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

Ni Chroinin M, Greenstone IR, Danish A, Magdolinos H, Masse V, Zhang X, Ducharme FM

THE COCHRANE COLLABORATION®

This is a reprint of a Cochrane review, prepared and maintained by The Cochrane Collaboration and published in *The Cochrane Library* 2006, Issue 4

http://www.thecochranelibrary.com

TABLE OF CONTENTS

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

Ni Chroinin M, Greenstone IR, Danish A, Magdolinos H, Masse V, Zhang X, Ducharme FM

This record should be cited as:
Ni Chroinin M, Greenstone IR, Danish A, Magdolinos H, Masse V, Zhang X, Ducharme FM. Long-acting beta2-agonists versus placebo in addition to inhaled corticosteroids in children and adults with chronic asthma. *Cochrane Database of Systematic Reviews* 2005, Issue 4. Art. No.: CD005535. DOI: 10.1002/14651858.CD005535.

This version first published online: 19 October 2005 in Issue 4, 2005.
Date of most recent substantive amendment: 24 June 2005

ABSTRACT

Background
Long-acting inhaled ß2-adrenergic agonists are recommended as 'add-on' medication to inhaled corticosteroids in the maintenance therapy of asthmatic adults and children aged two years and above.

Objectives
To quantify in asthmatic patients the safety and efficacy of the addition of long-acting ß2-agonists to inhaled corticosteroids on the incidence of asthma exacerbations, pulmonary function and other measures of asthma control.

Search strategy
We identified randomised controlled trials (RCTs) through electronic database searches (the Cochrane Airways Group Specialised Register, MEDLINE, EMBASE and CINAHL), bibliographies of RCTs and correspondence with manufacturers, until April 2004.

Selection criteria
RCTs were included that compared the addition of inhaled long-acting ß2-agonists to corticosteroids with inhaled corticosteroids alone for asthma therapy in children aged two years and above and in adults.

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. The primary endpoint was rate of asthma exacerbations requiring systemic corticosteroids. Secondary endpoints included pulmonary function tests (PFTs), symptom scores, adverse events and withdrawal rates.

Main results
Of 594 identified citations, 49 trials met the inclusion criteria: 27 full-text publications, one unpublished full-text report and 21 abstracts. Twenty-three citations (21 abstracts and two full-text publications) provided data in insufficient detail, 26 trials contributed to this systematic review. All but three trials were of high methodological quality. Most interventions (N = 26) were of four-month duration or less. Eight trials focused on children and 18 on adults, with participants generally symptomatic with moderate airway obstruction despite their current inhaled steroid regimen. If a trial had more than one intervention or control group, additional control to intervention comparisons were considered separately. Formoterol (N = 17) or salmeterol (N = 14) were most frequently added to low-dose inhaled corticosteroids (200 to 400 µg/day of beclomethasone (BDP) or equivalent).

The addition of a daily long-acting ß2-agonist (LABA) reduced the risk of exacerbations requiring systemic steroids by 19% (relative risk (RR) 0.81, 95% CI 0.73 to 0.90). The number needed to treat for one extra patient to be free from exacerbation for one year was 18 (95% CI 13 to 33). The addition of LABA significantly improved FEV1 (weighted mean difference (WMD) 170 mL, 95% CI 110 to 240) using a random-effects model, increased the proportion of symptom-free days (WMD 17%, 95% CI 12 to 22, N = 6 trials) and rescue-free days (WMD 19%, 95% CI 12 to 26, N = 2 trials). The group treated with LABA plus inhaled corticosteroid showed a

reduction in the use of rescue short-acting ß2-agonists (WMD -0.7 puffs/day, 95% CI -1.2 to -0.2), experienced less withdrawals due to poor asthma control (RR 0.5, 95% CI 0.4 to 0.7) and less withdrawals due to any reason (RR 0.9, 95% CI 0.8 to 0.98), using a random-effects model. There was no group difference in risk of overall adverse effects (RR 0.98, 95% CI 0.92 to 1.05), withdrawals due to adverse health events (RR 1.29, 95% CI 0.96 to 1.75) or specific adverse health events.

Authors' conclusions

In patients who are symptomatic on low to high doses of inhaled corticosteroids, the addition of a long-acting ß2-agonist reduces the rate of exacerbations requiring systemic steroids, improves lung function, symptoms and use of rescue short-acting ß2-agonists. The similar number of serious adverse events and withdrawal rates in both groups provides some indirect evidence of the safety of long-acting ß2-agonists as add-on therapy to inhaled corticosteroids.

PLAIN LANGUAGE SUMMARY

Long-acting beta ß2-agonists versus placebo in addition to inhaled corticosteroids in children and adults with chronic asthma

Most consensus statements recommend the use of long-acting ß2-agonists (LABA) as 'add-on' medication to inhaled corticosteroids for poorly-controlled asthma where asthma exacerbations may require additional treatment with oral steroids. The purpose of this review was to identify the benefits and safety profile of adding long-acting ß2-agonists to inhaled corticosteroids in asthmatic children and adults.

Based on the identified randomised trials, in people who remain symptomatic while on inhaled corticosteroids,the addition of long-acting ß2-agonists improved lung function and reduced the risk of asthma exacerbations compared to ongoing treatment with similar dose of inhaled corticosteroids alone. There was no evidence of increased serious side effects or withdrawal rates with the addition of long-acting ß2-agonists, thus providing some indirect evidence of the short- and medium-term safety profile of long-acting ß2-agonists when used in addition to inhaled corticosteroids.

BACKGROUND

With the recognition of asthma as an inflammatory disease the cornerstone of asthma management rests with the use of inhaled corticosteroids (GINA 2002). Inhaled ß2-agonists are powerful agents used to relieve the bronchoconstriction associated with asthma. They act by stimulating the ß2-receptors located in airway smooth muscle resulting in smooth muscle relaxation (Nelson 1995). Inhaled ß2-agonists can be differentiated one from another by their onset and duration of action. Short-acting ß2-agonists such as salbutamol and terbutaline are hydrophilic and interact directly with ß2-receptors leading to a fast onset of action with duration of effect of six hours or less (D'Alonzo 1997). Long-acting ß2-agonists (LABA) provide longer symptom control, which is a particularly useful feature for preventing night-time symptoms. There are two main LABA, namely salmeterol and formoterol. Salmeterol is highly lipophilic and diffuses through the lipid bilayer in muscle cell membranes to reach the ß2-receptors, explaining the slower onset and long duration of action (Nelson 1995). Formoterol, being less lipophilic, has a fast onset of action, similar to short-acting ß2-agonists, and is believed to be incorporated into the lipid bilayer to serve as a reservoir, accounting for its prolonged action (Nelson 1995).

Frequent use of short- or long-acting ß2-agonists generally indicates a significant inflammatory process that should be controlled with anti-inflammatory drugs such as inhaled corticosteroids. The role of long-acting ß2-agonists in the management of asthma has previously been debated. At present, the use of long-acting ß2-agonists as monotherapy clearly appears to be less effective than inhaled corticosteroids alone (Warner 1998) and has been associated with increased asthma deaths; this data resulted in an early trial termination (Smart). Therefore, all national and international asthma consensus statements recommend the use of long-acting ß2-agonists only in combination with inhaled corticosteroids (Australia, 2002; BTS guidelines 2003; GINA 2002; Lemiere 2004; NAEPP 2002).

While all guidelines recommend the addition of long-acting ß2-agonists (LABA) as a 'step three' option, that is in patients who are unsatisfactorily controlled on inhaled steroids, several variations across guidelines highlight ongoing uncertainties regarding the optimal use of LABA as add-on treatment to inhaled steroids. First, the lowest dose of inhaled steroids to which LABA could be considered as add-on therapy varies across guidelines. In adults, LABA can be added to chlorofluorocarbon-propelled beclomethasone dipropionate (BDP) at a dose level equivalent to or greater than 200 µg/day according to the American (NAEPP 2002), British (BTS guidelines 2003) and GINA guidelines (GINA 2002); 400 µg/day or more according to the Canadian consensus statement (Lemiere 2004); and 800 µg/day or more according to the Australian recommendations (Australia, 2002). Recommendations

also vary by age group. In children aged five years and over, the addition of LABA is recommended if inadequate control is achieved with 200 µg/day of BDP, according to the British (BTS guidelines 2003) and American guidelines (NAEPP 2002); 400 µg/day according to the GINA recommendations (GINA 2002); and 800 µg/day according to the Australian (Australia, 2002) and Canadian (Lemiere 2004) statements. Secondly, the preference of adding LABA to inhaled steroids as 'step three' option over other alternative strategies varies across age. Indeed, the Canadian (Lemiere 2004) and Australian (Australia, 2002) guidelines clearly favour increasing the dose of inhaled corticosteroid to 800 µg/day BDP-equivalent rather than adding LABA, as favoured by the British (BTS guidelines 2003) and American (NAEPP 2002) guidelines. In infants and preschool-aged children, LABA is not recommended as add-on therapy, except by the American guidelines which suggest LABA as add-on to 100 to 400 µg/day of BDP or equivalent (NAEPP 2002). Finally, the criteria to consider the addition of LABA are vaguely described as inadequate control with no clear instruction as whether the severity of baseline obstruction or atopy may be important factors. We believed that a systematic review of randomised controlled trials may clarify the ongoing uncertainties about the optimal use of LABA as add-on therapy to inhaled steroids.

OBJECTIVES

The objective of this review was to assess the safety and clinical benefit on asthma control resulting from the addition of long-acting ß2-agonists to inhaled corticosteroids in asthmatic patients. We also wished to examine whether the benefit of long-acting ß2-agonists was influenced by age, severity of airway obstruction, dose of inhaled corticosteroids to which long-acting ß2-agonists were added, use of one or two devices to deliver combination therapy, the dose and type of long-acting ß2-agonist and the duration of intervention.

CRITERIA FOR CONSIDERING STUDIES FOR THIS REVIEW

Types of studies

Only randomised controlled trials conducted in adults or children, or both, in whom long-acting ß2-agonists were added to inhaled corticosteroids were included.

Types of participants

Children aged two years and above or adults with chronic asthma and having received daily inhaled corticosteroids for at least 30 days prior to study entry.

Types of intervention

Long-acting ß2-agonist (for example, salmeterol or formoterol) or placebo administered daily for at least 30 days. The dose of inhaled corticosteroids had to be similar between the intervention and the control groups. Other co-interventions such as xanthines, anticholinergics and other anti-asthmatic medications were accepted provided that the dose remained unchanged throughout the study. Rescue inhaled short-acting ß2-agonists and short courses of systemic steroids were permitted.

Types of outcome measures

The primary outcome was the number of asthma exacerbations of moderate intensity; that is requiring a short course of systemic corticosteroids. Secondary outcomes included (1) other measures reflecting the severity of acute exacerbations, such as rate of hospital admissions; and (2) measures reflecting chronic asthma control, such as changes in pulmonary function tests, symptoms, days and nights without symptoms, functional status, quality of life and use of rescue short-acting ß2-agonists.

Changes in measures of inflammation such as serum eosinophils, serum eosinophil cationic protein and sputum eosinophils were also considered. Rates of clinical and biochemical adverse effects related to treatment were examined.

SEARCH METHODS FOR IDENTIFICATION OF STUDIES

See: Cochrane Airways Group methods used in reviews.

A 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))
An additional search of CENTRAL was completed using the above search strategy. Reference lists of all included studies and reviews were checked to identify potentially relevant citations. The most recent searches were carried out in April 2004.

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

METHODS OF THE REVIEW

Selection of trials

From the title, abstract or descriptors, one of the review authors (IRG, MNC or FMD) independently reviewed the literature searches. All studies that were clearly 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 assessing for inclusion based on study design, population, intervention and outcome.

Assessment of methodological quality

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

Grade A: adequate concealment.

Grade B: unclear concealment.

Grade C: clearly inadequate concealment.

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

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

Data extraction

Data for the trials were independently extracted by two review authors (MNC or IRG, and FMD) and entered into the Cochrane Collaboration software program Review Manager, Version 4.2. 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 and clarification for the trial, as needed.

We recorded as a 'User defined order' the mean daily dose of inhaled corticosteroids in both the intervention and control groups, 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 (NAEPP 2002). All doses of inhaled medications were reported based on ex-valve rather than ex-inhaler values.

Statistical considerations

The analysis focused on the following comparison.

Long-acting ß2-agonist (LABA) and inhaled corticosteroids (ICS) (LABA + ICS) versus a similar dose of inhaled corticosteroids (ICS alone) as second-line treatment, that is in patients already on inhaled corticosteroids.

Note that given the large size of the review, other comparisons originally stated in the protocol (published in 1999) are now assessed in separate reviews; this includes comparing the addition of LABA to inhaled corticosteroids to increased doses of inhaled corticosteroids (Greenstone et al) and to tapering doses of inhaled corticosteroids (Gibson et al). A similar comparison focusing only on steroid-naive patients is the object of another Cochrane review (Ni Chroinin 2004). When a trial had more than one intervention or control group, additional control to intervention comparisons were considered, if appropriate for this review. If two control to intervention comparisons used the same group twice as comparator (for example a 3-arm study had two LABA + ICS arms but only one ICS alone arm) the number of participants in the group used twice (in this instance the ICS alone group) was halved to avoid over-representation (Buhl BUD400(qd); Buhl BUD400(bd); Zetterstrom BUD4001d; Zetterstrom BUD4002d; Zimmerman ICS450F12; Zimmerman ICS450F6). For event rate, the denominator was also halved in the control group.

Treatment effects for dichotomous variables were calculated as relative risk (RR), risk difference (RD), or both, with 95% confidence intervals (CI). For continuous outcomes, such as pulmonary function tests, pooled statistics were calculated as weighted mean differences (WMD) or standardized mean differences (SMD), as indicated, and reported with 95% confidence intervals. Homogeneity of effect sizes between studies being pooled was tested with the I2 statistic with a value greater than 25% as the cut-off for heterogeneity (Higgins 2003), the Dersimonian and Laird method with a P value less than 0.05 used as the cut-off level for significance, or both. In absence of heterogeneity, the fixed-effect model (Greenland 1985) was used. If heterogeneity was suggested by the I2 or the Dersimonian and Laird method, the Dersimonian and Laird random-effects model (DerSimonian 1986) was applied to the summary estimates. Unless otherwise specified, the fixed-effect model is reported. Equivalence was assumed if the relative risk estimate and its confidence interval were between 0.9 and 1.1. Numbers needed to treat (NNT) were derived from the pooled odds ratios using Visual Rx (an online calculator at http://www.nntonline.net) (Cates 2002).

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

1. Magnitude of airway obstruction at baseline as determined by the mean per cent predicted forced expiratory volume in one

second (FEV1): classified as mild (FEV1 80% or more), moderate (FEV1 61 to 79%) or severe (FEV1 60% or less) (GINA 2002).
2. Children (less than 18 years of age) versus adults.
3. Mean dose (ex-valve) of inhaled corticosteroids in both groups, reported in CFC-propelled beclomethasone-equivalent doses (µg/day), portrayed as the user-defined number.
4. Usual versus higher than usual dose (reported as ex-valve in µg) of the long-acting ß2-agonist (salmeterol or formoterol).
5. Type of long-acting ß2-agonist (salmeterol versus formoterol).
6. Use of one or two devices to deliver the combination of ICS plus LABA.
7. Trial duration (in weeks).

Since the publication of the original protocol in 1999, and prior to data analysis, we have added the last two subgroups analyses. Subgroup 6 was added because of recent data (Nelson HR 2003) suggesting a differential effect when using one or two devices to deliver the combination of LABA plus ICS. We added subgroup 7 to investigate the risk of tachyphylaxis.

Differences in the magnitude of effect attributable to these subgroups were examined with the residual chi square test from the Peto Odds Ratios or with the t-test for weighted mean differences (Deeks 2001). We conducted a multivariate meta-regression to examine the simultaneous impact of and interaction between the above-named variables on the risk of patients with exacerbations requiring systemic steroids. Backward and forward models were built using these subgroups as well as using FEV1 (litres) and dose of inhaled corticosteroids (µg/day) as continuous variables (Stata for Windows, Version 8 2003, Stata Corporation, Texas, USA).

Sensitivity analyses were performed to investigate the potential effects of the (1) methodological quality, (2) publication bias and (3) funding source on the main outcome. Funnel plots were used to examine the possibility of publication bias (Egger 1997). The fail-safe N test was used to assess the robustness of the results (Gleser 1996). All estimates were reported with their 95% confidence interval. The meta-analysis was performed using MetaView, version 1.0.2 (Cochrane Review Manager, Cochrane Collaboration, Oxford).

DESCRIPTION OF STUDIES

The search updated in April 2004 identified 594 citations. Of these, 545 reports were excluded for the following mutually exclusive reasons: (1) duplicate references (N = 208), not a randomised controlled trial (N = 68) or an ongoing trial (N = 14), (3) participants were not asthmatics (N = 4), (4) no consistent intervention with inhaled corticosteroids in all participants (N = 41), (5) intervention was not daily inhaled long-acting ß2-agonists (N = 19), (6) control intervention was not inhaled corticosteroids alone (N = 63), (7) duration of intervention was less than 30 days (N = 45), (8) outcome measures did not reflect asthma control (N = 8), (9) the treatment and intervention groups compared the same medications either in combination or with different delivery devices (N = 30), (10) co-intervention with a non-permitted agent (N = 1), (11) patients were steroid-naive on study entry (N = 20), (12) control group had a higher dose of inhaled corticosteroid than the intervention group (N = 21) and (13) the dose of inhaled corticosteroid did not remain stable during the trial (N = 3). Due to the large number of citations considered, the reasons for exclusion are provided only for published randomised controlled trials.

A total of 49 citations met eligibility criteria including 27 full-text publications, 21 abstracts and the complete disclosure of one unpublished study report (Hultquist BUD400). The abstracts and two full-text publications (Gardiner ICS600; Leblanc 1996) provided data with insufficient details to be used in this meta-analysis. The abstracts are currently listed under Studies awaiting assessment, until full-text publication.
Eligible trials were identified by name of author followed by the generic name and (fixed or mean) daily dose in microgram of inhaled steroids, where BDP = beclomethasone dipropionate, BUD = budesonide, FP = fluticasone propionate, TAA = triamcinolone acetonide, ICS = variety of steroids used, and NR = not reported. When more than two interventions were compared within the same trial, differentiating criteria followed (od = one dose versus bd = two doses per day of inhaled steroids; F6 = formoterol (6µg); F12 = formoterol (12 µg); or 1d = one device versus 2d = two devices for delivering the combination of LABA plus ICS) (see below).

The current review, therefore, aggregated 26 trials that examined the addition of long-acting ß2-agonists to inhaled corticosteroids (LABA + ICS) as compared to similar inhaled corticosteroids alone (ICS alone) in patients already receiving inhaled corticosteroids prior to study enrolment. Five trials with more than two study groups contributed two control to intervention comparisons, namely Buhl BUD400(qd) (LABA + ICS once daily), Buhl BUD400(bd) (LABA+ICS twice daily), O'Byrne BUD200 (ICS 200 µg/day of BDP-equivalent in both groups), O'Byrne BUD400 (ICS 400 µg/day of BDP-equivalent in both groups), Pauwels BUD200 (ICS 200 µg/day of BDP-equivalent in both groups), Pauwels BUD800 (ICS 800 µg/day of BDP-equivalent in both groups), Zetterstrom BUD4001d (LABA + ICS delivered in one device), Zetterstrom BUD4002d (LABA + ICS delivered in two separate devices), Zimmerman ICS450F12 (formoterol 12 µg twice daily) and Zimmerman ICS450F6 (formoterol 6 µg twice daily). In total, there were 31 control to intervention comparisons derived from the 26 included studies.
All trials except one (Hultquist BUD400) was published in full-text. Trial size varied from 16 (Simons BUD150) to 663 participants (Price 2002).

Eighteen control to intervention comparisons pertained exclusively to adults, nine to children (Akpinarli ICS600; Langton Hewer ICS400; Meijer ICSNR; Russell ICS750; Si-

mons BUD150; Tal BUD400; Verberne 1998; Zimmerman ICS450F12; Zimmerman ICS450F6) while the remaining eight comparisons permitted the enrolment of an unspecified number of adolescents aged 12 years or more (D'Urzo ICSNR; Hultquist BUD400; Kavaru FP400; Kemp ICSNR; O'Byrne BUD200; O'Byrne BUD400; Price 2002; Shapiro FP1000). In adult trials, the mean age of participants was relatively homogeneous, varying from 35 years (Li ICS400) to 48 years (Zetterstrom BUD4001d); in pediatric studies, it ranged from 8.5 years (Zimmerman ICS450F6) to 14 years (Langton Hewer ICS400). The gender distribution varied widely from 30% males in Norhaya ICS890 to 71% in Langton Hewer ICS400.

In all but three trials participants clearly had inadequate asthma control (that is, ongoing symptoms and use of rescue short-acting ß2-agonists) at the time of enrolment. In the remaining three trials (Meijer ICSNR; Shapiro FP1000; Simons BUD150) participants appeared asymptomatic and well controlled according to the Canadian consensus guidelines (Lemiere 2004).

In most trials (N = 18) the mean severity of baseline airway obstruction was moderate (that is, FEV1 or PEF of 61% to 79% of predicted); while it was mild (FEV1 80% or more of predicted) in eight control to intervention comparisons (Langton Hewer ICS400; Li ICS400; Meijer ICSNR; O'Byrne BUD200; O'Byrne BUD400; Simons BUD150; Verberne 1998; Wallin FP800); and unreported in the remaining trial (D'Urzo ICSNR). The presence of atopic disease at baseline was reported in only ten studies, all of which reported atopy in 62% to 100% of participants (Akpinarli ICS600; Langton Hewer ICS400; Li ICS400; Meijer ICSNR; Russell ICS750; Simons BUD150; Tal BUD400; van der Molen ICSNR; Verberne 1998; Wallin FP800).

The long-acting ß2-agonist was salmeterol xinafoate in 14 control to intervention comparisons and formoterol in the remaining 17 comparisons. Most of the control to intervention comparisons tested the usual recommended dose of the long-acting ß2-agonist (that is, salmeterol 50 µg twice daily, formoterol 6 or 12 µg twice daily). In three trials a higher than usual dose of salmeterol (100 µg twice daily in Boyd ICS1675 and Langton Hewer ICS400) or formoterol (24 µg twice daily in van der Molen ICSNR) were used. All but one control to intervention comparison examined the combination of LABA plus ICS versus ICS alone in a twice-daily regimen; only Buhl BUD400(bd) examined the two options as a once-daily administration regimen (Buhl BUD400(bd)).

Within each comparison, the dose of inhaled corticosteroid to which LABA was added was similar to that in its own ICS-alone group, being a fixed dose for 23 control to intervention comparisons and a range or unspecified dose for the remaining eight comparisons. Of the 23 comparisons reporting a fixed dose, 12 tested the addition of LABA to low-dose inhaled corticosteroids (200 to 400 µg/day of beclomethasone, or equivalent), eight added LABA to a medium dose of ICS (401 to 799 µg/day of beclomethasone, or equivalent) and three comparisons used a high dose of ICS (800 µg/day or more of beclomethasone, or equivalent) (Ind 2003; Norhaya ICS890; Shapiro FP1000). LABA was added to budesonide (N = 7 trials), beclomethasone (N = 3 trials) (Meijer ICSNR; Shapiro FP1000; Verberne 1998), budesonide or beclomethasone (N = 1 trial) (Russell ICS750) or fluticasone propionate (4 als) (Ind 2003; Kavaru FP400; Shapiro FP1000; Wallin FP800). The remaining 11 trials failed to specify the inhaled corticosteroid used.

Most studies (N = 19) used two inhaler devices for ICS and LABA while six control to intervention comparisons used one device (Buhl BUD400(bd); Buhl BUD400(qd); Kavaru FP400; Li ICS400; Shapiro FP1000; Tal BUD400). One study tested both one and two delivery devices (Zetterstrom BUD4001d; Zetterstrom BUD4002d). Wallin FP800 failed to report the number of devices used. Compliance was assessed or monitored during 11 of the 26 studies.

Co-intervention with other prophylactic medications was permitted in five trials provided that doses remained unchanged throughout the trial. These included systemic steroids, anticholinergics and xanthines (Langton Hewer ICS400), cromoglycate and xanthines (Norhaya ICS890) and immunotherapy (Zimmerman ICS450F12; Zimmerman ICS450F6). Two studies (Ind 2003; Russell ICS750) permitted co-intervention with other agents but did not mention specifically which drugs. Patients taking prophylactic medications were excluded in 15 other trials and this factor was unreported in six trials. Rescue medications such as inhaled short-acting ß2-agonists and systemic steroids were permitted in all the trials.

The duration of the intervention in most trials (N = 13) was between 12 to 16 weeks (Boyd ICS1675; Buhl BUD400(bd); Buhl BUD400(qd); Kavaru FP400; Kemp ICSNR; Li ICS400; Meijer ICSNR; Molimard ICSNR; Russell ICS750; Shapiro FP1000; Tal BUD400; Wallin 2003; Zetterstrom BUD4001d; Zetterstrom BUD4002d; Zimmerman ICS450F12; Zimmerman ICS450F6) Six trials lasted between four to eight weeks (Akpinarli ICS600; Hultquist BUD400; Langton Hewer ICS400; Norhaya ICS890; Price 2002; Simons BUD150) and the remaining seven trials extended from 24 to 54 weeks (D'Urzo ICSNR; Fitzgerald ICS730; Ind 2003; O'Byrne BUD200; O'Byrne BUD400; Pauwels BUD200; Pauwels BUD800; van der Molen ICSNR; Verberne 1998).

The main outcome, the rate of patients with one or more exacerbations requiring systemic steroids, was reported in only 17 control to intervention comparisons. Most trials reported changes in lung function, use of rescue ß2-agonists, withdrawals due to any reason, withdrawals due to poor asthma control and overall adverse health events. There was a large variation in the way improvement in symptoms (symptom score, per cent symptom-free days, per cent days with symptoms, per cent night awakenings) and use of rescue short-acting ß2-agonist were reported, both using various parameters (average value, final value at end point, per cent change

and change in per cent values). These wide variations in reporting prevented the aggregation of all available data.

The overwhelming majority of trials (N = 24) were funded by producers of both LABA and ICS: 12 trials were supported by Glaxo Wellcome; seven by Astra Zeneca; two by Astra Draco (Pauwels BUD200; Pauwels BUD800; van der Molen ICSNR); two by Allen & Hanburys, a subsidiary of Glaxo Wellcome in the United Kingdom (Boyd ICS1675; Price 2002); and one by Novartis (Fitzgerald ICS730). Only one trial was independently supported by a charity organization (Langton Hewer ICS400) while one trial failed to identify the source of funding (Zimmerman ICS450F12; Zimmerman ICS450F6).

METHODOLOGICAL QUALITY

Twenty-four trials had a parallel group design studies and two were cross-over studies (Norhaya ICS890; Simons BUD150) which failed to provide results stratified by period.

All but three trials (Akpinarli ICS600; Molimard ICSNR; Wallin FP800) were of high quality (Jadad score 4 or greater). All trials were randomised though the method of randomisation was not described in 12 trials.

Twenty-seven trials were double blind with an appropriate means of blinding in all but two trials, in which it was not reported (D'Urzo ICSNR; Wallin FP800). The remaining one trial was open label (Molimard ICSNR).

The handling of withdrawals and dropouts were adequately described in all but two trials (Akpinarli ICS600; O'Byrne BUD200; O'Byrne BUD400).

With regards to possible selection bias, none of the studies stated how many patients were screened for eligibility. Thirteen trials reported the per cent of run-in participants that were successfully randomised, ranging from 58 to 95% of recruited patients.
Confirmation of methodology was obtained in 11 of the 26 studies.

RESULTS

The meta-analysis aggregated 31 control to intervention comparisons, hereafter referred to as comparisons, derived from 26 trials involving 8147 asthmatic participants.

In the 17 comparisons contributing data to the primary outcome (outcome 01.01), there was a 19% relative reduction in the risk of patients experiencing one or more exacerbations requiring systemic corticosteroids (relative risk (RR) 0.81, 95% CI 0.73 to 0.90). There was no evidence of heterogeneity (chi2 15.75, df 15, P value 0.4). The rate of patients with exacerbations decreased from 27% to 22% with the addition of long-acting ß2-agonist, an absolute risk reduction of 5% (95% CI 3% to 8%). The number needed to treat INNT) with LABA to prevent one exacerbation over one year is 18 (95% CI 13 to 33), Figure 01. The fail-safe N, that is the number of unpublished studies with null results needed to negate the current finding, is 81.

In the absence of heterogeneity, a priori subgroup analyses were conducted to examine the impact of the following variables on the magnitude of benefit observed with the addition of LABA (effect modification). Trends were observed between exacerbations and the severity of airway obstruction (outcome 02.01), (RR) 1.2, 95% CI 0.91 to 1.54) and the dose of inhaled steroids (outcome 02.03) (chi2 7.41, 3 df, P value 0.06) but they did not reach statistical significance. Although no significant protective effect of LABA was observed in the four pediatric trials contributing data to this outcome (RR 0.90, 95% CI 0.57 to 1.42), the effect was not statistically different from the 12 adult comparisons (RR 0.80, 95% CI 0.73 to 0.89; chi2 0.5, 1 df, P value > 0.10) (outcome 02.02). Dose of LABA (outcome 02.05) and type of LABA both showed significant differences between subgroups (RRR 1.4, 95% CI 1.0 to 2.0, for higher than usual dose; and RRR 1.27, 95% CI 1.04 to 1.56, for salmeterol) but it is difficult to interpret these results as they are not independent of each other. Use of one trial (N = 1) or two devices to deliver the combination of LABA plus ICS (outcome 02.04), and trial duration (outcome 02.07) did not modify the protective effect of LABA.
The meta-regression identified the impact of three variables modifying the relative risk of exacerbation with LABA versus placebo, namely the severity of airway obstruction, the dose of ICS and the LABA used. Because of multicollinearity (for example correlation between variables), once one of these independent predictors was selected in the model, no additional variable improved the fit. The following three bivariate models were generated. A model supported an inverse relationship between baseline severity and efficacy of LABA, where every 10% increase in baseline FEV1 was associated with a 14% increased protection (RR 0.86, 95 % CI 0.74 to 1.0) from exacerbations with LABA over placebo (Table 02). The other models suggested a greater protection against exacerbations with the lower dose as compared to higher doses of inhaled steroids (Table 03) and with formoterol as compared to salmeterol (Table 04). However, the relative importance of these factors could not be untangled as milder airway obstruction was associated with more use of formoterol and lower doses of inhaled steroids.

Sensitivity analysis confirmed the robustness of the results. The conclusions were unchanged with the exclusion of trials with lower methodological quality (Jadad score less than 4) (N = 12 comparisons, RR 0.81, 95% CI 0.73 to 0.90). Because only one trial was not funded by producers of LABA and all trials contributing data to this outcome were published, sensitivity analyses on funding and publication status could not be done. There was no evidence of systematic bias identified by the test for funnel plot asymmetry (intercept 0.239, 95% CI -0.87 to 1.34).

There was no significant group difference in the number of exacerbations requiring admission to hospital (N = 11 comparisons, RR 0.81, 95% CI 0.50 to 1.33; outcome 01.02). The use of LABA significantly reduced the risk of overall withdrawals (all reasons included) (N = 26 comparisons, RR 0.87, 95% CI 0.77 to 0.97; or RD -0.02, 95% CI -0.04 to 0.00) (outcome 01.31) and withdrawals due to poor asthma control (N = 22 comparisons, RR 0.50, 95% CI 0.36 to 0.70; or RD -0.02, 95% CI -0.03 to -0.01) (outcome 01.32).

The addition of LABA to ICS provided significantly greater improvement in lung function over using ICS alone (outcomes 01.03 to 01.14). This was irrespective of whether the group differences were reported as change from baseline FEV1 in litres (N = 9, WMD 0.170, 95% CI 0.11 to 0.24, random-effects model); change in per cent predicted (N = 4, WMD 2.79% predicted value, 95% CI 1.89 to 3.69); FEV1 at endpoint in litres (N = 9, WMD 0.15 litres, 95% CI 0.07 to 0.22); FEV1 at endpoint in per cent predicted (N = 3, WMD 5.93% predicted, 95% CI 3.74 to 8.11); change from baseline in morning peak expiratory flow (PEF) (N = 17, WMD 23.28 litres/min, 95% CI 18.38 to 28.18, random-effects model); or in evening PEF (N = 11, WMD 21.33 litres/min, 95% CI 14.53 to 28.12, random-effects model) and morning PEF at endpoint (N = 6, WMD 22.62 litres/min, 95% CI 4.34 to 40.90, random-effects model). There was insufficient data (fewer than two trials) to aggregate the change in PEF variability or evening PEF at endpoint. There was no apparent effect of duration of the intervention in the magnitude of improvement in FEV1 (outcome 01.07) as observed after 6 ± 2 weeks (N = 2, SMD 0.41, 95% CI 0.18 to 0.64); 12 ± 4 weeks (N = 11, SMD 0.38, 95% CI 0.24 to 0.52); 24 ± 4 weeks (N = 2, SMD 0.30, 95% CI 0.09 to 0.51) or 52 ± 4 weeks (N = 2, SMD 0.32, 95% CI 0.21 to 3) (chi2 7, 3 df).

Use of LABA significantly reduced daytime symptoms (N = 5, SMD -0.34, 95% CI -0.44 to -0.23); night-time symptoms (N= 2, SMD -0.18, 95% CI -0.31 to -0.05) and overall 24-hour symptoms (N = 2, SMD -0.28, 95% CI -0.45 to-0.11). The beneficial effect of LABA and ICS over ICS alone was also observed in the per cent symptom-free days during the observation period (N = 4, SMD 0.32, 95% CI 0.02 to 0.62, random-effects model); the change from baseline in symptom-free days (N = 6, WMD 17.21%, 95% CI 12.06 to 22.36, random-effects model) and in symptom-free nights (N = 4, SMD 0.51, 95% CI 0.28 to 0.74, random-effects model). The favourable effect of LABA was observed in the change in asthma-control days (N = 2, WMD 15.61%, 95% CI 8.51 to 22.70). There were no significant group differences for percentage of nights with no awakening (N = 2, WMD -1.37, 95% CI -2.75 to 0.02); the changes in per cent nights with no awakening (N = 2, WMD 3.24, 95% CI -0.89 to 7.38) and in night-time awakening (N = 3, WMD -0.22, 95% CI -2.24 to 1.81).

The addition of LABA to ICS also reduced the need for rescue short-acting ß2-agonists whether reported as daytime use at endpoint (N = 2, WMD -0.73 puffs/day, 95% CI -1.24 to -0.22, random-effects model); night-time use at endpoint (N = 2, WMD -0.44 puffs/night, 95% CI -0.81 to -0.07, random-effects model); change in overall 24-hour use (N = 8, WMD -0.81 puffs/day, 95% CI -1.17 to -0.44, random-effects model); change in night-time use (N = 6, WMD -0.33 puffs/night, 95% CI -0.57 to -0.1, random-effects model) or change in daytime use (N = 9, WMD -0.82 puffs/day ,95% CI -1.17 to -0.44, random-effects model). The change in per cent rescue-free days (N = 2, WMD 19.1%, 95% CI 12.19 to 26.01) and in quality of life (N = 2, WMD 0.33, 95% CI 0.05 to 0.6, random-effects model) also favoured LABA.

There was no apparent group difference in the risk of overall adverse effects (N = 11, RR 0.98, 95% CI 0.92 to 1.05), meeting our a priori definition of equivalence. There was also no group difference in the risk of serious adverse events (N = 4 comparisons, RR 1.16, 95% CI 0.30 to 4.42) or in any of the reported specific side effects including headache (N = 12, RR 1.13, 95% CI 0.92 to 1.41); hoarseness (N = 3 comparisons, RR 0.71, 95% CI 0.16 to 3.18, random-effects model); oral thrush (N = 4, RR 1.04, 95% CI 0.35 to 3.06); tachycardia or palpitations (N = 5, RR 2.13, 95% CI 0.77 to 5.88); cardiovascular adverse effects such as chest pain (N = 3, RR 0.90, 95% CI 0.32 to 2.54) or tremor (N = 7, RR 2.48, 95% CI 0.78 to 7.89, random-effects model). However, the upper confidence interval for some adverse events was high (for example tachycardia, palpitations and tremor), ruling out total reassurance. The effect on growth, adrenal function and methacholine challenge could not be aggregated due to insufficient number of trials (fewer than 2) reporting these outcomes. Only one study reported deaths, with three deaths reported overall. The risk of withdrawals due to adverse effects was similar in the intervention and control groups (N = 19, RR 1.29, 95% CI 0.96 to 1.75).

DISCUSSION

The available evidence confirms a beneficial effect of adding long-acting ß2-agonist (LABA) to inhaled corticosteroids (ICS) in patients with suboptimal asthma control despite the use of inhaled corticosteroids as compared to status quo?. The addition of long-acting ß2-agonist reduced by 19% the relative risk and by 5% the absolute risk of patients requiring systemic steroids for an asthma exacerbation, over 4 to 54 weeks. The beneficial effect of adding LABA to inhaled steroids was also supported by the greater improvement in FEV1 (by 170 ml in morning PEF (23 litres/min); in symptom-free days (by 17%); in rescue-free days (by 19%) and by a 50% lower relative risk or a 2% lower absolute risk of withdrawals due to poor asthma control) compared to treatment with a similar dose of inhaled steroids alone. The addition of LABA was not associated with an increase in overall or specific adverse health events (other than tremor) over those observed with inhaled steroids alone, but some of the confidence intervals were wide,

precluding total reassurance on the safety of LABA with regard to tachycardia and palpitations.

The strength of the evidence allows us to firmly conclude the beneficial effect of LABA as add-on to ICS, particularly on the risk of exacerbations. There was no evidence of heterogeneity between trials despite the participation of participants of different ages, with differing severity of airway obstruction and the use of various doses and combinations of LABA and ICS. Eighty-one new trials showing no protective effect of LABA on exacerbations would be required to negate the current findings, underlying the robustness of the conclusions. The reduction in patients requiring systemic steroids, by 27% to 22%, is probably clinically important in this population with its relatively high baseline rate of exacerbations; this is equivalent to 18 patients needing to be treated to prevent one exacerbation over the course of one year.

While the results seem to apply to all patients, irrespective of baseline characteristics and intervention variations, the meta-regression suggested three factors that might be associated with treatment effect, namely the baseline severity of airway obstruction, the dose of inhaled steroids and the LABA used. Of note, trials testing patients with less airway obstruction also tended to use a lower dose of ICS and more often formoterol than salmeterol. These factors may be important effect modifiers although caution is advised in the interpretation of the analyses because of the association observed between each of these three variables. We hypothesized that the baseline severity may be the major determinant of the increased protection associated with LABA since the dose and combination therapy to be tested probably guided the patient eligibility criteria. Perhaps the superior effect of LABA in those with normal lung function suggest greater efficacy in the absence of significant airway inflammation. The results clearly demonstrate the efficacy of LABA as add-on to ICS, even using low doses of 200 to 400 µg/day of BDP or equivalent. Whether the addition of LABA to ICS is superior to increasing the dose of ICS is addressed in another review (Greenstone et al, in preparation). The difference in protection between formoterol and salmeterol needs caution in interpretation at present in view of the association with baseline severity and dose of ICS, particularly with the single device combining formoterol (6 µg) with low dose ICS (100 or 200 µg of BUD) while salmeterol is combined with 100 or 250 µg of fluticasone, an inhaled steroid twice as potent as budesonide. Due to the small number of trials involving children that contributed data to the main outcome (N = 4) and using a single versus two devices for delivering combination therapy (N = 1) (Nelson HR 2003) the power for identifying the impact of these variables on the protection anticipated from LABA remains to be demonstrated. The benefits of once- versus twice-daily dosing need closer examination with additional trials. Finally, it remains unclear whether the addition of long-acting ß2-agonist to ICS in well-controlled patients is of any benefit as only four trials addressed this issue. Clearly the publication of the 21 identified eligible abstracts is likely to shed more light on the characteristics of patients and variation in treatment modalities that are associated with greater benefit from long-acting ß2-agonists.

The improvement in lung function with the use of LABAs may be surmised from their physiologic action, although most studies obtained these measurements at the trough of the dosage interval (12 hours or more after the last LABA inhalation). Improvements were seen in all lung function tests (FEV1 and PEF) whether measured in the respiratory laboratory or at home, in the morning or evening. The average improvement in FEV1 was 377 ml with LABA plus ICS compared to 151 ml with ICS alone; the improvement with LABA surpassed the 200 ml cut off for within-patient variability (ATS guideline 1994). While the addition of LABA reduced the need for rescue short-acting ß2-agonists slightly more than ICS the group difference was surprisingly small, an average reduction of only -0.8 puffs/24 hrs, -0.4 puffs/night and -0.8 puffs/day. Perhaps a baseline infrequent (not daily) use of short-acting ß2-agonists could explain this phenomenon, in which case the increase in percentage of rescue-free days (by 19%) may be a more useful indicator. Similarly, a group difference in the improvement in symptoms was present but modest (SMD of -0.2 to -0.3), suggesting perhaps little symptomatology at baseline. An alternative explanation may lie in the effectiveness of inhaled steroids per se in reducing symptoms and enhanced compliance in the use of rescue short-acting ß2 agonists in the context of a randomised controlled trial.

With regards to safety, the addition of long-acting ß2-agonists was not associated with any significant difference in overall or specific adverse effects, except for tremor; however, the upper confidence intervals of some adverse events were high. The similar withdrawal rate between groups due to adverse effects lends additional support to the safety of adding LABA to ICS, for up to 52 weeks. The long-term safety of long acting ß2-agonists remains to be demonstrated and could not be assessed in this context.

The absence of data on airway inflammation that could be aggregated was disappointing. The concern that use of LABA may hide symptoms of poor asthma control and lead to deterioration of the airways is not supported by the presented clinical evidence. Yet, it would have been quite reassuring to confirm the absence of increased airway inflammation with use of LABA. With similar improvement in FEV1 (outcome 01.07) irrespective of study duration, there was no evidence of tachyphylaxis associated with prolonged use of LABA.

To our knowledge this systematic review is the largest meta-analysis on the use of LABA add-on therapy to inhaled steroids, as currently recommended by International consensus statements. It provides complementary information to other reviews examining the overall efficacy of LABA in pediatrics (Bisgaard 2003) and with adults (Walters 2003) when used as monotherapy and/or inconsistent co-treatment with ICS. With 26 trials contributing data on over 8000 asthmatic patients there is enough power to firmly conclude the efficacy of LABA as add-on to ICS over and above similar dose of ICS alone. The benefits of addition of LABA to

ICS clearly apply to patients who are symptomatic on current dose of ICS, as low as 200 µg/day of beclomethasone or equivalent. However, the generalisability of the findings to a clinic population must be considered with care.

As for most asthma trials, the main eligibility criteria were presence of symptoms with significant (12 to 15% or more) reversibility in FEV1 with ß2-agonist; yet such reversibility is demonstrated in less than 10% of patients at a given point in time (Storms 2003). Major exclusion criteria relate to smokers, pregnant or lactating women as well as those of childbearing age without appropriate contraception, thus leading to the exclusion of probably half our patients. Finally, patients with severe airway obstruction, recent exacerbations, or both, were generally excluded. To how many of our patients do these results apply? Unfortunately none of the studies mentioned how many patients were screened for enrolment in the run-in period. Only 55% of studies reported the proportion of patients enrolled in the run-in period that were successfully randomised (varying between 58% and 95%). There was little reporting of adherence to treatment during the intervention period, mentioned in only 42% of studies, with no adjustment or stratification in the analyses. Whether treatment with LABA plus ICS leads to improved compliance and thus better asthma control than ICS alone could not be assessed in this review. Thus the results of this review may not be generalised to the majority of our patients particularly those with symptoms but little reversibility in FEV1.

Whether addition of long-acting ß2-agonists is more effective and safer than increasing the dose of inhaled corticosteroids (Greenstone), adding anti-leukotrienes (Ram 2005) or whether it exerts a steroid-sparing effect (Gibson) are addressed in other Cochrane reviews.

AUTHORS' CONCLUSIONS

Implications for practice

In symptomatic adults and children with mild to moderate airway obstruction who are symptomatic on their low to high dose of inhaled corticosteroids, the addition of long-acting ß2-agonist is superior to remaining on similar doses of inhaled steroids alone; for reducing the rate of exacerbations requiring systemic steroids and as well as for improving lung function, symptoms and quality of life. There is insufficient data to make firm conclusions on the use of LABA for preschool and school-aged children, on the starting dose of ICS to which to add LABA, the use of single versus two devices for administering combination therapy, and the preferred type of LABA. There was no apparent group difference in safety profile. Eighteen patients would need to receive LABA for one year to prevent one patient having an exacerbation requiring rescue systemic steroids.

Implications for research

Preschool-aged children with asthma, school-aged children with moderate or severe baseline obstruction and adults with severe airway obstruction warrant further investigation. Similarly, patients who are symptomatic on inhaled steroids, despite good compliance, but with little airway reversibility to short-acting ß2-agonists should be targeted for inclusion in future studies.

Interventions should include head-to-head comparisons or demonstrate more variations between studies permitting the evaluation of the effect of salmeterol versus formoterol, combined with various doses of inhaled steroids, use of one versus two devices to deliver combination treatment, once versus twice daily regimen, and flexible versus fixed dosing, of the combination of ICS and LABA.

Future trials should aim for the following design characteristics:

- double blinding, adequate randomisation and complete reporting of withdrawals and dropouts with intention-to-treat analysis;
- intervention period of 12 weeks or more to properly assess the impact on exacerbations requiring systemic corticosteroids;
- clear reporting of the per cent (and reasons) of non-eligibility of approached patients and of those enrolled in the run-in period;
- complete reporting of continuous (denominators, mean change and mean standard deviation of change) and dichotomous (denominators and rate) data.

Outcomes of particular importance to assess include:

- exacerbations requiring systemic corticosteroids and, in particular, the effect of different patient characteristics on outcome, such as baseline lung function, baseline dose of ICS;
- careful monitoring and reporting of compliance to ICS prior to randomisation and to ICS and LABA postrandomisation. The impact of compliance to combination therapy versus ICS alone on the magnitude of the effect size should be examined;
- reporting of the cost effectiveness of use of combination inhalers as compared to inhaled corticosteroids alone;
- long-term side effects of long-acting ß2-agonists.

POTENTIAL CONFLICT OF INTEREST

In the past five years, Francine Ducharme received some research funding from Glaxo Wellcome and Astra Zeneca and gave CME conferences supported by Merck Frost. M Ni Chroinin, IR Greenstone, A Danish, H Magalinos, V Masse and X Zhang report no conflict of interest.

ACKNOWLEDGEMENTS

We thank the Cochrane Airways Group, namely Stephen Milan, Toby Lasserson, Karen Blackhall, Liz Arnold, Veronica Stewart and Bettina Reuben for the literature search and ongoing support;

and Christopher Cates, Peter Gibson and Paul Jones for their constructive comments. We are indebted to the following corresponding authors or sponsors, namely G Boyd, X Li, A Tal, E Simons, F Price, JP Kemp, RA Pauwels, G Russell, Van der Molen and AAPH Verberne, as well as to Shailesh Patel, Karen Richardson, and Rob Pearson from GlaxoSmithKline, Nils Grundstrom and Roger Metcalf from AstraZeneca who cooperated enthusiastically to our requests for information and confirmation of methodology and data.

SOURCES OF SUPPORT

External sources of support

- Francine Ducharme was supported by a National Scientist Award from the Fonds de la Santé du Québec CANADA

Internal sources of support

- Canadian Cochrane Network, McGill University CANADA

REFERENCES

References to studies included in this review

Akpinarli ICS600 *{published data only}*

Akpinarli A, Tuncer A, Saraclar Y, Sekerel BE, Kalayci O. [Effect of formoterol on clinical parameters and lung functions in patients with bronchial asthma: a randomised controlled trial]. *Archives of Disease in Childhood* 1999;**81**:45–8.

Boyd ICS1675 *{published data only}*

Boyd G. Salmeterol xinafoate in asthmatic patients under consideration for maintenance oral corticosteroid therapy. *European Respiratory Journal* 1995;**8**:1494–98.

Buhl BUD400(bd) *{published data only}*

* Buhl R, Creemers JPHM, Vondra V, Martelli NA, Naya IP, Eksstrom T. Once daily budesonide /formoterol in a single inhaler in adults with moderate persistent asthma. *Respiratory Medicine* 2003; **97**(4):323–30.

Buhl BUD400(qd) *{published data only}*

Buhl R, Creemers JPHM, Vondra V, Martelli NA. Improved and maintained asthma control with once-daily budesonide/formoterol single inhaler in mild-to-moderate persistent asthma. European Respiratory Journal 2001; Vol. 18, issue Suppl 33:21s.

Buhl R, Creemers JPHM, Vondra V, Martelli NA. Once-daily budesonide/formoterol via a single inhaler is effective in mild-to-moderate persistent asthma. European Respiratory Journal 2001; Vol. 18, issue Suppl 33:21s.

Buhl R, Creemers JPHM, Vondra V, Martelli NA. Once daily symbicort (budesonide/eformoterol in a single inhaler) is effective in moderate-persistent asthma. *Thorax* 2001;**56**(Suppl 3):iii62.

* Buhl R, Creemers JPHM, Vondra V, Martelli NA, Naya IP, Eksstrom T. Once daily budesonide /formoterol in a single inhaler in adults with moderate persistent asthma. *Respiratory Medicine* 2003; **97**:323–330.

Buhl R, Zetterstrom O, Mellem H, Perpina M, Hedman J, O'Neill S, Peterson S. Improved asthma control with budesonide/formoterol via a single inhaler compared with budesonide alone, in moderate persistent asthma. European Respiratory Journal 2001; Vol. 18, issue Suppl 33:48s.

Buhl R, Creemers JPHM, Vondra V, Martelli NA. Symbicort® (budesonide and formoterol in a single inhaler) administered once daily is effective in mild to moderate asthma. Annual Thoracic Society 97th International Conference; San Francisco CA , May 18-23. 2001.

D'Urzo ICSNR *{published data only}*

D'Urzo AD, Chapman KR, Cartier A, Hargreave FE, Fitzgeerald M, Tesarowski D. Effectiveness and safety of salmeterol in nonspecialist practice settings. *Chest* 2001;**119**:714–9.

Fitzgerald ICS730 *{published data only}*

FitzGerald JM, Chapman KR, Della Cioppa G, Stubbing D, Fairbarn MS, Till MD, Brambilla R. Sustained bronchoprotection, bronchodilatation, and symptom control during regular formoterol use in asthma of moderate or greater severity. The Canadian FO/OD1 Study Group. *Journal of Allergy & Clinical Immunology* 1999;**103**(3 pt 1):427–35.

Gardiner ICS600 *{published data only}*

Gardiner PV, Ward C, Booth H, Allison A, Hendrick DJ, Walters EH. Bronchoalveolar Lavage Inflammatory Indices in Asthmatics. *American Journal of Respiratory & Critical Care Medicine* 1994;**150** (4):1006–11.

Hultquist BUD400 *{unpublished data only}*

Hultquist. [Unpublished].

Ind 2003 *{published data only}*

Ind P, Haughney J, Price D, Rosen J-P, Kennelly J. Four months adjustable or fixed BD dosing with budesonide /Formoterol in a single inhaler reduces symptom severity. Thorax 2002; Vol. 57, issue Suppl 3:iii88.

Ind PW, Dal Negro R, Colman N, Fletcher CP, Browning DC, James MH. Inhaled fluticasone propionate and salmeterol in moderate adult asthma I: lung function and symptoms. American Journal of Respiratory and Critical Care Medicine 1998; Vol. 157, issue Suppl 3:A416.

Ind PW, Dal Negro R, Colman N, Fletcher CP, Browning DC, James MH. Inhaled fluticasone propionate and salmeterol in moderate adult asthma II: exacerbations. American Journal of Respiratory and Critical Care Medicine 1998; Vol. 157, issue Suppl 3:A415.

* Ind PW, Dal Negro R, Colman NC, Fletcher CP, Browning D, James MH. Addition of salmeterol to fluticasone proprionate treatment in moderate to severe asthma. *Respiratory Medicine* 2003;**97**(5): 555–62.

Kavaru FP400 *{published data only}*

Edin HM, Payne E, Herrle MR, Schoaf L, Mather DB, Scott CA, Shah TP. Salmeterol/Fluticasone Propionate combination via HFA MDI improves quality of life in asthma patients. Journal of Allergy and Clinical Immunology 2001; Vol. 107, issue 2:S246.

Edin HM, Prillaman B, Baitinger LA, House K, Shah TP. Improved ability to perform strenuous avtivities after treatment with fluticasone propionate-salmeterol combination. American Journal of Respiratory and Critical Care Medicine 2002; Vol. 165, issue Suppl 8: A112.

Edwards T, Gross G, Mitchell D, Chervinsky P, Woodring A, Baitinger L, et al. The salmeterol xinafoate/fluticasone propionate dry powder combination product via diskus® inhaler improves asthma control compared to salmeterol xinafoate or fluticasone propionate dry powder alone. American Journal of Respiratory and Critical Care Medicine 1998; Vol. 157, issue Suppl 3:A414.

Johansson G, Price MJ, Sondhi S. Cost-effectiveness analysis of salmeterol/fluticasone propionate 50/100mug vs fluticasone propionate 100mug in adults and adolescents with asthma III. *Pharmacoeconomics* 1999;**16**(Suppl 2):15–21.

* Kavuru M, Melamed J, Gross G, Laforce C, House K, Prillaman B, et a'. Salmeterol and fluticasone proprionate combined in a new powder inhalation device for the treatment of asthma: A randomised, double blind,placebo controlled trial. *Journal of Allergy & Clinical Immunology* 2000;**105**(6):1108–16.

Nathan RA, Dorinsky P, Rosenzweig JR, Shah T, Edin H, Prillaman B. Improved ability to perfrom strenous acticities after treatment with fluticasone proprionate/salmeterol combination in patients with persistent asthma. *Journal of Asthma* 2003;**40**(7):815–22.

Kemp ICSNR *{published data only}*

Kemp JP, Cook DA, Incaudo GA, Corren J, Kalberg C, Emmett A, et al. Salmeterol improves quality of life in patients with asthma requiring inhaled corticosteroids. *Journal of Allergy & Clinical Immunology* 1998;**101**:188–95.

Langton Hewer ICS400 *{published data only}*

Langton Hewer S, Hobbs J, French D, Lenney W. Pilgrims progress: the effect of salmeterol in older chidlren with chronic severe asthma. *Respiratory Medicine* 1995;**89**:435–40.

Leblanc 1996 *{published data only}*

Leblanc P, Knight A, Kreisman H, Borkhoff CM, Johnston PR. A placebo-controlled, crossover comparison of salmeterol and salbutamol in patients with asthma. *American Journal of Respiratory & Critical Care Medicine* 1996;**154**:324–8.

Li ICS400 *{published data only}*

* Li X, Ward C, Thien F, Bish R, Bamford T, Bao X, et al. An anti-inflammatory effect of salmeterol, a long-acting B2-agonist, assessed in airway biopsies and bronchoalveolar lavage in asthma. *American Journal of Respiratory and Crtitical Care Medicine* 1999;**160**:1493–99.

Reid DW, Ward C, Wang N, Zheng L, Bish R, Orsida B, Walters EH. Possible anti-inflammatory effect of salmeterol against interleukin-8 and neutrophil activation in asthma in vivo. *European Respiratory Journal* 2003;**21**(6):994–9.

Meijer ICSNR *{published data only}*

Meijer GG, Postma DS, Mulder PG, van Aalderen WM. Long-term circadian effects of salmeterol in asthmatic children treated with inhaled corticosteroids. *American Journal of Respiratory & Critical Care Medicine* 1995;**152**:1887–92.

Molimard ICSNR *{published data only}*

* Molimard M, Bourcereau J, Le Gros V, Bourdeix I, Leynadier F, Duroux P. Comparison between formoterol 12 ug bid and on-demand salbutamol in moderate persistent asthma. *Respiratory Medicine* 2001;**95**(1):64–70.

Norhaya ICS890 *{published data only}*

* Norhaya MR, Yap TM, Zainudin BMZ. Addition of inhaled salmeterol to inhaled corticosteroids in patients with poorly controlled nocturnal asthma. *Repirology* 1999;**4**:77–81.

O'Byrne BUD200 *{published data only}*

Barnes PJ, O'Byrne PM, Rodriguez-Roisin R, Runnerstrom E, Sandstrom T, Svensson K, Tattersfield A. Oxis and Pulmicort turbuhaler in the management of asthma OPTIMA international study group. Treatment of mild persisitent asthma with low doses of inhaled Budesonide alone or in combination with Formoterol. *Thorax* 2000;**55** (Suppl 3):A4.

Barnes PJ, O'Byrne PM, Rodriguez-Roisin R, Runnerstrom E, Sandstrom T, Svensson K, Tattersfield A. Treatment of mild persistent asthma with low doses of inhaled budesonide alone or in combination with formoterol. For the Oxis and Pulmicort Turbuhaler in the Management of Asthma (OPTIMA) international study group. Thorax 2000; Vol. 55, issue Suppl 3:s5.

Jönsson BG, Berggren FE, Svensson K, O'Byrne PM. Budesonide and formoterol in mild persistent asthma compared with doubling the dose of budesonide - a cost-effectiveness analysis. European Respiratory Journal 2001; Vol. 18, issue Suppl 33:517s.

Jönsson BG, Berggren FE, Svensson K, O'Byrne PM. Economic results of adding formoterol to budesonide in mild persistent asthma. European Respiratory Journal 2001; Vol. 18, issue Suppl 33:331s.

* O'Byrne PM, Barnes PJ, Rodriguez-Roisin R, Runnerstrom E, Sandstrom T, Svensson K, Tattersfield A. Low dose inhaled budesonide and formoterol in mild persistent asthma: The OPTIMA randomized trial. *American Journal of Respiratory & Critical Care Medicine* 2001;**164**(8 pt 1):1392–7.

O'Byrne PM, Barnes PJ, Rodriguez-Roisin R, Sandtröm T, Tattersfield AE, Runnerström EM, Svensson K. Addition of formoterol Turbuhaler® to budesonide Tubuhaler® is safe and well tolerated in the long-term treatment of mild asthma: results from the OPTIMA trial. European Respiratory Journal 2001; Vol. 18, issue Suppl 33:330s.

O'Byrne BUD400 *{published data only}*

* O'Byrne PM, Barnes PJ, Rodriguez-Roisin R, Runnerstrom E, Sandstrom T, Svensson K, Tattersfield A. Low dose inhaled budesonide and formoterol in mild persistent asthma: The OPTIMA randomized trial. *American Journal of Respiratory & Critical Care Medicine* 2001;**164**(8 pt 1):1392–7.

Pauwels BUD200 *{published data only}*

Pauwels RA, Lofdahl CG, Postma DA, Tattersfield AE, O'Byrne P, Barnes PJ, Ullman A. Effect of inhaled formoterol and budesonide on exacerbations of asthma. *New England Journal of Medicine* 1997; **337**:1405–11.

Pauwels BUD800 *{published data only}*

Pauwels RA, Lofdahl CG, Postma DA, Tattersfield AE, O'Byrne P, Barnes PJ, Ullman A. [Effect of inhaled formoterol and budesonide on exacerbations of asthma]. *New England Journal of Medicine* 1997; **337**(20):1405–11.

Price 2002 *{published data only}*

Price D, Dutchman D, Mawson A, Bodalia B, Duggan S, Todd P, FLOW (Eformoterol in the management of mild asthma--eformoterol Turboinhaler with budesonide Turbohaler) research group. Early asthma control and maintenance with eformoterol following reduction of inhaled corticosteroid dose. *Thorax* 2002;**57**(9):791–8.

Price MJ, Briggs AH. Development of an economic model to assess the cost effectiveness of asthma management strategies. Pharmacoeconomics 2002; Vol. 20, issue 3:183–94.

Price MJ, Sondhi S, Yan S, Nyth A, House K. Salmeterol/fluticasone propionate combination inhaler is more cost effective than fluticasone propionate in patients with asthma. European Respiratory Society 1999 Annual Congress; Oct 9-13; Madrid, Spain. 1999.

Russell ICS750 *{published data only}*

Russell G, Williams DAJ, Weller P, Price JF. Salmeterol xinafoate on children on high dose inhaled steroids. *Annals of Allergy, Asthma and Immunology* 1995;**75**:423–28.

Shapiro FP1000 *{published data only}*

Shapiro G, Lumry W, Wolfe J, Given J, White MV, Woodring A, et al. Conbined salmeterol 50mcg and fluticasone proprionate 350mcg in the diskus device for the treatment of asthma. *American Journal of Respiratory & Critical Care Medicine* 2000;**161**:527–34.

Simons BUD150 *{published data only}*

Simons FE, Gerstner TV, Cheang MS. Tolerance to the bronchoprotective effect of salmeterol in adolescents with exercise-induced asthma using concurrent inhaled glucocorticoid treatment. *Pediatrics* May;**99**(5):655–9.

Tal BUD400 *{published data only}*

Tal A, Simon G, Vermeulen JH. Symbicort® (Budesonide and formoterol in a single inhaler) is effective and well tolerated in children with asthma. Annual Thoracic Society 97th International Conference; San Francisco CA ,May 18-23. 2001.

