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[Intervention Review]

Addition of long-acting beta2-agonists to inhaled steroids as first line therapy for persistent asthma in steroid-naive adults and children

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ABSTRACT

Background

Consensus statements recommend the addition of long-acting inhaled ß2-agonists (LABA) only in asthmatic patients who are inadequately controlled on inhaled corticosteroids (ICS). It is not uncommon for some patients to be commenced on ICS and LABA together as initial therapy.

Objectives

To compare the efficacy of combining inhaled corticosteroids with long-acting ß2-agonists (ICS+LABA) with inhaled corticosteroids alone (ICS alone) in steroid-naive children and adults with persistent asthma. We assessed two protocols: (1) LABA + ICS versus a similar dose of ICS (comparison 1) and (2) LABA + ICS versus a higher dose of ICS (comparison 2).

Search methods

We identified randomised controlled trials through electronic database searches (May 2008).

Selection criteria

Randomised trials comparing ICS + LABA with ICS alone in children and adults with asthma who had no inhaled corticosteroids in the preceding 28 days prior to enrolment.

Data collection and analysis

Each author assessed studies independently for risk of bias and extracted data. We obtained confirmation from the trialists when possible. The primary endpoint was rate of patients with one or more asthma exacerbations requiring rescue systemic corticosteroids. Results are expressed as relative risks (RR) for dichotomous data and as mean differences (MD) or standardised mean differences (SMD) for continuous data.

Main results

Twenty-eight study comparisons drawn from 27 trials (22 adult; five paediatric) met the review entry criteria (8050 participants). Baseline data from the studies indicated that trial populations had moderate or mild airway obstruction (FEV1≥65% predicted), and that they were symptomatic prior to randomisation. In comparison 1, the combination of ICS and LABA was not associated with a significantly lower risk of patients with exacerbations requiring oral corticosteroids (RR 1.04; 95% confidence interval (CI) 0.73 to 1.47) or requiring hospital admissions (RR 0.38; 95% CI 0.09 to 1.65) compared to a similar dose of ICS alone. The combination of LABA and ICS led to a significantly

greater improvement from baseline in FEV1 (0.12 L/sec; 95% CI 0.07 to 0.17), in symptoms (SMD -0.26; 95% CI -0.37 to -0.14) and in rescue ß2-agonist use (-0.41 puffs/day; 95% CI -0.73 to -0.09) compared with a similar dose of ICS alone. There was no significant group difference in the risk of serious adverse events (RR 1.15; 95% CI 0.64 to 2.09), any adverse events (RR 1.02; 95% CI 0.96 to 1.09), study withdrawals (RR 0.95; 95% CI 0.82 to 1.11), or withdrawals due to poor asthma control (RR 0.94; 95% CI 0.63 to 1.41).

In comparison 2, the combination of LABA and ICS was associated with a higher risk of patients requiring oral corticosteroids (RR 1.24; 95% CI 1 to 1.53) and study withdrawal (RR 1.31; 95% CI 1.07 to 1.59) than a higher dose of ICS alone. For every 100 patients treated over 43 weeks, nine patients using a higher dose ICS compared to 11 (95% CI 9 to 14) on LABA and ICS suffered one or more exacerbations requiring rescue oral corticosteroids. There was a high level of statistical heterogeneity for FEV1 and morning peak flow. There was no statistically significant group difference in the risk of serious adverse events. Due to insufficient data we could not aggregate results for hospital admission, symptoms and other outcomes.

Authors' conclusions

In steroid-naive patients with mild to moderate airway obstruction, the combination of ICS and LABA does not significantly reduce the risk of patients with exacerbations requiring rescue oral corticosteroids over that achieved with a similar dose of ICS alone. However, it significantly improves lung function, reduces symptoms and marginally decreases rescue ß2-agonist use. Initiation of a higher dose of ICS is more effective at reducing the risk of exacerbations requiring rescue systemic corticosteroids, and of withdrawals, than combination therapy. Although children appeared to respond similarly to adults, no firm conclusions can be drawn regarding combination therapy in steroid-naive children, given the small number of children contributing data.

PLAIN LANGUAGE SUMMARY

The effect of adding a long-acting beta-agonist to inhaled steroids in people not previously treated with inhaled steroids

In patients with asthma who require daily anti-inflammatory therapy, there is insufficient evidence to support initiating therapy with a combination of inhaled corticosteroids (ICS) and long-acting ß2-agonist (LABA) rather than with inhaled corticosteroids alone. Most consensus statements recommend the addition of LABA as second line therapy, only in asthmatic individuals who remain insufficiently controlled on maintenance inhaled corticosteroids. Yet, many physicians initiate combination therapy in patients with asthma, without a prior trial of inhaled corticosteroids alone. The purpose of this review was to compare the benefit and safety profile of initiating treatment with the combination of ICS and LABA as compared to a (1) similar and (2) higher dose of ICS alone in asthmatic patients who had not received ICS previously. This review identified 28 randomised controlled trials. The combination of ICS and LABA did not reduce the risk of patients with exacerbations requiring rescue oral corticosteroids but improved lung function, symptoms and minimally reduced the use of rescue ß2-agonists as compared to a similar dose of ICS alone. Initiating ICS at a higher dose than that used with LABA in the control group significantly reduced the risk of exacerbations and study withdrawals over that observed with the combination of LABA and a lower dose of ICS; there is insufficient evidence to comment on the impact on lung function, symptoms and use of rescue ß2-agonists. The current evidence does not support use of combination therapy with LABA and ICS as first line treatment in adults and children with asthma, without a prior trial of inhaled corticosteroids.

BACKGROUND

The cornerstone of asthma management is the use of inhaled corticosteroids (ICS) to alleviate the inflammatory reaction that characterises asthma (Adams 2007; Adams 2008a; Adams 2008b). Short-acting ß2-agonists are the primary agents in the management of acute asthma symptoms. This class of medication provides rapid onset bronchodilation by interaction with specific ß2-adrenergic receptors (Abramson 2003). Long-acting ß2-agonists (LABA), such as formoterol and salmeterol, were initially used in persistent asthmatics with severe nocturnal symptoms. Because of their lipophilicity, these agents achieve sustained bronchodilation for up to 12 hours (D'Alonzo 1997). Since bronchodilation with these agents is long-lasting, they are of potential use in managing the symptoms of asthma.

The use of salmeterol in combination with inhaled corticosteroids has been found to be superior to an increased dose of inhaled corticosteroids for improving symptoms and reducing exacerbations in patients with moderate to severe persistent asthma (Shrewsbury 2000). However, a subsequent larger systematic review found an absence of a statistically significant group difference in the rate of exacerbations requiring systemic steroids, while significantly greater improvements in lung function, symptoms and use of rescue ß2-agonists were documented with combination therapy than with higher ICS dose. Interestingly, a subgroup analysis suggested the superiority of a higher dose of ICS over combination therapy in patients with prolonged (> six months) therapy (Greenstone 2005). However, monotherapy with long-acting ß2-agonists alone had been associated with significant adverse events (Cates 2008a; Cates 2008b; Walters 2007).

Current national and international guidelines for asthma recommend long-acting ß2-agonists as an adjunctive therapy to inhaled corticosteroids in patients who are not controlled by inhaled corticosteroids alone (BTS 2008; GINA 2007; Lemiere 2004; NAEPP 2007). More specifically, guidelines recommend the initiation of therapy with low or moderate doses of inhaled corticosteroids alone in patients with mild or moderate persistent asthma, respectively. The addition of long-acting ß2-agonists to inhaled corticosteroids is generally recommended once a trial of inhaled corticosteroids alone has been insufficient to achieve adequate asthma control (GINA 2007). In fact, some national consensus statements have formally advised against the use of long-acting ß2-agonists without a prior trial of inhaled corticosteroids (Lemiere 2004).

Despite current guideline recommendations, data from observational studies indicate that the introduction of a long-acting ß2-agonist in mild asthma is still common in adults and children (Sazonov-Kocevar 2006; Stockl 2008). Perhaps because of the perception of greater efficacy of combination therapy, there is an increasing tendency for practitioners to initiate a combination of inhaled corticosteroids and long-acting ß2-agonists in patients with mild or moderate airway obstruction, without a prior trial of inhaled corticosteroids alone. The recent development of single inhalers delivering both an inhaled corticosteroid and long-acting ß2-agonist may have further facilitated this practice.

OBJECTIVES

The objective of this review was to examine the safety and efficacy of initiating a combination of long-acting ß2-agonists and inhaled corticosteroids compared to a similar dose or a higher dose of inhaled corticosteroids alone, in steroid-naive children and adults with persistent asthma.

More specifically, we wished to compare the impact of both treatment options on asthma control measured as exacerbations requiring systemic corticosteroids (main outcome), asthma symptoms, lung function, quality of life, withdrawals from the study, inflammatory mediator levels and adverse health events. We aimed to examine whether any observed benefit may be influenced by factors such as severity of baseline airway obstruction, age, dose of inhaled corticosteroids, use of one or two devices to deliver combination therapy, the long-acting ß2-agonist preparation used and trial duration.

METHODS

Criteria for considering studies for this review

Types of studies

We included only randomised controlled trials in which the combination of inhaled corticosteroids and long-acting ß2-agonists (ICS+LABA) was compared to a similar dose of inhaled corticosteroid (same ICS dose alone: Comparison 01), and to a higher dose of ICS (higher ICS dose alone: Comparison 02). Controlled studies with or without placebo were considered. Because of the requirement of participants to be steroid-naive, we excluded cross-over trials.

Types of participants

Adults and/or children aged two years and above with persistent asthma of any severity who were steroid-naive; that is, who had not received inhaled corticosteroids in the month preceding enrolment.

Types of interventions

1. Long-acting ß2-agonist (e.g. salmeterol or formoterol) plus inhaled steroids versus a **similar dose** of inhaled corticosteroids alone (+/- placebo) administered for four weeks or more (Comparison 1). We included trials that compared different inhaled corticosteroids at the same equivalent dose. Inhaled short-acting ß2-agonists and short courses of systemic corticosteroids were considered as rescue medications.
2. Long-acting ß2-agonist (e.g. salmeterol or formoterol) plus inhaled steroids versus a **higher dose** of inhaled corticosteroids alone (+/- placebo) administered for four weeks or more (Comparison 2). We included trials that compared different inhaled corticosteroids in each arm, at doses higher than the dose used in combination with LABA. Inhaled short-acting ß2-agonists and short courses of systemic corticosteroids were considered as rescue medications.

We only considered fixed-dose treatment arms, since maintenance and reliever therapy with budesonide and formoterol is subject to review elsewhere (Cates 2009).

Types of outcome measures

Primary outcomes

The primary outcome was the proportion of participants who experienced exacerbations of asthma requiring a short course of systemic corticosteroids (5 to 10 days).

Secondary outcomes

1. Hospital admission
2. Pulmonary function tests
3. Symptoms
4. Quality of life assessed with a validated questionnaire
5. Use of rescue short-acting ß2-agonists.
6. Measures of inflammation such as expired nitric oxide, serum eosinophils, serum eosinophil cationic protein, and sputum eosinophils
7. Rates of clinical and biochemical adverse effects
8. Withdrawals

Search methods for identification of studies

Electronic searches

We carried out a search in the Cochrane Airways Group Specialised Register of trials which is derived from systematic searches of bibliographic databases including the Cochrane Central Register of Controlled Trials (CENTRAL) (*The Cochrane Library)*, MEDLINE, EMBASE, CINAHL, AMED and PsycINFO, and handsearched respiratory journals and meeting abstracts (please see the Airways Group Module for further details). This register contains a variety of studies published in foreign languages. We did not exclude trials on the basis of language.

All records in the Specialised Register coded as 'asthma' were 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)).

The most recent search was conducted in May 2008.

Searching other resources

We reviewed reference lists of all included studies and of reviews to identify potentially relevant citations.

We also made enquiries regarding other published or unpublished studies known to the authors of the included studies or to pharmaceutical companies who produce the agents, namely GlaxoSmithKline (GSK) and AstraZeneca.

We handsearched the clinical trials websites of pharmaceutical firms which manufacture formoterol (AstraZeneca) and salmeterol (GSK). We undertook an additional search of Clinical Study Results. We conducted these additional handsearches in May 2008.

Data collection and analysis

Selection of studies

From the title, abstract, or descriptors, one of the authors (MNC, IG or TL) independently reviewed the literature searches. We excluded all studies that were clearly not randomised controlled trials or that clearly did not fit the inclusion criteria. Two authors ((MNC or TL) and FMD) reviewed all other citations independently in full text, assessing for inclusion based on study design, population, intervention and outcome.

Data extraction and management

Two authors (TL, MNC or FMD) independently extracted data for the trials and entered data into The Cochrane Collaboration software program Review Manager 5.0 (RevMan 2008). For the update in 2008, TL performed data extraction and corresponded with trialists and study sponsors to obtain missing data. FMD provided checks for accuracy of the data analysed in the primary outcome.

Assessment of risk of bias in included studies

We assessed the risk of bias for the allocation, blinding and the handling of missing data in the studies. This is in line with the recommendations made in the *Cochrane Handbook for Systematic Reviews of Interventions* (Handbook 2008).

Dealing with missing data

We contacted study investigators or study sponsors to verify data extraction for our primary outcome of exacerbations requiring systemic corticosteroids where this was reported in study publications. For study publications where no information was given on exacerbations, we attempted to establish the number of participants in each treatment group who had experienced one ore more oral steroid-treated exacerbation.

For partially reported continuous data endpoints (such as lung function outcomes where no or incomplete summary data were available), we sought necessary numerical values from study investigators or sponsors.

Where necessary, we performed expansions of graphic reproductions and estimations from other data presented in the papers.

Assessment of heterogeneity

We tested homogeneity of effect size between the studies being pooled the DerSimonian and Laird method with $I^2 \geq 25\%$ (Higgins 2003) being used as the threshold to prompt exploration of possible sources of variation. If heterogeneity was suggested, we applied the DerSimonian and Laird random-effects model to the summary estimates. Unless otherwise specified we reported the fixed-effect model.

Data synthesis

For dichotomous variables, we calculated individual and pooled statistics as relative risks with 95% confidence intervals. For continuous outcomes we calculated individual and pooled statistics as weighted mean differences or standardised mean differences, as indicated, with 95% confidence intervals.

We set limits of treatment equivalence a priori at +/- 0.10 on either side of the no-difference line for our primary outcome, the risk of exacerbations requiring oral corticosteroids. The null hypothesis tested whether the confidence interval for the difference between the two treatments included one of these limits.

Subgroup analysis and investigation of heterogeneity

For each outcome, we stratified trials according to the severity of baseline airway obstruction as determined by the mean percent predicted forced expiratory volume in one second (FEV1) where an FEV1 equal to, or greater than, 80% of predicted was indicative of mild obstruction; an FEV1 61% to 79% of predicted, indicative

of moderate obstruction; and an FEV1 equal to or less than 60% considered as severe obstruction (GINA 2007).

We recorded as a 'User defined order' the mean daily dose of inhaled corticosteroid in both groups reported in chlorofluorocarbon (CFC) propelled 'beclomethasone-equivalent', where 1 µg of beclomethasone dipropionate was equivalent to 1 µg of budesonide or 0.5 µg fluticasone propionate, irrespective of delivery device used (NAEPP 2007). All doses of inhaled corticosteroids were reported based on ex-valve rather than ex-inhaler values.

The following a priori defined subgroups were examined to explore influence on the magnitude of effect (effect modification), irrespective of the presence or absence of heterogeneity.

1. Severity of airway obstruction at baseline (FEV1: 80% of predicted and above; 61% to 79% of predicted ; 60% of predicted or less) (GINA 2007).
2. Children versus adults.
3. Dose of inhaled corticosteroids, reported in CFC-propelled beclomethasone or equivalent (µg/day) and portrayed as the user-defined number, was examined as the:
   a. Mean dose (ex-valve) used in both groups in studies where both groups used a similar dose of ICS, reported in CFC-propelled beclomethasone or equivalent (µg/day), portrayed as the user-defined number.
   b. Dose difference between groups in studies where a different ICS dose was used in the LABA + ICS versus ICS alone groups.
4. Use of one or two devices to deliver the combination of ICS plus LABA.
5. Long-acting ß2-agonist used (salmeterol versus formoterol).
6. Trial duration.

Sensitivity analysis

We performed sensitivity analyses to investigate the potential effect of:

1. risk of bias (blinding and completeness of outcome reporting);
2. publication status (data available from full text source versus non-full-text journal source (e.g. web-based company trial report, data made available on request or conference abstract);
3. funding source (producers of tested interventions versus independent source);
4. use of the same ICS versus similar dose-equivalent ICS on the study results.

We used funnel plots to test for the presence of possible publication bias (Egger 1997). The fail-safe N test was used to assess the robustness of the results (Gleser 1996).

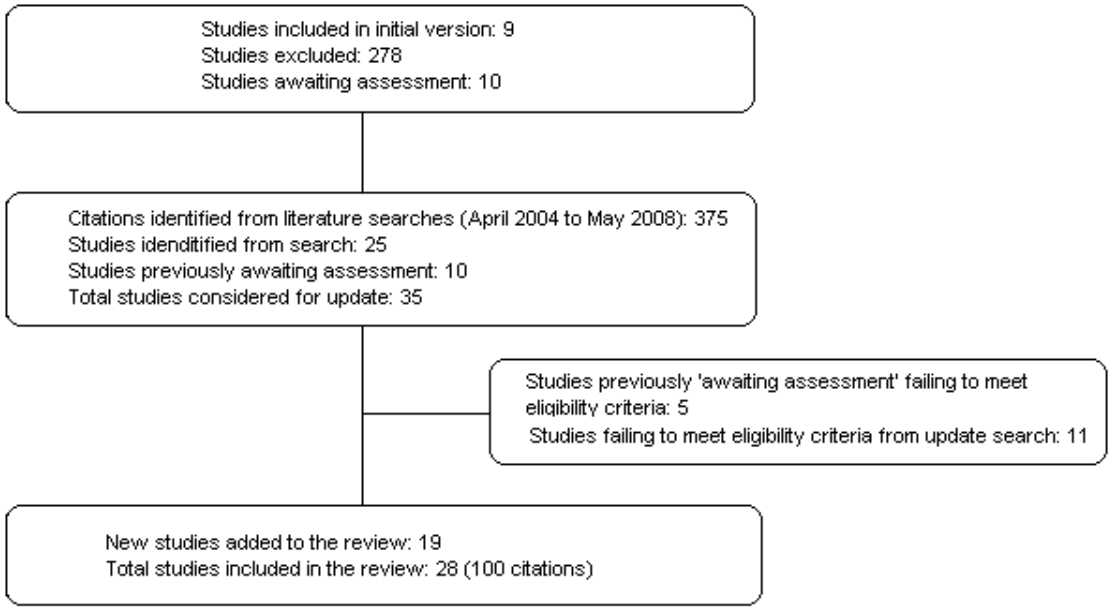
RESULTS

Description of studies

Results of the search

We considered 35 new studies for eligibility in this update of the review. Eighteen new studies met the review entry criteria, combining with the previous nine trials to yield a total of 27 included studies (reported in 100 citations). One study contributed two between-group comparisons: Pearlman 1999b; Pearlman 1999a, hereafter counted as two different studies for a total of 28 study comparisons. For full details of search history see Table 1, and for a literature flow diagram see Figure 1. The included trials randomised 8050 participants.

Figure 1. Flow diagram of literature added to update of the review (April 2004 to May 2008)



Included studies

There were two main comparisons: (1) the combination of LABA and ICS compared to a similar dose of ICS (N = 24 studies): Boonsawat 2008; Chuchalin 2002; Creticos 1999; Di Franco 1999; GOAL; Grutters 1999; Karaman 2007; Kerwin 2008; Miraglia del Giudice 2007; Murray 2004; Nelson 2003; O'Byrne 2001; Overbeek 2005; Pearlman 1999a; Pearlman 1999b; Prieto 2005; Rojas 2007; SAS30015; SAS30021; SAS40068; SLGF75; Stelmach 2008; Strand 2004; Weersink 1997) and (2) LABA + ICS versus higher dose ICS (N = four studies: Chuchalin 2008; SAM40034; SAM40036; Sorkness 2007). Assessment of the risk of bias and meta-analysis results are provided for each comparison.

Participants

Age

Five studies recruited children with mean ages of between 8 and 12 years. The youngest participants eligible for these studies was six years, and the oldest was 18 years (Karaman 2007; Miraglia del Giudice 2007; SAS30021; Sorkness 2007; Stelmach 2008). Twenty-three studies recruited adults with a mean age varying between 26 (Grutters 1999) and 45 years (Chuchalin 2002). Fifteen adult studies permitted the enrolment of an unspecified number of adolescents aged 12 years and above (Chuchalin 2008; Di Franco 1999; GOAL; Nelson 2003; O'Byrne 2001; Overbeek 2005; Pearlman 1999a; Pearlman 1999b; SAS30015; Murray 2004; Kerwin 2008; Boonsawat 2008; Rojas 2007; SAM40036; SAS40068). The gender distribution varied from 25% males in Chuchalin 2002 to 61% in Di Franco 1999.

Prior maintenance treatment

Participants were all naive to both long-acting ß2-agonists and inhaled corticosteroids; that is, they had never received inhaled corticosteroids (Creticos 1999; GOAL (stratum 1); Karaman 2007; Nelson 2003; Prieto 2005), had not received any inhaled corticosteroids for a minimum of one to six months (Boonsawat 2008; Di Franco 1999; Grutters 1999; Kerwin 2008; Miraglia del Giudice 2007; Murray 2004; O'Byrne 2001; Overbeek 2005; Pearlman 1999a; Pearlman 1999b; Rojas 2007; SAS30021; SAS40068; SLGF75; Sorkness 2007; Stelmach 2008; Strand 2004; Weersink 1997), or had abstained from corticosteroids for an unspecified period (Chuchalin 2002; Chuchalin 2008). In an additional study, the participants were described as uncontrolled at step 1 of the British Thoracic Society (BTS) guidelines (SAS30015), and therefore we considered them to be steroid naive, since these guidelines do not recommend the introduction of inhaled corticosteroids until step 2.

Asthma control

All participants had inadequate asthma control prior to enrolment, with ongoing symptoms and use of rescue short-acting ß2-agonists.

Ten studies (Chuchalin 2002; GOAL; Kerwin 2008; Miraglia del Giudice 2007; Murray 2004; Nelson 2003; Overbeek 2005; Pearlman 1999a; Pearlman 1999b; Rojas 2007) recruited patients with moderate airway obstruction (mean baseline FEV1 of 66% to 79% of predicted), whilst 12 trials recruited patients with minimal airway obstruction, for example, a mean baseline FEV1 of predicted 80% to 105% of predicted (Boonsawat 2008; Chuchalin 2008; Creticos 1999; Di Franco 1999; Grutters 1999; O'Byrne 2001; Prieto 2005;

SAM40034; SAM40036; Sorkness 2007; Stelmach 2008; Weersink 1997). For six studies (including four accessed from the GSK trials register), we were unable to determine baseline FEV1 predicted (Karaman 2007; SAS30015; SAS30021; SAS40068; SLGF75; Strand 2004). Strand 2004 reported baseline peak expiratory flow (PEF) predicted of 79%.

The presence of atopy was discussed in seven studies with three studies enrolling only atopic patients (Grutters 1999; Prieto 2005; Weersink 1997) and four reporting a 58%, 69%, 75% and 85% prevalence of atopy respectively (Di Franco 1999; GOAL; Overbeek 2005; Sorkness 2007).

Intervention

Type of LABA and ICS dosing

The long-acting ß2-agonist preparation was salmeterol xinafoate (50 µg twice daily) in 22 studies and formoterol (12 µg twice daily) in the remaining six trials (Chuchalin 2002; Karaman 2007; Miraglia del Giudice 2007; O'Byrne 2001; Overbeek 2005; Stelmach 2008). The dose and type of inhaled corticosteroid varied among the studies.

Fourteen studies tested the combination of LABA and low doses of inhaled corticosteroids (i.e. 200 to 400 µg/day of beclomethasone, or equivalent: Boonsawat 2008; Chuchalin 2002; Chuchalin 2008; Creticos 1999; Murray 2004; Nelson 2003; O'Byrne 2001; Overbeek 2005; Pearlman 1999a; Prieto 2005; SAS30015; SAS40068; SLGF75; Strand 2004). One study assessed LABA added to 500 mcg of beclomethasone equivalent (Kerwin 2008) and nine studies used high doses (i.e. 800 to 1000 mcg/day of BDP, or equivalent: Di Franco 1999; Grutters 1999; GOAL; Karaman 2007; Pearlman 1999b; Rojas 2007; SAM40034; Sorkness 2007; Weersink 1997). In the studies assessing adjunctive LABA therapy against a higher ICS dose, the control group received at least double the dose of ICS in the LABA group, with a BDP equivalent differential dose of 200 mcg (Chuchalin 2008 control group dose: 400 mcg BDP equivalent; Sorkness 2007 control group dose: 400 mcg BDP equivalent); or 300 mcg (SAM40034 control group dose: 1000 mcg BDP equivalent; SAM40036 control group dose: 400 mcg BDP equivalent).

Studies assessed the addition of LABA to beclomethasone (three studies: Di Franco 1999; Grutters 1999; SAS30015), budesonide (seven studies: Chuchalin 2002; Karaman 2007; Miraglia del Giudice 2007; O'Byrne 2001; Overbeek 2005; SAM40036; Stelmach 2008), triamcinolone (one study: Creticos 1999) or fluticasone (17 studies: Boonsawat 2008; Chuchalin 2008; GOAL; Kerwin 2008; Murray 2004; Nelson 2003; Pearlman 1999a; Pearlman 1999b; Prieto 2005; Rojas 2007; SAM40034; SAS30021; SAS40068; SLGF75; Sorkness 2007; Strand 2004; Weersink 1997).

Inhaler devices

Fifteen studies tested the combination of long-acting ß2-agonist and corticosteroid administered in a single inhaler (Boonsawat 2008; Chuchalin 2008; GOAL; Grutters 1999; Kerwin 2008; Murray 2004; Nelson 2003; Prieto 2005; Rojas 2007; SAM40034; SAM40036; SAS30015; SAS30021; SAS40068; Strand 2004). Thirteen studies used two separate inhalers (Chuchalin 2002; Creticos 1999; Di Franco 1999; Karaman 2007; Miraglia del Giudice 2007; O'Byrne 2001; Overbeek 2005; Pearlman 1999a; Pearlman 1999b; SLGF75; Sorkness 2007; Stelmach 2008; Weersink 1997). Compliance was monitored during the intervention period in only five studies (Di Franco 1999; Grutters 1999; Pearlman 1999a; Pearlman 1999b; Sorkness 2007).

Co-treatment and duration

Co-intervention with other prophylactic medications such as xanthines and sodium cromoglycate was clearly not permitted in four of the studies (Chuchalin 2002; Di Franco 1999; Nelson 2003; O'Byrne 2001) and unreported in the remaining studies. Rescue medication such as inhaled short-acting ß2-agonist was permitted in all trials.

Study duration varied: four to eight weeks (Grutters 1999; Karaman 2007; Miraglia del Giudice 2007; Overbeek 2005; Pearlman 1999a; Pearlman 1999b; Prieto 2005; Stelmach 2008; Weersink 1997), 12 weeks (Boonsawat 2008; Chuchalin 2002; GOAL; Kerwin 2008; Murray 2004; Nelson 2003; Rojas 2007; SAM40034; SAM40036; SAS30015; SAS30021), 24 weeks (Creticos 1999; SAS40068; Strand 2004), 48 weeks (Sorkness 2007) and 52 weeks (Chuchalin 2008; Di Franco 1999; O'Byrne 2001). One study of uncertain duration was included since it was reported to be longer than 12 weeks in a recent meta-analysis from GlaxoSmithKline (GSK) (SLGF75).

Outcomes

Eleven studies contributed data to our main outcome (number of patients with exacerbations requiring systemic corticosteroids) for Comparison 01 (Boonsawat 2008; Di Franco 1999; Kerwin 2008; Murray 2004; Nelson 2003; O'Byrne 2001; Rojas 2007; SAS30015; SAS30021; SAS40068; Strand 2004), and three studies to the same outcome under Comparison 02 (Chuchalin 2008; SAM40036; Sorkness 2007). We were able to obtain data relating to exacerbations requiring systemic corticosteroids for nine GSK-funded studies following correspondence with the study sponsors.

Most trials reported changes in lung function, albeit using various parameters, use of rescue ß2-agonists, cause-specific and all-cause withdrawals and overall adverse health events. Improvement in symptoms was reported in different ways (symptom score, percent symptom-free days, percent days with symptoms, percent night awakenings) using many parameters (average value, final value at endpoint, percent change, change in percent values) so aggregation could only be done on a few variables. Only one trial (Grutters 1999) reported the impact of treatment on inflammatory markers, serum eosinophils, eosinophilic cationic protein, platelet-activating factor and total IgE. Unfortunately, it failed to report change from baseline and could not be aggregated as no other trials reported these outcomes.

Funding status

Eighteen studies were funded by producers of long-acting ß2-agonists, namely GlaxoSmithKline (Boonsawat 2008; Chuchalin 2008; GOAL; Grutters 1999; Kerwin 2008; Murray 2004; Nelson 2003; Pearlman 1999a; Pearlman 1999b; Rojas 2007; SAM40034; SAM40036; SAS30015; SAS30021; SAS40068; SLGF75; Strand 2004; Weersink 1997) and AstraZeneca (O'Byrne 2001; Overbeek 2005). Two studies received funding from a charitable source (Sorkness 2007; Stelmach 2008). Source of funding was unspecified in the remaining six studies.

Excluded studies

We have listed the reason for the exclusion of 293 studies (411 citations) that did not meet the eligibility of the review in 'Characteristics of excluded studies'.

Risk of bias in included studies

See Figure 2 for a summary of our assessment of the risk of bias for each study.

Figure 2. Methodological quality summary: review authors' judgements about each methodological quality item for each included study.

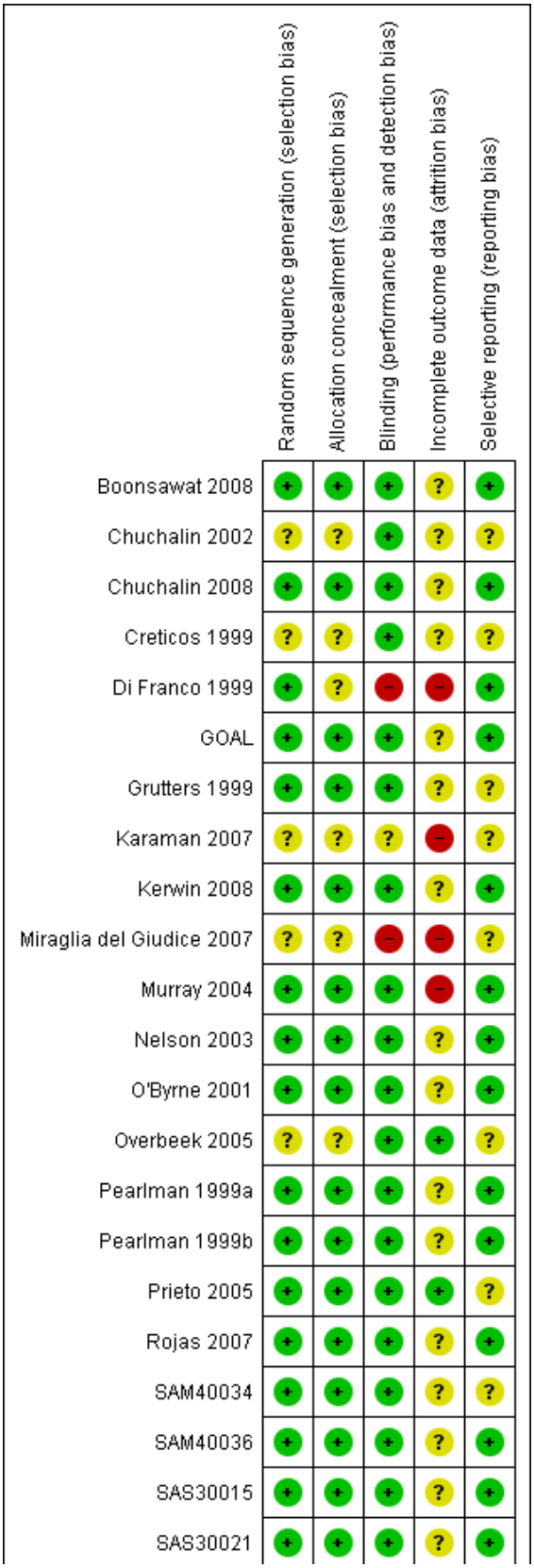


Figure 2. (Continued)

Comparison 01: LABA and ICS versus a similar dose of ICS alone

Based on correspondence with GSK who sponsored the salmeterol studies, we were able to verify that appropriate methods of randomisation had been undertaken for a total of 17 (71%) of 24 studies (see Appendix 1).

Nineteen (79%) studies were reported as double blind with an appropriate means of blinding (Boonsawat 2008; Chuchalin 2002; Creticos 1999; GOAL; Grutters 1999; Kerwin 2008; Murray 2004; Nelson 2003; O'Byrne 2001; Overbeek 2005; Pearlman 1999a; Pearlman 1999b; Prieto 2005; SAS30015; Rojas 2007; SAS40068; SLGF75; Strand 2004; Weersink 1997); one study was not blinded (Di Franco 1999).

The data was analysed by intention-to-treat in 15 (62.5%) studies, although detailed descriptions of how this was done when data was missing were infrequently available. One small study described its intention-to-treat analysis as one based on the last observation carried forward (SLGF75).

Only one study reported the proportion of the screened patients that were enrolled in the run-in period (GOAL: 67%). Only two trials reported the proportion of patients who were successfully randomised after the run-in period: Chuchalin 2002: 99%; Nelson 2003: 54%. The reasons for non-randomisation were not provided.

Comparison 02: LABA and ICS versus a higher dose of ICS alone

Based on correspondence with GSK who sponsored the salmeterol studies, we were able to verify that appropriate methods of randomisation had been undertaken for three of four studies (see Appendix 1).

Blinding of treatment was sufficient to categorise all four studies as being at a low risk of detection bias.

As with the studies under Comparison 01 the description of intention-to-treat analysis populations was not clear enough for us to determine how missing data were handled.

Only Sorkness 2007 provided information on the percentage of participants randomised from the screening population (44).

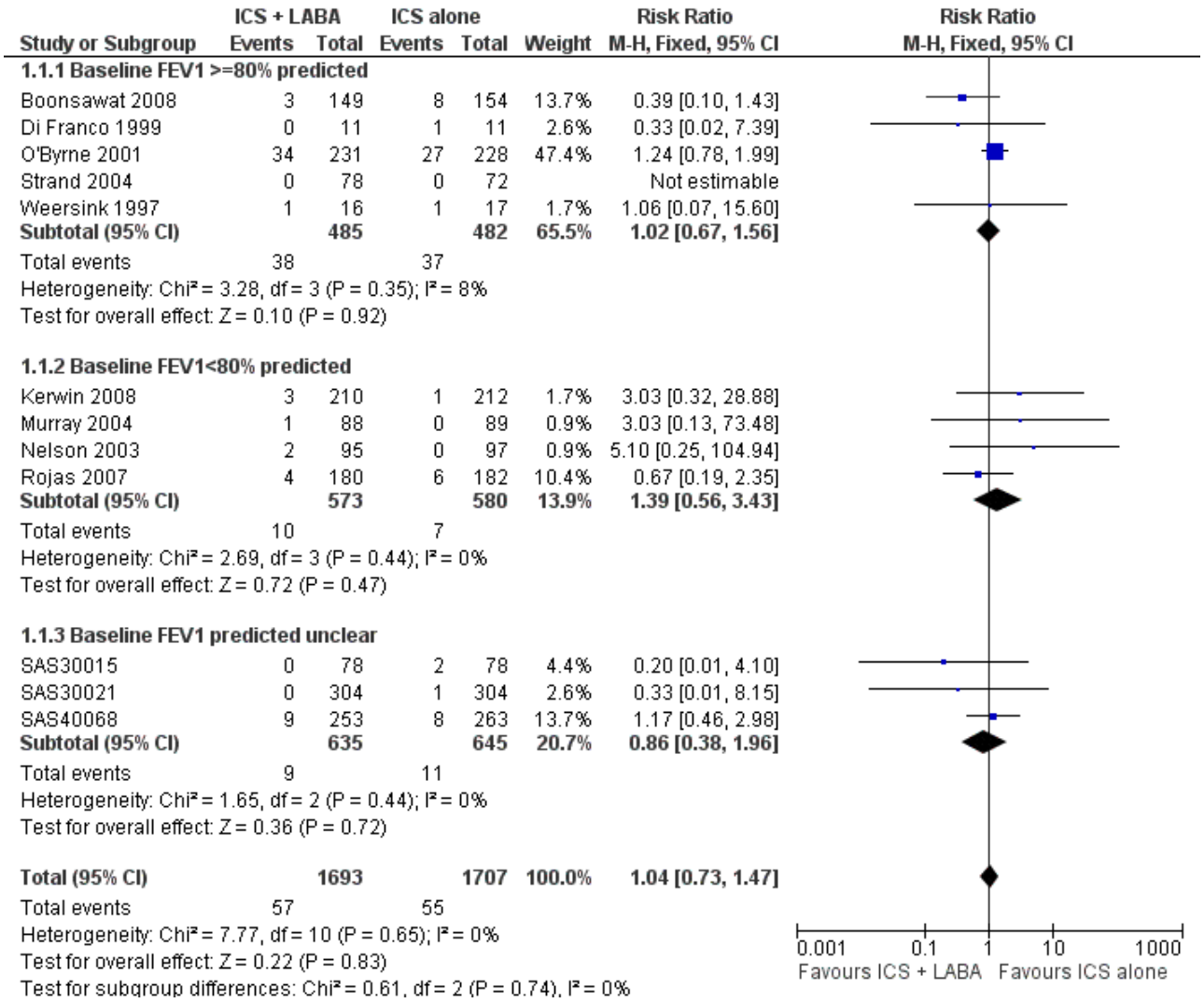
Effects of interventions

Comparison 01: LABA plus ICS versus a similar dose of ICS alone (24 studies)

Primary outcome: Patients with exacerbations requiring oral corticosteroids

In 12 (11 adult and one paediatric) trials contributing data to this outcome, there was no statistically significant group difference in the risk of patients requiring rescue oral steroids (RR 1.04; 95% CI 0.73 to 1.47; Figure 3).

Figure 3. Forest plot of comparison: 1 Addition of ICS + LABA versus same dose of ICS alone in steroid-naive patients as first line treatment, outcome: 1.1 # patients with exacerbations requiring systemic steroids.



Although there was some variation in the characteristics of the studies (enrolment of patients with mild and moderate airway obstruction, doses of inhaled corticosteroids varying between 200 µg/day to 1000 µg/day of beclomethasone or equivalent), we did not observe any statistical variation between the study results (I^2 = 0%). The subgroup analyses did not identify patient, intervention or study characteristics that might explain modify the magnitude of response. The Egger test did not support significant bias (-0.20; 95% CI -0.31 to 0.31).

Restricting the analyses to studies with a low or unclear risk of bias for blinding and those with acceptable proportion of follow up made little difference to our effect estimates (Analysis 4.1; Analysis 4.2). Removing from the analysis studies without a full-text publication also did not affect the direction of the effect (Analysis 4.3).

Secondary outcomes

Exacerbations requiring hospitalisation

Three studies contributed data to the outcome measuring patients with exacerbations requiring hospitalisation which showed no significant difference between treatment regimens (RR 0.38; 95% CI 0.09 to 1.65; Analysis 1.2).

Lung function & diary recorded peak flow

There was a significant group difference in favour of LABA with regards to the improvement from baseline in FEV1 (11 studies: 0.12 litres; 95% CI 0.07 to 0.17; random-effects modelling; Analysis 1.3), in morning peak expiratory flow (PEF) (11 studies: WMD 19.50 L/min; 95% CI 16.19 to 22.82; random-effects model; Analysis 1.6) and in evening PEF (eight studies: 10.45 L/min; 95% CI 7.08 to 13.82; Analysis 1.7). There was no statistically significant group difference in the morning PEF measured at endpoint (19.34 L/min; 95% CI -10.75 to 49.42; Analysis 1.8) or in the change in PEF variability (four studies: SMD -0.04; 95% CI -0.50 to 0.41; random-effects model; Analysis 1.12). There was an insufficient number of trials to allow

aggregation of data pertaining to FEV1 measured at endpoint and in airway hyperreactivity (measured as PC20).

We performed subgroup analyses on the change from baseline in FEV1. When restricting the analysis to the eight trials in which the average baseline FEV1 was reported, there was no significant group difference in the magnitude of effect between patients with a baseline FEV1 61% to 79% of predicted compared to those with FEV1 of >= 80% predicted (0.14 versus 0.12 L; P = 0.77 (Analysis 1.3). Similarly, the ICS dose to which LABA was added did not explain the statistical heterogeneity between the studies (<= 500: 0.11 L versus > 800 mcg: 0.18 L; P = 0.315) (Analysis 3.5). When studies were stratified by trial duration, there was a statistically significant group difference showing a weaker effect on FEV1 at 24 weeks compared with 12 weeks (mean difference: 0.08 L; P = 0.0101). With the small number of trials, it was impossible to perform a meta-regression to disentangle the independent effect of baseline severity, ICS dose, and study duration on the magnitude of effect on FEV1. Finally, there were insufficient studies to examine the effects of the type of LABA, age and number of devices to administer the combination therapy in the magnitude of improvement in FEV1.

Symptoms and rescue medication use

Patients treated with LABA experienced significantly greater improvements from baseline in symptom score (seven studies: SMD -0.26; 95% CI -0.37 to -0.14; random-effects modelling; Analysis 1.17) and in night-time symptom score (SMD -0.16; 95% CI -0.32 to 0.00; Analysis 1.19). There was no significant difference in change from baseline in night-time awakening (Analysis 1.21).

There was also a significant group difference in favour of combination therapy in reducing the use of rescue short-acting ß2-agonists (eight studies: WMD -0.41 puffs/day; 95% CI -0.73 to -0.09; random-effects model; Analysis 1.29) and in the increase in rescue-free days (9.29%; 95% CI 4.52 to 14.05; Analysis 1.24). There were insufficient data to report aggregated estimates for night-time awakenings (Analysis 1.22), percentage of symptom-free days (Analysis 1.25; Analysis 1.26) rescue-free days at endpoint (Analysis 1.23) or quality of life (Analysis 1.32; Analysis 1.33).

Inflammation

With only one trial (Grutters 1999) reporting inflammatory markers, the impact of either treatment option on airway inflammation could not be examined.

Withdrawals & tolerability

There was no statistically significant difference, nor equivalence, in the risk of serious adverse events between treatment options (10 studies; RR 1.15; 95% CI 0.64 to 2.09; Analysis 1.34).

The overall risk of withdrawals (18 trials; RR 0.95; 95% CI 0.82 to 1.11; Analysis 1.35) and withdrawals due to poor asthma control (13 studies; RR 0.94; 95% CI 0.63 to 1.41; Analysis 1.36) were not statistically different between groups. With regards to side effects, there were no statistically significant differences between treatments in the risk of any adverse effects (13 studies: RR 1.02; 95% CI 0.96 to 1.09; Analysis 1.38), reaching our a priori definition of equivalence. There was no significant group difference in withdrawals due to adverse effects (11 studies: RR 1.07; 95% CI 0.67 to 1.71; Analysis 1.37), oral candidiasis (six studies: RR 0.91; 0.39 to 2.12; Analysis 1.40), headache (11 studies: RR 1.03; 95% CI 0.86 to 1.23; Analysis 1.39) or hoarseness (three studies: RR 1.97; 95% CI 0.49 to 7.88; Analysis 1.41). There was a significant increase in the risk of tremor associated with the use of LABA (four studies: RR 4.71; 95% CI 1.38 to 16.08; Analysis 1.42). Other potential adverse effects such as tachycardia (Analysis 1.43) and adverse cardiovascular events (Analysis 1.44) could not be examined reliably due to insufficient trials reporting these outcomes. There were no reported deaths.

Comparison 02: LABA plus ICS versus higher dose ICS alone (four studies)

Primary outcome: Patients with exacerbations requiring oral corticosteroids

In two adult and one paediatric trial, the combination of LABA and ICS in steroid-naive participants led to a higher risk of patients with exacerbations requiring oral corticosteroids compared with those treated with a higher ICS dose alone (RR 1.24; 95% CI 1.00 to 1.53; Figure 4; Analysis 2.1), a group difference at the limit of statistical significance. For every 100 patients treated over 43 weeks, nine patients using a higher dose ICS compared to 11 (95% CI 9 to 14) on LABA and ICS required rescue oral corticosteroids for an exacerbation (Figure 5.) Three studies (two adult and one pediatric) contributed data to this outcome. Of note, the data were available only from trials in which patients had a mean baseline FEV1 of 80% or more of predicted. Three trials showing no group difference would reverse this conclusion (Gleser 1996).

Figure 4. Forest plot of comparison: 5 Addition of ICS + LABA versus higher dose of ICS alone in steroid-naive patients as first line treatment, outcome: 5.1 # patients with exacerbations requiring systemic steroids.

