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Addition of long-acting beta$_2$-agonists to inhaled corticosteroids for chronic asthma in children (Review)

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[Intervention Review]

Addition of long-acting beta$_2$-agonists to inhaled corticosteroids for chronic asthma in children

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ABSTRACT

Background

Long-acting beta$_2$-agonists (LABA) in combination with inhaled corticosteroids (ICS) are increasingly prescribed for children with asthma.

Objectives

To assess the safety and efficacy of adding a LABA to an ICS in children and adolescents with asthma. To determine whether the benefit of LABA was influenced by baseline severity of airway obstruction, the dose of ICS to which it was added or with which it was compared, the type of LABA used, the number of devices used to deliver combination therapy and trial duration.

Search methods

We searched the Cochrane Airways Group Asthma Trials Register until January 2015.

Selection criteria

We included randomised controlled trials testing the combination of LABA and ICS versus the same, or an increased, dose of ICS for at least four weeks in children and adolescents with asthma. The main outcome was the rate of exacerbations requiring rescue oral steroids. Secondary outcomes included markers of exacerbation, pulmonary function, symptoms, quality of life, adverse events and withdrawals.

Data collection and analysis

Two review authors assessed studies independently for methodological quality and extracted data. We obtained confirmation from trialists when possible.

Main results

We included in this review a total of 33 trials representing 39 control-intervention comparisons and randomly assigning 6381 children. Most participants were inadequately controlled on their current ICS dose. We assessed the addition of LABA to ICS (1) versus the same dose of ICS, and (2) versus an increased dose of ICS.

LABA added to ICS was compared with the same dose of ICS in 28 studies. Mean age of participants was 11 years, and males accounted for 59% of the study population. Mean forced expiratory volume in one second (FEV_1) at baseline was ≥ 80% of predicted in 18 studies, 61% to 79% of predicted in six studies and unreported in the remaining studies. Participants were inadequately controlled before randomisation in all but four studies.

There was no significant group difference in exacerbations requiring oral steroids (risk ratio (RR) 0.95, 95% confidence interval (CI) 0.70 to 1.28, 12 studies, 1669 children; moderate-quality evidence) with addition of LABA to ICS compared with ICS alone. There was no statistically significant group difference in hospital admissions (RR 1.74, 95% CI 0.90 to 3.36, seven studies, 1292 children; moderate-quality evidence)nor in serious adverse events (RR 1.17, 95% CI 0.75 to 1.85, 17 studies, N = 4021; moderate-quality evidence). Withdrawals occurred significantly less frequently with the addition of LABA (23 studies, 471 children, RR 0.80, 95% CI 0.67 to 0.94; low-quality evidence). Compared with ICS alone, addition of LABA led to significantly greater improvement in FEV_1 (nine studies, 1942 children, inverse variance (IV) 0.08 L, 95% CI 0.06 to 0.10; mean difference (MD) 2.99%, 95% CI 0.86 to 5.11, seven studies, 534 children; low-quality evidence), morning peak expiratory flow (PEF) (16 studies, 3934 children, IV 10.20 L/min, 95% CI 8.14 to 12.26), reduction in use of daytime rescue inhalations (MD -0.07 puffs/d, 95% CI -0.11 to -0.02, seven studies; 1798 children) and reduction in use of nighttime rescue inhalations (MD -0.08 puffs/d, 95% CI -0.13 to -0.03, three studies, 672 children). No significant group difference was noted in exercise-induced % fall in FEV_1, symptom-free days, asthma symptom score, quality of life, use of reliever medication and adverse events.

A total of 11 studies assessed the addition of LABA to ICS therapy versus an increased dose of ICS with random assignment of 1628 children. Mean age of participants was 10 years, and 64% were male. Baseline mean FEV_1 was ≥ 80% of predicted. All trials enrolled participants who were inadequately controlled on a baseline inhaled steroid dose equivalent to 400 µg/d of beclomethasone equivalent or less.

There was no significant group differences in risk of exacerbation requiring oral steroids with the combination of LABA and ICS versus a double dose of ICS (RR 1.69, 95% CI 0.85 to 3.32, three studies, 581 children; moderate-quality evidence) nor in risk of hospital admission (RR 1.90, 95% CI 0.65 to 5.54, four studies, 1008 children; moderate-quality evidence).