Tal A, Simon G, Vermeulen JH, Petru V, Cobos N, Everard ML, de Boeck C, Jerre F. Symbicort (budesonide and formoterol in a single inhaler) improves lung function in children with asthma. International Paediatric Respiratory and Allergy Congress, April 1-4; Prague. 2001:85.

Tal A, Simon G, Vermeulen JH, Petru V, Cobos N, Everard ML, de Boeck C, Jerre F. Symbicort (budesonide and formoterol in a single inhaler) is more effective that budesonide alone in children with asthma. International Paediatric Respiratory and Allergy Congress April 1-4; Prague. 2001:84–5.

Tal A, Simon G, Vermeulen JH, Petru V, Cobos N, Everard ML, De Boeck C, Naya I. Rapid and sustained improvements in lung function and symptom control with budesonide/ formoterol in adolescent asthma. European Respiratory Journal 2001; Vol. 18, issue Suppl 33: 494s.

* Tal A, Simon G, Vermeulen JH, Petru V, Cobos N, Everard ML, de Boeck K. Budesonide/Formoterol in a single Inhaler versus inhaled corticosteroids alone in the treatment of asthma. *Pediatric Pulmonology* 2002;**34**(5):342–50.

Vermeulen JH, Simon G, Tal A. Symbicort® (Budesonide and formoterol in a single inhaler) improves lung function in asthmatic children aged 4-17 years. Annual Thoracic Society 97th International Conference; San Francisco CA, May 18-23. 2001.

van der Molen ICSNR *{published data only}*

van de Molen T, Postma DS, Kraan J, Chapman K, Grossman R, Turner MO, Seares MR. No influence of six months treatment with formoterol on airway hyperresponsiveness in asthma subjects using inhaled corticosteroids. *American Journal of Respiratory and Critical Care Medicine* 1998;**157**(3 Suppl):A400.

* van der Molen T, Postma DS, Turner MO, Meyboom-de Jong B, Malo JL, Chapman K, Grossman R, et al. Effects of the long acting beta agonist formoterol on asthma control in asthmatic patients using inhaled corticosteroids. *Thorax* 1997;**52**:535–39.

van der Molen T, Sears MR, de Graaff CS, Postma DS, Meyboom-de Jong B. Quality of life during formoterol treatment: comparison between asthma-specific and generic questionnaires. *European Respiratory Journal* 1998;**12**(1):30–4.

Verberne 1998 *{published data only}*

Verberne AAPH, Frost C, Duiverman EJ, Grol MH, Kerribijn KF. Addition of salmeterol versus doubling the dose of beclomethasone in children with asthma. *American Journal of Respiratory & Critical Care Medicine* 1998;**158**:213–19.

Wallin FP800 *{published data only}*

Sue-Chu M, Wallin A, Wilson S, Ward J, Sandstrom T, Djukanovic R, et al. Bronchial biopsy study in asthmatics treated with low and high dose fluticasone propionate (FP) compared to low dose FP combined with salmeterol. European Respiratory Society 1999 Annual Congress Oct 9-13; Madrid, Spain. 1999.

Wallin A, Sandstrom T, Cioppa GD, Holgate S, Wilson S. The effects of regular inhaled formoterol and budesonide on preformed Th-2 cytokines in mild asthmatics. *Respiratory Medicine* 2002;**96**(12):1021–5.

Wallin A, Sue-Chu M, Bjermer L, Ward J, Sandstrom T, Lindberg A, et al. Effect of inhaled fluticasone with and without salmeterol on airway inflammation in asthma. *Journal of Allergy & Clinical Immunology* 2003;**112**(1):72–8.

Zetterstrom BUD4001d *{published data only}*

Zetterstrom O, Buhl R, Mellem H. Efficacy and safety of symbicort® (budesonide and formoterol in a single inhaler) in adults with asthma. Annual Thoracic Society 97th International Conference; San Francisco CA, May 18-23. 2001.

* Zetterstrom O, Buhl R, Mellem H, Perpina M, Hedman J, O'Neill S, Ekstrom T. Improved asthma control with budesonide /formoterol in a single inhaler, compared with budesonide alone. *European Respiratory Journal* 2001;**18**(2):262–8.

Zetterstrom O, Buhl R, Mellem H, Perpina M, Hedman J, O'Neill S, Ekstrom T. The new single inhaler product containing both budesonide/formoterol improves asthma control in adults. European Respiratory Journal 2000; Vol. 16, issue Suppl 31:455s.

Zetterström O, Buhl R, Mellem H, Perpiñá M, Hedman J, O'Neill S, Ekström T. Efficacy and safety of a new single inhaler product containing both budesonide and formoterol in adult asthma. European Respiratory Journal 2000; Vol. 16, issue 31:455s.

Zetterstrom BUD4002d *{published data only}*

Zetterstrom O, Buhl R, Mellem H, Perpina M, Hedman J, O'Neill S, Ekstrom T. Improved asthma control with budesonide /formoterol in a single inhaler, compared with budesonide alone. *European Respiratory Journal* 2001;**18**(2):262–8.

Zimmerman ICS450F12 *{published data only}*

* Zimmerman B, D'Urzo A, Berube D. Efficacy and safety of formoterol turbuhaler(R) when added to inhaled corticosteroid treatment in children with asthma. *Pediatric Pulmonology* 2004;**37**(2): 122–7.

Zimmerman B, D'Urzo A, Berube D. Efficacy and tolerability of formoterol turbuhaler(r) compared with placebo, in children (6-11 yr) with asthma poorly controlled with inhaled corticosteroids [abstract]. American Journal of Respiratory and Critical Care Medicine. 2002; Vol. 165, issue 8 Suppl:A746.

Zimmerman B, D'Urzo A, Berube D. Efficacy and tolerability of formoterol Turbuhaler in 6-11 year old children with asthma, not adequately controlled with inhaled corticosteroids. European Respiratory Society Annual Congress. 2002:P2734.

Zimmerman ICS450F6 *{published data only}*

* Zimmerman B, D'Urzo A, Berube D. Efficacy and safety of formoterol turbuhaler(R) when added to inhaled corticosteroid treatment in children with asthma. *Pediatric Pulmonology* 2004;**37**(2): 122–7.

References to studies excluded from this review

Aalbers 2003 a

R Aalbers, Backer V, Kava TT, Welte T, Omenaas ER, Bergqvist PBF, Sandstrom T. Is well controlled asthma weeks a useful measure? Fewer exacerbations in patients treated with budesonide/formoterol than salmeterol/Fluticasone. European Respiratory Society. 2003:P–2-18.

Aalbers 2003 b

Aalbers R, Backer V, Kava TT, Welte T, Omenaas ER, Bergqvist PB, Sandstrom T. Improvements in FEV1 are greater with budesonide/formotoerl than with salmerol/fluticasone. European Respiratory Society Annual Congress. 2003:P–2-19.

Aalbers 2003 c

Aalbers R, Backer V, Kava TT, Welte T, OmenaasER, Bergqvist PB, Sandstrom T. Adjustable dosing with budesonide/formoterol reduces the rate of asthma exacerbations compared with fixed dosing salmeterol/fluticasone. European Respiratory Society. 2003:p–2-20.

Aalbers 2004

Aalbers R, Backer V, Kava TT, Omenaas ER, Sandstrom T, Jorup C, Welte T. Adjustable maintenance dosing with budesonide/formoterol compared with fixed-dose salmeterol/fluticasone in moderate to severe asthma. *Current Medical Research & Opinion* 2004;**20** (2):225–40.

Adinoff 1998

Adinoff AD, Schwartz HJ, Rickard KA, Yancey SW, Swearingen BE. Salmeterol compared with current therapies in chronic asthma. *Journal of Family Practice* 1998;**47**(4):278–84.

Alonso 2001

Alonso JF, Badiola C, Kielhorn A. Economic evaluation of salmeterol/fluticasone combination vs budesonide plus formoterol in Spain. *European Respiratory Journal* 2001;**18**(Suppl 33):49s.

Ankerst 2001

Ankerst J, Persson G, Weibull E. Cardiovascular effects of a high dose of the budesonide/formoterol single inhaler in asthmatic patients. European Respiratory Journal 2001; Vol. 18, issue Suppl 33:53s.

Ankerst 2003

Ankerst J, Persson G, Weibull E. Tolerability of a high dose of budesonide /formoterol ina single inhaler in paitients with asthma. *Pulmonary Pharmacology & Therapeutics* 2003;**16**:147–51.

Anonymous 2003

Anonymous. Flexible dosing of combination inhaler cuts asthma exacerbations. *Pharmaceutical Journal* 2003;**271**(7271):535.

Arvidsson-P 1991

Arvidsson P, Larsson S, Lofdahl CG, Melander B, Svedmyr N, Wahlander L. Inhaled formoterol during one year in asthma: a comparison with salbutamol. *European Respiratory Journal* 1991;**4**(10): 1168–73.

Aubier 1999

Aubier M, Pieters WR, Schlosser NJ, Steinmetz KO. Salmeterol/fluticasone propionate (50/500 mug) in combination in a Diskus (TM) inhaler (Seretide(TM)) is effective and safe in the treatment of steroid-dependent asthma. *Respiratory Medicine* 1999;**93**(12):876–84.

Aziz 1999 c

Aziz I, Wilson AM, Lipworth BJ. Effects of formoterol (FM) and budesonide (BUD) alone or in combination (FM+BUD) on inflammatory markers in asthmatic patients. European Respiratory Society; 1999 Oct 9-13; Madrid, Spain. 1999:2854.

Aziz 1998

Aziz I, Hall IP, McFarlane LC, Lipworth BJ. Beta2-adrenoceptor regulation and bronchodilator sensitivity after regular treatment with formoterol in subjects with stable asthma. *Journal of Allergy & Clinical Immunology* 1998;**101**(3):337–41.

Aziz 1999 a

Aziz I, Lipworth BJ. A bolus of inhaled budesonide rapidly reverses airway subsensitivity and beta2-adrenoceptor down-regulation after regular inhaled formoterol. *Chest* 1999;**115**(3):623–8.

Aziz 1999 b

Aziz I, Lipworth BJ. In vivo effect of albuterol on methacholine-contracted bronchi in conjunction with salmeterol and formoterol. *Journal of Allergy & Clinical Immunology* 1999;**103**(5 pt 1):816–22.

Aziz 2000

Aziz I, Wilson AM, Lipworth BJ. Effects of once-daily formoterol and budesonide given alone or in combination on surrogate inflammatory markers in asthmatic adults. *Chest* 2000;**118**(4):1049–58.

Bacci 2002

Bacci E, Di Franco A, Bartoli ML, Carnevali S, Cianchetti S, Dente FL, et al. Comparison of anti-inflammatory and clinical effects of beclomethasone dipropionate and salmeterol in moderate asthma. *European Respiratory Journal* 2002;**20**(1):66–72.

Baker 1998

Baker J, Yancey S, Kalberg C, Petrocella V, Emmett A, Bowers B, et al. Added salmeterol versus increased-dose fluticasone in patients symptomatic on low-dose fluticasone. *American Journal of Respiratory and Critical Care Medicine* 1998;**157**(Suppl 3):A406.

Baki 1998

Baki A, Karaguzel G. Short-term effects of budesonide, nedocromil sodium and salmeterol on bronchial hyperresponsiveness in childhood asthma. *Acta Paediatrica Japonica* 1998;**40**(3):247–51.

Baraniuk 1999

Braniuk J, Murray JJ, Nathan RA, Berger WE, Johnson M, Edwards LD, et al. Fluticasone alone or in combination with salmeterol vs triamcinolone in asthma. *Chest* 1999;**116**(3):625–32.

Bateman 1998

Bateman ED, Britton M, Carrillo J, Almeida J, Wixon C. Salmeterol/fluticasone combination inhaler. A new, effective and well tolerated treatment for asthma. *Clinical Drug Investigation* 1998;**16**(3):193–201.

Bateman 2000

Bateman ED, Beasley R, Silins V, Bogolubov M. Comparison of salmeterol/fluticasone propionate combination 50/100 bid delivered via metered dose inhaler or diskus in patients with reversible airways obstruction. American Journal of Respiratory & Critical Care Medicine. 2000; Vol. 161, issue Suppl 3:A197.

Bateman 2001 a

Bateman ED, Silins V, Bogolubov M. Clinical equivalence of salmeterol/fluticasone proprionate in combination (50/100 mcg twice daily) when administered via a chlorofluorocarbon-free metered dose inhaler or dry powder inhaler to patients with mild-to-moderate asthma. *Respiratory Medicine* 2001;**95**(2):136–46.

Bateman 2001 b

Bateman ED, Bantje TA, Gomes M, Toumbis M, Huber R, Eliraz A, Pettersson E. Symbicort (budesonide and formoterol in a single inhaler) is a more effective treatment than fluticasone in asthma patients. Annual Thoracic Society 97th International Conference. 2001.

Bateman 2001 c

Bateman ED, Bantje TA, Joao Gomes M, Toumbis M, Huber R, Eliraz A, Pettersson E. Symbicort (Budesonide/eformoterol) turbohaler controls asthma more effectively than fluticasone diskus. Thorax 2001; Vol. 56, issue Suppl 3:iii 63.

Bateman 2001 d

Bateman ED, Bantje TA, Joao Gomes M, Toumbis M, Huber R, Eliraz A. Early and sustained benefits of budesonide and formoterol in a single inhaler vs fluticasone in moderate asthma. European Respiratory Journal 2001; Vol. 18, issue Suppl 33:157s.

Bateman a 2003

Bateman ED, Bantje TA, Joao Gomes M, Toumbis M, Huber R, Eliraz A. Early and sustained benefits of budesonide and formoterol in a single inhaler vs fluticasone in moderate asthma. European Respiratory Journal 2001; Vol. 18, issue Suppl 33:157s.

Bateman ED, Bantje TA, Joao Gomes M, Toumbis M, Huber R, Eliraz A, Pettersson E. Symbicort (Budesonide/eformoterol) turbohaler controls asthma more effectively than fluticasone diskus. Thorax 2001; Vol. 56, issue Suppl 3:iii 63.

Ericsson K, Bantje TA, Huber H, Borg S. Symbicort® turbuhaler® is more cost effective than fluticasone diskus™ in the treatment of asthma. Annual Thoracic Society 97th International Conference; San Francisco CA ,May 18-23. 2001.

Ericsson K, Bantje TA, Huber R, Borg S, Anderson F. Cost-effectiveness of budesonide and formoterol in a single inhaler compared to fluticasone in the treatment of asthma. European Respiratory Journal 2001; Vol. 18, issue Suppl 33:157s.

* RD Bateman, TA Bantje, MJ Gomes, MG Toumbis, RM Huber, I Naya, A Eliraz. Combination Therapy with a Single Inhaler Budesonide/Formoterol compared with high dose fluticasone proprionate alone in patients with moderate persistent asthma. *Am J Repir Med* 2003;**2**(3):275–281.

Bateman b 2003

Bateman ED, Akveld M, Ho M. Greater responder rate to fluticasone propionate/salmeterol combination over montelukast plus fluticasone in asthma. American Thoracic Society 99th International Conference. 2003:B036 Poster H90.

Becker 1999

Becker I, Kielborn A, Price MJ, Volmer T, Lloyd AC. Cost-effectiveness of salmeterol/fluticasone combination product and budesonide in asthma patients in Germany. European Respiratory Society; 1999 Oct 9-13; Madrid, Spain. 1999:854.

Behling

Behling B, Matthys H. Comparison of efficacy and safety of formoterol with terbutaline in children with mild to moderate asthma. European Respiratory Society; 1999 Oct 9-13; Madrid, Spain. 1999: 369.

Bensch 2002

Bensch G, Berger WE, Blokhnn M, Socolovshy AL, MH THomson, Till MD, Castellsague J, Della Cioppa G. One year efficacy and safety of inhaled formoterol dry powder in children with persistent asthma. *Annals of Allergy asthma and Immunology* 2002;**89**:180–90.

Berger 2001

Berger W, Bensch G, Blokhin BM, Socolovsky AL, Thompson MH, Till D. Addition of formoterol (foradil®) improves lung function and symptoms in children with persistent asthma not controlled by inhaled corticosteroids. Annual Thoracic Society 97th International Conference; San Francisco CA ,May 18-23. 2001.

Berggren 2001

Berggren F, Ekstrom T. A cost-effectiveness study comparing the as-needed use of formoterol (Oxis) and terbutaline (Bricanyl) in patients with moderate to severe asthma. *Respiratory Medicine* 2001;**95**(9): 753–8.

Bergmann 2004

Bergmann KC, Lindemann L, Braun R, Steinkamp G. Salmeterol/ fluticasone propionate (50/250 mug) combination is superior to double dose fluticasone (500 mug) for the treatment of symptomatic moderate asthma: A prospective, double-blind trial.. *Swiss Medical Weekly* 2004;**134**(3-4):50–58.

Bernstein 2002

Bernstein IL. Beta2-agonists: Deja vu all over again: the second-generation controversy. Chest 2002; Vol. 122, issue 3:763–5.

Bessmertny 2002

Bessmertny O, DiGregorio RV, Cohen H, Becker E, Looney D, Golden J, Kohl L, Johnson T. A randomized clinical trial of nebulized magnesium sulfate in addition to albuterol in the treatment of acute mild-to-moderate asthma exacerbations in adults. *Annals of Emergency Medicine* 2002;**39**(6):585–91.

Bijl-Hofland 2001

Bijl-Hofland ID, Cloosterman SG, Folgering HT, van den Elshout FJ, van Weel C, van Schayck CP. Inhaled corticosteroids, combined with long-acting beta(2)-agonists, improve the perception of bronchoconstriction in asthma. *American Journal of Respiratory & Critical Care Medicine* 2001;**164**(5):764–9.

Bjermer 2000

Bjermer L, Bisgaard H, Bousquet J, Fabbri LM, Greening A, Haahtela T, Holgate ST, Picado C, Leff JA. Montelukast or salmeterol combined with an inhaled steroid in adult asthma: design and rationale of a randomized, double-blind comparative study (the IMPACT Investigation of Montelukast as a Partner Agent for Complementary Therapy-trial). *Respiratory Medicine* 2000;**94**(6):612–21.

Bjermer 2002

Bjermer L, Greening A, Haahtela T, Bousquet J, Holgate ST, Picado C, et al. Addition of montelukast or salmeterol to fluticasone in patients with uncontrolled asthma: results of the IMPACT trial. Chest 2002; San Diego, CA. 2002:434.

Bjermer 2003

Bjermer L, Bisgaard H, Bousquet J, Fabbri LM, Greening AP, Haahtela T, at al. Montelukast and fluticasone compared with salmeterol and fluticasone in protecting against asthma exacerbation in adults: one year, double blind, randomised, comparative trial. *BMJ* 2003;**327**(7420):891.

Bloom 2003

Bloom J, Calhoun W, Koenig S, Yancey S, Reilly D, Edwards L, Stauffer J, Dorinsky P. Fluticasone propionate/salmeterol 100/50mcg is inhaled steroid sparing in patients who require fluticasone propionate 250mcg for asthma stability. American Thoracic Society 99th International Conference. 2003:D034 Poster C33.

Boonsawat 2003

Boonsawat W, Charoenratanakul S, Pothirat C, Sawanyawisuth K, Seearamroongruang T, Bengtsson T, Brander R, Selroos OW. Formoterol (OXIS) Turbuhaler as a rescue therapy compared with salbutamol pMDI plus spacer in patients with acute severe asthma. *Respiratory Medicine* 2003;**97**(9):1067–74.

Booth-H 1993

Booth H, Fishwick K Harkawat R Devereux G, Hendrick DJ, Walters EH. Changes in methacholine induced bronchoconstriction with the long acting beta 2 agonist salmeterol in mild to moderate asthmatic patients. *Thorax* 1993;**48**(11):1121–4.

Boskovska 2001

Boskovska MI, Dokic D, Busletic-Bozinovska K, Arbutina S, Goseva Z. Concomitant use of low-dose inhaled corticosteroids and a long-acting bronchodilatator visavi doubling the dose of inhaled corticosteroid in asthma patients. European Respiratory Journal 2001, issue Suppl 33:98s.

Boulet 2003

Boulet LP, Chapman K, Roberts J, Watson EG. Efficacy of salmetero/fluticasone proprionate HFA MDI versus high dose fluticasone proprioante HFA MDI in adolescent and adult asthma. European Respiratory Society Meeting. 2003.

Bouros 1999

Bouros D, Bachlitzanakis N, Kottakis J, Pfister P, Polychronopoulos V, Papadakis E, et al. Foromoterol and beclomethasone versus higher dose beclomethasone as maintenance therapy in adult asthma. *European Respiratory Journal* 1999;**14**:627–32.

Brambilla 1994

Brambilla C, Chastang C, Georges D, Bertin L. Salmeterol compared with slow-release terbutaline in nocturnal asthma. A multicenter, randomized, double-blind, double-dummy, sequential clinical trial. French Multicenter Study Group. *Allergy* 1994;**49**(6):421–6.

Brambilla 2003

Brambilla C, Le Gros V, Bourdeix I. Formoterol 12 mcg bid admisnistered via single dry powder inhaler in adults with asthma suboptimally controlled with salmeterol or on demaind salbutamol. *Clinical Therapeutics* 2003;**25**(7):2022–36.

Braniuk 1999

Braniuk J, Murray JJ, Nathan RA, Berger WE, Johnson M, Edwards LD, et al. Fluticasone alone or in combination with salmeterol vs triamcinolone in asthma. *Chest* 1999;**116**(3):625–32.

Brenner-M 1988

Brenner M, Berkowitz R, Marshall N, Strunk RC. Need for theophylline in severe steroid-requiring asthmatics. *Clinical Allergy* 1988; **18**(2):143–50.

Britton 1992

Britton MG, Earnshaw JS, Palmer JBD. A twelve month comparison of salmeterol with salbutamol in asthmatic patients. *European Respiratory Journal* 1992;**5**(9):1062–67.

Britton 1998

Britton MG, Carrillo T, Almeida J, Wixon C. Combined serevent™ and fluticasone propionate (50/100µg strength) bd via one diskus™ (accuhaler™) inhaler compared with salmeterol 50µg and fluticasone propionate 100µg bd via two separate diskus inhalers. American

Journal of Respiratory and Critical Care Medicine 1998; Vol. 157, issue Suppl 3:A415.

Brogden-RN 1991

Brogden RN, Faulds D. Salmeterol xinafoate. A review of its pharmacological properties and therapeutic potential in reversible obstructive airways disease. *Drugs* 1991;**42**(5):895–912.

Buchvald F

Buchvald F, Bisgaard H. Comparisons of the complementary effetct on exhaled nitric oside of salmeterol vs montelukast ina sthmatic children taking regular budesonide. *Annals of Allergy, Asthma & Immunology* 2003;**91**(3):309–13.

Busse 1999

Busse W, Nelson H, Wolfe J, Kalberg C, Yancey SW, Rickard KA. Comparison of inhaled salmeterol and oral zafirlukast in patients with asthma. *Journal of Allergy & Clinical Immunology* 1999;**103**(6): 1075–80.

Busse 2003 part 1

* Busse W, Koenig SM, Oppenheimer J, Sahn SA, Yancey SW, Reilly D, Edwards LD, Dorinsky PM. Steroid-sparing effects of fluticasone proprionate 100mcg and salmeterol 50mcg administered twice daily in a single product in patients previously controlled with fluticasone proprionate 250mcg administered twice daily. *Journal of Allergy & Clinical Immunology* 2003;**111**(2):57–65.

Sahn S, Yancey S, Reilly D, Edwards L, Rickard K, Dorinsky P. The fluticasone propionate/salmeterol (FSC) combination product 100/50 mcg BID is steroid sparing in patients who require FP250 mcg BID for asthma stability. Chest 2002; San Diego, CA. 2002.

Busse 2003 part 2

* Busse W, Koenig SM, Oppenheimer J, Sahn SA, Yancey SW, Reilly D, Edwards LD, Dorinsky PM. Steroid-sparing effects of fluticasone proprionate 100mcg and salmeterol 50mcg administered twice daily in a single product in patients previously controlled with fluticasone proprionate 250mcg administered twice daily. *Journal of Allergy & Clinical Immunology* 2003;**111**(2):57–65.

Byrnes 2000

Byrnes C, Shrewsbury S, Barnes PJ, Bush A. Salmeterol in paediatric asthma. *Thorax* 2000;**55**(9):780–4.

Calhoun 2001

Calhoun WJ, Nelson HS, Nathan RA, Pepsin PJ, Kalberg C, Emmett A, Rickard KA, Dorinsky P. Comparison of fluticasone propionate-salmeterol combination therapy and motelukast in patients who are symptomatic on short-acting 2-agonists alone. *American Journal of Respiratory & Critical Care Medicine* 2001;**164**(5):759–63.

Calverley 2002

Calverley PMA, Pauwels RA, Vestbo J, Jones PW, Pride NB, Gulsvik A, et al. Salmeterol / fluticasone propionate combination for one year provides greater clinical benefit than its individual coponents in COPD. American Journal of Respiratory and Critical Care Medicine 2002; Vol. 165, issue Suppl 8:A226.

Castle

Castle W, Fuller R, Hall J, Palmer J. Serevent nationwide surveillance study: comparison of salmeterol with salbuatmol in asthmantic patients who require regular bronchodialtor treatment. *BMJ* 1993;**306** (6884):1034–7.

Cazzola 2000

Cazzola M, Di Lorenzo G, Di Perna F, Calderaro F, Testi R, Centanni S. Additive effects of salmeterol and fluticasone or theophylline in COPD. *Chest* 2000;**118**(6):1576–81.

Chan 2001

Chan JS, Cowie RL, Lazarenko GC, Little C, Scott S, Ford GT. Comparison of intramuscular betamethasone and oral prednisone in the prevention of relapse of acute asthma. *Canadian Respiratory Journal* 2001;**8**(3):147–52.

Chapman 1999

Chapman KR, Ringdal N, Backer V, Palmqvist M, Saarelainen S, Briggs M. Salmeterol and fluticasone propionate (50/250 mug) administered via combination Diskus inhaler: As effective as when given via separate Diskus inhalers. *Canadian Respiratory Journal* 1999;**6**(1): 45–51.

Cheer 2003

Cheer SM, Warner GT, Easthope SE. Formoterol delivered by Turbuhaler: in pediatric asthma. *Paediatric Drugs* 2003;**5**(1):63–8.

Chuchalin 2001

Chuchalin AG, Chovan L, Ringdal N, Whitehead PJ. Advair™ seretide™ (250/50 mu-g bid) shows nocturnal benefit over budesonide 800mu-g + formoterol 12mu-g bid in moderate to severe asthma. Annual Thoracic Society 97th International Conference; San Francisco CA ,May 18-23. 2001.

Cloosterman 2001

Cloosterman SG, Bijl-Hofland ID, van Herwaarden CL, Akkermans RP, van Den Elshout FJ, Folgering HT, van Schayck CP. A placebo-controlled clinical trial of regular monotherapy with short-acting and long-acting beta(2)-agonists in allergic asthmatic patients. *Chest* 2001;**119**(5):1306–15.

Condemi 1999

Condemi JJ, Goldstein S, Kalberg C, Yancey S, Emmett A, Rickard K. The addition of salmeterol to fluticasone propionate versus increasing the dose of fluticasone propionate in patients with persistent asthma. *Annals of Allergy Asthma & Immunology* 1999;**82**:383–89.

Condemi 2001

Condemi JJ. Comparison of the efficacy of formoterol and salmeterol in patients with reversible obstructive airway disease: a multicenter, randomized, open-label trial. *Clinical Therapeutics* 2001;**23** (9):1529–41.

Cook 2001

Cook CK, Prillaman BA, House KW, Rickard KA, Shah TP. Concurrent use of salmeterol/fluticasone propionate diskus® powder combination product and fluticasone propionate aqueous nasal spray does not adversely affect hpa-axis function. *Annals of Allergy, Asthma & Immunology* 2001;**86**:98.

Crompton 1999

Crompton GK, Ayres JG, Basran G, Schiraldi G, Brusasco V, Eivindson A, Jamieson AH, Olsson H. Comparison of oral bambuterol and inhaled salme. *American Journal of Respiratory & Critical Care Medicine* 1999;**159**(3):824–8.

Currie 2002

Currie GP, Stenback S, Lipworth BJ. Dissociation in effects of fluticasone but not fluticasone/salmeterol on lung function and airway

hyperresponsiveness in mild persistent asthma. *European Respiratory Society Annual Congress* 2002:P2391.

Currie 2003 a

Currie GP, Lee DK, Haggart K, Bates CE, Lipworth BJ. Effects of montelukast on surrogate inflammatory markers in corticosteroid-treated patients with asthma. *American Journal of Respiratory and Critical Care Medicine* 2003;**167**(9):1232–8.

Currie 2003 b

Currie GP, Bates CE, Lee DK, Jackson CM, Lipworth BJ. Effects of fluticasone plus salmeterol versus twice the dose of fluticasone in asthmatic patients. *European Journal of Clinical Pharmacology* 2003; **59**(1):11–15.

Currie 2003 c

Currie GP, Stenback S, Lipworth BJ. Effects of fluticasone vs. fluticasone/salmeterol on airway calibre and airway hyperresponsiveness in mild persistent asthma. *British Journal of Clinical Pharmacology* 2003;**56**(1):11–7.

D'Alonzo 1994

D'Alonzo GE, Nathan RA, Henochowicz, Morris RJ, Ratner P, Rennard SI. Salmetrol xinafoate as maintenance therapy compared with albuterol in patients with asthma. *JAMA* 1994;**271**:1412–16.

Dahl 1989

Dahl R, Pedersen B, Hagglof B. Nocturnal asthma: effect of treatment with oral sustained-release terbutaline, inhaled budesonide, and the two in combination. *Journal of Allergy & Clinical Immunology* 1989; **83**(4):811–5.

Dahl 1991

Dahl R, Earnshaw JS, Palmer JBD. Salmeterol: a four week study of a long-acting beta-adrenoceptor agonist for the treatment of reversible airways disease. *European Respiratory Journal* 1991;**4**(10):1178–84.

Dal Negro 2001 a

Dal Negro R, Micheletto C, Tognella S, Trevisan F, Pomari C. Short-term bronchodilation following salmeterol 50mcg and combined salmeterol + fluticasone p(50/250mcg) via diskus: a randomized, double blind cross-over study in reversible airway obstruction. Annual Thoracic Society 97th International Conference; San Francisco CA ,May 18-23. 2001.

Dal Negro 2001 b

Dal Negro RW, Micheletto C, Pomari C, Trevisan F, Tognella S. The combination salmeterol (S) + fluticasone propionate (F) in mild-to-moderate asthma. European Respiratory Journal 2001; Vol. 18, issue Suppl 33:426s.

Dal Negro 2002 a

Dal Negro R, Micheletto C, Trevison F, Tognells S, Pomari C, Spencer S. Salmeterol & Fluticasone 50µg/250µg bid vs Salmeterol 50µg bid and vs Placebo in the log-term treatment of COPD. American Journal of Respiratory and Critical Care Medicine 2002, issue Suppl 8:A228.

Dal Negro 2002 b

Dal Negro RW, Micheletto C, Tognella S, Trevisan F, Pomari C. Is the sequence of salmeterol (SM) and fluticasone p. (FP) dry powder inhalation crucial in persistent mild asthma?. European Respiratory Society Annual Congress. 2002:P396.

Davis 2001

Davis ES, Bowers B, Pepsin P, Kalberg C, Dorinsky P. The impact of fluticasone propionate/salmeterol combination product compared to oral montelukast on asthma related quality of life. Annual Thoracic Society 97th International Conference; San Francisco CA ,May 18-23. 2001.

Del Rio-Navarro2001a

Del-Rio-Navarro BE, Sienra-Monge JJL, Alvarez-Amador M, Reyes-Ruiz N, Arevalo-Salas A, Berber A. Serum potassium levels, CPK-MB and ECG in children suffering asthma treated with beclomethasone or beclomethasone-salmeterol. *Allergologia et Immunopathologia* 2001;**29**(1):16–21.

Del-Rio-Navarro2001b

Del Rio BE, Corona L, Fregosa R, Berber A, Magana J, Sienra-Monge JL. Effect of Salmeterol and Salmeterol plus Beclomethasone on the saliva flow and saliva IgA levels on patients with chronic moderate persistent asthma (CMPA). Journal of Allergy and Clinical Immunology 2001; Vol. 107, issue 2:s11.

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

Dempsey 2000 a

Dempsey OJ, Wilson AM, Sims EJ, Lipworth BJ. Additive anti-inflammatory effects of montelukast but not salmeterol in asthmatics suboptimally controlled on inhaled steroids. American Journal of Respiratory and Critical Care Medicine 2000; Vol. 161, issue Suppl 3:A198.

Dempsey 2000 b

Dempsey OJ, Wilson AM, Sims EJ, Mistry C, Lipworth BJ. Additive bronchoprotective and bronchodilator effects with single doses of salmeterol and montelukast in asthmatic patients receiving inhaled corticosteroids.. *Chest* 2000;**117**(4):950–3.

Dente 2001 a

Dente FL, Scuotri L, Bacci E, Di Franco A, Giannini D, Taccola M, et al. Effects of combined treatment - fluticasone plus salmeterol - on allergen-induced asthmatic responses. American Journal of Respiratory and Critical Care Medicine. 2001; Vol. 463, issue Suppl 5: A419.

Dente 2001 b

Dente FL, Scuotri L, Bacci E, DeSanctis M, Di Franco A, Giannini D, et al. Combined treatment with fluticasone plus salmeterol protects against allergen-induced asthmatic responses better than each drug alone. European Respiratory Journal 2001; Vol. 18, issue Suppl 33: 349s.

Dicpinigaitis 2002

Dicpinigaitis PV, Dobkin JB, Reichel J. Antitussive effect of the leukotriene receptor antagonist zafirlukast in subjects with cough-variant asthma. *Journal of Asthma* 2002;**39**(4):291–7.

Didier 1997

Didier A, Campos Oriola R. A two-month comparison of salmeterol/beclomethasone and slow-release terbutaline/budesonide in moderate asthma management. *Clinical Drug Investigation* 1997;**14**(1):1–11.

Djordjevic 1999

Djordjevic D, Zickovic D, Stankovic I, Pejcic T, Ducic J, Rancic M, et al. Comparative study of three months treatment in combination

of salmeterol and beclomethasone dipropionate (bdp) with doubling the dose of bdp in mild asthma. European Respiratory Society; 1999 Oct 9-13; Madrid, Spain. 1999:p849.

Dorinsky 2001 a

Dorinsky PM, Kalberg C, Pepsin P, Emmett A, Rickard K. Greater onset of improvement in clinical efficacy measures with first line use of the fluticasone/salmeterol combination product compared to montelukast. Annual Thoracic Society 97th International Conference; San Francisco CA May 18-23. 2001.

Dorinsky 2001 b

Dorinsky P, Kalberg C, Pepsin P, Emmett A, Bowers B, Rickard K. The fluticasone/salmeterol combination product is superior to montelukast as first-line asthma control. European Respiratory Journal 2001; Vol. 18, issue Suppl 33:263s.

Eliraz 2001

Eliraz A, Ramirez-Rivera A, Ferranti P, Holzer R, Garcia JM, Turcotte C, et al. Similar efficacy following four weeks treatment of asthmatics with formoterol 12 mcg BD delivered by two different dry powder inhalers; differences in inhaler handling. *International Journal of Clinical Practice* 2001;**55**(3):164–70.

Eliraz 2002 a

Eliraz A, Fritscher CC, Perez CMR, Boonsawat W, Nang AN, Bardin, P Kao HP. Symbicort® (Budesonide/Formoterol) achieves more rapid control of asthma that fluticasone in patients with mild asthma. American Journal of Respiratory and Critical Care Medicine 2002; Vol. 165, issue Suppl 8:A567.

Eliraz 2002 b

Eliraz A, Fritscher CC, Perez CMR, Boonsawat W, Nang AN, Bardin P, Kao HP. Budesonide and formoterol in a single inhaler quickly gains asthma control compared with fluticasone propionate in mild asthma. European Respiratory Journal 2001; Vol. 18, issue Suppl 33: 48s.

Ericsson 2001 a

Ericsson K, Bantje TA, Huber H, Borg S. Symbicort® turbuhaler® is more cost effective than fluticasone diskus™ in the treatment of asthma. Annual Thoracic Society 97th International Conference; San Francisco CA , May 18-23. 2001.

Ericsson2001 b

Ericsson K, Bantje TA, Huber R, Borg S, Anderson F. Cost-effectiveness of budesonide and formoterol in a single inhaler compared to fluticasone in the treatment of asthma. European Respiratory Journal 2001; Vol. 18, issue Suppl 33:157s.

Everden 2002

Everden P, Lloyd A, Hutchinson J, Plumb J. Cost-effectiveness of eformoterol Turbohaler(R) versus salmeterol Accuhaler(R) in children with symptomatic asthma. *Respiratory Medicine* 2002;**96**(4): 250–8.

Faurschou 1996

Faurschou P, Steffensen I, Jacques L. Effect of addition of inhaled salmeterol to the treatment of moderate-to-severe asthmatics uncontrolled on high-dose inhaled steroids. *European Respiratory Journal* 1996;**9**(9):1885–90.

Faurschou-P 1994

Faurschou P, Engel AM, Haanaes OC. Salmeterol in two different doses in the treatment of nocturnal bronchial asthma poorly controlled by other therapies. *Allergy* 1994;**49**(40):827–32.

Fish 2000

Fish J, Boone R, Emmett A, Yancey S, Knobil K, Rickard K. Salmeterol added to inhaled corticosteroids (ICS) provides greater asthma control compared to montelukast. American Journal of Respiratory and Critical Care Medicine 2000; Vol. 161, issue Suppl 3:A203.

Fish 2001

Fish JE, Israel E, Murray JJ, Emmett A, Boone R, Yancey SW, Rickard KA. Salmeterol powder provides significantly better benefit than Montelukast in asthmatic patients receiving concomitant inhaled corticosteroid therapy. *Chest* 2001;**120**(2):423–430.

Fitzpatrick 1990

Fitzpatrick MF, Mackay T, Driver H, Douglas NJ. Salmeterol in nocturnal asthma: a double-blind, placebo controlled trial of long-acting inhaled beta2 agonist. *BMJ* 1990;**301**:1365–8.

Fowler 2002

SJ Fowler, PC Currie, BJ Lipworth. Step down therapy with low dose fluticasone-salmeterol combination or medium dose hydrofluoroalkane 134a-beclomethasone alone. *Journal of Allergy & Clinical Immunology* 2002;**109**(6):929–35.

Fuglsang-G 1995

Fuglsang G, Agertoft L, Vikre-Jorgensen J, Pedersen S. Influence of budesonide on the response to inhaled terbutaline in children with mild asthma. *Pediatric Allergy and Immunology* 1995;**6**(2):103–8.

Gabrijelcic 2004

Gabrijelcic J, Casas A, Rabinovich RA, Roca J, Barbera J A, Chung K F, Rodriguez-Rosin R. Formoterol protects against platelet-activating factor-induced effects in asthma. *European Respiratory Journal* 2004; **23**(1):71–75.

Giannini 1996

Giannini D, Carletti A, Dente FL, Testi R, Bacci D, Bancalari L, et al. Effect of inhaled beclomethasone dipropionate (BDP) on tolerance to salmeterol (S) in allergen induced bronchoconstriction. European Respiratory Journal 1996; Vol. 9, issue Suppl 23:272s.

Giannini 1998 a

Giannini D, Di Franco A, Bacci E, Conti I, Dente FL, Kotopulos C, et al. Long-term treatment with salmeterol and inhaled corticosteroids does not induce tolerance to the protective effect of salmeterol on allergen challenge. American Journal of Respiratory and Critical Care Medicine 1998; Vol. 157, issue Suppl 3:A414.

Giannini 1998 b

Giannini D, di Franco A, Bacci E, Conti I, Dente FL, Kotopulos C, et al. One-week regular treatment with salmeterol induces tolerance to the protective effect of salmeterol on allergen challenge only in subjects not regularly treated with salmeterol and inhaled corticosteroid. *European Respiratory Journal* 1998;**12**(Suppl 28):156s.

Giannini 1999

Giannini D, Bacci E, Dente FL, Di Franco A, Vagaggini B, Testi R, Paggiaro P. Inhaled beclomethasone dipropionate reverts tolerance to the protective effect of salmeterol on allergen challenge. *Chest* 1999; **115**(3):629–634.

Giannini 2000

Giannini D, Di Franco A, Bacci E, Dente FL, Taccola M, Vagaggini B, Paggiaro P. The protective effect of salbutamol inhaled using different devices on methacholine bronchoconstriction. *Chest* 2000;**117**(5): 1319–23.

Giannini 2001

Giannini D, Tonelli M, Di Franco A, Bacci E, Conti I, Dente FL, et al. Tolerance to the protective effect of salmeterol on allergen challenge in mild untreated asthmatics and in moderate asthmatics on inhaled corticosteroid treatment. European Respiratory Journal 2001; Vol. 18, issue Suppl 33:103s.

Giannini 2002 a

Giannini D, Tonelli M, Di Franco A, Bacci E, Conti I, Dente FL, et al. Tolerance to the protective effect of salmeterol + fluticasone combination (50/250 µg) on allergen challenge in mild untreated asthmatics. American Journal of Respiratory and Critical Care Medicine 2002; Vol. 165, issue Suppl 8:A566.

Giannini D 2002 b

Giannini D, di Franco A, Bacci E, Conti I, Dente FL, Kotopulos C, et al. One-week regular treatment with salmeterol induces tolerance to the protective effect of salmeterol on allergen challenge only in subjects not regularly treated with salmeterol and inhaled corticosteroid. *European Respiratory Journal* 1998;**12**(Suppl 28):156s.

Gizycki 2000

Gizycki MJ, Venge P, Dahl R, Jeffery PK. Comparison of the effects of six weeks treatment with fluticasone or salmeterol on the late phase response (LPR) in mild asthma - a bronchial biopsy study. American Journal of Respiratory and Critical Care Medicine 2000; Vol. 161, issue Suppl 3:A203.

Gold 2001

Gold M, Jõgi R, Mulder PGH, Akveld MLM. Salmeterol/fluticasone propionate combination 50/100µg bid is more effective than fluticasone propionate 100µg bid plus montelukast 10 mg once daily in reducing exacerbations. European Respiratory Journal 2001; Vol. 18, issue Suppl 33:262s.

Green 2002

Green RH, Brightling CE, McKenna S, Hargadon B, Parker D, Wardlaw AJ, Pavord ID. A placebo controlled comparison of formoterol, montelukast or higher dose of inhaled corticosteroids in subjects with symptomatic asthma despite treatment with low dose inhaled corticosteroids. Thorax 2002; Vol. 57, issue Suppl III:iii 11.

Greening 1994

Greening AP, Ind PW, Northfield M, Shaw G. Added salmeterol versus higher-dose corticosteroid in asthma patients with symptoms on existing inhaled corticosteroid. *Lancet* 1994;**344**:219–24.

Grosclaude 2003

Grosclaude M, Cerruti JL, Delannay B, Herent M, Spilthooren F, Desfougeres JL. The fixed fluticasone/salmeterol gives better control of asthma than the association of beclomethsone dipropronate-montelukast. *Allergie Et Immunologie* 2003;**35**(9):356–62.

Grzelewska-Rzymowska

Grzelewska-Rzymowska I, Malolepszy J, de Molina M, Sladek K, Zarkovic J, Siergiejko Z. Equivalent asthma control and systemic safety of inhaled budesonide delivered via HFA-134a or CFC propellant in a broad range of doses. *Respiratory Medicine* 2003;**97**(SUPPL. D):S10–S19.

Gustafsson 1994

Gustafsson PM, Von BA, Jenkins MM. Salmeterol 50 mug twice daily in the treatment of mild-to-moderate asthma in childhood - A comparison of two inhalation devices. *European Journal of Clinical Research* 1994;**5**:63–73.

Hasani 2003

Hasani A, Toms N, O'Connor J, Dilworth JP, Agnew JE. Effect of salmeterol xinafoate on lung mucociliary clearance in patients with asthma. *Respiratory Medicine* 2003;**97**(6):667–671.

Haughney 2002

Haughney J, Price D, Rosen JP, Kennelly J. Adjustable maintenance treatment with budesonide/formoterol combination rapidly improves and maintains quality of life in asthma patients. European Respiratory Society Annual Congress. 2002:P379.

Heuck 1999

Heuck C, Heickendorff L, Wolthers OD, Sygehus S. Short term growth and collagen turnover in asthmatics treated inhaled formoterol and budesonide. European Respiratory Society; Oct 9-13; Madrid, Spain. 1999:364.

Heuck 2000

Heuck C, Heickendorff L, Wolthers OD. A randomized controlled trial of short term growth and collagen turnover in asthmatics with inhaled formoterol and budesonide. *Archives of Disease in Childhood* 2000;**83**:334–339.

Hyland-ME 1995

Hyland ME, Crocker GR. Validation of an asthma quality of life diary in a clinical trial. *Thorax* 1995;**50**(7):724–730.

Ind 2002 a

Ind P, Haughney J, Price D, Rosen JP, Kennelly J. Managed adjustable dosing of budesonide/formoterol combination provides equivalent asthma control to fixed dosing at a lower overall dose. European Respiratory Society Annual Congress. 2002:P2450.

Ind 2002 b

Ind PW, Villasante C, Shiner RJ, Pietinalho A, Boszormenyi NG, Soliman S, Selroos O. Safety of formoterol by Turbuhaler as reliever medication compared with terbutaline in moderate asthma. *European Respiratory Journal* 2002;**20**(4):859–66.

Ind 2003 b

Haughney J, Price D, Rosen JP, Kennelly J. Adjustable maintenance treatment with budesonide/formoterol combination rapidly improves and maintains quality of life in asthma patients. European Respiratory Society Annual Congress. 2002:P379.

Ind P W, Price D, Haughney J, Rosen J P. Adjustable dosing with budesonide/formoterol in a single inhaler (symbicort(r)) provides similarly effective treatment of asthma compared with fixed dosing but at a lower overall dose [. American Thoracic Society 99th International Conference. 2003:D034 Poster C38.

Isabelle 2001

Isabelle P, Bjamer D, Neuparth N, Desfougeres JL. Efficacy and safety of salmeterol/fluticasone combination 50/100mug bd via two different powder devices in children. Annual Thoracic Society 97th International Conference; San Francisco CA ,May 18-23. 2001.

Jeffery 2002

Jeffery PK, Venge P, Gizycki MJ, Egerod I, Dahl R, Faurschou P. Effects of salmeterol on mucosal inflammation in asthma: a placebo-controlled study. *European Respiratory Journal* 2002;**20**(6):1378–85.

Jenkins 1995

Jenkins M. Clinical evaluation of CFC-free metered dose inhalers. *Journal of Aerosol Medicine: Deposition, Clearance, and Effects in the Lung* 1995;**8**(Suppl 1):s41–s47.

Jenkins 2000 a

Jenkins C, Woolcock AJ, Saarelainen P, Lundbaack B, James MH. Salmeterol /fluticasone proprionate combination therapy 50/250mcgs twice daily is more effective than budesonide 800 twice daily in treating moderate to severe asthma. *Repiratory Medicine* 2000;**94**:715–723.

Jenkins 2000 b

Jenkins C, Woolcock A, James M. Superior overall control of moderate to severe asthma with salmeterol/fluticasone propionate (FP) combination (50/250 mcg bd) compared with three-fold-higher dose of budesonide (800mcg bd). European Respiratory Journal 2000; Vol. 16, issue Suppl 31:456s.

Jenkins 2002 a

Jenkins C, Wilson J, Rutherford C, Perry AS, Whitehead PJ. Asthma management costs are lower with combination fluticasone/salmeterol (25/50 mcg BD) in a single inhaler than with budesonide (800 mcg BD) plus eformoterol (12 mcg BD) via separate inhalers. 2002. Respirology 2002; Vol. 7, issue supp:A20.

Jenkins 2002 b

Jenkins C. Combination therapy with fluticasone and salmeterol for symptomatic asthma produces similar benefits when given by accuhaler in a single or two separate devices over 24 weeks. Respirology 2002; Vol. 7, issue Suppl:A20.

Johansson 2001

Johansson G, McIvor RA, D'Ambrosio FP, Gratziou C, James MH. Comparison of Salmeterol/Flucticasone Propionate Combination with Budesonide in Patients with Mild-to-Moderate Asthma. *Clinical Drug Investigation* 2001;**21**(9):633–42.

Jones 1994

Jones KP. Salmeterol xinafoate in the treatment of mild to moderate asthma in primary care. *Thorax* 1994;**49**:971–5.

Juniper

Juniper EF, Johnston PR, Borkhoff CM, Guyatt GH, Boulet LP, Haukioja A. Quality of life in asthma clinical trials: comparison of salmeterol and salbutamol. *American Journal of Respiratory and Critical Care Medicien* 1995;**151**(1):66–70.

Juniper 1999

Juniper EF, Svenson K, O'Byrne PM, Barnes PJ, Bauer CA, Lofdahl CG, et al. Asthma quality of life during 1 year of treatment with budesonide with or without formoterol. *European Respiratory Journal* 1999;**14**:1038–43.

Kaik 2002

Kaik G, Kottakis I, Anagnostopoulou O, Sichletidis L, Bachlitzanakis N, D'Amato M, et al. Sequential flexible therapy with formoterol (Foradil(r)) plus budesonide (Miflonide(r)) versus a fixed combination of salmeterol and fluticasone (Seretide(r)) in asthma self-management. European Respiratory Society Annual Congress. 2002.

Kalberg 1998

Kalberg CJ, Nelson H, Yancey S, Petrocella V, Emmett AH, Rickard KA, et al. A comparison of added salmeterol versus increased-dose fluticasone in patients symptomatic on low-dose fluticasone [Abstract]. *Journal of Allergy & Clinical Immunology* 1998;**101**(suppl):S6.

Kalra 1996

Kalra S, Swystun VA, Bhagat R, Cockcroft DW. Inhaled corticosteroids do not prevent the development of tolerance to the bronchoprotective effect of salmeterol. *Chest* 1996;**109**(4):953–6.

Kardos 2001

Kardos P, Bruggenjurgen B, Martin A, Meyer-Sabellek W, Richter K, Vogelmeier C, Willlich SN, Buhl R. [Treatment of bronchial asthma using a new adjustable combination treatment plan: Asthma Control Plan (ATACO)]. *Pneumologie* 2001;**55**(5):253–7.

Kelsen 1999

Kelsen SG, Church NL, Gillman SA, Lanier BQ, Emmett AH, Rickard KA, Anderson WH. Salmeterol added to inhaled corticosteroids therapy is superior to doubling the dose of inhaled cotricosteroids: A randomized clinical trial. *Journal of Asthma* 1999;**36**(8):703–15.

Kerwin 2001

Kerwin E, Srebro S, Church N, Emmett A, Rickard K, Knobil K. Salmeterol added to low-dose fluticasone propionate (fp) improves pulmonary function and albuterol use more rapidly than adding montelukast. *Annals of Allergy, Asthma & Immunology* 2001;**86**:99.

Ketchell 2002

Ketchell RI, Jensen MW, Spina D, O'Connor BJ. Dose-related effects of formoterol on airway responsiveness to adenosine 5'-monophosphate and histamine. *European Respiratory Journal* 2002;**19**(4):611–616.

Kidney 1995

Kidney J, Pizzichini MMM, Wong B, Morris MM, Efthimadis A, Dolovich J, Hargreave FE. Salmeterol compared with beclomethasone and placebo on allergen induced asthmatic and inflammatory responses. European Respiratory Journal 1995; Vol. 8, issue Suppl 19:336s.

Kips 2000

Kips JC, O'Connor BJ, Inman MD, Svenson K, Pauwels RA, O'Byrne PM. A long-term study of the antiinflammatory effect of low-dose budesonide plus formoterol versus high-dose budesonide in asthma. *American Journal Respiratory Critical Care Medicine* 2000;**161**:996–1001.

Kirby 2000

Kirby S, Falcoz C, Daniel MJ, Milleri S, Squassante L, et al. Salmeterol and fluticasone propionate given as a combination: Lack of systemic pharmacodynamic and pharmacokinetic interactions. *European Journal of Clinical Pharmacology* 2000;**56**(11):781–91.

Knobil 2000

Knobil K, Dorinsky P, Yancey S, Emmett A, Rickard K. Salmeterol is superior to montelukast as add-on therapy to inhaled corticosteroids. European Respiratory Journal 2000; Vol. 16, issue suppl 31:457s.

Knorr 2001

Knorr B, Franchi LM, Bisgaard H, Vermeulen JH, LeSouef P, Santanello N, et al. [Montelukast, a leukotriene receptor antagonist, for the treatment of persistent asthma in children aged 2 to 5 years]. *Pediatrics* 2001;**108**(3):E48.

Kraft 2003

Kraft M, Martin RJ, Lazarus SC, Lemanske RF, Szefler SJ. Airway tissue mast cells in persistent asthma: Predictor of treatment failure when patients dixcontinue inhaled corticosteroids. *Chest* 2003;**124**(1):42–50.

LaForce 1994

LaForce C, Liddle RF, Yancey SW. Salmeterol response in asthmatic patients using inhaled corticosteroids and in those not using inhaled corticosteroids. Annals of Allergy 1994; Vol. 72:100.

Lai 1995

Lai CKW, Chan CHS, Ho SS, Hui ACF, Lai KN. Inhaled salmeterol and albuterol in asthmatic patinets receiving high-dose inhaled corticosteroids. *Chest* 1995;**108**:36–40.

Lalloo 2000

Lalloo UG, Bantje TA, Kozma D, Krofta K, Ankerst J, Johansen B, Thomson NC. Low-dose Symbicort (budesonide / formoterol) is more effective than double-dose inhaled corticosteroid in mild asthma. Allergy Clinical Immunology Int 2000; Vol. Suppl 2.

Lalloo 2001 a

Lalloo UG, Malolepszy J, Kozma D, Krofta K, Ankerst J, Johansen B, Thomson NC. Symbicort® (budesonide and formoterol in a single inhaler) is more effective than increasing the dose of inhaled corticosteroids in mild asthma. Annual Thoracic Society 97th International Conference; San Francisco CA ,May 18-23. 2001.

Lalloo 2001 b

Lalloo UG, Malolepszy J, Kozma D, Krofta K, Ankerst J, Johansen B, Thompson NC. Budesonide and formoterol in a single inhaler is more effective than a higher dose of inhaled corticosteroid in mild-moderate persistent asthma. *European Respiratory Journal* 2001;**18** (Suppl 33):159s.

Lalloo 2001 c

Lalloo UG, Malolepsky J, Kozma D, Krofta K, Ankerst J, Johansen B, Thompson NC. Budesonide and formoterol in a single inhaler controls exacerbations more effectively than a higher dose of inhaled corticosteroids alone, in mild-moderate persistent asthma. *European Respiratory Journal* 2001;**18**(Suppl 33):43s.

Lalloo 2003

Lalloo UG, Malolepszy D, Kozma K, Krofta J, Ankerst B, Johansen NC, Thomson NC. Budesonide and formoterol in a single inhaler improves asthma control compared with increasing the dose of corticosteroid in adults with mild to moderate asthma. *Chest* 2003;**123** (5):1480–87.

Lange 2001

Lange ML, House KW, Scott CA, Shah TP, Akveld MLM. The salmeterol/fluticasone propionate combination 50/100µg bid is effective as initial maintenance therapy in mild and moderate asthmatics. European Respiratory Journal 2001; Vol. 18, issue Suppl 33:176s.

Lazarus 2001

Lazarus SC, Boushey HA, Fahy JV, Chinchilli VM, Lemanske RF Jr, Sorkness CA, et al. Long-acting beta2 agonist monotherapy vs continued therapy with inhaled coricosteroids in patients with persistent asthma: A randomized controlled trial. *Journal of the American Medical Association* 2001;**285**(20):2583–93.

Lee 2003

Lee DK, Jackson CM, Currie GP, Cockburn WJ, Lipworth BJ. Comparison of combination inhalers vs inhaled corticosteroids alone in moderate persistent asthma. *British Journal of Clinical Pharmacology* 2003;**56**(5):194–500.

Lemanske 2001

Lemanske RF Jr, Sorkness CA, Mauger EA, Lazarus SC, Boushey HA, Fahy JV, et al. Inhaled Corticosteroid Reduction and Elimination in Patients with Persistent Asthma Receiving Salmeterol: A randomized controlled trial. *JAMA* 2001;**285**(20):2594–603.

Lenney 1995

Lenney W, Pedersen S, Boner AL, Ebbutt A, Jenkins MM. Efficacy and safety of salmeterol in childhood asthma. *European Journal of Pediatrics* 1995;**154**:983–90.

Leuppi 2003

Leuppi FD, Salzberg M, Meyer L, Bucher SE, Nief M, Brutsche MH, Tamm M. An individualized, adjustable maintenance regimen of budesonide/formoterol provides effective asthma symptom control at a lower overall dose than fixed dosing. *Swiss Medical Weekly* 2003; **133**(21-22):302–9.

LHSRG 2000

The Lung Health Study Research Group. Effect of inhaled triamcinolone on the decline in pulmonary function in chronic obstructive pulmonary disease. *New England Journal of Medicine* 2000;**343**(26): 1902–9.

Li 1999

Li X, Ward C, Thien F, Bish R, Bamford T, Bao X, et al. An anti-inflammatory effect of salmeterol, a long-acting B2-agonist, assessed in airway biopsies and bronchoalveolar lavage in asthma. *American Journal of Respiratory and Crtitical Care Medicine* 1999;**160**:1493–99.

Lindqvist

Lindqvist AE, Karjalainen EM, Laitinen LA, Kava T, Altraja A, Pulkkinen M, et al. Salmeterol (sim), fluticasone propionate (fp) or disodium cromoglycate (dscg) in the treatment of newly diagnosed asthma. Annual Thoracic Society 97th International Conference; San Francisco CA ,May 18-23. 2001.

Lindqvist 2003

Lindqvist A, Karjalainen EM, Laitinen L A, Kava T, Altraja A, Pulkkinen M, et al. Salmeterol resolves airway obstruction but does not possess anti-eosinophil efficacy in newly diagnosed asthma: a randomized, double-blind, parallel group biopsy study comparing the effects of salmeterol, fluticasone propionate, and disodium cromoglycate. *Journal of Allergy & Clinical Immunology* 2003;**112**(1):23–8.

Lipworth 1996

Lipworth BJ, Hall IP, Aziz I, Tan KS, Wheatley A. Beta2-adrenoceptor polymorphism and bronchoprotective sensitivity with regular short- and long-acting beta2-agonist therapy. *Clinical Science* 96;**3** (253-9).

Lipworth 1998

Lipworth B, Tan S, Devlin M, Aiken T, Baker R, Hendrick D. Effects of treatment with formoterol on bronchoprotection against methacholine. *American Journal of Medicine* 1998;**104**(5):431–8.

Lipworth 1999 a

Lipworth BJ, Aziz I. A high dose of albuterol does not overcome bronchoprotective subsensitivity in asthmatic subjects receiving regular salmeterol or formoterol. *Journal of Allergy & Clinical Immunology* 1999;**103**(1 part 1):88–92.

Lipworth 1999 b

Lipworth BJ, Hall IP, Aziz I, Tan KS, Wheatley A. Beta2-adrenoceptor polymorphism and bronchoprotective sensitivity with regular short- and long-acting beta2-agonist therapy. *Clinical Science* 96;**3** (253-9).

Lipworth 2000 a

Lipworth BJ, Dempsey OJ, Aziz I. Functional antagonism with formoterol and salmeterol in asthmatic patients expressing the homozygous glycine-16 beta(2)-adrenoceptor polymorphism. *Chest* 2000; **118**(2):321–8.

Lipworth 2000 b

Lipworth BJ, Dempsey OJ, Aziz I, Wilson AM. Effects of adding a leukotriene antagonist or a long-acting beta(2)-agonist in asthmatic patients with the glycine-16 beta(2)-adrenoceptor genotype. *American Journal of Medicine* 2000;**109**(2):114–21.

Lipworth ????

BJ Lipworth. Does genetic polymorphism of b2-adrenoceptors determine airway sensitivity to regular long-acting b2-agonist therapy?. National Research Register (UK).

Lockey 1999

Lockey RF, DuBuske LM, Friedman B, Petrocella V, Cox F, Rickard K. Nocturnal asthma: Effect of salmeterol on quality of life and clinical outcomes. *Chest* 1999;**115**(3):666–673.

Lowhagen 2002

Lowhagen O, Wever AM, Lusuardi M, Moscato G, De Backer WA, Gandola L, at al. The inflammatory marker serum eosinophil cationic protein (ECP) compared with PEF as a tool to decide inhaled corticosteroid dose in asthmatic patients. *Respiratory Medicine* 2002;**96** (2):95–101.

Lundback 2000

Lundback B, Jenkins C, Price MJ, Thwaites RM. Cost-effectiveness of salmeterol/fluticasone propionate combination product 50/250 microg twice daily and budesonide 800 microg twice daily in the treatment of adults and adolescents with asthma. *Respiratory Medicine* 2000;**94**(7):724–32.

Lundback 2001

Lundback B, Ronmark E, Jonsson AC, et al. Treatment effectiveness and exacerbations during one year with Seretide compared to fluticasone propionate and salmeterol in mild to moderate asthma. European Respiratory Journal 2001; Vol. 18, issue Suppl 33:176s.

Lundback 2002

Lundback B, Ronmark E, Jonsson AC, Larsson LG, Petavy F, James MH. Airway hyperresponsiveness and treatment effectiveness during a one year study of the combination of salmeterol and fluticasone propionate (FP) compared with FP and salmeterol alone in mild to moderate asthma. European Respiratory Society Annual Congress. 2002:P2397.