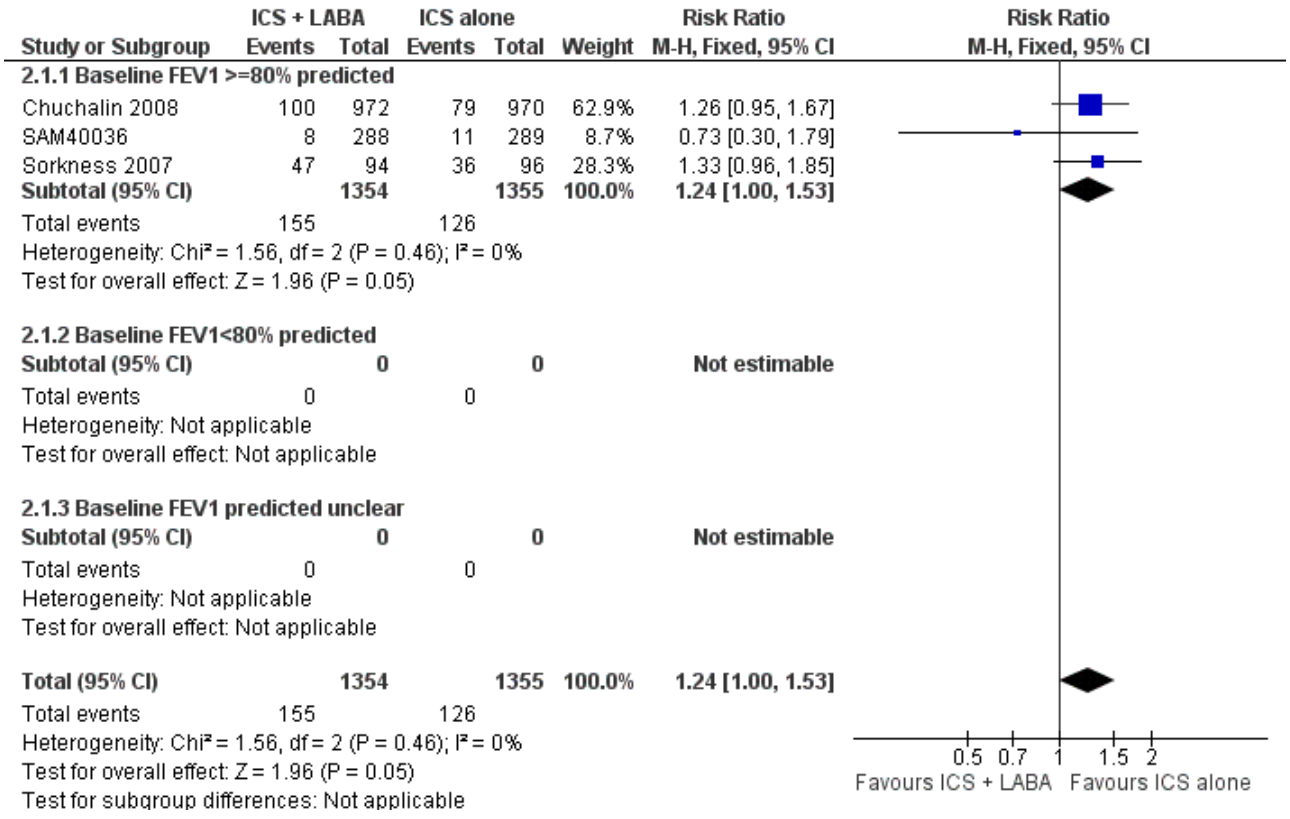
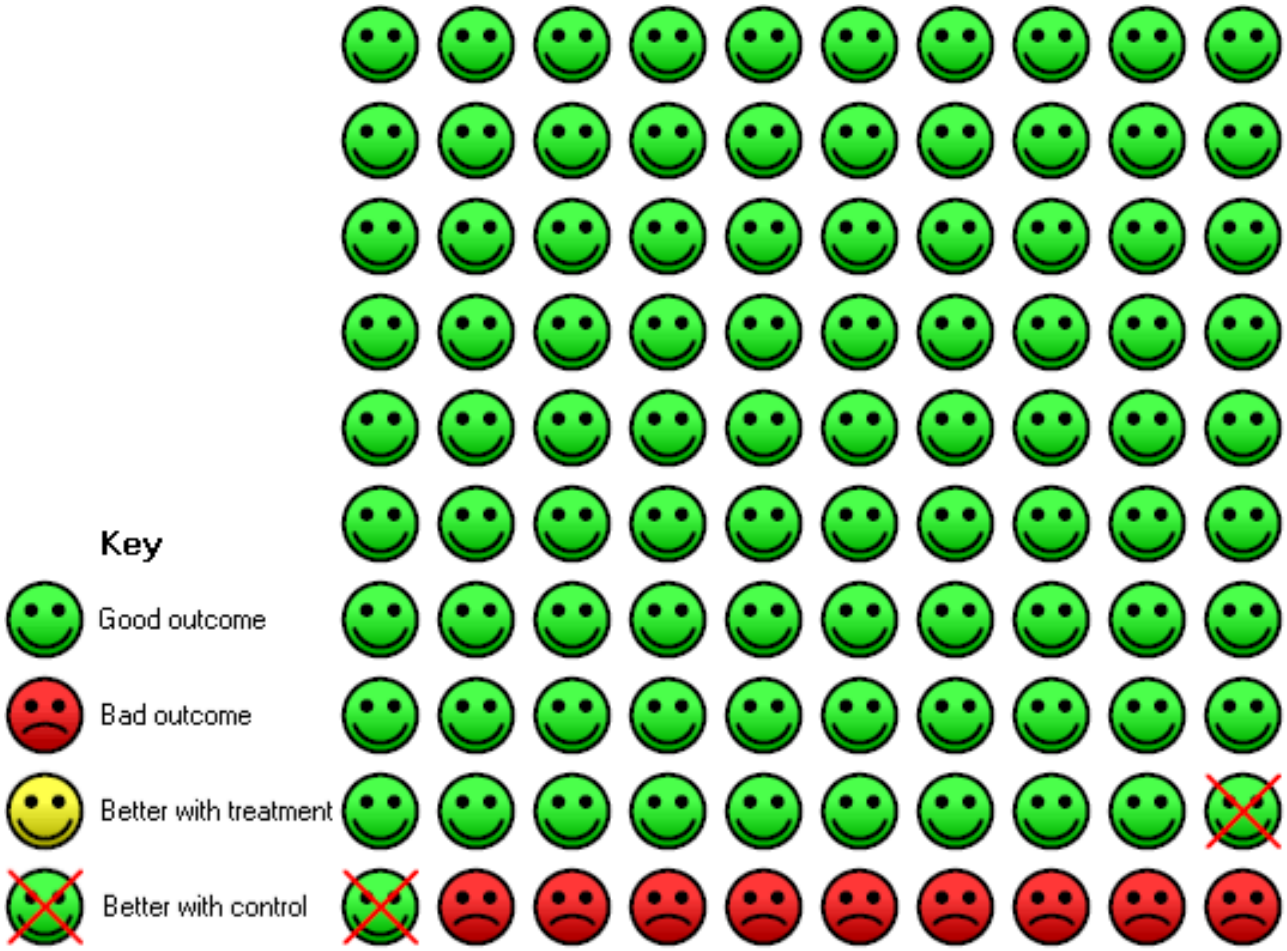


Figure 5. In the higher dose ICS group 9 people out of 100 had exacerbations requiring oral corticosteroids over 43 weeks, compared to 11 (95% CI 9 to 14) out of 100 for the LABA + ICS group.



Given the low number of studies contributing data to this outcome, we did not undertake subgroup analyses.

Secondary outcomes

Exacerbations requiring hospitalisation

There was no group difference in the risk of patients with exacerbations requiring hospital admission (RR 1.00; 95% CI 0.31 to 3.25; Analysis 2.2).

Lung function & diary recorded peak flow

There was a high level of statistical heterogeneity between two studies contributing estimates of change in FEV1 (I^2 72%; pooled random-effects model: 0.07 L; 95% CI -0.02 to 0.15; Analysis 2.3). Similarly, the findings for change in morning PEF indicated a high level of statistical heterogeneity (I^2 97%) (Analysis 2.6). This may be related to the design of Chuchalin 2008 in which fluticasone twice daily was compared to combination therapy administered once daily in the morning, before which PEF was measured (24 hours after previous dose).

Change in evening PEF significantly favoured LABA compared with a higher ICS dose (15.57 L/min; 95% CI 3.8 to 27.35; Analysis 2.8).

Symptoms and rescue medication use

Data for these outcomes could not be aggregated as they were only available for single studies (Analysis 2.10; Analysis 2.11).

Airway hyperreactivity

No aggregation of data was possible for these outcomes. A paediatric trial (Sorkness 2007) reported significantly fewer doubling doses of methacholine to induce a 20% fall in FEV1 following higher dose ICS (Analysis 2.18).

Withdrawals & tolerability

There was no statistically significant difference in the risk of serious adverse events between treatments (four studies: RR 1.03; 95% CI 0.63 to 1.69; Analysis 2.12), with insufficient power to reach equivalence.

All-cause withdrawals were more likely with the combination of LABA and ICS than with a higher ICS dose (RR 1.31; 95% CI 1.07 to 1.59; Analysis 2.13). Withdrawals due to adverse events were not significantly different between treatments (RR 1.00; 95% CI 0.54 to 1.84; Analysis 2.14). The risk of headache was not significantly different between treatments (RR 0.97; 95% CI 0.80 to 1.17; Analysis 2.16). Due to insufficient trials reporting hoarseness (Analysis 2.17)

or other adverse health events, we were unable to perform meta-analysis for additional safety endpoints.

DISCUSSION

In symptomatic steroid-naive asthmatic patients, the combination of long acting ß2-agonist (LABA) and inhaled corticosteroids does not significantly reduce the risk of patients with exacerbations requiring rescue systemic corticosteroids as compared to using a similar dose of ICS alone; however combination therapy improves lung function, symptoms and, marginally, the use of rescue ß2-agonists. Of the few specific adverse events recorded in the trials, significant group differences were only documented for tremor, which was more than four-fold more frequent with combination therapy than with ICS alone. Initiation of ICS at a slightly higher dose (by 200 to 300 mcg/day) was more effective than the combination of LABA and ICS at a lower dose reducing by 25% the risk of patients experiencing exacerbations requiring systemic corticosteroids and study withdrawals. Combination therapy achieved a higher evening PEF than a higher dose ICS, with no significant difference in improvement from baseline in FEV1 or morning PEF. Given the small number of children contributing data, no firm conclusions can be drawn regarding combination therapy in steroid-naive children although no age group differences are apparent.

Comparison 1: LABA + ICS versus same dose ICS

When comparing ICS alone with the combination of LABA with a similar dose of ICS, the available data did not show a statistically significant group difference between these strategies for the main outcome, namely patients with one or more exacerbations requiring rescue oral corticosteroids; however, the confidence interval exceeds our predefined limits of equivalence and thus we could not exclude clinically meaningful superiority of either strategy. Subgroup analyses did not detect differences in the magnitude of effect associated with the severity of baseline airway obstruction, the choice of LABA, the dose of ICS, or the duration of treatment. Our findings contrast with that of the steroid-naive stratum of GOAL (1098 patients). The GOAL data could not be included in this review because of the inability to obtain data pertaining only to rescue oral steroids. Using a composite definition of exacerbations including hospital admission, emergency visits and oral steroid, the GOAL study identified a small, but significant reduction in the *overall rate* of exacerbations over the 12 months, favouring combination therapy ($P < 0.009$). In contrast to included trials, the GOAL study design included step-up therapy with inhaled corticosteroid until asthma control was achieved, whereas we examined the effects of introducing LABA to a stable dose of ICS. Thus, in addition to the different study design, the definition of exacerbations also differed to our endpoint, which may explain the apparent discrepancy.

In this review, there was no group difference in the risk of hospital admission, but the rarity of the event with only four contributing trials prevents firm conclusion. In contrast, the combination of LABA and ICS was associated with a significantly greater improvement from baseline in lung function, by a magnitude of 0.12 L in FEV1 and 19.5 L/min in morning PEF as compared to those treated with a similar dose of ICS alone. Following the addition of five new studies contributing data to the change in FEV1, the magnitude of improvement in FEV1 due to combination therapy decreased from 210 mL in the original review, to 120 mL in this updated review. While this downward trend probably results from a more representative sample of the population and treatment protocols in which combination therapy can be used, the magnitude of improvement in FEV1 appeared to be significantly affected by trial duration, with data from 24-week or longer studies showing a smaller effect than those reporting outcome data at 12 weeks or less, suggesting that the benefit of combination therapy on lung function appears to wane with time. Because of the lack of power, the effect of the choice of LABA (i.e. formoterol versus salmeterol), and the number of devices to deliver combination therapy, on the improvement in FEV1 could not be examined.

Use of LABA and ICS also translated into significant improvements in the percentage of days without symptoms and in symptom scores over those observed with a similar ICS dose. It was also associated with a modest reduction of rescue fast-acting ß2-agonists (by less than a half-puff per day) compared to inhaled corticosteroids alone. With only one trial reporting data, the impact on airway inflammation could not be examined.

The risk of overall adverse events showed no group difference, meeting our a priori definition of equivalence. With the exception of tremor, which was almost five times more frequent in the combination therapy, there was also no group difference in specific adverse effects. Use of ICS and LABA therapy was not associated with a reduced risk of withdrawals due to either adverse effects or all reasons combined. However, due to the small number of trials, the absence of group difference did not meet our a priori definition of equivalence.

Comparison 2: LABA + ICS versus higher dose ICS

When comparing the combination of LABA and ICS to a higher (two-fold) dose of ICS, there is a statistically significant difference in favour of higher doses of ICS in reducing the risk of children and adults with exacerbations requiring oral corticosteroids. The findings were not particularly robust since only three additional trials with no group difference could change the conclusion. This finding is based on three (two adult and one paediatric) trials which all tested salmeterol in patients with a mean baseline FEV1 of 80% of predicted or higher. Whether the findings would be more or less positive in patients with more severe airway obstruction at baseline, receiving a higher ICS dose, or with other characteristics remains to be determined. The findings were supported by the superiority of a higher ICS dose for preventing study withdrawals.

With only four trials contributing few events, no firm conclusion could be made regarding the superiority of either treatment option for reducing the risk of patients with exacerbations requiring hospital admission. There was no significant group difference in most lung function tests, which displayed significant heterogeneity between studies in FEV1 and morning PEF; only the change from baseline in evening PEF favoured combination therapy in two trials with patients with mild airway obstruction. No data could be aggregated for other secondary outcomes.

Again, the risk of adverse events was not significantly different between groups, with insufficient power to prove equivalence and to rule out rare serious adverse health events. Due to the small number of trials leading to large confidence intervals, no equivalence in the safety profile can be assumed. Furthermore, the careful evaluation of the impact of a higher dose of corticosteroid requires the documentation of relevant outcomes such as bone

mineral density, adrenal function and, in children, growth in studies of long duration (≥ 26 to 52 weeks).

The non-superiority of LABA and ICS patients over ICS alone in steroid-naive patients is interesting in view of three previous large Cochrane Reviews. Indeed, as compared to ICS alone, the combination of LABA and ICS was clearly associated with a greater reduction in exacerbations in patients already on daily inhaled corticosteroids and who remained poorly controlled, in other words, when combination therapy was added at step 3 of the Global Initiative for Asthma guidelines (Ni Chroinin 2005). Moreover, the superiority of a higher ICS dose over the combination of LABA and ICS in steroid-naive patients is intriguing as no group difference was found when these strategies were compared in a large Cochrane Review focusing on patients at step 3 (Greenstone 2005). Bateman 2008, which summarised the evidence derived only from GlaxoSmithKline studies involving both steroid-naive and non steroid-naive patients, reported a significant reduction in the odds of exacerbations requiring systemic steroids in favour of adding LABA. Our linked Cochrane Reviews would indicate that the impact of LABA needs to be assessed separately in these different populations. Indeed, the divergence in response to LABA between steroid-naive patients and patients who remain poorly controlled while on ICS, exemplifies the heterogeneity in asthma sub-populations and reinforces the need for careful evaluation of all treatment strategies at each GINA step as well as within different subgroups.

The divergence in response for patients at step 2 versus step 3 suggests that, in steroid-naive patients, asthma control is achieved in the majority of patients with ICS alone. This assumption is supported by the negligible reduction in the need for rescue ß2-agonists with LABA (< 1/2 puff/day) despite baseline ß2-agonist use varying between 1 puff/day (O'Byrne 2001) and 2.5 to 4 puffs/day (Chuchalin 2002; Nelson 2003; Pearlman 1999a; Pearlman 1999b), thus leaving room for improvement. These observations confirm that the single most important intervention in steroid-naive patients, irrespective of severity of asthma, is to initiate inhaled corticosteroids at low or moderate doses.

Within each protocol, we were unable to demonstrate the impact of varying dose of ICS, LABA and duration of treatment on the magnitude of effects for our primary outcome. This may be explained by the small number of trials which under-powered the subgroup analyses, as well as by the relatively flat dose response of ICS. Indeed, the flat dose-response with inhaled corticosteroids indicates that the major part of the beneficial effect of inhaled corticosteroids is conferred at a low ICS dose, with minimal additional gain at higher doses (Powell 2003). Additional large trials with varying start-up doses of ICS are needed to clarify the relative efficacy of both treatment options and to characterise responders on age, severity of airway obstruction, smoking status etc.

Many proponents of initial treatment with combination therapy may argue that the rapid improvement in lung function, symptom control and reduction in ß2-agonists will lead to better compliance with treatment because of the patient's perception of immediate benefit with LABA. The validity of this argument could not be examined because compliance with treatment was infrequently reported and not apparently analysed in the trials. If compliance was indeed superior with the combination of ICS and LABA, it did not translate into a significant reductions in the risk of asthma exacerbation or a meaningful reduction use of rescue ß2-agonists, whether compared to the same or a higher dose of ICS.

The results of this review must be interpreted in light of the following strengths and limitations. Our review included studies examining the relative efficacy of three different strategies in asthma management for patients with no prior controller medication; that is at step 2 of the Global Initiative for Asthma guidelines. Unfortunately, a notable number of trials did not contribute to our primary outcome, because data on exacerbations treated with systemic steroids was not made available to us. However, we obtained a considerable amount of unpublished information directly from trialists and study sponsors that would not have been otherwise available. With regards to generalisability of study results, only one study reported the proportion of eligible patients amongst those approached and, in the two trials reporting the proportion of randomised patients among those enrolled in the run-in, this varied from 54% (Nelson 2003) to 99% (Chuchalin 2002). In view of this poor reporting, it is impossible to comment on how far the observed results may be replicated in clinical practice. However one must take note that patients included in the included trials were symptomatic and demonstrated significant (>= 12%) reversibility in FEV1 with a short-acting ß2 agonist. The reversibility to bronchodilator would tend to favour combination therapy with LABA over inhaled corticosteroids alone and may seriously limit generalisability since reversibility to bronchodilator is a criterion met in less than 10% of patients at a given point in time (Storms 2003), leading to regression towards the mean. We recognise that over-representation of short trials (<= 12 weeks) in the first comparison and the small number of trials in the second comparison may have limited the ability to identify group differences in specific adverse health events. Moreover, the review was not sufficiently powered to examine rare serious adverse health events. The long duration (>= 48 weeks) of two of the three trials contributing data to the main outcome probably explain the precision achieved for the second comparison. Paediatric trials represented 22% of identified studies, yet only one study in each comparison contributed data to the main outcome, thus preventing any subgroup analyses on age. While children seem to respond similarly to adults, no firm conclusion could be made with respect to the relative effectiveness of both treatment options in youth. The conclusion should not be generalised to preschool-aged children, who were not included in any identified trial.

AUTHORS' CONCLUSIONS

Implications for practice

In steroid-naive asthmatic patients who are symptomatic and exhibit mild or moderate airway obstruction, the risk in exacerbations requiring oral corticosteroids is similar between adding long-acting ß2-agonists (LABA) to inhaled steroids (ICS) and ICS alone. It does not provide sufficient justification for initiating a combination of ICS and LABA without a prior trial of ICS as a means of reducing exacerbations requiring systemic steroids. However, greater improvement in lung function and symptoms, and minimal reduction in use of rescue ß2-agonist would be expected with combination therapy. Interestingly, the benefits observed in lung function appear to wane by 24 weeks. Moreover, the use of higher dose ICS is superior to initiating combination therapy for preventing exacerbations and study withdrawals. The analyses are insufficiently powered to identify characteristics of patients (such as age group) or treatment modalities that may or may not

modify the magnitude of effect on the risk of rescue corticosteroids. Insufficient reporting of relevant outcomes and insufficient power preclude firm conclusions as to the relative safety profile of both treatment strategies, including rare serious adverse health events.

Implications for research

Long-term studies >= 24 to 52 weeks are needed to examine the relative safety profile of both treatment options and the characteristics of patients responders (age, gender, smoking status, airway obstruction) or treatment modalities (dose of ICS, number of inhalers, duration of treatment) associated with each treatment strategy (ICS versus the combination of LABA and ICS) as step 2 therapy in steroid naive patients. The safety profile, including serious adverse health events, adrenal function, bone mineralization and, in children, growth, are crucial. Trials in children are of a high priority, with 12-month duration to assess growth. These studies need to be adequately powered and preferably randomised by subgroups with subgroup analyses to identify factors which may modify outcomes (effect modifiers).

Given the flat dose-response curve of inhaled corticosteroids, future trials should focus on the comparison of long-acting ß2-agonists as:

1. Add-on to a low-dose of inhaled corticosteroids in patients with mild obstruction (or stratified on the severity of baseline obstruction);
2. Add-on to moderate doses of inhaled corticosteroids in patients with moderate or severe airway obstruction (or stratified on the severity of baseline obstruction).

Future trials should aim for the following design characteristics.

1. Enrol patients with asthma in whom the current reversibility with ß2-agonists is not a pre-requisite (in other words, asthma documented by provocation tests, prior documented reversibility with ß2-agonists or inhaled/oral corticosteroids).
2. Report separately the number of patients with exacerbations requiring systemic corticosteroids and patients requiring hospital admission, as these outcomes are less influenced by the LABA effect on smooth muscle than lung function, use of rescue ß2-agonists and symptoms.
3. Double blinding, adequate randomisation and complete reporting of withdrawals and drop-outs, with intention-to-treat analyses.
4. Parallel-groups
5. A minimal intervention period of 24 weeks or preferably more to properly assess the impact of treatment on exacerbations requiring systemic corticosteroids, and the possibility of an effect modification associated with treatment duration.
6. Clear reporting of the percentage of non-eligibility (with reasons) of approached patients and of those enrolled in the run-in period to assess the generalisability of findings.
7. Careful monitoring and reporting of compliance to treatment.
8. Complete reporting of continuous (denominators, mean change and mean standard deviation of change) and dichotomous (denominators and rate) data.
9. Systematic documentation of reasons for withdrawals and adverse effects, including those associated with inhaled corticosteroids, such as oral candidiasis, osteopenia, adrenal suppression and growth suppression.
10. Reporting of cost effectiveness of the use of combination inhalers as compared to inhaled corticosteroids alone.

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

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

Boonsawat 2008

Methods	Parallel group, 69 centres in Australia, Thailand, Philippines and Europe. 3 treatment groups: FP/SAL; FP and placebo
Participants	Asthmatic adults on short-acting beta-agonists alone % ELIGIBLE OF SCREENED POPULATION: Not reported % RUN-IN PARTICIPANTS RANDOMISED: 67 RANDOMISED: 306 (FP/SAL: 151; FP: 155) WITHDRAWALS: FP/SAL: 5; FP: 9 AGE: mean (SD): 34 (13.6) GENDER: (% male): 44 SEVERITY: Mild to moderate BASELINE % PRED. FEV1 (mean): 95 ASTHMA DURATION: Not reported ATOPY (%): Not reported ELIGIBILITY CRITERIA: 12 to 80 years of age; documented history of asthma for at least 6 months; treatment with short-acting beta-agonists only; symptomatic during run-in EXCLUSION CRITERIA: ICS treatment within 12 weeks of run-in; treatment with LABA, sodium cromoglycate, nedocromil, anticholinergic; upper/lower RTI; recent acute exacerbation; smoking history > 10 pack years

Boonsawat 2008 *(Continued)*

Interventions	PROTOCOL: Combination FP/SAL versus SAME DOSE FP OUTCOMES: 12 weeks RUN-IN: 2 weeks DOSE OF ICS DURING RUN-IN: 0 INTERVENTION PERIOD: 12 weeks TEST GROUP: Combination fluticasone and salmeterol 200/100 OD CONTROL GROUP: Fluticasone 200 OD DEVICE: HFA-MDI NUMBER OF DEVICES: 1 COMPLIANCE: Not assessed CO-TREATMENT: prn SABA
Outcomes	PULMONARY FUNCTION TEST: am PEF*; pm PEF; FEV1 SYMPTOM SCORES: Not reported FUNCTIONAL STATUS: Symptom-free days; rescue medication use; well controlled asthma; exacerbations requiring oral corticosteroids INFLAMMATORY MARKERS: Not reported ADVERSE EFFECTS: Reported by treatment group WITHDRAWALS: Reported by treatment group *Primary outcome
Notes	Unpublished full data set available from http://www.ctr.gsk.co.uk Source of funding: GSK Confirmation of methodology and data: Not obtained User defined number: 400

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	See Appendix 1
Allocation concealment (selection bias)	Low risk	See Appendix 1
Blinding (performance bias and detection bias) All outcomes	Low risk	Treatments given via identical inhaler devices
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Although the intention-to-treat population was described in the trial report, it was not clear how this was composed. Withdrawal in the study was low, however (<5%)

Boonsawat 2008 *(Continued)*

Selective reporting (reporting bias)	Low risk	Data on primary outcome were available from full-text publication

Chuchalin 2002

Methods	Parallel group, multicentre study. 3 treatment groups of which 2 considered for this review
Participants	Asthmatic adults % ELIGIBLE OF SCREENED POPULATION: Not reported % RUN-IN PARTICIPANTS RANDOMISED: 99% RANDOMISED: 338 randomised but 333 entered treatment period (F9/BUD: 111; BDP: 114; investigators choice = 108) WITHDRAWALS: Not described MEAN AGE years (RANGE): 46 (19 to 66) GENDER: (% male): 25 SEVERITY: Mild to moderate BASELINE FEV1 L (range): 1.96 (0.93 to 3.99) ASTHMA DURATION (range in years): Not reported ATOPY (%): Not reported ELIGIBILITY CRITERIA: Adult patients; diagnosis of asthma minimum 6 months; FEV1 50% to 85% predicted normal; 15% reversibility post-bronchodilator EXCLUSION CRITERIA: Current or recent users of inhaled, oral or parenteral corticosteroids; oral leukotriene antagonists; nedocromil sodium; sodium cromoglycate; betablockers including eye drops; smokers with a history of smoking > or = 10 pack years; all female patients were required to be post-menopausal, sterile or using contraception CRITERIA FOR RANDOMISATION DURING RUN-IN: No additional criteria
Interventions	LABA +ICS vs SAME dose of ICS OUTCOMES: reported monthly RUN-IN PERIOD: 2 weeks DOSE OF ICS DURING RUN-IN: No ICS during run-in DOSE OPTIMISATION PERIOD: None INTERVENTION PERIOD: 12 weeks TEST GROUP: Formoterol 9 mcg bid and budesonide 200 mcg bid CONTROL GROUP: Budesonide 200 mcg bid DEVICE: Turbuhaler NUMBER OF DEVICES: 2 COMPLIANCE: Not assessed

Chuchalin 2002 *(Continued)*

	CO-TREATMENT: prn SABA
Outcomes	PULMONARY FUNCTION TEST: FEV1 predicted; am PEF; pm PEF SYMPTOM SCORES: Score of 0 to 3 recorded in patient diary card FUNCTIONAL STATUS: Rescue medication use; contact with healthcare provider; inability to work or conduct normal activities; quality of life score INFLAMMATORY MARKERS: None ADVERSE EFFECTS: Reported WITHDRAWALS: Not described Primary outcome measure: Not reported
Notes	Full-text publication Source of funding: Not stated Confirmation of methodology and data: Not obtained User-defined number: 400

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Described as randomised; other information not available
Allocation concealment (selection bias)	Unclear risk	Information not available
Blinding (performance bias and detection bias) All outcomes	Low risk	Double-dummy design
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Intention-to-treat analysis stated, but explicit description of its composition not available and information on withdrawals was not reported
Selective reporting (reporting bias)	Unclear risk	No information on primary outcome available; exacerbation data were collected in the study but it is not clear if steroid-treated exacerbations were recorded

Chuchalin 2008

Methods	Parallel group, multicentre study. 175 centres in Australasia, South-East Asia, Middle East, Eastern Europe. 3 treatment groups of which 2 considered in the review. JADAD quality score = 4
Participants	Mild asthmatic adults % ELIGIBLE OF SCREENED POPULATION: Not reported % RUN-IN PARTICIPANTS RANDOMISED: Not reported

Chuchalin 2008 *(Continued)*

	RANDOMISED: 1964 (316 randomised to placebo not considered in this review) FP/SAL: 985; FP: 979 WITHDRAWALS: FP/SAL: 162; FP: 119 AGE: mean: 34 GENDER (% male): 58 SEVERITY: Mild BASELINE % PRED. FEV1(mean): 96 BASELINE DOSE OF ICS: 0 ASTHMA DURATION: Not reported ATOPY (%): Not reported ELIGIBILITY CRITERIA: 12 to 79 years of age; clinical history of asthma > 6 months; treatment with SABA prn only; symptomatic during run-in (symptom score > 1 on 3 to 6 days of last 7 days of run-in); > 15% reversibility in PEF post-SABA OR mean PEF < 85% predicted post-SABA EXCLUSION CRITERIA: Not reported
Interventions	LABA + ICS versus HIGHER dose ICS OUTCOMES: TIMING 52 weeks RUN-IN: 2 weeks DOSE OF ICS DURING RUN-IN: 0 INTERVENTION PERIOD: 52 weeks TEST GROUP: Combination fluticasone and salmeterol 100/50 OD CONTROL GROUP: Fluticasone 100 mcg bid DEVICE: Diskus NUMBER OF DEVICES: 1 COMPLIANCE: Not assessed CO-TREATMENT: prn SABA
Outcomes	PULMONARY FUNCTION TEST: am PEF*; FEV1 SYMPTOM SCORES: % symptom-free days FUNCTIONAL STATUS: Exacerbation rates; rescue medication use INFLAMMATORY MARKERS: Not reported ADVERSE EFFECTS: Reported WITHDRAWALS: Reported *Primary outcome
Notes	Full text article. Unpublished data available from GSK trial registry Source of funding: GSK Confirmation of methodology and data: Obtained for methods, not obtained for data

Chuchalin 2008 *(Continued)*

User defined number: 400

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	See Appendix 1
Allocation concealment (selection bias)	Low risk	See Appendix 1
Blinding (performance bias and detection bias) All outcomes	Low risk	Identical inhaled devices
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	"Analysis populations for this study included the ITT Population (all subjects randomised to study treatment who had taken at least one dose of study medication), and the PP Population (subjects in the ITT Population who had no major protocol violations."
Selective reporting (reporting bias)	Low risk	OCS-treated exacerbations available on request from study sponsor

Creticos 1999

Methods	Parallel group study
Participants	Symptomatic asthmatic adults % ELIGIBLE OF SCREENED POPULATION: Not reported % RUN-IN PARTICIPANTS RANDOMISED: Not reported RANDOMISED: 46 WITHDRAWALS: Not described AGE: mean: 35 GENDER (% male): 43.5 SEVERITY: Mild-moderate BASELINE FEV1 L (mean): 2.8 ASTHMA DURATION: Not described ATOPY (%): Not described ELIGIBILITY CRITERIA: FEV1 >= 65%; >= 12% reversibility; bronchodilator use >= 4 days/week EXCLUSION CRITERIA: None reported
Interventions	LABA + ICS vs. SAME dose of ICS OUTCOMES: Not described RUN-IN: 2 weeks

Creticos 1999 *(Continued)*

	DOSE OF ICS DURING RUN-IN: Zero
	INTERVENTION PERIOD: 6 months
	TEST GROUP: (TAA400 mcg bid + salm 50 mcg bid) Triamcinalone 400 mcg bid salmeterol 50 mcg bid
	CONTROL GROUP: (TAA400) Triamcinalone 400 mcg bid
	DEVICE: Not reported
	NUMBER OF DEVICES: 2
	COMPLIANCE: Not reported
	CO-TREATMENT: Not described
Outcomes	PULMONARY FUNCTION TEST: FEV1*; PEF
	SYMPTOM SCORES: Score of 0 to 4
	FUNCTIONAL STATUS: Not described
	INFLAMMATORY MARKERS: Not described
	ADVERSE EFFECTS: Not described
	WITHDRAWALS: Not reported
	*Primary outcome
Notes	Full text publication
	Source of funding: Not reported
	Confirmation of methodology and data not obtained
	User defined number: 400 (TAA 400 bid X 0.5)

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Described as randomised; other information not available
Allocation concealment (selection bias)	Unclear risk	Information not available
Blinding (performance bias and detection bias) All outcomes	Low risk	Identical placebo used
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Information not available
Selective reporting (reporting bias)	Unclear risk	No information on primary outcome available; not clear if exacerbation data were collected in the study

Di Franco 1999

Methods	Parallel group, single centre. 3 groups of which 2 are considered in this review
Participants	Symptomatic asthmatics teenagers and adults % ELIGIBLE OF SCREENED POPULATION: Not reported % RUN-IN PARTICIPANTS RANDOMISED: Not reported RANDOMISED: 22 (BDP/Sal: 11; BDP: 11) WITHDRAWALS: BDP/Sal: 1; BDP: 6 AGE mean (range): 37 (14 to 68) GENDER (% male): 59 SEVERITY: Mild to moderate BASELINE % PRED. FEV1: 96 BASELINE DOSE OF ICS: No ICS in the last 4 weeks before the study ASTHMA DURATION mean years (range): 10 (1 to 30) ATOPY (%): 68 ELIGIBILITY CRITERIA: A documented historical bronchial reversibility of at least 15% in FEV1 to 200 mg of salbutamol EXCLUSION CRITERIA: Well controlled asthma; previous treatment with corticosteroids; respiratory tract infections in the previous 4 weeks before ELIGILITY CRITERIA FOR RANDOMISATION DURING RUN-IN: Daily symptom score >/= 2 or within-day variation of at least 20% on at least 2 out of 7 days during the second baseline week
Interventions	LABA + ICS vs SAME dose of ICS OUTCOMES: Reported at 3, 6 and 12 months RUN-IN PERIOD: 2 weeks DOSE OF ICS DURING RUN-IN: Zero TREATMENT DURATION: 12 months DOSE OPTIMISATION PERIOD: None INTERVENTION PERIOD: 12 months TEST GROUP: (BDP 500 mg+ SALM 50 mg) beclomethasone dipropionate 500 mcg bid + salmeterol 50 mcg bid CONTROL GROUP: (BDP 500 mcg bid) Beclomethasone dipropionate 500 mcg bid DEVICE: Metered-dose aerosol inhaler NUMBER OF DEVICES: 2 COMPLIANCE: MDI inhalers weighed to assess compliance CO-TREATMENT: prn SABA
Outcomes	PULMONARY FUNCTION TEST: Diurnal variation in PEF (%); FEV1 % predicted; PC 20

Di Franco 1999 *(Continued)*

	SYMPTOM SCORES: Measured but not reported FUNCTIONAL STATUS: Rescue medication use (measured but not reported); exacerbations requiring oral corticosteroids INFLAMMATORY MARKERS: Not reported ADVERSE EFFECTS: Reported WITHDRAWALS: Described *Primary outcome: not reported
Notes	Full-text publication Source of funding: Not reported Confirmation of methodology and data obtained from Dr. Di Franco User defined number: 1000 (mean ICS dose in LABA group in mcg/day of BDP-equivalent: 1000 BDP)

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated random numbers schedule
Allocation concealment (selection bias)	Unclear risk	Information not available
Blinding (performance bias and detection bias) All outcomes	High risk	Open label study
Incomplete outcome data (attrition bias) All outcomes	High risk	Available case for spirometry outcomes
Selective reporting (reporting bias)	Low risk	Primary outcome data available

GOAL

Methods	Parallel group, 326 centres in Europe, North America, Latin America and Asia Pacific
Participants	Uncontrolled asthmatic adults % ELIGIBLE OF SCREENED POPULATION: 67 % RUN-IN PARTICIPANTS RANDOMISED: Not clear RANDOMISED: 3416 (of which 1098 were in stratum one with no ICS in previous 6 months) FP/SAL: 1707; FP: 1709 WITHDRAWALS: FP/SAL: 162; FP: 215 AGE mean (SD): 40 (16) GENDER (% male): 42

GOAL *(Continued)*

	SEVERITY: Moderate BASELINE % PRED. FEV1 (mean): 77 BASELINE DOSE OF ICS: Divided into 3 strata: 0; 500 mcg/d or less; between 500 and 1000 mcg/d ASTHMA DURATION: 0 to 1 year: FP/SAL: 56; FP: 97; 1 to 10 years: FP/SAL: 649; FP: 647; > 10 years: FP/SAL: 1004; FP: 992 ATOPY (%): 58 ELIGIBILITY CRITERIA: 12 to 80 years of age ;6-month history of asthma; FEV1 reversibility of 15%; smoking history of less than 10 pack years; no use of LABA or oral beta-agonists in previous 2 weeks EXCLUSION CRITERIA: Not reported
Interventions	LABA + ICS versus SAME dose ICS OUTCOMES: End of phase 1 (12 weeks) RUN-IN: 4 weeks DOSE OF ICS DURING RUN-IN: Usual maintenance dose of ICS (including 0 for participants not treated with ICS) INTERVENTION PERIOD: Two different phases: I = Dose step-up until total asthma control achieved, or until maximum dose of study drug given for 12 weeks; II = Constant dose of final dose of study drug until 52 weeks since randomisation had elapsed. TEST GROUP: Combination fluticasone and salmeterol 50/100; 50/250 or 50/500 mcg bid CONTROL GROUP: Fluticasone 100, 250 or 500 mcg bid DEVICE: Diskus NUMBER OF DEVICES: 1 COMPLIANCE: Not assessed CO-TREATMENT: prn SABA
Outcomes	PULMONARY FUNCTION TEST: FEV1 SYMPTOM SCORES: Not reported FUNCTIONAL STATUS: N achieving total asthma control*; exacerbations INFLAMMATORY MARKERS: Not reported ADVERSE EFFECTS: Reported by treatment group WITHDRAWALS: Reported by treatment group *Primary outcome
Notes	Full text publication Source of funding: GSK Confirmation of methodology and data: Not obtained User defined number: 1000

Risk of bias

GOAL *(Continued)*

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated randomisation schedule. Participants allocated to stratum according to pre-trial treatment (0 ICS, low dose & high dose). See Appendix 1
Allocation concealment (selection bias)	Low risk	Central system maintained by telephone. See Appendix 1
Blinding (performance bias and detection bias) All outcomes	Low risk	Identical inhaler devices
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Study population described as intention-to-treat; it is not clear whether last observation carried forward was applied: "...a minimum of 4 weeks of evaluable data were required to make an assessment of control... All unassessable patients were classified as uncontrolled."
Selective reporting (reporting bias)	Low risk	Primary outcome reported as a mean rate; dichotomous data requested and obtained from study sponsors

Grutters 1999

Methods	Parallel group, 2-centre study. 3 treatment arms of which 2 are considered for this review
Participants	Stable asthmatic adults % ELIGIBLE OF SCREENED POPULATION: Not reported % RUN-IN PARTICPANTS RANDOMISED: Not reported RANDOMISED: 40 (SALM 50 mcg + 400 BDP bid: 12; BDP 400 bid = 15) WITHDRAWALS: Not reported AGE: mean: 27 GENDER (% males): 52 SEVERITY: Moderate BASELINE % PRED. FEV1 mean: 84 BASELINE DOSE OF ICS (before start of run-in): 0 ASTHMA DURATION: Not reported ATOPY (%): 100 ELIGIBILITY CRITERIA: Adults; history of wheezing, impaired lung function, verified in GP or hospital records; regular rescue medication; no oral corticosteroids during 12 months prior to study; no systemic disease or respiratory illness; FEV1 at baseline >= 60% of its predicted value; PC 20 < 4.0 mg/ml; 15% reversibility following bronchodilator; blood eosinophilia > 5%; raised Total IgE and specific antibodies to certain allergens and positive skin tests EXCLUSION CRITERIA: History of hospitalisation for asthma; change in medication for acute exacerbation in 2 months prior to study
Interventions	LABA + ICS vs SAME dose of ICS

Grutters 1999 *(Continued)*

	OUTCOMES: At days 12, 14, 15, 43, 69, 71 and 72 RUN-IN PERIOD: 2 weeks DOSE OF ICS DURING RUN-IN: 0 DOSE OPTIMISATION PERIOD: None INTERVENTION PERIOD: 8 weeks TEST GROUP (LABA + SAME DOSE ICS): BDP 400 mcg bid + salmeterol 50 mcg bid CONTROL GROUP: BDP 400 mcg bid DEVICE: Diskhaler NUMBER OF DEVICES: 1 COMPLIANCE: Study medication counted CO-TREATMENT: Not stated
Outcomes	PULMONARY FUNCTION TEST: FEV1 SYMPTOM SCORES: Not given FUNCTIONAL STATUS: Not assessed INFLAMMATORY MARKERS: Serum ECP; respiratory burst defined as rate of oxygen uptake of eosinophils; release of PAF before and after allergen inhalation challenge ADVERSE EFFECTS: Not reported WITHDRAWALS: Not reported Primary outcome: Not reported
Notes	Full-text publication Supported by GlaxoWellcome Research and Development Confirmation of methodology and data extraction not obtained User defined number: 800 (mean ICS dose in LABA group in mcg/day of BDP-equivalent: 800)

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	See Appendix 1
Allocation concealment (selection bias)	Low risk	See Appendix 1
Blinding (performance bias and detection bias) All outcomes	Low risk	Identical inhaler devices
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Information not available

Grutters 1999 *(Continued)*

Selective reporting (reporting bias)	Unclear risk	No information on primary outcome available; not clear if exacerbation data were collected in the study

Karaman 2007

Methods	Parallel group trial, single centre in Turkey
Participants	Asthmatic children without prior treatment N RANDOMISED: 90 (60 for this review) N COMPLETED: 67 (46 for this review) GENDER (% MALE): 52 MEAN AGE: 10 years BASELINE FEV1 not reported ATOPY (%): 54 INCLUSION CRITERIA: 7 to 17 years; GINA diagnosed asthma; no prior treatment with anti-asthma medication; diagnosed within 3 months EXCLUSION: Mild or severe persistent asthma; hospitalisation in preceding 4 weeks; previous intubation
Interventions	LABA + ICS versus SAME dose ICS OUTCOMES: At 8 weeks RUN-IN PERIOD: 0 INTERVENTION PERIOD: 8 weeks TEST GROUP: Budesonide 400 mcg bid, plus 9 mcg formoterol bid CONTROL: Budesonide 400 mcg bid NUMBER OF INHALER DEVICES: 2 CO-TREATMENT: Not reported
Outcomes	PULMONARY FUNCTION TEST: FEV1; FVC; PEF SYMPTOMS: Not reported FUNCTIONAL STATUS: Change in paediatric AQLQ INFLAMMATORY MARKERS: Eosinophil counts Primary outcome: Not stated
Notes	Full-text article Additional data sought from trialists, but not forthcoming Funding source: not disclosed User defined number: 400

Karaman 2007 *(Continued)*

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Described as randomised; no other information available
Allocation concealment (selection bias)	Unclear risk	Information not available
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Information not available
Incomplete outcome data (attrition bias) All outcomes	High risk	Study completers analysed for outcomes
Selective reporting (reporting bias)	Unclear risk	No information on primary outcome available; not clear if exacerbation data were collected in the study

Kerwin 2008

Methods	Parallel group, multicentre study (121 centres in USA and Canada)
Participants	Mildly asthmatic adults % ELIGIBLE OF SCREENED POPULATION: Not reported % RUN-IN PARTICIPANTS RANDOMISED: Not reported RANDOMISED: 844 (FP/SAL bid: 210 (not considered for this review); FP/SAL qd: 212; FP qd: 212; placebo: 212 (not considered for this review)) WITHDRAWALS: FP/SAL qd: 36; FP: 30 AGE mean (SD): 33 (13) GENDER: (% male): 46 SEVERITY: Mild BASELINE % PRED. FEV1 (mean): 74 BASELINE DOSE OF ICS: 0 ASTHMA DURATION: Not reported ATOPY (%): Not reported ELIGIBILITY CRITERIA: > 12 years of age; 50% to 80% predicted; >/= 15% reversibility post-SABA; pm PEF 50% to 90% normal; symptom score of more than 2 on 4 or more days in week prior to randomisation; treatment with SABA alone; use of SABA on 4 or more days in week prior to randomisation EXCLUSION CRITERIA: Not reported
Interventions	LABA + ICS versus SAME dose ICS OUTCOMES TIMING: 12 weeks

Kerwin 2008 *(Continued)*

	RUN-IN: Not reported DOSE OF ICS DURING RUN-IN: 0 INTERVENTION PERIOD: 12 weeks TEST GROUP: Combination fluticasone and salmeterol 250/50mcg qd CONTROL GROUP: Fluticasone 250mcg qd DEVICE: Diskus NUMBER OF DEVICES: 1 COMPLIANCE: Not assessed CO-TREATMENT: prn SABA
Outcomes	PULMONARY FUNCTION TEST: am PEF predicted; pm PEF predicted* SYMPTOM SCORES: Combined symptoms FUNCTIONAL STATUS: Rescue medication use INFLAMMATORY MARKERS: Not reported ADVERSE EFFECTS: Reported WITHDRAWALS: Reported *Primary outcome
Notes	Unpublished full data set available from http://www.ctr.gsk.co.uk Source of funding: GSK Confirmation of methodology and data: obtained User defined number: 500

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	See Appendix 1
Allocation concealment (selection bias)	Low risk	See Appendix 1
Blinding (performance bias and detection bias) All outcomes	Low risk	Identical inhaler devices used
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Intention-to-treat analysis stated, but explicit description of its composition not available
Selective reporting (reporting bias)	Low risk	Data on OCS-treated exacerbations available on request from study sponsor

Miraglia del Giudice 2007

Methods	Parallel group, single centre in Italy
Participants	% ELIGIBLE OF SCREENED POPULATION: 94 % RUN-IN PARTICIPANTS RANDOMISED: Not stated RANDOMISED: 48 (N relevant to comparisons in this review: 24) WITHDRAWALS: All completed AGE mean (range) or mean (SD): 7 to 11 years SEVERITY: Moderate BASELINE % PRED. FEV1: 76% BASELINE DOSE OF ICS: 0 ASTHMA DURATION: Not stated ATOPY (%): 100 ELIGIBILITY CRITERIA: 7 to 11 years; HDM-sensitive; > 12% increase in FEV1 post-SABA EXCLUSION CRITERIA: Use of ICS, OCS or LTRAs in previous 4 weeks ELIGIBILITY CRITERIA DURING RUN-IN: Not applicable
Interventions	LABA + ICS versus SAME dose ICS OUTCOMES: 4 weeks RUN-IN PERIOD: 0 DOSE OPTIMISATION PERIOD: Not applicable INTERVENTION PERIOD: 4 weeks TEST GROUP: Budesonide 200 mcg bid + formoterol 9 mcg bid CONTROL GROUP: Budesonide 200 mcg bid NUMBER OF DEVICES: 2 COMPLIANCE: Not assessed CO-TREATMENT: SABA prn
Outcomes	PULMONARY FUNCTION TEST: FEV1 predicted SYMPTOM SCORES: NA FUNCTIONAL STATUS: NA INFLAMMATORY MARKERS: FEno ADVERSE EFFECTS: Not reported WITHDRAWALS: Reported
Notes	Full text article Funding: Non-commercial source Confirmation of methodology and data: Not obtained

Miraglia del Giudice 2007 *(Continued)*

User defined number: 400

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Described as randomised; other information not reported
Allocation concealment (selection bias)	Unclear risk	Information not reported
Blinding (performance bias and detection bias) All outcomes	High risk	Non-identical placebo (confectionary with similar shape to anti-leukotriene agent)
Incomplete outcome data (attrition bias) All outcomes	High risk	Study completers analysed for outcomes
Selective reporting (reporting bias)	Unclear risk	No information on primary outcome available; not clear if exacerbation data were collected in the study

Murray 2004

Methods	Parallel group, multicentre study (33 centres in USA). 3 treatment groups: FP/SAL; FP; SAL (not considered by this review)
Participants	Asthmatic adults not treated with inhaled corticosteroids % ELIGIBLE OF SCREENED POPULATION: Not reported % RUN-IN PARTICIPANTS RANDOMISED: Not reported RANDOMISED: 177 (FP/SAL: 88; FP: 89) WITHDRAWALS: FP/SAL: 12; FP: 11 AGE mean (SD): 33 (13.5) GENDER (% male): 49 SEVERITY: Moderate BASELINE % PRED. FEV1 (mean): 66 BASELINE DOSE OF ICS: 0 ASTHMA DURATION: Not reported ATOPY (%): Not reported ELIGIBILITY CRITERIA: ATS defined asthma for at least 6 months prior to screening; treatment with as-needed short-acting beta-agonists only for at least 1 month; FEV1 40% to 85% predicted EXCLUSION CRITERIA: Use of ICS or OCS within 1 month of study entry; use of LABA within 72 hours of study entry
Interventions	LABA + ICS versus SAME dose ICS

Murray 2004 *(Continued)*

	OUTCOMES: 12 weeks RUN-IN: Not reported DOSE OF ICS DURING RUN-IN: Not reported INTERVENTION PERIOD: 12 weeks TEST GROUP: Combination fluticasone and salmeterol 100/50 mcg bid CONTROL GROUP: Fluticasone 100 mcg bid DEVICE: Diskus NUMBER OF DEVICES: 1 COMPLIANCE: Not assessed CO-TREATMENT: prn SABA
Outcomes	PULMONARY FUNCTION TEST: am PEF; pm PEF; FEV1* SYMPTOM SCORES: Combined scores FUNCTIONAL STATUS: Rescue medication usage; night-time awakenings; withdrawal due to worsening asthma INFLAMMATORY MARKERS: Not reported ADVERSE EFFECTS: Reported by treatment group WITHDRAWALS: Reported by treatment group *Primary outcome
Notes	Full data set available from http://www.ctr.gsk.co.uk Source of funding: GSK Confirmation of methodology and data: Not obtained User defined number: 400

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	See Appendix 1
Allocation concealment (selection bias)	Low risk	See Appendix 1
Blinding (performance bias and detection bias) All outcomes	Low risk	Identical inhaler devices used
Incomplete outcome data (attrition bias) All outcomes	High risk	Described as intention-to-treat analysis, last observation carried forward used: ITT population "...defined as all randomised patients who had taken at least one dose of the study drug. To minimize the potential bias due to different withdrawal rates among the treatment groups, end point analyses were used when appropriate."