No statistical significant group difference was noted in serious adverse events (RR 1.54, 95% CI 0.81 to 2.94, seven studies, N = 1343; moderate-quality evidence) and no statistically significant differences in overall risk of all-cause withdrawals (RR 0.96, 95% CI 0.67 to 1.37, eight studies, 1491 children; moderate-quality evidence). Compared with double the dose of ICS, use of LABA was associated with significantly greater improvement in morning PEF (MD 8.73 L/min, 95% CI 5.15 to 12.31, five studies, 1283 children; moderate-quality evidence), but data were insufficient to aggregate on other markers of asthma symptoms, rescue medication use and nighttime awakening. There was no group difference in risk of overall adverse effects, A significant group difference was observed in linear growth over 12 months, clearly indicating lower growth velocity in the higher ICS dose group (two studies: MD 1.21 cm/y, 95% CI 0.72 to 1.70).

Authors' conclusions

In children with persistent asthma, the addition of LABA to ICS was not associated with a significant reduction in the rate of exacerbations requiring systemic steroids, but it was superior for improving lung function compared with the same or higher doses of ICS. No differences in adverse effects were apparent, with the exception of greater growth with the use of ICS and LABA compared with a higher ICS dose. The trend towards increased risk of hospital admission with LABA, irrespective of the dose of ICS, is a matter of concern and requires further monitoring.

PLAIN LANGUAGE SUMMARY

Addition of long-acting $beta_2$-agonists to inhaled corticosteroids for chronic asthma in children

Background

Most consensus statements recommend use of long-acting $beta_2$-agonists (LABA) as adjunct therapy to inhaled corticosteroids (ICS) for poorly controlled asthma, despite the use of low-dose ICS.

Review question

What are the benefits and safety of the combination of LABA and ICS in children with persistent asthma when compared with the same dose or a higher dose of ICS alone?

What evidence did we find?

From available evidence until January 2015, we found 39 eligible studies evaluating the combination of LABA and ICS in children with persistent asthma. Of these, 28 studies compared LABA with the same dose of ICS, and the remaining studies compared LABA with a larger dose of ICS.

The number of people who had an exacerbation (worsening of symptoms) that required treatment with oral steroids was not significantly different. However, lung function improved in people taking LABA and steroids compared with the same dose of steroids only or larger

doses of steroids. No evidence suggested increased serious adverse events or adverse events (also known as side effects) with the addition of LABA.

Compared with the same dose of ICS, people used less of their rescue/relief bronchodilator treatment. There was no benefit for control of asthma symptoms when LABA added to ICS was compared with higher doses of ICS. The higher dose of ICS was associated with 1.2 cm per year lower growth than was observed with the combination of LABA and a lower dose of ICS.

Conclusion

In children with persistent asthma, the combination of LABA and ICS did not reduce the risk of exacerbations requiring steroid treatment but did improve lung function when compared with the same, or a higher, dose of ICS. No differences in adverse effects were apparent, with the exception of better growth with use of ICS and LABA compared with a higher ICS dose. The trend towards increasing chances of hospital admission indicates the need for continuous monitoring and additional trials in children.

Quality of the evidence

Overall, we judged the quality of evidence to be moderate. Most outcomes showed wide confidence intervals, which led to downgrading of the quality of evidence to moderate. In a few outcomes for which open-label studies contributed data, we further downgraded evidence quality to low.

SUMMARY OF FINDINGS

Summary of findings for the main comparison.