Lyseng-Williamson 20

Lyseng-Williamson K A, Plosker G L. Inhaled salmeterol/fluticasone propionate combination: A pharmacoeconomic review of its use in the management of asthma. *Pharmacoeconomics* 2003;**21**(13):951–989.

Lötvall 2002

Lötvall J, van der Woude HJ, Palmqvist M, Arvidsson P, Beckman O, Boorsma M, Bergqvist PBF, Aalbers R. More rapid onset of action of budesonide/formoterol (Symbicort®) than salmeterol/fluticasone (seretide™). American Journal of Respiratory and Critical Care Medicine 2002; Vol. 165, issue Suppl 8:A567.

Magadle 2001

Magadle R, Berar-Yanay N, Weiner P. Long-acting bronchodilators in premenstrual exacerbation of asthma. *Respiratory Medicine* 2001; **95**(9):740–3.

Malmqvist-Granlund 2

Malmqvist-Granlund K, Asking L, Lindbald T, Rollwage U, Steckel H. An in vitro comparison of budesonide/formoterol and fluticasone/salmeterol in dry powder inhalers. European Respiratory Journal 2000; Vol. 16, issue suppl 31:455s.

Malolepszy 2001

Malolepszy J, Boszormenyi Nagy G, Selroos O, Larsson P, Brander R. Safety of formoterol turbuhaler at cumulative dose of 90 mug in patients with acute bronchial obstruction. *European Respiratory Journal* 2001;**18**(6):928–34.

Malolepszy 2002

Malolepszy J. Efficacy and tolerability of oral theophylline slow-release versus inhalative formoterol in moderate asthma poorly controlled on low-dose steroids. *Atemwegs- und Lungenkrankheiten* 2002; **28**(2):78–87.

Martin 2003

Martin A A, Whitehead PJ, McCarthy T P. Asthma costs with salmeterol/fluticasone combination 50/250mcg bd compared to budesonide 800mcg bd plus formoterol 12mcg bd. American Thoracic Society 99th International Conference. 2003:D034 Poster C43.

Martinat 2003

Martinat Y, Desfougeres JL. Fixed-dose fluticasone-salmeterol combination: At least effective and better tolerated than open-dose combinations. *Revue De Pneumologie Clinique* 2003;**59**(3):139–148.

Matz May 2001

Matz J, Emmett A, Rickard K, Kalberg C. Addition of salmeterol to low-dose fluticasone versus higher-dose fluticasone: An analysis of asthma exacerbations. *Journal of Allergy and Clinical Immunology* May 2001;**107**(5):783–9.

McCarthy 2000

McCarthy TP, Boone R, Yancey S, Rickard K. Salmeterol compared to Montelukast as adjunctive therapy to inhaled corticosteroids. Thorax 2000; Vol. 55, issue suppl 3:A63.

McCarthy 2001 a

McCarthy TP, Russell D, Baxter LE, et al. A comparison of the efficacy of salmeterol/fluticasone propionate combination (SF) with beclometasone dipropionate (BDP) delivered via metered dose inhaler (MDI) in patients not well controlled on bronchodilators alone. European Respiratory Journal 2001; Vol. 18, issue suppl 33:53–54s.

McCarthy 2001 b

McCarthy TP, Greening AP, Holgate SK, Whitehead C, Rice L. The efficacy of salmeterol/fluticasone propionate combination (SFC) metered dose inhaler compared with beclomethasone dipropionate (BDP) in patients not well controlled at step 1 of the British guidelines on asthma management (BGAM). Thorax 2001; Vol. 56, issue suppl 3:iii62.

McCarthy 2002

McCarthy TP, Grening AP, Holgate SK, Whitehead C, Rice L. Salmeterol/Fluticasone propionate combination (SFC) is more effective that beclometasone dipropionate (BDP) in patients not well con-

trolled on bronchodilators alone. American Journal of Respiratory and Critical Care Medicine 2002; Vol. 165, issue suppl 8:A566.

McCarthy 2003

McCarthy T P, Woodcock A A, Pavord I D, Allen DJ, Parker D, Rice L. A comparison of the anti-inflammatory and clinical effects of salmeterol 25mcg/fluticasone propionate 50mcg combination (SFC 50) with fluticasone propionate (FP) plus montelukast (M) in patients with mild to moderate asthma. American Thoracic Society 99th International Conference. 2003:B036 Poster H89.

Mcivor 1998

Mcivor RA, Pizzichini E, Turner MO, Hussack P, Hargreave FE, Sears MR. Potential masking effects of salmeterol on airway inflammation in asthma. *American Journal of Respiratory & Critical Care Medicine* 1998;**158**(3):924–30.

Michel 2000

Michel O, Olbrecht J, Moulard D, Sergysels R. Effect of anti-asthmatic drugs on the response to inhaled endotoxin. *Annals of Allergy, Asthma, & Immunology* 2000;**85**(4):305–10.

Midgren-B 1992

Midgren-B, Melander-B, Persson-G. Formoterol, a new long-acting beta 2 agonist, inhaled twice daily, in stable asthmatic subjects. *Chest* 1992;**101**(4):1019–22.

Mitchell 2000

Mitchell C, Jenkins C, Scicchitano R, Rubinfeld A. Adding formoterol is more effective and safer than doubling the dose of inhaled steroids in moderately severe asthma. American Journal of Respiratory and Critical Care Medicine 2000; Vol. 161, issue suppl 3:A197.

Mitchell 2003

Mitchell C, Jenkins C, Scicchitano R, Rubinfeld A, Kottakis J. Formoterol (Foradil) and medium-high doses of inhaled corticosteroids are more effective than high doses of corticosteroids in moderate-to-severe asthma. *Pulmonary Pharmacology & Therapeutics* 2003;**16**(5): 229–306.

Murray 1998

Murray JJ, Hagaman DD, Dworski R, Keane B, Sheller JR. Inhibition by salmeterol and beclomethasone of late phase response to segmental antigen challenge in asthmatics. American Journal of Respiratory and Critical Care Medicine 1998; Vol. 157, issue suppl 3: A872.

Murray 1999

Murray JJ, Church NL, Anderson WH, Bernstein DI, Wenzel SE, Emmett A, Rickard KA. Concurrent use of Salmeterol with inhaled corticosteroids is more effective than inhaled corticosteroid dose increases. *Allergy & Asthma Proceedings* 1999;**20**(3):173–80.

Nathan

Nathan RA, Mitchell D, Condemi J, Heller A, Schoaf L, Herrle M, at al. Cardiovascular and hypthalamic-pituitary-adrenal axis safety of fluticasone propionate/salmeterol hfa mdi in adolescent and adult patients with asthma. Annual Thoracic Society 97th International Conference; San Francisco CA ,May 18-23. 2001.

Nathan 1995

Nathan RA, Seltzer JM, Kemp JP, Chervinsky P, Alexander WJ, Liddle R, Mills R. Safety of salmeterol in the maintenance treatment of asthma. *Annals of Allergy, Asthma and Immunology* 1995;**75**:243–8.

Nathan 1999 a

Nathan RA, Pinnas JL, Schwartz HJ, Grossman J, Yancey SW, Emmett AH, Rickard KA. A six-month, placebo-controlled comparison of the safety and efficacy of salmeterol or beclomethasone for persistent asthma. *Annals of Allergy, Asthma, & Immunology* 1999;**82**: 521–29.

Nathan1999 b

Nathan R, Woodring A, Baitinger L, Prillaman B, Faris M, House K, Shah T. The salmeterol/fluticasone propionate diskus combination decreases the incidence of exacerbations compared to treatment with salmeterol or fluticasone propionate alone. European Respiratory Society; 1999 Oct 9-13; Madrid, Spain. 1999:848.

Nelson 1999

Nelson HS, Berkowitz RB, Tinkelman DA, Emmett AH, Rickard KA, Yancey SW. Lack of subsensitivity to albuterol after treatment with salmeterol in patients with asthma. *American Journal of Respiratory and Critical Care Medicine* 1999;**159**(5 part 1):1556–61.

Nelson 2000 a

Nelson HS, Busse WW, Kerwin E, Church N, Emmett A, Rickard K, Knobil K. [Fluticasone propionate/salmeterol combination provides more effective asthma control than low-dose inhaled corticosteroid plus montelukast]. *Journal of Allergy & Clinical Immunology* 2000; **106**(6):1088–95.

Nelson 2000 b

Nelson H, Chervinsky P, Greos L, Pelskow W, Baitinger L, Scott C, et al. The salmeterol/fluticasone propionate combination product improves asthma control compared with the individual products in asthmatics treated with prn short-acting beta2-agonists alone. American Journal of Respiratory and Critical Care Medicine 2000; Vol. 161, issue suppl 3:A196.

Nelson HS, Baitinger L, Scott C, House K, Payne E, Shah T. Salmeterol/fluticasone propionate (50/100µg dose) non-CFC metered dose inhaler is safe and effective in in patients with asthma using short-acting ß²-agonists alone. European Respiratory Journal 2000; Vol. 16, issue 31:53s.

Nelson HS, Busse WW, Kerwin E, Church N, Emmett A, Rickard K, Knobil K. Fluticasone propionate/salmeterol combination provides more effective asthma control than low-dose inhaled corticosteroid plus montelukast. *Journal of Allergy Clinical Immunology* 2000;**106** (6):1088–1095.

Nelson 2000 c

Nelson HS, Chervinsky P, Greos L, Pleskow W, Baitinger L, Scott C, et al. The salmeterol/fluticasone propionate combination product improves asthma control compared with the individual products in asthmatics treated with PRN short-acting beta2-agonists alone. American Journal of Respiratory and Critical Care Medicine 2000; Vol. 161, issue 3 suppl:A196.

Nelson 2001 b

Nelson HS, Nathan R A, Kalberg C, Yancey SW, Rickard K A. Comparison of inhaled salmeterol and oral zafirlukast in asthmatic patients using concomitant inhaled corticosteroids. Medscape General Medicine 2001; Vol. 3, issue 4:3.

Nelson 2001a

Nelson HS, Nathan RA, Kalberg C, Yancey SW, Rickard K A. Comparison of inhaled salmeterol and oral zafirlukast in asthmatic pa-

tients using concomitant inhaled corticosteroids. Medscape General Medicine 2001; Vol. 3, issue 4:3.

Newnham-DM 1995

Newnham-DM, Grove-A, McDevitt-DG, Lipworth-BJ. Subsensitivity of bronchodilator and systemic beta 2 adrenoceptor responses after regular twice daily treatment with eformoterol dry powder in asthmatic patients. *Thorax* 1995;**50**(5):497–504.

Nielsen 1999

Nielsen LP, Pedersen B, Faurschou P, Madsen F, Wilcke JTR, Dahl R. Salmeterol reduces the need for inhaled corticosteroids in steroid-dependent asthmatics. *Respiratory Medicine* 1999;**93**:863–68.

Nightingale 2002

Nightingale JA, Rogers D F, Barnes PJ. Comparison of the effects of salmeterol and formoterol in patients with severe asthma. *Chest* 2002;**121**(5):1401–6.

Nsouli 2001

Nsouli SM, McNutt WJ. The additive effects of montelukast and salmeterol in moderate asthmatics who are uncontrolled on a low dose on inhaled corticosteroids. *Annals of Allergy, Asthma & Immunology* 2001, (86):81.

O'Brian 2001

O'Brian J, Carlos-Palma A, Bogolubov M, Davies P, Payne E. Benefits of fluticasone propionate/salmeterol [fp/s] hfa mdi are apparent on the first day of dosing. Annual Thoracic Society 97th International Conference; San Francisco CA ,May 18-23. 2001.

Odeback 1998

Odeback P. Is the addition of salmeterol more effective than doubling the dose of budesonide in mild asthma?. American Journal of Respiratory and Critical Care Medicine 1998; Vol. 157, issue Suppl 3:A417.

Olsson 2002

Olsson P, Stallberg B, Ekstrom T, Lindarck N, Jorgensen LA. Adjustable maintenance treatment of asthma with budesonide and formoterol in a single inhaler. European Respiratory Society Annual Congress. 2002:P2451.

Ortega-Cisnero 1998

Ortega-Cisnero M, Maldonado-Alaniz ML, Rosas Vargas MA, Sierra-Monge JJL. Salmeterol and inhaled beclomethasone versus high dose inhaled beclomethasone in the control of pediatric patients with moderate asthma. *Annals of Allergy, Asthma and Immunology* 1998; **80**:131.

Overbeck 2003

Overbeck SE, Mulder PG, Baelemans SM, Hoogsteden HC, Prins JB. Comparison of budesonide plus formoterol with budesonide alone on airway inflammation in mild asthmatics. American Thoracic Society 99th International Conference. 2003:D034 Poster C36.

Ozkaya 1999

Ozkaya O, Turktas I, Cengizlier R. Low dose budesonide plus formoterol versus high dose budesonide in children with bronchial asthma. European Respiratory Society; 1999 Oct 9-13; Madrid, Spain. 1999.

Palmer 1992

Palmer JBD, Stuart AM, Shepherd GL, Viskum K. Inhaled salmeterol in the treatment of patients with moderate to severe reversible obstructive airways disease- a 3 month comparison of the efficacy and safety of twice-daily salmeterol (100 mcg) with salmeterol (50 mcg). *Respiratory Medicine* 1992;**86**:409–17.

Palmqvist 2001

Palmqvist M, Arvidsson P, Beckman O, Peterson S, Lotvall J. Onset of bronchodilation of budesonide/formoterol vs salmeterol/fluticasone in single inhalers. *Pulmonary Pharmacology & Therapeutics* 2001;**14** (1):29–34.

Paterson 1999

Paterson MC, Wilson AM, Dempsey OJ, Sims EJ, Lipworth BJ. The effect of combination therapy with salmeterol and montelukast in asthmatic patients receiving inhaled corticosteroids. European Respiratory Society; 1999 Oct 9-13; Madrid, Spain. 1999. P3490.

Pauwels 1997c

Pauwels RA, Lofdahl CG, Postma DA, Tattersfield AE, O'Byrne P, Barnes PJ, Ullman A. [Effect of inhaled formoterol and budesonide on exacerbations of asthma]. *New England Journal of Medicine* 1997; **337**(20):1405–11.

Pauwels 1998 a

Pauwels R. Additive effects of inhaled formoterol and budesonide in reducing asthma exacerbations. *Allergy* 1998;**53**:20–3.

Pauwels 1998 b

Pauwels RA, Yernault JC, Demedts MG, Geusens P. Safety and efficacy of fluticasone and beclomethasone in moderate to severe asthma. *American Journal of Respiratory & Critical Care Medicine* 1998;**157** (3 pt 1):827–32.

Pearlman

Pearlman DS, Kent E, Lanz MJ, Peden D, Baitinger L, Herrle M, et al. Fluticasone propionate/salmeterol hfa mdi has a rapid onset of effect in asthmatics treated with short or long-acting beta2-agonists (ba) or inhaled corticosteroids. Annual Thoracic Society 97th International Conference; San Francisco CA ,May 18-23. 2001.

Pearlman 1992

Pearlman DA, Chervinsky P, LaForce C, Seltzer JM, Southern DL, Kemp JP, et al. A comparison of salmeterol with albuterol in the treatment of mild to moderate asthma. *New England Journal of Medicine* 1992;**327**:1420–5.

Pearlman 1994

Pearlman DS, Liddle R. Controlling asthma symptoms: Salmeterol compared with salbutamol in large-scale multicentre studies. *European Respiratory Review* 1994;**4**(21):301–5.

Pearlman 2002

Pearlman DS, White MV, Lieberman AK, Pepsin PJ, Kalberg C, Emmett A, et al. Fluticasone propionate/salmeterol combination compared with montelukast for the treatment of persistent asthma. *Annals of Allergy, Asthma and Immunology* 2002;**88**(2):227–35.

Pearlman1999same 200

Pearlman DS, Stricker W, Weistein S, Gross G, Chervinsky P, Woodring A, et al. Inhaled salmeterol and fluticasone: a study comparing monotherapy and combination therapy in asthma. *Annals of Allergy, Asthma, & Immunology* 1999;**82**:257–65.

Pearlman1999same 500

* Pearlman DS, Stricker W, Weistein S, Gross G, Chervinsky P, Woodring A, et al. Inhaled salmeterol and fluticasone: a study comparing monotherapy and combination therapy in asthma. *Annals of Allergy, Asthma, & Immunology* 1999;**82**:257–65.

Peters 2000

Peters JI, Shelledy DC, Jones AP Jr, Lawson RW, Davis CP, LeGrand TS. A randomized, placebo-controlled study to evaluate the role of salmeterol in the in-hospital management of asthma. *Chest* 2000;**118** (2):313–20.

Pieters 1999 b

Pieters WR, Lundback B, Sondhi S, Price MJ. Cost effectiveness analysis of salmeterol/fluticasone proprionate 50/500mcg vs fluticasone proprionate 500mcg in patients with corticosteroid -dependent asthma. *Pharmacoeconomics* 1999;**16**(Suppl 2):29–34.

Pieters 2001

Pieters WR, Wilson KK, Smith HCE, Tamminga JJ. Cost-effectiveness of fluticasone propionate/salmeterol combination product and fluticasone propionate/montelukast in asthma. Annual Thoracic Society 97th International Conference; San Francisco CA ,May 18-23. 2001.

Pinnas 1998

Pinnas JL, Schwartz H, Yancey SW, Rickard K. Six month comparison of beclomethasone vs. salmeterol or placebo in adults with asthma. American Journal of Respiratory and Critical Care Medicine 1998; Vol. 157, issue Suppl 3:A417.

Pizzichini 1996

Pizzichini MM, Kidney JC, Wong BJ, Morris MM, Efthimiadis A, Dolovich J, Hargreave FE. Effect of salmeterol compared with beclomethasone on allergen-induced asthmatic and inflammatory responses. *European Respiratory Journal* 1996;**9**(3):449–55.

Price 2003

Price D, Haughney J, Rosen J P, Morrison K. Switching to symbicort (r) from beclomethasone dipropionate (BDP) with or without salmeterol signficantly improved symptom severity in patients with moderate asthma. American Thoracic Society 99th International Conference. 2003; Vol. D034 Poster C40.

Pujet 1995

Pujet JC, Evano CI. A randomized double-blind study comparing inhaled beclomethasone with long-acting theophylline for the first-line treatment of moderate asthma. *Semaine Des Hopitaux* 1995;**71** (27-28):865–72.

Pyke 2001

Pyke SD. Synergy with salmeterol and fluticasone propionate after administration from a single inhaler (Seretide(tm)). European Respiratory Journal. 2001; Vol. 18, issue Suppl 33:176s.

Rance 2002

Rance L, Musin L. Asthma management costs in Canada are lower with combination fluticasone propionate/salmeterol (250/50mcg BID) in as single inhaler than with budesonide 800mcg BID plus eformoterol 12 mcg BID via seperate inhalers. Chest 2002; San Diego, CA. S6.

Rickard 1999

Rickard KA, Yancey S, Emmett AH, Kalberg CJ. Salmeterol compared to zafirlukast when added to inhaled corticosteroid therapy in patients with persistent asthma. European Respiratory Society; 1999 Oct 9-13; Madrid, Spain. 1999:P839.

Rickard 2001

Rickard K, Dorinsky PM, Knobil K, Pepsin P, Akveld ML. The salmeterol/fluticasone propionate combination 50/100µg bid is more effective than oral montelukast 10mg of as a first line therapy in mild and moderate asthmatics. European Respiratory Journal 2001; Vol. 18, issue Suppl 33:262s.

Rijssenbeek-Nouwens

Rijssenbeek-Nouwens LH, Oosting AJ, De Monchy JG, Bregman I, Postma DS, De Bruin-Weller MS. The effect of anti-allergic mattress encasings on house dust mite-induced early- and late-airway reactions in asthmatic patients. A double-blind, placebo-controlled study. *Clinical & Experimental Allergy* 2002;**32**(1):117–25.

Ringbaek 1996

Ringbaek TJ, Soes-Petersen U, Christensen M, Iversen ET, Rasmussen FV. Salmeterol improves the control of disease in patients with moderate asthma. A comparative study of inhaled salmeterol 50 mg and salbutamol depot tablets 8 mg, both administered twice daily]. *Ugeskrift for Laeger* 1996;**158**(27):3940–43.

Ringdal 1997

Ringdal N, Eliraz A, Pruzinec R, Weber HH, Mulder PG, Akveld M, Bateman ED. The salmeterol/fluticasone combination is more effective than fluticasone plus oral montelukast in asthma. *Respiratory Medicine* 97;**3**:234–4.

Ringdal 2000

Ringdal N, Chuchalin AG, Chovan L, Whitehead PJ. A comparison of Advair™/Seretide™ (salmeterol 50 mcg/fluticasone propionate 250 mcg bid) with formoterol 12 mcg + budesonide 800 mcg bid in moderate-severe asthma. American Journal of Respiratory and Critical Care Medicine 2000; Vol. 161, issue 3 part 2 Supp1:A196.

Ringdal 2001

Ringdal NR, Chovan L, Chuchalin AG, Whitehead PJ. Advair™/Seretide™ (250/50mu-g bid) shows exacerbation benefit over budesonide plus formoterol bid in moderate-severe asthma. Annual Thoracic Society 97th International Conference; San Francisco CA ,May 18-23. 2001.

Ringdal 2002

Ringdal N, Chuchalin A, Chovan L, Tudoric N, Maggi E, Whitehead PJ. Evaluation of different inhaled combination therapies (EDICT): a randomised, double-blind comparison of Seretide (50/250 microg bd Diskus vs. formoterol (12 microg bd) and budesonide (800 microg bd) given concurrently (both via Turbuhaler) in patients with moderate-to- severe asthma. *Respiratory Medicine* 2002;**96**(11):851–61.

Ringdal 2003

Ringdal N, Eliraz A, Pruzinec R, Weber HH, Mulder PG, Akveld M, Bateman ED. The salmeterol/fluticasone combination is more effective than fluticasone plus oral montelukast in asthma. *Respiratory Medicine* 97;**3**:234–4.

Rocca-Serra 2002

Rocca-Serra JP, Vicaut E, Lefrancois G, Umile A. Efficacy and tolerability of a new non-extrafine formulation of beclomethasone HFA-134a in patients with asthma: comparison with beclomethasone CFC. *Clinical Drug Investigation* 2002;**22**(10):653–665.

Rooklin 2001

Rooklin A, Elkayam D, Weiler J, Windom H, Schoaf L, Scott C, et al. The fluticasone propionate/salmeterol HFA MDI is significantly more efficacious in treating asthma than placebo HFA MDI, fluticasone propionate CFC MDI or salmeterol CFC MDI. Journal of Allergy and Clinical Immunology 2001; Vol. 107, issue 2.

Rosenhall 2001 a

Rosenhall L, Stahl E, Heinig JH, Lindquist A, Leegard J, Bergqvist PBF. Health-related quality of life and asthma control in patients using symbicort® (budesonide and formoterol in a single inhaler). Annual Thoracic Society 97th International Conference; San Francisco CA ,May 18-23. 2001.

Rosenhall 2001 b

Rosenhall L, Heinig JH, Lindqvist A, Leegard J, Bergqvist PB. Budesonide and formoterol in a single inhaler is safe and effective in the treatment of asthma. *European Respiratory Journal* 2001;**18**(33):159s.

Rosenhall 2001 c

Rosenhall L, Stahl E, Heinig JH, Lindqvist A, Leegard J, Bergqvist PB. Health-related quality of life and asthma control in patients treated with budesonide and formoterol in a single inhaler. European Respiratory Journal 2001; Vol. 18, issue Suppl 33:46s.

Rosenhall 2002

Rosenhall L, Heinig JH, Lindqvist A, Leegaard J, Stahl E, Bergqvist PB. Budesonide/formoterol (Symbicort) is well tolerated and effective in patients with moderate persistent asthma. *International Journal of Clinical Practice* 2002;**56**(6):427–33.

Rosenhall 2003

Rosenhall L, Elvstrand A, Tilling B, Vinge I, Jemsby P, Stahl E, et al. One-year safety and efficacy of budesonide/formoterol in a single inhaler (Symbicort Turbuhaler) for the treatment of asthma. *Respiratory Medicine* 2003;**97**(6):702–8.

Rosenhall 56

Rosenhall L, Heinig JH, Lindqvist A, Leegard J, Bergqvist PB. Symbicort (Budesonide/eformoterol in a single inhaler) is safe and effective in the treatment of asthma. Thorax 56; Vol. Suppl 3:iii63.

Rosenthal 1999

Rosenthal RR, Busse WW, Kemp JP, Baker JW, Kalberg C, Emmett A, Rickard KA. Effect of long-term salmeterol therapy compared with as-needed albuterol use on airway hyperresponsiveness. *Chest* 1999; **116**(3):595–602.

Sahn 2002

Sahn S, Yancey S, Reilly D, Edwards L, Rickard K, Dorinsky P. The fluticasone propionate/salmeterol (FSC) combination product 100/50 mcg BID is steroid sparing in patients who require FP250 mcg BID for asthma stability. Chest 2002 (conference); San Diego, CA. 2002.

Schreurs 1996

Schreurs AJ, Sinninghe Damste HE, de Graaff CS, Greefhorst AP. A dose-response study with formoterol Turbuhaler as maintenance therapy in asthmatic patients. *European Respiratory Journal* 1996;**9**: 1678–83.

Sears 2003

Sears MR, McIvor A, Becker A, Fitzgearld JM, Boulet LP, Ernsy P, Georgijev NS, Lee J. Budesonide/formoterol adjustable maintenance dosing effectively improves asthma symptom severity: a multicentre Canadian study. *European Respiratory Journal* 2003;**22**(Suppl 45): P1695.

Serrier 2003

Serrier P, Roche N, Pello JY, Larguier JS, Mezzi K. Asthma control achieved with inhaled corticosteroids and long-acting beta2-agonists in a free or fixed combination: Results of the ALISE survey. *Presse Medicale* 2003;**32**(11):493–7.

Shapiro 2001

Shapiro GG, Mendelson LM, Pearlman DS. Once-daily budesonide inhalation powder (Pulmicort Turbuhaler) maintains pulmonary function and symptoms of asthmatic children previously receiving inhaled corticosteroids. *Ann Allergy Asthma & Immunology* 2001;**86** (6):633–40.

Sheth 2002

Sheth K, Borker R, Emmett A, Rickard K, Dorinsky P. Cost-effectiveness comparison of salmeterol/fluticasone propionate versus montelukast in the treatment of adults with persistent asthma. *Pharmacoeconomics* 2002;**20**(13):909–18.

Shrewsbury 2002

Shrewsbury SB, Pyke S. MIASMA: asthma exacerbation reduction with salmeterol [Letter]. Chest 2002; Vol. 121, issue 3:1002–1004.

Sienra-Monge 2001

Sienra-Monge JJL, Del Rio BE, Alvarez ME, Magana AJ. Comparison of quality of life and pulmonary function on moderate asthmatic children treated with Beclomethasone and Beclomethasone plus Salmeterol. Journal of Allergy and Clinical Immunology 2001; Vol. 107, issue 2:s263.

Simons 1997 b

Simons FER. A comparison of beclomethasone, salmeterol and placebo in children with asthma. *New England Journal of Medicine* 1997;**337**:1659–65.

Sims 2003

Sims EJ, Jackson C M, Lipworth B J. Add-on therapy with montelukast or formoterol in patients with the glycine-16 beta2-receptor genotype. *British Journal of Clinical Pharmacology* 2003;**56**(1):104–11.

Staehr 1995

Staehr P, Vestbo I. Salmeterol improves control in asthmatic patients treated in general practice. A comparative study of salmeterol (Serevent) and salbutamol. *Ugeskr-Laeger* 1995;**157**(1):36–40.

Stahl 2003

Stahl E, Postma DS, Svensson K, Tattersfield AE, Eivindson A, Schreurs A, Lofdahl CG. Formoterol used as needed improves health-related quality of life in asthmatic patients uncontrolled with inhaled corticosteroids. *Respiratory Medicine* 2003;**97**(9):1061–6.

Stallberg 2003

Stallberg B, Olsson P, Jorgensen L A, Lindarck N, Ekstrom T. Budesonide/formoterol adjustable maintenance dosing reduces asthma exacerbations versus fixed dosing. *International Journal of Clinical Practice* 2003;**57**(8):656–61.

Stanford 2002

Stanford RH, Borker R, Dorinsky P, Pepsin P, Kalberg C, Emmett A. The costs and efficacy of fluticasone propionate/salmeterol combination versus montelukast in the treatment of adults with persistent asthma. *Chest 2002; San Diego, CA* 2002:422.

Stankovic 2000

Stankovic IJ, Djordjevic DV, Pejcic TA, Zivkovic DS, Rancic MR, et al. Formoterol and beclomethasone dipropionate versus higher dose beclomethasome dipropionate in asthma patients. *European Respiratory Journal* 2000;**16**(Suppl 31):455s.

Stelmach 2001

Stelmach I, Grzelewski T, Majak P, Majak J, Bobrowska M, Jerzynska J, et al. The effect of triamcinolone, montelukast and formoterol on

serum levels of il-4, IgE and clin.ical parameters in children with asthma. *Polski Merkuriusz Lekarski* 2001;**11**(63):247–51.

Stelmach 2002 a

Stelmach I, Jerzynska J, Majak P, Grzelewski T, Gorski P, Stelmach W, Kuna P. Effect of triamcinolone acetonide, montelukast, nedocromil sodium, formoterol on serum levels of sICAM-1, sIL-2R and clinical parameters of asthma in children. *Polski Merkuriusz Lekarsk* 2002;**12**(68):99–103.

Stelmach 2002 b

Stelmach I, Jerzynska J, Kuna P. A randomized, double-blind trial of the effect of glucocorticoid, antileukotriene and [beta]-agonist treatment on IL-10 serum levels in children with asthma. *Clinical & Experimental Allergy* 2002;**32**(2):264–9.

Stojkovic-Andjelkovi

Stojkovic-Andjelkovic AK, Pajovic DM, Protrka OJ, Ugrinovic BS, Obradovic SM, Pavicevic MD. Effect of combination fluticasone propionate and salmeterol diskhaler in treatment of moderate to severe asthma: comparison of initial high dose, constant medium dose and placebo. European Respiratory Journal 2001; Vol. 18, issue Suppl 33:123s.

Stoloff 2002

Stoloff S, Poinsett-Holmes K, Dorinsky PM. Combination therapy with inhaled long-acting beta(2)-agonists and inhaled corticosteroids: A paradigm shift in asthma management. *Pharmacotherapy* 2002;**22**(2):212–6.

Tan 1997

Tan S, Hall IP, Dewar J, Dow E, Lipworth B. Association between beta 2-adrenoceptor polymorphism and susceptibility to bronchodilator desensitisation in moderately severe stable asthmatics. *Lancet* 1997;**350**(9083):995–9.

Tattersfield 1999

Tattersfield AE, Postma DS, Barnes PJ, Svensson K, Bauer C A, O'Byrne PM, et al. Exacerbations of asthma: a descriptive study of 425 severe exacerbations. The FACET International Study Group. *American Journal of Respiratory & Critical Care Medicine* 1999;**160**(2):594–9.

Tattersfield 2001

Tattersfield AE, Lofdahl CG, Postma DS, Eivindson A, Schreurs AG, Rasidakis A, Ekstrom T. Comparions of formoterol and terbutaline for as-needed treatment of asthma: a randomised trial. 2001;**357**(9252):257–61.

TLHSRG 2000

The Lung Health Study Research Group. Effect of inhaled triamcinolone on the decline in pulmonary function in chronic obstructive pulmonary disease. *New England Journal of Medicine* 2000;**343**(26):1902–9.

Tolley 2002

Tolley K, Martin A, Rice L, McCarthy TP. Salmeterol/fluticasone propionate combination (SFC) demonstrates improved health outcomes and good cost effectiveness compared with beclometasone dipropionate. *American Journal of Respiratory and Critical Care Medicine* 2002;**165**(Suppl 8):A112.

Tonelli 2001

Tonelli M, Giannini D, Di Franco A, Carnevali S, Bartoli ML, Cianchetti S, et al. Symptoms, induced sputum eosinophil percentages and treatment with salmeterol or fluticasone in mild asthmatics. European Respiratory Journal 2001, issue Suppl 33:336s.

Trautmann 2001

Trautmann M. Treatment with salmeterol/fluticasone propionate (50/250g) inhaler improves lung function, asthma symptoms and quality of life in a large group of patients with mild to moderate asthma. American Journal of Respiratory & Critical Care Medicine 2001; Vol. 163, issue 5:A864.

Turner 1998

Turner MO, Johnston PR, Pizzichini E, Pizzichini MM, Hussack PA, Hargreave FE. Anti-inflammatory effects of salmeterol compared with beclomethasone in eosinophilic mild exacerbations of asthma: A randomized, placebo controlled trial. *Canadian Respiratory Journal* 1998;**5**(4):261–8.

Ullman 1990

Ullman A, Hedner J, Svedmyr N. Inhaled salmeterol and salbutamol in asthmatic patients. An evaluation of asthma symptoms and the possible development of tachyphylaxis. *American Review of Respiratory Disease* 1990;**142**(3):571–5.

Van den Berg 2000

Van den Berg NJ, Ossip MS, Hederos CA, Anttila H, Ribeiro BL, Davies PI. Salmeterol/fluticasone propionate (50/100 ug) in combination in diskus inhaler (seretide) is effective and safe in children with asthma. *Pediatric Pulmonology* 2000;**30**:97–105.

van der Woude 2001

van der Woude HJ, Winter TH, Boorsma M, Bergqvist PBF, Aalbers R. More rapid relief of methacholine-induced bronchoconstriction with budesonide/formoterol than with salmeterol/fluticasone. European Respiratory Journal 2001; Vol. 18, issue Suppl 33:53s.

Van Der Woude 2004

Van Der Woude HJ, Boorsma M, Bergqvist PB, Winter T H, Aalbers R. Budesonide/formoterol in a single inhaler rapidly relieves methacholine-induced moderate-to-severe bronchoconstriction. *Pulmonary Pharmacology & Therapeutics* 2004;**17**(2):89–95.

Van der Woude 2004

Van Der Woude H J, Boorsma M, Bergqvist P B F, Winter T H, Aalbers R (H. Budesonide/formoterol in a single inhaler rapidly relieves methacholine-induced moderate-to-severe bronchoconstriction. . *Pulmonary Pharmacology & Therapeutics* 2004;**17**(2):89–95.

Van Noord 1999

Van Noord JA, Schreurs AJM, Mol SJM, Mulder PGH. Addition of salmeterol versus doubling the dose of fluticasone propionate in patients with mild to moderate asthma. *Thorax* 1999;**54**:207–12.

Van Noord 2001

Van Noord JA, Lill H, Carrillo Diaz T, Greefhorst AP, Davies P. Clinical equivalence of a salmeterol/fluticasone propionate combination product delivered via a chlorofluorocarbon-free metered-dose inhaler with the Diskus in patients with moderate to severe asthma. *Clinical Drug Investigation* 2001;**21**(4):243–55.

Van Schayck 2002

van Schayck CP, Cloosterman SG, Bijl-Hofland ID, van den Hoogen H, Folgering HT, van Weel C. Is the increase in bronchial responsiveness or FEV1 shortly after cessation of beta2-agonists reflecting a real deterioration of the disease in allergic asthmatic patients? A compari-

son between short-acting and long-acting beta2-agonists. *Respiratory Medicine* 2002;**96**(3):155–62.

Vastagh 2003

Vastagh E, Kuna P, Calistru P, Bogdan MA. Efficacy and safety of inhaled budesonide delivered once or twice daily via HFA-134a in mild to moderate persistent asthma in adult patients. Comparison with budesonide CFC. *Respiratory Medicine* 2003;**97**(Suppl D):S20–S28.

Verberne 1997

Verberne AA, Frost C, Roorda RJ, van der Laag H, Kerrebijn KF. One year treatment with salmeterol compared with beclomthasone in children with asthma. *American Journal of Respiratory & Critical Care Medicine* 1997;**156**:688–95.

Vermetten 1999

Vermetten AM, Boermans JM, Luiten WDVF, Mulder PGH, Vermue NA. Comparison of salmeterol with beclomethasone in adult patients with mild persistent asthma who are already on low-dose inhaled steroids. *Journal of Asthma* 1999;**36**(1):97–106.

Vestbo 2000

Vestbo J, Sorensen T, Lange P, Brix A, Torre P, Viskum K. Long-term effect of inhaled budesonide in patients with mild to moderate chronic obstructive lung disease. *Ugeskr-Laeger* 2000;**162**(4):493–7.

Vickers 2000

Vickers M. Assessment of long-term efficacy of early introduction of inhaled steroids in asthma. National Health Technology Assessment (NCCHTA).

Vilsvik 2001

Vilsvik J, Ankerst J, Palmqvist M, Persson G, Schaanning J, Schwabe G, Johansson A. Protection against cold air and exercise-induced bronchoconstriction while on regular treatment with Oxis. *Respiratory Medicine* 2001;**95**(6):484–90.

Virchow 2002

Virchow JC. Salmeterol powder provides significantly better benefit than montelukast in asthmatic patients receiving concomitant inhaled corticosteroid therapy. *Chest* 2002;**121**(6):2083–4.

Von Berg 1989

von-Berg A, Berdel D. Formoterol and salbutamol metered aerosols: comparison of a new and an established beta-2-agonist for their bronchodilating efficacy in the treatment of childhood bronchial asthma. *Pediatric Pulmonology* 1989;**7**(2):89–93.

Von Berg 2003

Von Berg A, Papageorgiou Saxoni F, Wille S, Carrillo T, Kattamis C, Helms PJ. Efficacy and tolerability of formoterol turbuhaler in children. *International Journal of Clinical Practice* 2003;**57**(10):852–856.

Wallaert 1999

Wallaert B, Brun P, Ostinelli J, Murciano D, Champel F, Blaive B, et al. A comparison of two long-acting beta-agonists, oral bambuterol and inhaled salmeterol, in the treatment of moderate to severe asthmatic patients with nocturnal symptoms. The French Bambuterol Study Group. *Respiratory Medicine* 1999;**93**(1):33–8.

Wallin 1990

Wallin A, Melander B, Rosenhall L, Sandstrom T, Wahlander L. Formoterol, a new long acting beta 2 agonist for inhalation twice daily, compared with salbutamol in the treatment of asthma. *Thorax* 1990;**45**(4):259–61.

Wallin 1998

Wallin A, Sandstrom T, Soderberg M, Howarth P, Djukanovic R, Wilson S, et al. Effects of Formoterol, Budesonide and placebo treatment on asthmatic airway inflammation. Annals of Allergy, Asthma and Immunology 1998; Vol. 80:88.

Wallin 1999

Wallin A, Sandstrom T, Soderberg M, Howarth P, Lundback B, Della-Cioppa G, et al. The effects of regular inhaled formoterol, budesonide, and placebo on mucosal inflammation and clinical indices in mild asthma. *American Journal of Respiratory & Critical Care Medicine* 1999;**159**(1):79–86.

Weinberger 2004

Weinberger M. Innovative therapies for asthma: Anti-IgE - The future?. *Paediatric Respiratory Reviews* 2004;**5**(SUPPL. A):S115–S118.

Weinstein 2001

Weinstein SF, Pearlman DS, Condemi JJ, Herrle MR, Scott CA, Payne JE, et al. Superior efficacy of the fluticasone propionate/salmeterol (88/42mcg) HFA-MDI combination product versus the individual components in asthmatics previously treated with either short- or long-acting beta2-agonists or inhaled corticosteroids. *Journal of Allergy and Clinical Immunology* 2001;**107**(2):S102.

Weinstein July 1998

Weinstein SF, Pearlman DS, Bronsky EA, Byrne A, Arledge T, Liddle R, Stahl E. Efficacy of salmeterol xinafoate powder in children with chronic persistent asthma. *Annals of Allergy, Asthma and Immunology* 1998;**81**:51–8.

Wempe-JB 1992

Wempe JB, Tammeling EP, Koeter GH, Hakansson L, Venge P, Postma DS. Blood eosinophil numbers and activity during 24 hours: effects of treatment with budesonide and bambutero. *Journal of Allergy and Clinical Immunology* 1992;**90**(5):757–65.

White 2001

White M, Scott C, Herrle MR, Pearlman D, Payne E, House K, Shah T. Salmeterol/fluticasone propionate (42/88mcg) hfa-mdi improves asthma control in asthmatics previously treated with short- or long-acting beta2-agonists or inhaled corticosteroids. Annals of Allergy, Asthma & Immunology 2001; Vol. 86:81.

Wilcke 1998

Wilcke JT, Iversen ET, Kok-Jensen A. Effect of salmeterol is independent of previously inhaled salbutamol: a clinical controlled study. *Lung* 1998;**176**(2):133–9.

Wilding 1997

Wilding P, Clark M, Thompson Coon J, Lewis S, Rushton L, Bennett J, et al. Effect of long term treatment with salmeterol on asthma control: a double-blind, randomised crossover study. *BMJ* 1997;**314**:1441–6.

Wilson 1999

Wilson AM, Dempsey OJ, Sims EJ, Lipworth BJ. A comparison of salmeterol and montelukast as second-line therapy in asthmatic patients not controlled on inhaled corticosteroids. Thorax 1999; Vol. 54, issue Suppl 3:A66, P189.

Wilson 2000

Wilson SJ, Ward JA, Djukanovic R, Wallin A, Sue-Chu M, Sandstrom T, ET AL. Effects of high and low dose inhaled fluticasone propionate (FP) compared to low dose FP combined with salmeterol (SAL) on airway inflammation in asthma. American Journal of Respiratory and Critical Care Medicine 2000; Vol. 161, issue Suppl 3: A196.

Wilson 2001 a

Wilson AM, Dempsey OJ, Sims EJ, Lipworth BJ. Evaluation of salmeterol or montelukast as second-line therapy for asthma not controlled with inhaled corticosteroids. *Chest* 2001;**119**(4):1021–6.

Wilson 2001 b

Wilson SJ, Wallin A, Della-Cioppa G, Sandstrom T, Holgate ST. Effects of budesonide and formoterol on NF-kappaB, adhesion molecules, and cytokines in asthma. *American Journal of Respiratory & Critical Care Medicine* 2001;**164**(6):1047–52.

Wong 1992

Wong-BJ, Dolovich-J, Ramsdale-EH, O'Byrne-P, Gontovnick-L, Denburg-JA, Hargreave-FE. Formoterol compared with beclomethasone and placebo on allergen-induced asthmatic responses. *American Review of Respiratory Disease* 1992;**146**(5 pt 1):1156–60.

Woolcock 1995

Woolcock A. Continuing patient care with metered-dose inhalers. *Journal of Aerosol Medicine: Deposition, Clearance, and Effects in the Lung* 1995;**8**(Suppl 2):s5–s10.

Woolcock 1996 s 50

Woolcock A, Lundback B, Ringdal N, Jacques LA. Comparison of addition of salmeterol to inhaled steroids with doubling the dose of inhaled steroids. *American Journal of Respiratory & Critical Care Medicine* 1996;**153**:1481–8.

Woolcock 1996 s100

* Woolcock A, Lunback B, Ringdal N, Jacques LA. Comparison of addition of salmeterol to inhlaed steroids with doubling the dose of inhaled steroids. *American Journal of Respiratory & Critical Care Medicine* 1996;**153**:1481–8.

Yates 1995

Yates DH, Sussman HS, Shaw MJ, Barnes PJ, Chung K F. Regular formoterol treatment in mild asthma: Effect on bronchial responsiveness during and after treatment. *American Journal of Respiratory and Critical Care Medicine* 1995;**152**(41):1170–4.

Yates 1996

Yates DH, Kharitonov SA, Barnes PJ. An inhaled glucocorticoid does not prevent tolerance to the bronchoprotective effect of a long-acting inhaled beta 2-agonist. *American Journal of Respiratory & Critical Care Medicine* 1996;**154**(6 pt 1):1603–7.

Youngchaiyud 1995

Youngchaiyud P, Permpikul C, Suthamsmai T, Wong E. A double-blind comparison of inhaled budesonide, long-acting theophylline, and their combination in treatment of nocturnal asthma. *Allergy* 1995;**50**:28–33.

Yurdakul 2002

Yurdakul AS, Calisir HC, Tunctan B, Ogretensoy M. Comparison of second controller medications in addition to inhaled corticosteroid in patients with moderate asthma. *Respiratory Medicine* 2002;**96**(5): 322–9.

Zarkovic 1998

Zarkovic J, Gotz MH, Holgate ST, Taak NK. Effect of long-term regular salmeterol treatment in children with moderate asthma. *Clinical Drug Investigation* 1998;**15**(3):169–75.

References to studies awaiting assessment

Beckett 2003

Beckett P, Hewitt L, Woodcock A, Smith J, Seghal N, Rice L, et al. Improvement in airway hyper-responsiveness (AHR) and lung function with salmeterol/fluticasone propionate combination (SFC) in persistent asthma [abstract]. American Thoracic Society 99th International Conference. 2003:D034 Poster C27.

Bouchard 2000

Bouchard J, Arkinstall W, Tesarowski D. Efficacy of salmeterol and fluticasone propionate (FP) combination therapy vs FP alone in mild/moderate asthma. American Journal of Respiratory and Critical Care Medicine. 2000; Vol. 161, issue Suppl 3:A197.

Cook 1998

Cook D, Srebro SH, Rogenes PR, Rickard K, Edwards L, Johnson MC. A comparison of the safety and efficacy of fluticasone, triamcinolone, and fluticasone plus salmeterol in patients with mild to moderate asthma. American Journal of Respiratory and Critical Care Medicine 1998; Vol. 157, issue 3 Suppl:A416.

Dorinsky 2002

Dorinsky P, Jones S, Kalberg C, Emmett A, Rickard K. Sustained protection against activity-induced bronchospasm (AIB) during chronic treatmet with the fluticasone propionate/salmeterol combination (FSC). American Journal of Respiratory and Critical Care Medicine 2002; Vol. 165, issue Suppl 8:A568.

Ericsson 2001 1

Ericsson K, Bantje TA, Huber R, Borg S, Andersson F. Symbicort turbohaler is more effective than fluticasone diskus in the treatment of asthma. Thorax 2001; Vol. 56, issue Suppl 3:iii63.

Green 2003

Green RH, Brightling CE, McKenna S, Hargadon B, Parker D, Pavord ID. A placebo controlled comparison of formoterol, montelukast or higher dose of inhaled budesonide in subjects with symptomatic asthma despite treatment with low dose inhaled budesonide. American Thoracic Society 99th International Conference. 2003: B036 Poster H82.

Johnson 1998

Johnson MC, Srebro SH, Rogenes PR, Rickard K, Edwards L. A comparison of physician-rated and patient-rated outcomes in a study with fluticasone, triamcinolone, and fluticasone plus salmeterol. American Journal of Respiratory and Critical Care Medicine 1998; Vol. 157, issue Suppl 3:A414.

Keith 2001

Keith P, D Urzo A, Stepner N, et al. Fluticasone/salmeterol combination (FSC) is safe and provides effective long-term (52 week) control in the management of patients with persistent asthma (PA). European Respiratory Journal 2001; Vol. 18, issue Suppl 33:176s.

Knobil 1998

Knobil K, Kalberg C, Emmett A, Rickard K. Adding salmeterol is more effective than increasing the dose of fluticasone for patients with asthma who are symptomatic on low dose fluticasone. European Respiratory Journal. 1998; Vol. 12, issue Suppl 29:19s, P160.

Lundback 2003

Lundback B, Ronmark E, Jonsson AC, Larsson LG, Lindberg A, Petavy F, James MH. Fluticasone propionate/salmeterol combination improves airway hyperresponsiveness and clinical outcomes compared with fluticasone or salmeterol alone in mild to moderate asthma. American Thoracic Society 99th International Conference. 2003:D034 Poster C28.

McCarthy 2001 1

McCarthy TP, Edin HM, House K, Vandermeer AK. Quality of life and asthma control assessment in patients previously on inhaled corticosteroids (ICS) treated with salmeterol/fluticasone combination (SFC) metered dose inhaler (MDI). Thorax 2001; Vol. 56, issue Suppl 3:iii63.

McCarthy TP, Ed2

McCarthy TP, Edin HM, House K, Yan SK, Vandermeer AK. The effects of salmeterol/fluticasone combination (SFC) dry powder inhaler (DPI) on asthma control and quality of life in patients previously treated with inhaled corticosteroids (ICS). Thorax 2001; Vol. 56, issue Suppl 3:iii 63.

Miraglia 2003

Miraglia del Giudice M, Capristo M, Amelio R, Rocco A, Fusco N, Brunese FP. Combined fluticasone propionate/salmeterol (diskus) vs fluticasone propionate (Diskus) in the control of persistent asthma in children. American Thoracic Society 99th International Conference. 2003:A117 Poster D78.

Parnaby 55

Parnaby A, Lloyd A, Browning D, McCarthy TP. A comparison of the cost-effectiveness of salmeterol/fluticasone combination inhaler and budesonide in the management of asthma. Thorax 55; Vol. Suppl 3, issue A64.

Pieters 1998

Pieters WR, Steinmetz KO, Aubier M, Johnson L, Gomez E, Bogolubov M. Effectiveness of a new salmeterol/fluticasone propionate (50/500µg) combination inhaler in patients with reversible airways obstruction. European Respiratory Journal 1998; Vol. 12, issue Suppl 28:35s.

Pieters 1999

Pieters WR, Sondhi S, Price MJ, Thwaites RM, Nyth A. The cost effectiveness of salmeterol/fluticasone propionate 50/500 microgramm combination inhaler versus fluticasone propionate 500 microgramm in patients with chronic asthma. European Respiratory Society; 1999 Oct 9-13; Madrid, Spain. 1999:P2458.

Pieters W; Ring2

Pieters W, Ringdal N, Aubier M, Chapman KR, Huskisson SC. A new inhaler combination containing salmeterol and fluticasone propionate is well-tolerated in longterm use. European Respiratory Journal. 1998; Vol. 12, issue Suppl 29:P164.

Pljaskic-Kamenov 200

Pljaskic-Kamenov SS, Filipovic MD, Kamenov BA. Comparison of addition of salmeterol xinafoate to budesonide with budesonide alone on symptoms and quality of life in asthmatic children. European Respiratory Journal 2000; Vol. 16, issue Suppl 31:518s.

Rumbak 1998

Rumbak M, Self T, Kelso T, Eberle L, Abou-Shala N, Learned S, et al. Moderate to high dose inhaled corticosteroids in adult asthmatics: does salmeterol facilitate step down therapy?. European Respiratory Journal. 1998; Vol. 12, issue Suppl 29:19s, P157.

Schlosser 1998

Schlosser NJ, Steinmetz KO, Aubier M, Gomez E, Wixon C. Evaluation of longterm safety of salmeterol/fluticasone propionate (50/500µg) combination inhaler in patients with reversible airways obstruction. European Respiratory Journal 1998; Vol. 12, issue Suppl 28:35s.

Schreurs 1998

Schreurs AJ, van Noord JA, Mulder PG. Fluticasone propionate (FP) and salmeterol xinafoate (SLM) in patients with mild to moderate asthma. European Respiratory Journal. 1998; Vol. 12, issue Suppl 29:19s, F159.

van 1998

van der Molen T, Postma DS, Kraan J, Chapman K, Grossman R, Turner MO, Sears MR. No influence of six months treatment with formoterol on airway hyperresponsiveness in asthma subjects using inhaled corticosteroids. American Journal of Respiratory and Critical Care Medicine 1998; Vol. 157, issue Suppl 3:A400.

Yancey 1997

Yancey SW, Rickard KA, Emmett A, Cox F. The response to salmeterol or theophylline in asthmatics either receiving or not-receiving inhaled corticosteroids. Annals of Allergy, Asthma and Immunology 1997; Vol. 78:110.

References to ongoing studies

Aziz

Aziz I. Comparison of anti inflammatory effect of once daily inhaled formoterol and once daily inhaled budesonide on inflammatory markers in asthmatic patients. Clinical Pharmacology, Ninewells Hospital and Medical School, University of Dundee, DUNDEE, DD1 9SY, Scotland, UK.

Barnes a

Barnes NC. Lung Function, Quality of Life Symptons Cost, Consultant Physicist, . A Randomized Parallel 3 Arm Study to Assess Asthma Control, Lung Function, Costs and Quality of Life in Patients With Asthma Treated With Formoterol Twice Daily and Either Budesonide Once or Twice Daily From a Novel Multidisc Dry Powder Inhaler. Respiratory Medicine, London Chest Hospital, Bonner Road, London, E2 9JX, United Kingdom.

Barnes b

Barnes PJ. Effect of low dose formoterol and budesonide on exhaled breath in asthma. Royal Brompton and Harefield NHS Trust.

Bush

Bush A. Efficacy and safety of Budesonide/Formoterol Turbuhaler , compared to Budesonide turbuhaler metred dose, in steroid using asthmatic adolescent patients, double blind, double dummy parallel group, Phase III, multicentre study. Department of Paediatrics, Imperial College School of Medicine, Brompton Campus, Dovehouse Street, London, SW3 6LY, United Kingdom). Royal Brompton and Harefield NHS Trust.

Currie

Currie GP. Are there additional anti-inflammatory effects of leukotriene receptor antagonists in persistent asthmatics receiving inhaled steroid alone and combined inhaled steroid/long acting B2-agonists?. Academic Publications.

Goves

Goves JR. Eformoterol in the management of mild asthma - eformoterol Turbohaler R with budesonide Turbohaler R. Department of Paediatrics, Level 4 John Radcliffe Hospital, Headley Way, Headington, Oxford, OX3 9DU.

Hill

Hill J. The ASSURE Study - the effectiveness and safety of an individualised Symbicort Turbohaler maintenance dosing regimen (Symbicort Asthma Control Plan) versus Symbicort Turbohaler given as standard regular twice daily therapy. Northern General Hospital NHS Trust.

Kharitonov

Kharitonov SA. Effect of inhaled corticosteroids (Budesonide 100micrograms/400micrograms vs placebo) and formoterol on localisation of glucocorticoid receptor and exhaled markers in asthma. *Royal Brompton and Harefield NHS Trust*.

Lipworth 2001

Lipworth BJ. Relative lung bioavailability with fluticasone via dry powder inhaler versus: (a) fluticasone/salmeterol combination vis dry powder inhaler; (b) fluticasone/salmeterol combination via HFA-pMDI plus spacer, in patients with moderate persistent asthma. Academic Publications 2001.

Millar

Millar AB. A randomised double-blind multi-centre study to evaluate the effect of adding alternative agents to inhaled steroids in adult asthmatics. [Telephone: 0117 9595348]. South West Regional Office, North Bristol NHS Trust. To Assess the Effects of 48 Weeks of Treatment With Drug Vs. Inhaled Salmeterol Concomitantly Administered With Inhaled Steroids on the Percent of Patients Who Have at Least One Asthma Attack. To Determine Tolerability Profile Over a 49 Treatment Period. 2001 May 31;. Lung Research Unit, Southmead Hospital, Southmead Road, Westbury-on-Trym, Bristol, BS10 5NB, UK.

Ruggins

Ruggins N. Pragmatic trial of add-on therapy in Paediatric Asthma. Southern Derbyhsire Acute Hospitals NHS Trust, Consultant Paediatrician, Chidren's Hospital, Uttoxeter Road, Derby, DE22 3NE, England 2003.

Sovani

Sovani MP. The effect of providing a single combination inhaler on steroid use and asthma control. Nottingham City Hospital NHS Trust.

Thomson

Thomson NC. Bundesonide/formoterol fixed combination in adults with asthma. Respiratory Medicine, Gartnavel General Hospital, Great Western Road, Glasgow, G12 0YN, Scotland.

Young

Young KM. Budesonide/formoterol fixed combination in adults with asthma. Cambridge Consortium - Addenbrookes.

Additional references

Adkins 1997

Adkins JC, McTavish D. Salmeterol: A review of its pharmacological properties and clinical efficacy in the management of children with asthma. *Drugs* 1997;**54**(2):331–54.

Anonymous 1997

Anonymous. [British Guidelines on Asthma Management]. *Thorax* 1997;**52**(Suppl):S1–S21.

Anonymous 2002

Asthma Management Handbook. 5th Edition. Melbourne: National Asthma Council of Australia, 2002.

ATS guideline 1994

Committee on Proficiency standards for clinical pulmonary function laboratories. Standardization of spirometry. *American Journal of Respiratory & Critical Care Medicine* 1995;**152**:1107–36.

Australia, 2002

Anonymous. *Asthma Management Handbook*. 5th Edition. Melbourne: National Asthma Campaign, 2002.

Bartow 1998

Bartow RA, Brogden RN. Formoterol: An update of its pharmacological properties and therapeutic efficacy in the management of asthma. *Drugs* 1998;**55**(2):302–22.

Bisgaard 2003

Bisgaard Hans. Effect of long acting beta 2 agonists on exacerbation rates of asthma in children. *Pediatric Pulmonology* 2003;**36**:391–8.

BTS guidelines 2003

Anonymous. [British Guidelines on Asthma Management]. *Thorax* 2003;**58**(suppl 1):i1–94.

Cates 2002

Cates CJ. Simpson's paradox and calculation of number needed to treat from meta-analysis. *Bio Med Central* 2002;**BMC Medical Research Methodology 2**:1.

D'Alonzo 1997

D'Alonzo GE, Tolep KA. Salmeterol in the treatment of chronic asthma. *American Family Physician* 1997;**56**(2):558–62.

Deeks 2001

Deeks JJ, Altman DG, Bradburn MJ. Statistical methods for examining heterogeneity and combining results from several studies in meta-analysis. In: EggerM, SmithGD, AltmanDG editor(s). *Systematic reviews in health care: meta-analysis in context*. London: BMJ Publishing, 2001:285–312.

DerSimonian 1986

DerSimonian R, Laird N. Meta-analysis in clinical trials. *Controlled Clinical Trials* 1986;**7**:177–88.

Egger 1997

Egger M, Smith GD, Schneider M, Minder C. [Bias in meta-analysis detected by a simple, graphical test]. *BMJ* 1997;**315**:629–34.

Fireman 1995

Fireman P. Beta2-agonists and their safety in the treatment of asthma. *Allergy Proceedings* 1995;**16**:235–39.

Georgitis 1999

Georgitis JW. The 1997 asthma management guidelines and therapeutic issues relating to the treatment of asthma. *Chest* 1999;**115**(1):210–17.

Gibson

Gibson PG, Powell H, Ducharme F. lnhaled long-acting beta-agonists as an inhaled corticosteroid-sparing agent for chronic asthma in adults and children (unpublished Cochrane review).

GINA 2002
Global Initiative for Asthma. Global Strategy for Asthma Management and Prevention. *NIH Publication 02-3659*. 2002:Available at: http://www.ginasthma.com.

Gleser 1996
Gleser LJ, Olkin I. [Models for estimating the number of unpublished studies]. *Statistics in Medicine* 1996;**15**:2493–507.

Global 2002
Global Initiative for Asthma. Global Strategy for Asthma Management and Prevention. *NIH Publication 02-3659*. 2002:Available at: http://www.ginasthma.com.

Greenland 1985
Greenland S, Robins JM. Estimation of a common effect parameter from sparse follow-up data. *Biometrics* 1985;**41**:55–68.

Greenstone
Greenstone IR, Ni Chroinin MN, Masse V, Danish A, Magdalinos H, Zhang X, Ducharme FM. Combination of inhaled long-acting beta2-agonists and inhaled steroids versus higher dose of inhaled steroids in children and adults with persistent asthma (unpublished Cochrane review).

Higgins 2003
Higgins JPT, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. *BMJ* 2003;**327**(557):560.

Kemp 1998
Kemp JP, Cool DA, Incaudo GA, et al. Salmeterol improves quality of life in patients with asthma requiring inhaled corticosteroids. *Journal of Allergy and Clinical Immunology* 1998;**101**:188–95.

Lemiere 2004
Lemiere C, Bai T, Balter M, Bayliff C, Becker A, Boulet LP, et al. Adult Asthma Guidelines Update 2003. *Canadian Respiratory Journal* 2004;**11**(Suppl A):9A–18A.

Moore 1998
Moore RH, Khan A, Dickey BF. Long-acting inhaled beta2-agonists in asthma therapy. *Chest* 1998;**113**:1095–108.

NAEPP 2002
National Asthma Education and Prevention Program. Expert Panel Report Guidelines for the Diagnosis and Management of Asthma. *NIH Publication 02-5075*. Bethesda, MD: National Heart, Lung and Blood Institute, 2002:Available at: http://www.nhlbi.nih.gov/guidelines/asthma/index.htm.

National 2002
National Asthma Education and Prevention Program. Expert Panel Report Guidelines for the Diagnosis and Management of Asthma. *NIH Publication 02-5075*. Bethesda, MD: National Heart, Lung and Blood Institute, 2002:Available at: http://www.nhlbi.nih.gov/guidelines/asthma/index.htm.

Nelson 1995
Nelson HS. Beta-adrenergic bronchodilators. *New England Journal of Medicine* 1995;**333**(8):499–506.

Nelson HR 2003
Nelson HS, Chapman KR, Pyke SD, Johnson M, Pritchard JN. Enhanced synergy between fluticasone propionate and salmeterol inhaled from a single inhaler versus separate inhalers. *Journal of Allergy and Clinical Immunology* 2003;**112**(1):29–36.