Murray 2004 *(Continued)*

Selective reporting (reporting bias)	Low risk	Data on exacerbations available on request from GSK

Nelson 2003

Methods	Parallel-group, multicentre study (33 centres). 3 treatment groups of which 2 are considered here
Participants	Symptomatic asthmatic patients over 12 years % ELIGIBLE OF SCREENED POPULATION: Not reported % RUN-IN PARTICIPANTS RANDOMISED: 54% (Of 525 patients screened 242 were not randomised reasons not stated) RANDOMISED: 192 total randomised to groups of interest (SAL + ICS: 95; placebo + ICS: 97) WITHDRAWALS: SAL + ICS: 9; placebo + ICS: 8 AGE: mean(range): 31.4 (12 to 76) GENDER (% male): 53 SEVERITY: Mild to moderate BASELINE FEV1 % PRED. MEAN : 66 BASELINE DOSE OF ICS: 0 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; FEV1 between 40% to 85%; 15% improvement in FEV1 post-bronchodilator; female patients negative pregnancy test, surgically sterile, post-menopausal or using birth control EXCLUSION CRITERIA: History of life threatening asthma; hypersensitivity reaction to sympathomimetic drugs or corticosteroids; smoking in year before study or smoking history of > 10 pack 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
Interventions	LABA + ICS vs SAME dose of ICS OUTCOMES: Reported weekly weeks 1 to 4 and thereafter 2-weekly RUN-IN PERIOD: 2 weeks DOSE OF ICS DURING RUN-IN: 0 DOSE OPTIMISATION PERIOD: None INTERVENTION PERIOD: 12 weeks TEST GROUP: (SAL 50 + ICS) Salmeterol 50 mg bid + ICS FP 100 mcg bid CONTROL GROUP: (placebo+ICS) placebo + ICS FP 100 mcg bid

Nelson 2003 *(Continued)*

	DEVICE: MDI
	NUMBER OF DEVICES: 2
	COMPLIANCE: Evaluated using diary cards (96% to 97%)
	CO-TREATMENT: prn SABA
Outcomes	PULMONARY FUNCTION TEST: am PEF; pm PEF; FEV1
	SYMTPOM SCORES: Mean change in patient-rated daily diary card asthma symptom scores (score 0 to 5)
	FUNCTIONAL STATUS: Symptom-free days; night awakenings; rescue medication use
	INFLAMMATORY MARKERS: Not described
	ADVERSE EFFECTS: Described
	WITHDRAWALS: Described
Notes	Full-text publication
	Funded by GSK
	Confirmation of methodology obtained from Shailesh Patel
	User-defined number: 400 (400 mcg/day BDP equivalent in control group)

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	See Appendix 1
Allocation concealment (selection bias)	Low risk	See Appendix 1
Blinding (performance bias and detection bias) All outcomes	Low risk	Identical placebos used
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Intention-to-treat analysis: unclear how population composed
Selective reporting (reporting bias)	Low risk	Data on exacerbations available on request from GSK

O'Byrne 2001

Methods	Parallel group, multicentre trial. 7 groups of which 2 considered here
Participants	Symptomatic asthmatic teenagers and adults
	% ELIGIBLE OF SCREENED POPULATION: Not reported
	% RUN-IN PARTICIPANTS RANDOMISED: Not reported

O'Byrne 2001 *(Continued)*

	RANDOMISED: 459 (F/BUD: 231; BUD: 228) WITHDRAWALS: Not reported by subgroup AGE mean: 31 GENDER (% male): 38 SEVERITY: Mild BASELINE % PRED. FEV1: 90 BASELINE DOSE OF ICS: 0 ASTHMA DURATION: Not reported ATOPY(%): Not reported ELIGIBILITY CRITERIA: >= 12 years of age with mild asthma; taking no inhaled corticosteroids for >/= 3 months; FEV1 >= 80% predicted normal after terbutaline EXCLUSION CRITERIA: Experienced 3 severe exacerbations during the initial 6 months or 5 exacerbations in total; 2 poorly controlled asthma days, defined as days with morning PEF values >= 2 above baseline, or with asthma awakening CRITERIA FOR RANDOMISATION DURING RUN-IN: Randomised patients demonstrated a need for 2 or more inhalations per week of rescue medication during the last 2 weeks of run-in; a >= 15% variability in peak expiratory flows; or a >= 12% increase in FEV1 after terbutaline
Interventions	LABA + ICS vs SAME dose ICS OUTCOMES: Reported at 52 weeks RUN-IN PERIOD: 4 weeks DOSE OF ICS DURING RUN- IN: 0 DOSE OPTIMISATION PERIOD: None INTERVENTION PERIOD: 52 weeks TEST GROUP: Formoterol 4.5 mcg and budesonide 100 mcg bid CONTROL GROUP: Budesonide 100 mcg bid DEVICE: Turbuhaler NUMBER OF DEVICES: 2 COMPLIANCE: Not reported CO-TREATMENT: prn SABA
Outcomes	PULMONARY FUNCTION TEST: am PEF; FEV1 SYMPTOM SCORES: Not reported FUNCTIONAL STATUS: Symptom-free days; nocturnal awakenings; rescue medication use; severe exacerbations (rate) INFLAMMATORY MARKERS: Not reported ADVERSE EFFECTS: Reported WITHDRAWAL: Reported

O'Byrne 2001 *(Continued)*

	*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 obtained User-defined order: 200

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer generated random numbers
Allocation concealment (selection bias)	Low risk	Opaque consecutive numbered envelopes containing assignment
Blinding (performance bias and detection bias) All outcomes	Low risk	Use of identical placebo
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Intention-to-treat analysis stated, but explicit description of its composition not available
Selective reporting (reporting bias)	Low risk	Primary outcome data available from study publication

Overbeek 2005

Methods	Parallel-group, single centre study
Participants	Asthmatic adults % ELIGIBLE OF SCREENED POPULATION: Not reported % RUN-IN PARTICIPANTS RANDOMISED: Not reported RANDOMISED: 40 WITHDRAWALS: 0 MEAN AGE years: 28.8 GENDER: (% male) 53 SEVERITY: Mild to moderate BASELINE FEV1 PREDICTED: 78% BASELINE DOSE OF ICS: 0 ASTHMA DURATION (range in years): Not reported ATOPY (%): 85

Overbeek 2005 *(Continued)*

	ELIGIBILITY CRITERIA: Non-smokers; receiving maximum of 800 mcg ICS/d prior to steroid-free run-in; 18 to 55 years of age; FEV1 between 50% and 90% of predicted; provocative concentration of methacholine causing 20% fall in FEV1 of 8 mg/mL EXCLUSION CRITERIA: Not reported CRITERIA FOR RANDOMISATION DURING RUN-IN: Not reported
Interventions	LABA + ICS vs SAME dose ICS OUTCOMES: Reported at 8 and 16 weeks RUN-IN PERIOD: 4 weeks DOSE OF ICS DURING RUN-IN: No ICS during run-in DOSE OPTIMISATION PERIOD: 0 INTERVENTION PERIOD: 8 weeks (ICS doubled between weeks 8 and 16) TEST GROUP: Formoterol 12 mcg bid and budesonide 100 mcg bid CONTROL GROUP: Budesonide 100 mcg bid DEVICE: Turbuhaler NUMBER OF DEVICES: 2 COMPLIANCE: Not assessed CO-TREATMENT: prn SABA
Outcomes	PULMONARY FUNCTION TEST: FEV1 predicted SYMPTOM SCORES: Not reported FUNCTIONAL STATUS: Not reported INFLAMMATORY MARKERS: Bronchoprovocation test*; exhaled nitric oxide ADVERSE EFFECTS: None WITHDRAWALS: None *Primary outcome measure
Notes	Full-text publication Funded by AstraZeneca Data and methodology confirmation: Not obtained User-defined number: 200

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Described as randomised; other information not available
Allocation concealment (selection bias)	Unclear risk	Information not available

Overbeek 2005 *(Continued)*

Blinding (performance bias and detection bias) All outcomes	Low risk	Identical inhaler devices used
Incomplete outcome data (attrition bias) All outcomes	Low risk	All participants completed the study
Selective reporting (reporting bias)	Unclear risk	No information on primary outcome available; not clear if exacerbation data were collected in the study

Pearlman 1999a

Methods	Parallel group, multicentre study (11 centres). 6 treatment groups of which 4 are considered for this review and 2 are described here
Participants	Asthmatic adults % ELIGIBLE OF SCREENED POPULATION: Not reported % RUN-IN PARTICIPANTS RANDOMISED: Not reported RANDOMISED: 48 (FP/SAL 25; FP: 23) WITHDRAWALS: FP/SAL: 2; FP: 1 AGE: mean (range): 30 (13 to 60) GENDER (% male): 57 SEVERITY: Moderate BASELINE % PRED. FEV1: 68 BASELINE DOSE OF ICS: 0 ASTHMA DURATION: >= 6 months & < 1 year = 0 >= 1 year & < 5 years = 11 >= 5 years & < 10 years = 7 >= 10 years & < 15 years = 7 >= 15 years = 23 ATOPY (%): Not recorded ELIGIBILITY CRITERIA: >= 12 years; FEV1 between 50% and 80% of predicted value for age, sex, height and race; medical history of asthma of at least 6 months requiring pharmacotherapy; >= 15% increase in FEV1 15 minutes after 2 puffs of inhaled albuterol; being treated with daily or as-needed short-acting beta-sympathomimetic bronchodilators; females had negative pregnancy tests, surgically sterile, postmenopausal for at least 1 year; or using acceptable birth control for at least 1 month prior to participation EXCLUSION CRITERIA: History of life threatening asthma; hypersensitivity reaction to sympathomimetic drugs or corticosteroids; smoking within the previous year or a history of > 10 pack-years; use of oral, inhaled, injectable, or intranasal corticosteroid therapy within the previous month; use of daily oral corticosteroid treatment within the previous 6 months; use of any other prescription or over-the-counter medication that may affect the course of asthma or interact with sympathomimetic amines; abnormal chest X-rays; clinically significant abnormal 12-lead electrocardiograms; history of significant concurrent disease

Pearlman 1999a *(Continued)*

	CRITERIA FOR RANDOMISATION DURING RUN-IN: Completion of daily dairy cards and report medication compliance; patients were not eligible for inclusion if they used 12 or more puffs of albuterol daily for more than 2 days or if they had more than 2 night-time awakenings due to asthma requiring treatment with albuterol during the 7 days immediately preceding the randomisation period; FEV 1 had to be between 50% and 80% of the predicted value and within 15% of the FEV1 obtained at the beginning of the screening period
Interventions	LABA + ICS vs SAME dose ICS OUTCOMES: reported at 2 and 4 weeks RUN-IN PERIOD: 2 weeks DOSE OF ICS DURING RUN-IN: Same as usual DOSE OPTIMISATION PERIOD: None INTERVENTION PERIOD: 4 weeks TEST GROUP: (SL50 + FP100) salmeterol 50 mg bid + fluticasone propionate 100 mg bid CONTROL GROUP: (FP 100) Fluticasone propionate 100 mg bid DEVICE: Metered-dose inhaler NUMBER OF DEVICES: 2 COMPLIANCE: Evaluated CO-TREATMENT: prn SABA
Outcomes	PULMONARY FUNCTION TEST: FEV1; am PEF SYMPTOM SCORE: Score of 0 to 4 mean change from baseline FUNCTIONAL STATUS: Rescue medication use; night awakenings; symptom-free days INFLAMMATORY MARKERS: Not measured ADVERSE EFFECTS: Reported WITHDRAWALS: Reported *Primary outcome measure (not reported)
Notes	Full-text publication Funded by Glaxo Wellcome Confirmation of methodology and data confirmed User defined number: 400 (F100 x 2 bid)

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer generated random numbers "Lowest available treatment number in accordance with their chronological presentation to the investigator"
Allocation concealment (selection bias)	Low risk	See Appendix 1

Pearlman 1999a *(Continued)*

Blinding (performance bias and detection bias) All outcomes	Low risk	Use of identical placebo (double dummy design)
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Intention-to-treat population defined as "all randomized subjects exposed to the study drug". Handling of withdrawals not explicit
Selective reporting (reporting bias)	Low risk	Exacerbations not assessed

Pearlman 1999b

Methods	See Pearlman 1999a
Participants	As for Pearlman 1999a, except for: RANDOMISED: 44 (FP/SAL: 21; FP: 23) WITHDRAWALS: FP/SAL: 0; FP: 1 AGE: mean (range) 29 (13 to 61) GENDER: (% male) 62 SEVERITY: Moderate BASELINE % PRED. FEV1: 67 BASELINE DOSE OF ICS: 0 ASTHMA DURATION: >= 6 months & < 1 year = 1 >= 1 year & < 5 years = 5 >= 5 years & < 10 years = 6 >= 10 years & < 15 years = 8 >= 15 years = 24
Interventions	As for Pearlman 1999a, except for TEST GROUP: (SL50 + FP250) salmeterol 50 mg bid and fluticasone propionate 250 mg bid CONTROL GROUP: (FP 250) Fluticasone propionate 250 mg bid DEVICE: Metered-dose inhaler NUMBER OF DEVICES: 2
Outcomes	See Pearlman 1999a
Notes	As for Pearlman 1999a, except for: User defined number: 1000 (F250 x 2 bid)

Risk of bias

Bias	Authors' judgement	Support for judgement

Pearlman 1999b *(Continued)*

Random sequence generation (selection bias)	Low risk	Computer generated random numbers "Lowest available treatment number in accordance with their chronological presentation to the investigator"
Allocation concealment (selection bias)	Low risk	See Appendix 1
Blinding (performance bias and detection bias) All outcomes	Low risk	Use of identical placebo (double dummy design)
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Intention-to-treat population defined as "all randomized subjects exposed to the study drug". Handling of withdrawals not explicit
Selective reporting (reporting bias)	Low risk	Exacerbations not assessed

Prieto 2005

Methods	Parallel group, single centre in Spain.
Participants	Mild asthmatic adults % ELIGIBLE OF SCREENED POPULATION: Not reported % RUN-IN PARTICIPANTS RANDOMISED: Not reported RANDOMISED: 42 (FP/SAL: 21; FP: 21) WITHDRAWALS: 0 AGE: mean: 41 GENDER (% male): 45 SEVERITY: Mild BASELINE % PRED. FEV1 (mean): 105 BASELINE DOSE OF ICS: 0 ASTHMA DURATION: Not reported ATOPY (%): 100 ELIGIBILITY CRITERIA: 18 to 72 years; sensitised to pollen; lifelong non-smoker EXCLUSION CRITERIA: Requirement for asthma therapy; symptoms outside pollen season
Interventions	LABA + ICS versus SAME dose ICS OUTCOMES: 6 weeks RUN-IN: None DOSE OF ICS DURING RUN-IN: NA INTERVENTION PERIOD: 6 weeks

Prieto 2005 *(Continued)*

	TEST GROUP: Combination fluticasone and salmeterol 100/50 mcg bid CONTROL GROUP: Fluticasone 100 mcg bid DEVICE: Accuhaler NUMBER OF DEVICES: 1 COMPLIANCE: Not assessed CO-TREATMENT: Not reported
Outcomes	PULMONARY FUNCTION TEST: FEV1 SYMPTOM SCORES: Not reported FUNCTIONAL STATUS: Not reported INFLAMMATORY MARKERS: PC20* ADVERSE EFFECTS: Reported WITHDRAWALS: Reported *Primary outcome
Notes	Full text publication and unpublished data available from http://www.ctr.gsk.co.uk Source of funding: GSK Confirmation of methodology and data: Not obtained User defined number: 400

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	See Appendix 1
Allocation concealment (selection bias)	Low risk	See Appendix 1
Blinding (performance bias and detection bias) All outcomes	Low risk	Identical inhaler devices used
Incomplete outcome data (attrition bias) All outcomes	Low risk	All participants completed the study
Selective reporting (reporting bias)	Unclear risk	No information on primary outcome available; not clear if exacerbation data were collected in the study

Rojas 2007

Methods	Parallel group, 48 centres in Argentina & Europe
Participants	Moderately severe asthmatic adults

Rojas 2007 *(Continued)*

	% ELIGIBLE OF SCREENED POPULATION: Not reported % RUN-IN PARTICIPANTS RANDOMISED: Not reported RANDOMISED: 362 (FP/SAL: 182; FP: 180) WITHDRAWALS: FP/SAL: 7; FP: 5 AGE mean (SD): 40 (15) GENDER (% male): 42 SEVERITY: Moderate BASELINE % PRED FEV1 (mean): 72 BASELINE DOSE OF ICS: 0 ASTHMA DURATION: Not reported ATOPY (%): Not reported ELIGIBILITY CRITERIA: 12 to 80 years of age; history of asthma of more than 6 months; FEV1 60% to 80% predicted; >/= 15% reversibility FEV1 post-SABA OR mean PEF <85% predicted post-SABA over last 7 days of run-in EXCLUSION CRITERIA: Use of corticosteroids within 12 weeks; anti-leukotrienes within 4 weeks; LABAs/nedocromil sodium/ketotifen/methylxanthines/anticholinergics within 2 weeks; acute exacerbation of asthma within 6 weeks
Interventions	LABA + ICS versus SAME dose ICS OUTCOMES: 12 weeks RUN-IN: 2 weeks DOSE OF ICS DURING RUN-IN: 0 INTERVENTION PERIOD: 12 weeks TEST GROUP: Combination fluticasone and salmeterol 250/50 mcg bid CONTROL GROUP: Fluticasone 250 mcg bid DEVICE: Diskus NUMBER OF DEVICES: 1 COMPLIANCE: Not assessed CO-TREATMENT: prn SABA
Outcomes	PULMONARY FUNCTION TEST: am PEF*; pm PEF; FEV1 SYMPTOM SCORES: Daytime symptoms; night-time symptoms FUNCTIONAL STATUS: Rescue medication use INFLAMMATORY MARKERS: Not reported ADVERSE EFFECTS: Reported by treatment group WITHDRAWALS: Reported by treatment group *Primary outcome

Rojas 2007 *(Continued)*

Notes	Unpublished full data set available from http://www.ctr.gsk.co.uk Source of funding: GSK Confirmation of methodology and data: Obtained User defined number: 1000

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	See Appendix 1
Allocation concealment (selection bias)	Low risk	See Appendix 1
Blinding (performance bias and detection bias) All outcomes	Low risk	Identical inhaler devices used
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Intention-to-treat analysis stated, but explicit description of its composition not available
Selective reporting (reporting bias)	Low risk	Data on OCS-treated exacerbations available on request from study sponsor

SAM40034

Methods	Parallel group, 27 centres in Scandinavia JADAD quality score = 4
Participants	Symptomatic mildly asthmatic adults % ELIGIBLE OF SCREENED POPULATION: Not reported % RUN-IN PARTICIPANTS RANDOMISED: Not reported RANDOMISED: 154 (FP/SAL: 75; FP: 79) WITHDRAWALS: FP/SAL: 4; FP: 5 AGE: mean (range) or mean: 37 GENDER (% male): 39 SEVERITY: Mild BASELINE % PRED. FEV1 (mean): 91 BASELINE DOSE OF ICS: 0 ASTHMA DURATION: Not reported ATOPY (%): Not reported

SAM40034 *(Continued)*

	ELIGIBILITY CRITERIA: 18 to 60 years; symptoms of asthma for at least 3 months; treatment with SABA only
	EXCLUSION CRITERIA: ICS treatment
Interventions	LABA+ICS versus HIGHER dose of ICS
	OUTCOMES TIMING: 4, 8 & 12 weeks
	RUN-IN: Not reported
	DOSE OF ICS DURING RUN-IN: NA
	INTERVENTION PERIOD: 12 weeks
	TEST GROUP: Combination fluticasone and salmeterol 100/50 mcg bid
	CONTROL GROUP: Fluticasone 250 mcg bid
	DEVICE: Diskus
	NUMBER OF DEVICES: 1
	COMPLIANCE: Not reported
	CO-TREATMENT: prn SABA
Outcomes	PULMONARY FUNCTION TEST: am PEF*; pm PEF; FEV1
	SYMPTOM SCORES: NA
	FUNCTIONAL STATUS: NA
	INFLAMMATORY MARKERS: NA
	ADVERSE EFFECTS: Reported
	WITHDRAWALS: Reported
	*Primary outcome
Notes	Full unpublished data set available from http://www.ctr.gsk.co.uk
	Source of funding: GSK
	Confirmation of methodology and data: Obtained for methods, not obtained for data
	User defined number: 1000

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	See Appendix 1
Allocation concealment (selection bias)	Low risk	See Appendix 1
Blinding (performance bias and detection bias) All outcomes	Low risk	Identical inhaler device

SAM40034 *(Continued)*

Incomplete outcome data (attrition bias) All outcomes	Unclear risk	"The primary population of patients analysed for safety and efficacy was the Intent-to-Treat (ITT) population that consisted of all subjects randomised to study treatment who received at least one dose of study treatment."
Selective reporting (reporting bias)	Unclear risk	Unclear whether data on OCS-treated exacerbations were collected. Request for data from study sponsors has not been successful.

SAM40036

Methods	Parallel group, multicentre study (74 centres in Europe) JADAD quality score = 4
Participants	Mildly asthmatic adults % ELIGIBLE OF SCREENED POPULATION: Not reported % RUN-IN PARTICIPANTS RANDOMISED: Not reported RANDOMISED: 577 (FP/SAL: 288; BUDL: 289) WITHDRAWALS: FP/SAL: 18; BUD: 16 AGE mean: 37 GENDER (% male): 43 SEVERITY: Mild BASELINE % PRED. FEV1: 95.4 BASELINE DOSE OF ICS: 0 ASTHMA DURATION: Not reported ATOPY (%): Not reported ELIGIBILITY CRITERIA: 12 to 80 years; diagnosis of asthma; treatment with inhaled short-acting beta-agonists alone EXCLUSION CRITERIA: Not reported
Interventions	LABA+ICS versus HIGHER dose ICS OUTCOMES TIMING: 12 weeks RUN-IN: 2 weeks DOSE OF ICS DURING RUN-IN: 0 INTERVENTION PERIOD: 12 weeks TEST GROUP: Combination fluticasone and salmeterol (100/50 mcg) once daily CONTROL GROUP: Budesonide 400 mcg once daily DEVICE: FP/SAL: Diskus; BUD: Turbuhaler NUMBER OF DEVICES: 1 (double-dummy design) COMPLIANCE: Not assessed

SAM40036 *(Continued)*

	CO-TREATMENT: prn SABA
Outcomes	PULMONARY FUNCTION TEST: am PEF*; FEV1 SYMPTOM SCORES: Daytime symptoms; night-time symptoms FUNCTIONAL STATUS: Rescue medication use INFLAMMATORY MARKERS: Not reported ADVERSE EFFECTS: Reported WITHDRAWALS: Reported *Primary outcome
Notes	Unpublished full data set available from http://www.ctr.gsk.co.uk Source of funding: GSK Confirmation of methodology and data: Obtained for methods; not obtained for data User defined number: 400

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	See Appendix 1
Allocation concealment (selection bias)	Low risk	See Appendix 1
Blinding (performance bias and detection bias) All outcomes	Low risk	Double dummy design with identical inhaler devices
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	"The Intent-to-Treat (ITT) population representing all subjects randomised to treatment who had taken at least one dose of study medication was also used for safety analyses."
Selective reporting (reporting bias)	Low risk	OCS-treated exacerbations available on request from study sponsor.

SAS30015

Methods	Parallel group, multicentre study (37 centres in UK)
Participants	Poorly controlled asthmatic adults at step 1 of BTS guidelines % ELIGIBLE OF SCREENED POPULATION: Not reported % RUN-IN PARTICIPANTS RANDOMISED: Not reported RANDOMISED: 156 (FP/SAL: 78; BDP: 78) WITHDRAWALS: FP/SAL: 9; BDP: 17 AGE mean (SD): 35 (15)

SAS30015 *(Continued)*

	GENDER (% male): 54 SEVERITY: Mild to moderate BASELINE % PRED. FEV1 (mean): Not reported BASELINE DOSE OF ICS: 0 ASTHMA DURATION: Not reported ATOPY (%): Not reported ELIGIBILITY CRITERIA: Step 1 of BTS asthma guidelines; am PEF 50% to 85% predicted over last 7 days of run-in; rescue medication use >/= 2 occasions on 3 or more days of last 7 of run-in period/symptom score >/= 1 on 3 of last 7 days of run-in EXCLUSION CRITERIA: Not reported
Interventions	LABA + ICS versus EQUIVALENT dose of BDP OUTCOMES: 12 weeks RUN-IN: 2 weeks DOSE OF ICS DURING RUN-IN: 0 INTERVENTION PERIOD: 12 weeks TEST GROUP: Combination fluticasone and salmeterol 100/50 mcg bid CONTROL GROUP: Beclomethasone 200 mcg bid DEVICE: FP/SAL: HFA-MDI; BDP: CFC-MDI NUMBER OF DEVICES: 1 COMPLIANCE: Not assessed CO-TREATMENT: prn SABA
Outcomes	PULMONARY FUNCTION TEST: am PEF*; pm PEF SYMPTOM SCORES: Combined symptoms FUNCTIONAL STATUS: Symptom-free days; % SABA-free nights; exacerbations; loss of control INFLAMMATORY MARKERS: Not reported ADVERSE EFFECTS: Reported by treatment group WITHDRAWALS: Reported by treatment group *Primary outcome
Notes	Full unpublished data set available from http://www.ctr.gsk.co.uk Source of funding: GSK Confirmation of methodology and data: Obtained User defined number: 400

Risk of bias

Bias	Authors' judgement	Support for judgement

SAS30015 *(Continued)*

Random sequence generation (selection bias)	Low risk	See Appendix 1
Allocation concealment (selection bias)	Low risk	See Appendix 1
Blinding (performance bias and detection bias) All outcomes	Low risk	Identical inhaler devices used
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Intention-to-treat analysis stated, but explicit description of its composition not available
Selective reporting (reporting bias)	Low risk	Data on OCS-treated exacerbations available on request from study sponsor

SAS30021

Methods	Parallel group, multicentre study
Participants	Steroid-naive asthmatic children % ELIGIBLE OF SCREENED POPULATION: Not reported % RUN-IN PARTICIPANTS RANDOMISED: Not reported RANDOMISED: 608 (FP/SAL 304; FP: 304) WITHDRAWAL: FP/SAL: 56; FP: 63 AGE mean: 7.8 years GENDER (male %): 61% ASTHMA SEVERITY: Mild-moderate BASELINE % PRED. FEV1: Not reported ASTHMA DURATION: Not reported ATOPY(%): Not reported ELIGIBILITY CRITERIA: Non-ICS controller medication for 6 months prior to entry; 50% to 85% predicted am PEF; 50% to 90% predicted PEF at screening visit >/= 15% response to beta-agonist EXCLUSION CRITERIA: Not reported CRITERIA FOR RANDOMISATION DURING RUN-IN: Symptomatic in week before study entry (score >/= 2 or used SABA on >/= 4 days of preceding week)
Interventions	LABA + ICS versus SAME dose ICS OUTCOMES: reported at 3 months RUN-IN PERIOD: Unclear DOSE OF ICS DURING RUN-IN: 0 DOSE OPTIMISATION PERIOD: None reported

SAS30021 *(Continued)*

	INTERVENTION PERIOD: 3 months TEST GROUP: Combination salmeterol 50/fluticasone 100 mcg once daily CONTROL GROUP: Fluticasone 100 mcg once daily DEVICE: Diskus NUMBER OF DEVICES: 1 COMPLIANCE: Not reported CO-TREATMENT: prn SABA
Outcomes	PULMONARY FUNCTION TEST: am PEF predicted; pm PEF predicted* SYMPTOM SCORES: % Symptom-free days FUNCTIONAL STATUS: Use of reliever medication; exacerbations (undefined) INFLAMMATORY MARKERS: Not reported ADVERSE EFFECTS: Reported WITHDRAWAL: Reported *Primary outcome
Notes	Data downloaded from GSK trials web site (http://www.ctr.gsk.co.uk) Source of funding: GSK Confirmation of methodology and data: Obtained User defined number: 400

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	See Appendix 1
Allocation concealment (selection bias)	Low risk	See Appendix 1
Blinding (performance bias and detection bias) All outcomes	Low risk	Identical inhaler devices
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	"An Intent-to-Treat Population was defined as all subjects who were randomized to treatment and received at least one dose of study drug. This population was used for all analyses of data from this trial (demographic, efficacy, and safety)."
Selective reporting (reporting bias)	Low risk	Data on OCS-treated exacerbations available on request from study sponsor

SAS40068

Methods	Parallel group, multicentre study (58 centres in Canada)
Participants	Asthmatic adults not adequately controlled on SABA alone % ELIGIBLE OF SCREENED POPULATION: Not reported % RUN-IN PARTICIPANTS RANDOMISED: Not reported RANDOMISED: 532 (FP/SAL: 262; FP: 270) WITHDRAWALS: FP/SAL: 53; FP: 46 AGE mean: 34.6 GENDER (% male): 36 SEVERITY: Mild to moderate BASELINE % PRED. FEV1(mean): Not reported BASELINE DOSE OF ICS: 0 ASTHMA DURATION: Not reported ATOPY (%): Not reported ELIGIBILITY CRITERIA: > 12 years; FEV1 > 80% over last 7 days of run-in; symptom score >/= 2 on 3 days of run-in; SABA use on more than 4 days of last 7 days of run-in EXCLUSION CRITERIA: ICS, anti-leukotriene agent, LABA in 1 month prior to study entry; smoking history of > 10 pack years; emergency room treatment within 6 weeks of study entry & hospitalization within 12 weeks
Interventions	ICS and LABA versus SAME DOSE ICS OUTCOMES: 24 weeks RUN-IN: Reported but duration not described DOSE OF ICS DURING RUN-IN: 0 INTERVENTION PERIOD: 24 weeks TEST GROUP: Combined fluticasone and salmeterol 100/50 mcg bid CONTROL GROUP: Fluticasone 100 mcg bid DEVICE: Diskus NUMBER OF DEVICES: 1 COMPLIANCE: Not reported CO-TREATMENT: prn SABA
Outcomes	PULMONARY FUNCTION TEST: am PEF*; pm PEF; FEV1 SYMPTOM SCORES: % symptom-free days; % rescue-free days FUNCTIONAL STATUS: Exacerbation rate INFLAMMATORY MARKERS: Not reported ADVERSE EFFECTS: Reported by treatment group WITHDRAWALS: Reported by treatment group

SAS40068 *(Continued)*

	*Primary outcome
Notes	Unpublished data set available from http://www.ctr.gsk.co.uk Source of funding GSK Confirmation of methodology and data: Obtained User defined number: 400

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	See Appendix 1
Allocation concealment (selection bias)	Low risk	See Appendix 1
Blinding (performance bias and detection bias) All outcomes	Low risk	Identical inhaler devices used
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Intention-to-treat analysis stated, but explicit description of its composition not available
Selective reporting (reporting bias)	Low risk	Data on OCS-treated exacerbations available on request from study sponsor

SLGF75

Methods	Parallel group, 7 centres in Italy
Participants	% ELIGIBLE OF SCREENED POPULATION: Not reported % RUN-IN PARTICIPANTS RANDOMISED: Not clear RANDOMISED: 31 (FP+SAL: 14; FP: 17) WITHDRAWALS: 4 (FP+SAL: 2; fp: 2) AGE mean (range) or mean (SD): 42 SEVERITY: Mild to moderate BASELINE % PRED. FEV1: Not reported BASELINE DOSE OF ICS: 0 ASTHMA DURATION: Not reported ATOPY (%): Not reported ELIGIBILITY CRITERIA: 16 to 65 years; asthma > 6 months duration; FEV1 > 60% predicted EXCLUSION CRITERIA: ICS within 3 months; upper RTI within 1 month ELIGIBILITY CRITERIA DURING RUN-IN: Not reported

SLGF75 *(Continued)*

Interventions	LABA + ICS versus SAME DOSE ICS OUTCOMES: 12 weeks RUN-IN PERIOD: 2 to 4 weeks DOSE OPTIMISATION PERIOD: NA TEST GROUP: Salmeterol 50 mcg bid plus fluticasone 100 mcg bid CONTROL GROUP: Fluticasone 100 mcg bid NUMBER OF DEVICES: 2 (DPI) CO-TREATMENT: SABA
Outcomes	PULMONARY FUNCTION TEST: NA SYMPTOM SCORES: NA FUNCTIONAL STATUS: Admission to hospital INFLAMMATORY MARKERS: Eosinophil count ADVERSE EFFECTS: Stated WITHDRAWALS: Stated
Notes	Unpublished data set available from http://www.ctr.gsk.co.uk Source of funding: GSK Confirmation of methodology and data: Not obtained User defined number: 400

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	See Appendix 1
Allocation concealment (selection bias)	Low risk	See Appendix 1
Blinding (performance bias and detection bias) All outcomes	Low risk	Identical inhaler devices used
Incomplete outcome data (attrition bias) All outcomes	High risk	Last observation carried forward: "Safety population: subjects randomised and with at least one dose of administered study drug. ITT population: subjects randomised and with at least one dose of administered study drug with eosinophils >5% were used for primary efficacy analysis. PP population: all subjects of ITT without any major protocol violation were used for secondary efficacy analysis."
Selective reporting (reporting bias)	Unclear risk	No information on primary outcome available

Sorkness 2007

Methods	Parallel group, multicentre study. 3 treatment groups (FP/SAL; FP and montelukast) JADAD quality score = 4
Participants	Mildly asthmatic children % ELIGIBLE OF SCREENED POPULATION: Not reported % RUN-IN PARTICIPANTS RANDOMISED 44 RANDOMISED: 190 (FP/SAL: 94; FP: 96. Montelukast not considered by this review: 95) WITHDRAWALS: FP/SAL: 13; FP: 10 AGE mean: 10 GENDER (% male): 62 SEVERITY: Mild BASELINE % PRED. FEV1: 97 BASELINE DOSE OF ICS: Not consistent (55% on ICS at baseline) ASTHMA DURATION: Not reported ATOPY (%): 75 ELIGIBILITY CRITERIA: Physician-diagnosed asthma; 6 to 14 years; ability to perform reproducible spirometry; post-dose FEV1 >/= 80% predicted normal at screening & >/= 70% predicted normal at randomisation; PC20 </= 12.5 mg/mL; mild-moderate persistent asthma (defined by symptoms or SABA use) or peak flows < 80% calculated from mean of morning and evening peak flows obtained during last week of run-in, on average >/= 3 times per week EXCLUSION CRITERIA: Other lung diseases; respiratory tract infection/asthma; exacerbation/systemic corticosteroid use within 4 weeks; 2 or more asthma hospitalisations in past year; history of life-threatening asthma exacerbation; >/= 4 courses of systemic corticosteroids in past year; cigarette smoking within the past year-pregnancy/lactation; adverse reactions to study medication; use of controller medications for at least 2 weeks before randomisation; inability to use study drug delivery systems/or adherence </= 75% of doses during the run-in
Interventions	LABA+ICS versus versus higher dose ICS OUTCOMES TIMING: 48 weeks RUN-IN: 4 weeks DOSE OF ICS DURING RUN-IN: 0 INTERVENTION PERIOD: 48 weeks TEST GROUP: Combination fluticasone/salmeterol 100/50 mcg qd + salmeterol qd CONTROL GROUP: Fluticasone 100 mcg bid DEVICE: Diskus NUMBER OF DEVICES: 2 COMPLIANCE: 95% adherence (diary card entry) CO-TREATMENT: prn SABA
Outcomes	PULMONARY FUNCTION TEST: am PEF; pm PEF; FEV1

Sorkness 2007 *(Continued)*

	SYMPTOM SCORES: Not stated FUNCTIONAL STATUS: Asthma control days (defined as: day without SABA rescue use; use of oral corticosteroids for asthma; use of non-study asthma medications; daytime symptoms; night-time awakenings; unscheduled health care visits, emergency department visits, or hospitalisations for asthma; and school absenteeism for asthma)*; episode-free days INFLAMMATORY MARKERS: Exhaled nitric oxide ADVERSE EFFECTS: Growth WITHDRAWALS: Stated *Primary outcome
Notes	Full text publication Source of funding: NHLBI Confirmation of methodology and data: Obtained for data User defined number: 800

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Stratified on lung function (method of randomisation/sequence generation not described)
Allocation concealment (selection bias)	Unclear risk	Information not available
Blinding (performance bias and detection bias) All outcomes	Low risk	Double-dummy design
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	"All analyses were performed under the intent-to-treat paradigm."
Selective reporting (reporting bias)	Low risk	Study presented adjusted estimates; n/N data for OCS-treated exacerbations available on request from investigators

Stelmach 2008

Methods	DESIGN: Parallel group; single centre study (Poland)
Participants	% ELIGIBLE OF SCREENED POPULATION: 67 % RUN-IN PARTICIPANTS RANDOMISED: NA RANDOMISED: 40 WITHDRAWALS: BUD/F: 2; BUD/MON: 3 AGE mean (range) or mean (SD): 12 years (6 to 18) SEVERITY: Not stated

Stelmach 2008 *(Continued)*

	BASELINE % PRED. FEV1: 91 BASELINE DOSE OF ICS: 0 ASTHMA DURATION: Not stated ATOPY (%): Not stated ELIGIBILITY CRITERIA: Age 6 to 18 years; diagnosis of bronchial asthma for at least 6 months; resting FEV1 of greater than 70%; a documented decrease in FEV1 of at least 20% post-exercise challenge test. EXCLUSION CRITERIA: Active upper respiratory tract infection 3 weeks before study entry; sinus disease requiring antibiotic treatment within 1 month; intubation, or asthma hospitalisation in last 3 months; other clinically significant diseases; participants taking beta-blockers and oral corticosteroids within 1 month before study; participants receiving immunotherapy ELIGIBILITY CRITERIA DURING RUN-IN: Not applicable
Interventions	LABA + ICS versus SAME dose ICS OUTCOMES: 8 weeks RUN-IN PERIOD: 4 weeks (LABAs, LTRAs and ICS stopped during run-in) DOSE OPTIMISATION PERIOD: NA INTERVENTION PERIOD: 8 weeks TEST GROUP: Budesonide 100 mcg bid/formoterol 9 mcg bid CONTROL GROUP: Budesonide 100 mcg bid NUMBER OF INHALER DEVICES: 2 CO-TREATMENT: prn SABA
Outcomes	PULMONARY FUNCTION TEST: AUC; fall in FEV1 post-exercise SYMPTOM SCORES: Not assessed FUNCTIONAL STATUS: Not assessed INFLAMMATORY MARKERS: Not assessed ADVERSE EFFECTS: Not reported WITHDRAWALS: Stated
Notes	Full text article Funding: Non-commercial source Confirmation of methodology and data: Not obtained User defined number: 200

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Described as randomised; other information not available

Stelmach 2008 *(Continued)*

Allocation concealment (selection bias)	Low risk	Undertaken by third party (hospital pharmacy)
Blinding (performance bias and detection bias) All outcomes	Low risk	Matching placebo
Incomplete outcome data (attrition bias) All outcomes	High risk	Completers analysed for outcomes
Selective reporting (reporting bias)	Low risk	Participants who experienced OCS-treated exacerbations were described in the study report, but distribution among treatment groups was not given. Correspondence has not been successful in retrieving these data.

Strand 2004

Methods	Parallel group multicentre study (45 centres in Denmark)
Participants	Asthmatic adults poorly controlled on SABA alone % ELIGIBLE OF SCREENED POPULATION: 68 RUN-IN PARTICIPANTS RANDOMISED: Not reported RANDOMISED: 150 (FP/SAL: 78; FP: 72) WITHDRAWALS: FP/SAL: 11; FP: 13 AGE mean (SD): 39 (15) GENDER (% male): 43 SEVERITY: Mild to moderate BASELINE % PRED. FEV1 (mean): Not reported BASELINE DOSE OF ICS: 0 ASTHMA DURATION: 12 years ATOPY (%): Not reported ELIGIBILITY CRITERIA: > 18 years; medical history of ATS defined asthma for at least 3 months; use of SABA only once per week for 2 months prior to visit 1; diary data during run-in for 11 days & 11 nights; PEF diurnal variation >/= 20% on > 2 days OR FEV1 reversibility > 15% within 3 years, PC20 </= 4 mg/mL, diurnal variation in PEF >/= 20%; SABA relief medication >/=once per week. Day or night symptom score >/= 1 once/week during run-in EXCLUSION CRITERIA: Use of ICS within 2 months prior to visit 1; use of OCS within1 month of visit 1; upper/lower RTI or middle ear infection within 1 month of visit; inadequate inhaler technique; lung diseases other than asthma; serious comorbid disease
Interventions	LABA + ICS versus SAME DOSE ICS OUTCOMES: 24 weeks RUN-IN: 2 weeks DOSE OF ICS DURING RUN-IN: 0

Strand 2004 *(Continued)*

	INTERVENTION PERIOD: 24 weeks TEST GROUP: Combined fluticasone and salmeterol 100/50 mcg bid CONTROL GROUP: Fluticasone 100 mcg bid DEVICE: Diskus NUMBER OF DEVICES: 1 COMPLIANCE: Not assessed CO-TREATMENT: prn SABA
Outcomes	PULMONARY FUNCTION TEST: am PEF; pm PEF; diurnal variation in PEF SYMPTOM SCORES: Day symptoms; night symptoms FUNCTIONAL STATUS: Rescue medication use; % 24-hour days without symptoms*; episode-free 24 hours INFLAMMATORY MARKERS: Not reported ADVERSE EFFECTS: Reported by treatment group WITHDRAWALS: Reported by treatment group *Primary outcome
Notes	Full text article, with unpublished data set available from http://www.ctr.gsk.co.uk Source of funding: GSK Confirmation of methodology and data: Not obtained User defined number: 400

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	See Appendix 1
Allocation concealment (selection bias)	Low risk	See Appendix 1
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Identical inhaler devices used
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Intention-to-treat population defined as: "All efficacy parameters were analysed on an intent-to-treat basis and data from all patients with at least one dose of study drug were included in the analysis."
Selective reporting (reporting bias)	Low risk	Primary outcome data available in study publication

Weersink 1997

Methods	Parallel group, single centre study. 3 treatment groups of which 2 are considered for this review
Participants	Stable asthmatic adults % ELIGIBLE OF SCREENED POPULATION: Not reported % RUN-IN PARTICIPANTS RANDOMISED: Not reported RANDOMISED: 33 (SAL + FP: 16; FP: 17) WITHDRAWALS: SAL + FP: 2; FP: 1 AGE years mean: 27 GENDER (% males): 47 SEVERITY: Mild BASELINE % PRED. FEV1: 86 BASELINE DOSE OF ICS : All ICS discontinued if taken at least 1 month before study commenced ASTHMA DURATION: Not reported ATOPY (%): 100 ELIGIBILITY CRITERIA: Non-smoking, atopic asthmatic subjects 18 to 45 years; circadian variation in PEF >/= 15%; history of episodic dyspnea or wheezing consistent with clinical diagnosis of asthma and no concomitant diseases; BHR to methacholine bromide (PC20 < 9.6 mg/ml); elevated specific immunoglobulin E (IgE) against house dust mite (RAST > 2) or positive intracutaneous tests against house dust mite or 2 other common aeroallergens; no use of oral corticosteroids; no respiratory tract infection or acute asthma during the 2 months prior to the study; inhaled corticosteroids if used were stopped 4 weeks before onset of the study whereas nedocromil sodium and long-acting beta2-agonists were discontinued 2 weeks before. Short-acting beta 2 agonists were allowed for symptom relief during 4-week period before study. EXCLUSION CRITERIA: History of hospitalisation for asthma; change in medication for acute exacerbation in 2 months prior to study
Interventions	LABA + ICS vs SAME dose of ICS OUTCOMES: At days 1, 2 and at 6 weeks RUN-IN PERIOD: None DOSE OF ICS DURING RUN-IN: NA DOSE OPTIMISATION PERIOD: None INTERVENTION PERIOD: 6 weeks TEST GROUP: Fluticasone 250 mcg bid and salmeterol 50 mcg bid CONTROL GROUP: Fluticasone propionate 250 mcg bid DEVICE: Diskhaler NUMBER OF DEVICES: 2 COMPLIANCE: Not reported CO-TREATMENT: Not stated
Outcomes	PULMONARY FUNCTION TEST: FEV1 % predicted; circadian variation in PEF; PC20 methacholine

Weersink 1997 *(Continued)*

	SYMPTOM SCORES: Not given FUNCTIONAL STATUS: Not assessed INFLAMMATORY MARKERS: Not reported ADVERSE EFFECTS: Not reported WITHDRAWALS: Not reported Primary outcome: Not reported
Notes	Full-text publication Supported by Glaxo BV Netherlands Confirmation of methodology and data extraction: Not obtained User defined number: 1000 (mean ICS dose in LABA group in mcg/day of BDP-equivalent: 1000)

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	See Appendix 1
Allocation concealment (selection bias)	Low risk	See Appendix 1
Blinding (performance bias and detection bias) All outcomes	Low risk	Identical placebo device used
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Handling of missing data not described
Selective reporting (reporting bias)	Low risk	Primary outcome data available

AQLQ = Asthma quality of life questionnaire
ATS = American Thoracic Society
AUC = Area under the curve
BDP = Beclomethasone dipropionate
BHR = Bronchial hyperresonsiveness
bid = Twice a day
BTS = British Thoracic Society
BUD = Budesonide
CFC-MDI = Chlorofluorocarbon metered dose inhaler
CXR = Chest X-ray
ECP = Eosinophil cationic protein
EKG (or ECG): Electrocardiogram
FeNO: Fixed exhalation nitric oxide
FEV1 = Forced expiratory volume in one second
FP = Fluticasone
FVC = Forced vital capacity
GINA = Global Initiative for Asthma
GSK = GlaxoSmithKline
HDM = House dust mite

HFA-MDI = Hydrofluoroalkane metered dose inhaler
ICS = Inhaled corticosteroid
IgE = Immunoglobulin E
LABA = long-acting inhaled ß2-agonist
LTRA = Leukotriene receptor antagonist (anti-leukotriene)
MDI = Metered dose inhaler
NA = not applicable
OCS = Oral corticosteroids
OD = Once daily
OTC = Over the counter
PAF = Platelet-activating factor
PC20 = Provocative concentration of adenosine 5'-monophosphate producing a 20% decline in FEV_1
PEF = Peak expiratory flow
prn = As needed
qd = Once daily
RAST = Radioallergosorbent test
RTI = Respiratory tract infection
SABA = Short-acting ß2-agonist
SAL = Salmeterol
vs = Versus

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

Study	Reason for exclusion
Aalbers 2004	No group with inhaled corticosteroids alone
Adinoff 1998	No consistent use of inhaled corticosteroids in either the intervention or control groups - co-intervention with other non-steroidal anti-asthmatic drugs not stable during the intervention period
Akpinarli 1999	Patients on inhaled corticosteroids prior to study commencement
Ankerst 2003	Cross-over study of inadequate duration
Anonymous 1999	Not relevant comparison
Anonymous 2003a	Control intervention not ICS alone
Anonymous 2003b	Duplicate citation
Anonymous 2003c	Duplicate publication of SMART study of salmeterol in asthma
Arvidsson 1991	Control intervention not inhaled corticosteroids alone
ASSURE	Fixed versus adjustable maintenance dosing of combination LABA/ICS
Aubier 1999	Patients were not steroid-naive
Aziz 1998	Intervention duration < 30 days
Aziz 1999a	Intervention duration < 30 days
Aziz 1999b	Outcome measure did not reflect asthma control
Aziz 2000	Duration of intervention < 30 days
Bacci 2002	No consistent co-intervention with ICS

