with exacerbations requiring oral steroids.

Figure 6.

Forest plot of comparison: 2 Long-acting beta2 agonist + ICS versus placebo + higher dose of ICS, outcome: 2.2 # patients with exacerbations requiring hospitalisation.