Ni Chroinin 2004
M Ni Chroinin, Greenstone I, Ducharme FM. Addition of inhaled long acting beta2-agonists to inhaled steroids as first line therapy for persistent asthma in steroid naive adults (Cochrane Review). In: *The Cochrane Database of Systematic Reviews*, 4, 2004.

Ram 2005
Ram FSF, Cates CJ, Ducharme FM. Long-acting beta2-agonists versus anti-leukotrienes as add-on therapy to inhaled corticosteroids for chronic asthma (Cochrane Review). In: *The Cochrane Database of Systematic Reviews*, 1, 2005.

Reference 1
[Le 9e Congres Annuel de la "European Respiratory Society"]. Madrid, Spain October 9-13, 1999.

Sears 1998
Sears MR. Asthma treatment: Inhaled beta0agonists. *Canadian Respiratory Journal* 1998;**5**(Suppl A):54A–59A.

Smart
FDA. Smart study site. www.fda.gov/bbs/topics/ANSWERS/2003/ANS01192.html.

Storms 2003
Storms W. Clinical trials: Are these your patients?. *Journal of Allergy & Clinical Immunology* 2003;**5**(Suppl):S107–S111.

Walters 2003
Walters EH, Walters JAE, Gibson MDP. Long acting beta agonists for stable chronic asthma. In: *The Cochrane Database of Systematic Reviews*, 3, 2003.

Warner 1998
Warner JO, Naspitz CK. Third International Pediatric Consensus statement on the management of childhood asthma. International Pediatric Asthma Consensus Group. *Pediatric Pulmonology* 1998;**25**(1):1–17.

** Indicates the major publication for the study*

TABLES

Characteristics of included studies

Study	Akpinarli ICS600
Methods	DESIGN: -parallel group, 2 groups -multicenter ALLOCATION: -random BLINDING: -double-blind -use of identical placebo WITHDRAWAL/ DROP-OUTS: -not described JADAD's Quality Score= 3 Confirmation of methodology unobtainable
Participants	Symptomatic asthmatic children % ELIGIBLE OF SCREENED POPULATION Not reported % RUN-IN PARTICIPANTS RANDOMISED Not reported RANDOMISED: 32 patients -ICS +F12 (BID)= 16 -ICS= 16 WITHDRAWALS: -not described AGE mean (range) or mean (SD): - 6 to 14 years GENDER:(% male): -ICS+F12= 43% -ICS = 50% -total= 47% SEVERITY: not reported BASELINE % PRED. FEV1: mean(SEM) -not described BASELINE DOSE OF ICS: - 400-800mcg ASTHMA DURATION: -not described

Characteristics of included studies (*Continued*)

	ATOPY (%) -ICS + F12 (BID)= 69% -ICS = 67% -total= 62.5 ELIGIBILITY CRITERIA: -met ATS criteria for asthma ->= 15%increase in FEV1 within the previous year EXCLUSION CRITERIA: -asthma exacerbation or respiratory infection in < month ELIGIBILITY CRITERIA DURING RUN IN Only patients requing salbutamol more than once a week were randomised
Interventions	PROTOCOL: -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 -not described
Outcomes	INTENTION TO TREAT ANALYSIS: not described PULMONARY FUNCTION TEST -% of predicted FEV1 -morning PEFR (L/min) -evening PEFP (L/min) -PEF variability (%) -PC 20 (mg/ml) SYMPTOM SCORES: -score of 0 to 3 (max 9) (Change) -nighttime symptom score -symptom-free days or nights

Characteristics of included studies (*Continued*)

	FUNCTIONAL STATUS: -rescue B2-agonist use per week (each use consisted of 2 puffs) -exacerbation requiring systemic steroids -exacerbations requiring admision INFLAMMATORY MARKERS: -not described ADVERSE EFFECTS: -described WITHDRAWALS: -not described primary outcome measure not reported
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)
Allocation concealment	A – Adequate

Study	**Boyd ICS1675**
Methods	DESIGN -parallel-group -multicentre (15 centres) ALLOCATION -random -computer generated random numbers -numbered coded inhalers supplied by Pharmacy BLINDING -double-blind -placebo-controlled -use of identical placebo WITHDRAWAL/ DROPOUTS -described by groups JADAD'S quality score=5 Confirmation of methodology: obtained
Participants	Symptomatic Asthmatic adults %ELIGIBLE OF SCREENED POPULATION Not reported %RUN-IN PARTICIPANTS RANDOMISED 66% RANDOMISED: 119 patients -Salm100 + ICS=55 -Placebo + ICS=64

Characteristics of included studies (*Continued*)

	WITHDRAWALS: -Salm100 + ICS=8 (15%) -Placebo + ICS=14 (22%) AGE: mean(range) -Salm100 + ICS=47(18-79) -Placebo + ICS=47(18-73) GENDER: (% male) -Salm100 + ICS=40% -Placebo + ICS=45% BASELINE % PRED. FEV1: mean(range) -Salm100 + ICS=66(33-105) -Placebo + ICS=66(16-115) BASELINE DOSE OF ICS: Salm100 + ICS: - 1000-2000 mcg/day=47(85%) - 2001-3000 mcg/day=6(11%) - 3001-4000 mcg/day=2(4%) Placebo + ICS: - 1000-2000 mcg/day=55(86%) - 2001-3000 mcg/day=7(11%) - 3001-4000 mcg/day=2(3%) ASTHMA DURATION (years): -Salm100 + ICS=15.5+/-14.3 -Placebo + ICS=14.1+/-12.7 ATOPY (%): -not described ELIGIBILITY CRITERIA: ->= 15% improvement from baseline in lung function following inhaled salbutamol -at least 2 acute asthma exacerbations in the preceding 18 months EXCLUSION CRITERIA: -concurrent uncontrolled systemic disease -having received treatment for an acute respiratory infection in the last 2 weeks - or had a FEV1 <40% predicted
Interventions	PROTOCOL: -LABA + ICS vs SAME dose of ICS OUTCOMES: -reported at 4, 8 and 12 weeks RUN-IN:

-	2 weeks DOSE OF ICS DURING RUN IN Usual ICS Intervention period:
-	12 weeks TEST GROUP: (Salm100 + ICS) -Salmeterol 100 mcg bid + ICS CONTROL GROUP: -Placebo + ICS DEVICE: -diskhaler NUMBER OF DEVICES: 2 COMPLIANCE: Assessed at each clinic visit CO-TREATMENT -Salbutamol metered dose inhaler
Outcomes	INTENTIqq1ON TO TREAT ANALYSIS: -yes PULMONARY FUNCTION TEST: -FEV1 -PEF(morning and evening)* SYMPTOM SCORE: -score of 0 to 4 (change) -changes in daytime and nighttime score FUNCTIONAL STATUS: -rescue B2-agonist (number of puffs per 24 hours) -nocturnal awakening(change in symptom free nights) - symptom free days change -severe exacerbation (requiring systemic steroids) INFLAMMATORY MARKERS: -none studied ADVERSE EFFECTS: -reported WITHDRAWALS: -reported * primary outcome variable
Notes	-Full text publication -Funded by Allen & Hanburys -Confirmation of methodology and data obtained

	-User-defined number: 1681 (mean ICS dose in LAB2 group in mcg/day of BDP-equivalent)
Allocation concealment	A – Adequate

Study	**Buhl BUD400(bd)**
Methods	Same as Buhl od except the following 2 groups considered: LABA + ICS twice a day versus ICS once a day
Participants	Symptomatic Asthmatic adults % ELIGIBLE OF SCREENED POPULATION: Not reported % RUN IN PATIENTS RANDOMISED: 95% 26 patients were recruited but were not randomised as they deteriorated during run in RANDOMISED 347 patients -Form 6 mcg+ ICS bid=176 -Placebo + ICS=171 (for analyisis of data half the placebo group data was compared to each treatment group) WITHDRAWALS: -Form 6 bid + ICS=14 (8%) -Placebo + ICS=14 (8%) AGE: mean(range) -Form 6 + ICS bid = 44.8(18-74) -Placebo + ICS=45.5(18-78) GENDER: (% male) -Form 6 + ICS bid =57%% -Placebo + ICS=40% BASELINE % PRED. FEV1: mean(range) -Form 6 + ICS bid= 77.6(43-111) -Placebo + ICS=77.6(33-132) BASELINE DOSE OF ICS mean: Form 6 + ICS bid: 592 mcg/day Placebo + ICS: 612mcg/day mcg/day Range only given for total population (400-1000) ASTHMA DURATION mean , (range) in years: -Form 6 + ICS bid = 12.3 (1-63) -Placebo + ICS=14.5 (0-62) ATOPY (%): -not described ELIGIBILITY CRITERIA:

Characteristics of included studies (*Continued*)

	Baseline FEV1 of 60-90% normal ->= 12% improvement from baseline in lung function following inhaled salbutamol -at least 2 acute asthma exacerbations in the preceding 18 months EXCLUSION CRITERIA: - systemic corticosteroids in 4 weeks before run in -concurrent respiratory infection in the 4 weeks before run in - severe cardiovascular disorder -use of beta blocker -heavy smoking.
Interventions	PROTOCOL: -LABA + ICS TWICE A DAY vs SAME dose of ICS ONCE A DAY OUTCOMES: -reported at 4, 8 and 12 weeks RUN-IN: - 4 weeks DOSE OF ICS DURING RUN IN BUD 200 bid INTERVENTION PERIOD: - 12 weeks TEST GROUP: (Form 6 + ICS) -Formoterol 6mcg bid + ICS bid CONTROL GROUP: -Placebo + ICS od DEVICE: -turbuhaler NUMBER OF DEVICES: active medication delivered in 1 device COMPLIANCE: Not reported CO-TREATMENT -Salbutamol metered dose inhaler
Outcomes	Same as Buhl od
Notes	Same as Buhl od
Allocation concealment	A – Adequate

Study	**Buhl BUD400(qd)**
Methods	DESIGN -parallel-group -multicentre (56 centres in 9 countries) 3 groups of which the following two groups are considered: LABA and ICS once and day versus ICS once a day

	ALLOCATION -random -numbered coded inhalers supplied by Pharmacy BLINDING -double-blind -placebo-controlled -use of identical placebo WITHDRAWAL/ DROPOUTS -described by groups JADAD'S quality score=4 Confirmation of methodology: not obtained
Participants	Symptomatic Asthmatic adults % ELIGIBLE OF SCREENED POPULATION: Not reported % RUN IN PATIENTS RANDOMISED: 95% 26 patients were recruited but were not randomised as they deteriorated during run in RANDOMISED 347 patients -Form 9 mcg+ ICS=176 -Placebo + ICS=171 (for analyisis of data half the placebo group data was compared to each treatment group) WITHDRAWALS: -Form 9 + ICS=14 (8%) -Placebo + ICS=14 (8%) AGE: mean(range) -Form 9+ ICS= 42.7(18-77) -Placebo + ICS=15.4(18-78) GENDER: (% male) -Form 9 + ICS=38% -Placebo + ICS=40% BASELINE % PRED. FEV1: mean(range) -Form 9 + ICS= 77.1(44-126) -Placebo + ICS=77.6(33-132) BASELINE DOSE OF ICS mean: Form 9 + ICS: 592 mcg/day Placebo + ICS: 612mcg/day mcg/day Range only given for total population (400-1000) ASTHMA DURATION mean , (range) in years): -Form 9 + ICS= 12.1 (0-62) -Placebo + ICS=14.5 (0-62)

Characteristics of included studies (*Continued*)

	ATOPY (%): -not described ELIGIBILITY CRITERIA: Baseline FEV1 of 60-90% normal ->= 12% improvement from baseline in lung function following inhaled salbutamol -at least 2 acute asthma exacerbations in the preceding 18 months EXCLUSION CRITERIA: - systemic corticosteroids in 4 weeks before run in -concurrent respiratory infection in the 4 weeks before run in - severe cardiovascular disorder -use of beta blocker -heavy smoking.
Interventions	PROTOCOL: -LABA + ICS ONCE A DAY vs SAME dose of ICS ONCE A DAY OUTCOMES: -reported at 4, 8 and 12 weeks RUN-IN PERIOD: - 4 weeks DOSE OF ICS DURING RUN IN BUD 200bid INTERVENTION PERIOD: - 12 weeks TEST GROUP: (Form 12 + ICS) -Formoterol 12 mcg bid + ICS CONTROL GROUP: -Placebo + ICS DEVICE: -turbuhaler NUMBER OF DEVICES: medication delivered in 1 device COMPLIANCE: Not reported CO-TREATMENT -Salbutamol metered dose inhaler
Outcomes	INTENTION TO TREAT ANALYSIS: -yes PULMONARY FUNCTION TEST: -FEV1 - change in morning PEF* - change in evening PEF SYMPTOM SCORE: -Score of 0 to 3 grading day-time and night -time symptoms

Characteristics of included studies (*Continued*)

	Total daily asthma score = sum of day time and night time scores FUNCTIONAL STATUS: -exacerbations -rescue B2-agonists use (change in inhalations per day) -nocturnal awakening (% nights with awakening) -%reliever use free days -%symptom free days -% asthma control days -% asthma control weeks INFLAMMATORY MARKERS: -none studied ADVERSE EFFECTS: -reported WITHDRAWALS: -reported Primary outcome*
Notes	-Full text publication -Funded by Astra-Zeneca -Confirmation of methodology and data obtained -User-defined number: 400
Allocation concealment	A – Adequate

Study	**D'Urzo ICSNR**
Methods	DESIGN: -parallel-group -multicenter in 253 centers predominantly general practices - 2 groups ALLOCATION: -Randomised -Method of randomisation: not described -Means of assignment: not described BLINDING: -double-blind -(means of blinding not described) WITHDRAWAL/DROP-OUTS: -described by groups JADAD'S quality score= 4 Confirmation of methodology: not obtained
Participants	Adults and adolescents with asthma %ELIGILBE OF SCREENED POPULATION: Not reported %RUN IN PARTICIPANTS RANDOMISED:

	Not reported RANDOMISED: 911 total randomised -Salm50 bid + ICS = 455 -Placebo + ICS=456 WITHDRAWALS: -Salm50 bid + ICS= 19% -Placebo + ICS= 24% AGE: mean(range) -Salm50 bid+ ICS=46.5(17-82) -Placebo + ICS=45.9(18-86) GENDER: (% male) -Salm50 bid+ ICS=47% -Placebo + ICS=45% SEVERITY: -moderate BASELINE FEV1 MEAN (SD): Not reported BASELINE DOSE OF ICS/day: -Sal 50 bid BDP up to 500mcg :19.3 % BDP 500-1000: 56.2% BDP >1000 = 24.6% -Placebo + ICS BDP up to 500mcg :16.8% BDP 500-1000: 61.6% BDP >1000 = 21.3% ASTHMA DURATION: Not reported ATOPY(%): -Not reported ELIGIBILITY CRITERIA: - History of Asthma (ATS criteria) -Required regular ICS but still required resuce bronchodilator more than twice daily EXCLUSION CRITERIA: -uncontrolled pulmonary or systemic disease or psyhological condition that in then opinion of investigator precluded their entry into study -concurrent beta blocker therapy
Interventions	PROTOCOL: -LABA + ICS vs SAME dose of ICS OUTCOMES: measured at 4 weekly intervals RUN IN PERIOD: none

	DOSE OF ICS DURING RUN-IN: not applicable DOSE OPTIMISATION PERIOD: -none INTERVENTION PERIOD: 6 months TEST GROUP (LABA + SINGLE DOSE ICS): usual ICS + salmeterol 50 mcgs bid CONTROL GROUP - Placebo + usual dose of ICS DEVICE: MDI NUMBER OF DEVICES: 2 COMPLIANCE: Not reported CO-TREATMENT not reported
Outcomes	INTENTION TO TREAT ANALYSIS: -yes PULMONARY FUNCTION TEST: -change in clinic PEF SYMPTOM SCORES: -not reported FUNCTIONAL STATUS: -rescue medication use day and night -Daytime and nighttime symptoms - nocturnal awakenings -Serious asthma exacerbation* defined as days in hospital,-days of prednisone treatment or ER visit -days requiring increased asthma medication -work or school days lost because of asthma limitation of activites because of asthma INFLAMMATORY MARKERS: -blood esoinophil count measured in subgroup with asthma exacerbation ADVERSE EFFECTS: heart rate higher in salmeterol group no other adverse effects reported WITHDRAWALS: Sal 50 bid + ICS : 19% Placebo + ICS 24% Primary outcome variable*
Notes	-Full-text publication Supported by Glaxo Wellcome Confirmation of methodology and data extraction not obtained

	-User defined number: Not reported (mean ICS dose in LAB2 group in mcg/day of BDP-equivalent: not reported
Allocation concealment	A – Adequate

Study	**Fitzgerald ICS730**
Methods	DESIGN: -parallel-group -multicenter in 15 centers in Canada - 3 groups of which 2 considered for this review (group which evaluated regular albuterol use not considered) ALLOCATION: -Randomised -Method of randomisation: not described -Means of assignment: not reported BLINDING: -double-blind -use of identical placebo (double dummy) WITHDRAWAL/DROP-OUTS: -reported JADAD'S quality score= 5 Confirmation of methodology: not obtained
Participants	Symptomatic Asthmatic adults % ELIGIBLE OF SCREENED POPULATION: Not reported %RUN IN PARTICIPANTS RANDOMISED: 72% RANDOMISED: 271 -F 12 bid +usual dose ICS =89 -Usual dose ICS and on demand albuterol= 91 - Usual dose ICS + regular albuterol=91 WITHDRAWALS: -total = 54 -F 12 bid +usual dose ICS = 17 (19%) -Usual dose ICS and on demand albuterol = 18 (20%) Mean AGE years(SD) -F 12 bid +usual ICS = 36(13) -Usual ICS and on demand albuterol = 36 (12) GENDER: (%male) -F 12 bid +usual ICS =53% -Usual ICS and on deman albuterol = 36% SEVERITY: -moderate

BASELINE FEV1 mean % Pred (SD):
-F 12 bid +usual ICS =79.1(16.3)
-Usual ICS and on demand albuterol 79.7(16.4)

BASELINE DOSE OF ICS Mean (SD):
--F 12 bid +usual ICS = 730(290)
-Usual ICS and on demand
albuterol =734(270)

ASTHMA DURATION (years):
Not reported

ATOPY (%):
-nor reported

ELIGIBILITY CRITERIA:
-Non smoking adults with asthma as defined by ATS criteria
- Treated with ICS 400-1200 mcg/day for at least 1 months prior to screening
->=15% reversibility after bronchodilator
-During the last 7 days of run in , had used albuterol on at least 5 days awakening on >=1 night due to asthma symptoms
-use of beta agonist>=10 puffs as weekly mean
-competance with turbuhaler
-compliance with dairy cards and assesments

EXCLUSION:
-Respiratory infection within 2 months of screening
-an acute asthma exacerbation requiring an ER visit in the previous 3 months

CRITERIA FOR RANDOMISATION DURING RUN-IN:
- Had used resuce albuterol on at least 5 of the last 7 days of the run-in period
-Were excluded from randomisation if asthma was poorly controlled as defined by 2 or more awakenings per week or a visit 2 premedication FEV1 less than 50% predicted or less than 1L

Interventions

PROTOCOL:
-LABA + ICS vs SAME dose of ICS

OUTCOMES:
after initial dose, 3,6 months and 2 days after end of last dose

RUN-IN PERIOD:
2 weeks

DOSE OF ICS DURING RUN-IN:
400-1200 mcgs BDP, BUD usual dose of patient

DOSE OPTIMISATION PERIOD:
-none

INTERVENTION PERIOD:
6 months

TEST GROUP (LABA + SINGLE DOSE ICS): Formoterol 12 mcgs bid +
beclomethasone,budesonide 400-1200mcg/day

CONTROL GROUP:
-Beclomethasone , budesonide 400-1200 mcg bid

DEVICE: Formoterol- dry powder inhalation capsules
Albuterol MDI

	NUMBER OF DEVICES: 2 COMPLIANCE: Not reported CO-TREATMENT not reported
Outcomes	INTENTION TO TREAT ANALYSIS: -not stated PULMONARY FUNCTION TEST: -change in morning PEF* -Change in FEV1 SYMPTOM SCORES: -change in daytime and nighttime scores FUNCTIONAL STATUS: -change in rescue medication use day and night (puffs per day or night) INFLAMMATORY MARKERS: -not described ADVERSE EFFECTS: -F 12 bid +usual ICS = 13 -Usual ICS and on demand =8 WITHDRAWALS: reported *Primary outcome: change in mean morning PEF.
Notes	-Full-text publication Supported by Novartis Confirmation of methodology and data extraction not obtained -User defined number: (mean ICS dose in LAB2 group in mcg/day of BDP-equivalent: 730
Allocation concealment	A – Adequate

Study	**Gardiner ICS600**
Methods	DESIGN: -crossover group - single center ALLOCATION: -random BLINDING: -double-blind -identical placebo WITHDRAWAL/ DROP-OUTS: - not described JADAD's Quality Score=3

Characteristics of included studies (*Continued*)

	Confirmation of methodology: not obtained
Participants	Stable asthmatic adults %ELIGIBLE OF SCREENED POPULATION Not reported %RUN IN PARTICIPANTS RANDOMISED Not reported RANDOMISED: 10 -SALM 50mcg bid + usual ICS -Placebo +Usual ICS AGE: median (range) 42 (23-64) GENDER: (%males) 60% SEVERITY: moderate BASELINE % PRED. FEV1: mean (SEM) Not reported BASELINE DOSE OF ICS (before start of run-in): 400-1000 BDP equivalent ASTHMA DURATION: not reported ATOPY (%): - 70% ELIGIBILITY CRITERIA: ->non smoking -Asthma diagnosed by ATS criteria - 15% reversibility following bronchodilator EXCLUSION CRITERIA: - respiratory infection or asthma exacerbation in 2 months prior to study
Interventions	PROTOCOL: -LABA + ICS vs SAME dose of ICS OUTCOMES: 2 and 4 months RUN-IN PERIOD: 2 weeks DOSE OF ICS DURING RUN-IN: Usual ICS (400-1000) DOSE OPTIMISATION PERIOD: -none INTERVENTION PERIOD:

	8 weeks TEST GROUP (LABA + SINGLE DOSE ICS): salmeterol 50 mcg bid DEVICE: Not stated NUMBER OF DEVICES: 2 COMPLIANCE: Not stated CO-TREATMENT Inhaled albuterol as rescue medication but no oral beta agonists, inhaled anticholinergic medication or theophylline
Outcomes	INTENTION TO TREAT ANALYSIS: -not stated PULMONARY FUNCTION TEST: -PEF SYMPTOM SCORES: -not given FUNCTIONAL STATUS: -not assessed INFLAMMATORY MARKERS: -BAL differential cell count and ly -BAL Mast cell tryptase &al -Serum ECP - respiratory burst -release of PAF before and after allergen inhalation challenge. ADVERSE EFFECTS: -not reported WITHDRAWALS: - not reported
Notes	Full-text publication Source of funding not reported Confirmation of methodology and data extraction not obtained -User defined number: (mean ICS dose in LAB2 group in mcg/day of BDP-equivalent: not reported range 400-1000
Allocation concealment	A – Adequate

Study	**Hultquist BUD400**
Methods	DESIGN: -parallel-group -multicenter in 49 clinical centers in 6 countries - 3 groups of which 2 are considered for this review ALLOCATION: -Randomised -Means of assignment:

	opaque consecutive numbered envelopes containing assignment BLINDING: -double-blind -use of identical placebo (double dummy) WITHDRAWAL/DROP-OUTS: -described by groups JADAD'S quality score= 5 Confirmation of methodology: obtained
Participants	Symptomatic Asthmatic patients aged 12-70 years % ELIGIBLE OF SCREENED POPULATION: Not reported %RUN IN PARTICIPANTS RANDOMISED: 74% 126 enrolled patients not ranodmised -reasons as follows- eligibility criteria not fulfilled 110 patients; adverse events 6 patients;lost to follow-up 1 patient; other reasons 9 patients. RANDOMISED: 352 -F 9 bid +Bud 200 bid = 118 -Bud 200 bid = 116 Bud +montelukast= 118 WITHDRAWALS: -F 9 bid +Bud 200 bid = 10% -Bud 200 bid = 7% Mean AGE years -F 9 bid +Bud 200 bid = 38.1 -Bud 200 bid = 38.1 GENDER: (%male) -F 9 bid +Bud 200 bid = 53% -Bud 200 bid = 49% SEVERITY: -moderate BASELINE FEV1 (% Pred): F 9 bid +Bud 200 bid = 69.71 -Bud 200 bid = 72.12 BASELINE DOSE OF ICS: - 400-1000mcgs per day. ASTHMA DURATION (years): F 9 bid +Bud 200 bid = 12.1 -Bud 200 bid =10.6 ATOPY (%): -information unavailable

Characteristics of included studies (*Continued*)

	ELIGIBILITY CRITERIA: -Aged 12-70 years - Treated with ICS 400-1000 mcg/day for at least 3 months prior to visit 1 - FEV1 between 50-80 % of pred normal ->=12% reversibility after bronchodilator -smoking history <= 10 years CRITERIA FOR RANDOMISATION DURING RUN-IN: -During the last 7 days of run in , having an asthma score >=1 on 4 days or awakening on >=1 night due to asthma symptoms -use of beta agonist>=10 puffs as weekly mean -competence with turbuhaler -compliance with dairy cards and assesments EXCLUSION CRITERIA: -Patients who had other diseases that may interfere with assesments - respiratory infection ,COPD or pumonary dysfunction other than asthma -pregnant or lactating women -use of LABA within 1 month prior to visit 1 -Previous use of lekotriene antagonist -known intolerance to study drugs or inhaled lactose
Interventions	PROTOCOL: -LABA + ICS vs SAME dose of ICS OUTCOMES: not reported RUN-IN PERIOD: 2 weeks DOSE OF ICS DURING RUN-IN: not stated DOSE OPTIMISATION PERIOD: -none INTERVENTION PERIOD: 8 weeks TEST GROUP (LABA + SINGLE DOSE ICS): budesonide 200 mcgs bid + formoterol 9 mcgs bid CONTROL GROUP -Budesonide 200 mcg bid DEVICE: turbuhaler NUMBER OF DEVICES: 2 COMPLIANCE: Not reported CO-TREATMENT not reported
Outcomes	INTENTION TO TREAT ANALYSIS: -modified

	PULMONARY FUNCTION TEST: -change in morning PEF* -Change in FEV1 SYMPTOM SCORES: -day time and night time score FUNCTIONAL STATUS: -change in resuce medication use per day (puffs per day) -change in resuce medication use per night(puffs per night) -change in rescue medication use per 24 hours -% night time awakenings INFLAMMATORY MARKERS: -not described ADVERSE EFFECTS: -descriptions and numbers of adverse events not described WITHDRAWALS: -reported *Primary outcome: change in mean morning PEF.
Notes	Abstract and full study report from sponsoring drug company Supported by Astra Zeneca Confirmation of methodology and data extraction obtained -User defined number: (mean ICS dose in LAB2 group in mcg/day of BDP-equivalent: 800
Allocation concealment	A – Adequate

Study	**Ind 2003**
Methods	DESIGN: -parallel-group -multicenter in 100 hospitals and general practices in 6 countries - 3 groups of which 2 are considered fo this review ALLOCATION: -Randomised -Method of randomisation: not described -Means of assignment: not described BLINDING: -double-blind -use of identical placebo (double dummy) WITHDRAWAL/DROP-OUTS: -described by groups JADAD'S quality score= 4 Confirmation of methodology: Not obtained
Participants	Symptomatic Asthmatic Adults % ELIGIBLE OF SCREENED POPULATION: Not reported

%RUN IN PARTICIPANTS RANDOMISED:
58%
Of 859 recruited 357 not randomised(improved during run in period)

RANDOMISED:
502 (496 with completed case report forms included in intent-to treat population)
-Salm50/FP250 = 171
-FP250 = 160

WITHDRAWALS:
Salm50/FP250 = 27 (16%)
-FP250 = 15 (9%)

mean AGE years (SD)
-Salm50/FP250 44.8(15.6)
-FP250 = 45.7 (15.2)

GENDER: (%male)
-Salm50/FP250= 41
-FP 250= 49

SEVERITY:
-moderate to severe

BASELINE FEV1 (SD):
-Salm50/FP 250= 2.3 (0.9) L
-FP250= 2.2 (0.8) L

% PREDICTED PEF am (SD)
Salm50/FP 250= 75.4 (17.4)
-FP250= 73.6 (18.6)

BASELINE DOSE OF ICS (Median):
SM/FP250 1000
FP 250 1000

ASTHMA DURATION (range in years):
Salm50/FP250 0.2-64
FP 250= 0.4-65

ATOPY (%):
-information unavailable

ELIGIBILITY CRITERIA:
-Aged 15-75
-Symptomatic on BDP500-800mcg BID or equivalent via MDI with good technique
-

2 documented exacerbations needing hospitalisation or change in treatment with one occuring in last 6 months
- PEF less than 85% of post bronchodilator PEF at first clinic visit

INCLUSION CRITERIA FOR RANODMISATION DURING RUN-IN:
-period variation in PEF over 10 days of >= 15% (highest evening PEF minus lowest morning PEF as a percentage of highest value)
-PEF not exceeding 90% of the post bronchodilator PEF at first clinic visit

Characteristics of included studies (*Continued*)

	EXCLUSION CRITERIA: -Patients receiving regular oral corticosteroid. -Patients who had serious uncontrolled systemic disease -Participation was deemed unsuitable by their physician from the study.
Interventions	PROTOCOL: -LABA + ICS vs SAME dose of ICS OUTCOMES: 6, 12 18 and 24 weeks RUN-IN PERIOD: 4 weeks DOSE OF ICS DURING RUN-IN: FP 250 mcg bid DOSE OPTIMISATION PERIOD: -none INTERVENTION PERIOD: 6 months TEST GROUP (LABA + SAME DOSE ICS): fluticasone proprionate 250 mcgs(MDI) bid + salmeterol (MDI) 50 ug bid in single device. CONTROL GROUP FP 500mcgs bid DEVICE: MDI NUMBER OF DEVICES: 2 COMPLIANCE: Not reported CO-TREATMENT rescue short-acting beta2-agonists (salbutamol MDI) as needed, other asthma drugs as needed except LABA
Outcomes	INTENTION TO TREAT ANALYSIS: -modified PULMONARY FUNCTION TEST: -change in morning* and evening PEF SYMPTOM SCORES: -Night-time scores 0-4 -Day-time score 0-5 FUNCTIONAL STATUS: -% symptom free days - % symptom free nights -% days with no relief medication -% nights with no relief medication - mild , moderate and severe exacerbations defined as :mild (requiring increase in relief medication), moderate(requiring the use of additional corticosteroid) and severe(requiring emergency hospital treatment) FUNCTIONAL STATUS: INFLAMMATORY MARKERS: -not described

Characteristics of included studies (*Continued*)

	ADVERSE EFFECTS: -numbers reported but not described WITHDRAWALS: -reported *Primary outcome:
Notes	Full-text publication Supported by GlaxoWellcome Research and Development Confirmation of methodology and data extraction not obtained -User defined number: (mean ICS dose in LAB2 group in mcg/day of BDP-equivalent: 1000)
Allocation concealment	A – Adequate

Study	**Kavaru FP400**
Methods -	DESIGN: -parallel-group -multicentre (42 centres) 4 groups of which 2 considered in this review ALLOCATION: -randomised -means of assignment not described BLINDING: -double-blind -placebo-controlled -identical placebo WITHDRAWAL/ DROP-OUTS: -described JADAD'S quality score= 4 Confirmation of methodology: -not obtained
Participants	Asthmatic Patients over 12 years %ELIGIBLE OF SCREENED POPULATION: Not reported %RUN IN PARTICIPANTS RANDOMISED: 68% 171 of total 527 patients found to be ineligible after recruitment RANDOMISED: 356 total randomised -Salm50 + ICS=92 -Placebo + ICS=90 WITHDRAWALS: -Salm50 + ICS=22% -Placebo + ICS=19% AGE: mean(range) -Salm50 + ICS=38(12-70) -Placebo + ICS=39(12-67)

	GENDER: (% male) -Salm50 + ICS=59% -Placebo + ICS=52% SEVERITY: -moderate BASELINE FEV1 MEAN %: -Salm50 + ICS= 64% -Placebo + ICS= 64% BASELINE DOSE OF ICS: RANGE (Not reported by treatment groups) BDP 300-500 mcgs/day; triamcinolone acetate 600-1000mcgs/day; flunisolide 1000 mcgs/day; FP 200mcgs/day ASTHMA DURATION: Not reported ATOPY(%): -Not reported ELIGIBILITY CRITERIA: - Asthma (ATS criteria) of at least 6 months duration -Required pharmacotherapy for at least 6 months before study and inhaled corticosteroids for at least 1 month without change before study - 15% improvement in FEV1 post bronchodilator - female patients negative pregnancy test, surgically sterile, postmenopausal or using birth control EXCLUSION CRITERIA: -history of life threatening asthma -hypersensitivity rxn to sympathomimetic drugs or corticosteroids -smoking in year before study or smoking history of >10pack years -received a course of systemic corticosteroids in 6 months before study of use of any other prescription or OTC medication that could affect asthma or interact with other medications -abnormal CXR or EKG -history of diabetes glaucoma, hypertension. EXCLUSION CRITERIA FOR RANODMISATION DURING RUN-IN: -unstable asthma during run in periods i.e. more than 3 nights with awakenings, during 7 days before randomisation,more than 12 puffs of rescue medication/day for more than 3 days, FEV1 not within 15% of value obtained at beginning of screening
Interventions	PROTOCOL: -LABA + ICS vs SAME dose of ICS OUTCOMES: -reported weekly weeks 1-4 and therafter 2 weekly RUN IN PERIOD: - 2 weeks DOSE OF ICS DURING RUN IN: placebo in addition to usual medication DOSE OPTIMISATION PERIOD: -none

Characteristics of included studies (*Continued*)

-	INTERVENTION PERIOD: 12 weeks TEST GROUP: (Salm 50 + ICS) -salmeterol 50 mg bid + FP 200mcg/day CONTROL GROUP: (Placebo+ICS) -Placebo + FP 200 mcg/day DEVICE: -diskhaler NUMBER OF DEVICES: 1 COMPLIANCE: measured using dose counter on DISKUS device CO-TREATMENT -Albuterol as needed - No other prophylactic asthma medication permitted
Outcomes	INTENTION TO TREAT ANALYSIS -Modified (21 patients from one site excluded from analysis as significant deviations from good clinical practice standards) PULMONARY FUNCTION TEST: -Change in morning and evening PEF - Change in FEV1* SYMPTOM SCORES: -Change in asthma symptom score symptoms were rated daily on a 6 point scale FUNCTIONAL STATUS: -change in rescue B2-agonists (puffs per day) -nocturnal awakenings (% of nights with no awakenings) - % of days with no asthma symptoms OTHER: Probability of remaining in study over time* INFLAMMATORY MARKERS: -not described ADVERSE EFFECTS: -described WITHDRAWALS: - FP 100 S 50bid = 22% FP 100bid + 19% Primary outcome measure*
Notes	Full-text publication

	-Funded by Glaxo Wellcome -Confirmation of methodology and data User-defined number: 400 (mean ICS dose in LAB2 group in mcg/day of BDP-equivalent: FP 200 x 2)
Allocation concealment	A – Adequate

Study	**Kemp ICSNR**
Methods	DESIGN: -parallel-group -multicenter (4 centers) ALLOCATION: -Random -computer generated -assignment by opaque consecutive numbered envelopes BLINDING: -double-blind -placebo-controlled -Identical placebo. WITHDRAWALS/DROP-OUTS: -described JADAD's Quality Score = 5 Confirmation of methodology obtained
Participants	Symptomatic Asthmatic Teenagers and Adults % ELIGIBLE OF SCREENED POPULATION: Not reported % RUN-IN PARTICPANTS RANDOMISED 87% RANDOMISED: 506 patients -Salm 50 + ICS= 252 -ICS= 254 WITHDRAWALS: -Salm 50 + ICS=25 (10%) -ICS=47 (19%) AGE: mean (range) -Salm 50 + ICS= 42 years (12-85) -ICS=41.6 years (12-78) GENDER: (%male) -Salm 50 + ICS=45 -ICS=48 SEVERITY: -moderate

	BASELINE % PRED. FEV1: -Salm 50 + ICS= 63 +/- 1% - Placebo + ICS= 63 +/- 1% BASELINE DOSE OF ICS: -see below ASTHMA DURATION: -not described ATOPY(%): -not described ELIGIBILITY CRITERIA: -average daytime symptom score of 1 on a 0 to 3 point scale over a 2 week screening period -use of a short-acting bronchodilator on a daily basis -FEV1 of 40 to 80% predicted ->= 15% improvement from baseline in FEV1 following inhaled albuterol -use of one of the following inhaled corticosteroids on a daily basis at a fixed dose that is within package insert guidelines for a minimum of 6 weeks prior to the screening visit: beclomethasone (300-900 mcg/day), flunisolide (1000-2000 mcg/day), triamcinolone (600-1600 mcg/day) EXCLUSION CRITERIA: -concurrent tobacco use -oral corticosteroid therapy -immunotherapy requiring dosage change -inability to withdraw asthma/allergy medication before PFTs at screening or clinic visits throughout the study -cystic fibrosis, COPD, any significant uncontrolled disease state other than asthma -any other significant illness -pregnancy or lactation -contraindication to study medications -unstable asthma requiring albuterol >= 12 puffs/day or 12 puffs for > 3 days/ week -hospitalisation for asthma within 3 months -mechanical ventilation during an asthma exacerbation within 2 years or > 2 albuterol (or equivalent) inhalers/month within 3 months of screening
Interventions	PROTOCOL: -LABA + ICS vs SAME dose of ICS OUTCOMES: -reported on day 1 and after 4, 8 and 12 weeks RUN-IN PERIOD: - 2 weeks DOSE OPTIMISATION PERIOD: -None INTERVENTION PERIOD: - 12 weeks TEST GROUP: (Salm 50 + ICS) salmeterol xinafoate 50 ug bid + usual but unspecified doses of ICS. CONTROL GROUP: (Placebo +ICS) -placebo 2 puffs bid + usual but unspecified doses of ICS

Characteristics of included studies (*Continued*)

	DEVICE: -metered dose inhaler NUMBER OF DEVICES: 2 COMPLIANCE Not reported CO-TREATMENT-rescue short-acting beta2-agonist (albuterol aerosol) as needed
Outcomes	INTENTION TO TREAT ANALYSIS: -Yes PULMONARY FUNCTION TEST: -change in morning and evening PEF -FEV1 SYMPTOM SCORES: -overall score FUNCTIONAL STATUS: -Asthma Quality of Life Questionnaire scores -daytime rescue short-acting beta2-agonists (change in puffs per day) -nighttime rescue short-acting beta2-agonists (change in puffs per night) -nocturnal awakenings -exacerbations (not defined) -% of symptom-free days -% days without supplemental albuterol -% nights withour supplementa albuterol INFLAMMATORY MARKERS: -not described ADVERSE EFFECTS: -described WITHDRAWALS:--reported Primary outcome measure* not reported
Notes	-Full text publication -Funded by Glaxo Welcome -Methodology and data extraction confirmed. User-defined number: 600 (mean ICS dose in LAB2 group in mcg/day of BDP-equivalent: between 300-900)
Allocation concealment	A – Adequate

Study	**Langton Hewer ICS400**
Methods	DESIGN: -parallel group -single centre ALLOCATION randomised BLINDING -double-blinding -placebo-

	controlled - use of identical placebo WITHDRAWAL/ DROP-OUTS: - described JADAD's Quality Score= 4 Confirmation of methodology not obtained
Participants	SYMPTOMATIC children %ELIGIBLE OF SCREENED POPULATION: Not reported % RUN IN PARTICIPANTS RANDOMISED: Not reported NUMBER RECRUITED NOT RANDOMISED: Not stated RANDOMISED: -usual ICS + S 100bid =11 -usual ICS = 12 WITHDRAWALS: -Usual ICS +S=0 0% - Usual ICS =2 17% AGE median (range) years -Uaual ICS +S= 15 (12-17) -Usual ICS = 14 (12-16) GENDER:(% male) -Usual ICS + S =83% - Usual ICS= 55% SEVERITY: -severe BASELINE % PRED. FEV1: mean -Usual ICS +S= 83.4 -Usual ICS= 79.3 BASELINE DOSE OF ICS (start of run in): mean(range) -LABA =400 (50-1000) -Usual ICS 400(50-1,000) mcg ASTHMA DURATION: -Usual ICS +S= 12 years -Usual ICS= 13 years ATOPY (%) - 100% ELIGIBILITY CRITERIA: - Severe asthma not defined but severe enough to be attending residential school for asthma and persistent symptoms

Characteristics of included studies (*Continued*)

	EXCLUSION CRITERIA: already on LABA CRITERIA FOR RANDOMISATION DURING RUN-IN: None specified
Interventions	PROTOCOL: -LABS +usual dose ICS vs 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: (BUD800) Usual ICS and placebo bid DEVICE: -diskhaler NUMBER OF DEVICES: 2 COMPLIANCE: supervised in school taking medication by investigators CO-TREATMENT -oral steroids Usual dose ICS + S= 2 Usual dose ICS= 2 Methylxanthines Usual dose ICS +S =2 Usual dose ICS =1 Anticholinergics: Usual dose ICS +S =1 Usual dose ICS=0
Outcomes	INTENTION TO TREAT ANALYSIS: yes PULMONARY FUNCTION TEST - Change in % of predicted FEV1 - Change in morning and evening PEF SYMPTOM SCORES: -Change in morning and evening symptom scores

	FUNCTIONAL STATUS: -rescue B2-agonist -symptom free nights -symptom free days -change in rescue free days -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
Allocation concealment	A – Adequate

Study	**Leblanc 1996**
Methods	DESIGN: -multicenter (15 centers) 4 groups of which 2 considered for this review -three-way CROSSOVER study ALLOCATION: -random -computer generated random numbers -numbered coded randomisation envelopes supplied by pharmacy BLINDING: -double blind -use of identical placebo WITHDRAWAL/ DROP-OUTS: - not described by groups JADAD's Quality score= 4 CONFIRMATION OF METHODOLOGY: obtained
Participants	Symptomatic Asthmatic Adults %ELIGIBLE OF SCREENED POPULATION: Not reported %RUN-IN PARTICIPANTS RANDOMISED: Not reported RANDOMISED:

	367 patients WITHDRAWALS: - 66 (18%) AGE: mean (range) or mean (SD) -Total male=40 -Total female=39 GENDER: (%male) -Total male=164 (45%) SEVERITY: moderate BASELINE % PRED. FEV1: -Total=77.1% BASELINE DOSE OF ICS: -not reported ASTHMA DURATION: -Total <1 yrs=10 1-5 yrs =89 6-10 yrs =71 >10 yrs =197 ATOPY (%): -Not reported ELIGIBILITY CRITERIA: - >= 18 to 70 years old -if they demonstrated both FEV1 of at least 60% of their predicted value and an increase in FEV1 of at least 15% after inhalation of 200ug salbutamol -on 4 of the last 7 days of the pre-randomisation period, patients had to be either symptomatic or demonstrate a greater than 20% diurnal variation in PEF

Characteristics of included studies (*Continued*)

	EXCLUSION CRITERIA: -aged <18 or >70 years, -FEV1<60% of predicted having withheld inhaler bronchodilators for at least 4 hours previously, -have lab or clinical evidence in the opinion of the investigator to suggest a serious or uncontrolled systemic disease, -clinically significant abnormalities at Visit 1 lab test, have had a lower respiratory tract infection within previous 1 month, -abnormal 12-lead ECG measurement, -experienced an acute asthma exacerbation requiring emergency room treatment within the past 3 months, -been hospitalised for any aspect of their reversible airways disease within the past 12 months, -required daily maintenance therapy with oral steroids within the past 3 months, -required a booster course of oral prednisolone in excess of 10mg prednisolone or equivalent per day within the previous month, -a history of acute sudden deterioration of their asthma symptoms, -are pregnant or lactating. Females of childbearing potential may be included in the study providing that in the opinion of the investigator is that they are taking adequate contraceptive precautions, -are hypersensitive to beta-receptor agonists -are being treated with beta-receptor antagonists, -known to abuse alcohol or drugs, -unable to use the peak flow meter properly, -unlikely to take their medication in the prescribed manner, complete daily record card properly or attend the clinic on the required occasions, -unwilling to sign consent form -in the opinion of the investigator are unsuitable for this clinical trial ELIGIBILITY CRITERIA FOR RANDOMISATION DURING RUN-IN Not other criteria other than above reported
Interventions	PROTOCOL: -UNCLEAR- assumed to be single dose -ICS and LABA versus same dose of ICS OUTCOMES: -reported from 14 daily observations from each 1 month treatment period RUN-IN PERIOD: - 2 weeks DOSE OF ICS DURING RUN-IN Usual ICS DOSE OPTIMISATION PERIOD: -none INTERVENTION PERIOD: - 12 weeks TEST GROUP: (Salm 50 bid) -Salmeterol 50 ug bid CONTROL GROUP: (Placebo) DEVICE: -not reported NUMBER OF DEVICES:

	2 COMPLIANCE: medications taken recorded by patients in diary card CO-TREATMENT -salbutamol as rescue medication -other medication which could be taken concurrently provided they had been initiated at least one month prior to visit 1 and that the dose remain constant throughout the study: inhaled and intranasal corticosteroids, inhaled sodium cromoglycate, antihistamines, and immunotherapy (eg. Pollinex anti-hayfever injection)
Outcomes	INTENTION TO TREAT ANALYSIS -yes PULMONARY FUNCTION TEST: -morning PEF* -evening PEF -diurnal variation in PEF SYMPTOM SCORES: - 0 to 10 FUNCTIONAL STATUS: -% Rescue medication free days -% nights with no sleep disturbance -% symptom -free days -% symptom -free mornings INFLAMMATORY MARKERS: -not described ADVERSE EFFECTS: -not described WITHDRAWALS: -described Primary outcome measure*
Notes	-Full-text publication -Funded by Glaxo Canada Inc. -Methodology confirmed but data extraction not confirmed User-defined number: Not reported
Allocation concealment	A – Adequate

Study	**Li ICS400**
Methods	DESIGN: -parallel group - 3 groups of which 2 are considered for this review ALLOCATION: -random -computer generated numbers in balanced blocks -opaque consecutive numbered envelopes containing assignment

	BLINDING: -double-blind -identical placebo WITHDRAWAL/ DROP-OUTS: -described JADAD's Quality Score=5 Confirmation of methodology: obtained
Participants	Symptomatic asthmatic adults %ELIGIBLE OF SCREENED POPULATION: Not reported %RUN-IN PARTICIPANTS RANDOMISED: 70% RANDOMISED: 34 -SALM 50mcg bid+ usual ICS=16 -Placebo + usual ICS=18 WITHDRAWALS: -SALM 50mcg bid+ usual ICS=3 (19%) -Placebo + usual ICS=2 (11%) AGE: mean (range) -SALM 50mcg bid+ usual ICS=38 yr (20-70) -Placebo + usual ICS=33 yr (22-68) GENDER: (%males) -SALM 50mcg bid+ usual ICS=62% (8) -Placebo + usual ICS=44% (7) SEVERITY: mild BASELINE % PRED. FEV1: median(range) -SALM 50mcg bid+ usual ICS=84(63-106) -Placebo + usual ICS=83(61-109) BASELINE DOSE OF ICS (median) : -SALM 50mcg bid + usual ICS=400 (200-500) -Placebo + usual ICS=400 (200-500) ASTHMA DURATION: not reported ATOPY (%): -SALM 50mcg bid+ usual ICS=100% (13) -Placebo + usual ICS= 75% (12) ELIGIBILITY CRITERIA: -> 20 to 70 years old -non smokers -diagnosed asthma treated for at least 12 months with ICS in a dose up to 500 mg of beclomethasone dipropionate or budesonide per day. -FEV1 at baseline) >= 60% of its predicted value

Characteristics of included studies (*Continued*)

	EXCLUSION CRITERIA: -having suffered from acute respiratory tract infection during the previous 4 weeks -change in asthma medication in < 4 weeks -admission to hospital with airway disease in the < 4 weeks -patients unable to discontinue use of methylxanthines, inhaled anticholinergics and oral steroids CRITERIA FOR RANDOMISATION DURING RUN-IN -symptom score of more than 2 on 7 of the last 14 days -required the use of rescue inhaled albuterol on more than 7 of the last 14 days had a variation of more than 15% in PEF over a 24 hour period on at least 7 of the last 14 days and some degree of symptoms and rescue medication use during that time
Interventions	PROTOCOL: -LABA + ICS vs SAME dose of ICS OUTCOMES: measured at 12 weeks RUN IN PERIOD: - 2 to 6 weeks DOSE OF ICS DURING RUN-IN Same as baseline dose of ICS DOSE OPTIMISATION PERIOD: -none INTERVENTION PERIOD: 12 weeks TEST GROUP: (Salm50+ICS) -Salmeterol 50mcg bid+ usual ICS CONTROL GROUP: -(FP100 + ICS) -Placebo + usual ICS (=similar dose) DEVICE: -dry powder diskhaler NUMBER OF DEVICES: 2 COMPLIANCE: Not reported CO-TREATMENT-not described
Outcomes	INTENTION TO TREAT ANALYSIS: -no PULMONARY FUNCTION TEST: -absolute morning PEF -absolute FEV1 SYMPTOM SCORES: -score of 0 to 4 (mean/day) FUNCTIONAL STATUS: -rescue short-acting B2-agonist (mean puffs per day) -nocturnal awakenings

	OTHER: Methacholine challenge- PD 20 methacholine before and after treatment INFLAMMATORY MARKERS: on BAL and bronchial biopsy -mast cells in BAL -eosinophils in BAL -lymphocytes in BAL -macrophages in BAL and bronchial biopsies ADVERSE EFFECTS: not reported WITHDRAWALS: -reported PRIMARY OUTCOME: not specified
Notes	-Full-text publication -Funded by Glaxo Wellcome, Alfred Foundation and the NH&MRC of Australia -Confirmation of methodology and data obtained -User-defined number: 400
Allocation concealment	A – Adequate

Study	**Meijer ICSNR**
Methods	DESIGN: -parallel group -single center ALLOCATION: -random BLINDING: -double blind -use of identical placebo WITHDRAWAL/ DROP-OUTS: -described by groups and numbers and reasons stated in manuscript JADAD's Quality Score= 4 Confirmation of Methodology: - not obtained
Participants	Asymptomatic asthmatic children %ELIGIBLE OF SCREENED POPULATION: Not reported %RUN-IN PARTICIPANTS RANDOMISED: Not reported RANDOMISED: -Salm50 mcg BID + ICS= 20 -ICS + Placebo= 20

	WITHDRAWALS: -Salm50 mcg BID + ICS= 0 (0%) -ICS + Placebo= 1 (5%) AGE: mean (SD) -Salm50 mcg BID + ICS= 11.4(+/- 2.4) yrs -ICS + placebo= 11.4 (+/-2.8) yrs GENDER: (%male) -Salm50 mcg BID + ICS= 11 (55%) -ICS + placebo= 12 (60%) male SEVERITY: -mild BASELINE % PRED. FEV1: -Salm50 mcg BID + ICS= 93.6 (+/-12.9) % -ICS + placebo= 93.8 (15.9) % BASELINE DOSE OF ICS: -twice daily 200 or 400 mcg beclomethasone dipropionate rotadisk ASTHMA DURATION: -Salm50 mcg BID + ICS= 8.9(2.3) yrs -ICS + placebo= 7.7(3.0) yrs ATOPY (%): -Salm50 mcg BID + ICS= 100% -ICS + placebo= 100% ELIGIBILITY CRITERIA: -none reported EXCLUSION CRITERIA: -none reported CRITERIA FOR RANDOMISATION DURING RUN IN: N/A
Interventions	PROTOCOL: -LABA + ICS vs 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)

Characteristics of included studies (*Continued*)

	NUMBER OF DEVICES: 2 COMPLIANCE: Returned powder disks counted CO-TREATMENT -rescue beta2 agonist
Outcomes	INTENTION TO TREAT ANALYSIS: -not specified PULMONARY FUNCTION TEST: -change in % pred. FEV1 -change in PC20 doubling doses (DD) -change in circadian variation (day-night differences in FEV1) SYMPTOM SCORES: -only individual symptoms reported (yes/no) FUNCTIONAL STATUS: -use of rescue beta2-agonist (yes/no) INFLAMMATORY MARKERS: not reported ADVERSE EFFECTS: not reported WITHDRAWALS: reported PRIMARY OUTCOME: not reported
Notes	-Full-text publication -Funded by Glaxo -User-defined number: 500 (BDP 250 bid) -Confirmation of data and methodology not obtained
Allocation concealment	A – Adequate

Study	**Molimard ICSNR**
Methods	DESIGN: -parallel group -multicenter ALLOCATION: -randomised -telephone notification of assignment by coordinating centre BLINDING: -No concealment WITHDRAWAL/ DROP-OUTS: -described by groups JADAD's Quality Score=2 Confirmation of methodology:

Characteristics of included studies (*Continued*)

	Not obtained
Participants	Symptomatic Asthmatic Adults %ELIGIBLE OF SCREENED POPULATION: Not reported %RUN-IN PARTICIPANTS RANDOMISED: 97% Of 7 patients who discontinued before randomisation 3 failed to fulfil the selection criteria, 2 withdrew their consent and 2 were lost to follow-up RANDOMISED: 259 -Form 12ug bid=130 -On-demand sabultamol (ODS)=129 WITHDRAWALS: 30 -Form12 mg bid=12 (9%) -ODS=18 (14%) AGE: mean (SD) -Form12 mg bid=38.5+/-14.9 yrs -ODS=39.5+/-15 yrs GENDER: (% male) -Form12 mg bid=58% (76/130) -ODS=55% (71/129) SEVERITY: -moderate BASELINE % PRED. FEV1: -Form12 mg bid=72.7+/-10 -ODS=73.7+/-9.4 BASELINE DOSE OF ICS (start of run-in): -not reported maximum dose 1000mcg BDP eqivalent ASTHMA DURATION: -Form12 mg bid=14.7+/-13.0 yrs -ODS=15.1 +/- 11.5 yrs ATOPY (%): -not reported ELIGIBILITY CRITERIA: - 18 years or over -moderate persistent asthma -taking daily treatment with an ICS, same one for at least 1 month prior to first visit -require daily treatment with inhaled bronchodilators -asthma defined according to criteria of ATS -FEV1 >= 60% of predicted normal value for patient -reversibility test (increase in FEV1>=10% of predicted value) had to be documented at first visit within 3 months prior to visit -refrain from taking salbutamol 6 hours before each spirometry

Characteristics of included studies (*Continued*)

	EXCLUSION CRITERIA: -known hypersensitivity to sympathetic amines or to lactose -pregnancy or breast-feeding -women of childbearing potential who did not use a reliable contraceptive method -significant change in the regular asthma medication -asthma exacerbation or respiratory tract infection in the month prior to the first visit -incapacity to use a metered-dose inhaler correctly or to complete patient diary -concomitant treatments with theophylline, anticholinergic bronchodilators and inhaled or oral B2 agonists other than the trial medications were not allowed CRITERIA FOR RANDOMISATION DURING RUN IN No addtional criteria reported
Interventions	PROTOCOL: -LABA + ICS vs SAME dose of ICS OUTCOMES: measured at 12 weeks RUN IN PERIOD: - 2 to 6 weeks DOSE OF ICS DURING RUN-IN Same as usual DOSE OPTIMISATION PERIOD: -none INTERVENTION PERIOD: - 12 weeks TEST GROUP: (Form12+ICS) -Formoterol 12 mcg BID + ICS CONTROL GROUP: -on-demand salbutamol + usual ICS (up to 1000 ucg beclomethasone or 800 mcg budesonide or 500 mcg fluticasone per day) DEVICE: -dry powder diskhaler NUMBER OF DEVICES 2 COMPLIANCE: Not reported CO-TREATMENT-salbutamol prn
Outcomes	INTENTION TO TREAT ANALYSIS: -yes PULMONARY FUNCTION TEST: -mean change in morning PEF* (average of 2 weeks) -FEV1 -Bronchial responsiveness to methacholine (PD20) SYMPTOM SCORES: -score of 0 to 4 (mean/day)

	FUNCTIONAL STATUS: -rescue short-acting B2-agonist (mean/day) -nocturnal awakenings INFLAMMATORY MARKERS: on BAL and bronchial biopsy -mast cells in BAL -eosinophils in BAL -lymphocytes in BAL -macrophages in BAL and bronchial biopsies ADVERSE EFFECTS: not reported WITHDRAWALS: -reported Primary outcome measure*
Notes	-Full-text publication -Funded by Glaxo Wellcome, Alfred Foundation and the NH&MRC of Australia -Confirmation of methodology and data not obtained -User-defined number: not reported
Allocation concealment	D – Not used

Study	**Norhaya ICS890**
Methods	DESIGN: -cross-over ALLOCATION: -random -means of assignment: not described BLINDING: -double-blind -placebo- controlled -identical placebo WITHDRAWAL/ DROP-OUTS: -described by groups JADAD'S Quality Score=4 CONFIRMATION OF METHODOLOGY Not obtained
Participants	Symptomatic Asthmatic Adults %ELIGIBLE OF SCREENED POPULATION: Not reported %RUN-IN PARTICIPANTS RANDOMISED: 83% (5 patients were withdrawn as they did not meet the selection criteria, 3 were unable to record their symptoms satisfactorily , one had no nocturnal symptoms or significant PEF variability and one had taken prednisolone in excess of 10mg per day). RANDOMISED:

Characteristics of included studies (*Continued*)

	25 patients (20 completed) Numbers assigned to each treatment group not stated WITHDRAWALS: -Salm50 + ICS=1 -Placebo + ICS=3 In addition one other patient was withdrawn as they took the placebo and active treatment concurrently during the second treatment period. AGE: mean (SD) - 41.8 +/- 9.5 years GENDER: (%male) - 30 SEVERITY: -moderate BASELINE % PRED.FEV1: -Total= 68+/-22% predicted (1.72+/-0.54 L) BASELINE DOSE OF ICS - 885 (not stated whether this value is mean or median) range (200-1600) ASTHMA DURATION: -not reported ATOPY (%): -not reported ELIGIBILITY CRITERIA: - 15% improvement from baseline in FEV1 following salbutamol via diskhaler -night time symptom score >= 2/5 or diurnal variation in peak flow >= 20% on at least 3 nights in the 1 week run-in EXCLUSION CRITERIA: -lower respiratory tract infection within previous 28 days -need for maintenance oral prednisolone > 10 mg/day within previous 28 days -pregnant or lactating women CRITERIA FOR RANDOMISATION DURING RUN-IN No additional criteria reprorted
Interventions	PROTOCOL: -LABA + ICS vs SAME dose ICS OUTCOMES: - 4 weeks RUN-IN PERIOD: - 1 week DOSE OF ICS DURING RUN IN: Same as usual

Characteristics of included studies (*Continued*)

-	INTERVENTION PERIOD: 4 weeks per group with 2 week wash-out in between. DOSE OPTIMISATION PERIOD: -none TEST GROUP: (Salm 50) -Salmeterol 50 ug bid + usual, but unspecified dose of ICS CONTROL GROUP: - Placebo + usual, but unspecified, dose of ICS DEVICE: -diskhaler NUMBER OF DEVICES 2 COMPLIANCE: Not reported CO-TREATMENT -sodium cromoglycate, -theophylline and short-acting b2-agonist (Salbutamol) as needed
Outcomes	INTENTION TO TREAT ANALYSIS -no PULMONARY FUNCTION TEST: -morning PEF* -evening PEF -FEV1 -FVC SYMPTOM SCORES: -score of 0 to 5 daytime -score of 0 to 4 nighttime FUNCTIONAL STATUS: -daytime dose of rescue bronchodilator -night time dose of rescue bronchodilator -episode-free days -exacerbations requiring systemic steroids INFLAMMATORY MARKERS: -not reported ADVERSE EFFECTS: -not reported WITHDRAWALS: -described *primary outcome measure
Notes	-Full-text publication -Funded by Glaxo Wellcome Malayisa -Confirmation of methodology and data not obtained. GSK unable to provide confirmation. -User-defined number: not reported

Allocation concealment A – Adequate

Study	**O'Byrne BUD200**
Methods	DESIGN: -parallel group - 7 groups of which 2 considered here ALLOCATION: -random -computer generated random numbers -opaque consecutive numbered envelopes containing assignment BLINDING: -double blind -use of identical placebo WITHDRAWALS/DROPOUTS: - described JADAD'S quality score=4 CONFIRMATION OF METHODOLOGY: Not Obtained
Participants	Symptomatic Asthmatic teenagers and adults %ELIGIBLE OF SCREENED POPULATION: Not reported %RUN-IN PARTICIPANTS RANDOMISED: Not reported RANDOMISED: -BUD200=322 -BUD200+F= 323 WITHDRAWALS: Not reported by sub- group AGE: mean -BUD200=38.1 yrs -BUD200+F= 36.5 yrs GENDER (%male): -BUD200=43.8 -BUD200+F= 44.6 SEVERITY: -mild BASELINE % PRED. FEV1: -BUD200=86.3 -BUD200+F= 86.4 BASELINE DOSE OF ICS : -Not reported (</= 400 mcg/d BUD) ASTHMA DURATION: -not reported

Characteristics of included studies (*Continued*)