Study	Reason for exclusion
Baki 1998	No consistent intervention with ICS
Balachandran 2001	Review article
Balzano 2002	Review article
Baraniuk 1999	Patients on inhaled corticosteroids prior to study commencement
Bateman 1998	Combination versus concomitant delivery of LABA and ICS
Bateman 2000	Comparison between different delivery devices
Bateman 2001	Prior ICS exposure
Bateman 2003a	Patients on inhaled corticosteroids prior to study commencement
Bateman 2003b	Comparison between combination therapy and montelukast in addition to ICS
Baumgarten 2002	Not randomised
Beeh 2002	Not randomised
Behling 1999	Inadequate study duration
Bennett 2002	Review article
Bensch 2002	No concurrent ICS therapy
Berggren 2001	Intervention not regular but prn inhaled long-acting beta2-agonists
Bergmann 2004	Control group received a higher dose of ICS than was given in the intervention group
Berlinski 2001	Comparison of different spacers
Bernstein 2002	Correspondence
Bessmertny 2002	Intervention not LABAs
Bijl-Hofland 2001	No consistent co-treatment with ICS
Bjermer 2000	Control intervention not inhaled corticosteroids alone but montelukast
Bjermer 2003	LABA not compared to ICS alone
Bloom 2003	Comparison of LABA/ICS with higher dose of ICS
Boonsawat 2003	Outcome measures not asthma control
Booth 1993	No consistent co-intervention with ICS
Boskovska 2001	Not a RCT
Bouchard 2000	Not steroid-naive at baseline
Boulet 1998	No concurrent ICS therapy

Study	Reason for exclusion
Boulet 2003	Patients on inhaled corticosteroids prior to study commencement
Bouros 1999	Patients on inhaled corticosteroids prior to study commencement
Boyd 1995	Not steroid-naive at baseline
Brambilla 1994	Control intervention not ICS but rather slow-release oral beta2-agonist
Brambilla 2003	No regular LABA
Braunstein 2002	Review article
Brenner 1998	Intervention not regular inhaled long-acting beta2-agonists
Britton 1992	Control intervention not inhaled corticosteroids alone
Britton 1998	ICS/LABA combination compared with separate administration of the same drugs
Brogden 1991	Review article
Buchvald 2002	Control intervention was not maintenance inhaled corticosteroids alone (it was a leukotriene receptor antagonist)
Buchvald 2003	Control intervention was not maintenance inhaled corticosteroids alone (it was a leukotriene receptor antagonist)
Buhl 2003a	Patients on inhaled corticosteroids prior to study commencement
Buhl 2003b	Not a RCT
Busse 1999	Control intervention not inhaled corticosteroids alone
Busse 2003	Patients on inhaled corticosteroids prior to study commencement
Byrnes 2000	Control intervention not inhaled corticosteroids alone
Calhoun 2001	Control intervention is not ICS (but rather anti-leukotrienes)
Calverley 2002	Study in COPD
Cazzola 2000	Study in COPD
Chalmers 1999	Study of methacholine induced asthma
Chan 2001	Intervention not regular inhaled long-acting beta2-agonist
Chapman 1999	Tx and intervention compared LABA and ICS but in combined vs concurrent devices
Cheer 2003	Review article
Cloosterman 2001	No consistent co-intervention with ICS Control intervention is not ICS alone (but rather regular short-acting beta2-agonist)
Condemi 1999	Patients on inhaled corticosteroids prior to study commencement

Study	Reason for exclusion
Condemi 2001	Control intervention not ICS alone (but rather another LABA)
Crompton 1999	Control intervention not ICS alone but oral bambuterol
Currie 2003a	Duration of intervention < 30 days
Currie 2003b	Co-intervention with non-permitted treatment
Currie 2003c	Duration < 1 month
D'Alonzo 1994	No consistent co-intervention with ICS - approximately 1/4 of participants were taking regular inhaled corticosteroids at baseline. Control intervention was a short-acting beta2-agonist.
D'Urzo 2001	Patients on inhaled corticosteroids prior to study commencement
Dahl 1989	Intervention not inhaled LABA
Dahl 1991	No consistent co-treatment with ICS
Dal Negro 2001a	Comparison of LABA with ICS/LABA
Dal Negro 2001b	Comparison of combination LABA and ICS with LABA and ICS administered via 2 separate inhalers
Davis 2001	Not a RCT
Dekhuijzen 2002	Review article
Del Rio-Navarro 2001	Outcome measures do not reflect asthma control (but rather serum potassium, CPK-MB, and ECG)
Del-Rio-Navarro 2001	Outcome measures do not reflect asthma control (but rather saliva flow and IgA)
Dempsey 2000	Assessment of antileukotriene agent in asthma
Dente 2001	Not a RCT
Dicpinigaitis 2002	Intervention not regular inhaled long-acting beta2-agonist
Didier 1997	Control intervention is not ICS: this is a randomised, open, parallel-group, multicentre study comparing salmeterol with an oral bronchodilator, terbutaline
Djordjevic 1999	Not randomised
Dorinsky 2001	Wrong comparison
Dorinsky 2002	Not steroid-naive at baseline
Durham 1999	Review article
Ek 2000	Study in healthy volunteers
Eliraz 2001	Both the treatment and control group compared ICS with LABA with different inhaler devices
Everden 2002	Different LABAs compared (formoterol versus salmeterol)
Faurschou 1994	Duration < 30 days

Study	Reason for exclusion
Faurschou 1996	Control intervention not ICS alone (but regular SABA)
Fish 2001	Control intervention is not ICS (but rather anti-leukotrienes)
Fitzgerald 1999	Patients on inhaled corticosteroids prior to study commencement
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	Patients on inhaled corticosteroids prior to study commencement
Fuglsang 1995	Duration < 30 days
Garcia-Marcos 2002	Review article
Gardiner 1994	Patients on inhaled corticosteroids prior to study commencement
Gessner 2003	Not randomised
Giannini 1998a	Duration < 30 days
Giannini 1998b	Duration < 30 days
Giannini 1999	Duration < 30 days
Giannini 2000	Duration < 30 days
Giannini 2001	Duration < 30 days
Giannini 2002	Duration < 30 days
Gizycki 2000	Duration < 30 days
Gold 2001	Control intervention not inhaled corticosteroids alone
Green 2003	Not steroid-naive at baseline
Greening 1994	Patients on inhaled corticosteroids prior to study commencement
Grootendorst 2001	Wrong comparison
Gustafsson 1994	Tx and intervention compared ICS + LABA combination therapy using 2 different devices
Hacki 2001	Review article
Hasani 2003	No consistent intervention with inhaled corticosteroids in all subjects
Heuck 2000	Patients on inhaled corticosteroids prior to study commencement
Heyneman 2002	Systematic review
Hultquist 2000	Study of LABA & ICS versus increased dose ICS

Study	Reason for exclusion
Ind 2002	Formoterol versus SABA as relief medication
Ind 2003	Patients on inhaled corticosteroids prior to study commencement
Isabelle 2001	Comparison of 2 different devices to deliver ICS & LABA
Jarvis 1999	Review article
Jeffery 2002	Control intervention not inhaled corticosteroids alone
Jenkins 1995	Control intervention is not ICS (but LABA delivered with new propellant HFA134a)
Jenkins 2000	Patients on inhaled corticosteroids prior to study commencement
Jenkins 2002	Comparison of combination ICS & LABA versus separate administration
Johansson 2001	Patients on inhaled corticosteroids prior to study commencement
Johnson 1998	Not steroid-naive at baseline
Jones 1994	No consistent intervention with ICS (< 1/3 of participants were taking regular ICS at entry)
Juniper 1995	No consistent co-intervention with ICS (80% were taking regular ICS at entry). No subgroup analyses available.
Juniper 1999	Duplicate of Pauwels's study (NEJM 1997;337:1405-11)
Kalberg 1998	Patients on inhaled corticosteroids prior to study commencement
Kalra 1996	Duration < 30 days
Kardos 2001	Tx and intervention compared ICS + LABA in a fixed vs flexible schedule
Kavuru 2000	ICS permitted
Keith 2001	Not a RCT
Kelsen 1999	Patients on inhaled corticosteroids prior to study commencement
Kemp 1984	Wrong comparison
Kemp 1998	Not steroid-naive at baseline
Ketchell 2002	Duration of intervention < 30 days
Kidney 1995	No consistent intervention with inhaled corticosteroids in all subjects
Kips 2000	Patients on inhaled corticosteroids prior to study commencement
Kirby 2000	Subjects not asthmatics
Knobil 1998	Not steroid-naive at baseline
Knobil 2000	Assessment of LABA versus anti-leukotriene

Study	Reason for exclusion
Knorr 2001	Intervention is not LABA (but rather an anti-leukotriene agent: montelukast)
Kraft 2003	Not a RCT
LaForce 1994	Not a RCT
Lai 1995	Control intervention was not ICS alone but regular short-acting beta2-agonist instead of placebo Duration of intervention < 30 days: the treatment period was only 2 weeks long Co-intervention with non-permitted drugs: oral steroids
Lalloo 2003	Patients on inhaled corticosteroids prior to study commencement
Lange 2001	Inadequate duration
Langton-Hewer 1995	Patients on inhaled corticosteroids prior to study commencement
Lazarus 2001	No consistent co-intervention with ICS - intervention is monotherapy with LABA
Leblanc 1996	Patients on inhaled corticosteroids prior to study commencement
Lemanske 2001	Complicated protocol. No data provided for comparison groups of interest.
Lenney 1995	Not a RCT
LHSRG 2000	Subjects not asthmatics (but rather have COPD)
Li 1999	Patients on inhaled corticosteroids prior to study commencement
Lindqvist 2001	No consistent co-treatment with ICS
Lipworth 1998	Duration < 30 days
Lipworth 1999	Duration < 30 days
Lipworth 2000a	Duration < 30 days
Lipworth 2000b	Duration < 30 days
Lockey 1999	No consistent co-intervention with inhaled corticosteroids
Lowhagen 2002	Intervention not regular inhaled long-acting beta2-agonists
Lundbäck 2006	Mixture of ICS and non-ICS users
Lötvall 2002	Comparison of different ICS/LABA combinations
Magadle 2001	Duration < 30 days
Malmqvist-Granlund 2000	Not a RCT
Malolepszy 2002	Control intervention not ICS (but oral theophylline)
Matz 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

Study	Reason for exclusion
McCarthy 2000	Control intervention not inhaled corticosteroids alone
McCarthy 2001	Not randomised
Mcivor 1998	No consistent co-treatment with a stable dose of ICS (tapering)
Meier 1997	Case control study
Meijer 1995	Patients on inhaled corticosteroids prior to study commencement
Michel 2000	Duration < 30 days
Midgren 1992	Control intervention not ICS alone
Mitchell 2000	Study of LABA+ICS versus double-dose ICS
Molimard 2001	Study recruited patients who were taking ICS
Murray 1998	Inadequate duration
Murray 1999	Patients on inhaled corticosteroids prior to study commencement
Nagel 2002	Duplicate
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	Patients on inhaled corticosteroids prior to study commencement
Nathan 2006	Participants recruited who were prior users of ICS
Nelson 1999	Duration < 30 days
Nelson 2000	Control intervention is not ICS alone (but rather ICS with an anti-leukotriene agent (montelukast))
Nelson 2001	Control intervention not ICS alone (but LTRA- zafirlukast)
Newnham 1995	No consistent co-treatment with ICS
Nielsen 1999	Participants pre-treated with steroids
Nightingale 2002	Comparison of different LABAs (formoterol versus salmeterol)
Norhaya 1999	Participants pre-treated with ICS
Nsouli 2001	Control intervention not inhaled corticosteroids alone
O'Brian 2001	Duration of intervention < 30 days
O'Byrne 2005	Comparison between combination ICS/LABA and higher dose ICS
O'Connor 2002	Retrospective design

Study	Reason for exclusion
Odeback 1998	Participants were pre-treated with ICS
Ortega-Cisneros 1998	Patients on inhaled corticosteroids prior to study commencement
Palmer 1992	Control intervention is not ICS alone: both treatment groups received long-acting beta2-agonists but in different doses
Palmqvist 2001	Both the treatment and control groups compared ICS and LABA with different drugs and inhaler devices
Paterson 1999	Comparison of anti-leukotriene agent with LABA
Pauwels 1997	Patients on inhaled corticosteroids prior to study commencement
Pauwels 1998a	DUPLICATE REPORT - this study is a review of the FACET study which is already included in this analysis (Pauwels 1997)
Pauwels 1998b	Intervention not LABA but another ICS
Pearlman 1992	No consistent co-intervention with ICS (< 1/2 the participants were taking regular inhaled corticosteroids at entry) Control intervention was not ICS but short-acting beta2-agonist
Pearlman 1994	No consistent co-treatment with ICS 26%
Pearlman 2002	Control intervention is not ICS alone (but anti-leukotriene - montelukast - as maintenance)
Pearlman 2004	Mixed population of ICS and non-ICS users
Perez 2000	Wrong comparison
Peters 2000	CONTROL intervention is not ICS alone (but oral steroids, SABA and anticholinergics - in hospital setting)
Pieters 1998	Participants pre-treated with ICS
Pinnas 1998	No consistent intervention with inhaled corticosteroids in all subjects
Pizzichini 1996	Duration < 4 weeks
Pljaskic-Kamenov 2000	Pre-treatment with steroids
Price 2002	Patients on inhaled corticosteroids prior to study commencement
Pujet 1995	Intervention is not LABA (but theophylline)
Rance 2002	Comparison of combined and concomitant inhaled ICS and LABA
Rickard 2001	Control intervention not inhaled corticosteroids alone
Rijssenbeek-Nouwens 2002	Intervention is not LABA (but anti-allergic casing)
Ringbaek 1996	Control intervention not ICS alone but oral SABA as maintenance

Study	Reason for exclusion
Ringdal 2002	Treatment and intervention groups compared the same medications either in combination or with different delivery devices
Ringdal 2003	Control intervention no inhaled corticosteroids alone
Rocca-Serra 2002	Intervention not regular long-acting beta2-agonist
Rosenhall 2002	Treatment and intervention groups compared the same medications either in combination or with different delivery devices
Rosenhall 2003	Treatment and intervention groups compared the same medications either in combination or with different delivery devices
Rosenthal 1999	No consistent co-intervention with ICS
Russell 1995	Participants pre-treated with ICS
Saari 2002	Inadequate duration
SAM40004	ICS treatment permitted prior to study entry
SAM40104	Prior treatment with ICS
SAS10006	Cross-over study
SAS30013	Prior treatment with ICS
Schreurs 1996	No consistent co-intervention with ICS - 90% used regular ICS at entry
Scicchitano 2004	Combination given as maintenance as well as relief inhaler
Sears 2003	Fixed versus adjustable dosing regimen
Serrier 2003	Treatment and intervention groups compared the same medications either in combination or with different delivery devices
Shapiro 2000	Participants pre-treated with ICS
Shapiro 2001	Intervention is not LABA
Sheth 2002	Control intervention not inhaled corticosteroids alone
Sienra-Monge 2001	Comparison of LABA & ICS delivered as combination or concomitant therapy
Simons 1997a	Patients on inhaled corticosteroids prior to study commencement
Simons 1997b	No consistent co-intervention with inhaled corticosteroids. Treatment groups compared ICS to long-acting beta2-agonist alone.
SNS	Comparison of salmeterol with salbutamol
Sovani 2008	Assessment of combination therapy with usual care
Staehr 1995	Control intervention not ICS (but SABA maintenance)

Study	Reason for exclusion
Stanford 2002	Assessment of combination therapy with an anti-leukotriene agent
Stelmach 2001	The treatment and intervention groups compared the same medications either in combination or with different delivery devices
Stelmach 2002a	No co-intervention with ICS
Stelmach 2002b	No co-intervention with ICS
Stelmach 2007	Prior ICS exposure
Stojkovic-Andjelkovi 2001	No comparison with ICS alone
Tal 2003	Participants pre-treated with ICS
Tan 1997	Outcomes measures did not reflect asthma control
Tattersfield 2001	Intervention is not daily LABA (but rather on-demand LABA)
Trautmann 2001	Study did not assess equivalent ICS dose in control arm; participants pre-treated with ICS
Turner 1998	No consistent co-intervention with ICS
Ullman 1990	Duration < 30 days
Van den Berg 2000	No consistent co-intervention with LABA - both groups received LABA but compared delivery devices
van der Molen 1997	Patients on inhaled corticosteroids prior to study commencement
van der Woude 2001	Inadequate duration
van Noord 1999	Patients on inhaled corticosteroids prior to study commencement
van Noord 2001	Different propellants used to deliver FP & FP/SAL in the treatment groups
van Schayck 2002	No concurrent ICS treatment
Verberne 1997	No consistent co-intervention with ICS - approximately 20% were taking regular ICS at entry
Verberne 1998	Patients on inhaled corticosteroids prior to study commencement
Vermetten 1999	Patients on inhaled corticosteroids prior to study commencement
Vestbo 2000	Patients are not asthmatics (but rather have COPD)
Vickers 2000	The intervention is not LABA but placebo No consistent co-intervention with ICS Ongoing study - protocol only published
Vilsvik 2001	Outcome measures did not reflect asthma control
Von Berg 1989	Duration < 30 days
Wallaert 1999	Control intervention not ICS alone (but another LABA)

Study	Reason for exclusion
Wallin 1990	Control intervention not ICS alone (but regular SABA)
Wallin 1998	No consistent co-treatment with ICS
Wallin 2003	Patients on inhaled corticosteroids prior to study commencement
Weinstein 1998	No consistent co-intervention with ICS - only 57% were on ICS
Wempe 1992	No consistent co-treatment with ICS
Wilcke 1998	Duration < 30 days
Wilding 1997	Cross-over study design
Wilson 2001	Control intervention is not ICS alone (but rather ICS with an anti-leukotriene agent - montelukast)
Wong 1992	Duration < 30 days
Woolcock 1996	Patients on inhaled corticosteroids prior to study commencement
Yates 1995	Duration < 30 days. No co-treatment with ICS
Yates 1996	Duration < 30 days
Youngchaiyud 1995	Intervention not LABA (but theophylline)
Yurdakul 2002	Control intervention not regular inhaled long-acting beta2-agonists alone
Zarkovic 1998	No consistent co-intervention with ICS Control intervention is placebo
Zetterstrom 2003	Participants pre-treated with ICS
Zimmerman 2004	Patients were not steroid-naive

COPD = chronic obstructive pulmonary disease
ECG = electrocardiogram
ICS = inhaled corticosteroid
LABA = long-acting inhaled ß2-agonist
RCT = randomised controlled trial
SABA = short-acting ß2-agonist
Tx = treatment
vs = versus

DATA AND ANALYSES

Comparison 1. Addition of ICS + LABA versus same dose of ICS alone in steroid-naive patients as first line treatment

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 # patients with exacerbations requiring systemic steroids	12	3400	Risk Ratio (M-H, Fixed, 95% CI)	1.04 [0.73, 1.47]
1.1 Baseline FEV1 >=80% predicted	5	967	Risk Ratio (M-H, Fixed, 95% CI)	1.02 [0.67, 1.56]
1.2 Baseline FEV1<80% predicted	4	1153	Risk Ratio (M-H, Fixed, 95% CI)	1.39 [0.56, 3.43]
1.3 Baseline FEV1 predicted unclear	3	1280	Risk Ratio (M-H, Fixed, 95% CI)	0.86 [0.38, 1.96]
2 # patients with exacerbations requiring hospitalisation	10	2806	Risk Ratio (M-H, Fixed, 95% CI)	0.38 [0.09, 1.65]
2.1 Baseline FEV1 >=80% predicted	2	325	Risk Ratio (M-H, Fixed, 95% CI)	0.21 [0.01, 4.27]
2.2 Baseline FEV1 <80% predicted	3	1009	Risk Ratio (M-H, Fixed, 95% CI)	0.34 [0.01, 8.31]
2.3 Baseline FEV1 not reported	5	1472	Risk Ratio (M-H, Fixed, 95% CI)	0.58 [0.08, 4.38]
3 Change in FEV1 at endpoint	11	3014	L (Random, 95% CI)	0.12 [0.07, 0.17]
3.1 Baseline FEV1 <80% predicted	7	2172	L (Random, 95% CI)	0.14 [0.08, 0.20]
3.2 Baseline FEV1 >=80% predicted	3	370	L (Random, 95% CI)	0.12 [0.00, 0.25]
3.3 Baseline FEV1 not reported	1	472	L (Random, 95% CI)	0.06 [0.01, 0.11]
4 Change in FEV1 predicted at endpoint	2	489	Mean Difference (IV, Fixed, 95% CI)	1.75 [0.20, 3.29]
4.1 Baseline FEV1 <80% predicted	0	0	Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
4.2 Baseline FEV1 >/= 80% predicted	2	489	Mean Difference (IV, Fixed, 95% CI)	1.75 [0.20, 3.29]
4.3 Baseline FEV1 not reported	0	0	Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
5 FEV1 predicted at endpoint	2	64	Mean Difference (IV, Fixed, 95% CI)	4.39 [-1.27, 10.05]
5.1 Baseline FEV1 <80% predicted	2	64	Mean Difference (IV, Fixed, 95% CI)	4.39 [-1.27, 10.05]
5.2 Baseline FEV1 >/= 80% predicted	0	0	Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
5.3 Baseline FEV1 not reported	0	0	Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
6 Change in morning PEF (L/min) at endpoint	11	2894	Mean Difference (IV, Fixed, 95% CI)	19.50 [16.19, 22.82]
6.1 Baseline FEV1 < 80% predicted	7	1465	Mean Difference (IV, Fixed, 95% CI)	23.03 [17.95, 28.10]
6.2 Baseline FEV1 >=80% predicted	2	765	Mean Difference (IV, Fixed, 95% CI)	15.32 [9.63, 21.00]
6.3 Baseline FEV1 not reported	2	664	Mean Difference (IV, Fixed, 95% CI)	19.15 [12.27, 26.03]
7 Change in evening PEF (L/min) at endpoint	8	2725	Mean Difference (IV, Fixed, 95% CI)	14.16 [11.48, 16.84]
7.1 Baseline FEV1 <80% predicted	4	1149	Mean Difference (IV, Fixed, 95% CI)	20.88 [15.68, 26.09]
7.2 Baseline FEV1 >=80% predicted	1	306	Mean Difference (IV, Fixed, 95% CI)	19.8 [11.34, 28.26]
7.3 Baseline FEV1 not reported	3	1270	Mean Difference (IV, Fixed, 95% CI)	10.45 [7.08, 13.82]
8 Morning PEF at endpoint	3		L/min (Fixed, 95% CI)	19.34 [-10.75, 49.42]
8.1 Baseline FEV1 <80% predicted	2		L/min (Fixed, 95% CI)	20.72 [-21.47, 62.91]
8.2 Baseline FEV1 not reported	1		L/min (Fixed, 95% CI)	17.9 [-23.00, 60.80]
9 Evening PEF (L/min) at endpoint	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
9.1 Baseline FEV1 <80% predicted	0		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
9.2 Baseline FEV1 not reported	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
10 Change in am PEF predicted (%)	3	1207	Mean Difference (IV, Fixed, 95% CI)	3.41 [2.24, 4.58]
10.1 Baseline FEV1 <80% predicted	2	599	Mean Difference (IV, Fixed, 95% CI)	4.90 [3.37, 6.43]
10.2 Baseline FEV1 >=80% predicted	0	0	Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
10.3 Baseline FEV1 not reported	1	608	Mean Difference (IV, Fixed, 95% CI)	1.30 [-0.52, 3.12]
11 Change in pm PEF predicted (%)	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
11.1 Baseline FEV1 <80% predicted	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
11.2 Baseline FEV1 >=80% predicted	0		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
11.3 Baseline FEV1 not reported	0		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
12 Change in PEF variability at endpoint	4	292	Std. Mean Difference (IV, Random, 95% CI)	-0.04 [-0.50, 0.41]
12.1 Baseline FEV1 <80% predicted	3	270	Std. Mean Difference (IV, Random, 95% CI)	-0.18 [-0.42, 0.06]
12.2 Baseline FEV1 >=80% predicted	1	22	Std. Mean Difference (IV, Random, 95% CI)	1.02 [0.12, 1.92]
13 Diurnal PEF variability at endpoint	1		Std. Mean Difference (IV, Random, 95% CI)	Totals not selected
13.1 Baseline FEV1 <80% predicted	0		Std. Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]
13.2 Baseline FEV1 >=80% predicted	0		Std. Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]
13.3 Baseline FEV1 not reported	1		Std. Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]
14 % days with symptoms at endpoint	2	593	Mean Difference (IV, Fixed, 95% CI)	-0.18 [-4.47, 4.10]
14.1 Baseline FEV1 <80% predicted	0	0	Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
14.2 Baseline FEV1 >=80% predicted	1	459	Mean Difference (IV, Fixed, 95% CI)	-1.60 [-6.20, 3.00]
14.3 Baseline FEV1 not reported	1	134	Mean Difference (IV, Fixed, 95% CI)	9.20 [-2.65, 21.05]
15 Change in % symptom-free days at endpoint	4	795	Mean Difference (IV, Fixed, 95% CI)	8.72 [3.75, 13.68]
15.1 Baseline FEV1<80% predicted	3	284	Mean Difference (IV, Fixed, 95% CI)	10.74 [1.86, 19.62]
15.2 Baseline FEV1 >=80% predicted	0	0	Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
15.3 Baseline FEV1 not reported	1	511	Mean Difference (IV, Fixed, 95% CI)	7.80 [1.82, 13.78]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
16 Day symptom score at endpoint	1		Std. Mean Difference (IV, Fixed, 95% CI)	Totals not selected
16.1 Baseline FEV1 <80% predicted	0		Std. Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
16.2 Baseline FEV1 >=80% predicted	0		Std. Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
16.3 Baseline FEV1 not reported	1		Std. Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
17 Change in symptom score at endpoint	7	1464	Std. Mean Difference (IV, Random, 95% CI)	-0.26 [-0.37, -0.14]
17.1 Baseline FEV1 <80% predicted	7	1464	Std. Mean Difference (IV, Random, 95% CI)	-0.26 [-0.37, -0.14]
17.2 Baseline FEV1 >=80% predicted	0	0	Std. Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]
17.3 Baseline FEV1 not reported	0	0	Std. Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]
18 % nights with awakenings at endpoint	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
18.1 Baseline FEV1 <80% predicted	0		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
18.2 Baseline FEV1 >=80% predicted	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
19 Change in night-time symptoms at endpoint	2	584	Std. Mean Difference (IV, Fixed, 95% CI)	-0.16 [-0.32, 0.00]
19.1 Baseline FEV1 <80% predicted	1	359	Std. Mean Difference (IV, Fixed, 95% CI)	-0.10 [-0.31, 0.11]
19.2 Baseline FEV1 >=80% predicted	1	225	Std. Mean Difference (IV, Fixed, 95% CI)	-0.25 [-0.51, 0.01]
19.3 Baseline FEV1 not reported	0	0	Std. Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
20 Night symptom score at endpoint	1		Std. Mean Difference (IV, Fixed, 95% CI)	Totals not selected
20.1 Baseline FEV1 <80% predicted	0		Std. Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
20.2 Baseline FEV1 >=80% predicted	0		Std. Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
20.3 Baseline FEV1 not reported	1		Std. Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
21 Change in % nights with no awakenings at 12 weeks	2	369	Mean Difference (IV, Fixed, 95% CI)	3.53 [-2.98, 10.05]
21.1 Baseline FEV1 <80% predicted	2	369	Mean Difference (IV, Fixed, 95% CI)	3.53 [-2.98, 10.05]
21.2 Baseline FEV1 >=80% predicted	0	0	Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
22 % nights with symptoms at endpoint	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
22.1 Baseline FEV1 <80% predicted	0		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
22.2 Baseline FEV1 >=80% predicted	0		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
22.3 Baseline FEV1 not reported	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
23 Mean % rescue-free days at endpoint	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
23.1 Baseline FEV1 <80% predicted	0		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
23.2 Baseline FEV1 >=80% predicted	0		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
23.3 Baseline FEV1 not reported	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
24 Change in mean % rescue-free days at 12 weeks	2	703	Mean Difference (IV, Fixed, 95% CI)	9.29 [4.52, 14.05]
24.1 Baseline FEV1 <80% predicted	1	192	Mean Difference (IV, Fixed, 95% CI)	13.5 [2.06, 24.94]
24.2 Baseline FEV1 >=80% predicted	0	0	Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
24.3 Baseline FEV1 not reported	1	511	Mean Difference (IV, Fixed, 95% CI)	8.40 [3.15, 13.65]
25 % 24 hrs with symptoms at endpoint	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
25.1 Baseline FEV1 >=80% predicted	0		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
25.2 Baseline FEV1 <80% predicted	0		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
25.3 Baseline FEV1 not reported	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
26 % symptom-free days	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
26.1 Baseline FEV1 >=80% predicted	0		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
26.2 Baseline FEV1 <80% predicted	0		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
26.3 Baseline FEV1 not reported	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
27 Use of rescue fast-acting b2-agonists (puffs/24 hrs) at endpoint	1		Mean Difference (IV, Random, 95% CI)	Totals not selected
27.1 Baseline FEV1 <80% predicted	0		Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]
27.2 Baseline FEV1 >=80% predicted	0		Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]
27.3 Baseline FEV1 not reported	1		Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]
28 Change in awakenings requiring SABA/nt	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
28.1 Baseline FEV1 <80% predicted	0		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
28.2 Baseline FEV1 >=80% predicted	0		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
28.3 Baseline FEV1 not reported	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
29 Change in use of rescue fast-acting b2-agonists (puffs/24 hrs) at endpoint	8	2172	Mean Difference (IV, Random, 95% CI)	-0.41 [-0.73, -0.09]
29.1 Baseline FEV1 <80% predicted	6	1105	Mean Difference (IV, Random, 95% CI)	-0.67 [-0.94, -0.41]
29.2 Baseline FEV1 >=80% predicted	1	459	Mean Difference (IV, Random, 95% CI)	0.0 [-0.14, 0.14]
29.3 Baseline FEV1 not reported	1	608	Mean Difference (IV, Random, 95% CI)	-0.10 [-0.46, 0.26]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
30 Change in daytime rescue medication (puffs)	1		Mean Difference (IV, Random, 95% CI)	Totals not selected
30.1 Baseline FEV1 <80% predicted	1		Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]
30.2 Baseline FEV1 >=80% predicted	0		Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]
30.3 Baseline FEV1 not reported	0		Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]
31 Change in night-time rescue medication (puffs)	1		Mean Difference (IV, Random, 95% CI)	Totals not selected
31.1 Baseline FEV1 <80% predicted	1		Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]
31.2 Baseline FEV1 >=80% predicted	0		Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]
31.3 Baseline FEV1 not reported	0		Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]
32 Change in quality of life (AQLQ score) at 12 weeks	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
32.1 Baseline FEV1 <80% predicted	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
32.2 Baseline FEV1 >=80% predicted	0		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
33 Paediatric AQLQ scores	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
33.1 FEV1 not reported	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
34 Serious adverse events	15	3751	Risk Ratio (M-H, Fixed, 95% CI)	1.15 [0.64, 2.09]
34.1 Baseline FEV1 >=80% predicted	3	804	Risk Ratio (M-H, Fixed, 95% CI)	1.54 [0.53, 4.45]
34.2 Baseline FEV1 <80% predicted	7	1470	Risk Ratio (M-H, Fixed, 95% CI)	1.36 [0.47, 3.90]
34.3 Baseline FEV1 not reported	5	1477	Risk Ratio (M-H, Fixed, 95% CI)	0.76 [0.28, 2.10]
35 Total withdrawals	18	3658	Risk Ratio (M-H, Fixed, 95% CI)	0.95 [0.82, 1.11]
35.1 Baseline FEV1 >=80% predicted	5	860	Risk Ratio (M-H, Fixed, 95% CI)	0.84 [0.60, 1.17]

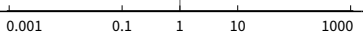
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
35.2 Baseline FEV1 <80% predicted	7	1268	Risk Ratio (M-H, Fixed, 95% CI)	1.12 [0.80, 1.56]
35.3 Baseline FEV1 not reported	6	1530	Risk Ratio (M-H, Fixed, 95% CI)	0.94 [0.76, 1.16]
36 # patients withdrawing due to poor asthma control or exacerbation	13	3350	Risk Ratio (M-H, Fixed, 95% CI)	0.94 [0.63, 1.41]
36.1 Baseline FEV1 <80% predicted	6	1244	Risk Ratio (M-H, Fixed, 95% CI)	0.92 [0.40, 2.10]
36.2 Baseline FEV1 >=80% predicted	4	817	Risk Ratio (M-H, Fixed, 95% CI)	1.41 [0.45, 4.42]
36.3 Baseline FEV1 not reported	3	1289	Risk Ratio (M-H, Fixed, 95% CI)	0.87 [0.52, 1.44]
37 # patient withdrawals due to adverse effects	13	3470	Risk Ratio (M-H, Fixed, 95% CI)	1.07 [0.67, 1.71]
37.1 Baseline FEV1<80% predicted	6	1244	Risk Ratio (M-H, Fixed, 95% CI)	2.14 [0.70, 6.55]
37.2 Baseline FEV1 >=80% predicted	3	787	Risk Ratio (M-H, Fixed, 95% CI)	1.39 [0.55, 3.51]
37.3 Baseline FEV1 not reported	4	1439	Risk Ratio (M-H, Fixed, 95% CI)	0.72 [0.37, 1.39]
38 # Patient with any adverse event	14	3286	Risk Ratio (M-H, Fixed, 95% CI)	1.02 [0.96, 1.09]
38.1 Baseline FEV1 <80% predicted	7	1470	Risk Ratio (M-H, Fixed, 95% CI)	1.03 [0.91, 1.17]
38.2 Baseline FEV1 >=80% predicted	3	370	Risk Ratio (M-H, Fixed, 95% CI)	0.86 [0.64, 1.14]
38.3 Baseline FEV1 not reported	4	1446	Risk Ratio (M-H, Fixed, 95% CI)	1.04 [0.98, 1.11]
39 # patients with headache	11	2863	Risk Ratio (M-H, Fixed, 95% CI)	1.03 [0.86, 1.23]
39.1 Baseline FEV1 <80% predicted	6	1245	Risk Ratio (M-H, Fixed, 95% CI)	0.97 [0.67, 1.41]
39.2 Baseline FEV1 >=80% predicted	2	328	Risk Ratio (M-H, Fixed, 95% CI)	0.55 [0.23, 1.35]
39.3 Baseline FEV1 not reported	3	1290	Risk Ratio (M-H, Fixed, 95% CI)	1.10 [0.89, 1.35]
40 # patients with oral thrush	6	1325	Risk Ratio (M-H, Fixed, 95% CI)	0.91 [0.39, 2.12]
40.1 Baseline FEV1<80% predicted	4	1153	Risk Ratio (M-H, Fixed, 95% CI)	0.89 [0.34, 2.36]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
40.2 Baseline FEV1 >=80% predicted	1	22	Risk Ratio (M-H, Fixed, 95% CI)	0.33 [0.02, 7.39]
40.3 Baseline FEV1 not reported	1	150	Risk Ratio (M-H, Fixed, 95% CI)	1.85 [0.17, 19.93]
41 # patients with hoarseness	3	934	Risk Ratio (M-H, Fixed, 95% CI)	1.97 [0.49, 7.88]
41.1 Baseline FEV1 <80%	2	784	Risk Ratio (M-H, Fixed, 95% CI)	1.41 [0.28, 7.12]
41.2 Baseline FEV1 not reported	1	150	Risk Ratio (M-H, Fixed, 95% CI)	4.62 [0.23, 94.64]
42 # patients with tremor	5	761	Risk Ratio (M-H, Fixed, 95% CI)	4.71 [1.38, 16.08]
42.1 Baseline FEV1 <80% predicted	4	739	Risk Ratio (M-H, Fixed, 95% CI)	4.71 [1.38, 16.08]
42.2 Baseline FEV1 >=80% predicted	1	22	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
43 # patients with tachycardia or palpitations	3	114	Risk Ratio (M-H, Fixed, 95% CI)	2.77 [0.12, 64.76]
43.1 Baseline FEV1 <80% predicted	2	92	Risk Ratio (M-H, Fixed, 95% CI)	2.77 [0.12, 64.76]
43.2 Baseline FEV1 >=80% predicted	1	22	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
44 # patients with adverse cardiovascular events	2	92	Risk Ratio (M-H, Fixed, 95% CI)	2.77 [0.12, 64.76]
44.1 Baseline FEV1 <80%	2	92	Risk Ratio (M-H, Fixed, 95% CI)	2.77 [0.12, 64.76]
45 Deaths	1	225	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
45.1 Baseline FEV1 <80% predicted	1	225	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
45.2 Baseline FEV1 >=80% predicted	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
46 Change in PC20 (methacholine) at 8 weeks	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
46.1 Baseline FEV1 <80% predicted	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
46.2 Baseline FEV1 >=80% predicted	0		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
47 PC20 (methacholine) at 8 weeks	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
47.1 Baseline FEV1 <80% predicted	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
47.2 Baseline FEV1 >=80% predicted	0		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]

Analysis 1.1. Comparison 1 Addition of ICS + LABA versus same dose of ICS alone in steroid-naive patients as first line treatment, Outcome 1 # patients with exacerbations requiring systemic steroids.

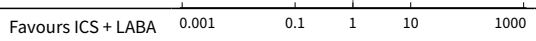
Study or subgroup	ICS + LABA n/N	ICS alone n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
1.1.1 Baseline FEV1 >=80% predicted					
Boonsawat 2008	3/149	8/154		13.73%	0.39[0.1,1.43]
Di Franco 1999	0/11	1/11		2.62%	0.33[0.02,7.39]
O'Byrne 2001	34/231	27/228		47.42%	1.24[0.78,1.99]
Strand 2004	0/78	0/72			Not estimable
Weersink 1997	1/16	1/17		1.69%	1.06[0.07,15.6]
Subtotal (95% CI)	**485**	**482**		**65.45%**	**1.02[0.67,1.56]**
Total events: 38 (ICS + LABA), 37 (ICS alone)					
Heterogeneity: Tau^2=0; Chi^2=3.28, df=3(P=0.35); I^2=8.46%					
Test for overall effect: Z=0.1(P=0.92)					
1.1.2 Baseline FEV1<80% predicted					
Kerwin 2008	3/210	1/212		1.74%	3.03[0.32,28.88]
Murray 2004	1/88	0/89		0.87%	3.03[0.13,73.48]
Nelson 2003	2/95	0/97		0.86%	5.1[0.25,104.94]
Rojas 2007	4/180	6/182		10.41%	0.67[0.19,2.35]
Subtotal (95% CI)	**573**	**580**		**13.88%**	**1.39[0.56,3.43]**
Total events: 10 (ICS + LABA), 7 (ICS alone)					
Heterogeneity: Tau^2=0; Chi^2=2.69, df=3(P=0.44); I^2=0%					
Test for overall effect: Z=0.72(P=0.47)					
1.1.3 Baseline FEV1 predicted unclear					
SAS30015	0/78	2/78		4.36%	0.2[0.01,4.1]
SAS30021	0/304	1/304		2.62%	0.33[0.01,8.15]
SAS40068	9/253	8/263		13.69%	1.17[0.46,2.98]
Subtotal (95% CI)	**635**	**645**		**20.67%**	**0.86[0.38,1.96]**
Total events: 9 (ICS + LABA), 11 (ICS alone)					
Heterogeneity: Tau^2=0; Chi^2=1.65, df=2(P=0.44); I^2=0%					
Test for overall effect: Z=0.36(P=0.72)					
Total (95% CI)	**1693**	**1707**		**100%**	**1.04[0.73,1.47]**
Total events: 57 (ICS + LABA), 55 (ICS alone)					
Heterogeneity: Tau^2=0; Chi^2=7.77, df=10(P=0.65); I^2=0%					
Test for overall effect: Z=0.22(P=0.83)					
Test for subgroup differences: Chi^2=0.61, df=1 (P=0.74), I^2=0%					



Favours ICS + LABA | Favours ICS alone

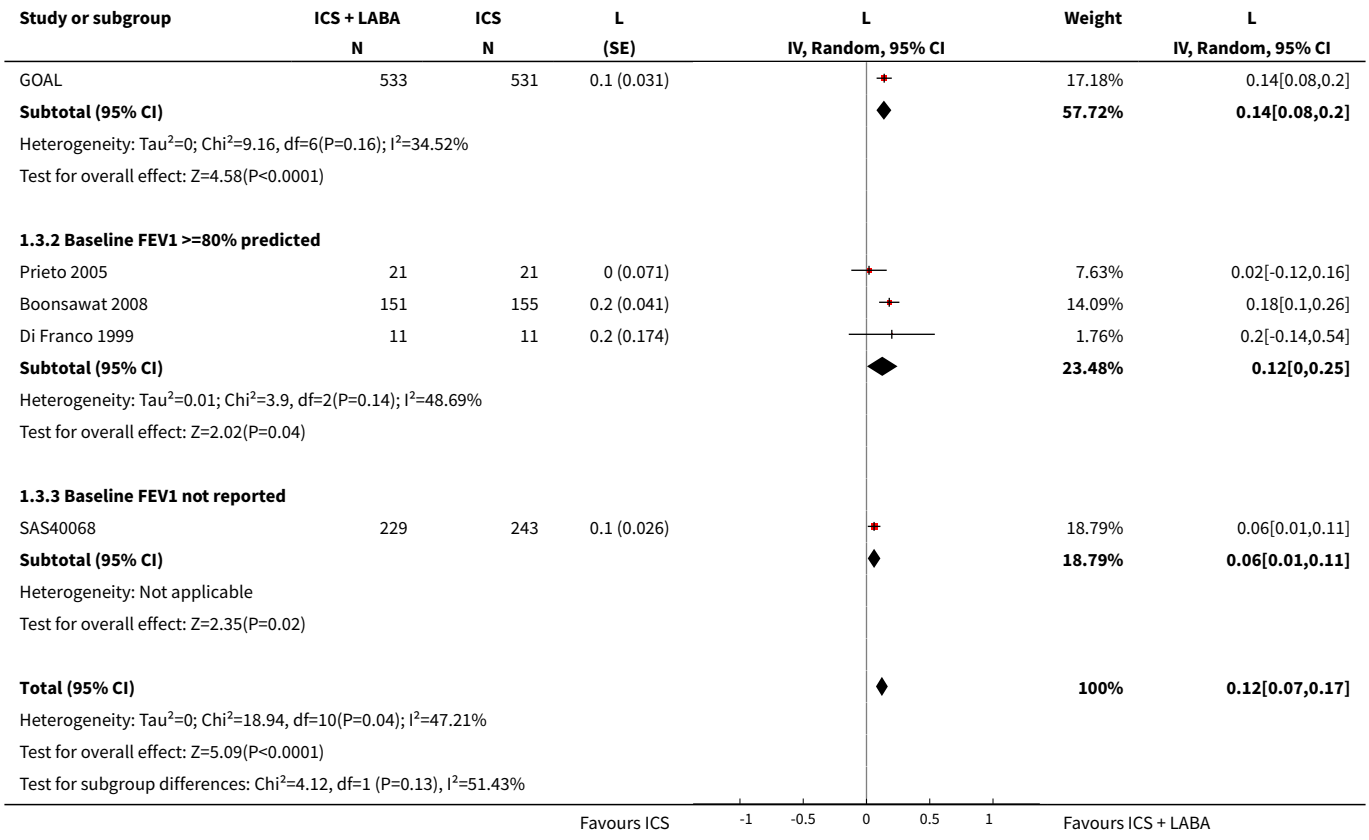
Analysis 1.2. Comparison 1 Addition of ICS + LABA versus same dose of ICS alone in steroid-naive patients as first line treatment, Outcome 2 # patients with exacerbations requiring hospitalisation.

Study or subgroup	LABA + ICS n/N	ICS alone n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
1.2.1 Baseline FEV1 >=80% predicted					
Boonsawat 2008	0/149	2/154		37.98%	0.21[0.01,4.27]
Di Franco 1999	0/11	0/11			Not estimable
Subtotal (95% CI)	**160**	**165**		**37.98%**	**0.21[0.01,4.27]**
Total events: 0 (LABA + ICS), 2 (ICS alone)					
Heterogeneity: Not applicable					
Test for overall effect: Z=1.02(P=0.31)					
1.2.2 Baseline FEV1 <80% predicted					
Chuchalin 2002	0/111	1/114		22.86%	0.34[0.01,8.31]
Kerwin 2008	0/210	0/212			Not estimable
Rojas 2007	0/180	0/182			Not estimable
Subtotal (95% CI)	**501**	**508**		**22.86%**	**0.34[0.01,8.31]**
Total events: 0 (LABA + ICS), 1 (ICS alone)					
Heterogeneity: Tau^2=0; Chi^2=0, df=0(P<0.0001); I^2=100%					
Test for overall effect: Z=0.66(P=0.51)					
1.2.3 Baseline FEV1 not reported					
SLGF75	0/14	0/17			Not estimable
Strand 2004	1/75	1/70		15.98%	0.93[0.06,14.64]
SAS30021	0/304	1/304		23.17%	0.33[0.01,8.15]
SAS40068	0/262	0/270			Not estimable
SAS30015	0/78	0/78			Not estimable
Subtotal (95% CI)	**733**	**739**		**39.15%**	**0.58[0.08,4.38]**
Total events: 1 (LABA + ICS), 2 (ICS alone)					
Heterogeneity: Tau^2=0; Chi^2=0.23, df=1(P=0.63); I^2=0%					
Test for overall effect: Z=0.53(P=0.6)					
Total (95% CI)	**1394**	**1412**		**100%**	**0.38[0.09,1.65]**
Total events: 1 (LABA + ICS), 5 (ICS alone)					
Heterogeneity: Tau^2=0; Chi^2=0.57, df=3(P=0.9); I^2=0%					
Test for overall effect: Z=1.29(P=0.2)					
Test for subgroup differences: Chi^2=0.32, df=1 (P=0.85), I^2=0%					

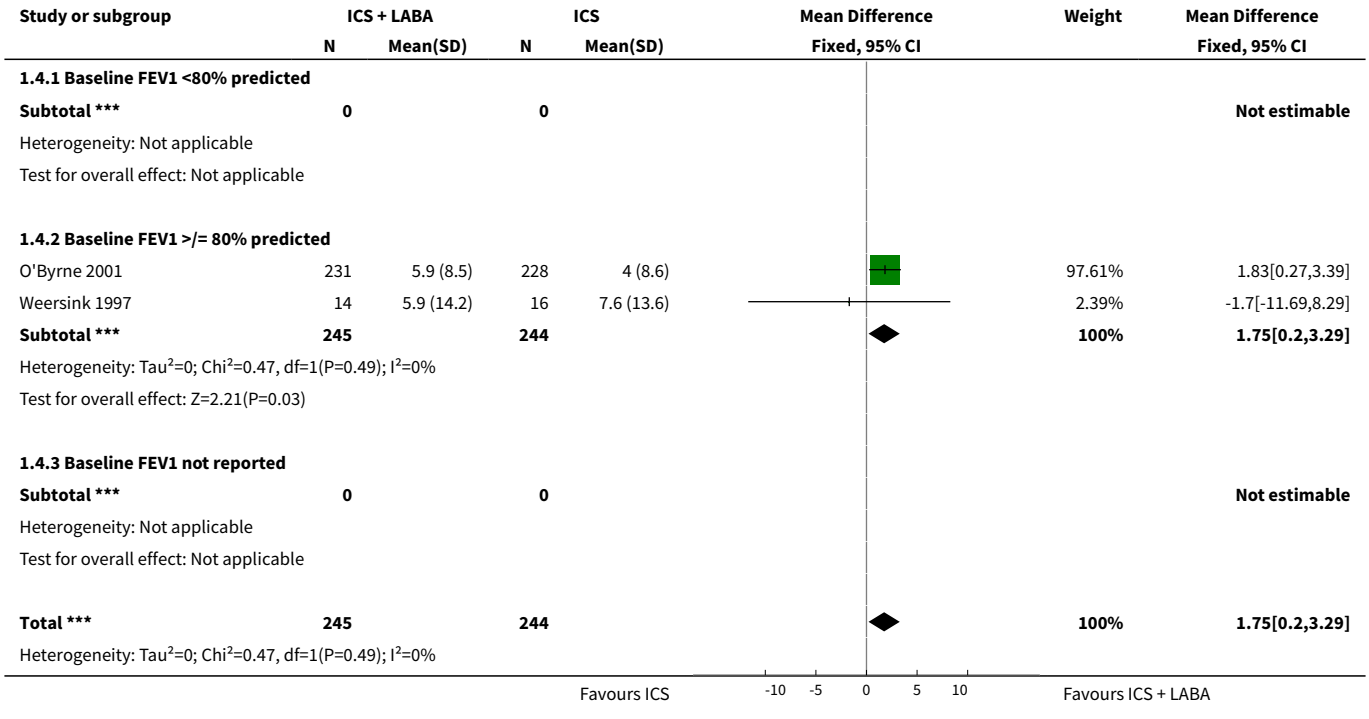


Analysis 1.3. Comparison 1 Addition of ICS + LABA versus same dose of ICS alone in steroid-naive patients as first line treatment, Outcome 3 Change in FEV1 at endpoint.