	ATOPY(%): -not reported ELIGIBILITY CRITERIA: ->=12 years of age with mild asthma. -Taking <= 400 mcg/daily of inhaled budesonide or its equivalent for >= 3 months. -FEV1 >= 70% predicted normal after terbutaline. CRITERIA FOR RANDOMISATION DURING RUN-IN: -randomised patients demonstrated a need for two or more inhalations per week of rescue medication during the last 2 wks of run-in, a >=15% variability in peak expiratory flows, or a >= 12% increase in FEV1 after terbutaline. EXCLUSION CRITERIA: -Experience 3 severe exacerbations during the initial 6 months or five exacerbations in total - 2 poorly controlled asthma days, defined as days with morning PEF values >= 2 above baseline, or with asthma awakening.
Interventions	PROTOCOL: -LABA + ICS vs SAME dose ICS OUTCOMES: -reported at 52 weeks RUN IN PERIOD: - 4 weeks DOSE OF ICS DURING RUN- IN: BDP 100 bid DOSE OPTIMISATION PERIOD: -none INTERVENTION PERIOD: - 52 weeks CONTROL GROUP vs TEST GROUP: -BUD200 vs BUD200+F 9 DEVICE: -Turbuhaler NUMBER OF DEVICES 2 COMPLIANCE: Not reported CO-TREATMENT -None, unless exacerbation
Outcomes	INTENTION TO TREAT ANALYSIS: -Yes PULMONARY FUNCTION TEST: -change in morning PEF -change in FEV1 SYMPTOM SCORES: -not reported

	FUNCTIONAL STATUS: -percentage of days with symptoms -percentage of asthma awakenings - number of rescue inhalations -rate per patient per year of severe asthma exacerbations INFLAMMATORY MARKERS: -not reported ADVERSE EFFECTS: -reported WITHDRAWAL: -reported * primary outcome: time to the first severe asthma exacerbation defined as need for treatment with oral corticosteroids or hospital admission or emergency treatment for worsening asthma or a decrease in morning PEF > 25% from baseline
Notes	-Full-text publication -Funded by AstraZeneca -Confirmation of methodology and data not obtained -User-defined order: 400 (BUD 200 bid)
Allocation concealment	A – Adequate

Study	**O'Byrne BUD400**
Methods	DESIGN: -parallel group - 7 groups of which 2 considered here ALLOCATION: -random -computer generated random numbers -opaque consecutive numbered envelopes containing assignment BLINDING: -double blind -use of identical placebo WITHDRAWALS/DROPOUTS: - described JADAD'S quality score=4 CONFIRMATION OF METHODOLOGY: Not obtained
Participants	Symptomatic Asthmatic teenagers and adults %ELIGIBLE OF SCREENED POPULATION: Not reported %RUN-IN PARTICIPANTS RANDOMISED: Not reported RANDOMISED: -BUD400=312 -BUD400+F= 315

	WITHDRAWALS: Not reported by sub -group AGE: mean -BUD400=37.5 yrs -BUD400+F= 36.8 yrs GENDER (%male): -BUD400=42.6 -BUD400+F= 40.9 SEVERITY: -mild BASELINE % PRED. FEV1: -BUD400=87.0 -BUD400+F= 86.5 BASELINE DOSE OF ICS : -Not reported </= 400 mcg/d BUD ASTHMA DURATION: -not reported ATOPY(%): -not reported ELIGIBILITY CRITERIA: ->=12 years of age with mild asthma. -Taking <= 400 mcg/daily of inhaled budesonide or its equivalent for >= 3 months. -FEV1 >= 70% predicted normal after terbutaline. CRITERIA FOR RANSOMISATION FOLLOWING RUN-IN: -randomized patients demonstrated a need for two or more inhalations per week of rescue medication during the last 2 wks of run-in, a >=15% variability in peak expiratory flows, or a >= 12% increase in FEV1 after terbutaline. EXCLUSION CRITERIA: -Experience 3 severe exacerbations during the initial 6 months or five exacerbations in total - 2 poorly controlled asthma days, defined as days with morning PEF values >= 2 above baseline, or with asthma awakening.
Interventions	PROTOCOL: -LABA + ICS vs SAME dose ICS OUTCOMES: -reported at 52 weeks RUN- IN PERIOD: - 4 weeks DOSE OF ICS DURING RUN IN: BUD 100bid DOSE OPTIMISATION PERIOD: -none INTERVENTION PERIOD:

-	
	52 weeks CONTROL GROUP vs TEST GROUP: -BUD400 vs BUD400+F 9 DEVICE: -Turbuhaler NUMBER OF DEVICES 2 COMPLIANCE Not reported CO-TREATMENT -None, unless exacerbation
Outcomes	INTENTION TO TREAT ANALYSIS: -Yes PULMONARY FUNCTION TEST: -change in morning PEF -change in FEV1 SYMPTOM SCORES: -not reported FUNCTIONAL STATUS: -percentage of days with symptoms -percentage of asthma awakenings - number of rescue inhalations -rate per patient per year of severe asthma exacerbations INFLAMMATORY MARKERS: -not reported ADVERSE EFFECTS: -reported WITHDRAWAL: -reported * primary outcome: time to the first severe asthma exacerbation defined as need for treatment with oral corticosteroids or hospital admission or emergency treatment for worsening asthma or a decrease in morning PEF > 25% from baseline
Notes	-Full-text publication -Funded by AstraZeneca -Confirmation of methodology and data not obtained. User-defined number: 800 (BUD 400 bid)
Allocation concealment	A – Adequate

Characteristics of included studies (*Continued*)

Study	Pauwels BUD200
Methods	DESIGN: -parallel-group -multicentre study (71 centers) - 4 groups of which 2 considered here -four groups -bud 100 + placebo bid -F12 + bud 100 bid -bud 400 + placebo bid -F12 + Bud 400 bid ALLOCATION: -Random -computer generated BLINDING: -double blind -identical placebo WITHDRAWALS/DROPOUTS: -described by group JADAD'S quality score=5 CONFIRMATION OF METHODOLOGY: Obtained
Participants	Symptomatic Asthmatic Adults %ELIGIBLE OF SCREENED POPULATION: Not reported %RUN-IN PARTICIPANTS RANDOMISED: 77% RANDOMISED: -F12 + Bud 100 bid=210 -Bud 100 bid= 213 WITHDRAWAL: -F12 + Bud 100 mcg (bid)= 62/210 (30%) -Bud 100 mcg (bid)= 82/213 (39%) AGE: mean (range) -F12 + Bud 100 (bid)= 41 (18-68) yrs -Bud 100 (bid)= 42 (18/70) yrs GENDER (%male): -F12 + Bud 100 (bid)= 50% -Bud 100 (bid)= 51% SEVERITY: -moderate BASELINE % PRED. FEV1: mean -F12 + Bud 100 (bid)= 75.7% -Bud 100 (bid)=75.5% BASELINE DOSE OF ICS : mean(range) -F12 + Bud 100 (bid) = 821 (150-2000) -Bud 100 mcg (bid)= 823 (100-2000)

Characteristics of included studies (*Continued*)

	ASTHMA DURATION: -not reported ATOPY(%): -not reported ELIGIBILITY CRITERIA: - asthma for at least six months - had been treated with an inhaled corticosteroid for at least 3 months -baseline FEV1 >= 50% predicted - >= 15% improvement following inhalation of 1mg of terbutaline EXCLUSION CRITERIA: - use of beclomethasone > 2000 ug/day or budesonide by MDI > 1600 ug/day or budesonide by turbuhaler >800 ug/day or fluticasone >800 ug/day - >= 3 courses of oral steroids in past 6 months - hospitalization for asthma in past 6 months CRITERIA FOR RANDOMISATION DURING RUN-IN: -Compliance with 75 to 125 % of the recommended dose of budesonide -Stable asthma over the preceding 10 days as defined by the absence of thefollowing criteria: diurnal variation of more than 20% in PEF on 2 consecutive days; use of 4 or more inhalations of resuce medication per day on 2 consecutive days;awakening due to asthma on 2 consecutive nights or the need to use oral glucocorticoids.
Interventions	PROTOCOL: -LABA + ICS vs SAME dose ICS OUTCOMES: 1, 2, 3, 6, 9, and 12 months of treatment RUN-IN PERIOD: - 4 weeks to document stability and compliance DOSE OF ICS DURING RUN IN: BUD 800 bid DOSE OPTIMISATION PERIOD: -none INTERVENTION PERIOD: - 12 months TEST GROUP: -budesonide 100 mcg bid + formoterol 12 mcg bid CONTROL GROUP: -budesonide 100 mcg bid + placebo DEVICE: - Turbuhaler NUMBER OF DEVICES: 2 COMPLIANCE: yes- hidden mechanical counter built into inhaler which could only be seen by investigators CO-TREATMENT -rescue short-acting beta2-agonist (terbutaline) as needed
Outcomes	INTENTION TO TREAT ANALYSIS: -yes

	OUTCOMES: -reported at 1,2,3,6,9 and 12 months PULMONARY FUNCTION TEST: -% of predicted FEV1 - change in morning and evening PEF SYMPTOM SCORES: -mean day time and night time symptom scores at end of study (4-point scale: averaged over 10 days) FUNCTIONAL STATUS: -rescue short-acting B2-agonist by day and night (number of inhalations) -nocturnal awakening (number per night) *-severe exacerbation (requiring systemic steroids) -episode free days (mean % of year) INFLAMMATORY MARKERS: not reported ADVERSE EFFECTS: reported WITHDRAWAL: -reported * primary outcome: rates of severe and mild exacerbations of asthma per patient per year
Notes	-Full-text publication -Funded by Astra Draco, Lund, Sweden - Confirmation of methodology and data obtained -User-defined order: 200 (BUD 100 bid)
Allocation concealment	A – Adequate

Study	**Pauwels BUD800**
Methods	DESIGN: -parallel-group -multicentre study (71 centers) - 4 groups of which 2 considered here -four groups -bud 100 + placebo bid -F12 + bud 100 bid -bud 400 + placebo bid -F12 + Bud 400 bid ALLOCATION: -Random -computer generated BLINDING: -double blind -identical placebo WITHDRAWALS/DROPOUTS: -described by group JADAD'S quality score=5

Characteristics of included studies (*Continued*)

	CONFIRMATION OF METHODOLOGY: Obtained
Participants	Symptomatic Asthmatic Adults %ELIGIBLE OF SCREENED POPULATION: Not reported %RUN-IN PARTICIPANTS RANDOMISED: 77% RANDOMISED: -F12 bid + Bud 400 bid=215 -Bud 400mcg bid= 214 WITHDRAWAL: -F12 bid + Bud 400 bid = 41/215 (19%) -Bud 400mcg bid= 60/214 (28%) AGE: mean (range) -F12 bid + Bud 400 bid =42 yrs (17-70) -Bud 400mcg bid= 44 (18-70) yrs GENDER (male%): - F12 bid + Bud 400 bid =48% -Bud 400mcg bid= 48% SEVERITY: -moderate BASELINE % PRED. FEV1: mean -F12 bid + Bud 400 bid = 76.3% - Bud 400mcg bid= 75.4% BASELINE DOSE OF ICS (start of run in): -F12 bid + Bud 400 bid = 856 (100-2000) -Bud 400 bid=818 (100-2000) ASTHMA DURATION: -not reported ATOPY(%): -not reported ELIGIBILITY CRITERIA: - asthma for at least six months - had been treated with an inhaled corticosteroid for at least 3 months -baseline FEV1 >= 50% predicted - >= 15% improvement following inhalation of 1mg of terbutaline EXCLUSION CRITERIA: - use of beclomethasone > 2000 ug/day or budesonide by MDI > 1600 ug/day or budesonide by turbuhaler >800 ug/day or fluticasone >800 ug/day - >= 3 courses of oral steroids in past 6 months - hospitalization for asthma in past 6 months CRITERIA FOR RANDOMISATION DURING RUN-IN: -Compliance with 75 to 125 % of the recommended dose of budesonide -Stable asthma over the preceding 10 days as defined by the absence of thefollowing criteria: diurnal variation of more than 20% in PEF on 2 consecutive days; use of 4 or more inhalations of resuce medication per day on 2 consecutive days;awakening due to asthma on 2 consecutive nights or the need to use oral glucocorticoids.

Characteristics of included studies (*Continued*)

Interventions	PROTOCOL: -LABA + ICS vs SAME dose ICS OUTCOMES: -reported at 1,2,3,6,9 and 12 months RUN-IN PERIOD: - 4 weeks to document stability and compliance DOSE OF ICS DURING RUN IN: BUD 800 bid DOSE OPTIMISATION PERIOD: -none INTERVENTION PERIOD: - 12 months TEST GROUP: -Formoterol 12 mcg bid + Budesonide 400 mcg bid CONTROL GROUP: -budesonide 400 mcg bid + placebo DEVICE: - Turbuhaler NUMBER OF DEVICES: 2 COMPLIANCE: yes- hidden mechanical counter built into inhaler which could only be seen by investigators CO-TREATMENT -rescue short-acting beta2-agonist (terbutaline) as needed
Outcomes	INTENTION TO TREAT ANALYSIS: -yes OUTCOMES: -reported at 1,2,3,6,9 and 12 months PULMONARY FUNCTION TEST: -% of predicted FEV1 - change in morning and evening PEF SYMPTOM SCORES: -mean day time and night time symptom scores at end of study (4-point scale: averaged over 10 days) FUNCTIONAL STATUS: -rescue short-acting B2-agonist by day and night (number of inhalations) -nocturnal awakening (number per night) *-severe exacerbation (requiring systemic steroids) -episode free days (mean % of year) INFLAMMATORY MARKERS: not reported ADVERSE EFFECTS: reported WITHDRAWAL: -reported

Characteristics of included studies (*Continued*)

	* primary outcome: rates of severe and mild exacerbations of asthma per patient per year
Notes	-Full-text publication -Funded by Astra Draco, Lund, Sweden - Confirmation of methodology and data obtained -User-defined order: 800 (BUD 400 bid)
Allocation concealment	A – Adequate

Study	**Price 2002**
Methods	DESIGN: -parallel-group -multicentre (72 centers in 14 countries) - 3 groups of which 2 are considered here ALLOCATION: -random -computer generated random numbers -numbered coded solutions supplied by pharmacy BLINDING: -double-blind -identical placebo WITHDRAWAL/ DROP-OUTS: -described JADAD'S quality score=5 Confirmation of methodology obtained
Participants	Symptomatic Asthmatic patients aged > 12 years %ELIGIBLE OF SCREENED POPULATION: Not reported %RUN-IN PARTICIPANTS RANDOMISED: 88% Of a total of 750 patients 87 were discontinued before randomisation ; 15 due to adverse event, 51 failed eligiblity criteria and 21 discontinued for other reasons RANDOMISED 1: 663 -F12 bid +Bud 400 bid = 332 -Bud 400 bid = 331 WITHDRAWALS: -F12 bid +Bud 400 bid = 19 (6%) -Bud 400 bid = 18 (5%) Mean AGE years(SD) -F12 bid +Bud 400 bid = 38.9(16.7) -Bud 400 bid = 37.7(16.1) GENDER: (%male) -F12 bid +Bud 400 bid = 41% -Bud 400 bid = 43%

	SEVERITY: -mild to moderate BASELINE PEF % Pred(SD): F12 bid +Bud 400 bid = 74.2(12.6) -Bud 400 bid = 73.8 (13.5) BASELINE DOSE OF ICS Mean (SD): F12bid +Bud 400 bid = 368.7(162.6) -Bud 400 bid = 348.7(90.9) ASTHMA DURATION : n (%) F12bid +Bud 400 bid < 1year =28 (8) 1-5 years =83(25) >5 years =221 (67) -Bud 400 bid = < 1year =19 (6) 1-5 years= 63(19) >5 years =223(67) ATOPY (%): -information unavailable ELIGIBILITY CRITERIA: At Baseline -Aged >12 years -asthma diagnosed > 3 months - Treated with ICS <400 mcg/day at constant dose for at least 1 month prior to entry - asthma symptoms on at least 3 days per week EXCLUSION CRITERIA: -Severe or recent unstable asthma -PEF <50% predicted -Oral corticosteroids, nebulised therapy, leukotriene antagonist or LABA within 4 weeks of study entry - upper respiratory infection, COPD CRITERIA FOR RANDOMISATION DURING RUN-IN: To randomise into part 1 - asthma symptoms on 3 of previous 7 days ->=reversibility after bronchodilator of > 12% or (% of predicted normal -diurnal variation of >20% on at least one day during run in period.
Interventions	PROTOCOL: -LABA + ICS vs SAME dose of ICS OUTCOMES: 4 weeks RUN- IN PERIOD: 2 weeks DOSE OF ICS DURING RUN IN: usual ICS DOSE OPTIMISATION PERIOD: -none

Characteristics of included studies (*Continued*)

	INTERVENTION PERIOD: 4 weeks TEST GROUP (LABA + SINGLE DOSE ICS): budesonide 400 mcgs bid + formoterol 9 mcgs bid -Budesonide 400 mcg bid DEVICE: turbuhaler NUMBER OF DEVICES: 2 COMPLIANCE: missed doses recorded by patients in diary CO-TREATMENT not allowed
Outcomes	INTENTION TO TREAT ANALYSIS: -yes PULMONARY FUNCTION TEST: -change in morning PEF -change in FEV1 SYMPTOM SCORES: -change in day and night time score FUNCTIONAL STATUS: - time to asthma control ie 3 consecutive nights with a symptom score of 0* -resuce medication use day and night (inhalations per day or night) -Daytime and nighttime symptoms -nights per week with sleep disturbance INFLAMMATORY MARKERS: -not described ADVERSE EFFECTS: -not described primary outcome measure*
Notes	-Full-text publication Supported by Astra Zeneca Confirmation of methodology and data extraction pending -User defined number: (mean ICS dose in LAB2 group in mcg/day of BDP-equivalent: 800
Allocation concealment	A – Adequate

Study	**Russell ICS750**
Methods	DESIGN: -parallel-group -multicentre (78 centres) ALLOCATION: -consecutive allocation -computer generated random numbers -numbered coded envelopes supplied by Pharmacy

	BLINDING: -double-blind -placebo-controlled -identical placebo WITHDRAWAL/ DROP-OUTS: -described JADAD'S quality score= 4 Confirmation of methodology: -confirmed
Participants	Symptomatic Asthmatic Children %ELIGIBLE OF SCREENED POPULATION: Not reported %RUN-IN PARTICIPANTS RANDOMISED: Not reported RANDOMISED: 208 patients -Salm50 + ICS=99 -Placebo + ICS=109 WITHDRAWALS: -Salm50 + ICS=22% -Placebo + ICS=16.8% AGE: mean(SD) -Salm50 + ICS=10.2(2.7) -Placebo + ICS=10.3(2.7) GENDER: (% male) -Salm50 + ICS=60 -Placebo + ICS=61 SEVERITY: -moderate BASELINE MEAN % PRED. FEV1: -Salm50 + ICS=79.5 -Placebo + ICS=74.7 BASELINE DOSE OF ICS: -Salm50 + ICS=400-2400 mcg/day (avg750mcg BDP or BUD/day) -Placebo + ICS=400-2400 mcg/day (avg 750 mcg BDP or BUD/day) ASTHMA DURATION: -Salm50 + ICS: <1 year= 5(6%) 1 to 5 years= 17(20%) >5 years= 62 (74%) -Placebo + ICS: <1 year= 1(1%) 1 to 5 years= 19 (22%) >5years= 67 (77%) ATOPY(%): -Salm50 + ICS= 77 -Placebo + ICS=

Characteristics of included studies (*Continued*)

	76 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 -had 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 - or had recorded a diurnal variation in PEF of >= 15% on at least 7 occasions during baseline period EXCLUSION CRITERIA: -received a course of oral corticosteroids -a change in prophylactic therapy during the previous 2 weeks
Interventions	PROTOCOL: -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	INTENTION TO TREAT ANALYSIS -total population used, this comprised of all subjects who received at least one puff of medication and recorded at least one day of valid diary or clinic data during the treatment period. Where a subject withdrew before completion of the study, data recorded after this withdrawal data was excluded.

	PULMONARY FUNCTION TEST: -Change in mean monring PEF percent predicted from baseline* -Change in mean evening PEF percent predicted SYMTPOM SCORES: -symptoms were recorded daily as either being present or absent, wheeze or cough during day or night FUNCTIONAL STATUS -median change form baseline in proportion symptom free days - median change from baseline in proportion symptom free nights -median change from baseline in use of relief medication by day (blisters per day) - median change from baeline in use of relief medicaion by night (blisters per night) 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)
Allocation concealment	A – Adequate

Study	**Shapiro FP1000**
Methods	DESIGN: -parallel-group -multicentre (42 centres) - 4 groups of which 2 are considered for this review ALLOCATION: -randomised -means of assignment not described BLINDING: -double-blind -placebo-controlled -identical placebo WITHDRAWAL/ DROP-OUTS: -described JADAD'S quality score= 4 Confirmation of methodology: not obtained
Participants	Asthmatic Patients over 12 years %ELIGIBLE OF SCREENED POPULATION: Not reported %RUN-IN PARTICIPANTS RANDOMISED: 72% (of 484 patients sceened 135 not eligible)

RANDOMISED:
349 total randomised
181 received placebo or salmeterol alone
168 patients randomised ot groups of interest
-Salm50 + ICS=84
-Placebo + ICS=84

WITHDRAWALS:
-Salm50 + ICS= 13 (15%)
-Placebo + ICS= 22 (26%)

AGE: mean(range)
-Salm50 + ICS=38(12-69) -Placebo + ICS=40(12-67)

GENDER: (% male)
-Salm50 + ICS=48%
-Placebo + ICS=54%

SEVERITY:
-moderate

BASELINE FEV1 MEAN (SD):
-Salm50 + ICS= 2.23 (0.63)
-Placebo + ICS=2.12 (0.54)

BASELINE DOSE OF ICS:
mcg/day
-Not reported by treatment groups
BDP 462-672mcgs/day; triamcinolone acetate 1100-1600mcgs/day; flunisolide 1250-2000 mcgs/day; FP 440mcgs/day

ASTHMA DURATION:
-Not reported

ATOPY(%):
-Not reported

ELIGIBILITY CRITERIA:
- Asthma (ATS criteria) of at least 6 months duration
-Required pharmacotherapy for at least 6 months before study and inhaled corticosteroids for at least 12 weeks before study
- 15% improvement in FEV1 post bronchodilator
- female patients negative pregnancy test, surgically sterile, postmenopausal or using birth control

EXCLUSION CRITERIA:
-history of life threatening asthma
-hypersensitivity rxn to sympathomimetic drugs or corticosteroids
-smoking in year before study or smoking history of >10pack years
-received a course of systemic corticosteroids in 6 months before study of use of any other prescription or OTC medication that could affect asthma or interact with other medications
-abnormal CXR
or EKG
-history of diabetes glaucoma, hypertension.

CRITERIA FOR RANDOMISATION DURING RUN-IN:
-unstable asthma during run in periods i.e. more than 3 nights with awakenings during 7 days before randomisation,more than 12 puffs of rescue medication/day for more than 3 days, FEV1 not within 15% of value obtained at beginning of screening

Characteristics of included studies (*Continued*)

Interventions	PROTOCOL: -LABA + ICS vs SAME dose of ICS OUTCOMES: -reported weekly weeks 1-4 and therafter 2 weekly RUN IN PERIOD: - 2 weeks DOSE OF ICS DURING RUN-IN: -Not reported DOSE OPTIMISATION PERIOD: -none INTERVENTION PERIOD: - 12 weeks TEST GROUP: (Salm 50 + ICS) -salmeterol 50 mg bid + ICS FP 350mcg bid CONTROL GROUP: (Placebo+ICS) -Placebo + FP 250 mcg bid DEVICE: -diskhaler NUMBER OF DEVICES: 1 COMPLIANCE measured with dose counter CO-TREATMENT -Albuterol as needed -No other prophylactic asthma medication permitted
Outcomes	INTENTION TO TREAT ANALYSIS -Modified ie. 13 patients form one site excluded from analysis as data did not meet study standards PULMONARY FUNCTION TEST: -mean change in morning and evening PEF -FEV1* SYMTPOM SCORES: - mean change in asthma symptom score (symptoms were rated daily on a 6 point scale) FUNCTIONAL STATUS: -mean change in rescue B2-agonists use (puffs per day) -mean change in % nights with no awakenings -mean change in % days with no asthma symptoms INFLAMMATORY MARKERS: -not described

Characteristics of included studies (*Continued*)

	ADVERSE EFFECTS: -described WITHDRAWALS: -described primary outcome measure*
Notes	Full-text publication -Funded by Glaxo Wellcome Inc -Confirmation of methodology not obtained -User-defined number: 1000(1000 mcg/day)
Allocation concealment	A – Adequate

Study	**Simons BUD150**
Methods	DESIGN: -cross-over study -single center ALLOCATION: -random -computer generated random numbers BLINDING: -double blind -use of identical placebo WITHDRAWAL/ DROP-OUTS: -described by groups and numbers and reasons stated in manuscript JADAD's Quality Score= 5 CONFIRMATION OF METHODOLOGY: obtained
Participants	Asymptomatic Children %ELIGIBLE OF SCREENED POPULATION: Not reported %RUN-IN PARTICIPANTS RANDOMISED: Not reported RANDOMISED: - 16 WITHDRAWALS: -Salm50 mcg once daily + BDP 100-200 mcg BID= 0 -BDP 100-200 mcg BID + Placebo= 2 (13%) AGE: mean (range) or mean (SD) - 13.1 +/- 1.3 yrs (12-16 yrs) GENDER: (%male) - 7 male (44%)

Characteristics of included studies (*Continued*)

	SEVERITY: -not described BASELINE % PRED. FEV1: - 93.4 +/- 12.7 BASELINE DOSE OF ICS: - 100-200 mcg BDP BID ASTHMA DURATION: 5.9 +/- 3.4 yrs ATOPY (%): -all 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, and use a Nebulizer Chronolog correctly EXCLUSION CRITERIA: -any significant medical conditions other than mild asthma, allergic rhinitis, or eczema -if they had a respiratory tract infection, or an acute asthma exacerbation within the previous month -if they had required prednisone treatment, and emergency department visit or hospitalization within 3 months -if they had ever had a 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
Interventions	PROTOCOL: -LABA + ICS vs SAME dose of ICS 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

Characteristics of included studies (*Continued*)

	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 as needed albuterol (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
Outcomes	INTENTION TO TREAT ANALYSIS: -not reported OUTCOMES measured at: day 1 and 28 PULMONARY FUNCTION TEST: -exercise challenge (max % fall in FEV1 from pre-exercise baseline) SYMPTOM SCORES: measured but not reported FUNCTIONAL STATUS: -rescue beta2-agonist measured but not reported -exacerbations requiring systemic steroids INFLAMMATORY MARKERS: not reported ADVERSE EFFECTS: reported (headache) WITHDRAWALS: -described PRIMARY OUTCOME: not reported
Notes	-Full-text publication -Funded by Glaxo Wellcome -Confirmation of data and methodology obtained -User defined number: 300 (1/2 with BDP 100 bid; 1/2 with BDP 200 bid)
Allocation concealment	A – Adequate

Study	**Tal BUD400**
Methods	DESIGN: -parallel study -multi-center 48 centers in 7 countries ALLOCATION: -random -computer generated random numbers BLINDING: -double blind -use of identical placebo WITHDRAWAL/

	DROP-OUTS: -described by groups and numbers and reasons stated in manuscript JADAD's Quality Score= 5 CONFIRMATION OF METHODOLOGY: obtained
Participants	Asymptomatic children %ELIGIBLE OF SCREENED POPULATION: Not reported %RUN-IN PARTICIPANTS RANDOMISED: Not reported RANDOMISED: - 286 WITHDRAWALS: -F12 mcg bid + BDP 200 mcg BID= 9 (6%) -BDP 200 mcg BID + Placebo= 9 (7%) AGE: mean (range) or mean (SD) -F12 mcg bid + BDP 200mcg BID= 11(4-17) -BDP 200 mcg BID + Placebo= 11 (5-17) GENDER: (%male) -F12 mcg bid + BDP 200 mcg BID= 61% -BDP 200 mcg BID + Placebo= 63% SEVERITY: -mild BASELINE % PRED. FEV1: -F12 mcg bid + BDP 200 mcg BID= 74(40-114) -BDP 200 mcg BID + Placebo= 76(40-100) BASELINE DOSE OF ICS: -F12 mcg bid + BDP 200 mcg BID= 547(400-1500) -BDP 200 mcg BID + Placebo= 548(400-2000) ASTHMA DURATION: F12 mcg bid + BDP 200 mcg BID= 6.5(0-15) -BDP 200 mcg BID + Placebo=7.1(1-17 ATOPY (%): -not reported ELIGIBILITY CRITERIA: - 4-17rs old, asthma diagnosed minimum 6 months - FEVI 40-90%predicted and >15% reversibility in FEV1 within 15 mins of bronchodilator -Constant dose ICS for prior 6 weeks(>400mcg budesonide turbuhaler, >600mcg Budesonide via MDI, >375 mcg fluticasone proprionate or > 600mcg CFC beclomethasone diproprionate

Characteristics of included studies (*Continued*)

	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 stufy 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	PROTOCOL: -LABA + ICS vs SAME dose of ICS 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: 1 COMPLIANCE: Not reported CO-TREATMENT: Inhaled salbutanol or terbutaline as required -if subjects had allergic rhinitis, they were permitted to use nasal corticosteroids -treatment with other asthma medication not permitted
Outcomes	INTENTION TO TREAT ANALYSIS: - yes OUTCOMES measured at: 4,8 and 12 weeks PULMONARY FUNCTION TEST: - Change in morning* and evening PEF (L/min) -Change in % pred FEV1 in subgroup N=81 SYMPTOM SCORES: daily and nocturnal on 4 point scale FUNCTIONAL STATUS: -rescue beta2-agonist measured inhalations per 24 hours -mean night time awakening % - % symptom free days

Characteristics of included studies (*Continued*)

	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
Allocation concealment	A – Adequate

Study	**Verberne 1998**
Methods	DESIGN: -parallel group -multicentre (9 centres) - 3 groups of which 2 are considered in this review ALLOCATION: -random -computer generated random numbers -telephone notification of assignment by coordinating centre BLINDING: -double-blind -identical placebo WITHDRAWAL/ DROP-OUTS: -described JADAD'S quality score=5 Confirmation of methodology: obtained
Participants	Asthmatic Children %ELIGIBLE OF SCREENED POPULATION: Not reported %RUN-IN PARTICIPANTS RANDOMISED: Not reported RANDOMISED: - 117 patients -BDP400 + Salm=60 -BDP400=57 WITHDRAWALS: -BDP400 + Salm= 5 (8%) -BDP400= 4 (7%)

AGE: mean (SD)
-BDP400 + Salm=10.8(2.5) yrs
-BDP400=11.1 (2.7) yrs

GENDER: (% male)
-BDP400 + Salm=66%
-BDP400=63%

SEVERITY:
-mild

BASELINE % PRED.FEV1:
-BDP400 + Salm= 89.7
-BDP400= 86.5

BASELINE DOSE OF ICS (SD):
-BDP400 + Salm=490(154)
-BDP400=488
(149)

ASTHMA DURATION:
means(SD)
-BDP400 + Salm=7.8(3.5) yrs
-BDP400=8.5 (3.1) yrs

ATOPY(%):
-BDP400 + Salm=88%
-BDP400=88%

ELIGIBILITY CRITERIA:
-FEV1 between 55 and 90% predicted or a FEV1/FVC ratio of 50 to 75%
->=10% improvement in FEV1 after inhalation of salbutamol
-airway hyper-responsiveness to methacholine (PD20)
-ability to reproduce lung function test
-history of stable asthma for >= 1 month without exacerbation or respiratory tract infection
-use of inhaled steroids between 200 and 800 mg/day for at least 3 months prior to the beginning of the study

EXCLUSION CRITERIA:
Operations for congenital heart disease, oesophageal atresia, congenital or acquired anatomical malformation of the lungs or airways, dyskinetic cilia syndrome
-bronchiectasis
-bronchopulmonary dysplasia
-diabetes
-renal disease
-other serious conditions which may influence the possibility of continuation of the study
-were using oral corticosteroids continuously or inhaled corticosteroids at a dose of more than 800 mcg daily
-were using B-blocking agents or had used cromoglycate or nedocromil sodium within the previous 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

Characteristics of included studies (*Continued*)

	CRITERIA FOR RANODOMISATION DURING RUN IN: No additonal criteria
Interventions	PROTOCOL: -LABA + ICS vs SAME 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 INTERVENTION PERIOD: 54 weeks DOSE OPTIMISATION PERIOD: -none TEST GROUP: (Salm50 + BDP200) -Salmeterol 50 mcg bid and Beclomethasone 200 mcg bid CONTROL GROUP: (BDP 200 + placebo) -Beclomethasone 200 mcg bid + placebo DEVICE: -rotadisks in combination with a diskhaler NUMBER OF DEVICES: 2 COMPLIANCE: Not reported CO-TREATMENT -salbutamol 200 mg rotadisk
Outcomes	INTENTION TO TREAT ANALYSIS: -modified(when patients failed to complete their daily record cards for more than 7 days in any 14 day period such assessments were not included in the analysis). PULMONARY FUNCTION TEST: -Mean change in FEV1 -Mean change in Morning and evening 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 - % children reporting no symptoms FUNCTIONAL STATUS: -mean number of addtional rescue B2-agonist inhalations per day -exacerbation (requiring systemic steroids) -height, body weight, heart rate, systolic and diastolic blood pressure were measured

	INFLAMMATORY MARKERS: mean (SD) -Total IgE ADVERSE EFFECTS: -reported WITHDRAWALS: -reported *primary outcome: airway caliber measured as FEV1 and airway responsiveness to methacholine
Notes	-Full-text publication -Funded by Glaxo Wellcome -Confirmation of methodology and data obtained -User-defined number: 400
Allocation concealment	A – Adequate

Study	**Wallin FP800**
Methods	DESIGN: -parallel group - 3 groups of which 2 are considered for this review ALLOCATION: -randomised BLINDING: -double-blind WITHDRAWAL/ DROP-OUTS: - described JADAD's Quality Score=3 CONFIRMATION OF METHODOLOGY: Not obtained
Participants	Asthmatic Adults %ELIGIBLE OF SCREENED POPULATION: Not reported %RUN-IN PARTICIPANTS RANDOMISED: Not reported RANDOMISED: 37 - FP 200 bid + Sal 50 bid=18 -FP 200 bid=19 WITHDRAWALS: FP 200 bid + Sal 50 bid=4 (22%) -FP 200 bid=3 (16%) AGE: mean (SE)

	FP 200 bid + Sal 50 bid=43 (16) -FP 200 bid= 42(12) GENDER: (% male) -FP 200 bid + Sal 50 bid= (61%) -FP 200 bid= (42%) SEVERITY: -not stated BASELINE FEV1 % PRED (SE): -FP 200 bid + Sal 50 bid= 80(16) -FP 200 bid= 91 (20) BASELINE DOSE OF ICS bdp equiv:(SD) -fP 200 bid + Sal 50 bid= 600-1200 -FP 200 bid=800-1200 ASTHMA DURATION months (SE): -FP 200 bid + Sal 50 bid= 202 (140) -FP 200 bid= 206(130) ATOPY(%): - FP 200 + Sal 50bid= 66% -FP 200bid=57% ELIGIBILITY CRITERIA: -Free of respiratory tract infection for 4 weeks before study CRITERIA FOR RANDOMISATION DURING RUN-IN: - despite use of BUD/BDP 800-1200mcg/day or FP 400-500mcg/day patients were included if they had: - One or more of the following symptoms: symptoms on 6 or more days, symptoms on 4 or more nights, need for rescue bronchodilator on 6 or more nights,greater than 20% variation between AM and PM PEF on four or more days - One or more of the following pulmonary function criteria: At least 15% improvement in FEV1 after bronchodilator, 15% increase in PEF post bronchodilator compared to mean PEF on previous week, more than 20% variation between AM and PM PEF on at least 4 consecutive days, PC20 methacholine <4mg/ml EXCLUSION CRITERIA: none specified
Interventions	PROTOCOL: -LABA + ICS vs SAME dose of ICS OUTCOMES: -before and after 12 weeks treatment RUN-IN PERIOD: - 2-4 weeks DOSE OF ICS DURING RUN-IN:(mean) 876

Characteristics of included studies (*Continued*)

	DOSE OPTIMSIATION PERIOD: -none INTERVENTION PERIOD: - 12 weeks TEST GROUP: (FP200+ Sal 50 bid) -Fluticasone proprionate 200 mcg bid+ Salmeterol 50 mcg bid CONTROL GROUP: (FP200 bid) -Fluticasone proprionate 200 mcg bid DEVICE: -Diskhaler (dry powder inhaler) NUMBER OF DEVICES: Not reported COMPLIANCE: Not reported CO-TREATMENT -rescue short-acting beta2-agonist (Salbutamol) as needed via diskhaler or MDI
Outcomes	INTENTION TO TREAT ANALYSIS: -No PULMONARY FUNCTION TEST: -% of predicted monring and evening PEF -FEV1 litres before and after each treatment SYMPTOM SCORES: -none FUNCTIONAL STATUS: -measured but not reported INFLAMMATORY MARKERS: -submucosal mast cells -submucosal eosinophils -adhesion molecules and cytokines ADVERSE EFFECTS: - not reported by group WITHDRAWALS -reported
Notes	Full-text publication -Funded by Glaxo Wellcome -Confirmation of methodology and data not obtained -User-defined number: 800 (FP 200 bid)

Allocation concealment	B – Unclear

Study	**Zetterstrom BUD4001d**
Methods	DESIGN: -parallel-group -multicenter in 59 clinical centers in 6 countries - 3 groups comparing LABA/ICS single inhaler combination , separate inhalers for LABA and ICS and ICS alone - 2 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. ALLOCATION: -Randomised -Method of randomisation: computer generated random numbers -Means of assignment: opaque consecutive numbered envelopes containing assignment BLINDING: -double-blind -use of identical placebo (double dummy) WITHDRAWAL/DROP-OUTS: -described by groups JADAD'S quality score= 5 Confirmation of methodology: not obtained
Participants	Symptomatic Asthmatic patients aged >= 18 years %ELIGIBLE OF SCREENED POPULATION: Not reported %RUN-IN PARTICIPANTS RANDOMISED: 89% RANDOMISED: 247 -F 6 bid +Bud 200 bid = 123 -Bud 200 bid = 124 WITHDRAWALS: -F 4.5 bid +Bud 160 bid = 16% -Bud 200 bid = 13% Mean AGE years(range) -F 6 bid +Bud 200 bid = 46.7(18-78) -Bud 200 bid = 48.5(21-78) GENDER: (%male) -F 6 bid +Bud 200 bid = 53% -Bud 200 bid = 50% SEVERITY: -moderate BASELINE FEV1 (% Pred):

	F 6 bid +Bud 200 bid = 73.6 -Bud 200 bid = 73.1 BASELINE DOSE OF ICS: F 6 bid +Bud 200 bid = 971 -Bud 200 bid = 936 ASTHMA DURATION (years): F 6bid +Bud 200 bid = 19.1 -Bud 200 bid =17.1 ATOPY (%): -information unavailable ELIGIBILITY CRITERIA: -Aged >= 18 - Treated with ICS >= 500 mcg/day for at least 1 month prior to entry - FEV1 between 50-90 % of pred normal ->=15% reversibility after bronchodilator EXCLUSION CRITERIA: - Systemic corticosteroids within 30 days of study entry -smoking history <= 10 years - respiratory infection, seasonal asthma, severe cardiovascular disorder beta blocker therapy -pregnant or failure to use accpetable contraceptives in women of childbearing potential
Interventions	PROTOCOL: -LABA + ICS (COMBINATION INHALER) vs SAME dose of ICS OUTCOMES: measured at 4 weekly intervals RUN -IN PERIOD: 2 weeks DOSE OF ICS DURING RUN-IN: Usual ICS DOSE OPTIMISATION PERIOD: -none INTERVENTION PERIOD: 12 weeks TEST GROUP (LABA + SINGLE DOSE ICS COMBINATION INHALER): budesonide 200mcgs bid + formoterol 6 mcgs bid CONTROL GROUP -Budesonide 200 mcg bid DEVICE: turbuhaler NUMBER OF DEVICES: 1 COMPLIANCE: Not reported CO-TREATMENT

	not reported
Outcomes	INTENTION TO TREAT ANALYSIS: -yes PULMONARY FUNCTION TEST: -change in morning* and evening PEF -Change in FEV1 SYMPTOM SCORES: -Change from baseline in total sdathma symptom score (day time and night time score graded 1-3 1 mild ;2 moderate ;3 severe) FUNCTIONAL STATUS: -Change in rescue medication use (inhalations per day) - Change in % reliever use free days -Change in % nightime awakenings -Change in % symptom free days - Change in asthma control days INFLAMMATORY MARKERS: -not described ADVERSE EFFECTS: No medication related side effect WITHDRAWALS: described Primary outcome measure*
Notes	-Full-text publication Supported by Astra Zeneca Confirmation of methodology and data extraction not obtained -User defined number: (mean ICS dose in LAB2 group in mcg/day of BDP-equivalent: 400
Allocation concealment	A – Adequate

Study	**Zetterstrom BUD4002d**
Methods	DESIGN: -parallel-group -multicenter in 59 clinical centers in 6 countries - 3 groups comparing LABA/ICS single inhaler combination , separate inhalers for LABA and ICS and ICS alone - 2 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. ALLOCATION: -Randomised -Method of randomisation: computer generated random numbers -Means of assignment: opaque consecutive numbered envelopes containing assignment

Characteristics of included studies (*Continued*)

	BLINDING: -double-blind -use of identical placebo (double dummy) WITHDRAWAL/DROP-OUTS: -described by groups JADAD'S quality score= 5 Confirmation of methodology: not obtained
Participants	Symptomatic Asthmatic patients aged >= 18 years %ELIGIBLE OF SCREENED POPULATION: Not reported %RUN-IN PARTICIPANTS RANDOMISED: 89% RANDOMISED: 239 -F6 bid +Bud 200 bid = 123 -Bud 200 bid = 124 WITHDRAWALS: -F 6 bid +Bud 200 bid = 17 (15%) -Bud 200 bid = 16 (13%) Mean AGE years(range) -F 6 bid +Bud 200 bid = 44.7(18-77) -Bud 200 bid = 48.5(21-78) GENDER: (%male) -F 6 bid +Bud 200 bid = 58% -Bud 200 bid = 50% SEVERITY: -moderate BASELINE FEV1 (% Pred): F 6 bid +Bud 200 bid = 74.7 -Bud 200 bid = 73.1 BASELINE DOSE OF ICS: F 6 bid +Bud 200 bid = 973 -Bud 200 bid = 936 ASTHMA DURATION (years): F 6bid +Bud 200 bid = 16.9 -Bud 200 bid =17.1 ATOPY (%): -information unavailable ELIGIBILITY CRITERIA: -Aged >= 18 - Treated with ICS >= 500 mcg/day for at least 1 month prior to entry - FEV1 between 50-90 % of pred normal ->=15% reversibility after bronchodilator

	EXCLUSION CRITERIA: - Systemic corticosteroids within 30 days of study entry -smoking history <= 10 years - respiratory infection, seasonal asthma, severe cardiovascular disorder beta blocker therapy -pregnant or failure to use accpetable contraceptives in women of childbearing potential
Interventions	PROTOCOL: -LABA + ICS IN SEPARATE INHALERES vs SAME dose of ICS OUTCOMES: measured at 4 weekly intervals RUN -IN PERIOD: 2 weeks DOSE OF ICS DURING RUN-IN: Usual ICS DOSE OPTIMISATION PERIOD: -none INTERVENTION PERIOD: 12 weeks TEST GROUP (LABA + SINGLE DOSE ICS SEPARATE INHALERS): budesonide 200mcgs bid + formoterol 6 mcgs bid CONTROL GROUP: -Budesonide 200 mcg bid DEVICE: turbuhaler NUMBER OF DEVICES: 2 COMPLIANCE: Not reported CO-TREATMENT not reported
Outcomes	INTENTION TO TREAT ANALYSIS: -yes PULMONARY FUNCTION TEST: -change in morning* and evening PEF -Change in FEV1 SYMPTOM SCORES: -Change from baseline in total sdathma symptom score (day time and night time score graded 1-3 1 mild ;2 moderate ;3 severe) FUNCTIONAL STATUS: -Change in rescue medication use (inhalations per day) - Change in % reliever use free days -Change in % nightime awakenings -Change in % symptom free days - Change in asthma control days INFLAMMATORY MARKERS: -not described

Characteristics of included studies (*Continued*)

	ADVERSE EFFECTS: No medication related side effect WITHDRAWALS: described Primary outcome measure*
Notes	-Full-text publication Supported by Astra Zeneca Confirmation of methodology and data extraction not obtained -User defined number: (mean ICS dose in LAB2 group in mcg/day of BDP-equivalent: 400
Allocation concealment	A – Adequate

Study	**Zimmerman ICS450F12**
Methods	DESIGN: -parallel-group -multicenter in 27 clinical centers in Canada - 3 groups comparing LABA/ICS with 2 doses of LABA and ICS alone - 2 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. ALLOCATION: -Randomised -Method of randomisation: not stated -Means of assignment: not stated BLINDING: -double-blind -use of placebo WITHDRAWAL/DROP-OUTS: -described by groups JADAD'S quality score= 4 Confirmation of methodology: not obtained
Participants	Children aged >= 6-11 years %ELIGIBLE OF SCREENED POPULATION: Not reported %RUN-IN PARTICIPANTS RANDOMISED: 68% RANDOMISED: 196 -F12 bid +Usual ICS bid = 95 -Usual ICS bid = 101

	WITHDRAWALS: -F 12 bid +Usual ICS = 7 (7%) -Usual ICS bid = 16 (16%) Mean AGE years(range) -F 12 bid +Usual ICS bid = 9(6-11) -Usual ICS bid = 9(6-11) GENDER: (%male) -F 12 bid +Usual ICS bid = 61% -Usual ICS bid = 64% SEVERITY: -moderate BASELINE FEV1 (% Pred): F 12 bid +Usual ICS bid = 77.5 -Usual ICS bid = 77.2 BASELINE DOSE OF ICS: F 12 bid +Usual ICS bid =422 -Usual ICS bid = 464 ASTHMA DURATION (years): F 6bid +Usual ICS bid = 5.6 -Usual ICS bid =5.8 ATOPY (%): -information unavailable ELIGIBILITY CRITERIA: -Aged >=12-11 -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 % of pred normal ->=15% reversibility after bronchodilator - asthma symptoms suggestive that additional therapy might be needed -Able to use peak flow meter and turbuhaler, answer questions form the Pediatric Asthma Quality of Life Questionnaire and parent or guardian had to complete a daily diary card EXCLUSION CRITERIA: - Systemic corticosteroids or anit-leukotrieneswithin 30 days of study entry, astemizole within 120 days , sodium cromoglycate or ketotifen within 7 days, salmeterolor 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 repectively prior to study entry. -smoking history RANDOMISATION CRITERIA FOLLOWING RUN-IN: -post-bronchodilator reversibility of at least 12 % of the prebronchodilator value or at least 9% of predicted normal or diurnal varialbility or at least 15% on any 5 of the last 10 days of run-in. - 75-124% compliance with prescribed dose as assessed by diary card -symptoms during the last 10 days of run-in (defined as having one or more of the following: four or more inhalations of rescue medication; daytime symptoms on 4 or more days, or night time awakening on 1 or more nights)
Interventions	PROTOCOL: -LABA + Usual ICS vs 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 LABA + 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 disallowed except for immunotherapy and nasal steroids if dose not altered during study
Outcomes	INTENTION TO TREAT ANALYSIS: -not reported PULMONARY FUNCTION TEST: -change in morning* and evening PEF -Change in FEV1 Note: Mean value during treatment for 12 weeks reported rather than value at endpoint SYMPTOM SCORES: -Change from baseline in total asthma symptom score FUNCTIONAL STATUS: -Change in rescue medication use (inhalations per day) - Pedistric asthma qualtiy of life score (based on questionnaire) 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
Allocation concealment	A – Adequate

Study	**Zimmerman ICS450F6**
Methods	DESIGN: -parallel-group -multicenter in 27 clinical centers in Canada - 3 groups comparing LABA/ICS with 2 doses of LABA and ICS alone - 2 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. ALLOCATION: -Randomised -Method of randomisation: not stated -Means of assignment: not stated BLINDING: -double-blind -use of placebo WITHDRAWAL/DROP-OUTS: -described by groups JADAD'S quality score= 4 Confirmation of methodology: not obtained
Participants	Children aged >= 6-11 years %ELIGIBLE OF SCREENED POPULATION: Not reported %RUN-IN PARTICIPANTS RANDOMISED: 68% RANDOMISED: 207 -F6 bid +Usual ICS bid = 106 -Usual ICS bid = 101 WITHDRAWALS: -F 6 bid +Usual ICS = 7 (7%) -Usual ICS bid = 16 (16%) Mean AGE years(range) -F 6 bid +Usual ICS bid = 8(6-11) -Usual ICS bid = 9(6-11) GENDER: (%male) -F 6 bid +Usual ICS bid = 61% -Usual ICS bid = 64%

	SEVERITY: -moderate BASELINE FEV1 (% Pred): F 6 bid +Usual ICS bid = 78.3 -Usual ICS bid = 77.2 BASELINE DOSE OF ICS: F 6 bid +Usual ICS bid =450 -Usual ICS bid = 464 ASTHMA DURATION (years): F 6bid +Usual ICS bid = 5.4 -Usual ICS bid =5.8 ATOPY (%): -information unavailable ELIGIBILITY CRITERIA: -Aged >=6-11 -Clinical diagnosis of asthma according to ATS criteria for at least 6 months - Treated with ICS for at least 3 month prior to entry - FEV1 between 50-90 % of pred normal ->=15% reversibility after bronchodilator - asthma symptoms suggestive that additional therapy might be needed -Able to use peak flow meter and turbuhaler, answer questions form the Pediatric Asthma Quality of Life Questionnaire and parent or guardian had to complete a daily diary card EXCLUSION CRITERIA: - Systemic corticosteroids or anit-leukotrieneswithin 30 days of study entry, astemizole within 60 days , sodium cromoglycate or ketotifen within 7 days, salmeterolor 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 repectively prior to study entry. -smoking history RANDOMISATION CRITERIA FOLLOWING RUN-IN: -post-bronchodilator reversibility of at least 12 % of the prebronchodilator value or at least 9% of predicted normal or diurnal varialbility or at least 15% on any 5 of the last 10 days of run-in. - 75-124% compliance with prescribed dose as assessed by diary card -symptoms during the last 10 days of run-in (defined as having one or more of the following: four or more inhalations of rescue medication; daytime symptoms on 4 or more days, or night time awakening on 1 or more nights)
Interventions	PROTOCOL: -LABA + Usual ICS vs 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

Characteristics of included studies (*Continued*)

	INTERVENTION PERIOD: 12 weeks TEST GROUP LABA + Usual DOSE ICS formoterol 6 mcgs bid CONTROL GROUP: -Usual dose ICS + placebo bid DEVICE: turbuhaler NUMBER OF DEVICES: 2 COMPLIANCE: measured during run-in CO-TREATMENT disallowed except for immunotherapy and nasal steroids if dose not altered during study
Outcomes	INTENTION TO TREAT ANALYSIS: -not reported PULMONARY FUNCTION TEST: -change in morning* and evening PEF -Change in FEV1 Note: Mean value during treatment for 12 weeks reported rather than value at endpoint SYMPTOM SCORES: -Change from baseline in total asthma symptom score FUNCTIONAL STATUS: -Change in rescue medication use (inhalations per day) - Pedistric asthma qualtiy of life score (based on questionnaire) 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: 456
Allocation concealment	A – Adequate

Study	**van der Molen ICSNR**
Methods	DESIGN: -parallel-group -multicenter trial

	ALLOCATION: -Random: computer generated random numbers BLINDING: -triple-blind -placebo-controlled WITHDRAWAL/ DROPOUTS -described JADAD'S quality score=5 CONFIRMATION OF METHODOLOGY: Obtained
Participants	Asthmatic Adults %ELIGIBLE OF SCREENED POPULATION: Not reported %RUN-IN PARTICIPANTS RANDOMISED: Not reported RANDOMISED: 239 total randomised -ICS + F 48 (bid) = 125 -ICS = 114 WITHDRAWALS: -ICS + F 48 (bid) = 18, 14 % -ICS = 13, 11% AGE: mean 42.8 -ICS + F 48 (bid) = 40.5 -ICS = 45.4 GENDER: (% male) -ICS + F 48 (bid) = 48.8 -ICS = 49.2 SEVERITY: -moderate BASELINE FEV1 MEAN (SD): Mean 67.1% -ICS + F 48 (bid) = 68 -ICS = 66 BASELINE DOSE OF ICS: mean (range) -ICS +F48 <= 400mcg=23 401-800=28 801-1600=51 >=1600mcg =20 -ICS <= 400mcg=22 401-800=19

	801-1600=48 >=1600mcg =48 ASTHMA DURATION: mean - 20.6 years ATOPY(%): - ICS +F48 (bid) =68.8 -ICS =66.6 ELIGIBILITY CRITERIA: - Asthma according to the definition of the ATS -regular use of any dose of inhaled corticosteroids -use of >= 5 inhalations of short acting beta 2 agonist/week before entry visit ->15% reversibility in baseline FEV1 after 2 inhalations of terbutaline or equivalent EXCLUSION CRITERIA: -use of oral steroids at any time in the last month -smoking history of >20 pack years -FEV1 <40% predicted -exacerbation of asthma symptoms in the last month -use of cromoglycate, thephylline or anticholinergics CRITERIA FOR RANDOMISATION DURING RUN IN: No additional criteria
Interventions	PROTOCOL: -LABA + ICS vs SAME dose of ICS OUTCOMES: -reported at 4, 12 and 24 weeks RUN IN PERIOD: - 4 weeks DOSE OF ICS DURING RUN IN: usual dose of ICS WASH OUT PERIOD: - 4 weeks DOSE OPTIMISATION PERIOD: -none INTERVENTION PERIOD: - 24 weeks TEST GROUP: -Formoterol 24 mcg bid -usual dose of ICS 400-1600/d (mean: 980 /day) CONTROL GROUP: -placebo - usual dose of ICS (400-1600/d) (mean: 1030/day)

	DEVICE: -Turbohaler NUMBER OF DEVICES: 2 COMPLIANCE Not reported CO-TREATMENT -rescue short-acting beta2-agonist (terbutaline turbuhaler) as needed. - cromoglycate, theophylline and anticholinergic drugs were not permitted. - The dose of inhaled corticosteroids remained constant thromcghout
Outcomes	INTENTION TO TREAT ANALYSIS: -not described PULMONARY FUNCTION TEST: -Mean change in FEV1 -Mean change in morning and evening PEF SYMPTOM SCORES: -Change in sypmtom score (score 0 to 3) FUNCTIONAL STATUS: -blood pressure and pulse rate were measured -change in mean daytime and nighttime use of rescue B2-agonist -asthma exacerbations (number of courses of oral prednisolone) INFLAMMATORY MARKERS: -not reported ADVERSE EFFECTS: -reported WITHDRAWALS: -described *primary outcome: total asthma symptom score and morning PEF
Notes	-Full- text publication -Funded by Astra Draco -Confirmation of methodology and data extraction: obtained -User-defined number: 980 -Methodology and data extraction pending -User-defined number:
Allocation concealment	A – Adequate

Characteristics of excluded studies

Study	Reason for exclusion
Aalbers 2003 a	Not an RCT
Aalbers 2003 b	Not an RCT

Aalbers 2003 c	Not an RCT
Aalbers 2004	No group with inhaled corticosteroids alone.
Adinoff 1998	No consistent use of inhaled corticosteroids in either the intervention or control groups - Co-intervention with other non-steroidal anti-asthmatic drugs not stable during the intervention period.
Alonso 2001	Control intervention not inhaled glucocorticoids alone.
Ankerst 2001	No consistent co-intervention with ICS. Duplicate references.
Ankerst 2003	No group with inhaled corticosteroids alone
Anonymous 2003	No group with inhaled corticosteroids alone.
Arvidsson-P 1991	No group with inhaled corticosteroids alone.
Aubier 1999	The treatment and intervention groups compared the same classes of medications either in combination or with different delivery devices.
Aziz 1999 c	Not an RCT
Aziz 1998	Duration of intervention < 30 days.
Aziz 1999 a	Intervention duration <30 days.
Aziz 1999 b	outcome measure did not reflect asthma control.
Aziz 2000	Duration of intervention < 30 days.
Bacci 2002	No consistent co-intervention with ICS.
Baker 1998	Duplicate references.
Baki 1998	No consistent intervention with ICS.
Baraniuk 1999	Compared LABA and ICS to increase dose of ICS.
Bateman 1998	The treatment and intervention groups compared the same classes of medications either in combination or with different delivery devices.
Bateman 2000	The treatment and intervention groups compared the same classes of medications either in combination or with different delivery devices. Duplicate references.
Bateman 2001 a	Both the treatment and intervention groups compared ICS and LAB2 agonists, using different delivery devices. (Tx and intervention compared ICS + LAB2 in 2 different devices - combination)
Bateman 2001 b	Duplicate references.
Bateman 2001 c	Not an RCT
Bateman 2001 d	Not an RCT
Bateman a 2003	Increased dose of ICS in control group
Bateman b 2003	Control not ICS alone
Becker 1999	Duplicate references (Jenkins).
Behling	Duration < 30 days.
Bensch 2002	Not an RCT
Berger 2001	Duplicate references.
Berggren 2001	Intervention not regular but prn inhaled long-acting beta2-agonists. PM LABA vs PM SAB. Duplicate references.
Bergmann 2004	Compared LABA and ICS to increase dose of ICS.
Bernstein 2002	Not an RCT
Bessmertny 2002	Intervention not LAB2 agonists.
Bijl-Hofland 2001	No consistent co-treatment with ICS.

Bjermer 2000	Control not inhaled glucocorticoids alone but montelukast LABA not compared to ICS alone.
Bjermer 2002	Duplicate references.
Bjermer 2003	No group with ICS alone
Bloom 2003	Compared LABA and ICS to increased dose ICS
Boonsawat 2003	Outcome measures not asthma control.
Booth-H 1993	No consistent co-intervention with ICS.
Boskovska 2001	Not an RCT
Boulet 2003	Increased dose of ICS in control group
Bouros 1999	Increased dose of ICS in control group
Brambilla 1994	Control intervention not ICS but rather slow-release oral bela2-agonists.
Brambilla 2003	Duration of intervention < 30 days
Braniuk 1999	Not an RCT
Brenner-M 1988	Intervention not regular inhaled long-acting beta2-agonists. Control intervention not ICS alone.
Britton 1992	No group with inhaled corticosteroids alone (control is regular SAB2). No consistent intervention with inhaled glucocorticoids in all subjects.
Britton 1998	The treatment and intervention groups compared the same classes of medications either in combination or with different delivery devices. Duplicate references.
Brogden-RN 1991	Not an RCT
Buchvald F	No group with inhaled corticosteroids alone
Busse 1999	No group with inhaled corticosteroids alone (control is LTRA). No consistent intervention with inhaled glucocorticoids in all subjects.
Busse 2003 part 1	Increased dose of ICS in control group
Busse 2003 part 2	Increased dose of ICS in control group
Byrnes 2000	No group with inhaled corticosteroids alone (Control is LAB2 at a different dose and SAB2 as maintenance Tx).
Calhoun 2001	No group with inhaled corticosteroids alone. (Control intervention is anti-leukotrienes) Duplicate references.
Calverley 2002	Subjects not asthmatics.
Castle	Not an RCT
Cazzola 2000	Patients not asthmatics.
Chan 2001	Intervention not regular inhaled long-acting beta2-agonists. Control intervention not ICS alone (but oral predniosone) Seting - Acute asthma ED Duplicate references.
Chapman 1999	Tx and Intervention compared LAB2 and ICS but in combined vs concurrent devices.
Cheer 2003	Duplicate references.
Chuchalin 2001	Duplicate references.
Cloosterman 2001	No consistent co-intervention with ICS. No group with inhaled corticosteroids alone. (Control is regular short-acting beta2-antagonist)
Condemi 1999	Increased dose of ICS in control group
Condemi 2001	No group with inhaled corticosteroids alone. (Control is another LAB2) Duplicate references.