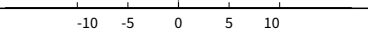
Study or subgroup	ICS + LABA N	ICS N	L (SE)	L IV, Random, 95% CI	Weight	L IV, Random, 95% CI
1.3.1 Baseline FEV1 <80% predicted						
Kerwin 2008	210	212	0.1 (0.041)		14.09%	0.1[0.02,0.18]
Murray 2004	88	89	0 (0.071)		7.63%	0.01[-0.13,0.15]
Nelson 2003	95	97	0.2 (0.071)		7.63%	0.18[0.04,0.32]
Chuchalin 2002	111	114	0.2 (0.082)		6.32%	0.16[0,0.32]
Pearlman 1999a	25	23	0.3 (0.122)		3.29%	0.32[0.08,0.56]
Pearlman 1999b	21	23	0.4 (0.184)		1.58%	0.43[0.07,0.79]



Analysis 1.4. Comparison 1 Addition of ICS + LABA versus same dose of ICS alone in steroid-naive patients as first line treatment, Outcome 4 Change in FEV1 predicted at endpoint.



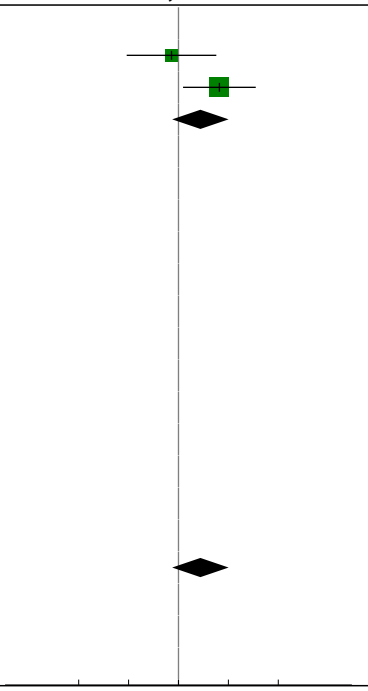
Study or subgroup	ICS + LABA N	ICS + LABA Mean(SD)	ICS N	ICS Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
Test for overall effect: Z=2.21(P=0.03)							
Test for subgroup differences: Not applicable							



Favours ICS | Favours ICS + LABA

Analysis 1.5. Comparison 1 Addition of ICS + LABA versus same dose of ICS alone in steroid-naive patients as first line treatment, Outcome 5 FEV1 predicted at endpoint.

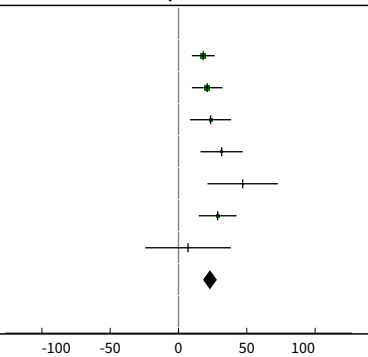
Study or subgroup	ICS + LABA N	ICS + LABA Mean(SD)	ICS N	ICS Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
1.5.1 Baseline FEV1 <80% predicted							
Miraglia del Giudice 2007	12	94.2 (11.9)	12	95.6 (10.5)		39.69%	-1.4[-10.38,7.58]
Overbeek 2005	20	89 (12)	20	80.8 (11.5)		60.31%	8.2[0.92,15.48]
Subtotal ***	**32**		**32**			**100%**	**4.39[-1.27,10.05]**
Heterogeneity: Tau^2=0; Chi^2=2.65, df=1(P=0.1); I^2=62.24%							
Test for overall effect: Z=1.52(P=0.13)							
1.5.2 Baseline FEV1 >/= 80% predicted							
Subtotal ***	**0**		**0**				**Not estimable**
Heterogeneity: Not applicable							
Test for overall effect: Not applicable							
1.5.3 Baseline FEV1 not reported							
Subtotal ***	**0**		**0**				**Not estimable**
Heterogeneity: Not applicable							
Test for overall effect: Not applicable							
Total ***	**32**		**32**			**100%**	**4.39[-1.27,10.05]**
Heterogeneity: Tau^2=0; Chi^2=2.65, df=1(P=0.1); I^2=62.24%							
Test for overall effect: Z=1.52(P=0.13)							
Test for subgroup differences: Not applicable							



Favours ICS | Favours ICS + LABA

Analysis 1.6. Comparison 1 Addition of ICS + LABA versus same dose of ICS alone in steroid-naive patients as first line treatment, Outcome 6 Change in morning PEF (L/min) at endpoint.

Study or subgroup	ICS + LABA N	ICS + LABA Mean(SD)	ICS alone N	ICS alone Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
1.6.1 Baseline FEV1 < 80% predicted							
Kerwin 2008	210	51.7 (43.5)	212	33.6 (43.7)		15.91%	18.1[9.79,26.41]
Rojas 2007	179	72 (54)	180	51 (54)		8.81%	21[9.83,32.17]
Nelson 2003	95	66.5 (54.2)	97	43 (51.9)		4.88%	23.5[8.48,38.52]
Murray 2004	87	68.1 (51.9)	89	36.5 (52.8)		4.6%	31.6[16.13,47.07]
Pearlman 1999a	25	57 (52)	23	10 (38.4)		1.66%	47[21.28,72.72]
Chuchalin 2002	111	65 (55.9)	114	36.3 (49.6)		5.76%	28.7[14.88,42.52]
Pearlman 1999b	21	32 (60.9)	22	25 (41.3)		1.13%	7[-24.25,38.25]
Subtotal ***	**728**		**737**			**42.74%**	**23.03[17.95,28.1]**
Heterogeneity: Tau^2=0; Chi^2=7.65, df=6(P=0.26); I^2=21.6%							



Favours ICS alone | Favours ICS + LABA

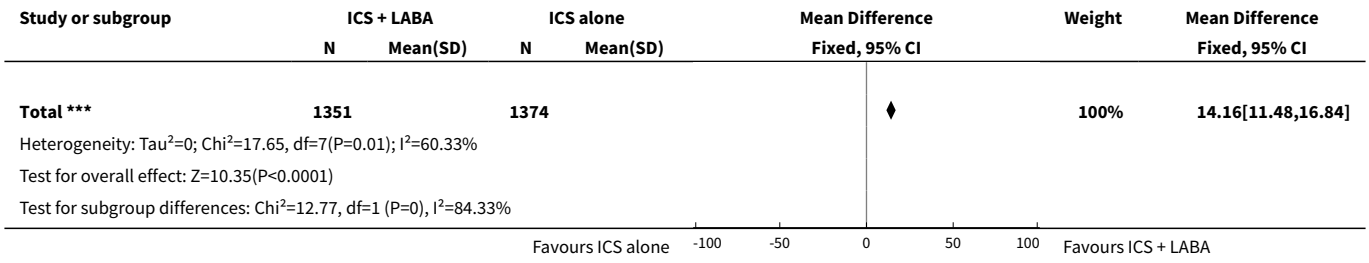
Study or subgroup	ICS + LABA N	ICS + LABA Mean(SD)	ICS alone N	ICS alone Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
Test for overall effect: Z=8.9(P<0.0001)							
1.6.2 Baseline FEV1 >=80% predicted							
O'Byrne 2001	231	31.8 (44.2)	228	15.1 (44.6)		16.66%	16.69[8.57,24.81]
Boonsawat 2008	151	35.8 (36)	155	21.8 (35)		17.37%	14[6.04,21.96]
Subtotal ***	**382**		**383**			**34.03%**	**15.32[9.63,21]**
Heterogeneity: Tau²=0; Chi²=0.21, df=1(P=0.64); I²=0%							
Test for overall effect: Z=5.28(P<0.0001)							
1.6.3 Baseline FEV1 not reported							
SAS30015	74	68 (60.4)	75	30 (40.5)		4.02%	38[21.47,54.53]
SAS40068	253	47.8 (44.1)	262	32.6 (43.5)		19.2%	15.2[7.63,22.77]
Subtotal ***	**327**		**337**			**23.23%**	**19.15[12.27,26.03]**
Heterogeneity: Tau²=0; Chi²=6.04, df=1(P=0.01); I²=83.44%							
Test for overall effect: Z=5.45(P<0.0001)							
Total ***	**1437**		**1457**			**100%**	**19.5[16.19,22.82]**
Heterogeneity: Tau²=0; Chi²=17.85, df=10(P=0.06); I²=43.98%							
Test for overall effect: Z=11.53(P<0.0001)							
Test for subgroup differences: Chi²=3.94, df=1 (P=0.14), I²=49.3%							

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

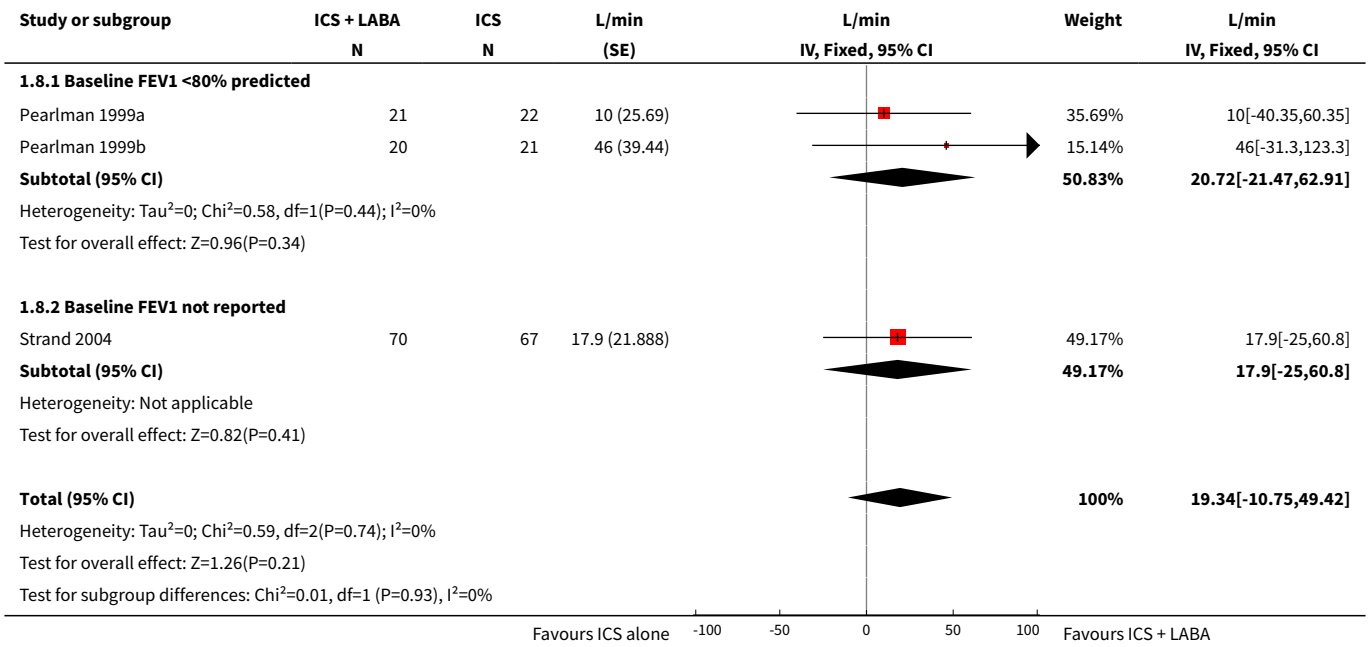
Analysis 1.7. Comparison 1 Addition of ICS + LABA versus same dose of ICS alone in steroid-naive patients as first line treatment, Outcome 7 Change in evening PEF (L/min) at endpoint.

Study or subgroup	ICS + LABA N	ICS + LABA Mean(SD)	ICS alone N	ICS alone Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
1.7.1 Baseline FEV1 <80% predicted							
Kerwin 2008	210	48.7 (40.6)	212	27.9 (40.8)		11.94%	20.8[13.04,28.56]
Rojas 2007	179	64.4 (50)	180	43 (49)		6.86%	21.4[11.16,31.64]
Nelson 2003	95	51 (46.2)	97	30.4 (49.6)		3.91%	20.6[7.04,34.16]
Murray 2004	87	50.7 (46.2)	89	30.2 (46.7)		3.82%	20.5[6.78,34.22]
Subtotal ***	**571**		**578**			**26.53%**	**20.88[15.68,26.09]**
Heterogeneity: Tau²=0; Chi²=0.01, df=3(P=1); I²=0%							
Test for overall effect: Z=7.86(P<0.0001)							
1.7.2 Baseline FEV1 >=80% predicted							
Boonsawat 2008	151	37.5 (38)	155	17.7 (37.5)		10.05%	19.8[11.34,28.26]
Subtotal ***	**151**		**155**			**10.05%**	**19.8[11.34,28.26]**
Heterogeneity: Not applicable							
Test for overall effect: Z=4.59(P<0.0001)							
1.7.3 Baseline FEV1 not reported							
SAS30021	304	22.2 (11.3)	304	14 (33.5)		45.57%	8.2[4.23,12.17]
SAS30015	74	44.4 (45.8)	75	24 (37.5)		3.98%	20.4[6.95,33.85]
SAS40068	251	42.3 (41.8)	262	27.3 (41.4)		13.87%	15[7.8,22.2]
Subtotal ***	**629**		**641**			**63.42%**	**10.45[7.08,13.82]**
Heterogeneity: Tau²=0; Chi²=4.87, df=2(P=0.09); I²=58.91%							
Test for overall effect: Z=6.08(P<0.0001)							

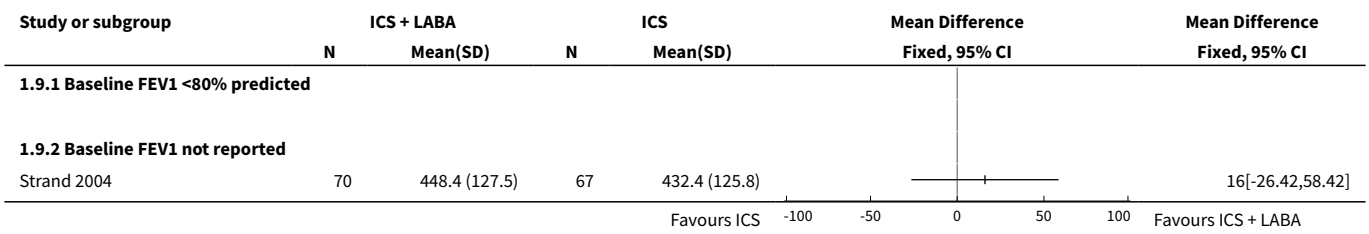
Favours ICS alone -100 -50 0 50 100 Favours ICS + LABA



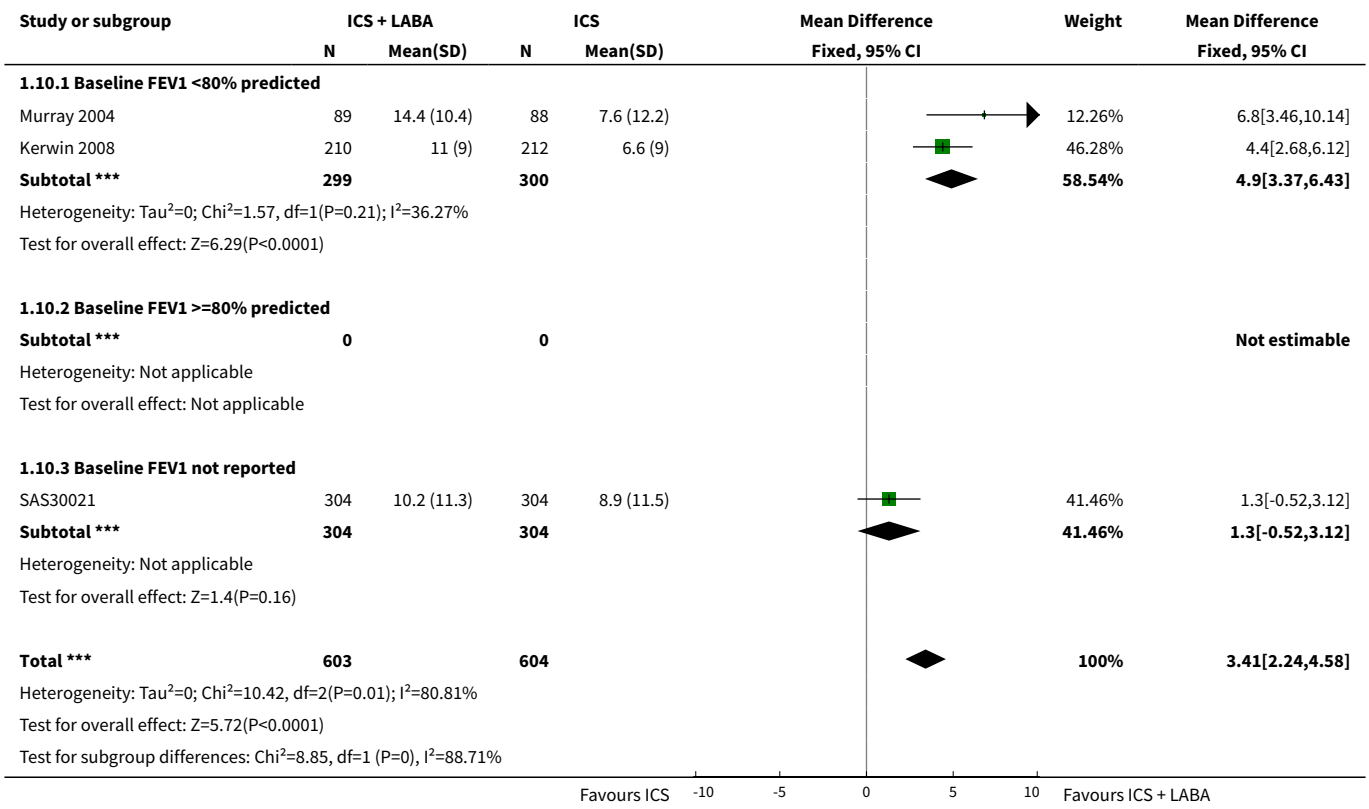
Analysis 1.8. Comparison 1 Addition of ICS + LABA versus same dose of ICS alone in steroid-naive patients as first line treatment, Outcome 8 Morning PEF at endpoint.



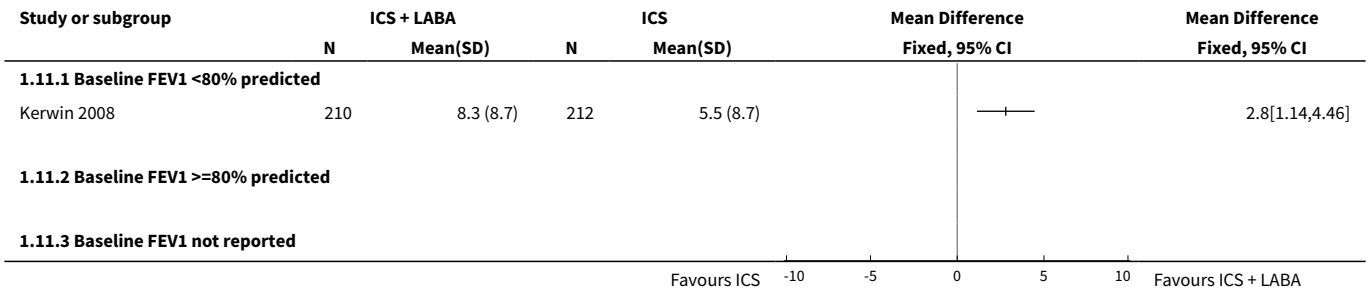
Analysis 1.9. Comparison 1 Addition of ICS + LABA versus same dose of ICS alone in steroid-naive patients as first line treatment, Outcome 9 Evening PEF (L/min) at endpoint.



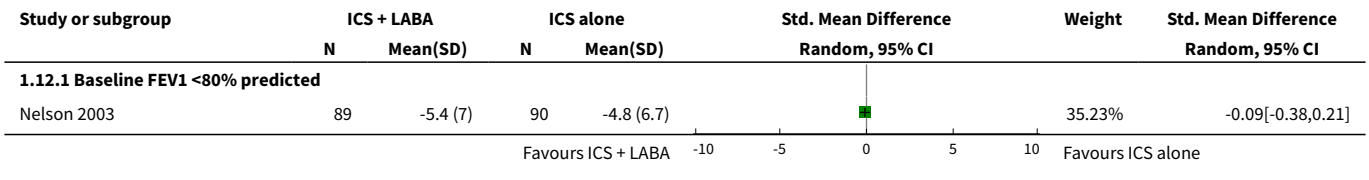
Analysis 1.10. Comparison 1 Addition of ICS + LABA versus same dose of ICS alone in steroid-naive patients as first line treatment, Outcome 10 Change in am PEF predicted (%).

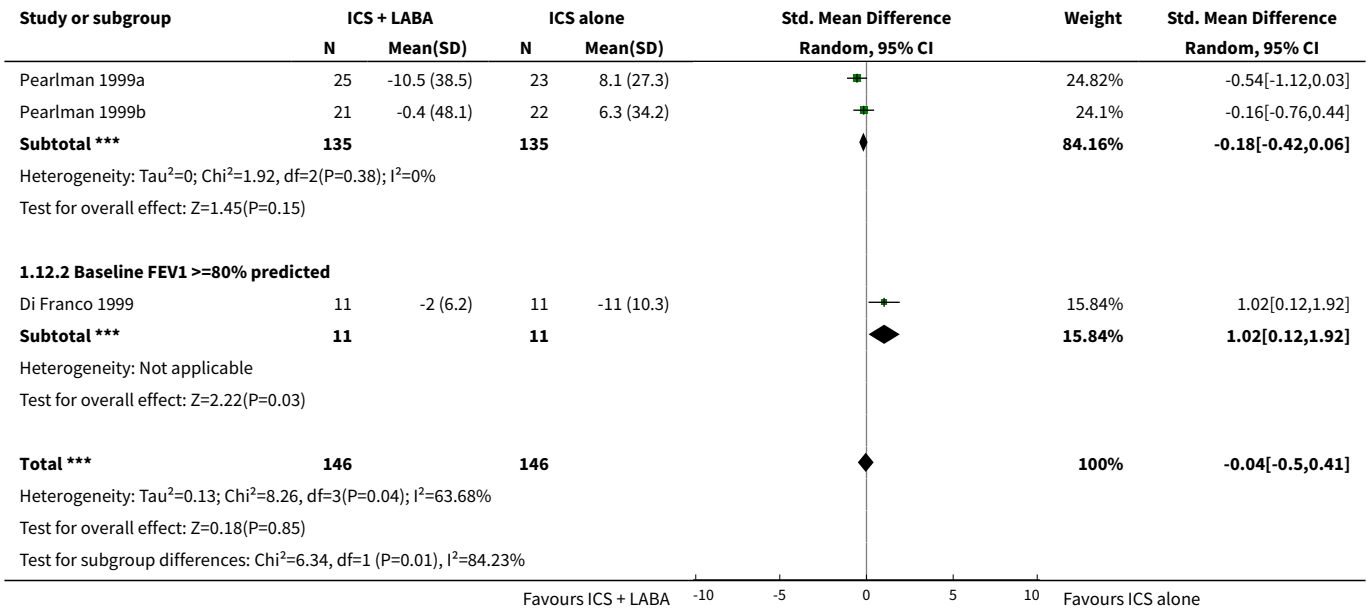


Analysis 1.11. Comparison 1 Addition of ICS + LABA versus same dose of ICS alone in steroid-naive patients as first line treatment, Outcome 11 Change in pm PEF predicted (%).

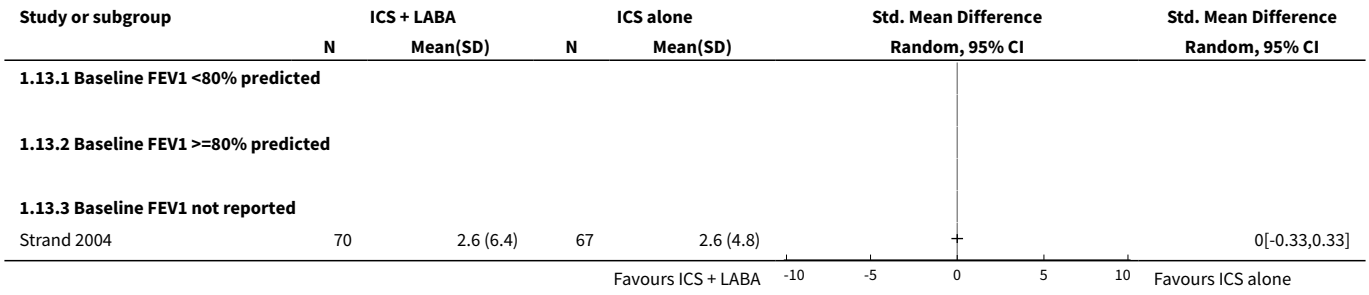


Analysis 1.12. Comparison 1 Addition of ICS + LABA versus same dose of ICS alone in steroid-naive patients as first line treatment, Outcome 12 Change in PEF variability at endpoint.

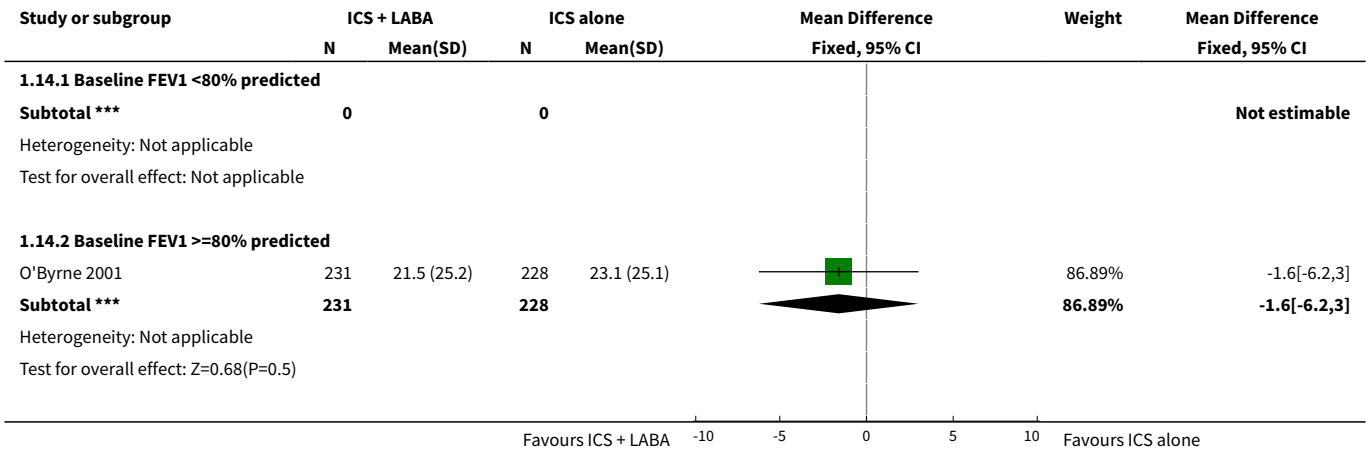


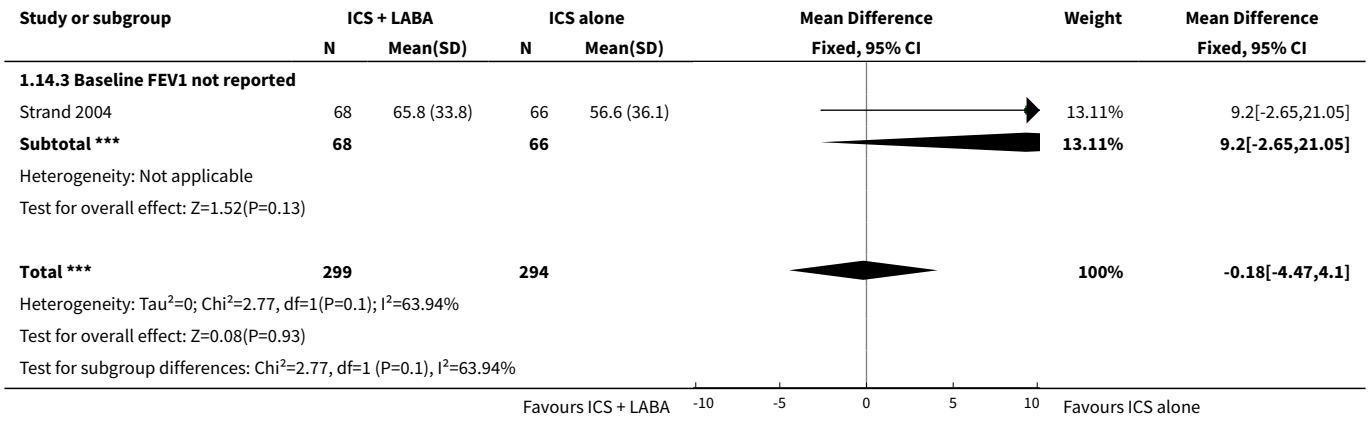


Analysis 1.13. Comparison 1 Addition of ICS + LABA versus same dose of ICS alone in steroid-naive patients as first line treatment, Outcome 13 Diurnal PEF variability at endpoint.

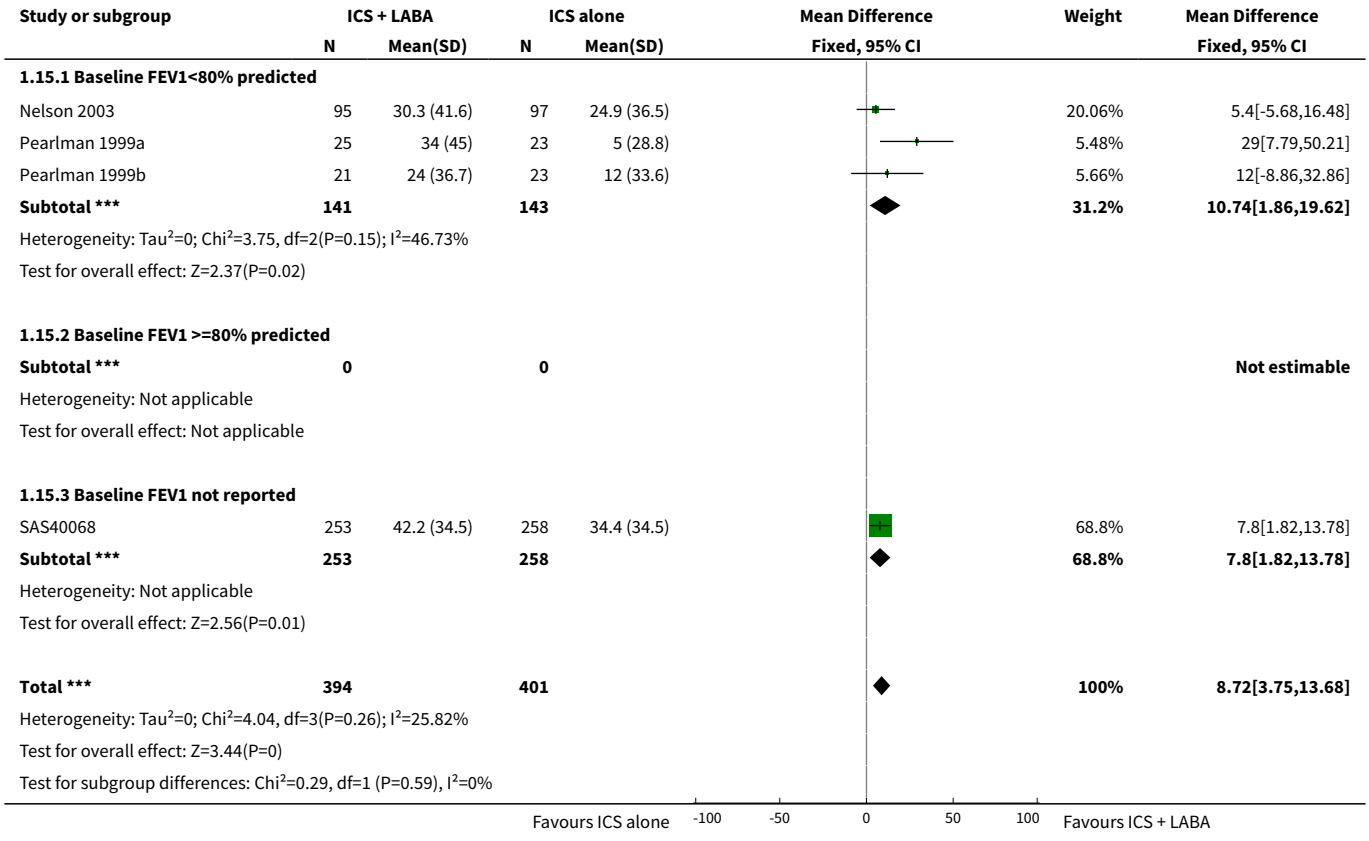


Analysis 1.14. Comparison 1 Addition of ICS + LABA versus same dose of ICS alone in steroid-naive patients as first line treatment, Outcome 14 % days with symptoms at endpoint.



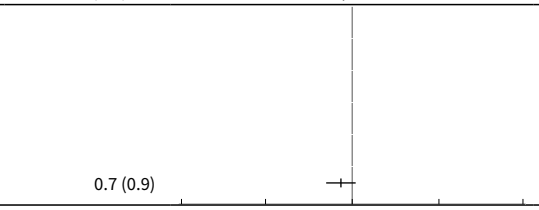


Analysis 1.15. Comparison 1 Addition of ICS + LABA versus same dose of ICS alone in steroid-naive patients as first line treatment, Outcome 15 Change in % symptom-free days at endpoint.



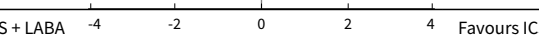
Analysis 1.16. Comparison 1 Addition of ICS + LABA versus same dose of ICS alone in steroid-naive patients as first line treatment, Outcome 16 Day symptom score at endpoint.

Study or subgroup	ICS + LABA N	ICS + LABA Mean(SD)	ICS alone N	ICS alone Mean(SD)	Std. Mean Difference Fixed, 95% CI	Std. Mean Difference Fixed, 95% CI
1.16.1 Baseline FEV1 <80% predicted						
1.16.2 Baseline FEV1 >=80% predicted						
1.16.3 Baseline FEV1 not reported						
Strand 2004	68	0.5 (0.6)	66	0.7 (0.9)		-0.26[-0.6,0.08]



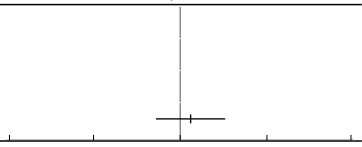
Analysis 1.17. Comparison 1 Addition of ICS + LABA versus same dose of ICS alone in steroid-naive patients as first line treatment, Outcome 17 Change in symptom score at endpoint.

Study or subgroup	ICS + LABA N	ICS + LABA Mean(SD)	ICS alone N	ICS alone Mean(SD)	Std. Mean Difference Random, 95% CI	Weight	Std. Mean Difference Random, 95% CI
1.17.1 Baseline FEV1 <80% predicted							
Kerwin 2008	210	-1.3 (1.5)	212	-1.1 (1.5)		26.07%	-0.14[-0.33,0.05]
Rojas 2007	179	-1.5 (1)	180	-1.3 (1)		23.21%	-0.2[-0.41,0.01]
Chuchalin 2002	111	-0.6 (0.6)	114	-0.5 (0.6)		16.2%	-0.22[-0.48,0.04]
Murray 2004	87	-1.3 (0.9)	89	-0.9 (0.9)		13.04%	-0.43[-0.72,-0.13]
Pearlman 1999a	25	-0.8 (1)	23	-0.1 (0.5)		3.73%	-0.87[-1.46,-0.27]
Nelson 2003	95	-1.1 (1.1)	97	-0.8 (0.9)		14.16%	-0.31[-0.59,-0.02]
Pearlman 1999b	21	-0.4 (0.5)	21	-0.3 (0.5)		3.59%	-0.21[-0.82,0.39]
Subtotal ***	**728**		**736**			**100%**	**-0.26[-0.37,-0.14]**
Heterogeneity: Tau^2=0; Chi^2=7.23, df=6(P=0.3); I^2=17.05%							
Test for overall effect: Z=4.27(P<0.0001)							
1.17.2 Baseline FEV1 >=80% predicted							
Subtotal ***	**0**		**0**				**Not estimable**
Heterogeneity: Not applicable							
Test for overall effect: Not applicable							
1.17.3 Baseline FEV1 not reported							
Subtotal ***	**0**		**0**				**Not estimable**
Heterogeneity: Not applicable							
Test for overall effect: Not applicable							
Total ***	**728**		**736**			**100%**	**-0.26[-0.37,-0.14]**
Heterogeneity: Tau^2=0; Chi^2=7.23, df=6(P=0.3); I^2=17.05%							
Test for overall effect: Z=4.27(P<0.0001)							
Test for subgroup differences: Not applicable							



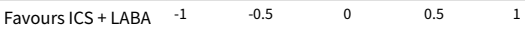
Analysis 1.18. Comparison 1 Addition of ICS + LABA versus same dose of ICS alone in steroid-naive patients as first line treatment, Outcome 18 % nights with awakenings at endpoint.

Study or subgroup	ICS + LABA N	ICS + LABA Mean(SD)	ICS alone N	ICS alone Mean(SD)	Mean Difference Fixed, 95% CI	Mean Difference Fixed, 95% CI
1.18.1 Baseline FEV1 <80% predicted						
1.18.2 Baseline FEV1 >=80% predicted						
O'Byrne 2001	231	3.1 (10.9)	228	2.5 (10.9)		0.6[-1.39,2.59]



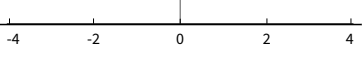
Analysis 1.19. Comparison 1 Addition of ICS + LABA versus same dose of ICS alone in steroid-naive patients as first line treatment, Outcome 19 Change in night-time symptoms at endpoint.

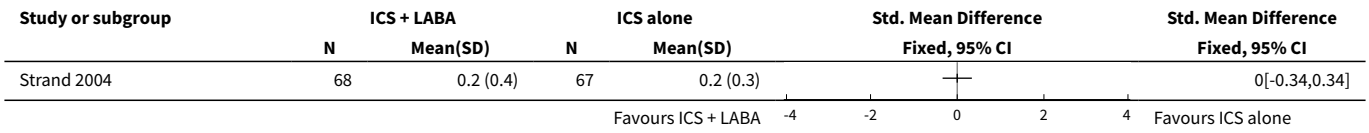
Study or subgroup	ICS + LABA N	ICS + LABA Mean(SD)	ICS alone N	ICS alone Mean(SD)	Std. Mean Difference Fixed, 95% CI	Weight	Std. Mean Difference Fixed, 95% CI
1.19.1 Baseline FEV1 <80% predicted							
Rojas 2007	179	-0.8 (1)	180	-0.7 (1)		61.64%	-0.1[-0.31,0.11]
Subtotal ***	**179**		**180**			**61.64%**	**-0.1[-0.31,0.11]**
Heterogeneity: Not applicable							
Test for overall effect: Z=0.94(P=0.34)							
1.19.2 Baseline FEV1 >=80% predicted							
Chuchalin 2002	111	-0.6 (0.6)	114	-0.4 (0.6)		38.36%	-0.25[-0.51,0.01]
Subtotal ***	**111**		**114**			**38.36%**	**-0.25[-0.51,0.01]**
Heterogeneity: Not applicable							
Test for overall effect: Z=1.88(P=0.06)							
1.19.3 Baseline FEV1 not reported							
Subtotal ***	**0**		**0**				**Not estimable**
Heterogeneity: Not applicable							
Test for overall effect: Not applicable							
Total ***	**290**		**294**			**100%**	**-0.16[-0.32,0]**
Heterogeneity: Tau^2=0; Chi^2=0.79, df=1(P=0.37); I^2=0%							
Test for overall effect: Z=1.9(P=0.06)							
Test for subgroup differences: Chi^2=0.79, df=1 (P=0.37), I^2=0%							



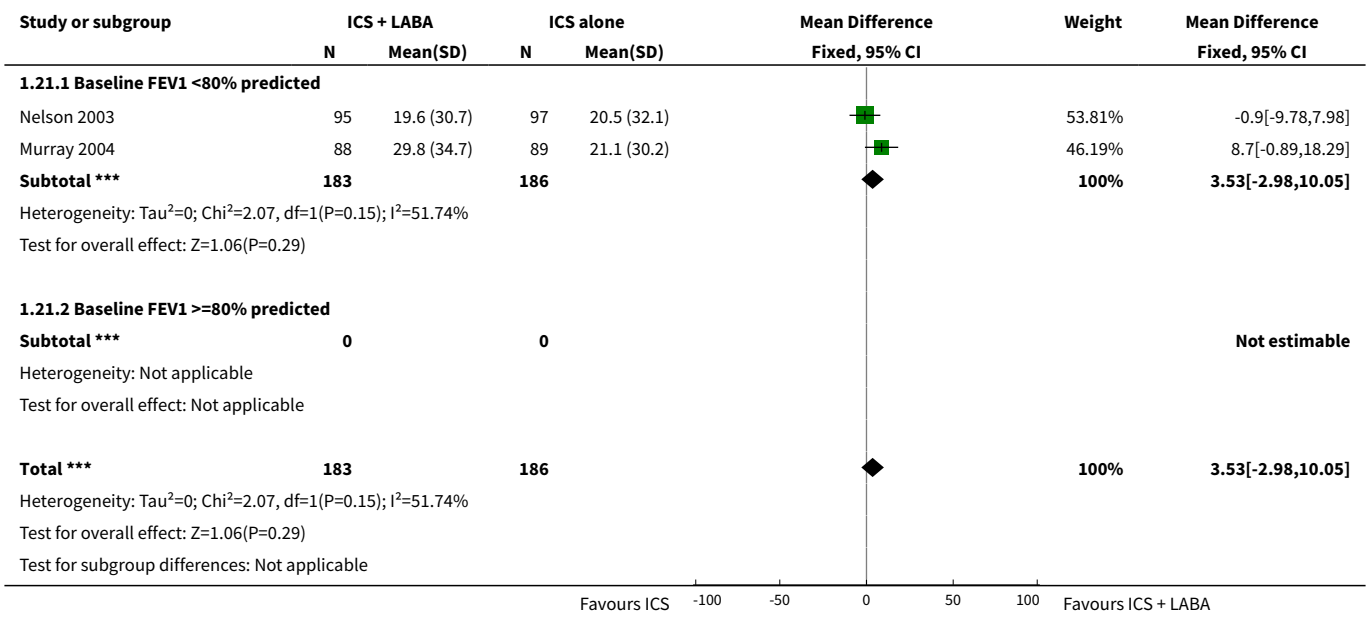
Analysis 1.20. Comparison 1 Addition of ICS + LABA versus same dose of ICS alone in steroid-naive patients as first line treatment, Outcome 20 Night symptom score at endpoint.

Study or subgroup	ICS + LABA N	ICS + LABA Mean(SD)	ICS alone N	ICS alone Mean(SD)	Std. Mean Difference Fixed, 95% CI	Std. Mean Difference Fixed, 95% CI
1.20.1 Baseline FEV1 <80% predicted						
1.20.2 Baseline FEV1 >=80% predicted						
1.20.3 Baseline FEV1 not reported						

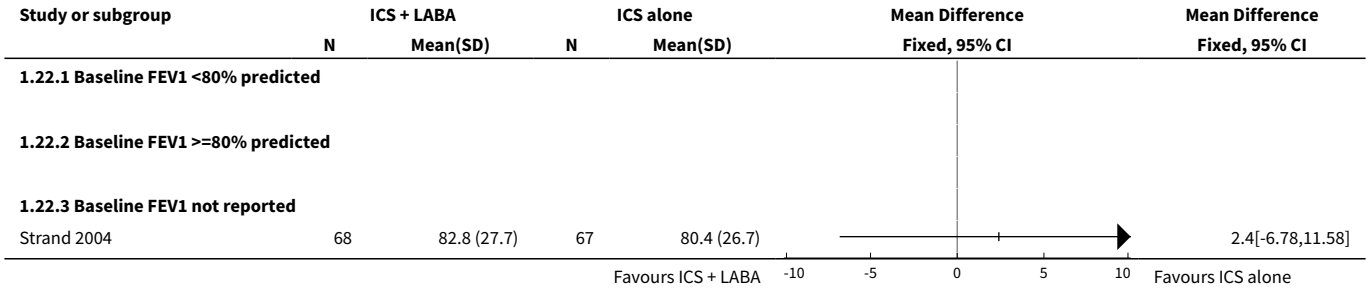




Analysis 1.21. Comparison 1 Addition of ICS + LABA versus same dose of ICS alone in steroid-naive patients as first line treatment, Outcome 21 Change in % nights with no awakenings at 12 weeks.

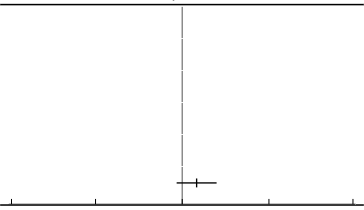


Analysis 1.22. Comparison 1 Addition of ICS + LABA versus same dose of ICS alone in steroid-naive patients as first line treatment, Outcome 22 % nights with symptoms at endpoint.



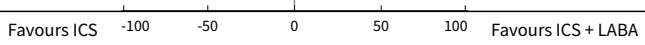
Analysis 1.23. Comparison 1 Addition of ICS + LABA versus same dose of ICS alone in steroid-naive patients as first line treatment, Outcome 23 Mean % rescue-free days at endpoint.

Study or subgroup	ICS + LABA N	ICS + LABA Mean(SD)	ICS alone N	ICS alone Mean(SD)	Mean Difference Fixed, 95% CI	Mean Difference Fixed, 95% CI
1.23.1 Baseline FEV1 <80% predicted						
1.23.2 Baseline FEV1 >=80% predicted						
1.23.3 Baseline FEV1 not reported						
Strand 2004	68	70.8 (33.4)	66	62.5 (34.6)		8.3[-3.22,19.82]



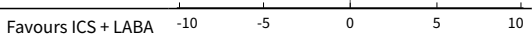
Analysis 1.24. Comparison 1 Addition of ICS + LABA versus same dose of ICS alone in steroid-naive patients as first line treatment, Outcome 24 Change in mean % rescue-free days at 12 weeks.

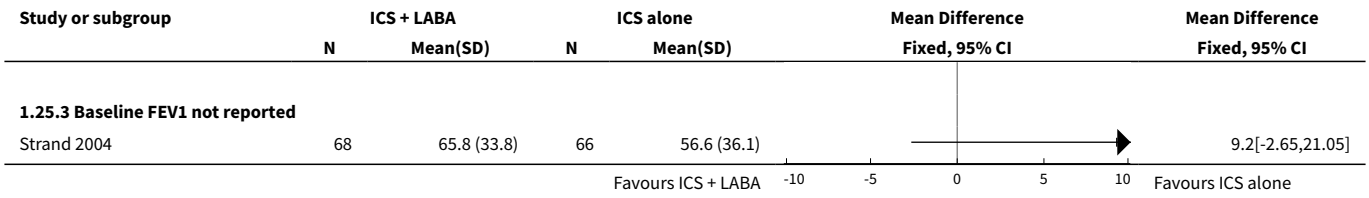
Study or subgroup	ICS + LABA N	ICS + LABA Mean(SD)	ICS alone N	ICS alone Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
1.24.1 Baseline FEV1 <80% predicted							
Nelson 2003	95	40 (43.7)	97	26.5 (36.8)		17.38%	13.5[2.06,24.94]
Subtotal ***	**95**		**97**			**17.38%**	**13.5[2.06,24.94]**
Heterogeneity: Not applicable							
Test for overall effect: Z=2.31(P=0.02)							
1.24.2 Baseline FEV1 >=80% predicted							
Subtotal ***	**0**		**0**				**Not estimable**
Heterogeneity: Not applicable							
Test for overall effect: Not applicable							
1.24.3 Baseline FEV1 not reported							
SAS40068	252	47.4 (30.2)	259	39 (30.3)		82.62%	8.4[3.15,13.65]
Subtotal ***	**252**		**259**			**82.62%**	**8.4[3.15,13.65]**
Heterogeneity: Not applicable							
Test for overall effect: Z=3.14(P=0)							
Total ***	**347**		**356**			**100%**	**9.29[4.52,14.05]**
Heterogeneity: Tau^2=0; Chi^2=0.63, df=1(P=0.43); I^2=0%							
Test for overall effect: Z=3.82(P=0)							
Test for subgroup differences: Chi^2=0.63, df=1 (P=0.43), I^2=0%							



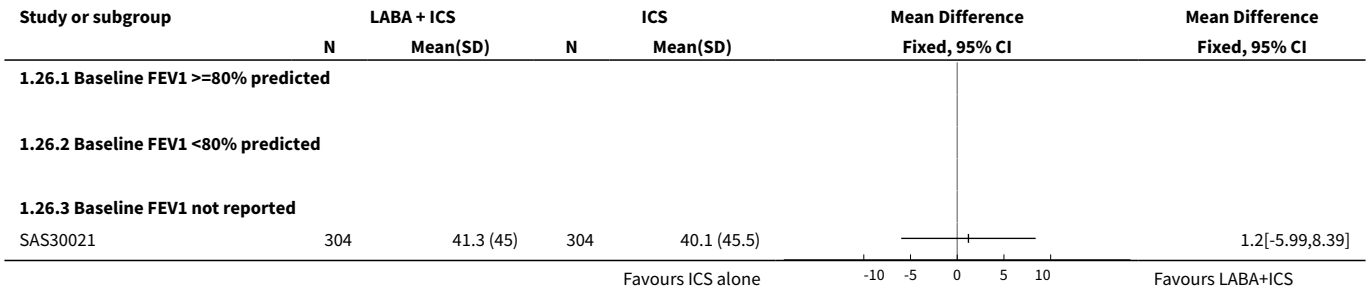
Analysis 1.25. Comparison 1 Addition of ICS + LABA versus same dose of ICS alone in steroid-naive patients as first line treatment, Outcome 25 % 24 hrs with symptoms at endpoint.

Study or subgroup	ICS + LABA N	ICS + LABA Mean(SD)	ICS alone N	ICS alone Mean(SD)	Mean Difference Fixed, 95% CI	Mean Difference Fixed, 95% CI
1.25.1 Baseline FEV1 >=80% predicted						
1.25.2 Baseline FEV1 <80% predicted						

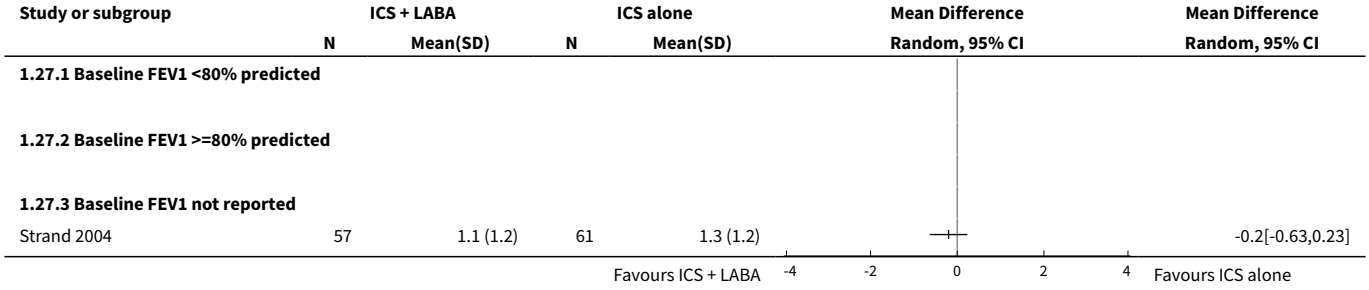




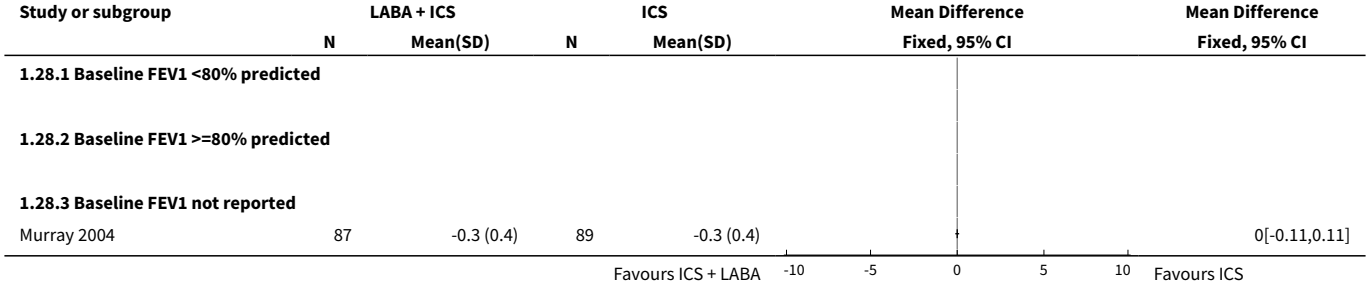
Analysis 1.26. Comparison 1 Addition of ICS + LABA versus same dose of ICS alone in steroid-naive patients as first line treatment, Outcome 26 % symptom-free days.



Analysis 1.27. Comparison 1 Addition of ICS + LABA versus same dose of ICS alone in steroid-naive patients as first line treatment, Outcome 27 Use of rescue fast-acting b2-agonists (puffs/24 hrs) at endpoint.

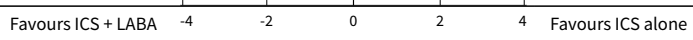


Analysis 1.28. Comparison 1 Addition of ICS + LABA versus same dose of ICS alone in steroid-naive patients as first line treatment, Outcome 28 Change in awakenings requiring SABA/nt.



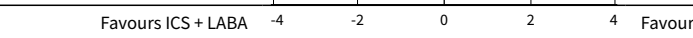
Analysis 1.29. Comparison 1 Addition of ICS + LABA versus same dose of ICS alone in steroid-naive patients as first line treatment, Outcome 29 Change in use of rescue fast-acting b2-agonists (puffs/24 hrs) at endpoint.

Study or subgroup	ICS + LABA N	ICS + LABA Mean(SD)	ICS alone N	ICS alone Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
1.29.1 Baseline FEV1 <80% predicted							
Kerwin 2008	210	-1.9 (2.8)	212	-1.5 (2.6)		13.97%	-0.4[-0.91,0.11]
Nelson 2003	95	-2.4 (3)	97	-1.8 (2.1)		10.15%	-0.6[-1.33,0.13]
Murray 2004	87	-2.8 (2.1)	89	-1.8 (2.1)		12.15%	-1[-1.61,-0.39]
Pearlman 1999a	24	-1.5 (2.5)	23	-1.1 (1.4)		5.72%	-0.4[-1.54,0.74]
Chuchalin 2002	111	-2.5 (1.9)	114	-1.6 (1.6)		14.88%	-0.87[-1.34,-0.4]
Pearlman 1999b	21	-1.4 (2.3)	22	-1.4 (1.9)		4.97%	0[-1.26,1.26]
Subtotal ***	**548**		**557**			**61.84%**	**-0.67[-0.94,-0.41]**
Heterogeneity: Tau^2=0; Chi^2=4.23, df=5(P=0.52); I^2=0%							
Test for overall effect: Z=4.97(P<0.0001)							
1.29.2 Baseline FEV1 >=80% predicted							
O'Byrne 2001	231	-0.5 (0.8)	228	-0.5 (0.8)		21.03%	0[-0.14,0.14]
Subtotal ***	**231**		**228**			**21.03%**	**0[-0.14,0.14]**
Heterogeneity: Not applicable							
Test for overall effect: Not applicable							
1.29.3 Baseline FEV1 not reported							
SAS30021	304	-1.2 (2.1)	304	-1.1 (2.4)		17.13%	-0.1[-0.46,0.26]
Subtotal ***	**304**		**304**			**17.13%**	**-0.1[-0.46,0.26]**
Heterogeneity: Not applicable							
Test for overall effect: Z=0.54(P=0.59)							
Total ***	**1083**		**1089**			**100%**	**-0.41[-0.73,-0.09]**
Heterogeneity: Tau^2=0.12; Chi^2=23.32, df=7(P=0); I^2=69.99%							
Test for overall effect: Z=2.51(P=0.01)							
Test for subgroup differences: Chi^2=19.1, df=1 (P<0.0001), I^2=89.53%							



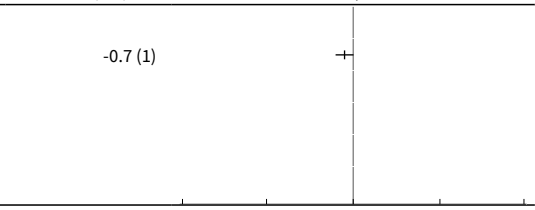
Analysis 1.30. Comparison 1 Addition of ICS + LABA versus same dose of ICS alone in steroid-naive patients as first line treatment, Outcome 30 Change in daytime rescue medication (puffs).

Study or subgroup	ICS + LABA N	ICS + LABA Mean(SD)	ICS alone N	ICS alone Mean(SD)	Mean Difference Random, 95% CI	Mean Difference Random, 95% CI
1.30.1 Baseline FEV1 <80% predicted						
Rojas 2007	179	-1.3 (1)	180	-1.1 (1)		-0.2[-0.41,0.01]
1.30.2 Baseline FEV1 >=80% predicted						
1.30.3 Baseline FEV1 not reported						



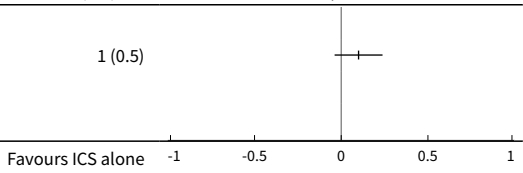
Analysis 1.31. Comparison 1 Addition of ICS + LABA versus same dose of ICS alone in steroid-naive patients as first line treatment, Outcome 31 Change in night-time rescue medication (puffs).

Study or subgroup	ICS + LABA N	ICS + LABA Mean(SD)	ICS alone N	ICS alone Mean(SD)	Mean Difference Random, 95% CI	Mean Difference Random, 95% CI
1.31.1 Baseline FEV1 <80% predicted						
Rojas 2007	179	-0.9 (1)	180	-0.7 (1)		-0.2[-0.41,0.01]
1.31.2 Baseline FEV1 >=80% predicted						
1.31.3 Baseline FEV1 not reported						



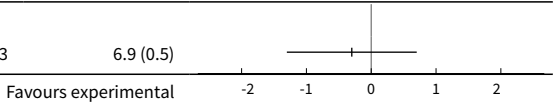
Analysis 1.32. Comparison 1 Addition of ICS + LABA versus same dose of ICS alone in steroid-naive patients as first line treatment, Outcome 32 Change in quality of life (AQLQ score) at 12 weeks.

Study or subgroup	ICS + LABA N	ICS + LABA Mean(SD)	ICS alone N	ICS alone Mean(SD)	Mean Difference Fixed, 95% CI	Mean Difference Fixed, 95% CI
1.32.1 Baseline FEV1 <80% predicted						
Chuchalin 2002	111	1.1 (0.6)	114	1 (0.5)		0.1[-0.04,0.24]
1.32.2 Baseline FEV1 >=80% predicted						



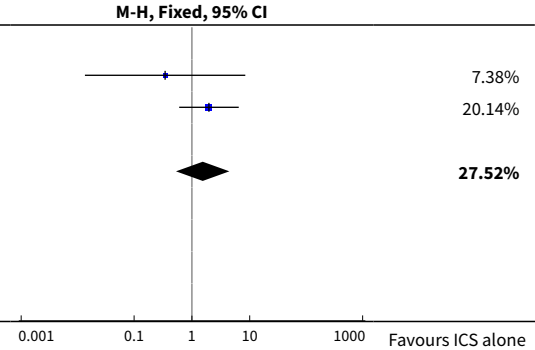
Analysis 1.33. Comparison 1 Addition of ICS + LABA versus same dose of ICS alone in steroid-naive patients as first line treatment, Outcome 33 Paediatric AQLQ scores.

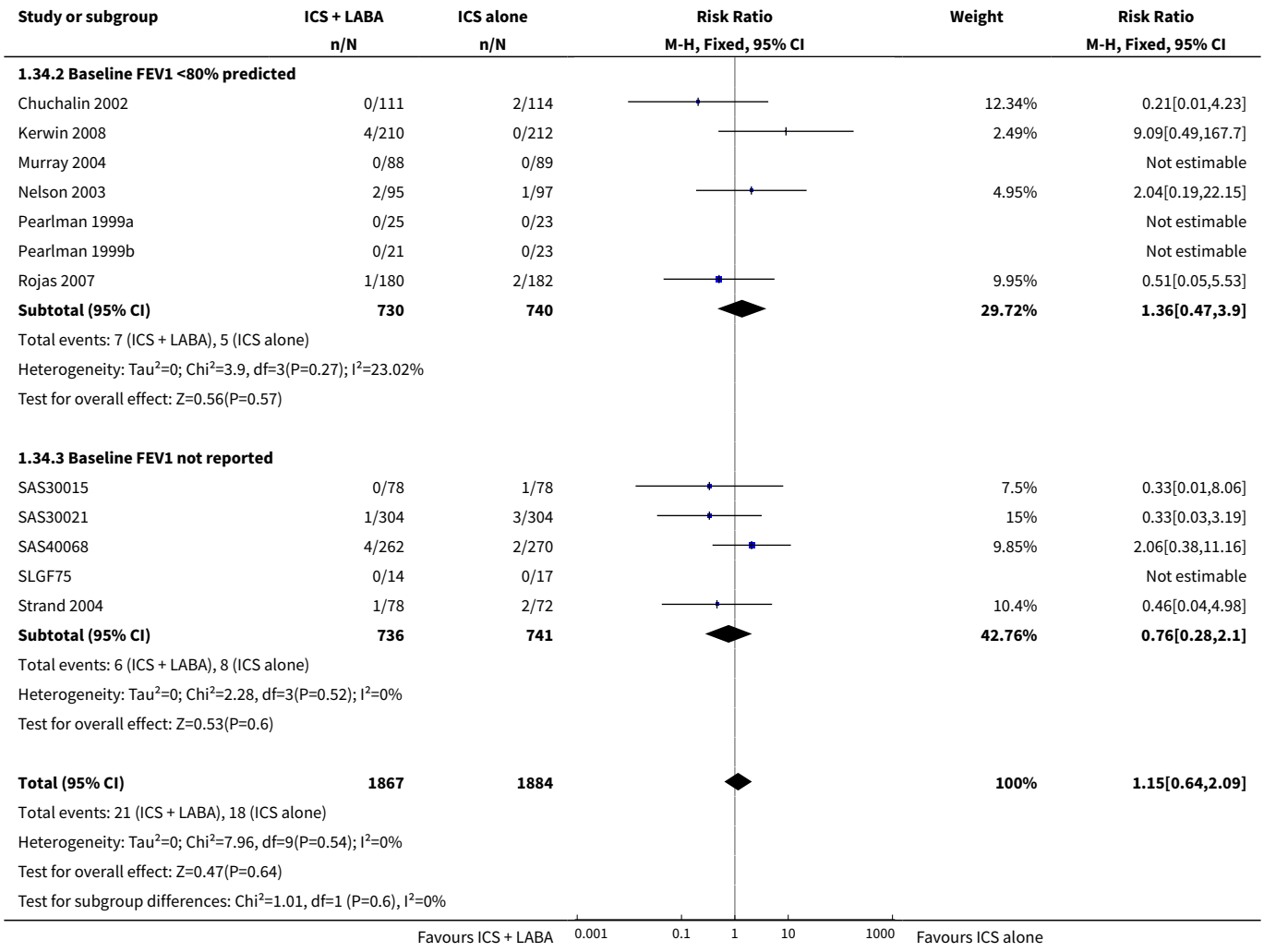
Study or subgroup	LABA + ICS N	LABA + ICS Mean(SD)	ICS alone N	ICS alone Mean(SD)	Mean Difference Fixed, 95% CI	Mean Difference Fixed, 95% CI
1.33.1 FEV1 not reported						
Karaman 2007	23	6.6 (2.4)	23	6.9 (0.5)		-0.3[-1.3,0.7]



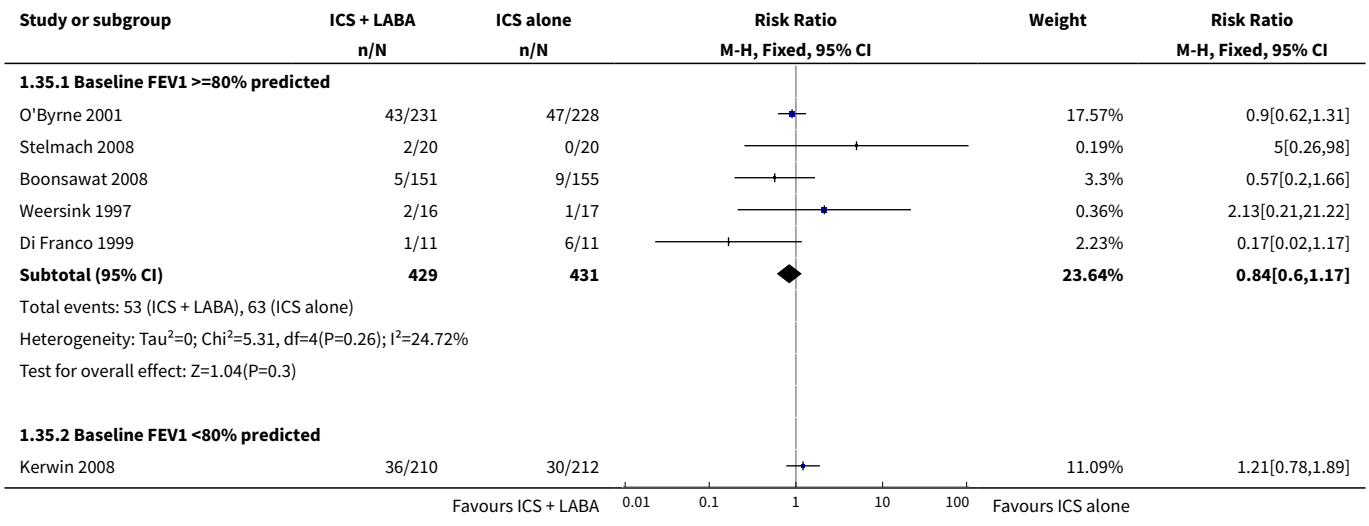
Analysis 1.34. Comparison 1 Addition of ICS + LABA versus same dose of ICS alone in steroid-naive patients as first line treatment, Outcome 34 Serious adverse events.

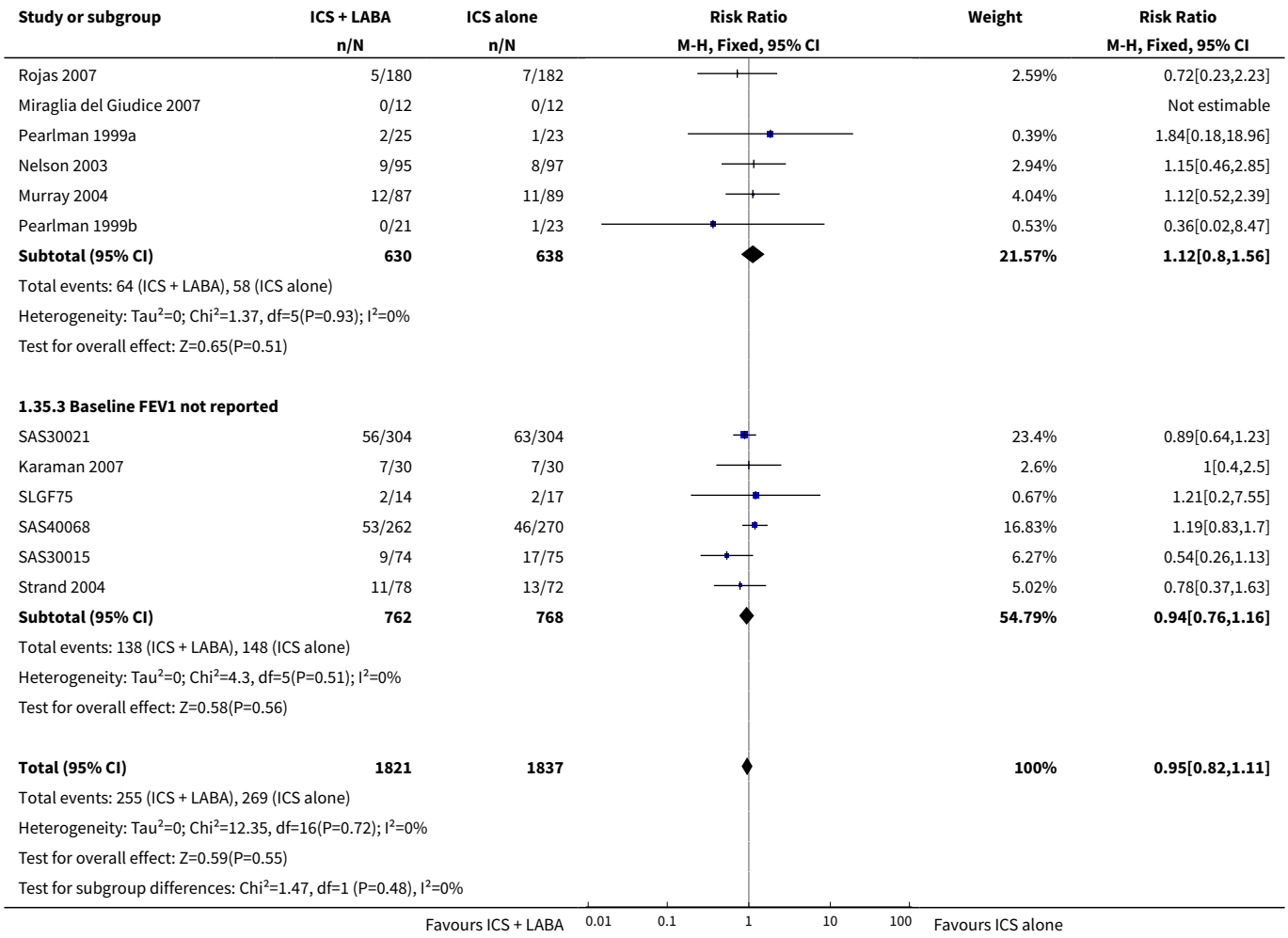
Study or subgroup	ICS + LABA n/N	ICS alone n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
1.34.1 Baseline FEV1 >=80% predicted					
Boonsawat 2008	0/149	1/154		7.38%	0.34[0.01,8.39]
O'Byrne 2001	8/231	4/228		20.14%	1.97[0.6,6.46]
Prieto 2005	0/21	0/21			Not estimable
Subtotal (95% CI)	**401**	**403**		**27.52%**	**1.54[0.53,4.45]**
Total events: 8 (ICS + LABA), 5 (ICS alone)					
Heterogeneity: Tau^2=0; Chi^2=1.01, df=1(P=0.31); I^2=1.38%					
Test for overall effect: Z=0.79(P=0.43)					



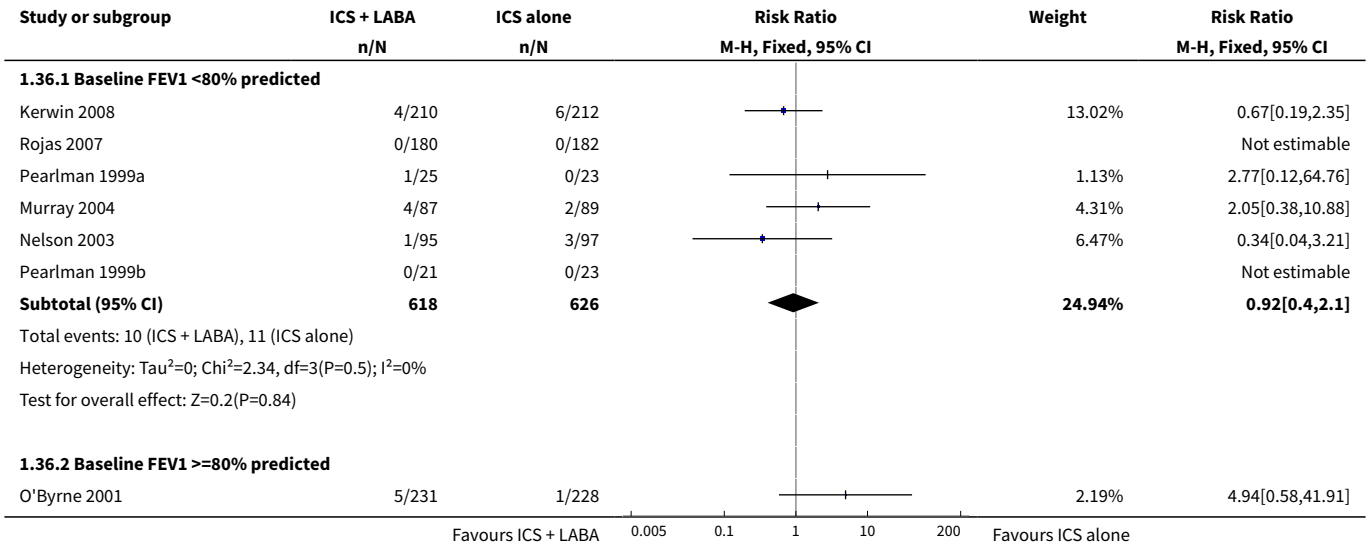


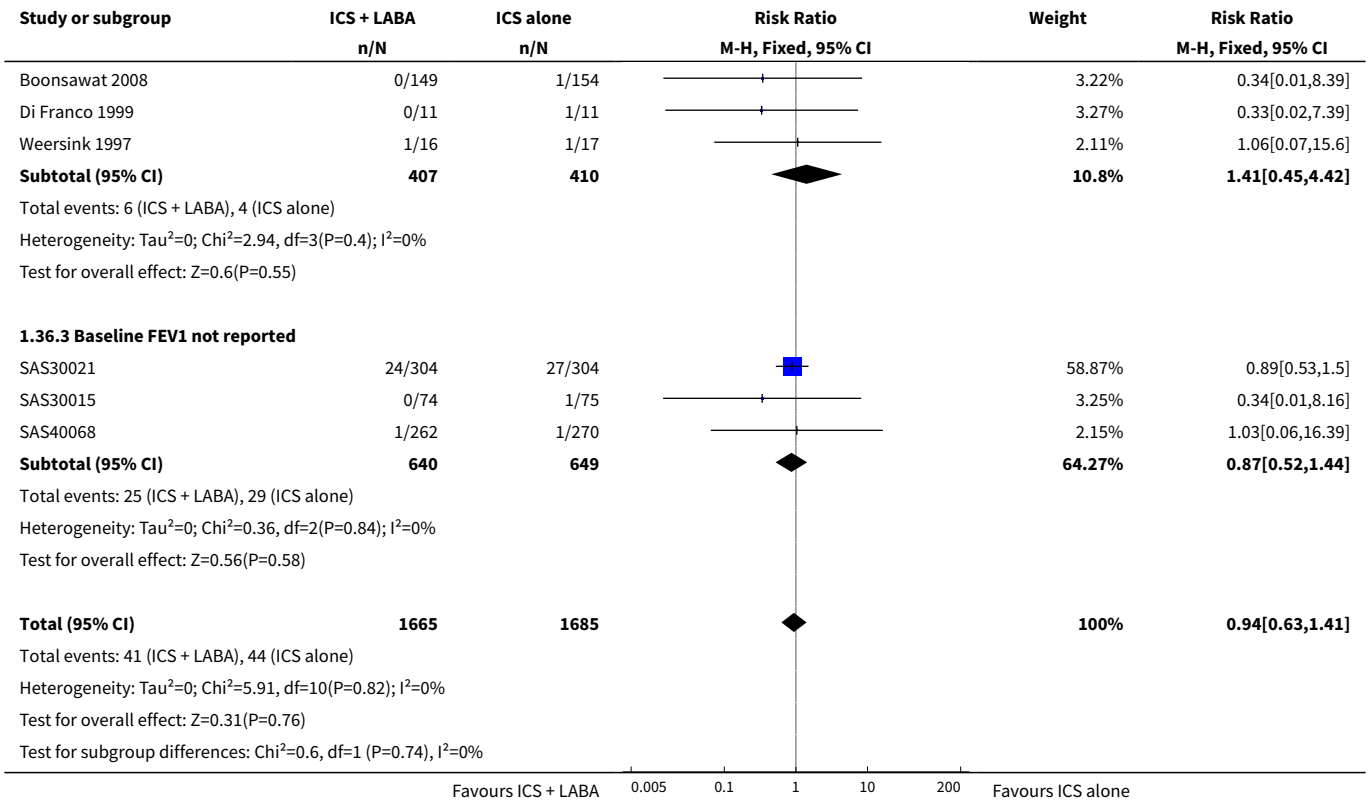
Analysis 1.35. Comparison 1 Addition of ICS + LABA versus same dose of ICS alone in steroid-naive patients as first line treatment, Outcome 35 Total withdrawals.



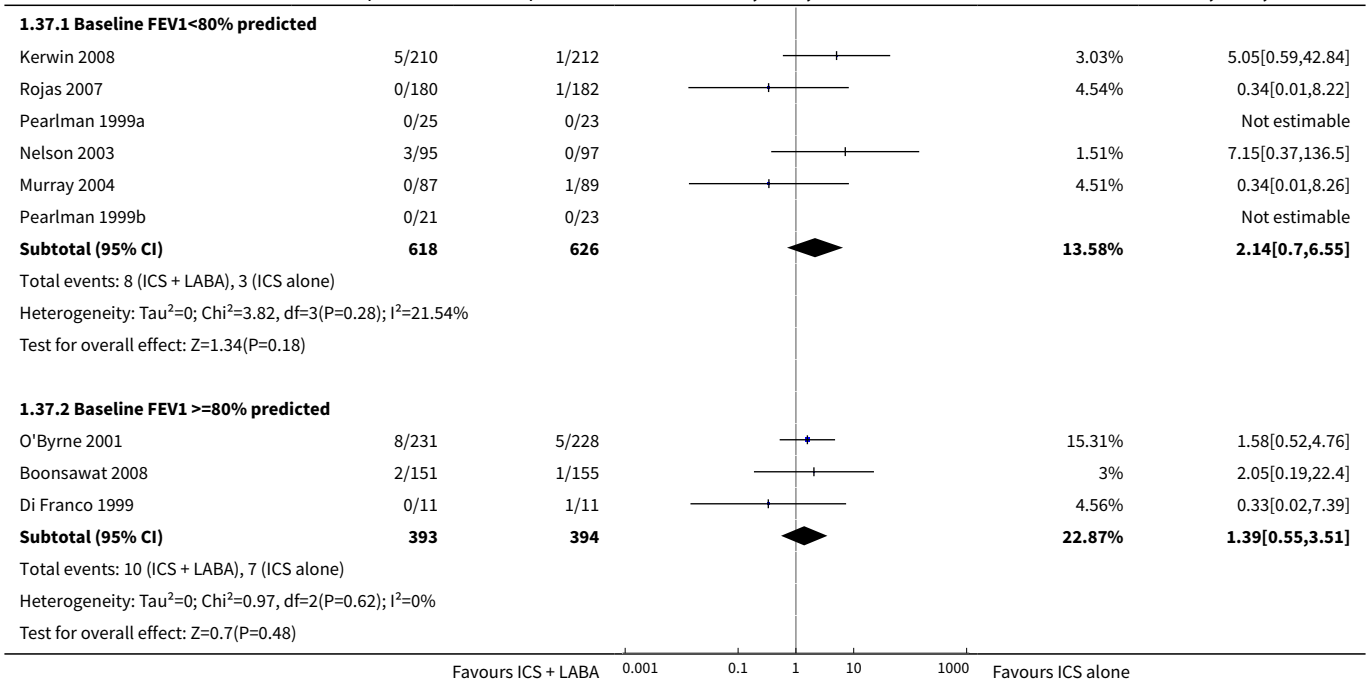


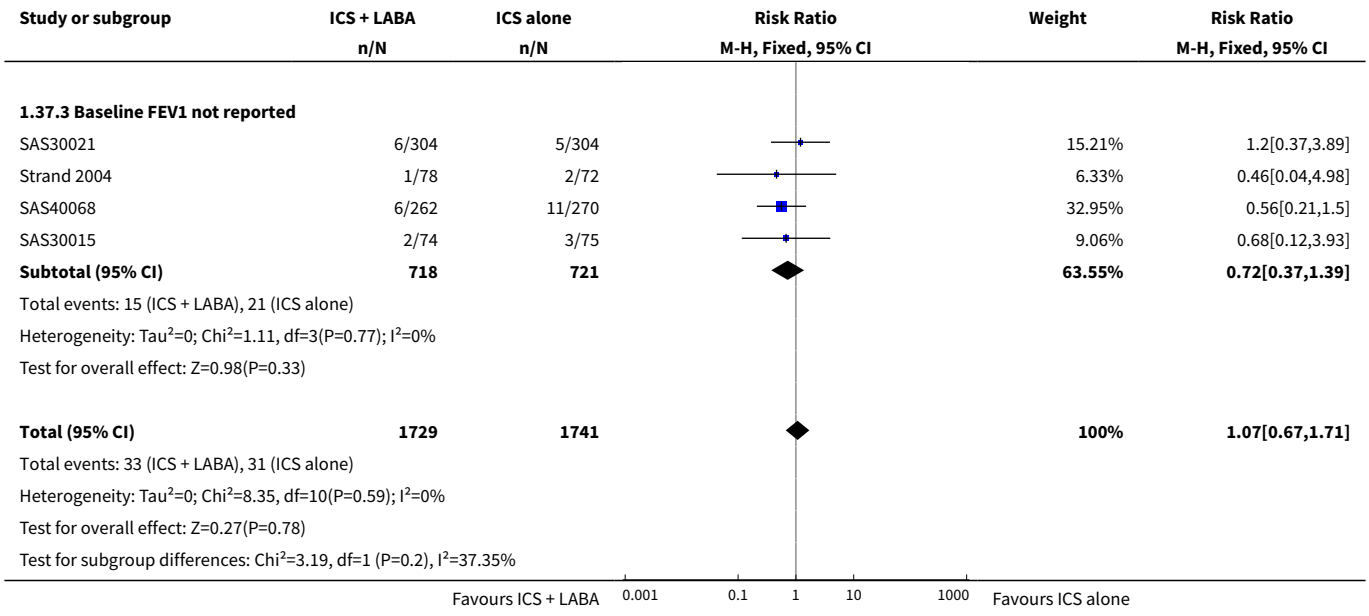
Analysis 1.36. Comparison 1 Addition of ICS + LABA versus same dose of ICS alone in steroid-naive patients as first line treatment, Outcome 36 # patients withdrawing due to poor asthma control or exacerbation.



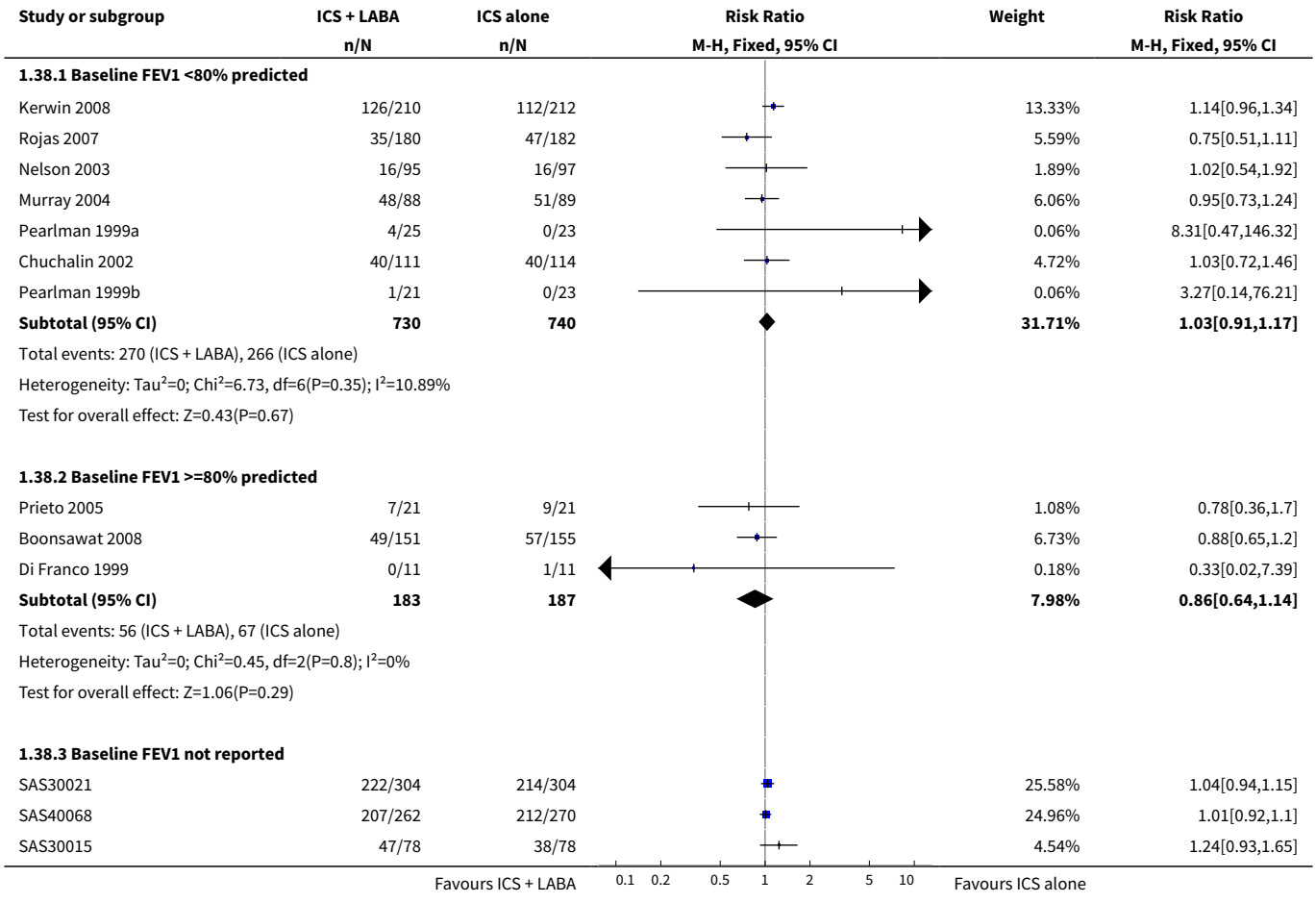


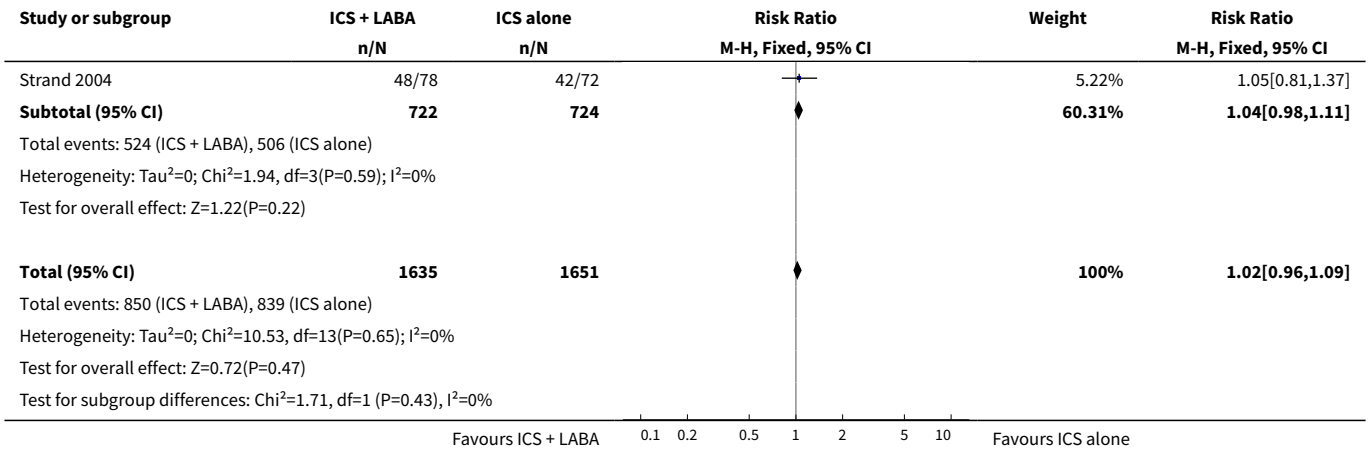
Analysis 1.37. Comparison 1 Addition of ICS + LABA versus same dose of ICS alone in steroid-naive patients as first line treatment, Outcome 37 # patient withdrawals due to adverse effects.



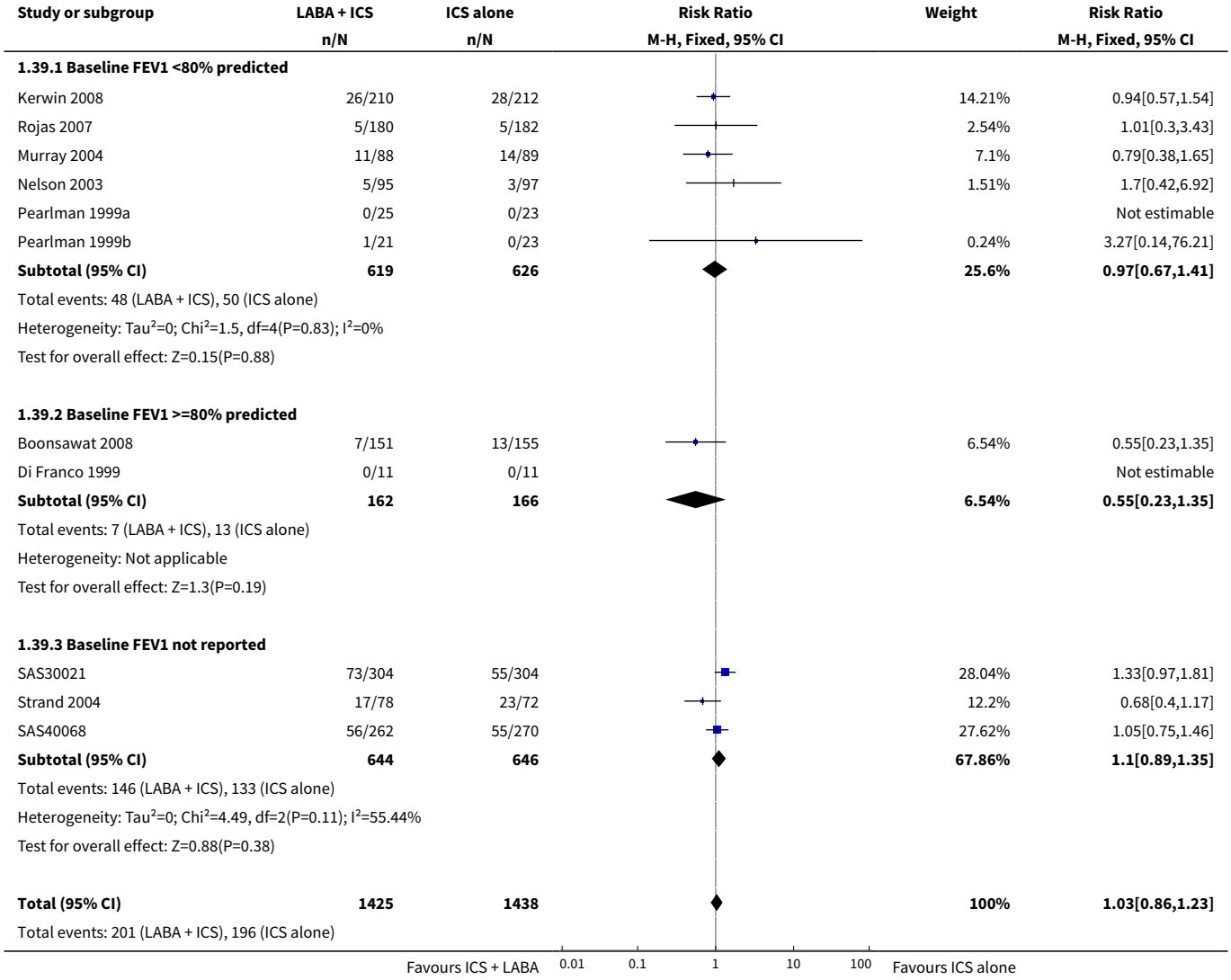


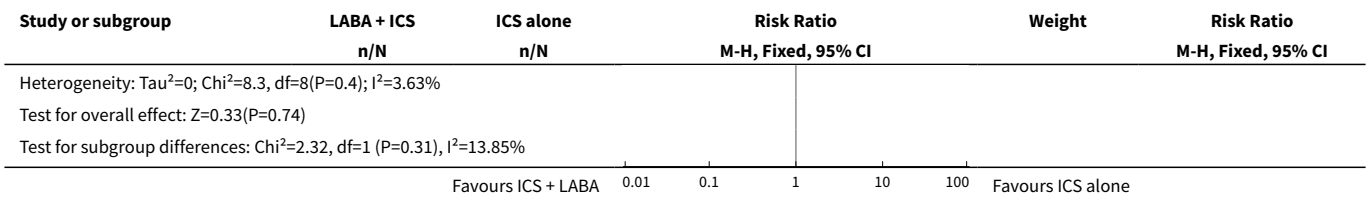
Analysis 1.38. Comparison 1 Addition of ICS + LABA versus same dose of ICS alone in steroid-naive patients as first line treatment, Outcome 38 # Patient with any adverse event.