Cook 2001	Duplicate references.
Crompton 1999	No group with inhaled corticosteroids alone. (Control is oral bambuterol)
Currie 2002	Control is increased dose of ICS
Currie 2003 a	Duration of intervention <30 days. Co-intervention with non permitted Rx.
Currie 2003 b	Co intervention with non permitted treatment. Duration of intervention < 30 days.
Currie 2003 c	Duration < 1month.
D'Alonzo 1994	No consistent co-intervention with ICS - approximately 1/4 of participants were taking regular inhaled corticosteroids at baseline. Control intervention was a short-acting beta2 agonist.
Dahl 1989	Intervention not inhaled LAB2.
Dahl 1991	No consistent co- treatment with ICS.
Dal Negro 2001 a	Not an RCT
Dal Negro 2001 b	The treatment and intervention groups compared the same medications either in combination or with different delivery devices.
Dal Negro 2002 a	Not an RCT
Dal Negro 2002 b	Cotrl not ICS alone
Davis 2001	Not an RCT
Del Rio-Navarro2001a	Outcome measures do not reflect asthma control (but rather serum potassium, CPK-MB, and ECG).
Del-Rio-Navarro2001b	Outcome measures do not reflect asthma control (but rather saliva flow and IgA).
Dempsey 2000 a	Control intervention not inhaled glucocorticoids alone. No consistent intervention with inhaled glucocorticoids in all subjects.
Dempsey 2000 b	Not an RCT
Dente 2001 a	Duplicate references.
Dente 2001 b	Not an RCT
Dicpinigaitis 2002	Intervention not regular inhaled long-acting beta2 agonist.
Didier 1997	Control intervention is not ICS: this is a randomised, open, parallel-group, multicentre study comparing salmeterol with an oral bronchodilator, terbutaline.
Djordjevic 1999	Not an RCT
Dorinsky 2001 a	Not an RCT
Dorinsky 2001 b	Duplicate references.
Eliraz 2001	Both the treatment and control group compared ICS with LAB2 with different inhaler devices.
Eliraz 2002 a	Not an RCT
Eliraz 2002 b	Not an RCT
Ericsson 2001 a	Duplicate references.
Ericsson2001 b	Not an RCT
Everden 2002	The treatment and intervention groups compared the same medications either in combination or with different delivery devices.
Faurschou 1996	Control intervention not ICS alone (but regular SAB2).
Faurschou-P 1994	Duration of intervention < 30 days. Intervention not regular inhaled long-acting beta2-agonists.
Fish 2000	Duplicate references.
Fish 2001	Control intervention not ICS (but rather anti-leukotrienes).
Fitzpatrick 1990	Duration of intervention < 30 days: The treatment period was only 2 weeks.

	No consistent intervention with ICS in all patients: 19/20 participants were taking regular ICS and 6 were taking oral steroids at baseline. Both treatment groups received different doses of long-acting beta2-agonists.
Fowler 2002	Increased dose of ICS in control group
Fuglsang-G 1995	Duration < 30 days.
Gabrijelcic 2004	Outcomes not related to asthma control.
Giannini 1996	Duration < 30 days.
Giannini 1998 a	Duration < 30 days. Duplicate references.
Giannini 1998 b	Duration < 30 days.
Giannini 1999	Duration < 30 days.
Giannini 2000	Duration < 30 days. Intervention is not LAB2 but 1 dose of salbutamol. Control intervention is not ICS alone (but placebo).
Giannini 2001	Duration of intervention < 30 days.
Giannini 2002 a	No consistent intervention with inhaled glucocorticoids in all subjects.
Giannini D 2002 b	Not an RCT
Gizycki 2000	No consistent intervention with inhaled glucocorticoids in all subjects. Duplicate references.
Gold 2001	Control intervention not inhaled glucocorticoids alone.
Green 2002	No consistent intervention with inhaled glucocorticoids in all subjects.
Greening 1994	Increased dose of ICS in control group
Grosclaude 2003	No group with inhaled corticosteroids alone.
Grzelewska-Rzymowska	No treatment with LABA.
Gustafsson 1994	Tx and intervention compared ICS + LAB2 combination therapy using 2 different devices.
Hasani 2003	No consistent intervention with inhaled glucocorticoids in all subjects.
Haughney 2002	Not an RCT
Heuck 1999	Not an RCT
Heuck 2000	Increased dose of ICS in control group
Hyland-ME 1995	Not an RCT
Ind 2002 a	No ICS alone.
Ind 2002 b	No ICS alone.
Ind 2003 b	Increased dose of ICS in control group
Isabelle 2001	Not an RCT
Jeffery 2002	No group with inhaled corticosteroids alone. Intervention not regular inhaled long-acting beta2-agonists.
Jenkins 1995	No group with inhaled corticosteroids alone. (LAB2 delivered with new propellant HFA134a)
Jenkins 2000 a	Increased dose of ICS in control group
Jenkins 2000 b	Not an RCT
Jenkins 2002 a	The treatment and intervention groups compared the same medications either in combination or with different delivery devices.
Jenkins 2002 b	The treatment and intervention groups compared the same medications either in combination or with different delivery devices.
Johansson 2001	Increased dose of ICS in control group

Jones 1994	No consistent intervention with ICS - < 1/3 of participants were taking regular ICS at entry.
Juniper	No consistent co-intervention with ICS - 80% were taking regular ICS at entry. No subgroup analyses available.
Juniper 1999	Duplicate of Pauwel's study (NEJM 1997;337:1405-11).
Kaik 2002	No ICS alone
Kalberg 1998	Increased dose of ICS in control group
Kalra 1996	Duration < 30 days.
Kardos 2001	Tx and intervention compared ICS + LAB2 in a fixed vs flexible schedule.
Kelsen 1999	Increased dose of ICS in control group
Kerwin 2001	Duplicate references.
Ketchell 2002	Duration < 30 days.
Kidney 1995	No consistent intervention with inhaled glucocorticoids in all subjects.
Kips 2000	Increased dose of ICS in control group
Kirby 2000	Subjects not asthmatics.
Knobil 2000	Control intervention not inhaled glucocorticoids alone.
Knorr 2001	Intervention is not LAB2 (but rather an anti-leukotriene agent: Montelukast).
Kraft 2003	No consistent co-treatment with ICS
LHSRG 2000	Subjects not asthmatics (but rather have COPD).
LaForce 1994	Not an RCT
Lai 1995	Control intervention was not ICS alone but regular short-acting beta2-agonists instead of placebo. Duration < 30 days. (2 weeks) Co-intervention with non-permitted drugs: oral steroids.
Lalloo 2000	Duplicate references.
Lalloo 2001 a	Duplicate references.
Lalloo 2001 b	Duplicate references.
Lalloo 2001 c	Not an RCT
Lalloo 2003	Increased dose of ICS in control group
Lange 2001	Not an RCT.
Lazarus 2001	No consistent co-intervention with ICS - intervention is monotherapy with LAB2.
Lee 2003	Duration of control period less than 4 weeks.
Lemanske 2001	Complicated protocol. No data provided for comparison groups of interest. No consistent intervention with inhaled glucocorticoids in all subjects.
Lenney 1995	Not an RCT
Leuppi 2003	No consistent co-treatment with ICS.
Li 1999	Increased dose of ICS in control group
Lindqvist	No consistent co-treatment with ICS.
Lindqvist 2003	No consistent co-treatment with ICS.
Lipworth 1996	Not an RCT
Lipworth 1998	Duration < 30 days.
Lipworth 1999 a	Duration < 30 days.
Lipworth 1999 b	Duration < 30 days.

Lipworth 2000 a	Duration < 30 days.
Lipworth 2000 b	Duration < 30 days.
Lipworth ????	Not an RCT
Lockey 1999	No consistent co-treatment with ICS.
Lowhagen 2002	Intervention not regular inhaled long-acting beta2-agonists.
Lundback 2000	Duplicate references.
Lundback 2001	Duplicate references.
Lundback 2002	No group with ICS alone
Lyseng-Williamson 20	Outcomes not related to asthma control -pharmacoeconomic review
Lötvall 2002	The treatment and intervention groups compared the same medications either in combination or with different delivery devices.
Magadle 2001	Duration < 30 days. Duplicate references.
Malmqvist-Granlund 2	Not an RCT
Malolepszy 2001	Outcome of LABA in acute asthma rather than asthma control.
Malolepszy 2002	Cotrol intervention not ICS (but oral theophylline). Duplicate references.
Martin 2003	No ICS alone group
Martinat 2003	No group with inhaled corticosteroids alone.
Matz May 2001	Duplicate publication of 2 RCTS, namely that of Condemi JJ (Ann Allergy Asthma Immunol 1999;82:383-9) and of Kalberg CJ (J Allergy Clin Immunol 1998;101 (Suppl):S6.
McCarthy 2000	Control intervention not inhaled glucocorticoids alone.
McCarthy 2001 a	Not an RCT
McCarthy 2001 b	Not an RCT
McCarthy 2002	Not an RCT
McCarthy 2003	No ICS alone group
Mcivor 1998	No consistent co-treatment with a stable dose of ICS (tapering).
Michel 2000	Compared LABA with increased doses of ICS rather than the same dose. Intervention duration <30 days.
Midgren-B 1992	No group with inhaled corticosteroids alone.
Mitchell 2000	Duration < 30 days. Duplicate references.
Mitchell 2003	Control group had increased dose of ICS
Murray 1998	No consistent intervention with inhaled glucocorticoids in all subjects. Duplicate references.
Murray 1999	Increased dose of ICS in control group
Nathan	Not an RCT
Nathan 1995	No consistent co-intervention with ICS in all patients: Only 1/4 of participants were taking regular ICS at entry. The usual dose of inhaled corticosteroids taken by participants was not stated in the manuscript. The control intervention was not ICS but a short-acting beta2-agonist.
Nathan 1999 a	Not an RCT
Nathan1999 b	Not an RCT

Nelson 1999	Not an RCT
Nelson 2000 a	Control intervention is not ICS alone (but rather ICS with an anti-leukotriene agent (montelukast)).
Nelson 2000 b	Not an RCT
Nelson 2000 c	Duplicate references.
Nelson 2001 b	Control intervention [1]ICS alone (but LTRA- zafirlukast).
Nelson 2001a	Control intervention [1]ICS alone (but LTRA- zafirlukast).
Newnham-DM 1995	No consistent co-treatment with ICS.
Nielsen 1999	Not an RCT
Nightingale 2002	Treatment and intervention groups compared the same medications either in combination or with different delivery devices.
Nsouli 2001	No group with inhaled corticosteroids alone. Duplicate references.
O'Brian 2001	Duration < 30 days.
Odeback 1998	Duplicate references.
Olsson 2002	Comparison of adjustable maintenance treatment with LABA +ICS rather than ICS alone
Ortega-Cisnero 1998	Increased dose of ICS in control group
Overbeck 2003	Patients were steroid naive
Ozkaya 1999	Not an RCT
Palmer 1992	No group with inhaled corticosteroids alone. (Treatment groups received different doses of long-acting beta2-antagonists.
Palmqvist 2001	Both the treament and control groups compared ICS and LAB2 with different drugs and inhaler devices (concurrent vs combined therapy)
Paterson 1999	Treatment and intervention groups compared the same medications either in combination or with different delivery devices.
Pauwels 1997c	Not an RCT
Pauwels 1998 a	DUPLICATE REPORT - This study is a review of the FACET study which is already included in this analysis (Pauwels 1997).
Pauwels 1998 b	Intervention not LAB2 but another ICS.
Pearlman	Not an RCT
Pearlman 1992	No consistent co-intervention with ICS - < 1/2 the participants were taking regular inhaled corticosteroids at entry. No group with inhaled corticosteroids alone. (Control was short-acting beta2-agonists).
Pearlman 1994	No consistent co-treatment with ICS 26 %.
Pearlman 2002	No group with inhaled corticosteroids alone. (Control is anti-leukotriene - montelukast - as maintenance) Duplicate references.
Pearlman1999same 200	Not an RCT
Pearlman1999same 500	Not an RCT
Peters 2000	No group with inhaled corticosteroids alone. (Control is oral steroids, SAB2 and anicholnergics) In Hospital setting.
Pieters 1999 b	Duplicate references.
Pieters 2001	Duplicate references.
Pinnas 1998	No consistent intervention with inhaled glucocorticoids in all subjects. Duplicate references.
Pizzichini 1996	Duration < 30 days. Outcomes measures did not reflect athsma control.

Price 2003	No ICS alone
Pujet 1995	Intervention is not LAB2 (but theophylline).
Pyke 2001	Comparison of LABA and ICS in separate versus combination devices. No ICS alone. Duplicate references.
Rance 2002	Abstract.
Rickard 1999	Outcomes measures did not reflect asthma control.
Rickard 2001	Control intervention not inhaled glucocorticoids alone.
Rijssenbeek-Nouwens	Intervention is not LAB2 (but anti-allegic casing)
Ringbaek 1996	No group with inhaled corticosteroids alone. (Control is oral SAB2 as maintenance)
Ringdal 1997	Not an RCT
Ringdal 2000	Duplicate references.
Ringdal 2001	Not an RCT
Ringdal 2002	Abstract.
Ringdal 2003	Control intervention no inhaled glucocorticoids alone. Outcomes measures did not reflect asthma control.
Rocca-Serra 2002	Intervention not regular long acting beta2 agonists. Duration < 30 days.
Rooklin 2001	Not an RCT
Rosenhall 2001 a	Duplicate references.
Rosenhall 2001 b	Duplicate references.
Rosenhall 2001 c	Duplicate references.
Rosenhall 2002	Treatment and intervention groups compared the same medications either in combination or with different delivery devices. Abstract.
Rosenhall 2003	Treatment and intervention groups compared the same medications either in combination or with different delivery devices.
Rosenhall 56	Not an RCT
Rosenthal 1999	No consistent co-intervention with ICS. Control intervention not ICS alone but SAB2 on demand.
Sahn 2002	Duplicate references.
Schreurs 1996	No consistent co-intervention with ICS. 90 % used regular ICS at entry. Control intervention not inhaled glucocorticoids alone (but a different dose of LAB2)
Sears 2003	Not an RCT
Serrier 2003	Treatment and intervention groups compared the same medications either in combination or with different delivery devices. Abstract. Duplicate references.
Shapiro 2001	Intervention is not LAB2.
Sheth 2002	Outcomes measures did not reflect asthma control.
Shrewsbury 2002	Duplicate references.
Sienra-Monge 2001	The treatment and intervention groups compared the same medications either in combination or with different delivery devices.
Simons 1997 b	No consistent co-intervention with inhaled corticosteroids. Treatment groups compared ICS to long-acting beta2-agonist alone.

Sims 2003	Duration < 30 days.
Staehr 1995	Control intervention not ICS (but SAB2 maintenance).
Stahl 2003	No regular LABA rather prn LABA vs SABA.
Stallberg 2003	No group with inhaled glucocorticoids alone.
Stanford 2002	Outcomes measures did not reflect asthma control.
Stankovic 2000	Not an RCT
Stelmach 2001	Duplicate references. No consistent intervention with inhaled glucocorticoids in all subjects.
Stelmach 2002 a	No co-intervention with ICS. Duplicate references.
Stelmach 2002 b	No co-intervention with ICS.
Stojkovic-Andjelkovi	Not an RCT
Stoloff 2002	Not an RCT.
TLHSRG 2000	Not an RCT
Tan 1997	Outcomes measures did not reflect asthma control.
Tattersfield 1999	Intervention is not daily LAB2 (but rather on-demand LAB2).
Tattersfield 2001	Not an RCT
Tolley 2002	Not an RCT
Tonelli 2001	No consistent intervention with inhaled glucocorticoids in all subjects.
Trautmann 2001	Not an RCT
Turner 1998	No consistent co-intervention with ICS alone. Intervention duration <30 days.
Ullman 1990	Duration < 30 days.
Van Der Woude 2004	No consistent intervention with ICS alone.
Van Noord 1999	Increased dose of ICS in control group
Van Noord 2001	Tx and intervention compared ICS + LAB2 in 2 different combination devices.
Van Schayck 2002	Duplicate references.
Van den Berg 2000	No consistent co-intervention with LAB2-both groups received LAB2 but compared delivery devices. Duplicate references.
Van der Woude 2004	No ICS alone
Vastagh 2003	No LABA.
Verberne 1997	No consistent co-intervention with ICS - approximatley 20% were taking regular ICS at entry.
Vermetten 1999	Not an RCT
Vestbo 2000	Patients are not asthmatics (but rather have COPD).
Vickers 2000	The intervention is not LAB2 but placebo No consistent co-intervention with ICS Ongoing study - protocol only published.
Vilsvik 2001	Intervention duration <30 days.
Virchow 2002	Duplicate references.
Von Berg 1989	Duration < 30 days.
Von Berg 2003	No concurrent ICS.
Wallaert 1999	No group with inhaled corticosteroids alone. (Control is another LAB2)
Wallin 1990	No group with inhaled corticosteroids alone. (Control is regular SAB2) No consistent intervention with inhaled glucocorticoids in all subjects.

Characteristics of excluded studies (*Continued*)

	Outcomes measures did not reflect asthma control.
Wallin 1998	Not an RCT
Wallin 1999	No consistent co-treatment with ICS.
Weinberger 2004	No LABA.
Weinstein 2001	Not an RCT
Weinstein July 1998	No consistent co-inervention with ICS -only 57% were on ICS.
Wempe-JB 1992	No consistent co-treatment with ICS.
White 2001	Duplicate references.
Wilcke 1998	Duration < 30 days.
Wilding 1997	Not an RCT
Wilson 1999	Duplicate references.
Wilson 2000	Duplicate references.
Wilson 2001 a	Control intervention is not ICS alone (but rather ICS with an anti-leukotriene agent - Montelukast).
Wilson 2001 b	Not an RCT
Wong 1992	Duration < 30 days.
Woolcock 1995	Not an RCT
Woolcock 1996 s 50	Increased dose of ICS in control group
Woolcock 1996 s100	Increased dose of ICS in control group
Yates 1995	No consistent co-treatment with ICS. Duration < 30 days.
Yates 1996	Duration < 30 days. Outcomes measures did not reflect asthma control.
Youngchaiyud 1995	Intervention not LAB2 (but theophylline)
Yurdakul 2002	Control not regular long-acting beta2-agonists alone. Outcomes measures did not reflect asthma control.
Zarkovic 1998	No consistent co-intervention with ICS. No group with inhaled corticosteroids alone. (Control is placebo)
van der Woude 2001	Duplicate references. The treatment and intervention groups compared the same medications either in combination or with different delivery devices.

ADDITIONAL TABLES

Table 01. Metagression of LABA vs RR of exacerbations

Variable	Coefficient	Standard Error	Z	P	95% CI of coeff (LL)	95% CI of coeff (UL)	Variable coding
LABA	0.244	0.099	2.5	0.013	0.051	0.437	0=Formoterol; 1= Salmeterol
Constant	-0.313	0.075	-4.2	0.000	-0.459	-0.167	

Table 02. Metagression of % predicted FEV1 vs RR of exacerbations

Variable	Coefficient	Standard Error	Z	P	95% CI of coeff (LL)	95% CI of coeff (UL)	Variable coding
FEV1	-0.015	0.008	-2.02	0.043	-0.030	-0.0005	0=FEV1 >=80% of predicted; continuous variable (% predicted FEV1 based on reference values)
Constant	0.925	0.577	1.60	0.109	-0.205	2.06	

Table 03. Metagression ICS dose vs RR of exacerbations

Variable	Coefficient	Standard Error	Z	P	95% CI of coeff (LL)	95% CI of coeff (UL)	Variable coding
Dose of ICS	0.114	0.058	2.0	0.049	0.0006	0.22705	0= ICS dose <400 mcg/day; 1=ICS dose 400-800 mcg/day; 2= ICS dose>800 mcg/day
Constant	-0.306	0.081	-3.75	0.000	-0.465	-0.146	

Table 04. Metagression of LABA vs RR of exacerbations

Variable	Coefficient	Standard Error	Z	P	95% CI of coeff (LL)	95% CI of coeff (UL)	Variable coding
LABA	0.244	0.099	2.5	0.013	0.051	0.437	0=Formoterol; 1= Salmeterol
LABA	0.244	0.099	2.5	0.013	0.051	0.437	0=Formoterol; 1= Salmeterol
Constant	-0.313	0.075	-4.2	0.000	-0.459	-0.167	
Constant	-0.313	0.075	-4.2	0.000	-0.459	-0.167	

ANALYSES

Comparison 01. Long-acting beta2 vs placebo: both groups receiving similar dose ICS

Outcome title	No. of studies	No. of participants	Statistical method	Effect size
01 # patients with exacerbations requiring systemic steroids	17	4027	Relative Risk (Fixed) 95% CI	0.81 [0.73, 0.90]
02 # patients with exacerbations requiring hospitalisation	11	4162	Relative Risk (Fixed) 95% CI	0.81 [0.50, 1.33]
03 FEV1 (L) at endpoint	6	914	Weighted Mean Difference (Fixed) 95% CI	0.15 [0.07, 0.22]
04 Change in FEV1 at endpoint (L) stratifying on baseline FEV1	9	1847	Weighted Mean Difference (Random) 95% CI	0.17 [0.11, 0.24]

05 Change in FEV1 at endpoint (% predicted) stratifying on baseline FEV1	4	1428	Weighted Mean Difference (Fixed) 95% CI	2.79 [1.89, 3.69]
06 FEV1 % predicted at endpoint	3	881	Weighted Mean Difference (Fixed) 95% CI	5.93 [3.74, 8.11]
07 Change in FEV1 (L or % pred)stratifying on trial duration	17	3926	Standardised Mean Difference (Random) 95% CI	0.35 [0.28, 0.42]
08 Morning PEF (L/min) at endpoint	6	1156	Weighted Mean Difference (Random) 95% CI	22.62 [4.34, 40.90]
09 Change in morning PEF (L/min) at endpoint stratifying on baseline FEV1	17	4885	Weighted Mean Difference (Random) 95% CI	23.28 [18.38, 28.18]
10 Evening PEF (L/min) at endpoint			Weighted Mean Difference (Fixed) 95% CI	Totals not selected
11 Change in evening PEF (L/min) at endpoint	9	2230	Weighted Mean Difference (Random) 95% CI	21.33 [14.53, 28.12]
12 Change in PEF variability at endpoint			Weighted Mean Difference (Fixed) 95% CI	Totals not selected
13 Change in daytime symptom score at endpoint	5	1371	Standardised Mean Difference (Fixed) 95% CI	-0.34 [-0.44, -0.23]
14 Change in nighttime symptom score at endpoint	2	922	Standardised Mean Difference (Fixed) 95% CI	-0.18 [-0.31, -0.05]
15 Change in 24 hour symptom score at endpoint	2	362	Weighted Mean Difference (Fixed) 95% CI	-0.28 [-0.45, -0.11]
16 % symptom-free days	4	1678	Standardised Mean Difference (Random) 95% CI	0.32 [0.02, 0.62]
17 Change in % symptom-free days at endpoint	6	1317	Weighted Mean Difference (Random) 95% CI	17.21 [12.06, 22.36]
18 % symptom-free nights at 12 +/- 4 weeks			Weighted Mean Difference (Fixed) 95% CI	Totals not selected
19 Change in % symptom-free nights at endpoint	4	1052	Standardised Mean Difference (Random) 95% CI	0.51 [0.28, 0.74]
20 Change in Asthma Control days % @ 12 +/- 4 weeks	2	362	Weighted Mean Difference (Fixed) 95% CI	15.61 [8.51, 22.70]
21 # daytime rescue inhalations (puffs per day) at endpoint	2	277	Weighted Mean Difference (Random) 95% CI	-0.73 [-1.24, -0.22]
22 Change in # daytime rescue inhalations (puffs per day) at endpoint	9	3003	Weighted Mean Difference (Random) 95% CI	-0.82 [-1.17, -0.47]
23 # nighttime rescue inhalations (puffs per night) at endpoint	2	546	Weighted Mean Difference (Random) 95% CI	-0.44 [-0.81, -0.07]
24 Change in # nighttime rescue inhalations at endpoint	6	2051	Weighted Mean Difference (Random) 95% CI	-0.33 [-0.57, -0.10]
25 Change in # overall daily rescue inhalations at endpoint	8	2745	Weighted Mean Difference (Random) 95% CI	-0.81 [-1.17, -0.44]
26 Change in mean % rescue free days at 12 +/- 4 weeks	2	362	Weighted Mean Difference (Fixed) 95% CI	19.10 [12.19, 26.01]
27 Change in % nights with no awakening at 12 +/- 4 weeks	2	334	Weighted Mean Difference (Fixed) 95% CI	3.24 [-0.89, 7.38]
28 % nights with awakening	2	913	Weighted Mean Difference (Fixed) 95% CI	-1.37 [-2.75, 0.02]

29 Change in night time awakening (number of nights) at endpoint	3	648	Weighted Mean Difference (Fixed) 95% CI	-0.22 [-2.24, 1.81]
30 Change in quality of life (AQLQ score) at endpoint	2	1169	Weighted Mean Difference (Random) 95% CI	0.33 [0.05, 0.60]
31 Total # withdrawals	26	6571	Relative Risk (Fixed) 95% CI	0.87 [0.77, 0.97]
32 # withdrawals due to poor asthma control or exacerbation	23	5409	Relative Risk (Fixed) 95% CI	0.50 [0.36, 0.70]
33 # withdrawals due to adverse events	23	5892	Relative Risk (Fixed) 95% CI	1.29 [0.96, 1.75]
34 # withdrawals due to serious non-respiratory event			Relative Risk (Random) 95% CI	Totals not selected
35 Total # adverse events	12	2393	Relative Risk (Fixed) 95% CI	0.98 [0.92, 1.05]
36 Serious adverse event including respiratory	4	886	Relative Risk (Fixed) 95% CI	1.16 [0.30, 4.42]
37 # patients with headache	14	3221	Relative Risk (Fixed) 95% CI	1.13 [0.92, 1.41]
38 # patients with hoarseness	3	544	Relative Risk (Random) 95% CI	0.71 [0.16, 3.18]
39 # patients with oral thrush	6	828	Relative Risk (Fixed) 95% CI	1.04 [0.35, 3.06]
40 # patients with tremor	10	2419	Relative Risk (Random) 95% CI	2.48 [0.78, 7.89]
41 # patients with tachycardia or palpitations	11	2580	Relative Risk (Fixed) 95% CI	2.13 [0.77, 5.88]
42 # patients with adverse cardiovascular events	4	792	Relative Risk (Fixed) 95% CI	0.90 [0.32, 2.54]
43 Change in height (cm) as SD scores at 24 +/- 4 weeks			Weighted Mean Difference (Fixed) 95% CI	Totals not selected
44 PC20 Methacholine-adjusted odds ratio increase from baseline			Weighted Mean Difference (Random) 95% CI	Totals not selected
45 ACTH induced cortisol <18microg/dl at endpoint			Relative Risk (Fixed) 95% CI	Totals not selected
46 Am cortisol < 5 microg/dl at endpoint			Relative Risk (Fixed) 95% CI	Totals not selected
47 Deaths			Relative Risk (Fixed) 95% CI	Totals not selected
48 Change in # of symptom-free nights at endpoint			Weighted Mean Difference (Fixed) 95% CI	Totals not selected
49 # Worsening asthma			Relative Risk (Fixed) 95% CI	Totals not selected
50 Change in % PC 20 at endpoint	1	39	Weighted Mean Difference (Fixed) 95% CI	0.30 [-0.68, 1.28]

Comparison 02. Additional comparisons for same dose

Outcome title	No. of studies	No. of participants	Statistical method	Effect size
01 # patients with exacerbations requiring oral steroids by FEV1 % predicted at baseline	17	4027	Relative Risk (Fixed) 95% CI	0.81 [0.73, 0.90]
02 # patients with exacerbations requiring oral steroids children versus adults	17	4027	Relative Risk (Fixed) 95% CI	0.81 [0.73, 0.90]
03 # patients with exacerbations requiring oral steroids by dose of ICS in both groups	17	4027	Relative Risk (Fixed) 95% CI	0.81 [0.73, 0.90]

04 # patients with exacerbations requiring oral steroids by combination inhaler or separate inhaler for LABA	17	4027	Relative Risk (Fixed) 95% CI	0.81 [0.73, 0.90]
05 # patients with exacerbations requiring oral steroids by whether LABA dose is usual or higher than usual	17	4027	Relative Risk (Fixed) 95% CI	0.81 [0.73, 0.90]
06 # patients with exacerbations requiring oral steroids by type of LABA	17	4027	Relative Risk (Fixed) 95% CI	0.81 [0.73, 0.90]
07 # patients with exacerbations requiring oral steroids by trial duration	17	4027	Relative Risk (Fixed) 95% CI	0.81 [0.73, 0.90]
08 # patients with exacerbations requiring oral steroids study unsupported by pharmaceutical industry excluded	17	4027	Relative Risk (Fixed) 95% CI	0.81 [0.73, 0.90]
09 # patients with exacerbations requiring oral steroids with studies with Jadad score < 4 excluded	14	3855	Relative Risk (Fixed) 95% CI	0.81 [0.73, 0.90]
10 Change in FEV1 at endpoint (L or % predicted) stratifying by adult or pediatric study	13	3275	Standardised Mean Difference (Random) 95% CI	0.37 [0.26, 0.48]
11 Change in FEV1 at endpoint (L or % predicted) stratifying by type of LABA used.	13	3275	Standardised Mean Difference (Random) 95% CI	0.37 [0.26, 0.48]

INDEX TERMS

Medical Subject Headings (MeSH)

Administration, Inhalation; Adrenal Cortex Hormones [*therapeutic use]; Adrenergic beta-Agonists [*therapeutic use]; Anti-Asthmatic Agents [*therapeutic use]; Asthma [*drug therapy]; Chronic Disease; Randomized Controlled Trials

MeSH check words

Adult; Child; Humans

COVER SHEET

Title

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

Authors

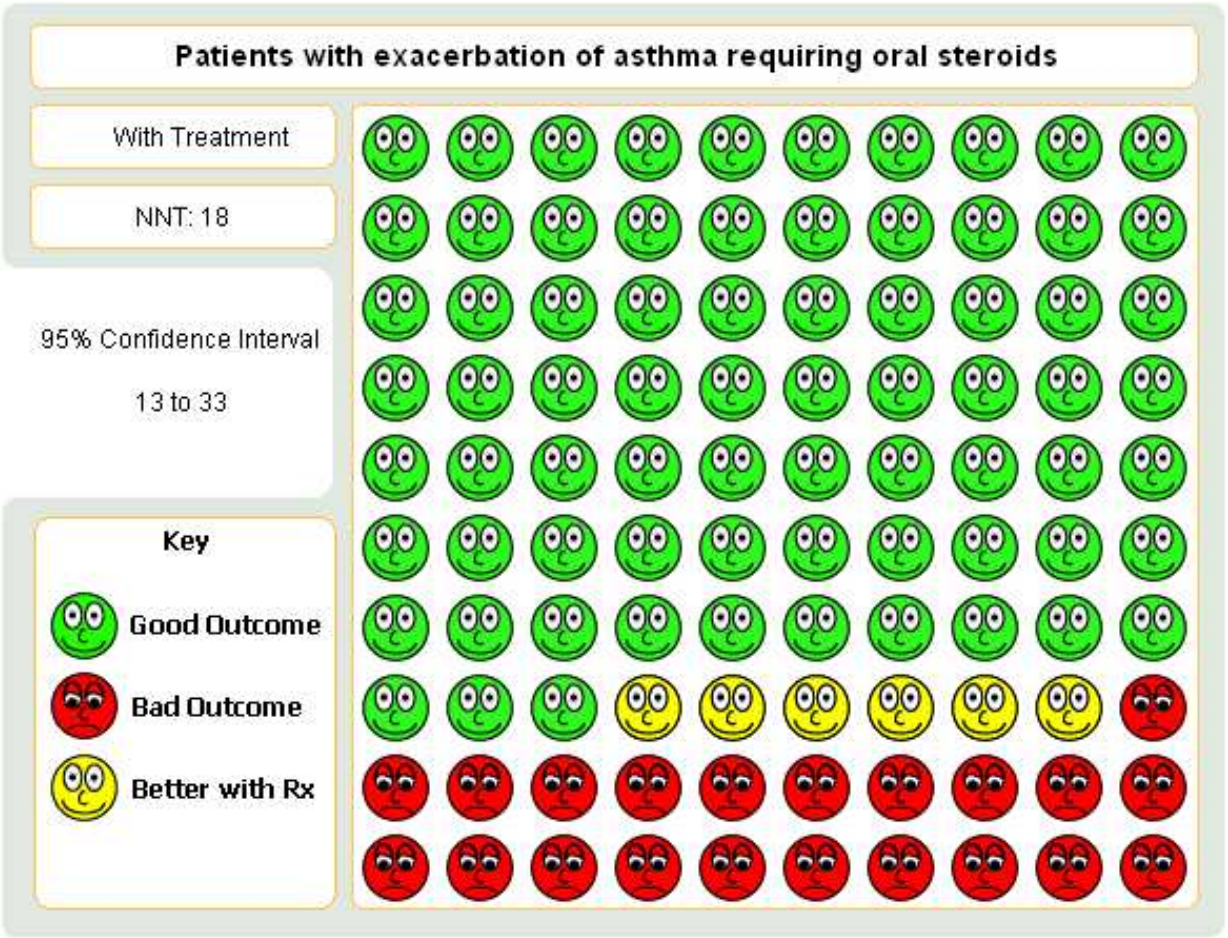
Ni Chroinin M, Greenstone IR, Danish A, Magdolinos H, Masse V, Zhang X, Ducharme FM

Contribution of author(s)

Muireann Ni Chroinin reviewed the literature searches from 2002-2004, identified and reviewed the full-text publication of all citations of potential or potentially eligible RCTs, extracted the methodology and data, entered the description of studies and data entry in RevMan, analysed and interpreted results of the meta-analysis and wrote the final review.
Dr Ilana Greestone conceived the protocol, requested the literature search, identified and reviewed the full-text publication of all citations of potential or potentially eligibible RCTs

	from 1999-2001, drafted the correspondance to authors and/or the pharmaceutical companies to solicit their collaboration in this review and to identify other possibly relevant trials, participated in extraction of the methodology and data, entering the description of studies and data entry in RevMan, interpreted results of the meta-analysis and approved the final review. Three research assistants participated in some aspects of the review. Helen Magdalinos (May-July 2001), Alya Danish (November 2001-March 2002), Vincent Masse (June-August 2004) participated in the entry of data, references, characteristics of included and excluded studies, and revision of the table of comparisons. Xu Zhang performed and assisted in the interpretation of the meta-regression. Francine Ducharme supervised Muireann Ni Chroinin, Ilana Greenstone and the research assistants. She revised the protocol, supervised the literature search, created the methodology and data extraction forms, reviewed all full-text publications for relevance, participated in the selection of trials, methodology assessment, and data extraction, corresponded with authors and/or the pharmaceutical companies to identify other possibly relevant trials, verify methodology and data extraction and request additional information, supervised the analysis, interpretation, and writing up of the review.
Issue protocol first published	2000/1
Review first published	2005/4
Date of most recent amendment	12 July 2005
Date of most recent SUBSTANTIVE amendment	24 June 2005
What's New	Information not supplied by author
Date new studies sought but none found	Information not supplied by author
Date new studies found but not yet included/excluded	Information not supplied by author
Date new studies found and included/excluded	01 April 2004
Date authors' conclusions section amended	Information not supplied by author
Contact address	Dr Muireann Ni Chroinin Consultant in Paediatrics and Respiratory Medicine Paediatrics Norfolk and Norwich University Hospital Norfolk and Norwich University Hospital NHS Trust Colney Lane Norwich NR4 7UY UK E-mail: muireann.nichroinin@nnuh.nhs.uk
DOI	10.1002/14651858.CD005535
Cochrane Library number	CD005535
Editorial group	Cochrane Airways Group
Editorial group code	HM-AIRWAYS

Figure 01. In one hundred patients given LABA as well as ICS, there would be six patients who avoid an exacerbation giving a number needed to treat (NNT) of 18.



Analysis 01.01. Comparison 01 Long-acting beta2 vs placebo: both groups receiving similar dose ICS, Outcome 01 # patients with exacerbations requiring systemic steroids

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

Comparison: 01 Long-acting beta2 vs placebo: both groups receiving similar dose ICS

Outcome: 01 # patients with exacerbations requiring systemic steroids

Study	LABA + ICS n/N	ICS alone n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
01 Mean baseline FEV 1 >/= 80% of predicted					
Langton Hewer ICS400	3/11	3/12		0.5	1.09 [0.28, 4.32]
Li ICS400	2/13	1/16		0.2	2.46 [0.25, 24.21]
O'Byrne BUD200	58/323	81/322		14.6	0.71 [0.53, 0.96]
O'Byrne BUD400	39/315	61/312		11.1	0.63 [0.44, 0.92]
Simons BUD150	0/16	1/16		0.3	0.33 [0.01, 7.62]
Verberne 1998	10/60	10/57		1.9	0.95 [0.43, 2.11]
Wallin FP800	1/18	5/19		0.9	0.21 [0.03, 1.64]
Subtotal (95% CI)	756	754		29.4	0.70 [0.56, 0.86]
Total events: 113 (LABA + ICS), 162 (ICS alone)					
Test for heterogeneity chi-square=3.96 df=6 p=0.68 I^2 =0.0%					
Test for overall effect z=3.27 p=0.001					
02 Mean baseline FEV1 61-79% of predicted					
× Akpinarli ICS600	0/16	0/16		0.0	Not estimable
Boyd ICS1675	19/55	15/64		2.5	1.47 [0.83, 2.61]
Fitzgerald ICS730	3/89	6/91		1.1	0.51 [0.13, 1.98]
Kemp ICSNR	53/252	59/254		10.6	0.91 [0.65, 1.26]
Norhaya ICS890	1/30	3/30		0.5	0.33 [0.04, 3.03]
Pauwels BUD200	62/210	82/213		14.7	0.77 [0.59, 1.00]
Pauwels BUD800	41/215	60/214		10.9	0.68 [0.48, 0.96]
Russell ICS750	16/99	18/99		3.2	0.89 [0.48, 1.64]
van der Molen ICSNR	33/125	32/114		6.0	0.94 [0.62, 1.42]
Subtotal (95% CI)	1091	1095		49.6	0.83 [0.72, 0.97]
Total events: 228 (LABA + ICS), 275 (ICS alone)					
Test for heterogeneity chi-square=7.25 df=7 p=0.40 I^2 =3.4%					
Test for overall effect z=2.38 p=0.02					
03 Mean baseline FEV 1 not reported					
Ind 2003	111/171	113/160		21.1	0.92 [0.79, 1.07]
Subtotal (95% CI)	171	160		21.1	0.92 [0.79, 1.07]

(*Continued . . .*)

(. . . *Continued*)

Study	LABA + ICS n/N	ICS alone n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
Total events: 111 (LABA + ICS), 113 (ICS alone)					
Test for heterogeneity: not applicable					
Test for overall effect z=1.11 p=0.3					
Total (95% CI)	2018	2009		100.0	0.81 [0.73, 0.90]
Total events: 452 (LABA + ICS), 550 (ICS alone)					
Test for heterogeneity chi-square=15.75 df=15 p=0.40 I^2 =4.8%					
Test for overall effect z=4.05 p=0.00005					

Analysis 01.02. Comparison 01 Long-acting beta2 vs placebo: both groups receiving similar dose ICS, Outcome 02 # patients with exacerbations requiring hospitalisation

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

Comparison: 01 Long-acting beta2 vs placebo: both groups receiving similar dose ICS

Outcome: 02 # patients with exacerbations requiring hospitalisation

Study	LABA + ICS n/N	ICS alone n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
01 Mean baseline FEV 1 >/= 80% of predicted					
Langton Hewer ICS400	1/11	0/12		1.4	3.25 [0.15, 72.36]
Verberne 1998	1/60	2/56		6.1	0.47 [0.04, 5.01]
Subtotal (95% CI)	71	68		7.5	0.99 [0.18, 5.39]
Total events: 2 (LABA + ICS), 2 (ICS alone)					
Test for heterogeneity chi-square=0.95 df=1 p=0.33 I^2 =0.0%					
Test for overall effect z=0.01 p=1					
02 Mean baseline FEV 1 61-79% of predicted					
Kemp ICSNR	2/261	0/264		1.5	5.06 [0.24, 104.83]
Pauwels BUD200	1/210	3/213		8.7	0.34 [0.04, 3.22]
Pauwels BUD800	2/215	5/214		14.7	0.40 [0.08, 2.03]
× Price 2002	0/332	0/331		0.0	Not estimable
Russell ICS750	9/99	9/107		25.3	1.08 [0.45, 2.61]
Tal BUD400	5/158	0/138		1.6	9.62 [0.54, 172.36]
van der Molen ICSNR	0/125	1/114		4.6	0.30 [0.01, 7.39]
Subtotal (95% CI)	1400	1381		56.3	1.06 [0.58, 1.96]
Total events: 19 (LABA + ICS), 18 (ICS alone)					

(*Continued* . . .)

(. . . *Continued*)

Study	LABA + ICS n/N	ICS alone n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
Test for heterogeneity chi-square=6.24 df=5 p=0.28 I² =19.8%					
Test for overall effect z=0.20 p=0.8					
03 Mean baseline FEV 1 not reported					
× D'Urzo ICSNR	0/455	0/456		0.0	Not estimable
Ind 2003	5/171	12/160		36.3	0.39 [0.14, 1.08]
Subtotal (95% CI)	626	616		36.3	0.39 [0.14, 1.08]
Total events: 5 (LABA + ICS), 12 (ICS alone)					
Test for heterogeneity: not applicable					
Test for overall effect z=1.81 p=0.07					
Total (95% CI)	2097	2065		100.0	0.81 [0.50, 1.33]
Total events: 26 (LABA + ICS), 32 (ICS alone)					
Test for heterogeneity chi-square=9.27 df=8 p=0.32 I² =13.7%					
Test for overall effect z=0.82 p=0.4					

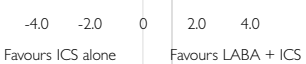
Analysis 01.03. Comparison 01 Long-acting beta2 vs placebo: both groups receiving similar dose ICS, Outcome 03 FEV1 (L) at endpoint

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

Comparison: 01 Long-acting beta2 vs placebo: both groups receiving similar dose ICS

Outcome: 03 FEV1 (L) at endpoint

Study	LABA + ICS N	LABA + ICS Mean(SD)	ICS alone N	ICS alone Mean(SD)	Weighted Mean Difference (Fixed) 95% CI	Weight (%)	Weighted Mean Difference (Fixed) 95% CI
01 Mean Baseline FEV1 >/-80% of predicted							
Subtotal (95% CI)	0		0			0.0	Not estimable
Test for heterogeneity: not applicable							
Test for overall effect: not applicable							
02 Mean baseline FEV 1 61-79% of predicted							
Boyd ICS1675	47	1.99 (0.78)	49	2.01 (0.68)		6.4	-0.02 [-0.31, 0.27]
Fitzgerald ICS730	89	2.92 (0.80)	91	2.68 (0.78)		10.4	0.24 [0.01, 0.47]
Norhaya ICS890	20	1.74 (0.61)	20	1.67 (0.57)		4.1	0.07 [-0.30, 0.44]
Zetterstrom BUD4001d	123	2.47 (0.42)	62	2.35 (0.42)		33.7	0.12 [-0.01, 0.25]
Zetterstrom BUD4002d	115	2.50 (0.41)	62	2.35 (0.42)		33.5	0.15 [0.02, 0.28]
van der Molen ICSNR	125	2.51 (0.85)	111	2.25 (0.84)		11.9	0.26 [0.04, 0.48]



(*Continued* . . .)

(. . . *Continued*)

Study	LABA + ICS N	LABA + ICS Mean(SD)	ICS alone N	ICS alone Mean(SD)	Weighted Mean Difference (Fixed) 95% CI	Weight (%)	Weighted Mean Difference (Fixed) 95% CI
Subtotal (95% CI)	519		395			100.0	0.15 [0.07, 0.22]
Test for heterogeneity chi-square=3.26 df=5 p=0.66 I² =0.0%							
Test for overall effect z=3.90 p=0.0001							
Total (95% CI)	519		395			100.0	0.15 [0.07, 0.22]
Test for heterogeneity chi-square=3.26 df=5 p=0.66 I² =0.0%							
Test for overall effect z=3.90 p=0.0001							

-4.0 -2.0 0 2.0 4.0

Favours ICS alone Favours LABA + ICS

Analysis 01.04. Comparison 01 Long-acting beta2 vs placebo: both groups receiving similar dose ICS, Outcome 04 Change in FEV1 at endpoint (L) stratifying on baseline FEV1

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

Comparison: 01 Long-acting beta2 vs placebo: both groups receiving similar dose ICS

Outcome: 04 Change in FEV1 at endpoint (L) stratifying on baseline FEV1

Study	LABA + ICS N	LABA + ICS Mean(SD)	ICS alone N	ICS alone Mean(SD)	Weighted Mean Difference (Random) 95% CI	Weight (%)	Weighted Mean Difference (Random) 95% CI
01 Mean baseline FEV1 >=80% of predicted							
Langton Hewer ICS400	11	0.22 (0.32)	10	-0.20 (0.16)		6.3	0.42 [0.21, 0.63]
Subtotal (95% CI)	11		10			6.3	0.42 [0.21, 0.63]
Test for heterogeneity: not applicable							
Test for overall effect z=3.86 p=0.0001							
02 Mean baseline FEV1 61-79% of predicted							
Boyd ICS1675	47	0.19 (0.38)	49	0.15 (0.44)		8.8	0.04 [-0.12, 0.20]
Hultquist BUD400	117	0.22 (0.54)	116	0.10 (0.54)		10.5	0.12 [-0.02, 0.26]
Kavaru FP400	87	0.51 (0.46)	85	0.28 (0.46)		10.6	0.23 [0.09, 0.37]
Kemp ICSNR	252	0.42 (0.48)	254	0.15 (0.48)		15.2	0.27 [0.19, 0.35]
Molimard ICSNR	130	0.17 (0.50)	129	0.06 (0.42)		12.6	0.11 [0.00, 0.22]
Russell ICS750	76	0.12 (0.41)	87	0.03 (0.37)		11.9	0.09 [-0.03, 0.21]
Shapiro FP1000	81	0.48 (0.45)	81	0.25 (0.45)		10.5	0.23 [0.09, 0.37]
van der Molen ICSNR	124	0.14 (0.44)	111	0.02 (0.37)		13.4	0.12 [0.02, 0.22]
Subtotal (95% CI)	914		912			93.7	0.16 [0.10, 0.22]
Test for heterogeneity chi-square=13.51 df=7 p=0.06 I² =48.2%							
Test for overall effect z=5.21 p<0.00001							
Total (95% CI)	925		922			100.0	0.17 [0.11, 0.24]
Test for heterogeneity chi-square=18.70 df=8 p=0.02 I² =57.2%							
Test for overall effect z=5.23 p<0.00001							

-10.0 -5.0 0 5.0 10.0

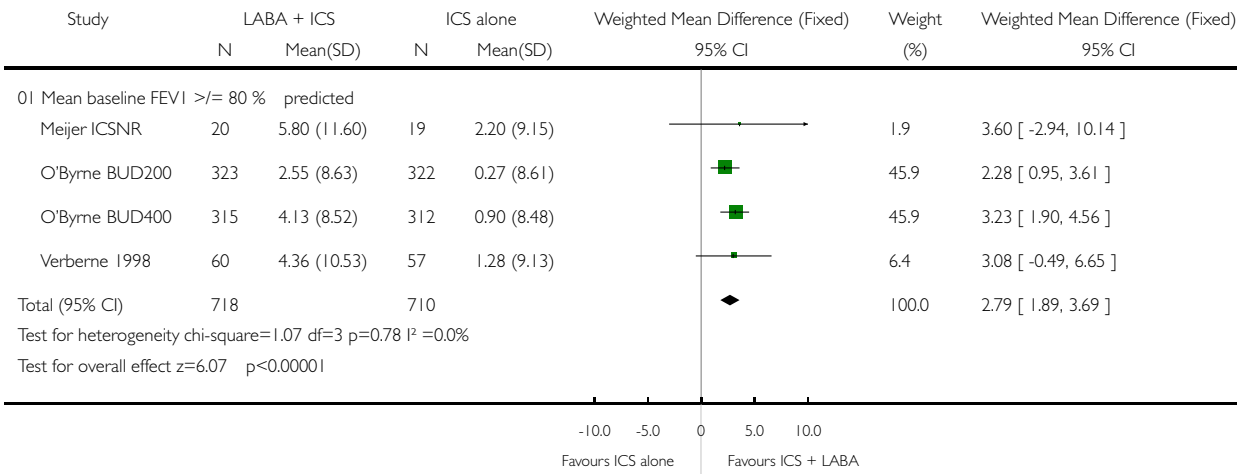
Favours ICS alone Favours LABA + ICS

Analysis 01.05. Comparison 01 Long-acting beta2 vs placebo: both groups receiving similar dose ICS, Outcome 05 Change in FEV1 at endpoint (% predicted) stratifying on baseline FEV1

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

Comparison: 01 Long-acting beta2 vs placebo: both groups receiving similar dose ICS

Outcome: 05 Change in FEV1 at endpoint (% predicted) stratifying on baseline FEV1

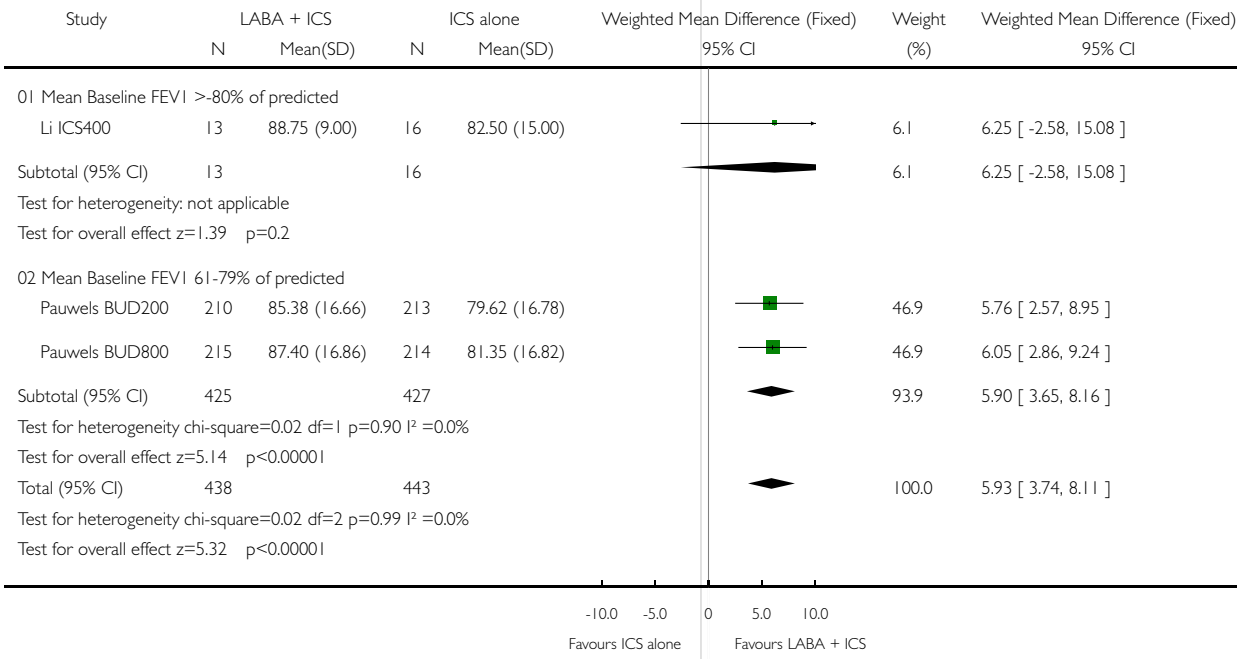


Analysis 01.06. Comparison 01 Long-acting beta2 vs placebo: both groups receiving similar dose ICS, Outcome 06 FEV1 % predicted at endpoint

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

Comparison: 01 Long-acting beta2 vs placebo: both groups receiving similar dose ICS

Outcome: 06 FEV1 % predicted at endpoint



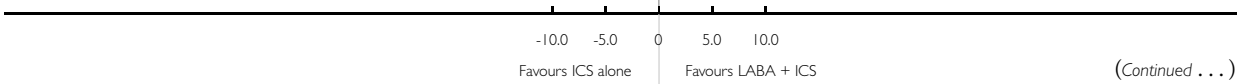
Analysis 01.07. Comparison 01 Long-acting beta2 vs placebo: both groups receiving similar dose ICS, Outcome 07 Change in FEV1 (L or % pred)stratifying on trial duration

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

Comparison: 01 Long-acting beta2 vs placebo: both groups receiving similar dose ICS

Outcome: 07 Change in FEV1 (L or % pred)stratifying on trial duration

Study	LABA + ICS N	LABA + ICS Mean(SD)	ICS alone N	ICS alone Mean(SD)	Standardised Mean Difference (Random) 95% CI	Weight (%)	Standardised Mean Difference (Random) 95% CI
01 Change in FEV1 (L) or (% predicted) at 6 +/- 2 weeks of treatment							
Meijer ICSNR	20	2.90 (8.90)	20	-0.30 (11.20)		1.3	0.31 [-0.31, 0.93]
Molimard ICSNR	130	0.15 (0.42)	129	-0.01 (0.33)		7.0	0.42 [0.18, 0.67]
Subtotal (95% CI)	150		149			8.4	0.41 [0.18, 0.64]
Test for heterogeneity chi-square=0.11 df=1 p=0.74 I² =0.0%							
Test for overall effect z=3.48 p=0.0005							
02 Change in FEV1 (L) or (% predicted) at 12 +/- 4 weeks of treatment							
Boyd ICS1675	47	0.19 (0.38)	49	0.15 (0.44)		3.0	0.10 [-0.30, 0.50]
Hultquist BUD400	117	0.22 (0.54)	116	0.10 (0.54)		6.5	0.22 [-0.04, 0.48]
Kavaru FP400	87	0.51 (0.47)	85	0.28 (0.46)		5.0	0.49 [0.19, 0.80]
Kemp ICSNR	252	0.42 (0.48)	254	0.15 (0.48)		11.4	0.56 [0.38, 0.74]
Langton Hewer ICS400	11	0.22 (0.32)	10	-0.20 (0.16)		0.5	1.57 [0.56, 2.57]
Meijer ICSNR	20	5.80 (11.60)	19	2.20 (9.15)		1.3	0.34 [-0.30, 0.97]
Molimard ICSNR	130	0.17 (0.50)	129	0.06 (0.42)		7.1	0.24 [-0.01, 0.48]
Russell ICS750	76	0.12 (0.41)	87	0.03 (0.37)		4.8	0.23 [-0.08, 0.54]
Shapiro FP1000	81	0.48 (0.45)	81	0.25 (0.45)		4.7	0.51 [0.20, 0.82]
Verberne 1998	60	4.64 (8.83)	57	1.30 (8.61)		3.6	0.38 [0.01, 0.75]
van der Molen ICSNR	124	0.13 (0.42)	111	0.03 (0.42)		6.6	0.24 [-0.02, 0.49]
Subtotal (95% CI)	1005		998			54.6	0.36 [0.24, 0.49]
Test for heterogeneity chi-square=17.34 df=10 p=0.07 I² =42.3%							
Test for overall effect z=5.67 p<0.00001							
03 Change in FEV1 (L) or (% predicted) at 24 +/- 4 weeks of treatment							
Verberne 1998	60	4.36 (10.53)	57	1.28 (9.13)		3.6	0.31 [-0.05, 0.67]
van der Molen ICSNR	124	0.14 (0.44)	111	0.02 (0.37)		6.6	0.29 [0.04, 0.55]
Subtotal (95% CI)	184		168			10.2	0.30 [0.09, 0.51]
Test for heterogeneity chi-square=0.01 df=1 p=0.94 I² =0.0%							
Test for overall effect z=2.78 p=0.005							
04 Change in FEV1 (L) or (% predicted) at 52 +/- 4 weeks of treatment							
O'Byrne BUD200	323	2.55 (8.63)	322	0.27 (8.61)		13.6	0.26 [0.11, 0.42]



(*Continued . . .*)

(... *Continued*)

Study	LABA + ICS N	LABA + ICS Mean(SD)	ICS alone N	ICS alone Mean(SD)	Standardised Mean Difference (Random) 95% CI	Weight (%)	Standardised Mean Difference (Random) 95% CI
O'Byrne BUD400	315	4.13 (8.52)	312	0.90 (8.48)		13.3	0.38 [0.22, 0.54]
Subtotal (95% CI)	638		634			26.9	0.32 [0.21, 0.43]
Test for heterogeneity chi-square=1.04 df=1 p=0.31 I² =4.2%							
Test for overall effect z=5.56 p<0.00001							
Total (95% CI)	1977		1949			100.0	0.35 [0.28, 0.42]
Test for heterogeneity chi-square=19.48 df=16 p=0.24 I² =17.9%							
Test for overall effect z=9.38 p<0.00001							

-10.0 -5.0 0 5.0 10.0

Favours ICS alone Favours LABA + ICS

Analysis 01.08. Comparison 01 Long-acting beta2 vs placebo: both groups receiving similar dose ICS, Outcome 08 Morning PEF (L/min) at endpoint

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

Comparison: 01 Long-acting beta2 vs placebo: both groups receiving similar dose ICS

Outcome: 08 Morning PEF (L/min) at endpoint

Study	LABA + ICS N	LABA + ICS Mean(SD)	ICS alone N	ICS alone Mean(SD)	Weighted Mean Difference (Random) 95% CI	Weight (%)	Weighted Mean Difference (Random) 95% CI
01 Mean baseline FEV1 >/= 80%							
Li ICS400	13	496.00 (89.80)	16	410.00 (99.20)		5.9	86.00 [17.11, 154.89]
Subtotal (95% CI)	13		16			5.9	86.00 [17.11, 154.89]
Test for heterogeneity: not applicable							
Test for overall effect z=2.45 p=0.01							
04 Mean baseline FEV1 61-79% of predicted							
Boyd ICS1675	48	319.20 (97.50)	52	321.20 (121.10)		12.1	-2.00 [-44.94, 40.94]
Norhaya ICS890	20	297.00 (70.00)	20	275.00 (77.00)		11.2	22.00 [-23.61, 67.61]
Pauwels BUD200	205	412.00 (114.00)	206	385.00 (118.00)		23.6	27.00 [4.57, 49.43]
Pauwels BUD800	207	420.00 (118.00)	206	383.00 (106.00)		24.2	37.00 [15.37, 58.63]
Russell ICS750	75	260.00 (75.00)	88	260.00 (76.00)		23.0	0.00 [-23.24, 23.24]
Subtotal (95% CI)	555		572			94.1	19.14 [2.93, 35.34]
Test for heterogeneity chi-square=6.60 df=4 p=0.16 I² =39.4%							
Test for overall effect z=2.31 p=0.02							
Total (95% CI)	568		588			100.0	22.62 [4.34, 40.90]
Test for heterogeneity chi-square=9.99 df=5 p=0.08 I² =50.0%							
Test for overall effect z=2.43 p=0.02							

-1000.0 -500.0 0 500.0 1000.0

Favours ICS alone Favours LABA + ICS

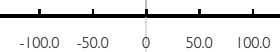
Analysis 01.09. Comparison 01 Long-acting beta2 vs placebo: both groups receiving similar dose ICS, Outcome 09 Change in morning PEF (L/min) at endpoint stratifying on baseline FEV1

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

Comparison: 01 Long-acting beta2 vs placebo: both groups receiving similar dose ICS

Outcome: 09 Change in morning PEF (L/min) at endpoint stratifying on baseline FEV1

Study	LABA + ICS		ICS alone		Weighted Mean Difference (Random)	Weight	Weighted Mean Difference (Random)
	N	Mean(SD)	N	Mean(SD)	95% CI	(%)	95% CI
01 Mean Baseline FEV1 >/= 80% of predicted							
Langton Hewer ICS400	11	26.00 (49.00)	10	-35.00 (63.00)		0.9	61.00 [12.39, 109.61]
O'Byrne BUD200	323	12.89 (44.40)	322	2.78 (44.30)		7.7	10.11 [3.26, 16.96]
O'Byrne BUD400	315	18.50 (44.40)	312	1.73 (44.20)		7.7	16.77 [9.83, 23.71]
Verberne 1998	60	30.92 (33.00)	57	15.89 (43.41)		5.2	15.03 [1.00, 29.06]
Subtotal (95% CI)	709		701			21.5	14.76 [7.47, 22.04]
Test for heterogeneity chi-square=5.46 df=3 p=0.14 I² =45.1%							
Test for overall effect z=3.97 p=0.00007							
02 Mean Baseline FEV1 61-79% of predicted							
Boyd ICS1675	48	54.00 (41.60)	52	28.00 (50.10)		4.1	26.00 [8.00, 44.00]
Hultquist BUD400	117	33.86 (63.71)	116	16.25 (63.22)		4.5	17.61 [1.31, 33.91]
Kavaru FP400	87	52.50 (49.44)	85	17.30 (40.57)		5.4	35.20 [21.70, 48.70]
Kemp ICSNR	252	47.00 (58.73)	254	14.00 (52.59)		6.7	33.00 [23.28, 42.72]
Molimard ICSNR	130	25.70 (36.50)	129	4.50 (32.70)		7.2	21.20 [12.76, 29.64]
Price 2002	332	36.80 (61.95)	331	17.80 (61.85)		6.8	19.00 [9.58, 28.42]
Russell ICS750	75	27.00 (36.00)	88	18.50 (43.00)		5.8	8.50 [-3.63, 20.63]
Shapiro FP1000	81	53.50 (50.40)	81	15.20 (41.40)		5.2	38.30 [24.10, 52.50]
Tal BUD400	148	23.10 (28.50)	138	11.10 (28.50)		7.8	12.00 [5.39, 18.61]
Zetterstrom BUD4001d	123	35.70 (41.26)	62	0.20 (41.76)		5.6	35.50 [22.80, 48.20]
Zetterstrom BUD4002d	115	32.00 (40.75)	62	0.20 (41.76)		5.6	31.80 [19.01, 44.59]
van der Molen ICSNR	125	26.70 (41.60)	113	-5.70 (30.70)		6.9	32.40 [23.17, 41.63]
Subtotal (95% CI)	1633		1511			71.6	25.46 [19.47, 31.44]
Test for heterogeneity chi-square=38.59 df=11 p=<0.0001 I² =71.5%							
Test for overall effect z=8.33 p<0.00001							
04 Mean Baseline FEV1 not reported							
Ind 2003	171	47.70 (47.40)	160	23.40 (38.30)		6.9	24.30 [15.04, 33.56]
Subtotal (95% CI)	171		160			6.9	24.30 [15.04, 33.56]
Test for heterogeneity: not applicable							
Test for overall effect z=5.15 p<0.00001							



(*Continued . . .*)

(. . . *Continued*)

Study	LABA + ICS N	LABA + ICS Mean(SD)	ICS alone N	ICS alone Mean(SD)	Weighted Mean Difference (Random) 95% CI	Weight (%)	Weighted Mean Difference (Random) 95% CI
Total (95% CI)	2513		2372		◆	100.0	23.28 [18.38, 28.18]
Test for heterogeneity chi-square=56.18 df=16 p=<0.0001 I^2 =71.5%							
Test for overall effect z=9.31 p<0.00001							

Analysis 01.10. Comparison 01 Long-acting beta2 vs placebo: both groups receiving similar dose ICS, Outcome 10 Evening PEF (L/min) at endpoint

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

Comparison: 01 Long-acting beta2 vs placebo: both groups receiving similar dose ICS

Outcome: 10 Evening PEF (L/min) at endpoint

Study	LABA + ICS N	LABA + ICS Mean(SD)	ICS alone N	ICS alone Mean(SD)	Weighted Mean Difference (Fixed) 95% CI	Weighted Mean Difference (Fixed) 95% CI
01 Mean baseline FEV1 61-79% of predicted						
Boyd ICS1675	47	330.30 (97.70)	52	343.70 (114.70)		-13.40 [-55.26, 28.46]

Analysis 01.11. Comparison 01 Long-acting beta2 vs placebo: both groups receiving similar dose ICS, Outcome 11 Change in evening PEF (L/min) at endpoint

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

Comparison: 01 Long-acting beta2 vs placebo: both groups receiving similar dose ICS

Outcome: 11 Change in evening PEF (L/min) at endpoint

Study	LABA + ICS N	LABA + ICS Mean(SD)	ICS alone N	ICS alone Mean(SD)	Weighted Mean Difference (Random) 95% CI	Weight (%)	Weighted Mean Difference (Random) 95% CI
01 Mean baseline FEV1 61-79% of predicted							
Hultquist BUD400	117	24.02 (62.63)	116	11.39 (62.04)		9.0	12.63 [-3.38, 28.64]
Ind 2003	171	31.60 (57.60)	160	15.40 (38.30)		12.6	16.20 [5.72, 26.68]
Kavaru FP400	87	35.00 (43.84)	85	18.00 (12.40)		13.3	17.00 [7.42, 26.58]
Price 2002	332	26.00 (59.04)	331	10.20 (58.95)		13.7	15.80 [6.82, 24.78]
Shapiro FP1000	81	45.40 (46.80)	81	7.90 (40.50)		10.5	37.50 [24.02, 50.98]
Tal BUD400	148	20.00 (27.70)	138	8.30 (27.70)		15.5	11.70 [5.28, 18.12]
Zetterstrom BUD4001d	123	24.80 (37.38)	62	-3.70 (37.75)		11.9	28.50 [17.01, 39.99]
Zetterstrom BUD4002d	115	22.30 (36.88)	62	-3.70 (37.75)		11.8	26.00 [14.44, 37.56]
Subtotal (95% CI)	1174		1035			98.3	19.93 [14.09, 25.77]
Test for heterogeneity chi-square=17.59 df=7 p=0.01 I² =60.2%							
Test for overall effect z=6.69 p<0.00001							
02 Mean baseline FEV1 > /= 80% of predicted							
Langton Hewer ICS400	11	48.00 (52.00)	10	-42.00 (64.00)		1.7	90.00 [39.82, 140.18]
Subtotal (95% CI)	11		10			1.7	90.00 [39.82, 140.18]
Test for heterogeneity: not applicable							
Test for overall effect z=3.52 p=0.0004							
Total (95% CI)	1185		1045			100.0	21.33 [14.53, 28.12]
Test for heterogeneity chi-square=25.41 df=8 p=0.001 I² =68.5%							
Test for overall effect z=6.15 p<0.00001							

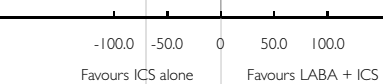
Analysis 01.12. Comparison 01 Long-acting beta2 vs placebo: both groups receiving similar dose ICS, Outcome 12 Change in PEF variability at endpoint

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

Comparison: 01 Long-acting beta2 vs placebo: both groups receiving similar dose ICS

Outcome: 12 Change in PEF variability at endpoint

Study	LABA + ICS N	LABA + ICS Mean(SD)	ICS alone N	ICS alone Mean(SD)	Weighted Mean Difference (Fixed) 95% CI	Weighted Mean Difference (Fixed) 95% CI
03 Mean baseline FEV 1 61-79% of predicted						
Russell ICS750	75	-4.64 (9.01)	88	-3.35 (7.15)		-1.29 [-3.82, 1.24]



Analysis 01.13. Comparison 01 Long-acting beta2 vs placebo: both groups receiving similar dose ICS, Outcome 13 Change in daytime symptom score at endpoint

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

Comparison: 01 Long-acting beta2 vs placebo: both groups receiving similar dose ICS

Outcome: 13 Change in daytime symptom score at endpoint

Study	LABA + ICS N	LABA + ICS Mean(SD)	ICS alone N	ICS alone Mean(SD)	Standardised Mean Difference (Fixed) 95% CI	Weight (%)	Standardised Mean Difference (Fixed) 95% CI
03 Mean baseline FEV1 61-79% of predicted							
Boyd ICS1675	53	-0.21 (0.41)	62	-0.12 (0.32)		8.4	-0.25 [-0.61, 0.12]
Kavaru FP400	87	-0.70 (1.03)	85	-0.20 (0.83)		12.3	-0.53 [-0.84, -0.23]
Molimard ICSNR	130	-0.30 (0.48)	129	-0.10 (0.43)		18.7	-0.44 [-0.68, -0.19]
Price 2002	332	-0.50 (0.60)	331	-0.35 (0.61)		48.8	-0.25 [-0.40, -0.09]
Shapiro FP1000	81	-0.80 (1.08)	81	-0.40 (0.81)		11.8	-0.42 [-0.73, -0.11]
Total (95% CI)	683		688			100.0	-0.34 [-0.44, -0.23]

Test for heterogeneity chi-square=4.01 df=4 p=0.40 I^2 =0.3%

Test for overall effect z=6.20 p<0.00001

Analysis 01.14. Comparison 01 Long-acting beta2 vs placebo: both groups receiving similar dose ICS, Outcome 14 Change in nightime symptom score at endpoint

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

Comparison: 01 Long-acting beta2 vs placebo: both groups receiving similar dose ICS

Outcome: 14 Change in nightime symptom score at endpoint

Study	LABA + ICS N	LABA + ICS Mean(SD)	ICS alone N	ICS alone Mean(SD)	Standardised Mean Difference (Fixed) 95% CI	Weight (%)	Standardised Mean Difference (Fixed) 95% CI
01 Mean baseline FEV 1 61-79% of predicted							
Molimard ICSNR	130	-0.10 (0.43)	129	0.00 (0.35)		28.0	-0.25 [-0.50, -0.01]
Price 2002	332	-0.38 (0.66)	331	-0.28 (0.65)		72.0	-0.15 [-0.30, 0.00]
Total (95% CI)	462		460			100.0	-0.18 [-0.31, -0.05]

Test for heterogeneity chi-square=0.48 df=1 p=0.49 I^2 =0.0%

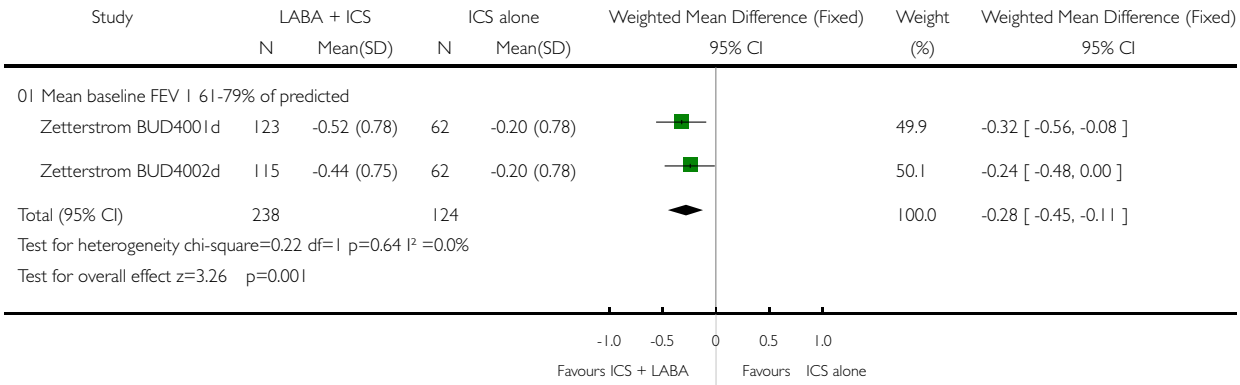
Test for overall effect z=2.74 p=0.006

Analysis 01.15. Comparison 01 Long-acting beta2 vs placebo: both groups receiving similar dose ICS, Outcome 15 Change in 24 hour symptom score at endpoint

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

Comparison: 01 Long-acting beta2 vs placebo: both groups receiving similar dose ICS

Outcome: 15 Change in 24 hour symptom score at endpoint

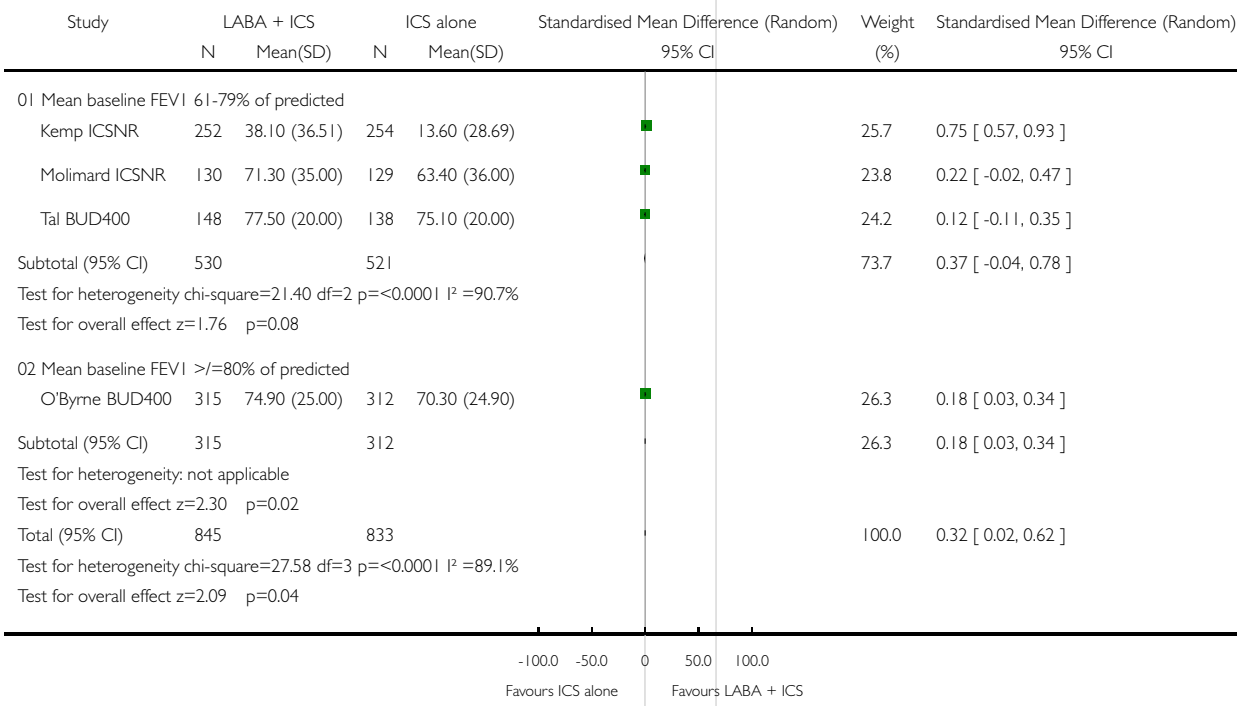


Analysis 01.16. Comparison 01 Long-acting beta2 vs placebo: both groups receiving similar dose ICS, Outcome 16 % symptom-free days

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

Comparison: 01 Long-acting beta2 vs placebo: both groups receiving similar dose ICS

Outcome: 16 % symptom-free days



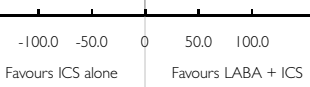
Analysis 01.17. Comparison 01 Long-acting beta2 vs placebo: both groups receiving similar dose ICS, Outcome 17 Change in % symptom-free days at endpoint

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

Comparison: 01 Long-acting beta2 vs placebo: both groups receiving similar dose ICS

Outcome: 17 Change in % symptom-free days at endpoint

Study	LABA + ICS N	LABA + ICS Mean(SD)	ICS alone N	ICS alone Mean(SD)	Weighted Mean Difference (Random) 95% CI	Weight (%)	Weighted Mean Difference (Random) 95% CI
01 Mean baseline FEV 1 >/=80% of predicted							
Subtotal (95% CI)	0		0			0.0	Not estimable
Test for heterogeneity: not applicable							
Test for overall effect: not applicable							
02 Mean baseline FEV 1 61-79% of predicted							
Boyd ICS1675	53	22.00 (30.00)	62	13.00 (22.00)		16.3	9.00 [-0.76, 18.76]
Kavaru FP400	87	22.60 (42.81)	85	7.20 (37.70)		12.5	15.40 [3.35, 27.45]
Kemp ICSNR	252	38.10 (36.50)	254	13.60 (28.69)		26.4	24.50 [18.78, 30.22]
Shapiro FP1000	81	33.80 (41.40)	81	15.40 (37.80)		12.2	18.40 [6.19, 30.61]
Zetterstrom BUD4001d	123	25.00 (31.39)	62	8.00 (31.85)		16.4	17.00 [7.32, 26.68]
Zetterstrom BUD4002d	115	22.30 (31.21)	62	8.00 (31.85)		16.2	14.30 [4.53, 24.07]
Subtotal (95% CI)	711		606			100.0	17.21 [12.06, 22.36]
Test for heterogeneity chi-square=8.92 df=5 p=0.11 I² =43.9%							
Test for overall effect z=6.55 p<0.00001							
Total (95% CI)	711		606			100.0	17.21 [12.06, 22.36]
Test for heterogeneity chi-square=8.92 df=5 p=0.11 I² =43.9%							
Test for overall effect z=6.55 p<0.00001							



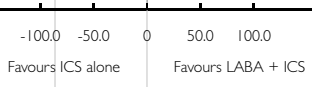
Analysis 01.18. Comparison 01 Long-acting beta2 vs placebo: both groups receiving similar dose ICS, Outcome 18 % symptom-free nights at 12 +/- 4 weeks

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

Comparison: 01 Long-acting beta2 vs placebo: both groups receiving similar dose ICS

Outcome: 18 % symptom-free nights at 12 +/- 4 weeks

Study	LABA + ICS N	LABA + ICS Mean(SD)	ICS alone N	ICS alone Mean(SD)	Weighted Mean Difference (Fixed) 95% CI	Weighted Mean Difference (Fixed) 95% CI
01 Mean baseline FEV 1 61-79% of predicted						
Molimard ICSNR	130	81.70 (28.40)	129	76.40 (29.70)		5.30 [-1.78, 12.38]

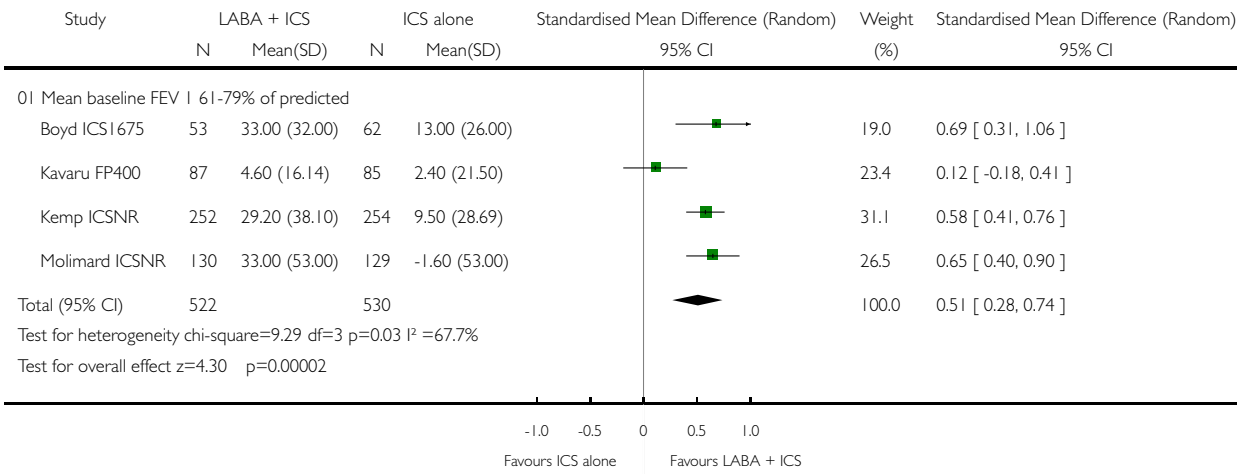


Analysis 01.19. Comparison 01 Long-acting beta2 vs placebo: both groups receiving similar dose ICS, Outcome 19 Change in % symptom-free nights at endpoint

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

Comparison: 01 Long-acting beta2 vs placebo: both groups receiving similar dose ICS

Outcome: 19 Change in % symptom-free nights at endpoint

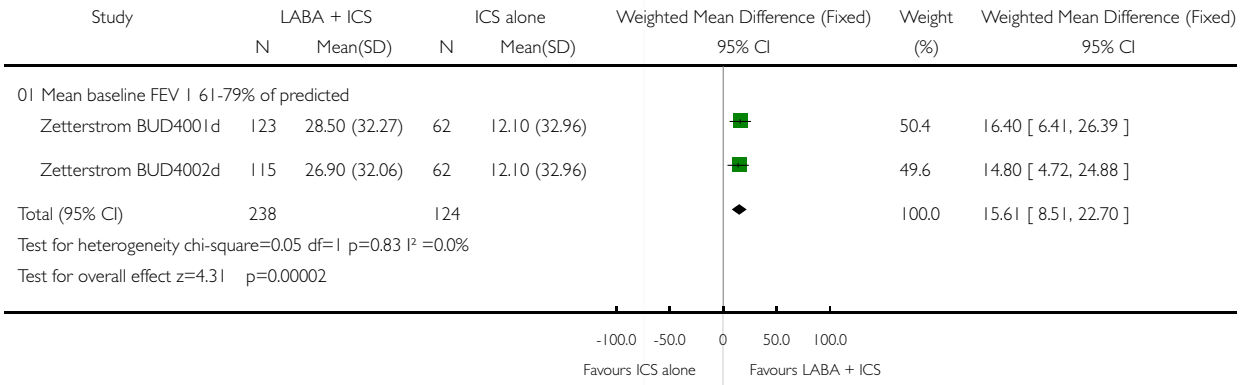


Analysis 01.20. Comparison 01 Long-acting beta2 vs placebo: both groups receiving similar dose ICS, Outcome 20 Change in Asthma Control days % @ 12 +/- 4 weeks

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

Comparison: 01 Long-acting beta2 vs placebo: both groups receiving similar dose ICS

Outcome: 20 Change in Asthma Control days % @ 12 +/- 4 weeks



Analysis 01.21. Comparison 01 Long-acting beta2 vs placebo: both groups receiving similar dose ICS, Outcome 21 # daytime rescue inhalations (puffs per day) at endpoint

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

Comparison: 01 Long-acting beta2 vs placebo: both groups receiving similar dose ICS

Outcome: 21 # daytime rescue inhalations (puffs per day) at endpoint

Study	LABA + ICS N	LABA + ICS Mean(SD)	ICS alone N	ICS alone Mean(SD)	Weighted Mean Difference (Random) 95% CI	Weight (%)	Weighted Mean Difference (Random) 95% CI
01 Mean baseline FEV 1 61-79% of predicted							
Norhaya ICS890	20	1.32 (1.12)	20	1.65 (1.50)		29.5	-0.33 [-1.15, 0.49]
van der Molen ICSNR	124	0.90 (1.30)	113	1.80 (1.80)		70.5	-0.90 [-1.30, -0.50]
Total (95% CI)	144		133			100.0	-0.73 [-1.24, -0.22]
Test for heterogeneity chi-square=1.49 df=1 p=0.22 I² =33.0%							
Test for overall effect z=2.81 p=0.005							

Analysis 01.22. Comparison 01 Long-acting beta2 vs placebo: both groups receiving similar dose ICS, Outcome 22 Change in # daytime rescue inhalations (puffs per day) at endpoint

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

Comparison: 01 Long-acting beta2 vs placebo: both groups receiving similar dose ICS

Outcome: 22 Change in # daytime rescue inhalations (puffs per day) at endpoint

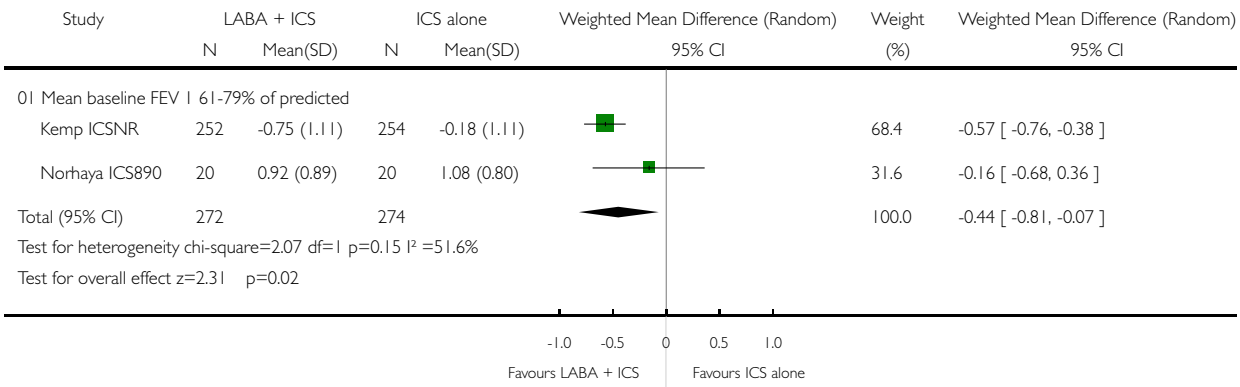
Study	LABA + ICS N	LABA + ICS Mean(SD)	ICS alone N	ICS alone Mean(SD)	Weighted Mean Difference (Random) 95% CI	Weight (%)	Weighted Mean Difference (Random) 95% CI
01 Mean baseline FEV 1 61-79% of predicted							
Kavaru FP400	87	-1.90 (2.43)	85	-0.40 (1.94)		9.2	-1.50 [-2.16, -0.84]
Kemp ICSNR	252	-2.73 (2.54)	254	-1.06 (1.91)		11.6	-1.67 [-2.06, -1.28]
Molimard ICSNR	130	-0.80 (1.32)	129	0.10 (0.85)		12.5	-0.90 [-1.17, -0.63]
O'Byrne BUD200	323	-0.29 (0.79)	322	-0.06 (0.79)		13.3	-0.23 [-0.35, -0.11]
Price 2002	332	-1.18 (1.45)	331	-0.85 (1.26)		12.9	-0.33 [-0.54, -0.12]
Russell ICS750	73	-0.75 (1.78)	86	-0.38 (1.73)		10.2	-0.37 [-0.92, 0.18]
Zetterstrom BUD4001d	123	-0.99 (1.66)	62	-0.44 (1.78)		10.3	-0.55 [-1.08, -0.02]
Zetterstrom BUD4002d	115	-1.13 (3.11)	62	-0.44 (1.78)		8.6	-0.69 [-1.41, 0.03]
van der Molen ICSNR	124	-1.50 (1.70)	113	-0.20 (1.50)		11.4	-1.30 [-1.71, -0.89]
Total (95% CI)	1559		1444			100.0	-0.82 [-1.17, -0.47]
Test for heterogeneity chi-square=88.25 df=8 p=<0.0001 I² =90.9%							
Test for overall effect z=4.53 p<0.00001							

Analysis 01.23. Comparison 01 Long-acting beta2 vs placebo: both groups receiving similar dose ICS, Outcome 23 # nighttime rescue inhalations (puffs per night) at endpoint

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

Comparison: 01 Long-acting beta2 vs placebo: both groups receiving similar dose ICS

Outcome: 23 # nighttime rescue inhalations (puffs per night) at endpoint

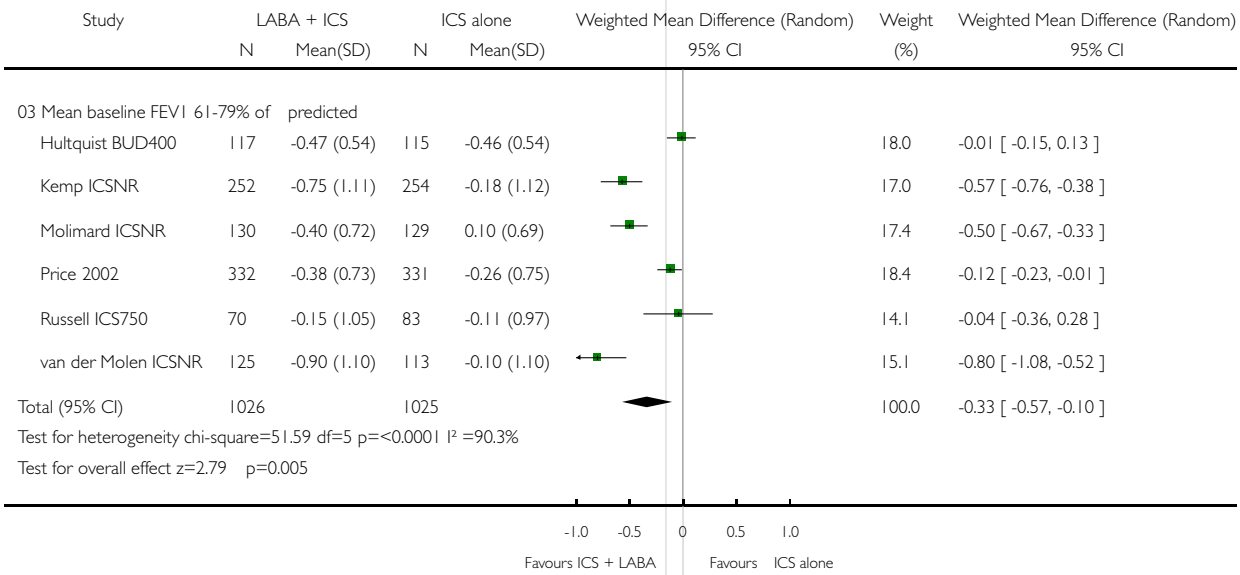


Analysis 01.24. Comparison 01 Long-acting beta2 vs placebo: both groups receiving similar dose ICS, Outcome 24 Change in # nighttime rescue inhalations at endpoint

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

Comparison: 01 Long-acting beta2 vs placebo: both groups receiving similar dose ICS

Outcome: 24 Change in # nighttime rescue inhalations at endpoint



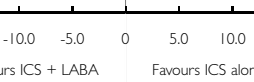
Analysis 01.25. Comparison 01 Long-acting beta2 vs placebo: both groups receiving similar dose ICS, Outcome 25 Change in # overall daily rescue inhalations at endpoint

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

Comparison: 01 Long-acting beta2 vs placebo: both groups receiving similar dose ICS

Outcome: 25 Change in # overall daily rescue inhalations at endpoint

Study	LABA + ICS		ICS alone		Weighted Mean Difference (Random)	Weight	Weighted Mean Difference (Random)
	N	Mean(SD)	N	Mean(SD)	95% CI	(%)	95% CI
01 Mean baseline FEV 1 >/=80% of predicted							
O'Byrne BUD200	323	-0.29 (0.79)	322	-0.06 (0.79)		16.8	-0.23 [-0.35, -0.11]
O'Byrne BUD400	315	-0.31 (0.78)	312	-0.20 (0.78)		16.8	-0.11 [-0.23, 0.01]
Subtotal (95% CI)	638		634			33.6	-0.17 [-0.29, -0.05]
Test for heterogeneity chi-square=1.86 df=1 p=0.17 I^2 =46.2%							
Test for overall effect z=2.83 p=0.005							
02 Mean baseline FEV 1 61-79% of predicted							
Boyd ICS1675	53	-5.10 (4.70)	62	-2.50 (4.00)		3.9	-2.60 [-4.21, -0.99]
Hultquist BUD400	117	-1.86 (1.84)	115	-1.35 (1.83)		13.3	-0.51 [-0.98, -0.04]
Kavaru FP400	87	-1.90 (2.43)	85	-0.40 (1.94)		11.0	-1.50 [-2.16, -0.84]
Kemp ICSNR	252	-3.48 (3.02)	254	-1.25 (2.55)		13.1	-2.23 [-2.72, -1.74]
Shapiro FP1000	81	-2.30 (3.60)	81	-0.90 (1.80)		8.6	-1.40 [-2.28, -0.52]
Tal BUD400	148	-0.11 (0.70)	138	-0.09 (0.70)		16.6	-0.02 [-0.18, 0.14]
Subtotal (95% CI)	738		735			66.4	-1.29 [-2.20, -0.38]
Test for heterogeneity chi-square=98.24 df=5 p=<0.0001 I^2 =94.9%							
Test for overall effect z=2.78 p=0.005							
Total (95% CI)	1376		1369			100.0	-0.81 [-1.17, -0.44]
Test for heterogeneity chi-square=105.75 df=7 p=<0.0001 I^2 =93.4%							
Test for overall effect z=4.35 p=0.00001							

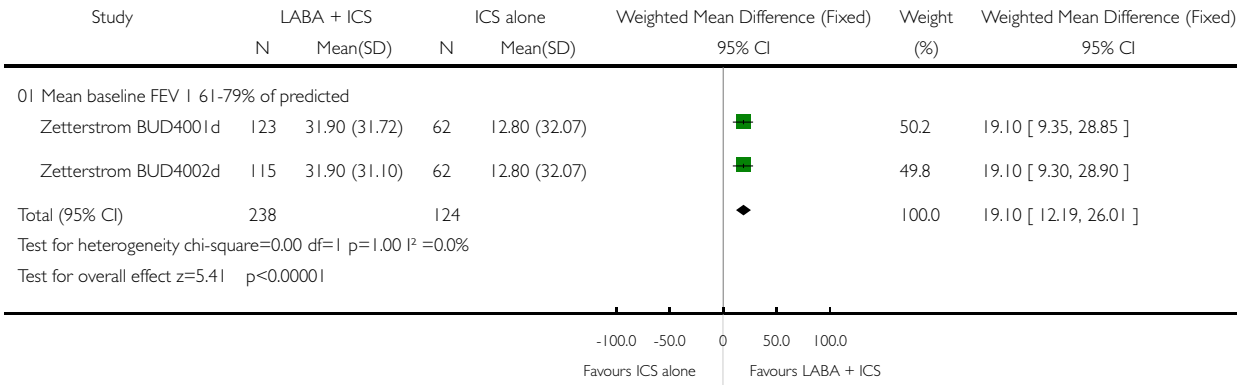


Analysis 01.26. Comparison 01 Long-acting beta2 vs placebo: both groups receiving similar dose ICS, Outcome 26 Change in mean % rescue free days at 12 +/- 4 weeks

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

Comparison: 01 Long-acting beta2 vs placebo: both groups receiving similar dose ICS

Outcome: 26 Change in mean % rescue free days at 12 +/- 4 weeks

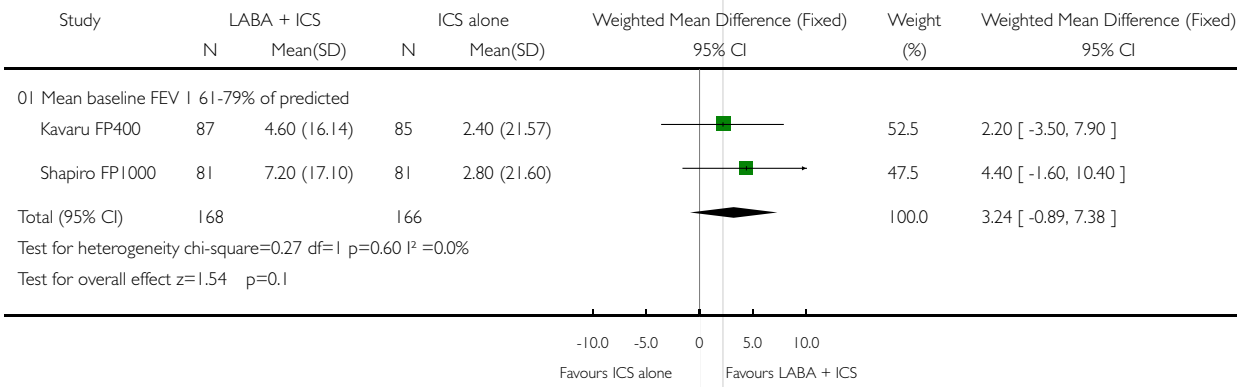


Analysis 01.27. Comparison 01 Long-acting beta2 vs placebo: both groups receiving similar dose ICS, Outcome 27 Change in % nights with no awakening at 12 +/- 4 weeks

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

Comparison: 01 Long-acting beta2 vs placebo: both groups receiving similar dose ICS

Outcome: 27 Change in % nights with no awakening at 12 +/- 4 weeks

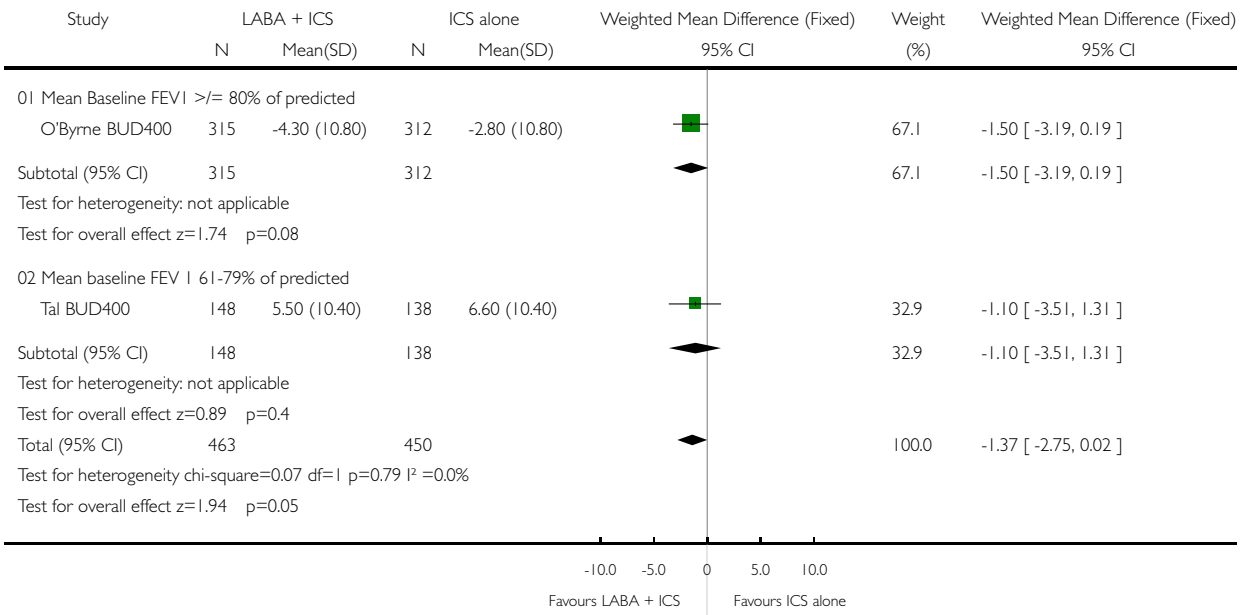


Analysis 01.28. Comparison 01 Long-acting beta2 vs placebo: both groups receiving similar dose ICS, Outcome 28 % nights with awakening

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

Comparison: 01 Long-acting beta2 vs placebo: both groups receiving similar dose ICS

Outcome: 28 % nights with awakening

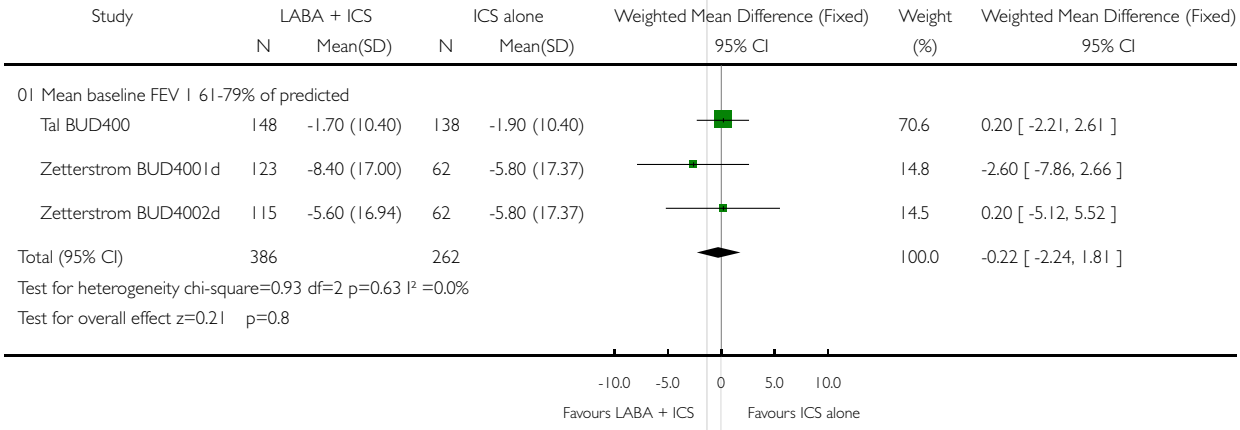


Analysis 01.29. Comparison 01 Long-acting beta2 vs placebo: both groups receiving similar dose ICS, Outcome 29 Change in night time awakening (number of nights) at endpoint

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

Comparison: 01 Long-acting beta2 vs placebo: both groups receiving similar dose ICS

Outcome: 29 Change in night time awakening (number of nights) at endpoint

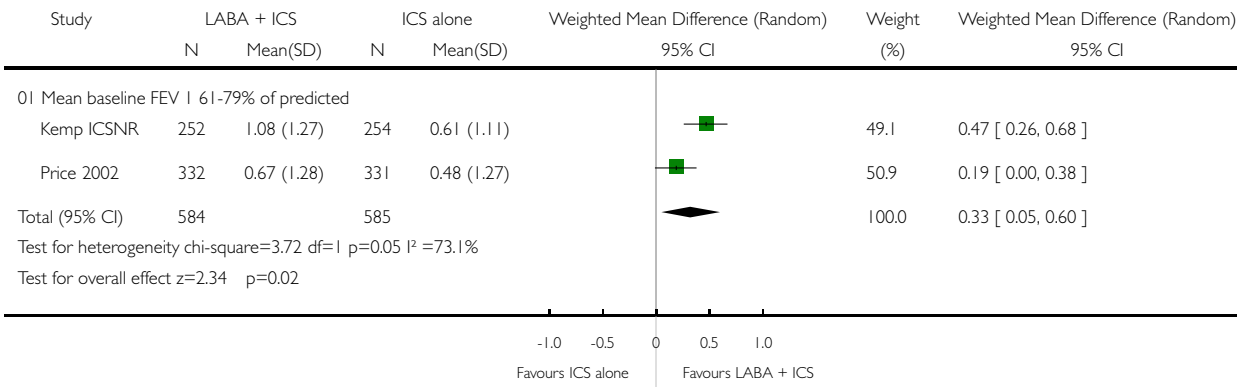


Analysis 01.30. Comparison 01 Long-acting beta2 vs placebo: both groups receiving similar dose ICS, Outcome 30 Change in quality of life (AQLQ score) at endpoint

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

Comparison: 01 Long-acting beta2 vs placebo: both groups receiving similar dose ICS

Outcome: 30 Change in quality of life (AQLQ score) at endpoint

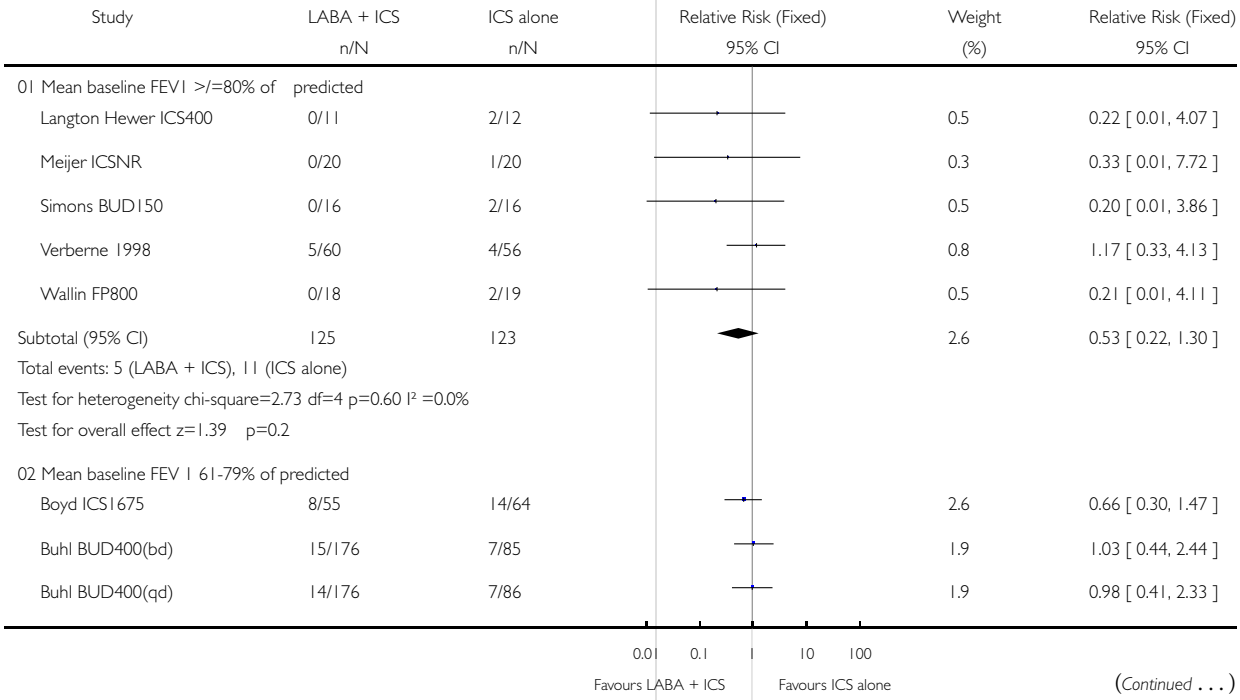


Analysis 01.31. Comparison 01 Long-acting beta2 vs placebo: both groups receiving similar dose ICS, Outcome 31 Total # withdrawals

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

Comparison: 01 Long-acting beta2 vs placebo: both groups receiving similar dose ICS

Outcome: 31 Total # withdrawals



(*Continued . . .*)

(. . . *Continued*)

Study	LABA + ICS n/N	ICS alone n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
Fitzgerald ICS730	17/89	18/91		3.5	0.97 [0.53, 1.75]
Hultquist BUD400	12/118	9/116		1.8	1.31 [0.57, 2.99]
Kavaru FP400	20/92	27/90		5.4	0.72 [0.44, 1.19]
Kemp ICSNR	25/252	47/254		9.2	0.54 [0.34, 0.84]
Molimard ICSNR	12/130	18/129		3.6	0.66 [0.33, 1.32]
Pauwels BUD200	47/210	53/213		10.4	0.90 [0.64, 1.27]
Pauwels BUD800	39/215	41/214		8.1	0.95 [0.64, 1.41]
Price 2002	19/332	18/331		3.6	1.05 [0.56, 1.97]
Russell ICS750	22/99	18/107		3.4	1.32 [0.75, 2.31]
Shapiro FP1000	13/84	22/84		4.3	0.59 [0.32, 1.09]
Tal BUD400	9/148	9/138		1.8	0.93 [0.38, 2.28]
Zetterstrom BUD4001d	20/123	8/62		2.1	1.26 [0.59, 2.70]
Zetterstrom BUD4002d	17/115	8/62		2.1	1.15 [0.52, 2.50]
Zimmerman ICS450F12	11/95	8/50		2.1	0.72 [0.31, 1.68]
Zimmerman ICS450F6	7/106	8/51		2.1	0.42 [0.16, 1.10]
van der Molen ICSNR	18/125	13/114		2.7	1.26 [0.65, 2.46]
Subtotal (95% CI)	2740	2341		72.5	0.87 [0.75, 0.99]
Total events: 345 (LABA + ICS), 353 (ICS alone)					
Test for heterogeneity chi-square=16.47 df=18 p=0.56 I^2 =0.0%					
Test for overall effect z=2.06 p=0.04					
04 Mean baseline FEV1 not reported					
D'Urzo ICSNR	88/455	111/456		21.9	0.79 [0.62, 1.02]
Ind 2003	27/171	15/160		3.1	1.68 [0.93, 3.05]
Subtotal (95% CI)	626	616		25.0	0.90 [0.72, 1.13]
Total events: 115 (LABA + ICS), 126 (ICS alone)					
Test for heterogeneity chi-square=5.27 df=1 p=0.02 I^2 =81.0%					
Test for overall effect z=0.88 p=0.4					
Total (95% CI)	3491	3080		100.0	0.87 [0.77, 0.97]
Total events: 465 (LABA + ICS), 490 (ICS alone)					
Test for heterogeneity chi-square=25.00 df=25 p=0.46 I^2 =0.0%					
Test for overall effect z=2.41 p=0.02					

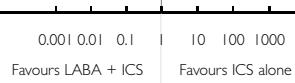
Analysis 01.32. Comparison 01 Long-acting beta2 vs placebo: both groups receiving similar dose ICS, Outcome 32 # withdrawals due to poor asthma control or exacerbation

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

Comparison: 01 Long-acting beta2 vs placebo: both groups receiving similar dose ICS

Outcome: 32 # withdrawals due to poor asthma control or exacerbation

Study	LABA + ICS n/N	ICS alone n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
01 Mean baseline FEV 1 >/=80% of predicted					
× Langton Hewer ICS400	0/11	0/12		0.0	Not estimable
Li ICS400	2/13	1/16		0.8	2.46 [0.25, 24.21]
Verberne 1998	0/60	1/56		1.5	0.31 [0.01, 7.49]
Wallin FP800	0/18	1/19		1.4	0.35 [0.02, 8.09]
Subtotal (95% CI)	102	103		3.7	0.82 [0.20, 3.40]
Total events: 2 (LABA + ICS), 3 (ICS alone)					
Test for heterogeneity chi-square=1.53 df=2 p=0.47 I^2 =0.0%					
Test for overall effect z=0.27 p=0.8					
02 Mean baseline FEV 1 61-79% of predicted					
Boyd ICS1675	2/55	2/64		1.8	1.16 [0.17, 7.99]
Buhl BUD400(bd)	4/176	2/86		2.5	0.98 [0.18, 5.23]
Buhl BUD400(qd)	5/176	3/86		3.8	0.81 [0.20, 3.33]
Hultquist BUD400	3/118	2/116		1.9	1.47 [0.25, 8.66]
Kavaru FP400	3/92	9/90		8.6	0.33 [0.09, 1.17]
Kemp ICSNR	2/252	9/254		8.5	0.22 [0.05, 1.03]
Molimard ICSNR	0/130	3/129		3.3	0.14 [0.01, 2.72]
Norhaya ICS890	1/30	3/30		2.8	0.33 [0.04, 3.03]
Pauwels BUD200	7/210	10/213		9.4	0.71 [0.28, 1.83]
Pauwels BUD800	0/215	4/214		4.3	0.11 [0.01, 2.04]
Russell ICS750	3/99	2/107		1.8	1.62 [0.28, 9.50]
Shapiro FP1000	3/81	18/81		17.1	0.17 [0.05, 0.54]
Tal BUD400	5/148	6/138		5.9	0.78 [0.24, 2.49]
Zetterstrom BUD4001d	5/123	2/62		2.5	1.26 [0.25, 6.31]
Zetterstrom BUD4002d	8/115	2/62		2.5	2.16 [0.47, 9.84]
Zimmerman ICS450F12	1/95	1/50		1.2	0.53 [0.03, 8.24]
Zimmerman ICS450F6	0/106	1/51		1.9	0.16 [0.01, 3.91]
van der Molen ICSNR	1/125	6/114		5.9	0.15 [0.02, 1.24]



(*Continued . . .*)

(. . . *Continued*)

Study	LABA + ICS n/N	ICS alone n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
Subtotal (95% CI)	2346	1947	◆	85.9	0.52 [0.37, 0.73]
Total events: 53 (LABA + ICS), 85 (ICS alone)					
Test for heterogeneity chi-square=19.01 df=17 p=0.33 I^2 =10.6%					
Test for overall effect z=3.73 p=0.0002					
03 Mean baseline FEV 1 not reported					
D'Urzo ICSNR	3/455	11/456		10.4	0.27 [0.08, 0.97]
Subtotal (95% CI)	455	456	◆	10.4	0.27 [0.08, 0.97]
Total events: 3 (LABA + ICS), 11 (ICS alone)					
Test for heterogeneity: not applicable					
Test for overall effect z=2.00 p=0.05					
Total (95% CI)	2903	2506	◆	100.0	0.50 [0.36, 0.70]
Total events: 58 (LABA + ICS), 99 (ICS alone)					
Test for heterogeneity chi-square=22.06 df=21 p=0.40 I^2 =4.8%					
Test for overall effect z=4.15 p=0.00003					

0.001 0.01 0.1 1 10 100 1000

Favours LABA + ICS Favours ICS alone

Analysis 01.33. Comparison 01 Long-acting beta2 vs placebo: both groups receiving similar dose ICS, Outcome 33 # withdrawals due to adverse events

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

Comparison: 01 Long-acting beta2 vs placebo: both groups receiving similar dose ICS

Outcome: 33 # withdrawals due to adverse events

Study	LABA + ICS n/N	ICS alone n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
01 Mean baseline FEV 1 >/=80% of predicted					
× Langton Hewer ICS400	0/11	0/11		0.0	Not estimable
Verberne 1998	2/60	0/56		0.7	4.67 [0.23, 95.24]
× Wallin FP800	0/18	0/19		0.0	Not estimable
Subtotal (95% CI)	89	86	◆	0.7	4.67 [0.23, 95.24]
Total events: 2 (LABA + ICS), 0 (ICS alone)					
Test for heterogeneity: not applicable					
Test for overall effect z=1.00 p=0.3					
02 Mean baseline FEV 1 61-79% of predicted					
Boyd ICS1675	4/55	2/64		2.5	2.33 [0.44, 12.22]
Hultquist BUD400	4/118	2/116		2.8	1.97 [0.37, 10.53]

0.001 0.01 0.1 1 10 100 1000

Favours LABA + ICS Favours ICS alone

(*Continued* . . .)

(. . . *Continued*)

Study	LABA + ICS n/N	ICS alone n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
Kavaru FP400	0/92	1/90		2.1	0.33 [0.01, 7.90]
Kemp ICSNR	7/252	5/254		6.9	1.41 [0.45, 4.39]
Molimard ICSNR	2/130	3/129		4.1	0.66 [0.11, 3.89]
Norhaya ICS890	1/30	3/30		4.1	0.33 [0.04, 3.03]
Pauwels BUD200	6/210	6/213		8.2	1.01 [0.33, 3.09]
Pauwels BUD800	9/215	8/214		11.0	1.12 [0.44, 2.85]
Price 2002	4/332	6/331		8.3	0.66 [0.19, 2.33]
Russell ICS750	4/99	2/107		2.6	2.16 [0.40, 11.54]
× Shapiro FP1000	0/84	0/84		0.0	Not estimable
Tal BUD400	2/148	0/138		0.7	4.66 [0.23, 96.30]
× Wallin FP800	0/18	0/19		0.0	Not estimable
Zetterstrom BUD4001d	8/123	3/62		5.5	1.34 [0.37, 4.89]
Zetterstrom BUD4002d	5/115	3/62		5.4	0.90 [0.22, 3.64]
Zimmerman ICS450F12	1/95	0/50		0.9	1.59 [0.07, 38.42]
Zimmerman ICS450F6	2/106	0/51		0.9	2.43 [0.12, 49.70]
van der Molen ICSNR	5/125	1/114		1.4	4.56 [0.54, 38.45]
Subtotal (95% CI)	2347	2128		67.6	1.24 [0.85, 1.79]
Total events: 64 (LABA + ICS), 45 (ICS alone)					
Test for heterogeneity chi-square=7.55 df=15 p=0.94 I^2 =0.0%					
Test for overall effect z=1.12 p=0.3					
03 Mean baseline FEV 1 not reported					
D'Urzo ICSNR	24/455	21/456		28.9	1.15 [0.65, 2.03]
Ind 2003	7/171	2/160		2.8	3.27 [0.69, 15.53]
Subtotal (95% CI)	626	616		31.7	1.34 [0.79, 2.27]
Total events: 31 (LABA + ICS), 23 (ICS alone)					
Test for heterogeneity chi-square=1.55 df=1 p=0.21 I^2 =35.6%					
Test for overall effect z=1.08 p=0.3					
Total (95% CI)	3062	2830		100.0	1.29 [0.96, 1.75]
Total events: 97 (LABA + ICS), 68 (ICS alone)					
Test for heterogeneity chi-square=9.90 df=18 p=0.94 I^2 =0.0%					
Test for overall effect z=1.67 p=0.1					

Analysis 01.34. Comparison 01 Long-acting beta2 vs placebo: both groups receiving similar dose ICS, Outcome 34 # withdrawals due to serious non-respiratory event

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

Comparison: 01 Long-acting beta2 vs placebo: both groups receiving similar dose ICS

Outcome: 34 # withdrawals due to serious non-respiratory event

Study	LABA + ICS n/N	ICS alone n/N	Relative Risk (Random) 95% CI	Relative Risk (Random) 95% CI
01 Mean baseline FEV 1 61-79% of predicted				
× Akpinarli ICS600	0/1	0/1		Not estimable
Tal BUD400	2/148	0/138		4.66 [0.23, 96.30]

Analysis 01.35. Comparison 01 Long-acting beta2 vs placebo: both groups receiving similar dose ICS, Outcome 35 Total # adverse events

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

Comparison: 01 Long-acting beta2 vs placebo: both groups receiving similar dose ICS

Outcome: 35 Total # adverse events

Study	LABA + ICS n/N	ICS alone n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
01 Mean baseline FEV 1 >/=80% of predicted					
Langton Hewer ICS400	10/11	9/12		1.5	1.21 [0.83, 1.77]
Verberne 1998	59/60	52/57		9.0	1.08 [0.99, 1.18]
Subtotal (95% CI)	71	69		10.4	1.10 [1.00, 1.20]
Total events: 69 (LABA + ICS), 61 (ICS alone)					
Test for heterogeneity chi-square=0.42 df=1 p=0.52 I^2 =0.0%					
Test for overall effect z=1.95 p=0.05					
02 Mean baseline FEV 1 61-79% of predicted					
Boyd ICS1675	44/55	53/64		8.3	0.97 [0.81, 1.15]
Buhl BUD400(bd)	60/176	39/86		8.8	0.75 [0.55, 1.02]
Buhl BUD400(qd)	71/176	39/86		8.8	0.89 [0.66, 1.19]
Fitzgerald ICS730	13/89	9/91		1.5	1.48 [0.66, 3.28]
Kemp ICSNR	134/252	130/254		21.8	1.04 [0.88, 1.23]
Molimard ICSNR	47/130	46/129		7.8	1.01 [0.73, 1.40]
Norhaya ICS890	2/30	3/30		0.5	0.67 [0.12, 3.71]
Russell ICS750	84/99	94/105		15.4	0.95 [0.85, 1.05]

(*Continued . . .*)

(. . . *Continued*)

Study	LABA + ICS n/N	ICS alone n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
× Shapiro FP1000	0/81	0/81		0.0	Not estimable
van der Molen ICSNR	104/125	94/114		16.6	1.01 [0.90, 1.13]
Subtotal (95% CI)	1213	1040		89.6	0.97 [0.90, 1.05]
Total events: 559 (LABA + ICS), 507 (ICS alone)					
Test for heterogeneity chi-square=5.53 df=8 p=0.70 I^2 =0.0%					
Test for overall effect z=0.78 p=0.4					
Total (95% CI)	1284	1109		100.0	0.98 [0.92, 1.05]
Total events: 628 (LABA + ICS), 568 (ICS alone)					
Test for heterogeneity chi-square=11.08 df=10 p=0.35 I^2 =9.8%					
Test for overall effect z=0.47 p=0.6					

Analysis 01.36. Comparison 01 Long-acting beta2 vs placebo: both groups receiving similar dose ICS, Outcome 36 Serious adverse event including respiratory

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

Comparison: 01 Long-acting beta2 vs placebo: both groups receiving similar dose ICS

Outcome: 36 Serious adverse event including respiratory

Study	LABA + ICS n/N	ICS alone n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
01 Mean baseline FEV 1 61-79% of predicted					
Buhl BUD400(bd)	2/176	1/86		33.4	0.98 [0.09, 10.63]
Buhl BUD400(qd)	1/176	1/86		33.4	0.49 [0.03, 7.72]
Zetterstrom BUD4001d	4/123	1/62		33.1	2.02 [0.23, 17.66]
× Zetterstrom BUD4002d	0/115	0/62		0.0	Not estimable
Total (95% CI)	590	296		100.0	1.16 [0.30, 4.42]
Total events: 7 (LABA + ICS), 3 (ICS alone)					
Test for heterogeneity chi-square=0.65 df=2 p=0.72 I^2 =0.0%					
Test for overall effect z=0.21 p=0.8					

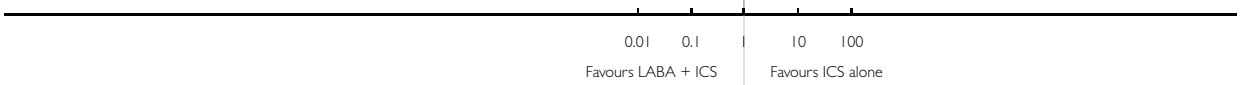
Analysis 01.37. Comparison 01 Long-acting beta2 vs placebo: both groups receiving similar dose ICS, Outcome 37 # patients with headache

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

Comparison: 01 Long-acting beta2 vs placebo: both groups receiving similar dose ICS

Outcome: 37 # patients with headache

Study	LABA + ICS n/N	ICS alone n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
01 Mean baseline FEV 1 >/=80%% of predicted					
Verberne 1998	25/60	23/57		19.3	1.03 [0.67, 1.60]
Subtotal (95% CI)	60	57		19.3	1.03 [0.67, 1.60]
Total events: 25 (LABA + ICS), 23 (ICS alone)					
Test for heterogeneity: not applicable					
Test for overall effect z=0.14 p=0.9					
02 Mean baseline FEV 1 61-79% of predicted					
× Akpinarli ICS600	0/16	0/16		0.0	Not estimable
Boyd ICS1675	17/55	17/64		12.8	1.16 [0.66, 2.05]
Kavaru FP400	2/92	0/90		0.4	4.89 [0.24, 100.51]
Kemp ICSNR	8/261	14/264		11.4	0.58 [0.25, 1.35]
Pauwels BUD200	1/210	0/213		0.4	3.04 [0.12, 74.27]
× Pauwels BUD800	0/215	0/214		0.0	Not estimable
Russell ICS750	20/99	9/107		7.1	2.40 [1.15, 5.02]
Tal BUD400	9/148	6/138		5.1	1.40 [0.51, 3.83]
Zetterstrom BUD4001d	3/123	3/62		3.3	0.50 [0.10, 2.43]
Zetterstrom BUD4002d	3/115	2/62		2.1	0.81 [0.14, 4.71]
Zimmerman ICS450F12	10/95	7/50		7.5	0.75 [0.30, 1.86]
Zimmerman ICS450F6	13/105	7/51		7.7	0.90 [0.38, 2.12]
van der Molen ICSNR	37/125	27/114		23.1	1.25 [0.82, 1.91]
Subtotal (95% CI)	1659	1445		80.7	1.16 [0.91, 1.48]
Total events: 123 (LABA + ICS), 92 (ICS alone)					
Test for heterogeneity chi-square=10.24 df=10 p=0.42 I^2 =2.3%					
Test for overall effect z=1.18 p=0.2					
Total (95% CI)	1719	1502		100.0	1.13 [0.92, 1.41]
Total events: 148 (LABA + ICS), 115 (ICS alone)					
Test for heterogeneity chi-square=10.43 df=11 p=0.49 I^2 =0.0%					
Test for overall effect z=1.15 p=0.2					



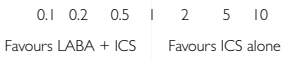
Analysis 01.38. Comparison 01 Long-acting beta2 vs placebo: both groups receiving similar dose ICS, Outcome 38 # patients with hoarseness

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

Comparison: 01 Long-acting beta2 vs placebo: both groups receiving similar dose ICS

Outcome: 38 # patients with hoarseness

Study	LABA + ICS n/N	ICS alone n/N	Relative Risk (Random) 95% CI	Weight (%)	Relative Risk (Random) 95% CI
01 Mean baseline FEV 1 61-79% of predicted					
Kavaru FP400	3/92	2/90		38.9	1.47 [0.25, 8.58]
Zetterstrom BUD4001d	0/123	3/62		19.8	0.07 [0.00, 1.38]
Zetterstrom BUD4002d	4/115	2/62		41.3	1.08 [0.20, 5.72]
Total (95% CI)	330	214		100.0	0.71 [0.16, 3.18]
Total events: 7 (LABA + ICS), 7 (ICS alone)					
Test for heterogeneity chi-square=3.28 df=2 p=0.19 I² =38.9%					
Test for overall effect z=0.44 p=0.7					



Analysis 01.39. Comparison 01 Long-acting beta2 vs placebo: both groups receiving similar dose ICS, Outcome 39 # patients with oral thrush

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

Comparison: 01 Long-acting beta2 vs placebo: both groups receiving similar dose ICS

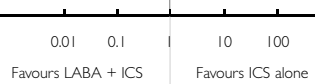
Outcome: 39 # patients with oral thrush

Study	LABA + ICS n/N	ICS alone n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
01 Mean baseline FEV 1 61-79% of predicted					
Boyd ICS1675	1/55	2/64		29.1	0.58 [0.05, 6.24]
Kavaru FP400	1/92	2/90		31.8	0.49 [0.05, 5.30]
Russell ICS750	1/99	0/107		7.6	3.24 [0.13, 78.62]
Shapiro FP1000	3/84	2/84		31.5	1.50 [0.26, 8.75]
Subtotal (95% CI)	330	345		100.0	1.04 [0.35, 3.06]
Total events: 6 (LABA + ICS), 6 (ICS alone)					
Test for heterogeneity chi-square=1.27 df=3 p=0.74 I² =0.0%					
Test for overall effect z=0.08 p=0.9					
02 FEV1 >/=80% predicted					
× Verberne 1998	0/60	0/56		0.0	Not estimable
× Wallin FP800	0/18	0/19		0.0	Not estimable

(*Continued . . .*)

(. . . *Continued*)

Study	LABA + ICS n/N	ICS alone n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
Subtotal (95% CI)	78	75		0.0	Not estimable
Total events: 0 (LABA + ICS), 0 (ICS alone)					
Test for heterogeneity: not applicable					
Test for overall effect: not applicable					
Total (95% CI)	408	420		100.0	1.04 [0.35, 3.06]
Total events: 6 (LABA + ICS), 6 (ICS alone)					
Test for heterogeneity chi-square=1.27 df=3 p=0.74 I^2 =0.0%					
Test for overall effect z=0.08 p=0.9					



Analysis 01.40. Comparison 01 Long-acting beta2 vs placebo: both groups receiving similar dose ICS, Outcome 40 # patients with tremor

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

Comparison: 01 Long-acting beta2 vs placebo: both groups receiving similar dose ICS

Outcome: 40 # patients with tremor

Study	LABA + ICS n/N	ICS alone n/N	Relative Risk (Random) 95% CI	Weight (%)	Relative Risk (Random) 95% CI
01 Mean baseline FEV 1 >/=80% of predicted					
× Verberne 1998	0/60	0/56		0.0	Not estimable
Subtotal (95% CI)	60	56		0.0	Not estimable
Total events: 0 (LABA + ICS), 0 (ICS alone)					
Test for heterogeneity: not applicable					
Test for overall effect: not applicable					
02 Mean baseline FEV 1 61-79% of predicted					
Boyd ICS1675	3/55	3/64		25.5	1.16 [0.24, 5.53]
Kemp ICSNR	4/261	0/264		11.8	9.10 [0.49, 168.23]
Norhaya ICS890	1/30	3/30		17.4	0.33 [0.04, 3.03]
Pauwels BUD200	2/210	0/213		11.2	5.07 [0.24, 105.00]
Pauwels BUD800	2/215	0/214		11.2	4.98 [0.24, 103.06]
× Russell ICS750	0/99	0/107		0.0	Not estimable
× Zimmerman ICS450F12	0/95	0/50		0.0	Not estimable
Zimmerman ICS450F6	1/106	0/51		10.3	1.46 [0.06, 35.18]
van der Molen ICSNR	13/125	0/114		12.5	24.64 [1.48, 409.86]

(*Continued* . . .)