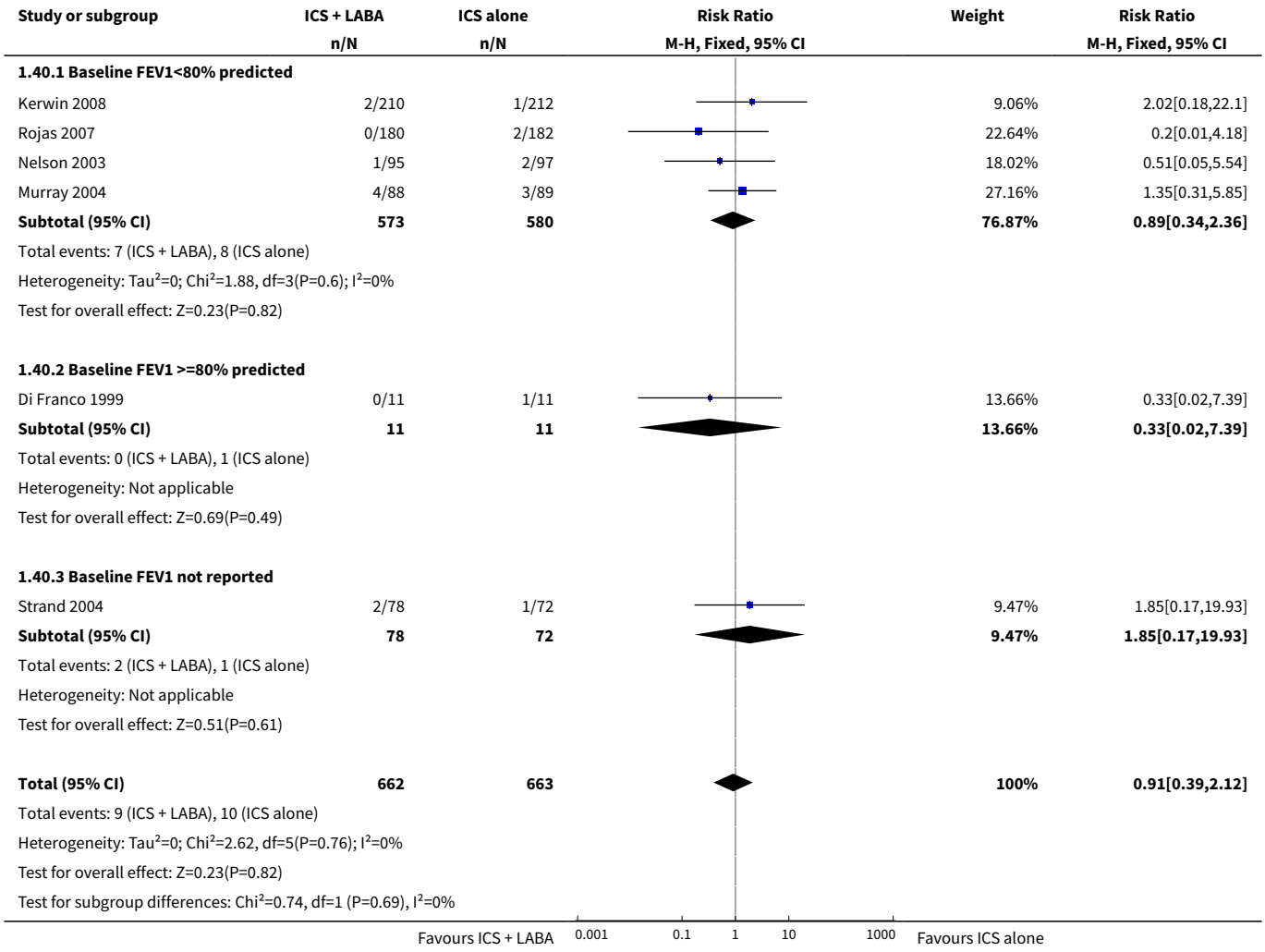


Analysis 1.39. Comparison 1 Addition of ICS + LABA versus same dose of ICS alone in steroid-naive patients as first line treatment, Outcome 39 # patients with headache.

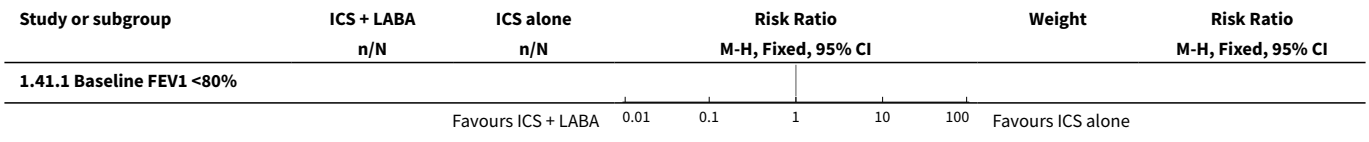


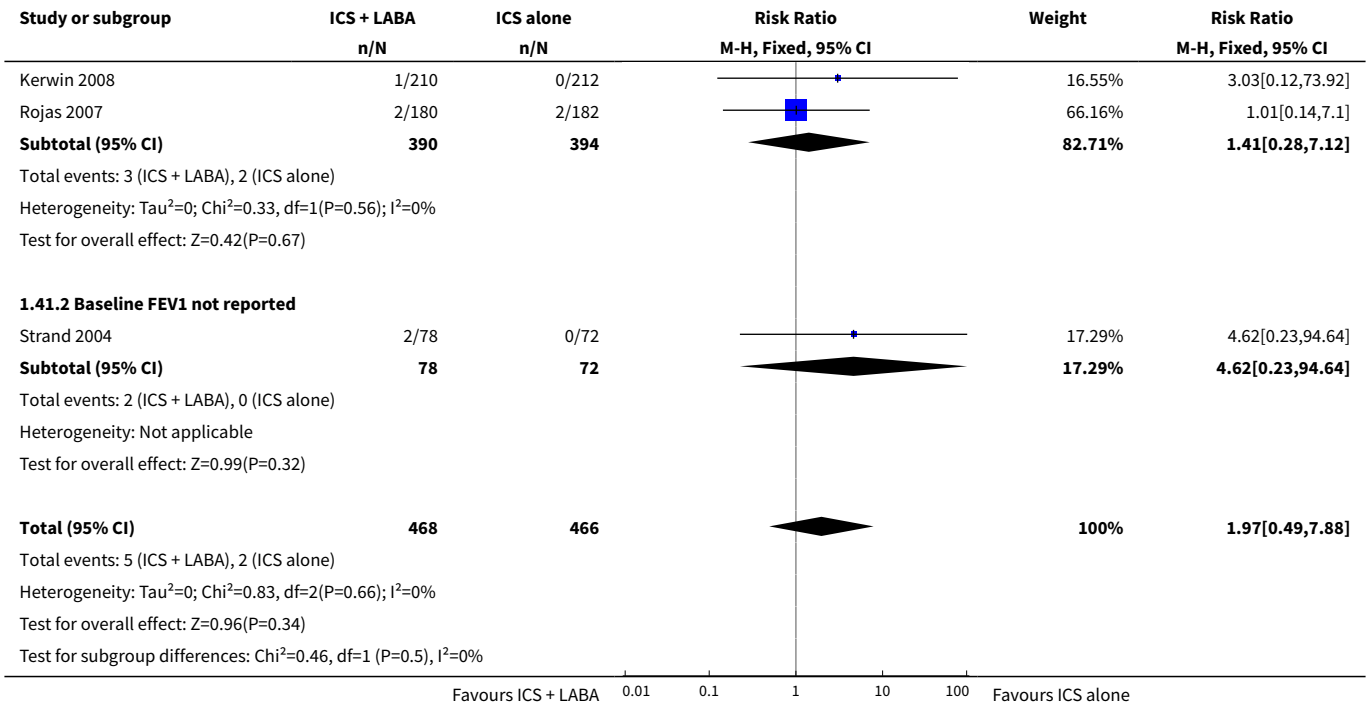


Analysis 1.40. Comparison 1 Addition of ICS + LABA versus same dose of ICS alone in steroid-naive patients as first line treatment, Outcome 40 # patients with oral thrush.

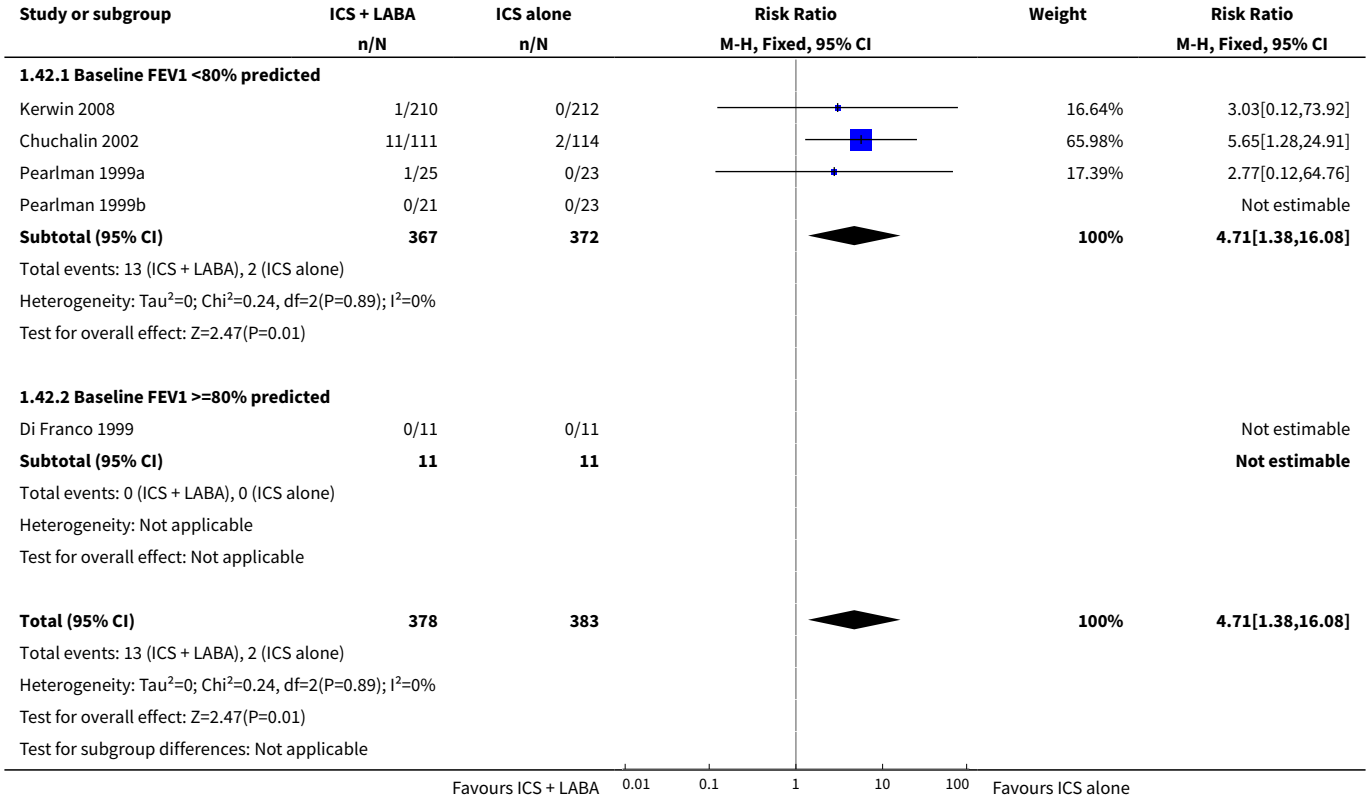


Analysis 1.41. Comparison 1 Addition of ICS + LABA versus same dose of ICS alone in steroid-naive patients as first line treatment, Outcome 41 # patients with hoarseness.



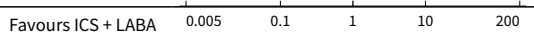


Analysis 1.42. Comparison 1 Addition of ICS + LABA versus same dose of ICS alone in steroid-naive patients as first line treatment, Outcome 42 # patients with tremor.



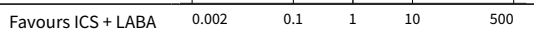
Analysis 1.43. Comparison 1 Addition of ICS + LABA versus same dose of ICS alone in steroid-naive patients as first line treatment, Outcome 43 # patients with tachycardia or palpitations.

Study or subgroup	LABA + ICS n/N	ICS alone n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
1.43.1 Baseline FEV1 <80% predicted					
Pearlman 1999a	1/25	0/23		100%	2.77[0.12,64.76]
Pearlman 1999b	0/21	0/23			Not estimable
Subtotal (95% CI)	**46**	**46**		**100%**	**2.77[0.12,64.76]**
Total events: 1 (LABA + ICS), 0 (ICS alone)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.63(P=0.53)					
1.43.2 Baseline FEV1 >=80% predicted					
Di Franco 1999	0/11	0/11			Not estimable
Subtotal (95% CI)	**11**	**11**			**Not estimable**
Total events: 0 (LABA + ICS), 0 (ICS alone)					
Heterogeneity: Not applicable					
Test for overall effect: Not applicable					
Total (95% CI)	**57**	**57**		**100%**	**2.77[0.12,64.76]**
Total events: 1 (LABA + ICS), 0 (ICS alone)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.63(P=0.53)					
Test for subgroup differences: Not applicable					



Analysis 1.44. Comparison 1 Addition of ICS + LABA versus same dose of ICS alone in steroid-naive patients as first line treatment, Outcome 44 # patients with adverse cardiovascular events.

Study or subgroup	ICS + LABA n/N	ICS alone n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
1.44.1 Baseline FEV1 <80%					
Pearlman 1999a	1/25	0/23		100%	2.77[0.12,64.76]
Pearlman 1999b	0/21	0/23			Not estimable
Subtotal (95% CI)	**46**	**46**		**100%**	**2.77[0.12,64.76]**
Total events: 1 (ICS + LABA), 0 (ICS alone)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.63(P=0.53)					
Total (95% CI)	**46**	**46**		**100%**	**2.77[0.12,64.76]**
Total events: 1 (ICS + LABA), 0 (ICS alone)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.63(P=0.53)					

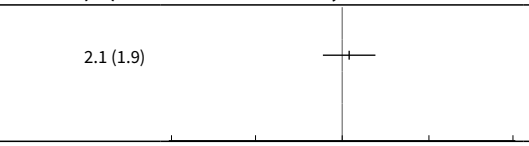


Analysis 1.45. Comparison 1 Addition of ICS + LABA versus same dose of ICS alone in steroid-naive patients as first line treatment, Outcome 45 Deaths.

Study or subgroup	ICS + LABA n/N	ICS alone n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
1.45.1 Baseline FEV1 <80% predicted					
Chuchalin 2002	0/111	0/114			Not estimable
Subtotal (95% CI)	**111**	**114**			**Not estimable**
Total events: 0 (ICS + LABA), 0 (ICS alone)					
Heterogeneity: Not applicable					
Test for overall effect: Not applicable					
1.45.2 Baseline FEV1 >=80% predicted					
Subtotal (95% CI)	**0**	**0**			**Not estimable**
Total events: 0 (ICS + LABA), 0 (ICS alone)					
Heterogeneity: Not applicable					
Test for overall effect: Not applicable					
Total (95% CI)	**111**	**114**			**Not estimable**
Total events: 0 (ICS + LABA), 0 (ICS alone)					
Heterogeneity: Not applicable					
Test for overall effect: Not applicable					
Test for subgroup differences: Not applicable					

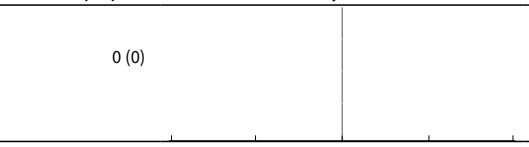
Analysis 1.46. Comparison 1 Addition of ICS + LABA versus same dose of ICS alone in steroid-naive patients as first line treatment, Outcome 46 Change in PC20 (methacholine) at 8 weeks.

Study or subgroup	ICS + LABA N	ICS + LABA Mean(SD)	ICS alone N	ICS alone Mean(SD)	Mean Difference Fixed, 95% CI	Mean Difference Fixed, 95% CI
1.46.1 Baseline FEV1 <80% predicted						
Weersink 1997	14	2.5 (2.3)	16	2.1 (1.9)		0.4[-1.11,1.91]
1.46.2 Baseline FEV1 >=80% predicted						



Analysis 1.47. Comparison 1 Addition of ICS + LABA versus same dose of ICS alone in steroid-naive patients as first line treatment, Outcome 47 PC20 (methacholine) at 8 weeks.

Study or subgroup	ICS + LABA N	ICS + LABA Mean(SD)	ICS alone N	ICS alone Mean(SD)	Mean Difference Fixed, 95% CI	Mean Difference Fixed, 95% CI
1.47.1 Baseline FEV1 <80% predicted						
Overbeek 2005	1	0 (0)	1	0 (0)		Not estimable
1.47.2 Baseline FEV1 >=80% predicted						



Comparison 2. Addition of ICS + LABA versus increased dose of ICS alone in steroid-naive patients as first line treatment

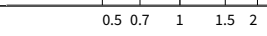
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 # patients with exacerbations requiring systemic steroids	3	2709	Risk Ratio (M-H, Fixed, 95% CI)	1.24 [1.00, 1.53]
1.1 Baseline FEV1 >=80% predicted	3	2709	Risk Ratio (M-H, Fixed, 95% CI)	1.24 [1.00, 1.53]
1.2 Baseline FEV1<80% predicted	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
1.3 Baseline FEV1 predicted unclear	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
2 # patients with exacerbations requiring hospitalisation	4	2864	Risk Ratio (M-H, Fixed, 95% CI)	1.00 [0.31, 3.25]
2.1 Baseline FEV1 >=80% predicted	4	2864	Risk Ratio (M-H, Fixed, 95% CI)	1.00 [0.31, 3.25]
2.2 Baseline FEV1 <80% predicted	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
2.3 Baseline FEV1 not reported	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
3 Change in FEV1 at endpoint	2		L (Random, 95% CI)	0.07 [-0.02, 0.15]
3.1 Baseline FEV1 >=80% predicted	2		L (Random, 95% CI)	0.07 [-0.02, 0.15]
3.2 Baseline FEV1 <80% predicted	0		L (Random, 95% CI)	0.0 [0.0, 0.0]
3.3 Baseline FEV1 not reported	0		L (Random, 95% CI)	0.0 [0.0, 0.0]
4 Change in FEV1 predicted at endpoint	1		L (Random, 95% CI)	Totals not selected
4.1 Baseline FEV1 >=80% predicted	1		L (Random, 95% CI)	0.0 [0.0, 0.0]
4.2 Baseline FEV1 <80% predicted	0		L (Random, 95% CI)	0.0 [0.0, 0.0]
4.3 Baseline FEV1 not reported	0		L (Random, 95% CI)	0.0 [0.0, 0.0]
5 Morning PEF at endpoint	1		L/min (Random, 95% CI)	Totals not selected
5.1 Baseline FEV1 >=80% predicted	1		L/min (Random, 95% CI)	0.0 [0.0, 0.0]
5.2 Baseline FEV1 <80% predicted	0		L/min (Random, 95% CI)	0.0 [0.0, 0.0]
5.3 Baseline FEV1 not reported	0		L/min (Random, 95% CI)	0.0 [0.0, 0.0]
6 Change in morning PEF at endpoint	3	2642	L/min (Random, 95% CI)	13.27 [-8.60, 35.15]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
6.1 Baseline FEV1 >=80% predicted	3	2642	L/min (Random, 95% CI)	13.27 [-8.60, 35.15]
6.2 Baseline FEV1 <80% predicted	0	0	L/min (Random, 95% CI)	0.0 [0.0, 0.0]
6.3 Baseline FEV1 not reported	0	0	L/min (Random, 95% CI)	0.0 [0.0, 0.0]
7 Change in morning PEF predicted at endpoint	1		% (Fixed, 95% CI)	Totals not selected
7.1 Baseline FEV1 >=80% predicted	1		% (Fixed, 95% CI)	0.0 [0.0, 0.0]
7.2 Baseline FEV1 <80% predicted	0		% (Fixed, 95% CI)	0.0 [0.0, 0.0]
7.3 Baseline FEV1 not reported	0		% (Fixed, 95% CI)	0.0 [0.0, 0.0]
8 Change in evening PEF at endpoint	2		L/min (Random, 95% CI)	15.57 [3.80, 27.35]
8.1 Baseline FEV1 >=80% predicted	2		L/min (Random, 95% CI)	15.57 [3.80, 27.35]
8.2 Baseline FEV1 <80% predicted	0		L/min (Random, 95% CI)	0.0 [0.0, 0.0]
8.3 Baseline FEV1 not reported	0		L/min (Random, 95% CI)	0.0 [0.0, 0.0]
9 Change in evening PEF predicted at endpoint	1		% (Random, 95% CI)	Totals not selected
9.1 Baseline FEV1 >=80% predicted	1		% (Random, 95% CI)	0.0 [0.0, 0.0]
9.2 Baseline FEV1 <80% predicted	0		% (Random, 95% CI)	0.0 [0.0, 0.0]
9.3 Baseline FEV1 not reported	0		% (Random, 95% CI)	0.0 [0.0, 0.0]
10 % symptom-free days at endpoint	1		Mean Difference (IV, Random, 95% CI)	Totals not selected
10.1 Baseline FEV1 >= 80 % predicted	1		Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]
10.2 Baseline FEV1 61%-79% predicted	0		Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]
10.3 Baseline FEV1 % predicted not reported	0		Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]
11 Absolute (or %) change in # rescue inhalations (per 24 hrs) at endpoint	1		Std. Mean Difference (IV, Random, 95% CI)	Totals not selected
11.1 Baseline FEV1 >= 80% predicted	1		Std. Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]
11.2 Baseline FEV1 61%-79% predicted	0		Std. Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
11.3 Baseline FEV1 <= 60% predicted	0		Std. Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]
11.4 Baseline FEV1 not reported	0		Std. Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]
12 Serious adverse events	4	2864	Risk Ratio (M-H, Fixed, 95% CI)	1.03 [0.63, 1.69]
12.1 Baseline FEV1 >= 80% predicted	4	2864	Risk Ratio (M-H, Fixed, 95% CI)	1.03 [0.63, 1.69]
13 Total # withdrawals	4	2881	Risk Ratio (M-H, Fixed, 95% CI)	1.31 [1.07, 1.59]
13.1 Baseline FEV1 >= 80% predicted	4	2881	Risk Ratio (M-H, Fixed, 95% CI)	1.31 [1.07, 1.59]
14 # withdrawals due to adverse events	3	2691	Risk Ratio (M-H, Fixed, 95% CI)	1.00 [0.54, 1.84]
14.1 Baseline FEV1 >= 80% predicted	3	2691	Risk Ratio (M-H, Fixed, 95% CI)	1.00 [0.54, 1.84]
15 # withdrawals due to poor asthma control or exacerbation	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
15.1 Baseline FEV1 >= 80% predicted	1		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
16 # patients with headache	3	2674	Risk Ratio (M-H, Fixed, 95% CI)	0.97 [0.80, 1.17]
16.1 Baseline FEV1 >= 80% predicted	3	2674	Risk Ratio (M-H, Fixed, 95% CI)	0.97 [0.80, 1.17]
17 # patients with hoarseness	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
17.1 Baseline FEV1 >/=80% predicted	1		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
18 Change in PC20	1		Doubl'g doses (Fixed, 95% CI)	Totals not selected
18.1 Baseline FEV1 >= 80% predicted	1		Doubl'g doses (Fixed, 95% CI)	0.0 [0.0, 0.0]
18.2 Baseline FEV1 61%-79 % predicted	0		Doubl'g doses (Fixed, 95% CI)	0.0 [0.0, 0.0]
18.3 Baseline FEV1 <= 60% predicted	0		Doubl'g doses (Fixed, 95% CI)	0.0 [0.0, 0.0]
18.4 Baseline FEV1 not reported	0		Doubl'g doses (Fixed, 95% CI)	0.0 [0.0, 0.0]
19 Growth (paediatric data)	1		cm (Random, 95% CI)	Totals not selected

Analysis 2.1. Comparison 2 Addition of ICS + LABA versus increased dose of ICS alone in steroid-naive patients as first line treatment, Outcome 1 # patients with exacerbations requiring systemic steroids.

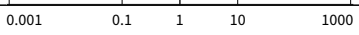
Study or subgroup	ICS + LABA n/N	ICS alone n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
2.1.1 Baseline FEV1 >=80% predicted					
Chuchalin 2008	100/972	79/970		62.92%	1.26[0.95,1.67]
SAM40036	8/288	11/289		8.74%	0.73[0.3,1.79]
Sorkness 2007	47/94	36/96		28.34%	1.33[0.96,1.85]
Subtotal (95% CI)	**1354**	**1355**		**100%**	**1.24[1,1.53]**
Total events: 155 (ICS + LABA), 126 (ICS alone)					
Heterogeneity: Tau^2=0; Chi^2=1.56, df=2(P=0.46); I^2=0%					
Test for overall effect: Z=1.96(P=0.05)					
2.1.2 Baseline FEV1<80% predicted					
Subtotal (95% CI)	**0**	**0**			**Not estimable**
Total events: 0 (ICS + LABA), 0 (ICS alone)					
Heterogeneity: Not applicable					
Test for overall effect: Not applicable					
2.1.3 Baseline FEV1 predicted unclear					
Subtotal (95% CI)	**0**	**0**			**Not estimable**
Total events: 0 (ICS + LABA), 0 (ICS alone)					
Heterogeneity: Not applicable					
Test for overall effect: Not applicable					
Total (95% CI)	**1354**	**1355**		**100%**	**1.24[1,1.53]**
Total events: 155 (ICS + LABA), 126 (ICS alone)					
Heterogeneity: Tau^2=0; Chi^2=1.56, df=2(P=0.46); I^2=0%					
Test for overall effect: Z=1.96(P=0.05)					
Test for subgroup differences: Chi^2=0, df=1 (P<0.0001), I^2=100%					



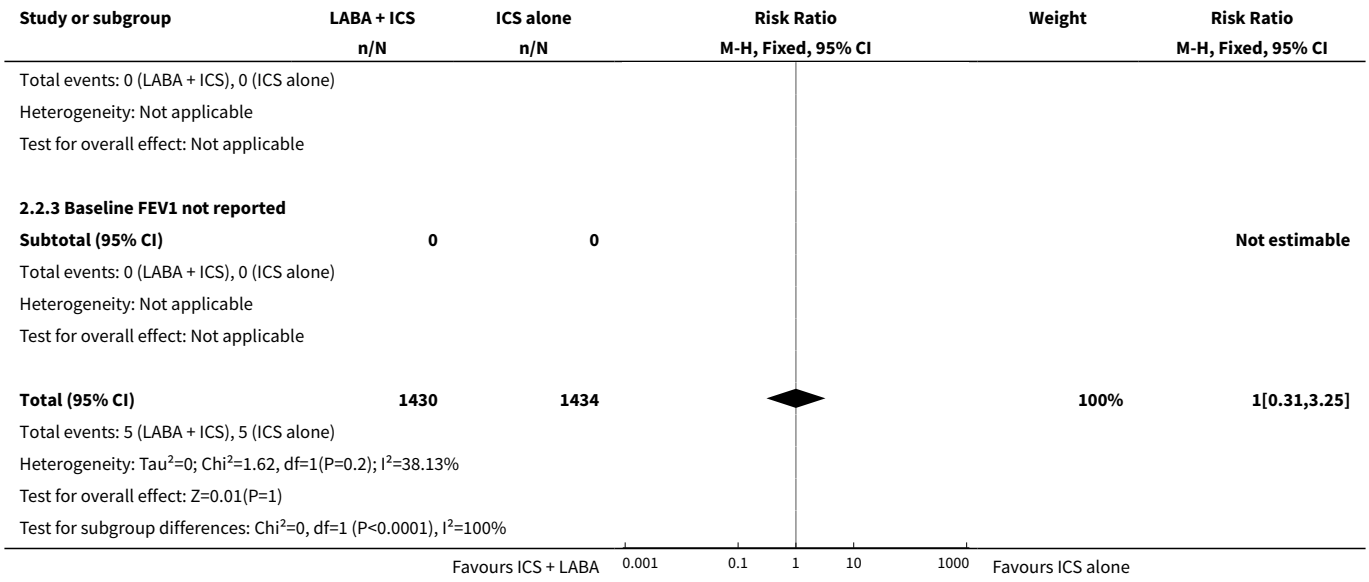
Favours ICS + LABA — Favours ICS alone

Analysis 2.2. Comparison 2 Addition of ICS + LABA versus increased dose of ICS alone in steroid-naive patients as first line treatment, Outcome 2 # patients with exacerbations requiring hospitalisation.

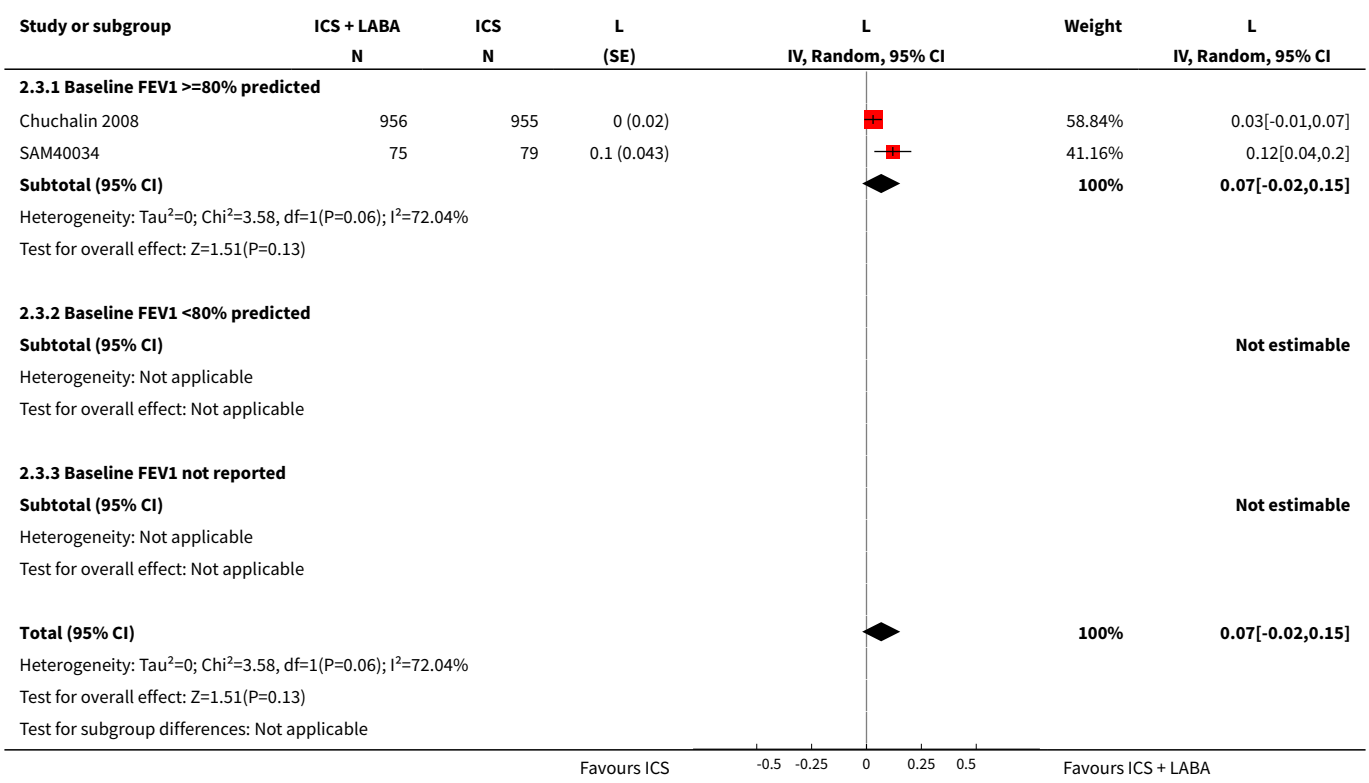
Study or subgroup	LABA + ICS n/N	ICS alone n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
2.2.1 Baseline FEV1 >=80% predicted					
SAM40036	0/288	0/289			Not estimable
Chuchalin 2008	3/973	5/970		91.01%	0.6[0.14,2.5]
SAM40034	0/75	0/79			Not estimable
Sorkness 2007	2/94	0/96		8.99%	5.11[0.25,104.94]
Subtotal (95% CI)	**1430**	**1434**		**100%**	**1[0.31,3.25]**
Total events: 5 (LABA + ICS), 5 (ICS alone)					
Heterogeneity: Tau^2=0; Chi^2=1.62, df=1(P=0.2); I^2=38.13%					
Test for overall effect: Z=0.01(P=1)					
2.2.2 Baseline FEV1 <80% predicted					
Subtotal (95% CI)	**0**	**0**			**Not estimable**



Favours ICS + LABA — Favours ICS alone

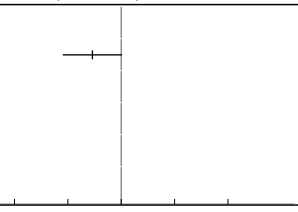


Analysis 2.3. Comparison 2 Addition of ICS + LABA versus increased dose of ICS alone in steroid-naive patients as first line treatment, Outcome 3 Change in FEV1 at endpoint.



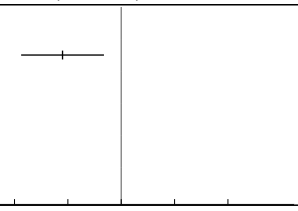
Analysis 2.4. Comparison 2 Addition of ICS + LABA versus increased dose of ICS alone in steroid-naive patients as first line treatment, Outcome 4 Change in FEV1 predicted at endpoint.

Study or subgroup	ICS + LABA N	ICS N	L (SE)	L IV, Random, 95% CI	L IV, Random, 95% CI
2.4.1 Baseline FEV1 >=80% predicted					
Sorkness 2007	81	86	-2.7 (1.416)		-2.7[-5.47,0.07]
2.4.2 Baseline FEV1 <80% predicted					
2.4.3 Baseline FEV1 not reported					



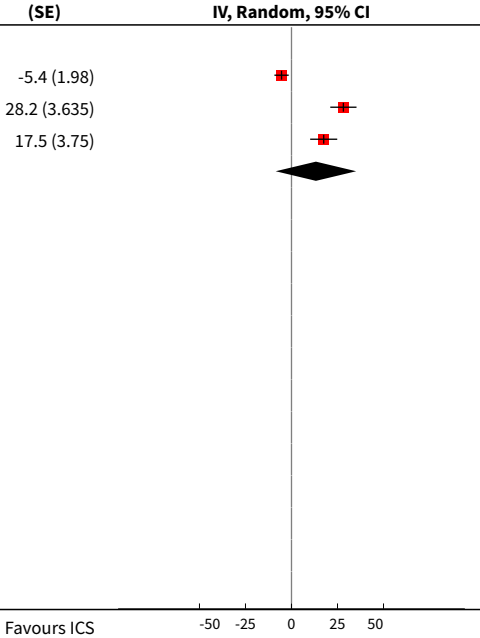
Analysis 2.5. Comparison 2 Addition of ICS + LABA versus increased dose of ICS alone in steroid-naive patients as first line treatment, Outcome 5 Morning PEF at endpoint.

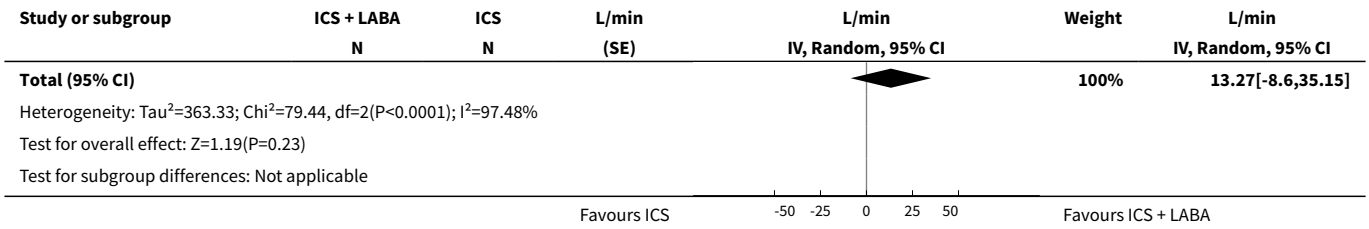
Study or subgroup	ICS + LABA N	ICS N	L/min (SE)	L/min IV, Random, 95% CI	L/min IV, Random, 95% CI
2.5.1 Baseline FEV1 >=80% predicted					
Chuchalin 2008	956	955	-5.5 (1.98)		-5.5[-9.38,-1.62]
2.5.2 Baseline FEV1 <80% predicted					
2.5.3 Baseline FEV1 not reported					



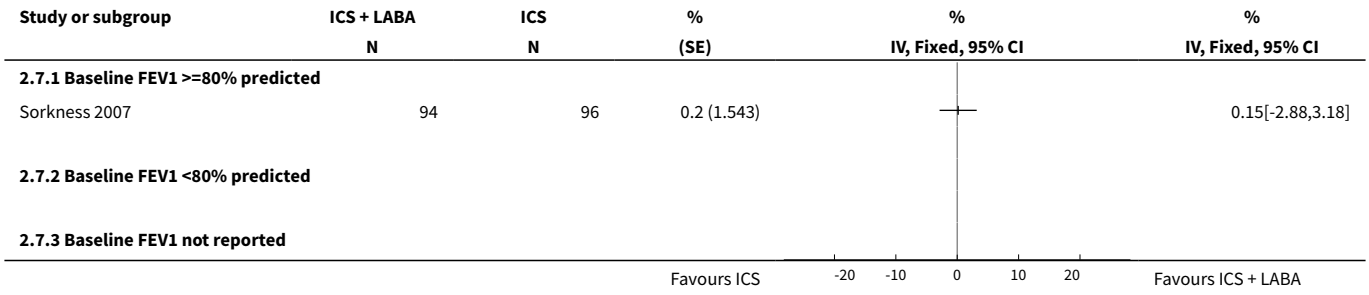
Analysis 2.6. Comparison 2 Addition of ICS + LABA versus increased dose of ICS alone in steroid-naive patients as first line treatment, Outcome 6 Change in morning PEF at endpoint.

Study or subgroup	ICS + LABA N	ICS N	L/min (SE)	L/min IV, Random, 95% CI	Weight	L/min IV, Random, 95% CI
2.6.1 Baseline FEV1 >=80% predicted						
Chuchalin 2008	956	955	-5.4 (1.98)		33.92%	-5.4[-9.28,-1.52]
SAM40034	75	79	28.2 (3.635)		33.08%	28.2[21.08,35.32]
SAM40036	288	289	17.5 (3.75)		33%	17.5[10.15,24.85]
Subtotal (95% CI)					**100%**	**13.27[-8.6,35.15]**
Heterogeneity: Tau²=363.33; Chi²=79.44, df=2(P<0.0001); I²=97.48%						
Test for overall effect: Z=1.19(P=0.23)						
2.6.2 Baseline FEV1 <80% predicted						
Subtotal (95% CI)						**Not estimable**
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						
2.6.3 Baseline FEV1 not reported						
Subtotal (95% CI)						**Not estimable**
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						

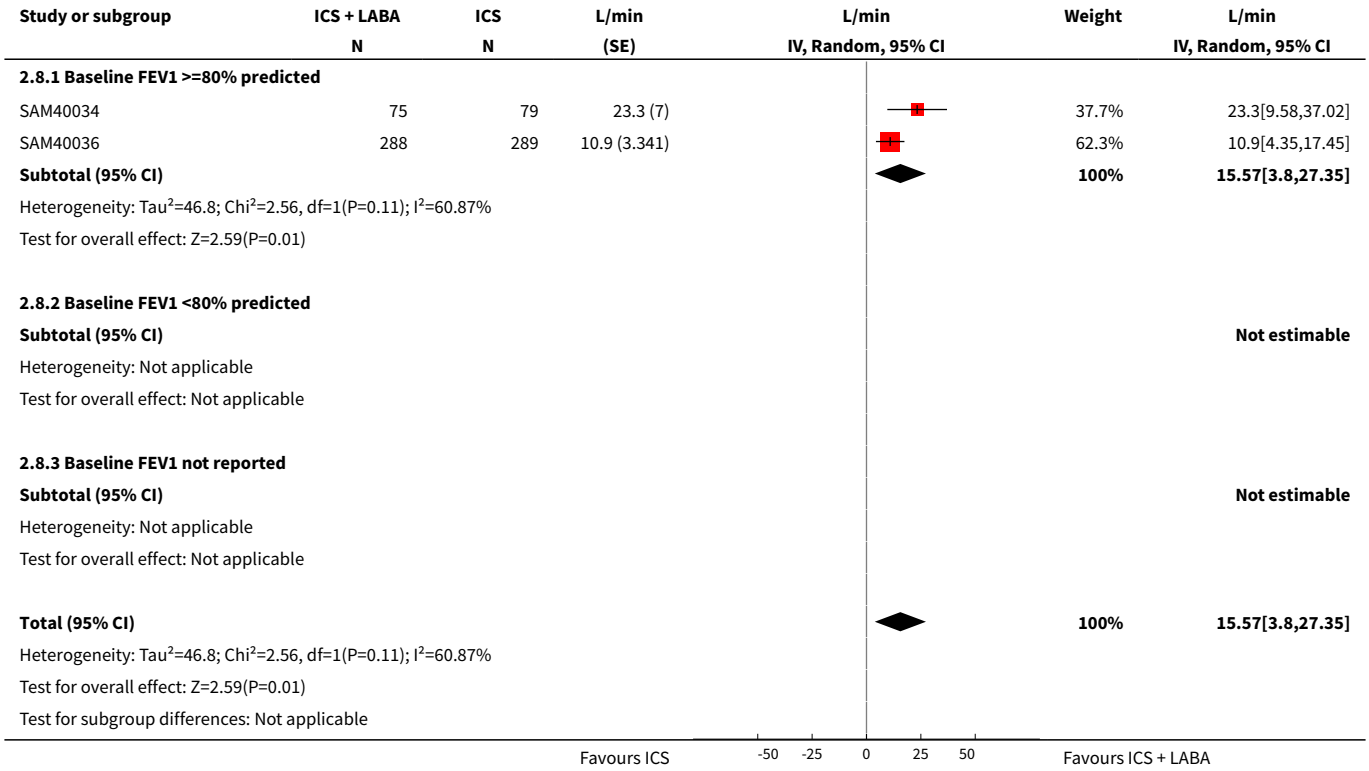




Analysis 2.7. Comparison 2 Addition of ICS + LABA versus increased dose of ICS alone in steroid-naive patients as first line treatment, Outcome 7 Change in morning PEF predicted at endpoint.

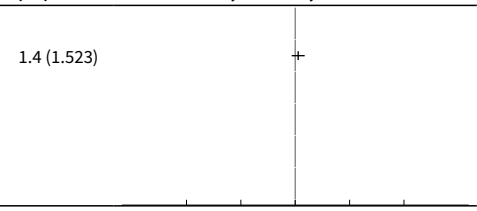


Analysis 2.8. Comparison 2 Addition of ICS + LABA versus increased dose of ICS alone in steroid-naive patients as first line treatment, Outcome 8 Change in evening PEF at endpoint.



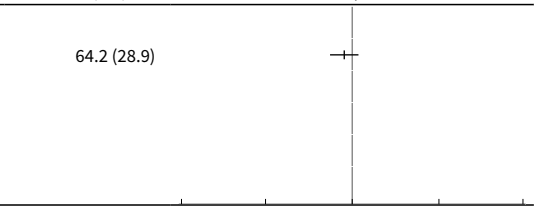
Analysis 2.9. Comparison 2 Addition of ICS + LABA versus increased dose of ICS alone in steroid-naive patients as first line treatment, Outcome 9 Change in evening PEF predicted at endpoint.

Study or subgroup	ICS + LABA N	ICS N	% (SE)	% IV, Random, 95% CI	% IV, Random, 95% CI
2.9.1 Baseline FEV1 >=80% predicted					
Sorkness 2007	94	96	1.4 (1.523)		1.36[-1.63,4.35]
2.9.2 Baseline FEV1 <80% predicted					
2.9.3 Baseline FEV1 not reported					



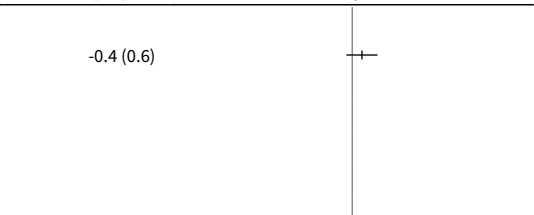
Analysis 2.10. Comparison 2 Addition of ICS + LABA versus increased dose of ICS alone in steroid-naive patients as first line treatment, Outcome 10 % symptom-free days at endpoint.

Study or subgroup	LABA + ICS N	LABA + ICS Mean(SD)	Increased ICS N	Increased ICS Mean(SD)	Mean Difference Random, 95% CI	Mean Difference Random, 95% CI
2.10.1 Baseline FEV1 >= 80 % predicted						
Sorkness 2007	96	59.6 (28.7)	94	64.2 (28.9)		-4.6[-12.79,3.59]
2.10.2 Baseline FEV1 61%-79% predicted						
2.10.3 Baseline FEV1 % predicted not reported						

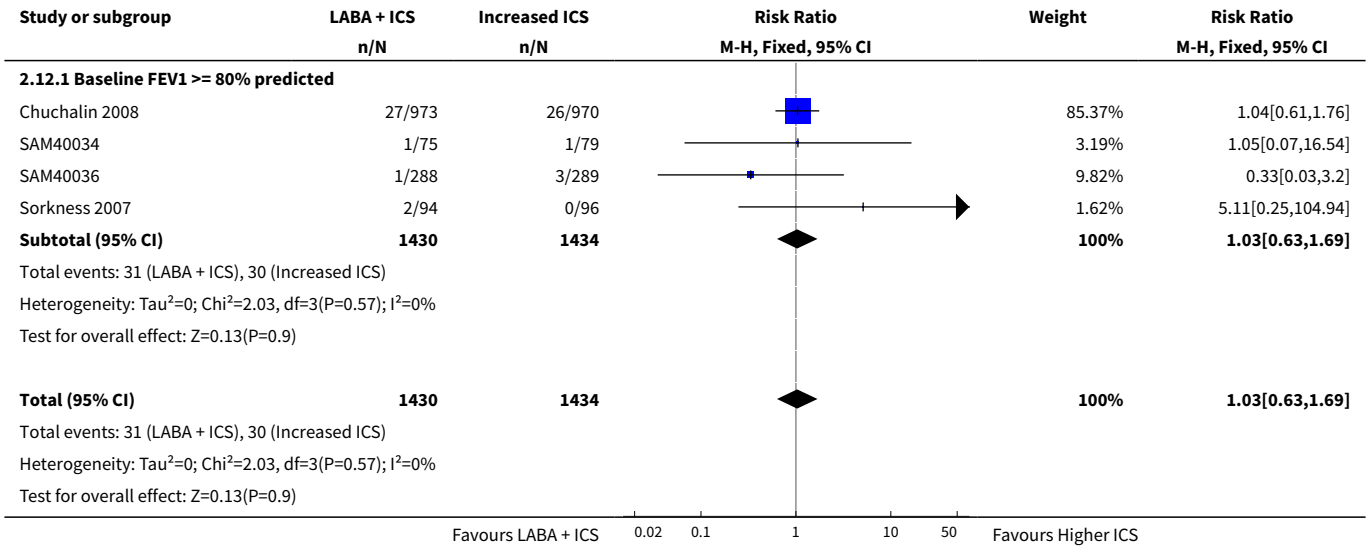


Analysis 2.11. Comparison 2 Addition of ICS + LABA versus increased dose of ICS alone in steroid-naive patients as first line treatment, Outcome 11 Absolute (or %) change in # rescue inhalations (per 24 hrs) at endpoint.