(. . . *Continued*)

Study	LABA + ICS n/N	ICS alone n/N	Relative Risk (Random) 95% CI	Weight (%)	Relative Risk (Random) 95% CI
Subtotal (95% CI)	1196	1107		100.0	2.48 [0.78, 7.89]
Total events: 26 (LABA + ICS), 6 (ICS alone)					
Test for heterogeneity chi-square=8.65 df=6 p=0.19 I^2 =30.7%					
Test for overall effect z=1.54 p=0.1					
Total (95% CI)	1256	1163		100.0	2.48 [0.78, 7.89]
Total events: 26 (LABA + ICS), 6 (ICS alone)					
Test for heterogeneity chi-square=8.65 df=6 p=0.19 I^2 =30.7%					
Test for overall effect z=1.54 p=0.1					

Analysis 01.41. Comparison 01 Long-acting beta2 vs placebo: both groups receiving similar dose ICS, Outcome 41 # patients with tachycardia or palpitations

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

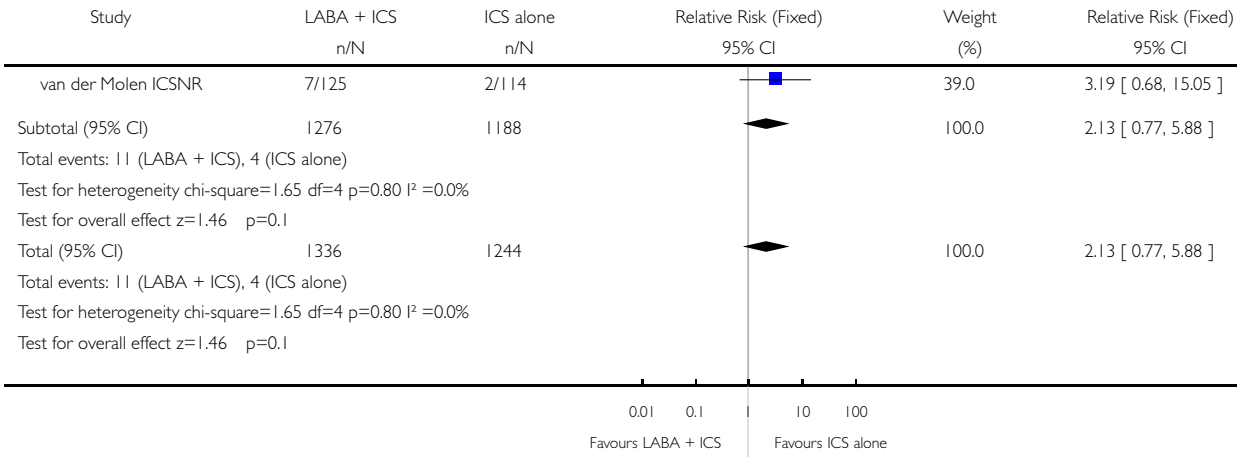
Comparison: 01 Long-acting beta2 vs placebo: both groups receiving similar dose ICS

Outcome: 41 # patients with tachycardia or palpitations

Study	LABA + ICS n/N	ICS alone n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
01 Mean baseline FEV 1 >/=80% of predicted					
× Verberne 1998	0/60	0/56		0.0	Not estimable
Subtotal (95% CI)	60	56		0.0	Not estimable
Total events: 0 (LABA + ICS), 0 (ICS alone)					
Test for heterogeneity: not applicable					
Test for overall effect: not applicable					
02 Mean baseline FEV 1 61-79% of predicted					
Boyd ICS1675	1/55	1/64		17.2	1.16 [0.07, 18.17]
Kemp ICSNR	1/261	0/264		9.3	3.03 [0.12, 74.15]
× Norhaya ICS890	0/30	0/30		0.0	Not estimable
× Pauwels BUD200	0/210	0/213		0.0	Not estimable
Pauwels BUD800	1/215	0/214		9.3	2.99 [0.12, 72.89]
× Russell ICS750	0/99	0/107		0.0	Not estimable
× Shapiro FP1000	0/81	0/81		0.0	Not estimable
× Zimmerman ICS450F12	0/95	0/50		0.0	Not estimable
Zimmerman ICS450F6	1/105	1/51		25.1	0.49 [0.03, 7.61]

(*Continued* . . .)

(. . . *Continued*)

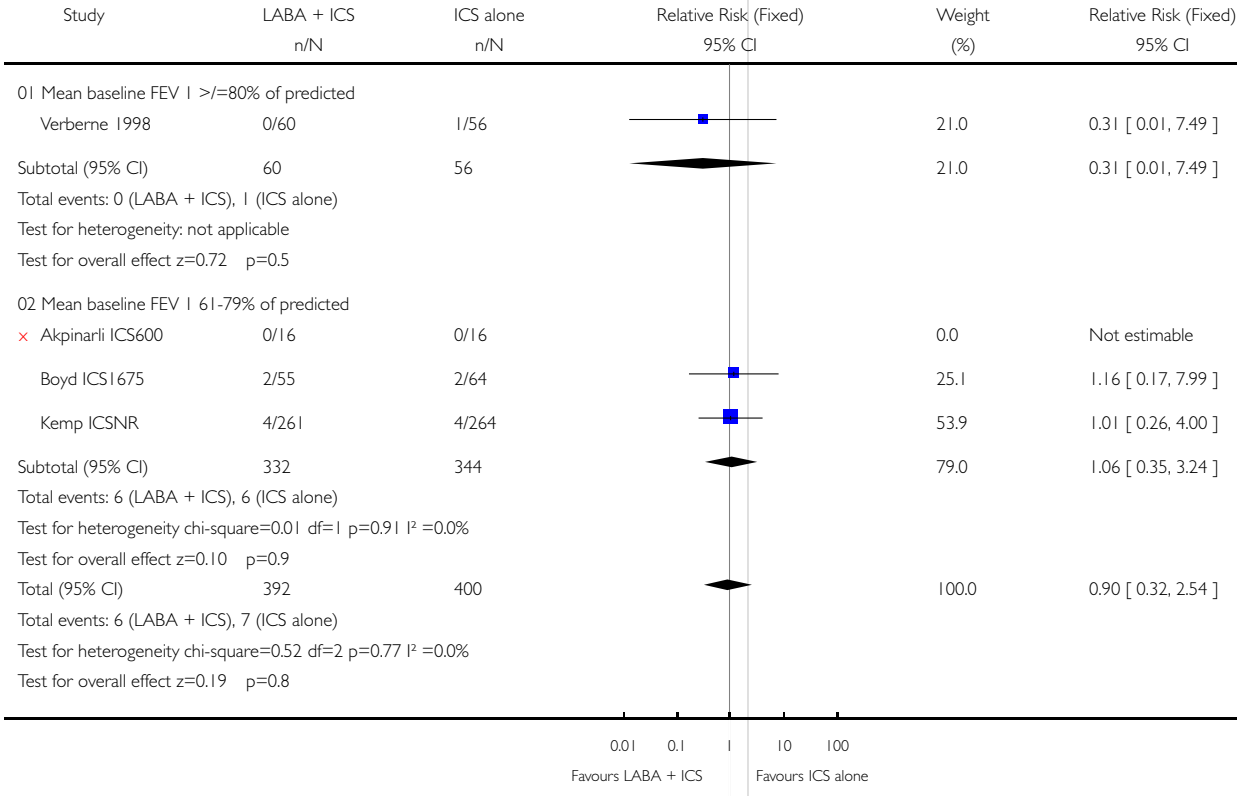


Analysis 01.42. Comparison 01 Long-acting beta2 vs placebo: both groups receiving similar dose ICS, Outcome 42 # patients with adverse cardiovascular events

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

Comparison: 01 Long-acting beta2 vs placebo: both groups receiving similar dose ICS

Outcome: 42 # patients with adverse cardiovascular events

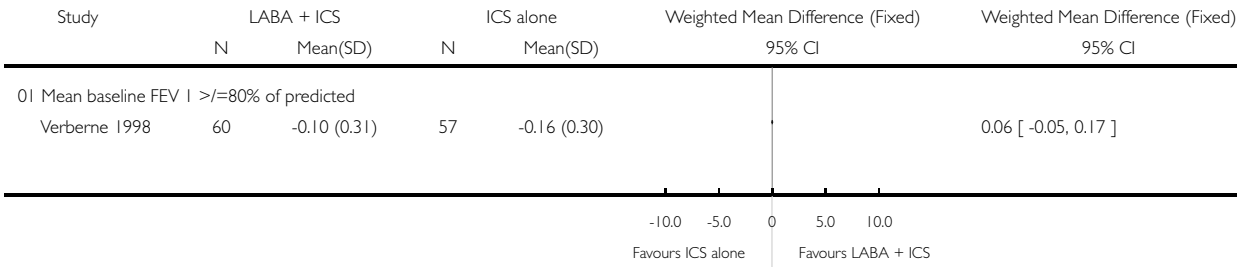


Analysis 01.43. Comparison 01 Long-acting beta2 vs placebo: both groups receiving similar dose ICS, Outcome 43 Change in height (cm) as SD scores at 24 +/- 4 weeks

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

Comparison: 01 Long-acting beta2 vs placebo: both groups receiving similar dose ICS

Outcome: 43 Change in height (cm) as SD scores at 24 +/- 4 weeks

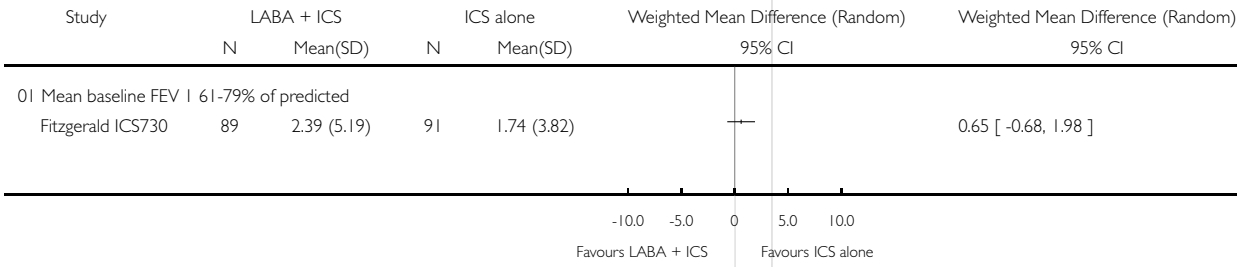


Analysis 01.44. Comparison 01 Long-acting beta2 vs placebo: both groups receiving similar dose ICS, Outcome 44 PC20 Methacholine-adjusted odds ratio increase from baseline

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

Comparison: 01 Long-acting beta2 vs placebo: both groups receiving similar dose ICS

Outcome: 44 PC20 Methacholine-adjusted odds ratio increase from baseline

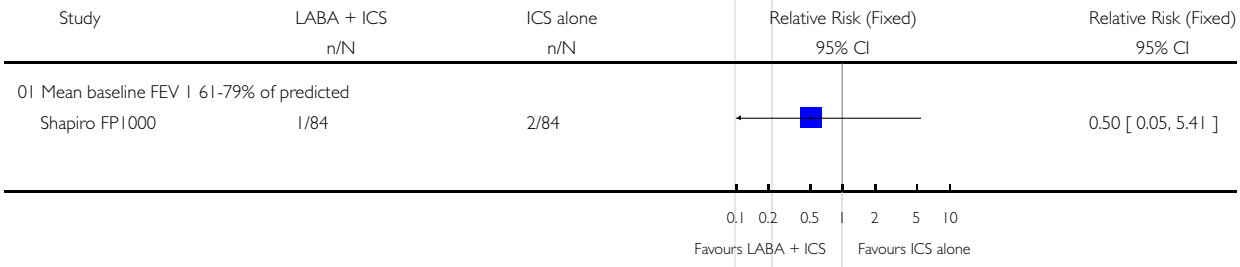


Analysis 01.45. Comparison 01 Long-acting beta2 vs placebo: both groups receiving similar dose ICS, Outcome 45 ACTH induced cortisol <18microg/dl at endpoint

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

Comparison: 01 Long-acting beta2 vs placebo: both groups receiving similar dose ICS

Outcome: 45 ACTH induced cortisol <18microg/dl at endpoint

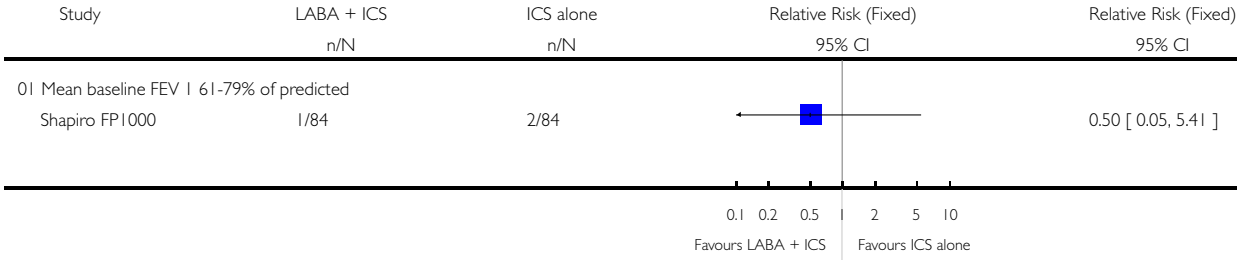


Analysis 01.46. Comparison 01 Long-acting beta2 vs placebo: both groups receiving similar dose ICS, Outcome 46 Am cortisol < 5 microg/dl at endpoint

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

Comparison: 01 Long-acting beta2 vs placebo: both groups receiving similar dose ICS

Outcome: 46 Am cortisol < 5 microg/dl at endpoint

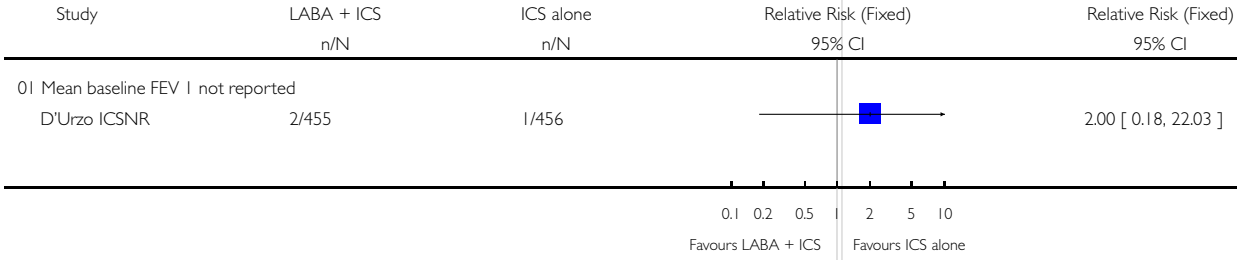


Analysis 01.47. Comparison 01 Long-acting beta2 vs placebo: both groups receiving similar dose ICS, Outcome 47 Deaths

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

Comparison: 01 Long-acting beta2 vs placebo: both groups receiving similar dose ICS

Outcome: 47 Deaths

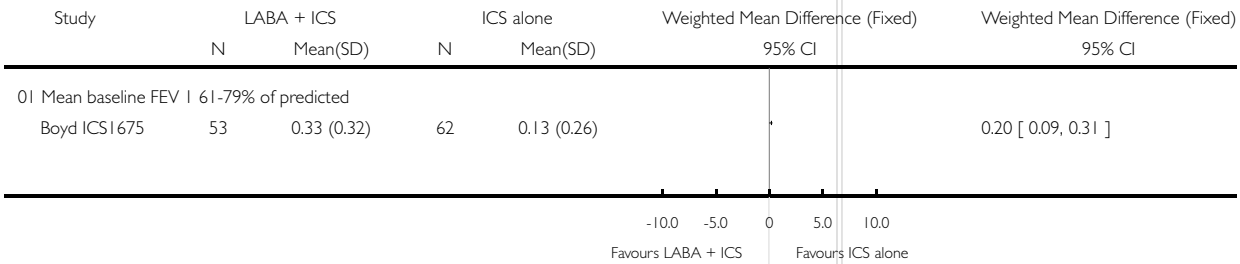


Analysis 01.48. Comparison 01 Long-acting beta2 vs placebo: both groups receiving similar dose ICS, Outcome 48 Change in # of symptom-free nights at endpoint

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

Comparison: 01 Long-acting beta2 vs placebo: both groups receiving similar dose ICS

Outcome: 48 Change in # of symptom-free nights at endpoint

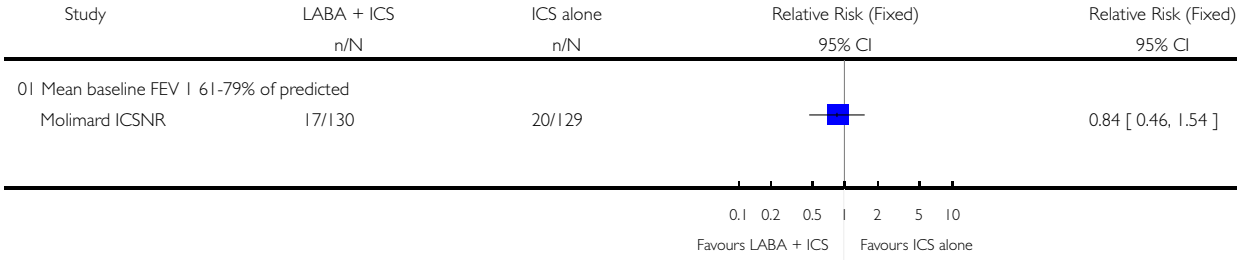


Analysis 01.49. Comparison 01 Long-acting beta2 vs placebo: both groups receiving similar dose ICS, Outcome 49 # Worsening asthma

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

Comparison: 01 Long-acting beta2 vs placebo: both groups receiving similar dose ICS

Outcome: 49 # Worsening asthma

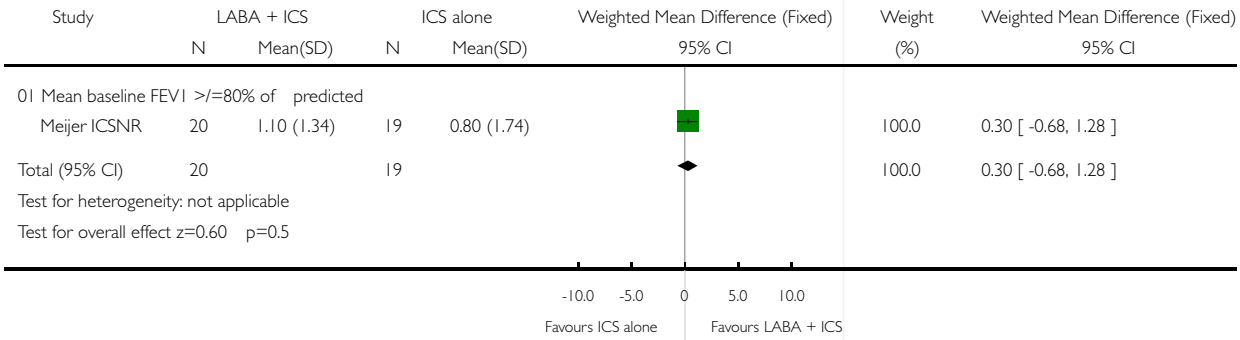


Analysis 01.50. Comparison 01 Long-acting beta2 vs placebo: both groups receiving similar dose ICS, Outcome 50 Change in % PC 20 at endpoint

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

Comparison: 01 Long-acting beta2 vs placebo: both groups receiving similar dose ICS

Outcome: 50 Change in % PC 20 at endpoint



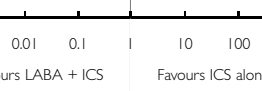
Analysis 02.01. Comparison 02 Additional comparisons for same dose, Outcome 01 # patients with exacerbations requiring oral steroids by FEV1 % predicted at baseline

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

Comparison: 02 Additional comparisons for same dose

Outcome: 01 # patients with exacerbations requiring oral steroids by FEV1 % predicted at baseline

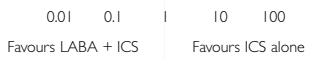
Study	LABA + ICS n/N	ICS alone n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
01 Mean baseline FEV 1 >/= 80% of predicted					
Langton Hewer ICS400	3/11	3/12		0.5	1.09 [0.28, 4.32]
Li ICS400	2/13	1/16		0.2	2.46 [0.25, 24.21]
O'Byrne BUD200	58/323	81/322		14.6	0.71 [0.53, 0.96]
O'Byrne BUD400	39/315	61/312		11.1	0.63 [0.44, 0.92]
Simons BUD150	0/16	1/16		0.3	0.33 [0.01, 7.62]
Verberne 1998	10/60	10/57		1.9	0.95 [0.43, 2.11]
Wallin FP800	1/18	5/19		0.9	0.21 [0.03, 1.64]
Subtotal (95% CI)	756	754		29.4	0.70 [0.56, 0.86]
Total events: 113 (LABA + ICS), 162 (ICS alone)					
Test for heterogeneity chi-square=3.96 df=6 p=0.68 I^2 =0.0%					
Test for overall effect z=3.27 p=0.001					
02 Mean baseline FEV1 61-79% of predicted					
× Akpinarli ICS600	0/16	0/16		0.0	Not estimable
Boyd ICS1675	19/55	15/64		2.5	1.47 [0.83, 2.61]
Fitzgerald ICS730	3/89	6/91		1.1	0.51 [0.13, 1.98]
Kemp ICSNR	53/252	59/254		10.6	0.91 [0.65, 1.26]
Norhaya ICS890	1/30	3/30		0.5	0.33 [0.04, 3.03]
Pauwels BUD200	62/210	82/213		14.7	0.77 [0.59, 1.00]
Pauwels BUD800	41/215	60/214		10.9	0.68 [0.48, 0.96]
Russell ICS750	16/99	18/99		3.2	0.89 [0.48, 1.64]
van der Molen ICSNR	33/125	32/114		6.0	0.94 [0.62, 1.42]
Subtotal (95% CI)	1091	1095		49.6	0.83 [0.72, 0.97]
Total events: 228 (LABA + ICS), 275 (ICS alone)					
Test for heterogeneity chi-square=7.25 df=7 p=0.40 I^2 =3.4%					
Test for overall effect z=2.38 p=0.02					
03 Mean baseline FEV 1 not reported					
Ind 2003	111/171	113/160		21.1	0.92 [0.79, 1.07]
Subtotal (95% CI)	171	160		21.1	0.92 [0.79, 1.07]



(*Continued . . .*)

(. . . *Continued*)

Study	LABA + ICS n/N	ICS alone n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
Total events: 111 (LABA + ICS), 113 (ICS alone)					
Test for heterogeneity: not applicable					
Test for overall effect z=1.11 p=0.3					
Total (95% CI)	2018	2009		100.0	0.81 [0.73, 0.90]
Total events: 452 (LABA + ICS), 550 (ICS alone)					
Test for heterogeneity chi-square=15.75 df=15 p=0.40 I^2 =4.8%					
Test for overall effect z=4.05 p=0.00005					



Analysis 02.02. Comparison 02 Additional comparisons for same dose, Outcome 02 # patients with exacerbations requiring oral steroids children versus adults

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

Comparison: 02 Additional comparisons for same dose

Outcome: 02 # patients with exacerbations requiring oral steroids children versus adults

Study	LABA + ICS n/N	ICS alone n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
01 Children					
× Akpinarli ICS600	0/16	0/16		0.0	Not estimable
Langton Hewer ICS400	3/11	3/12		0.5	1.09 [0.28, 4.32]
Russell ICS750	16/99	18/99		3.2	0.89 [0.48, 1.64]
Simons BUD150	0/16	1/16		0.3	0.33 [0.01, 7.62]
Verberne 1998	10/60	10/57		1.9	0.95 [0.43, 2.11]
Subtotal (95% CI)	202	200		5.9	0.90 [0.57, 1.42]
Total events: 29 (LABA + ICS), 32 (ICS alone)					
Test for heterogeneity chi-square=0.48 df=3 p=0.92 I^2 =0.0%					
Test for overall effect z=0.45 p=0.6					
02 Adults					
Boyd ICS1675	19/55	15/64		2.5	1.47 [0.83, 2.61]
Fitzgerald ICS730	3/89	6/91		1.1	0.51 [0.13, 1.98]
Ind 2003	111/171	113/160		21.1	0.92 [0.79, 1.07]
Kemp ICSNR	53/252	59/254		10.6	0.91 [0.65, 1.26]
Li ICS400	2/13	1/16		0.2	2.46 [0.25, 24.21]
Norhaya ICS890	1/30	3/30		0.5	0.33 [0.04, 3.03]

(*Continued* . . .)

(. . . *Continued*)

Study	LABA + ICS n/N	ICS alone n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
O'Byrne BUD200	58/323	81/322		14.6	0.71 [0.53, 0.96]
O'Byrne BUD400	39/315	61/312		11.1	0.63 [0.44, 0.92]
Pauwels BUD200	62/210	82/213		14.7	0.77 [0.59, 1.00]
Pauwels BUD800	41/215	60/214		10.9	0.68 [0.48, 0.96]
Wallin FP800	1/18	5/19		0.9	0.21 [0.03, 1.64]
van der Molen ICSNR	33/125	32/114		6.0	0.94 [0.62, 1.42]
Subtotal (95% CI)	1816	1809		94.1	0.80 [0.73, 0.89]
Total events: 423 (LABA + ICS), 518 (ICS alone)					
Test for heterogeneity chi-square=15.23 df=11 p=0.17 I^2 =27.8%					
Test for overall effect z=4.08 p=0.00005					
Total (95% CI)	2018	2009		100.0	0.81 [0.73, 0.90]
Total events: 452 (LABA + ICS), 550 (ICS alone)					
Test for heterogeneity chi-square=15.75 df=15 p=0.40 I^2 =4.8%					
Test for overall effect z=4.05 p=0.00005					

Analysis 02.03. Comparison 02 Additional comparisons for same dose, Outcome 03 # patients with exacerbations requiring oral steroids by dose of ICS in both groups

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

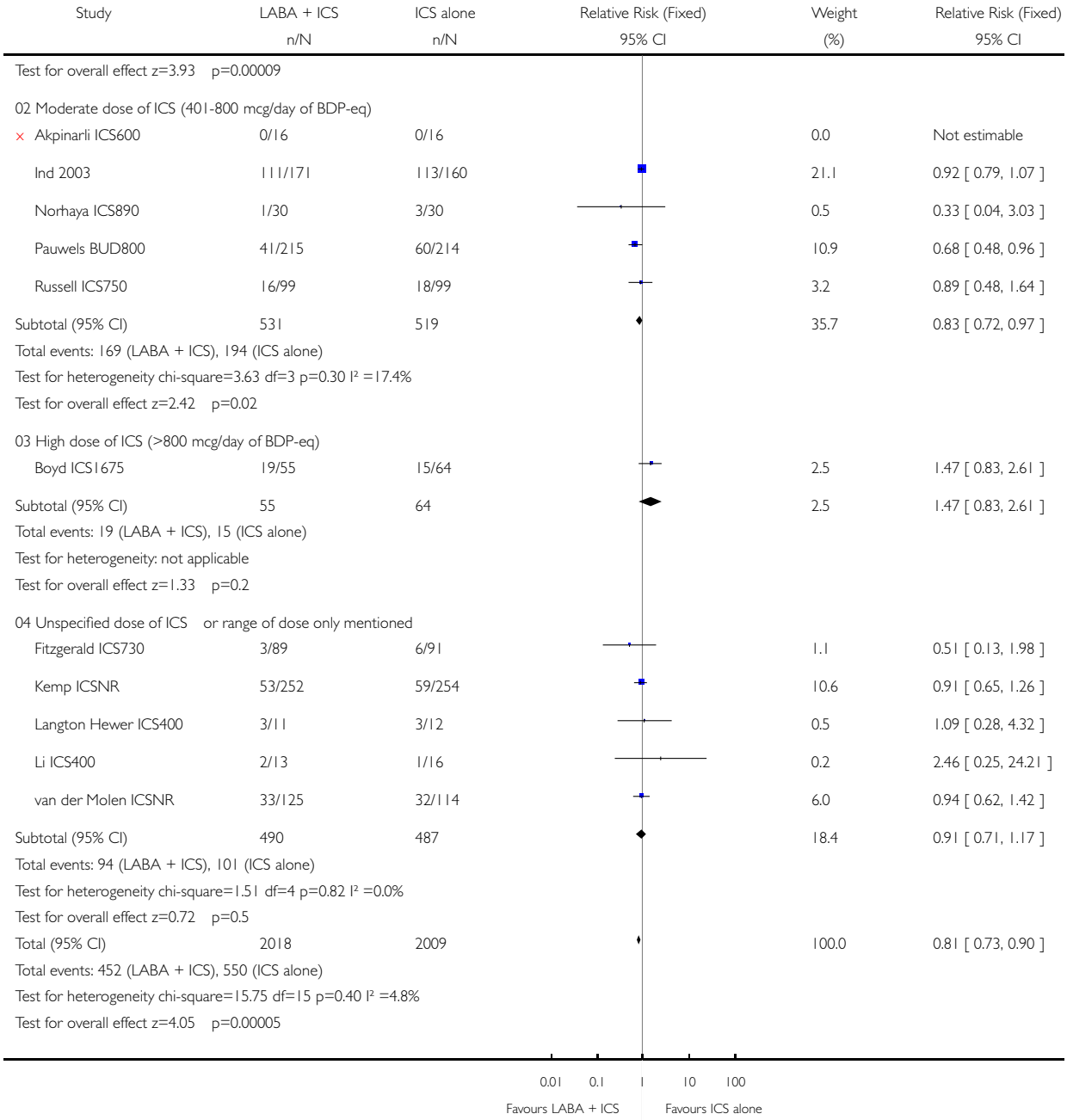
Comparison: 02 Additional comparisons for same dose

Outcome: 03 # patients with exacerbations requiring oral steroids by dose of ICS in both groups

Study	LABA + ICS n/N	ICS alone n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
01 Low dose of ICS (<= 400 mcg/day of BDP-eq)					
O'Byrne BUD200	58/323	81/322		14.6	0.71 [0.53, 0.96]
O'Byrne BUD400	39/315	61/312		11.1	0.63 [0.44, 0.92]
Pauwels BUD200	62/210	82/213		14.7	0.77 [0.59, 1.00]
Simons BUD150	0/16	1/16		0.3	0.33 [0.01, 7.62]
Verberne 1998	10/60	10/57		1.9	0.95 [0.43, 2.11]
Wallin FP800	1/18	5/19		0.9	0.21 [0.03, 1.64]
Subtotal (95% CI)	942	939		43.4	0.71 [0.60, 0.84]
Total events: 170 (LABA + ICS), 240 (ICS alone)					
Test for heterogeneity chi-square=2.77 df=5 p=0.74 I^2 =0.0%					

(*Continued* . . .)

(. . . *Continued*)



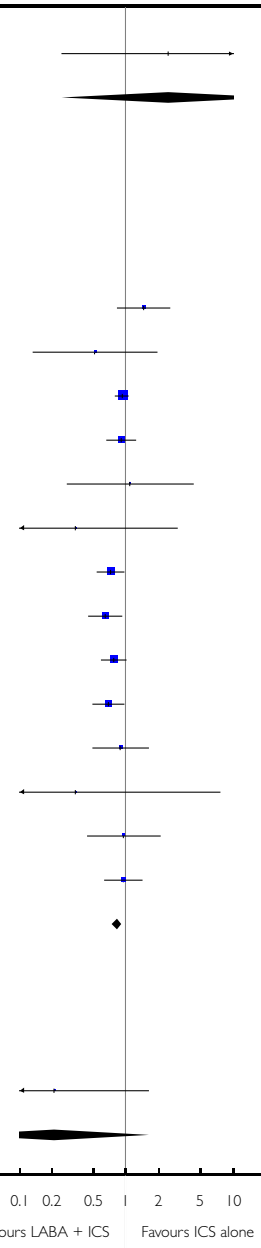
Analysis 02.04. Comparison 02 Additional comparisons for same dose, Outcome 04 # patients with exacerbations requiring oral steroids by combination inhaler or separate inhaler for LABA

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

Comparison: 02 Additional comparisons for same dose

Outcome: 04 # patients with exacerbations requiring oral steroids by combination inhaler or separate inhaler for LABA

Study	LABA + ICS n/N	ICS alone n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
01 Combination inhaler					
Li ICS400	2/13	1/16		0.2	2.46 [0.25, 24.21]
Subtotal (95% CI)	13	16		0.2	2.46 [0.25, 24.21]
Total events: 2 (LABA + ICS), 1 (ICS alone)					
Test for heterogeneity: not applicable					
Test for overall effect z=0.77 p=0.4					
02 Separate inhaler					
× Akpinarli ICS600	0/16	0/16		0.0	Not estimable
Boyd ICS1675	19/55	15/64		2.5	1.47 [0.83, 2.61]
Fitzgerald ICS730	3/89	6/91		1.1	0.51 [0.13, 1.98]
Ind 2003	111/171	113/160		21.1	0.92 [0.79, 1.07]
Kemp ICSNR	53/252	59/254		10.6	0.91 [0.65, 1.26]
Langton Hewer ICS400	3/11	3/12		0.5	1.09 [0.28, 4.32]
Norhaya ICS890	1/30	3/30		0.5	0.33 [0.04, 3.03]
O'Byrne BUD200	58/323	81/322		14.6	0.71 [0.53, 0.96]
O'Byrne BUD400	39/315	61/312		11.1	0.63 [0.44, 0.92]
Pauwels BUD200	62/210	82/213		14.7	0.77 [0.59, 1.00]
Pauwels BUD800	41/215	60/214		10.9	0.68 [0.48, 0.96]
Russell ICS750	16/99	18/99		3.2	0.89 [0.48, 1.64]
Simons BUD150	0/16	1/16		0.3	0.33 [0.01, 7.62]
Verberne 1998	10/60	10/57		1.9	0.95 [0.43, 2.11]
van der Molen ICSNR	33/125	32/114		6.0	0.94 [0.62, 1.42]
Subtotal (95% CI)	1987	1974		99.0	0.81 [0.73, 0.90]
Total events: 449 (LABA + ICS), 544 (ICS alone)					
Test for heterogeneity chi-square=13.09 df=13 p=0.44 I^2 =0.7%					
Test for overall effect z=3.97 p=0.00007					
03 Not reported					
Wallin FP800	1/18	5/19		0.9	0.21 [0.03, 1.64]
Subtotal (95% CI)	18	19		0.9	0.21 [0.03, 1.64]



(*Continued . . .*)

(. . . *Continued*)

Study	LABA + ICS n/N	ICS alone n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
Total events: 1 (LABA + ICS), 5 (ICS alone)					
Test for heterogeneity: not applicable					
Test for overall effect z=1.49 p=0.1					
Total (95% CI)	2018	2009	◆	100.0	0.81 [0.73, 0.90]
Total events: 452 (LABA + ICS), 550 (ICS alone)					
Test for heterogeneity chi-square=15.75 df=15 p=0.40 I^2 =4.8%					
Test for overall effect z=4.05 p=0.00005					

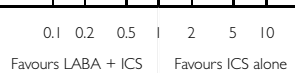
Analysis 02.05. Comparison 02 Additional comparisons for same dose, Outcome 05 # patients with exacerbations requiring oral steroids by whether LABA dose is usual or higher than usual

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

Comparison: 02 Additional comparisons for same dose

Outcome: 05 # patients with exacerbations requiring oral steroids by whether LABA dose is usual or higher than usual

Study	LABA + ICS n/N	ICS alone n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
02 LABA at usual dose					
× Akpinarli ICS600	0/16	0/16		0.0	Not estimable
Fitzgerald ICS730	3/89	6/91		1.1	0.51 [0.13, 1.98]
Ind 2003	111/171	113/160		21.1	0.92 [0.79, 1.07]
Kemp ICSNR	53/252	59/254		10.6	0.91 [0.65, 1.26]
Li ICS400	2/13	1/16		0.2	2.46 [0.25, 24.21]
Norhaya ICS890	1/30	3/30		0.5	0.33 [0.04, 3.03]
O'Byrne BUD200	58/323	81/322		14.6	0.71 [0.53, 0.96]
O'Byrne BUD400	39/315	61/312		11.1	0.63 [0.44, 0.92]
Pauwels BUD200	62/210	82/213		14.7	0.77 [0.59, 1.00]
Pauwels BUD800	41/215	60/214		10.9	0.68 [0.48, 0.96]
Russell ICS750	16/99	18/99		3.2	0.89 [0.48, 1.64]
Simons BUD150	0/16	1/16		0.3	0.33 [0.01, 7.62]
Verberne 1998	10/60	10/57		1.9	0.95 [0.43, 2.11]
Wallin FP800	1/18	5/19		0.9	0.21 [0.03, 1.64]



(*Continued* . . .)

(. . . *Continued*)

Study	LABA + ICS n/N	ICS alone n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
Subtotal (95% CI)	1827	1819	◆	90.9	0.78 [0.70, 0.87]
Total events: 397 (LABA + ICS), 500 (ICS alone)					
Test for heterogeneity chi-square=11.71 df=12 p=0.47 I^2 =0.0%					
Test for overall effect z=4.49 p<0.00001					
03 LABA at higher than usual dose					
Boyd ICS1675	19/55	15/64		2.5	1.47 [0.83, 2.61]
Langton Hewer ICS400	3/11	3/12		0.5	1.09 [0.28, 4.32]
van der Molen ICSNR	33/125	32/114		6.0	0.94 [0.62, 1.42]
Subtotal (95% CI)	191	190	◆	9.1	1.10 [0.79, 1.52]
Total events: 55 (LABA + ICS), 50 (ICS alone)					
Test for heterogeneity chi-square=1.55 df=2 p=0.46 I^2 =0.0%					
Test for overall effect z=0.56 p=0.6					
Total (95% CI)	2018	2009	◆	100.0	0.81 [0.73, 0.90]
Total events: 452 (LABA + ICS), 550 (ICS alone)					
Test for heterogeneity chi-square=15.75 df=15 p=0.40 I^2 =4.8%					
Test for overall effect z=4.05 p=0.00005					

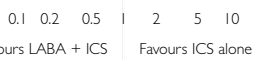
Analysis 02.06. Comparison 02 Additional comparisons for same dose, Outcome 06 # patients with exacerbations requiring oral steroids by type of LABA

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

Comparison: 02 Additional comparisons for same dose

Outcome: 06 # patients with exacerbations requiring oral steroids by type of LABA

Study	LABA + ICS n/N	ICS alone n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
01 Formoterol					
× Akpinarli ICS600	0/16	0/16		0.0	Not estimable
Fitzgerald ICS730	3/89	6/91		1.1	0.51 [0.13, 1.98]
O'Byrne BUD200	58/323	81/322		14.6	0.71 [0.53, 0.96]
O'Byrne BUD400	39/315	61/312		11.1	0.63 [0.44, 0.92]
Pauwels BUD200	62/210	82/213		14.7	0.77 [0.59, 1.00]
Pauwels BUD800	41/215	60/214		10.9	0.68 [0.48, 0.96]
van der Molen ICSNR	33/125	32/114		6.0	0.94 [0.62, 1.42]



(*Continued* . . .)

(. . . *Continued*)

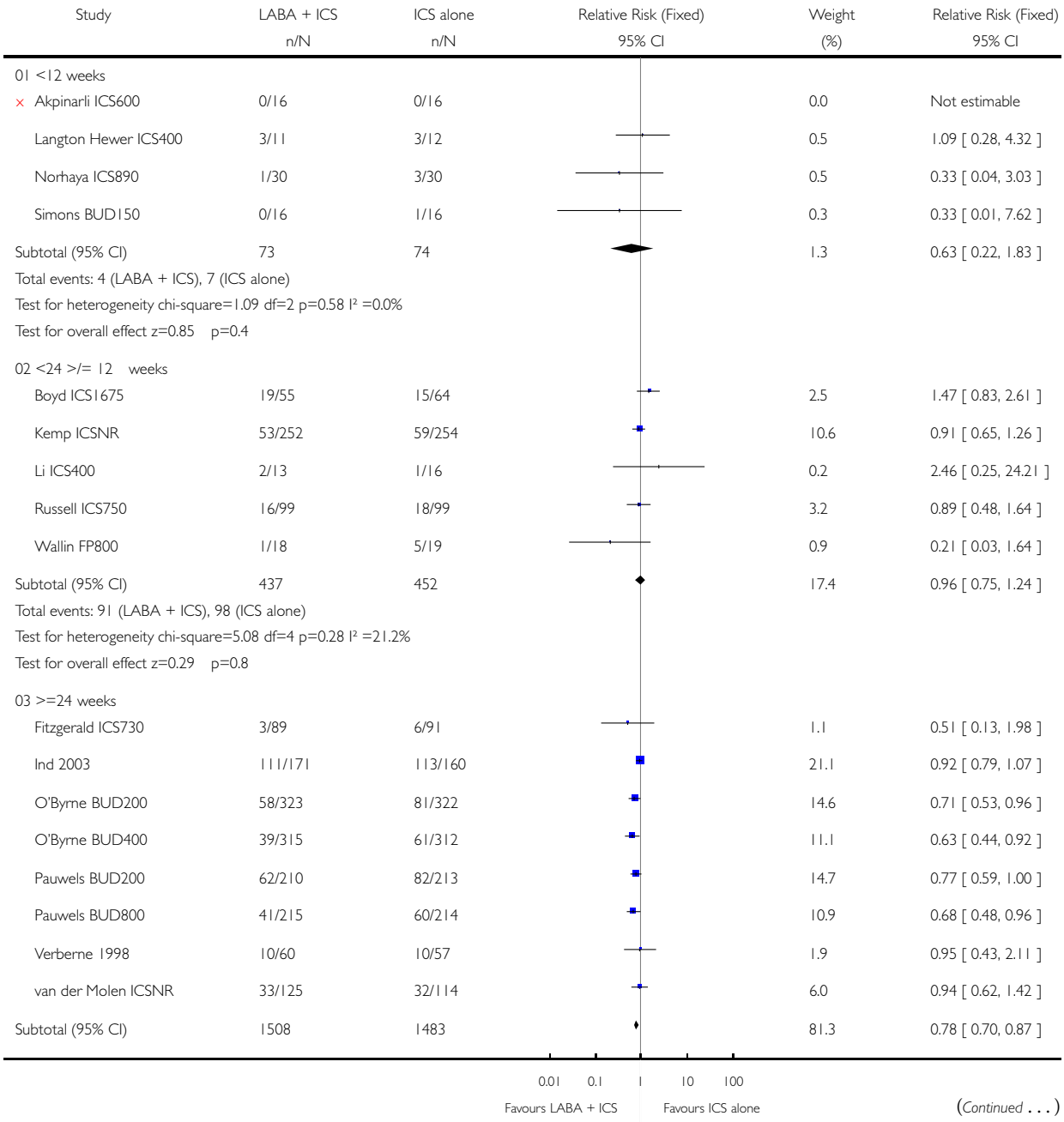
Study	LABA + ICS n/N	ICS alone n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
Subtotal (95% CI)	1293	1282		58.4	0.73 [0.63, 0.84]
Total events: 236 (LABA + ICS), 322 (ICS alone)					
Test for heterogeneity chi-square=2.59 df=5 p=0.76 I^2 =0.0%					
Test for overall effect z=4.29 p=0.00002					
02 Salmeterol					
Boyd ICS1675	19/55	15/64		2.5	1.47 [0.83, 2.61]
Ind 2003	111/171	113/160		21.1	0.92 [0.79, 1.07]
Kemp ICSNR	53/252	59/254		10.6	0.91 [0.65, 1.26]
Langton Hewer ICS400	3/11	3/12		0.5	1.09 [0.28, 4.32]
Li ICS400	2/13	1/16		0.2	2.46 [0.25, 24.21]
Norhaya ICS890	1/30	3/30		0.5	0.33 [0.04, 3.03]
Russell ICS750	16/99	18/99		3.2	0.89 [0.48, 1.64]
Simons BUD150	0/16	1/16		0.3	0.33 [0.01, 7.62]
Verberne 1998	10/60	10/57		1.9	0.95 [0.43, 2.11]
Wallin FP800	1/18	5/19		0.9	0.21 [0.03, 1.64]
Subtotal (95% CI)	725	727		41.6	0.93 [0.81, 1.07]
Total events: 216 (LABA + ICS), 228 (ICS alone)					
Test for heterogeneity chi-square=6.56 df=9 p=0.68 I^2 =0.0%					
Test for overall effect z=1.03 p=0.3					
Total (95% CI)	2018	2009		100.0	0.81 [0.73, 0.90]
Total events: 452 (LABA + ICS), 550 (ICS alone)					
Test for heterogeneity chi-square=15.75 df=15 p=0.40 I^2 =4.8%					
Test for overall effect z=4.05 p=0.00005					

Analysis 02.07. Comparison 02 Additional comparisons for same dose, Outcome 07 # patients with exacerbations requiring oral steroids by trial duration

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

Comparison: 02 Additional comparisons for same dose

Outcome: 07 # patients with exacerbations requiring oral steroids by trial duration



(*Continued . . .*)

(. . . *Continued*)

Study	LABA + ICS n/N	ICS alone n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
Total events: 357 (LABA + ICS), 445 (ICS alone)					
Test for heterogeneity chi-square=8.19 df=7 p=0.32 I^2 =14.6%					
Test for overall effect z=4.35 p=0.00001					
Total (95% CI)	2018	2009		100.0	0.81 [0.73, 0.90]
Total events: 452 (LABA + ICS), 550 (ICS alone)					
Test for heterogeneity chi-square=15.75 df=15 p=0.40 I^2 =4.8%					
Test for overall effect z=4.05 p=0.00005					

Analysis 02.08. Comparison 02 Additional comparisons for same dose, Outcome 08 # patients with exacerbations requiring oral steroids study unsupported by pharmaceutical industry excluded

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

Comparison: 02 Additional comparisons for same dose

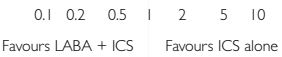
Outcome: 08 # patients with exacerbations requiring oral steroids study unsupported by pharmaceutical industry excluded

Study	LABA + ICS n/N	ICS alone n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
01 Charity Funded					
Langton Hewer ICS400	3/11	3/12		0.5	1.09 [0.28, 4.32]
Subtotal (95% CI)	11	12		0.5	1.09 [0.28, 4.32]
Total events: 3 (LABA + ICS), 3 (ICS alone)					
Test for heterogeneity: not applicable					
Test for overall effect z=0.12 p=0.9					
02 Funded by pharmaceutical industry					
× Akpinarli ICS600	0/16	0/16		0.0	Not estimable
Boyd ICS1675	19/55	15/64		2.5	1.47 [0.83, 2.61]
Fitzgerald ICS730	3/89	6/91		1.1	0.51 [0.13, 1.98]
Ind 2003	111/171	113/160		21.1	0.92 [0.79, 1.07]
Kemp ICSNR	53/252	59/254		10.6	0.91 [0.65, 1.26]
Li ICS400	2/13	1/16		0.2	2.46 [0.25, 24.21]
Norhaya ICS890	1/30	3/30		0.5	0.33 [0.04, 3.03]
O'Byrne BUD200	58/323	81/322		14.6	0.71 [0.53, 0.96]
O'Byrne BUD400	39/315	61/312		11.1	0.63 [0.44, 0.92]
Pauwels BUD200	62/210	82/213		14.7	0.77 [0.59, 1.00]

(*Continued* . . .)

(. . . *Continued*)

Study	LABA + ICS n/N	ICS alone n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
Pauwels BUD800	41/215	60/214		10.9	0.68 [0.48, 0.96]
Russell ICS750	16/99	18/99		3.2	0.89 [0.48, 1.64]
Simons BUD150	0/16	1/16		0.3	0.33 [0.01, 7.62]
Verberne 1998	10/60	10/57		1.9	0.95 [0.43, 2.11]
Wallin FP800	1/18	5/19		0.9	0.21 [0.03, 1.64]
van der Molen ICSNR	33/125	32/114		6.0	0.94 [0.62, 1.42]
Subtotal (95% CI)	2007	1997		99.5	0.81 [0.73, 0.90]
Total events: 449 (LABA + ICS), 547 (ICS alone)					
Test for heterogeneity chi-square=15.63 df=14 p=0.34 I^2 =10.4%					
Test for overall effect z=4.07 p=0.00005					
Total (95% CI)	2018	2009		100.0	0.81 [0.73, 0.90]
Total events: 452 (LABA + ICS), 550 (ICS alone)					
Test for heterogeneity chi-square=15.75 df=15 p=0.40 I^2 =4.8%					
Test for overall effect z=4.05 p=0.00005					



Analysis 02.09. Comparison 02 Additional comparisons for same dose, Outcome 09 # patients with exacerbations requiring oral steroids with studies with Jadad score < 4 excluded

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

Comparison: 02 Additional comparisons for same dose

Outcome: 09 # patients with exacerbations requiring oral steroids with studies with Jadad score < 4 excluded

Study	LABA + ICS n/N	ICS alone n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
01 Jadad score < 4					
× Akpinarli ICS600	0/16	0/16		0.0	Not estimable
Wallin FP800	1/18	5/19		0.9	0.21 [0.03, 1.64]
Subtotal (95% CI)	34	35		0.9	0.21 [0.03, 1.64]
Total events: 1 (LABA + ICS), 5 (ICS alone)					
Test for heterogeneity: not applicable					
Test for overall effect z=1.49 p=0.1					
02 Jadad score > 4					
Boyd ICS1675	19/55	15/64		2.6	1.47 [0.83, 2.61]
Fitzgerald ICS730	3/89	6/91		1.1	0.51 [0.13, 1.98]

(*Continued* . . .)

(. . . *Continued*)

Study	LABA + ICS n/N	ICS alone n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
Ind 2003	111/171	113/160		21.6	0.92 [0.79, 1.07]
Kemp ICSNR	53/252	59/254		10.9	0.91 [0.65, 1.26]
Li ICS400	2/13	1/16		0.2	2.46 [0.25, 24.21]
Norhaya ICS890	1/30	3/30		0.6	0.33 [0.04, 3.03]
O'Byrne BUD200	58/323	81/322		15.0	0.71 [0.53, 0.96]
O'Byrne BUD400	39/315	61/312		11.4	0.63 [0.44, 0.92]
Pauwels BUD200	62/210	82/213		15.1	0.77 [0.59, 1.00]
Pauwels BUD800	41/215	60/214		11.1	0.68 [0.48, 0.96]
Russell ICS750	16/99	18/99		3.3	0.89 [0.48, 1.64]
van der Molen ICSNR	33/125	32/114		6.2	0.94 [0.62, 1.42]
Subtotal (95% CI)	1897	1889		99.1	0.81 [0.73, 0.90]
Total events: 438 (LABA + ICS), 531 (ICS alone)					
Test for heterogeneity chi-square=13.36 df=11 p=0.27 I^2 =17.7%					
Test for overall effect z=3.93 p=0.00008					
Total (95% CI)	1931	1924		100.0	0.81 [0.73, 0.90]
Total events: 439 (LABA + ICS), 536 (ICS alone)					
Test for heterogeneity chi-square=15.21 df=12 p=0.23 I^2 =21.1%					
Test for overall effect z=4.07 p=0.00005					

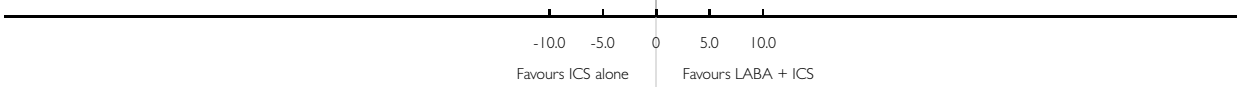
Analysis 02.10. Comparison 02 Additional comparisons for same dose, Outcome 10 Change in FEV1 at endpoint (L or % predicted) stratifying by adult or pediatric study

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

Comparison: 02 Additional comparisons for same dose

Outcome: 10 Change in FEV1 at endpoint (L or % predicted) stratifying by adult or pediatric study

Study	LABA + ICS N	LABA + ICS Mean(SD)	ICS alone N	ICS alone Mean(SD)	Standardised Mean Difference (Random) 95% CI	Weight (%)	Standardised Mean Difference (Random) 95% CI
01 Pediatric							
Langton Hewer ICS400	11	0.22 (0.32)	10	-0.20 (0.16)		1.1	1.57 [0.56, 2.57]
Meijer ICSNR	20	5.80 (11.60)	19	2.20 (9.15)		2.6	0.34 [-0.30, 0.97]
Russell ICS750	76	0.12 (0.41)	87	0.03 (0.37)		7.6	0.23 [-0.08, 0.54]
× Verberne 1998	60	4.30 (0.00)	57	4.30 (0.00)		0.0	Not estimable
Subtotal (95% CI)	167		173			11.3	0.56 [-0.06, 1.18]
Test for heterogeneity chi-square=6.23 df=2 p=0.04 I² =67.9%							
Test for overall effect z=1.76 p=0.08							
02 Adult							
Boyd ICS1675	47	0.19 (0.38)	49	0.15 (0.44)		5.4	0.10 [-0.30, 0.50]
Hultquist BUD400	117	0.22 (0.54)	116	0.10 (0.54)		9.3	0.22 [-0.04, 0.48]
Kavaru FP400	87	0.51 (0.46)	85	0.28 (0.46)		7.7	0.50 [0.19, 0.80]
Kemp ICSNR	252	0.42 (0.48)	254	0.15 (0.48)		12.6	0.56 [0.38, 0.74]
Molimard ICSNR	130	0.17 (0.50)	129	0.06 (0.42)		9.8	0.24 [-0.01, 0.48]
O'Byrne BUD200	323	2.55 (8.63)	322	0.27 (8.61)		13.7	0.26 [0.11, 0.42]
O'Byrne BUD400	315	4.13 (8.52)	312	0.90 (8.48)		13.6	0.38 [0.22, 0.54]
Shapiro FP1000	81	0.48 (0.45)	81	0.25 (0.05)		7.3	0.72 [0.40, 1.03]
van der Molen ICSNR	124	0.14 (0.44)	111	0.02 (0.37)		9.3	0.29 [0.04, 0.55]
Subtotal (95% CI)	1476		1459			88.7	0.37 [0.26, 0.48]
Test for heterogeneity chi-square=16.02 df=8 p=0.04 I² =50.1%							
Test for overall effect z=6.58 p<0.00001							
Total (95% CI)	1643		1632			100.0	0.37 [0.26, 0.48]
Test for heterogeneity chi-square=22.27 df=11 p=0.02 I² =50.6%							
Test for overall effect z=6.57 p<0.00001							



Analysis 02.11. Comparison 02 Additional comparisons for same dose, Outcome 11 Change in FEV1 at endpoint (L or % predicted) stratifying by type of LABA used.

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

Comparison: 02 Additional comparisons for same dose

Outcome: 11 Change in FEV1 at endpoint (L or % predicted) stratifying by type of LABA used.

Study	LABA + ICS N	LABA + ICS Mean(SD)	ICS alone N	ICS alone Mean(SD)	Standardised Mean Difference (Random) 95% CI	Weight (%)	Standardised Mean Difference (Random) 95% CI
01 Formoterol							
Hultquist BUD400	117	0.22 (0.54)	116	0.10 (0.54)		9.3	0.22 [-0.04, 0.48]
Molimard ICSNR	130	0.17 (0.50)	129	0.06 (0.42)		9.8	0.24 [-0.01, 0.48]
O'Byrne BUD200	323	2.55 (8.63)	322	0.27 (8.61)		13.7	0.26 [0.11, 0.42]
O'Byrne BUD400	315	4.13 (8.52)	312	0.90 (8.48)		13.6	0.38 [0.22, 0.54]
van der Molen ICSNR	124	0.14 (0.44)	111	0.02 (0.37)		9.3	0.29 [0.04, 0.55]
Subtotal (95% CI)	1009		990			55.6	0.30 [0.21, 0.38]
Test for heterogeneity chi-square=1.78 df=4 p=0.78 I² =0.0%							
Test for overall effect z=6.56 p<0.00001							
02 Salmeterol							
Boyd ICS1675	47	0.19 (0.38)	49	0.15 (0.44)		5.4	0.10 [-0.30, 0.50]
Kavaru FP400	87	0.51 (0.46)	85	0.28 (0.46)		7.7	0.50 [0.19, 0.80]
Kemp ICSNR	252	0.42 (0.48)	254	0.15 (0.48)		12.6	0.56 [0.38, 0.74]
Langton Hewer ICS400	11	0.22 (0.32)	10	-0.20 (0.16)		1.1	1.57 [0.56, 2.57]
Meijer ICSNR	20	5.80 (11.60)	19	2.20 (9.15)		2.6	0.34 [-0.30, 0.97]
Russell ICS750	76	0.12 (0.41)	87	0.03 (0.37)		7.6	0.23 [-0.08, 0.54]
Shapiro FP1000	81	0.48 (0.45)	81	0.25 (0.05)		7.3	0.72 [0.40, 1.03]
× Verberne 1998	60	4.30 (0.00)	57	4.30 (0.00)		0.0	Not estimable
Subtotal (95% CI)	634		642			44.4	0.47 [0.27, 0.68]
Test for heterogeneity chi-square=13.64 df=6 p=0.03 I² =56.0%							
Test for overall effect z=4.59 p<0.00001							
Total (95% CI)	1643		1632			100.0	0.37 [0.26, 0.48]
Test for heterogeneity chi-square=22.27 df=11 p=0.02 I² =50.6%							
Test for overall effect z=6.57 p<0.00001