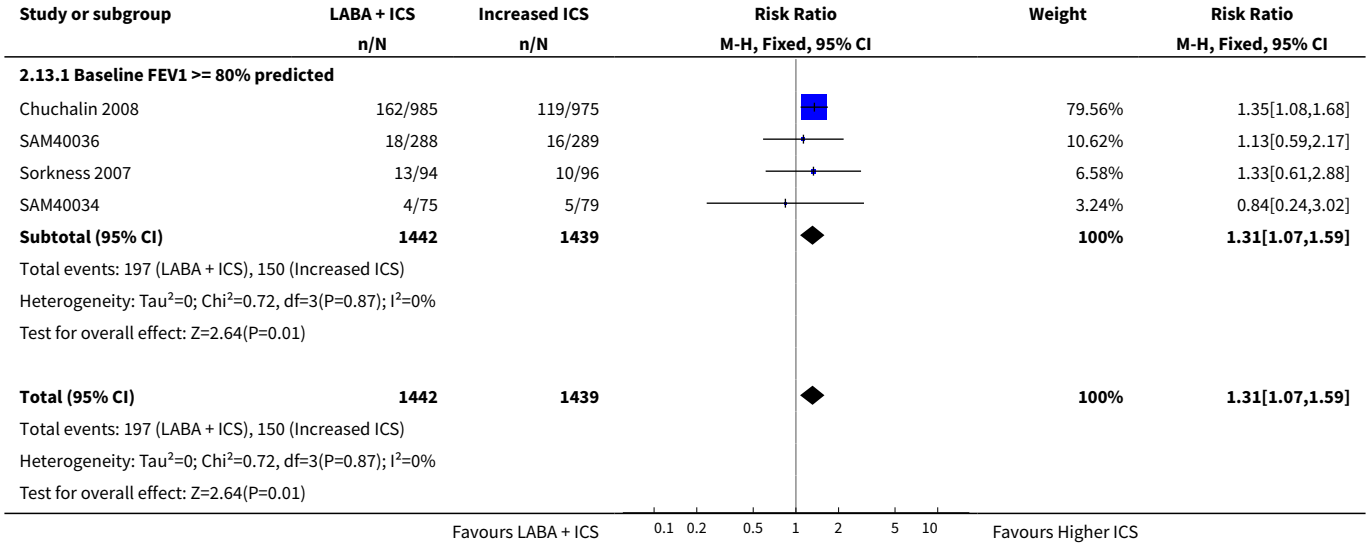
Study or subgroup	LABA + ICS N	LABA + ICS Mean(SD)	Increased ICS N	Increased ICS Mean(SD)	Std. Mean Difference Random, 95% CI	Std. Mean Difference Random, 95% CI
2.11.1 Baseline FEV1 >= 80% predicted						
Chuchalin 2008	957	-0.4 (0.5)	955	-0.4 (0.6)		0.06[-0.03,0.15]
2.11.2 Baseline FEV1 61%-79% predicted						
2.11.3 Baseline FEV1 <= 60% predicted						
2.11.4 Baseline FEV1 not reported						



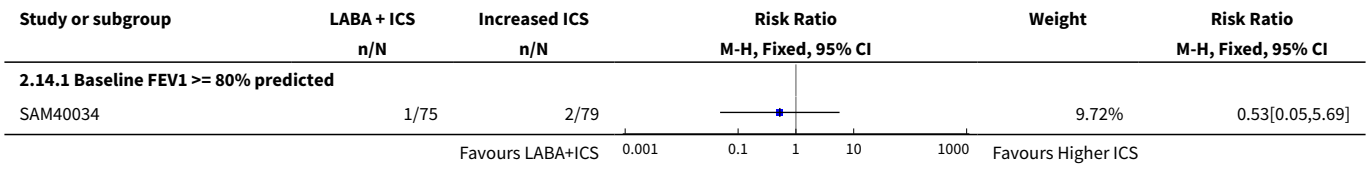
Analysis 2.12. Comparison 2 Addition of ICS + LABA versus increased dose of ICS alone in steroid-naive patients as first line treatment, Outcome 12 Serious adverse events.

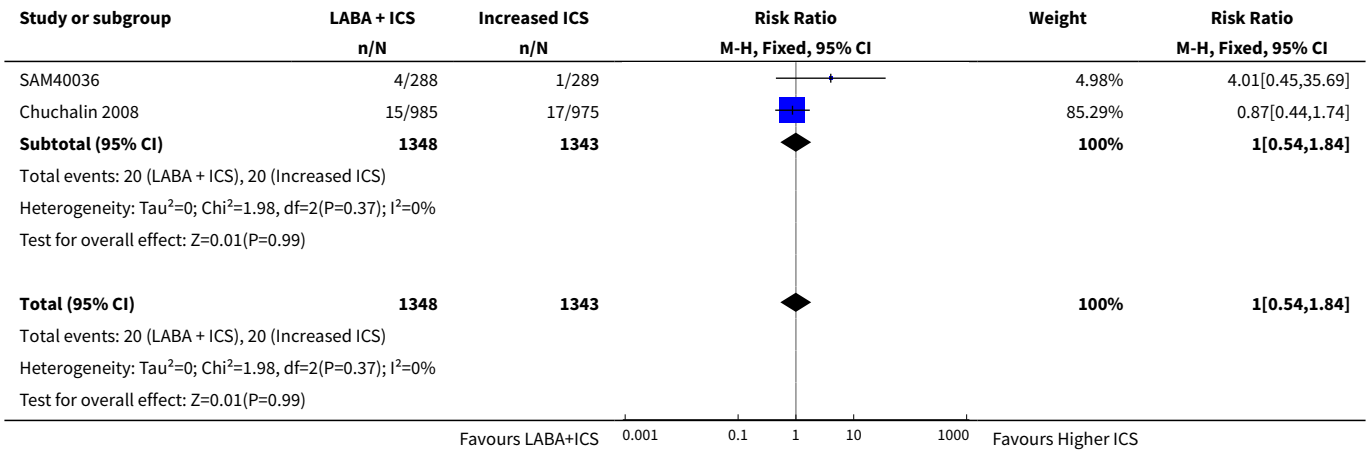


Analysis 2.13. Comparison 2 Addition of ICS + LABA versus increased dose of ICS alone in steroid-naive patients as first line treatment, Outcome 13 Total # withdrawals.

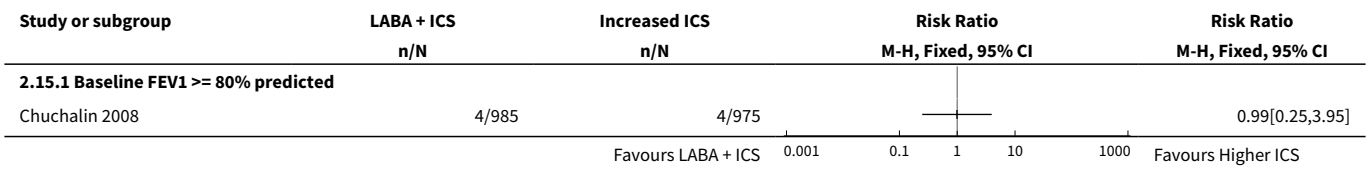


Analysis 2.14. Comparison 2 Addition of ICS + LABA versus increased dose of ICS alone in steroid-naive patients as first line treatment, Outcome 14 # withdrawals due to adverse events.

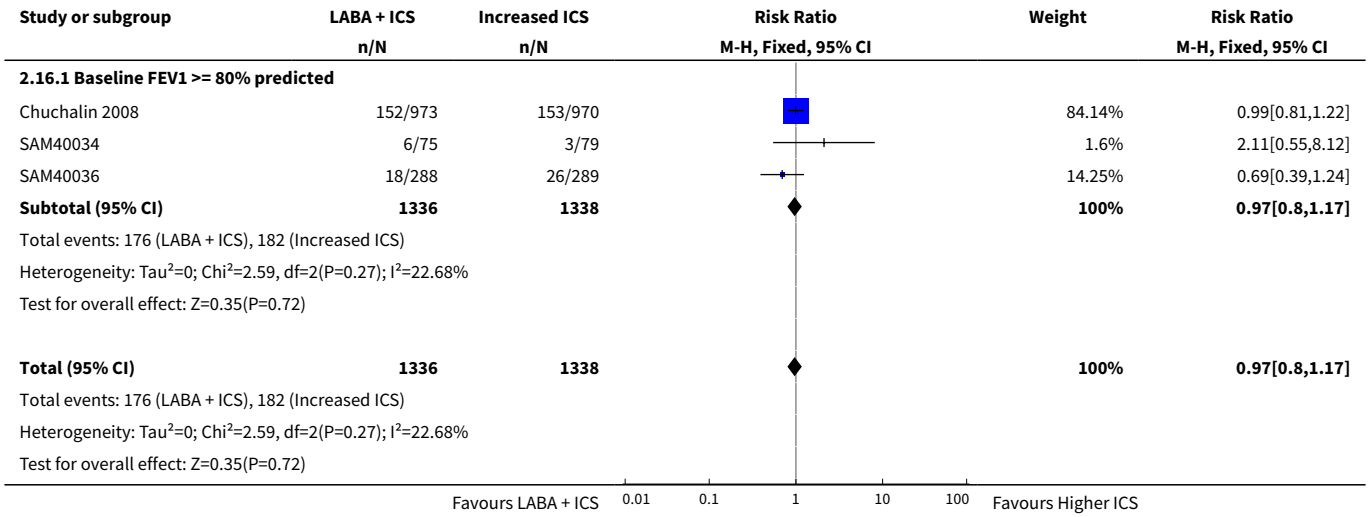




Analysis 2.15. Comparison 2 Addition of ICS + LABA versus increased dose of ICS alone in steroid-naive patients as first line treatment, Outcome 15 # withdrawals due to poor asthma control or exacerbation.

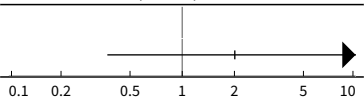


Analysis 2.16. Comparison 2 Addition of ICS + LABA versus increased dose of ICS alone in steroid-naive patients as first line treatment, Outcome 16 # patients with headache.



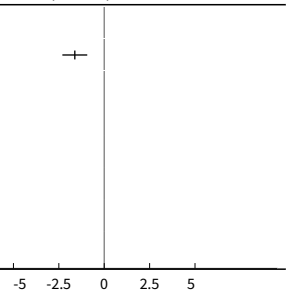
Analysis 2.17. Comparison 2 Addition of ICS + LABA versus increased dose of ICS alone in steroid-naive patients as first line treatment, Outcome 17 # patients with hoarseness.

Study or subgroup	LABA + ICS n/N	Increased ICS n/N	Risk Ratio M-H, Fixed, 95% CI	Risk Ratio M-H, Fixed, 95% CI
2.17.1 Baseline FEV1 >/=80% predicted				
SAM40036	4/288	2/289		2.01[0.37,10.87]



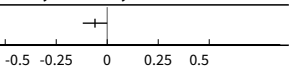
Analysis 2.18. Comparison 2 Addition of ICS + LABA versus increased dose of ICS alone in steroid-naive patients as first line treatment, Outcome 18 Change in PC20.

Study or subgroup	LABA + ICS N	Increased ICS N	Doubl'g doses (SE)	Doubl'g doses IV, Fixed, 95% CI	Doubl'g doses IV, Fixed, 95% CI
2.18.1 Baseline FEV1 >= 80% predicted					
Sorkness 2007	81	86	-1.6 (0.35)		-1.62[-2.31,-0.93]
2.18.2 Baseline FEV1 61%-79 % predicted					
2.18.3 Baseline FEV1 <= 60% predicted					
2.18.4 Baseline FEV1 not reported					



Analysis 2.19. Comparison 2 Addition of ICS + LABA versus increased dose of ICS alone in steroid-naive patients as first line treatment, Outcome 19 Growth (paediatric data).

Study or subgroup	LABA+ICS N	Higher dose ICS N	cm (SE)	cm IV, Random, 95% CI	cm IV, Random, 95% CI
Sorkness 2007	1	1	-0.1 (0.031)		-0.06[-0.12,-0]



Comparison 3. Subgroup analyses (comparison 01)

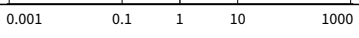
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 # patients with exacerbations requiring systemic steroids, stratified on LABA	12		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
1.1 Formoterol 12 mcg bid	1	459	Risk Ratio (M-H, Fixed, 95% CI)	1.24 [0.78, 1.99]
1.2 Salmeterol 50 mcg bid	11	2941	Risk Ratio (M-H, Fixed, 95% CI)	0.86 [0.51, 1.44]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
2 # patients with exacerbations requiring systemic steroids, stratified on ICS dose	12		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
2.1 Low ICS dose (<=400 mcg/day of BDP or equivalent)	8	2561	Risk Ratio (M-H, Fixed, 95% CI)	1.07 [0.73, 1.55]
2.2 Moderate dose of ICS (>400 to <800 mcg)	1	422	Risk Ratio (M-H, Fixed, 95% CI)	3.03 [0.32, 28.88]
2.3 High ICS dose (>=800 mcg/day of BDP or equivalent)	3	417	Risk Ratio (M-H, Fixed, 95% CI)	0.66 [0.23, 1.88]
3 # patients with exacerbations requiring systemic steroids, stratified on duration of intervention	12		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
3.1 <24 weeks	8	2253	Risk Ratio (M-H, Fixed, 95% CI)	0.78 [0.41, 1.48]
3.2 ≥24 weeks	4	1147	Risk Ratio (M-H, Fixed, 95% CI)	1.19 [0.79, 1.80]
4 # patients with exacerbations requiring systemic steroids, stratified on number of inhaler devices	12		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
4.1 One inhaler device	9	2886	Risk Ratio (M-H, Fixed, 95% CI)	0.88 [0.51, 1.50]
4.2 Two inhaler devices	3	514	Risk Ratio (M-H, Fixed, 95% CI)	1.19 [0.75, 1.88]
5 Change in FEV1 at endpoint by ICS dose	11		L (Random, 95% CI)	Subtotals only
5.1 200-500 mcg/day of CFC-BDP or equivalent	8		L (Random, 95% CI)	0.11 [0.06, 0.17]
5.2 800-1000 mcg/day of CFC-BDP or equivalent	3		L (Random, 95% CI)	0.18 [0.05, 0.30]
6 Change in FEV1 (L) at endpoint by LABA	11		L (Random, 95% CI)	Subtotals only
6.1 Formoterol	1		L (Random, 95% CI)	0.16 [0.00, 0.32]
6.2 Salmeterol	10		L (Random, 95% CI)	0.12 [0.07, 0.17]
7 Change in FEV1 (L) at endpoint by trial duration	11		L (Random, 95% CI)	Subtotals only
7.1 4 +/- 2 weeks	3		L (Random, 95% CI)	0.22 [-0.04, 0.49]
7.2 12 +/- 4 weeks	6		L (Random, 95% CI)	0.14 [0.10, 0.17]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
7.3 24 +/- 4 weeks	2		L (Random, 95% CI)	0.06 [0.01, 0.11]

Analysis 3.1. Comparison 3 Subgroup analyses (comparison 01), Outcome 1 # patients with exacerbations requiring systemic steroids, stratified on LABA.

Study or subgroup	ICS + LABA n/N	ICS alone n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
3.1.1 Formoterol 12 mcg bid					
O'Byrne 2001	34/231	27/228		100%	1.24[0.78,1.99]
Subtotal (95% CI)	**231**	**228**		**100%**	**1.24[0.78,1.99]**
Total events: 34 (ICS + LABA), 27 (ICS alone)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.9(P=0.37)					
3.1.2 Salmeterol 50 mcg bid					
Boonsawat 2008	3/149	8/154		26.11%	0.39[0.1,1.43]
Di Franco 1999	0/11	1/11		4.98%	0.33[0.02,7.39]
Kerwin 2008	3/210	1/212		3.3%	3.03[0.32,28.88]
Murray 2004	1/88	0/89		1.65%	3.03[0.13,73.48]
Nelson 2003	2/95	0/97		1.64%	5.1[0.25,104.94]
Rojas 2007	4/180	6/182		19.8%	0.67[0.19,2.35]
SAS30015	0/78	2/78		8.3%	0.2[0.01,4.1]
SAS30021	0/304	1/304		4.98%	0.33[0.01,8.15]
SAS40068	9/253	8/263		26.03%	1.17[0.46,2.98]
Strand 2004	0/78	0/72			Not estimable
Weersink 1997	1/16	1/17		3.22%	1.06[0.07,15.6]
Subtotal (95% CI)	**1462**	**1479**		**100%**	**0.86[0.51,1.44]**
Total events: 23 (ICS + LABA), 28 (ICS alone)					
Heterogeneity: Tau²=0; Chi²=6.73, df=9(P=0.66); I²=0%					
Test for overall effect: Z=0.58(P=0.56)					

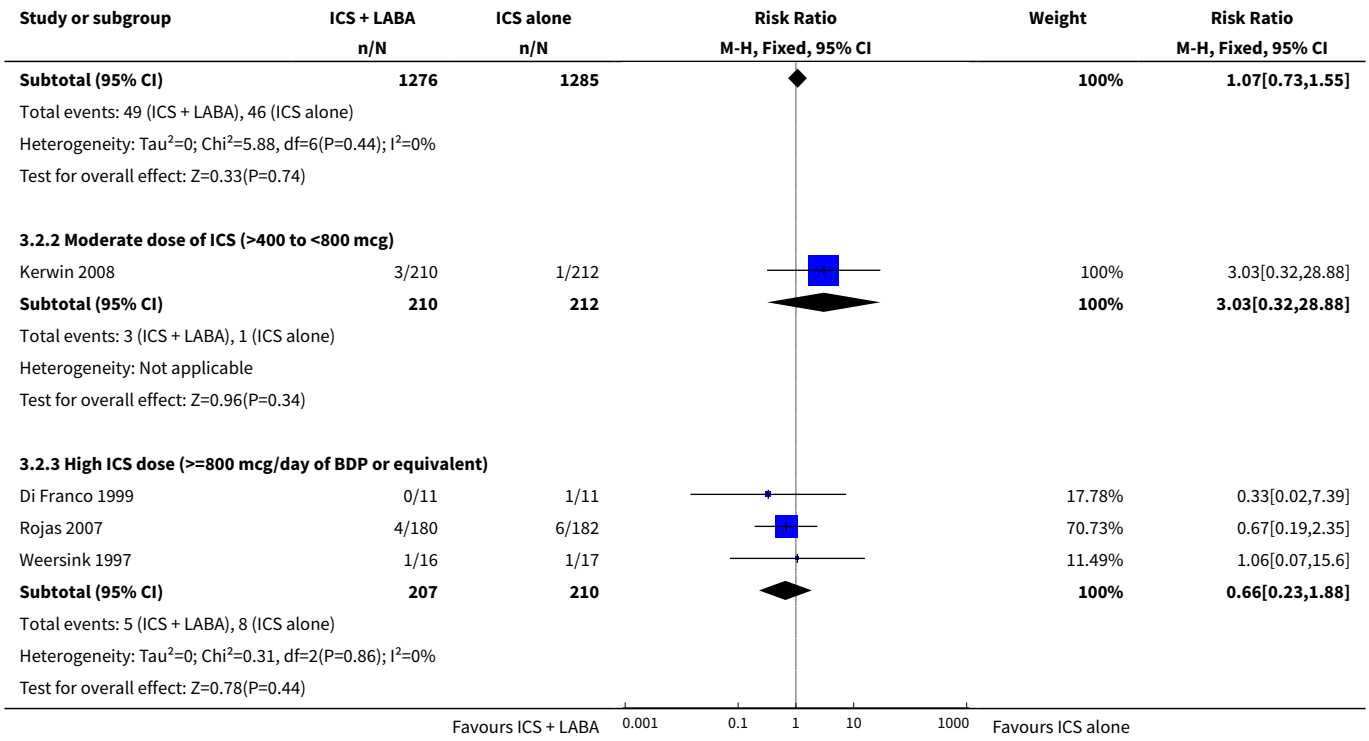


Favours LABA + ICS | Favours ICS alone

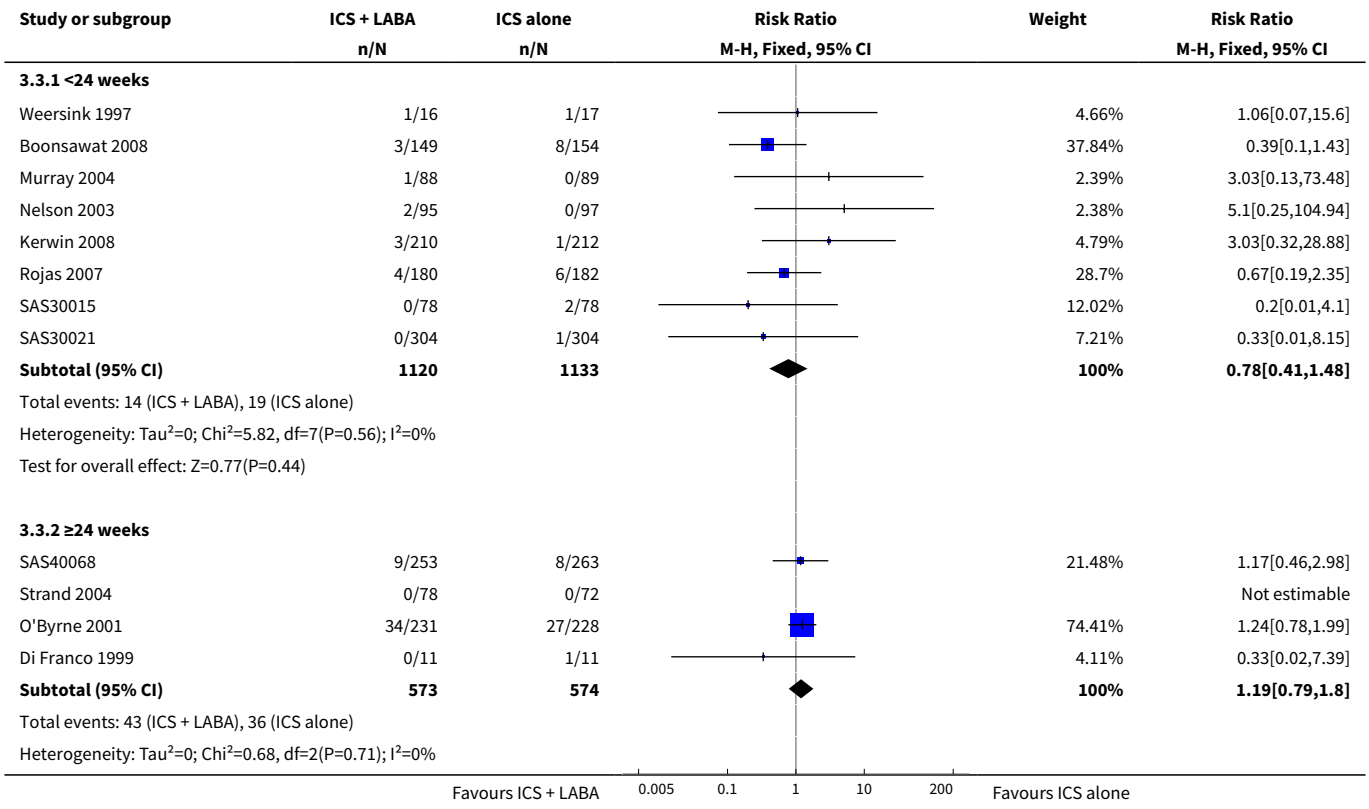
Analysis 3.2. Comparison 3 Subgroup analyses (comparison 01), Outcome 2 # patients with exacerbations requiring systemic steroids, stratified on ICS dose.

Study or subgroup	ICS + LABA n/N	ICS alone n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
3.2.1 Low ICS dose (<=400 mcg/day of BDP or equivalent)					
Boonsawat 2008	3/149	8/154		16.43%	0.39[0.1,1.43]
Murray 2004	1/88	0/89		1.04%	3.03[0.13,73.48]
Nelson 2003	2/95	0/97		1.03%	5.1[0.25,104.94]
O'Byrne 2001	34/231	27/228		56.76%	1.24[0.78,1.99]
SAS30015	0/78	2/78		5.22%	0.2[0.01,4.1]
SAS30021	0/304	1/304		3.13%	0.33[0.01,8.15]
SAS40068	9/253	8/263		16.38%	1.17[0.46,2.98]
Strand 2004	0/78	0/72			Not estimable

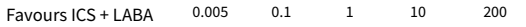
Favours ICS + LABA | Favours ICS alone



Analysis 3.3. Comparison 3 Subgroup analyses (comparison 01), Outcome 3 # patients with exacerbations requiring systemic steroids, stratified on duration of intervention.

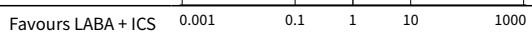


Study or subgroup	ICS + LABA n/N	ICS alone n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Test for overall effect: Z=0.82(P=0.41)					



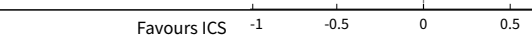
Analysis 3.4. Comparison 3 Subgroup analyses (comparison 01), Outcome 4 # patients with exacerbations requiring systemic steroids, stratified on number of inhaler devices.

Study or subgroup	ICS + LABA n/N	ICS alone n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
3.4.1 One inhaler device					
Murray 2004	1/88	0/89		1.8%	3.03[0.13,73.48]
Boonsawat 2008	3/149	8/154		28.44%	0.39[0.1,1.43]
Strand 2004	0/78	0/72			Not estimable
Nelson 2003	2/95	0/97		1.79%	5.1[0.25,104.94]
SAS30015	0/78	2/78		9.04%	0.2[0.01,4.1]
SAS30021	0/304	1/304		5.42%	0.33[0.01,8.15]
SAS40068	9/253	8/263		28.35%	1.17[0.46,2.98]
Kerwin 2008	3/210	1/212		3.6%	3.03[0.32,28.88]
Rojas 2007	4/180	6/182		21.57%	0.67[0.19,2.35]
Subtotal (95% CI)	**1435**	**1451**		**100%**	**0.88[0.51,1.5]**
Total events: 22 (ICS + LABA), 26 (ICS alone)					
Heterogeneity: Tau^2=0; Chi^2=6.35, df=7(P=0.5); I^2=0%					
Test for overall effect: Z=0.47(P=0.64)					
3.4.2 Two inhaler devices					
Weersink 1997	1/16	1/17		3.27%	1.06[0.07,15.6]
Di Franco 1999	0/11	1/11		5.06%	0.33[0.02,7.39]
O'Byrne 2001	34/231	27/228		91.67%	1.24[0.78,1.99]
Subtotal (95% CI)	**258**	**256**		**100%**	**1.19[0.75,1.88]**
Total events: 35 (ICS + LABA), 29 (ICS alone)					
Heterogeneity: Tau^2=0; Chi^2=0.69, df=2(P=0.71); I^2=0%					
Test for overall effect: Z=0.75(P=0.45)					



Analysis 3.5. Comparison 3 Subgroup analyses (comparison 01), Outcome 5 Change in FEV1 at endpoint by ICS dose.

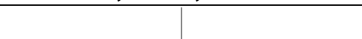
Study or subgroup	ICS + LABA N	ICS N	L (SE)	L IV, Random, 95% CI	Weight	L IV, Random, 95% CI
3.5.1 200-500 mcg/day of CFC-BDP or equivalent						
Kerwin 2008	210	212	0.1 (0.041)		17.68%	0.1[0.02,0.18]
Chuchalin 2002	111	114	0.2 (0.082)		8.02%	0.16[0,0.32]
SAS40068	229	243	0.1 (0.026)		23.4%	0.06[0.01,0.11]
Boonsawat 2008	151	155	0.2 (0.041)		17.68%	0.18[0.1,0.26]
Murray 2004	88	89	0 (0.071)		9.67%	0.03[-0.11,0.17]
Prieto 2005	21	21	0 (0.071)		9.67%	0.02[-0.12,0.16]
Nelson 2003	95	97	0.2 (0.071)		9.67%	0.18[0.04,0.32]
Pearlman 1999a	25	23	0.3 (0.122)		4.2%	0.32[0.08,0.56]
Subtotal (95% CI)					**100%**	**0.11[0.06,0.17]**



Study or subgroup	ICS + LABA N	ICS N	L (SE)	L IV, Random, 95% CI	Weight	L IV, Random, 95% CI
Heterogeneity: Tau²=0; Chi²=13.55, df=7(P=0.06); I²=48.32%						
Test for overall effect: Z=4.14(P<0.0001)						
3.5.2 800-1000 mcg/day of CFC-BDP or equivalent						
Di Franco 1999	11	11	0.2 (0.174)		11.73%	0.2[-0.14,0.54]
GOAL	533	531	0.1 (0.031)		77.66%	0.14[0.08,0.2]
Pearlman 1999b	21	23	0.4 (0.184)		10.61%	0.43[0.07,0.79]
Subtotal (95% CI)					**100%**	**0.18[0.05,0.3]**
Heterogeneity: Tau²=0; Chi²=2.51, df=2(P=0.28); I²=20.4%						
Test for overall effect: Z=2.8(P=0.01)						

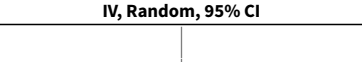
Analysis 3.6. Comparison 3 Subgroup analyses (comparison 01), Outcome 6 Change in FEV1 (L) at endpoint by LABA.

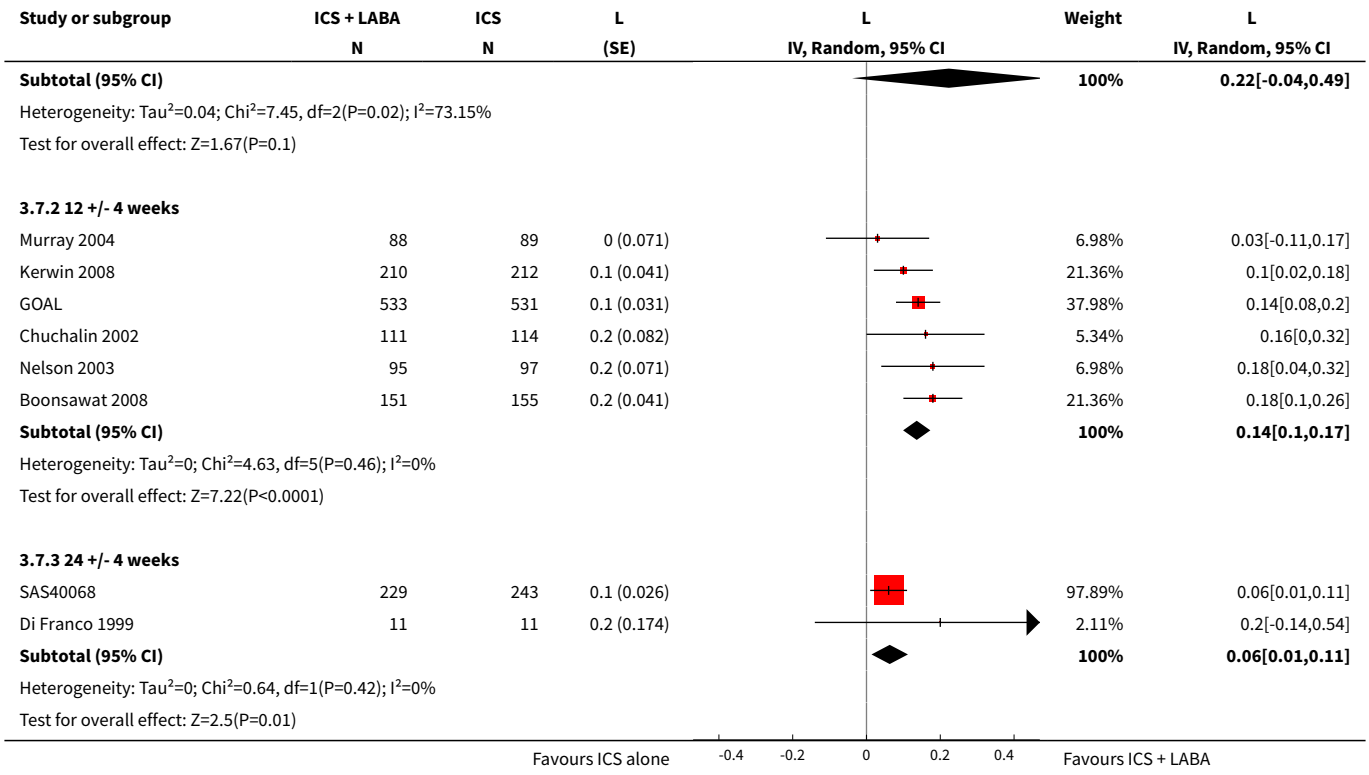
Study or subgroup	LABA + ICS N	ICS alone N	L (SE)	L IV, Random, 95% CI	Weight	L IV, Random, 95% CI
3.6.1 Formoterol						
Chuchalin 2002	111	114	0.2 (0.082)		100%	0.16[0,0.32]
Subtotal (95% CI)					**100%**	**0.16[0,0.32]**
Heterogeneity: Not applicable						
Test for overall effect: Z=1.96(P=0.05)						
3.6.2 Salmeterol						
Kerwin 2008	210	212	0.1 (0.041)		15.02%	0.1[0.02,0.18]
SAS40068	229	243	0.1 (0.026)		19.88%	0.06[0.01,0.11]
Pearlman 1999a	25	23	0.3 (0.122)		3.57%	0.32[0.08,0.56]
Prieto 2005	21	21	0 (0.071)		8.22%	0.02[-0.12,0.16]
Nelson 2003	95	97	0.2 (0.071)		8.22%	0.18[0.04,0.32]
Boonsawat 2008	151	155	0.2 (0.041)		15.02%	0.18[0.1,0.26]
Murray 2004	88	89	0 (0.071)		8.22%	0.03[-0.11,0.17]
Di Franco 1999	11	11	0.2 (0.174)		1.91%	0.2[-0.14,0.54]
GOAL	533	531	0.1 (0.031)		18.22%	0.14[0.08,0.2]
Pearlman 1999b	21	23	0.4 (0.184)		1.72%	0.43[0.07,0.79]
Subtotal (95% CI)					**100%**	**0.12[0.07,0.17]**
Heterogeneity: Tau²=0; Chi²=17.86, df=9(P=0.04); I²=49.61%						
Test for overall effect: Z=4.85(P<0.0001)						



Analysis 3.7. Comparison 3 Subgroup analyses (comparison 01), Outcome 7 Change in FEV1 (L) at endpoint by trial duration.

Study or subgroup	ICS + LABA N	ICS N	L (SE)	L IV, Random, 95% CI	Weight	L IV, Random, 95% CI
3.7.1 4 +/- 2 weeks						
Prieto 2005	21	21	0 (0.071)		41.4%	0.02[-0.12,0.16]
Pearlman 1999a	25	23	0.3 (0.122)		33.7%	0.32[0.08,0.56]
Pearlman 1999b	21	23	0.4 (0.184)		24.91%	0.43[0.07,0.79]

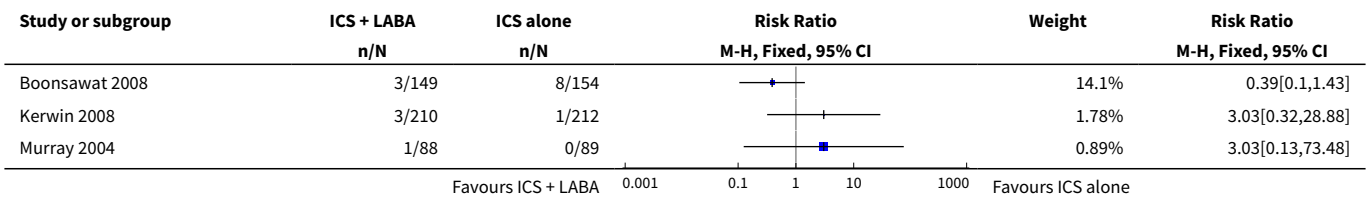




Comparison 4. Sensitivity analysis (comparison 01)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 # patients with exacerbations requiring systemic steroids (low or unclear risk of detection bias)	11	3378	Risk Ratio (M-H, Fixed, 95% CI)	1.06 [0.75, 1.50]
2 # patients with exacerbations requiring systemic steroids (low or unclear risk of bias in completeness of follow up)	11	3223	Risk Ratio (M-H, Fixed, 95% CI)	1.02 [0.72, 1.45]
3 # patients with exacerbations requiring systemic steroids	9	2120	Risk Ratio (M-H, Fixed, 95% CI)	1.09 [0.74, 1.60]

Analysis 4.1. Comparison 4 Sensitivity analysis (comparison 01), Outcome 1 # patients with exacerbations requiring systemic steroids (low or unclear risk of detection bias).



Study or subgroup	ICS + LABA n/N	ICS alone n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Nelson 2003	2/95	0/97		0.89%	5.1[0.25,104.94]
O'Byrne 2001	34/231	27/228		48.69%	1.24[0.78,1.99]
Rojas 2007	4/180	6/182		10.69%	0.67[0.19,2.35]
SAS30015	0/78	2/78		4.48%	0.2[0.01,4.1]
SAS30021	0/304	1/304		2.69%	0.33[0.01,8.15]
SAS40068	9/253	8/263		14.06%	1.17[0.46,2.98]
Strand 2004	0/78	0/72			Not estimable
Weersink 1997	1/16	1/17		1.74%	1.06[0.07,15.6]
Total (95% CI)	**1682**	**1696**		**100%**	**1.06[0.75,1.5]**
Total events: 57 (ICS + LABA), 54 (ICS alone)					
Heterogeneity: Tau^2=0; Chi^2=7.22, df=9(P=0.61); I^2=0%					
Test for overall effect: Z=0.32(P=0.75)					

Analysis 4.2. Comparison 4 Sensitivity analysis (comparison 01), Outcome 2 # patients with exacerbations requiring systemic steroids (low or unclear risk of bias in completeness of follow up).

Study or subgroup	ICS + LABA n/N	ICS alone n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Boonsawat 2008	3/149	8/154		13.85%	0.39[0.1,1.43]
Di Franco 1999	0/11	1/11		2.64%	0.33[0.02,7.39]
Kerwin 2008	3/210	1/212		1.75%	3.03[0.32,28.88]
Nelson 2003	2/95	0/97		0.87%	5.1[0.25,104.94]
O'Byrne 2001	34/231	27/228		47.83%	1.24[0.78,1.99]
Rojas 2007	4/180	6/182		10.5%	0.67[0.19,2.35]
SAS30015	0/78	2/78		4.4%	0.2[0.01,4.1]
SAS30021	0/304	1/304		2.64%	0.33[0.01,8.15]
SAS40068	9/253	8/263		13.81%	1.17[0.46,2.98]
Strand 2004	0/78	0/72			Not estimable
Weersink 1997	1/16	1/17		1.71%	1.06[0.07,15.6]
Total (95% CI)	**1605**	**1618**		**100%**	**1.02[0.72,1.45]**
Total events: 56 (ICS + LABA), 55 (ICS alone)					
Heterogeneity: Tau^2=0; Chi^2=7.35, df=9(P=0.6); I^2=0%					
Test for overall effect: Z=0.12(P=0.9)					

Analysis 4.3. Comparison 4 Sensitivity analysis (comparison 01), Outcome 3 # patients with exacerbations requiring systemic steroids.

Study or subgroup	ICS + LABA n/N	ICS alone n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Boonsawat 2008	3/149	8/154		17.3%	0.39[0.1,1.43]
Di Franco 1999	0/11	1/11		3.3%	0.33[0.02,7.39]
Kerwin 2008	3/210	1/212		2.19%	3.03[0.32,28.88]
Murray 2004	1/88	0/89		1.09%	3.03[0.13,73.48]

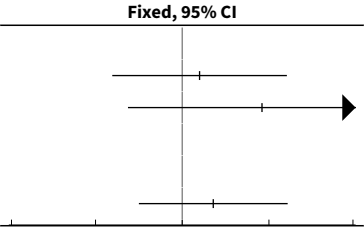
Study or subgroup	ICS + LABA n/N	ICS alone n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Nelson 2003	2/95	0/97		1.09%	5.1[0.25,104.94]
O'Byrne 2001	34/231	27/228		59.77%	1.24[0.78,1.99]
Rojas 2007	4/180	6/182		13.12%	0.67[0.19,2.35]
Strand 2004	0/78	0/72			Not estimable
Weersink 1997	1/16	1/17		2.13%	1.06[0.07,15.6]
Total (95% CI)	**1058**	**1062**		**100%**	**1.09[0.74,1.6]**
Total events: 48 (ICS + LABA), 44 (ICS alone)					
Heterogeneity: Tau^2=0; Chi^2=6.02, df=7(P=0.54); I^2=0%					
Test for overall effect: Z=0.43(P=0.67)					

Comparison 5. WMD archive

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Morning PEF (L/min) at endpoint	3		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
1.1 Baseline FEV1 <80% predicted	2		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
1.2 Baseline FEV1 not reported	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
2 Change in FEV1 (L) at endpoint	10		Mean Difference (IV, Random, 95% CI)	Totals not selected
2.1 Baseline FEV1 <80% predicted	7		Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]
2.2 Baseline FEV1 >=80% predicted	1		Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]
2.3 Baseline FEV1 not reported	2		Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]

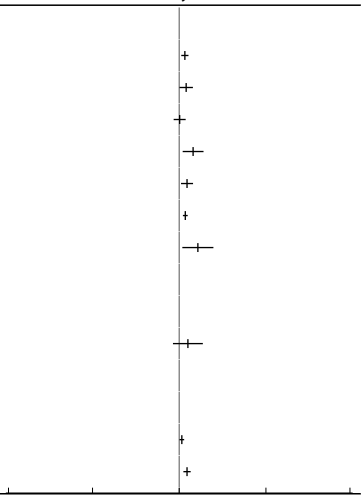
Analysis 5.1. Comparison 5 WMD archive, Outcome 1 Morning PEF (L/min) at endpoint.

Study or subgroup	ICS + LABA N	ICS + LABA Mean(SD)	ICS alone N	ICS alone Mean(SD)	Mean Difference Fixed, 95% CI	Mean Difference Fixed, 95% CI
5.1.1 Baseline FEV1 <80% predicted						
Pearlman 1999a	21	457 (93.5)	22	447 (73.2)		10[-40.35,60.35]
Pearlman 1999b	20	490 (156.9)	21	444 (82.5)		46[-31.29,123.29]
5.1.2 Baseline FEV1 not reported						
Strand 2004	70	424.9 (130.2)	67	407 (126)		17.9[-25,60.8]



Analysis 5.2. Comparison 5 WMD archive, Outcome 2 Change in FEV1 (L) at endpoint.

Study or subgroup	ICS + LABA N	ICS + LABA Mean(SD)	ICS alone N	ICS alone Mean(SD)	Mean Difference Random, 95% CI	Mean Difference Random, 95% CI
5.2.1 Baseline FEV1 <80% predicted						
Kerwin 2008	210	0.5 (0.4)	212	0.4 (0.4)		0.13[0.05,0.21]
Chuchalin 2002	111	0.6 (0.6)	114	0.4 (0.6)		0.16[0,0.32]
Murray 2004	88	0.5 (0.5)	89	0.5 (0.5)		0.01[-0.13,0.15]
Pearlman 1999a	25	0.6 (0.5)	23	0.3 (0.3)		0.32[0.08,0.56]
Nelson 2003	95	0.7 (0.5)	97	0.5 (0.5)		0.18[0.04,0.32]
GOAL	533	0.5 (0.5)	531	0.3 (0.5)		0.14[0.08,0.2]
Pearlman 1999b	21	0.7 (0.7)	23	0.3 (0.4)		0.43[0.07,0.79]
5.2.2 Baseline FEV1 >=80% predicted						
Di Franco 1999	11	0.3 (0.3)	11	0.1 (0.5)		0.2[-0.14,0.54]
5.2.3 Baseline FEV1 not reported						
SAS40068	229	0.1 (0.3)	243	0.1 (0.3)		0.06[0.01,0.11]
Boonsawat 2008	151	0.2 (0.4)	155	0 (0.4)		0.18[0.1,0.26]



ADDITIONAL TABLES

Table 1. Search history

Search year	Detail
All years to April 2004	Citations identified: 594 Excluded: 576 due to: (1) duplicate references (N = 209); (2) not a randomised controlled trial (N = 68), or an ongoing trial (N = 14); (3) participants were not asthmatics (N = 4); (4) no consistent intervention with inhaled corticosteroids in all participants (N = 41); (5) intervention was not maintenance, inhaled long-acting ß2-agonists (N = 19); (6) control intervention was not maintenance, inhaled corticosteroids alone (N = 64); (7) duration of intervention was less than 30 days (N = 45); (8) outcome measures did not reflect asthma control (N = 8); (9) treatment and intervention groups compared the same medications either in combination or with different delivery devices (N = 30); (10) co-intervention with non-permitted agent (N = 1); (11) patients were not steroid-naive, or did not examine the same dose of inhaled corticosteroids in each group (N = 73). Unique studies identified meeting entry criteria: 9 References pertaining to these studies: 16
April 2004 to May 2007	Citations identified: 293 Excluded: 231 due to: (1) duplicate references (N = 50); (2) not a randomised controlled trial (N = 14), or an ongoing trial (N = 0); (3) crossover study (N = 17) (4) participants were not asthmatics (N = 4); (5) study conducted in children (N = 8) (6) no consistent intervention with inhaled corticosteroids in all participants (N = 4);

Table 1. Search history *(Continued)*

(7) intervention was not maintenance, inhaled long-acting ß2-agonists (N = 16);
(8) control intervention was not maintenance, inhaled corticosteroids alone (N = 76);
(9) duration of intervention was less than 30 days (N = 2);
(10) outcome measures did not reflect asthma control (N = 8);
(11) treatment and intervention groups compared the same medications either in combination or with different delivery devices (N = 7);
(12) co-intervention with non-permitted agent (N = 0);
(13) patients were not steroid-naive, or did not examine the same dose of inhaled corticosteroids in each group (N = 25).

References identified of relevance to the review: 62
New unique studies identified meeting entry criteria: 10

APPENDICES

Appendix 1. Details of GSK randomisation processes

The procedures for randomising GSK sponsored studies has been detailed in correspondence between Richard Follows and TL, the details of which are given below:

The randomisation software is a computer-generated, centralised programme (RandAll). After verification that the randomisation sequence is suitable for the study design (cross-over, block or stratification), Clinical Supplies then package the treatments according the randomisation list generated. Concealment of allocation is maintained by a third party, since the sites phone in and are allocated treatments on that basis. Alternatively a third party may dispense the drug at the sites. Unblinding of data for interim analyses can only be done through RandAll, and are restricted so that only those reviewing the data are unblinded to treatment group allocation.

WHAT'S NEW

Date	Event	Description
11 April 2013	Amended	NIHR acknowledgement added

HISTORY

Protocol first published: Issue 1, 2000
Review first published: Issue 2, 2005

Date	Event	Description
14 January 2010	Amended	New title; minor spelling mistakes corrected
12 June 2008	New citation required and conclusions have changed	We added 19 studies to this review in the June 2008 update; four trials added data to our primary outcome. Confidence intervals tightened around pooled effect. We added an additional comparison comparing long-acting inhaled ß2-agonists (LABA) and inhaled corticosteroids (ICS) to increased dose of ICS, indicating that higher dose ICS is more effective than combining ICS with a LABA in reducing exacerbations.
2 May 2008	New search has been performed	New literature search performed (2004 to 2008).

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

CONTRIBUTIONS OF AUTHORS

Muireann Ni Chroinin, under the supervision of Francine Ducharme, identified and reviewed the full-text publication of all citations of potential or potentially eligible RCTs identified in the 2004 literature search, extracted the methodology and data, analysed and interpreted results of the meta-analysis and wrote the review. Ilana Greenstone participated in the selection of trials from the literature search. Toby Lasserson assessed studies for eligibility from the 2008 literature and company website search update, extracted and entered data, and wrote up the results.

Francine Ducharme supervised Muireann Ni Chroinin, Ilana Greenstone and Toby Lasserson. She conceived the protocol, supervised the literature search, 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, analysed and interpreted results of the meta-analysis and supervised the writing up of the review.

DECLARATIONS OF INTEREST

Francine M. Ducharme has received travel support for meeting attendance, research funds, fees for speaking and/or consulting fees from AstraZeneca (producer of formoterol and budesonide), GlaxoSmithKline (producer of fluticasone, beclomethasone, salmeterol) and Novartis (producer of formoterol). Muireann Ni Chroinin has received some research funds and fees for speaking from AstraZeneca and has attended CME conferences with support from GlaxoSmithKline. Toby Lasserson and Ilana Greenstone report no conflict of interest.

SOURCES OF SUPPORT

Internal sources

- Canadian Cochrane Network - McGill University, Canada.

External sources

- Francine Ducharme was supported by a senior clinical scientist award from the Fonds de la Santé du Québec, Canada.

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

This review has now been amended to include to two treatment comparisons:

1. the addition of LABA to ICS versus the same dose of ICS;
2. the addition of LABA to ICS versus a higher dose of ICS.

We have continued to require that the participants be steroid-naive prior to study entry.

We have incorporated a new method to assess the risk of bias, and based sensitivity analyses on sources of bias relating to blinding and completeness of follow up. Jadad scores have still been calculated for each study, but these findings are not the primary source of assessing the credibility of the results for each study.

INDEX TERMS

Medical Subject Headings (MeSH)

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

MeSH check words

Adult; Child; Humans