LABA + ICS compared with same dose of ICS for children with chronic asthma

Patient or population: children with chronic asthma

Settings: outpatients

Intervention: LABA + ICS

Comparison: same dose of ICS

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	Number of participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Increased dose of ICS	LABA + ICS				
Number of participants with exacerbations requiring systemic steroids	**86 per 1000**	**94 per 1000**	**RR 0.95** (0.70 to 1.28)	1669 (12 studies)	⊕⊕⊕⊖ **Moderate**[a]	
Number of participants with exacerbations requiring hospitalisation	**19 per 1000**	**33 per 1000**	**RR 1.74** (0.90 to 3.36)	1292 (6 studies)	⊕⊕⊕⊖ **Moderate**[a]	
Serious adverse events	**16 per 1000**	**18 per 1000**	**RR 1.17** (0.75 to 1.85)	4022 (16 studies)	⊕⊕⊕⊖ **Moderate**[a]	
Total number of withdrawals	**127 per 1000**	**94 per 1000**	**RR 0.80** (0.67 to 0.94)	4374 (23 studies)	⊕⊕⊖⊖ **Low**[a,b]	
Change in FEV_1 (L) at endpoint	Baseline mean FEV_1 ranged from 1.65 L to 1.9 L (baseline data reported in 4 studies only)	Mean FEV_1 change from baseline with LABA + ICS was 0.08 L higher (0.06 to 0.1 higher)		1942 (9 studies)	⊕⊕⊖⊖ **Low**[a,b]	
Change in morning PEF (L/min) at endpoint	Illustrative post-treatment PEFs range from 235 to 290 L/min (data from 3 recent studies)	Mean PEF change from baseline with LABA + ICS was 10.20 L/min higher (8.14 to 12.26 higher)		3934 (16 studies)	⊕⊕⊕⊖ **Moderate**[a]	

Total number of adverse events	**547 per 1000**	**568 per 1000**	**RR 1.04** (0.98 to 1.10)	3284 (15 studies)	⊕⊕⊕⊝ **Moderate**[b]

*The basis for the **assumed risk** (e.g. median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: Confidence interval; **FEV$_1$:** Forced expiratory volume in 1 second;**ICS:** Inhaled corticosteroids; **LABA:** Long-acting beta$_2$-agonists; **RR:** Risk ratio.

GRADE Working Group grades of evidence.
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

[a]Larger sample size may change the outcome.
[b]Open-label study contributed data.

Summary of findings 2.

LABA + ICS compared with increased dose of ICS for children with chronic asthma

Patient or population: children with chronic asthma

Settings: outpatients

Intervention: LABA + ICS

Comparison: increased dose of ICS

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	Number of participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Increased dose of ICS	LABA + ICS				
Number of participants with exacerbations requiring systemic steroids	**41 per 1000**	**69 per 1000**	**RR 1.69** (0.85 to 3.32)	581 (3 studies)	⊕⊕⊕⊝ **Moderate**[a]	
Number of participants with exacerbations requiring hospitalisation	**8 per 1000**	**18 per 1000**	**RR 1.90** (0.65 to 5.54)	1008 (4 studies)	⊕⊕⊕⊝ **Moderate**[a]	
Serious adverse events	**24 per 1000**	**39 per 1000**	**RR 1.54**	1343	⊕⊕⊕⊝	

			(0.81 to 2.94)	(7 studies)	**Moderate**[a]
Total number of withdrawals	**70 per 1000**	**67 per 1000**	**RR 0.96** (0.67 to 1.37)	1491 (7 studies)	⊕⊕⊕⊖ **Moderate**[a]
Change in FEV_1 (L) at endpoint	Mean baseline FEV_1 ranged from 1.6 to 1.7 L	Mean FEV_1: change from baseline with LABA + ICS was 0.01 L higher (-0.03 to 0.05 higher)		526 (2 studies)	⊕⊕⊕⊖ **Moderate**[a]
Change in morning PEF (L/min) at endpoint	Mean change in end of treatment PEF ranged from 16.7 to 39.2 L/min	Mean PEF: change from baseline with LABA + ICS was 8.73 L/min higher (5.15 to 12.31 higher)		1283 (5 studies)	⊕⊕⊕⊖ **Moderate**[a]
Total number of adverse events	**569 per 1000**	**576 per 1000**	**RR 1.01** (0.92 to 1.10)	1254 (6 studies)	⊕⊕⊕⊕ **High**

*The basis for the **assumed risk** (e.g. median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: Confidence interval; **FEV_1:** Forced expiratory volume in 1 second; **ICS:** Inhaled corticosteroids; **LABA:** Long-acting $beta_2$-agonists; **PEF:** Peak expiratory flow; **RR:** Risk ratio.

GRADE Working Group grades of evidence.
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

[a]Larger sample size may change the outcome.

BACKGROUND

Description of the condition

Inhaled corticosteroids (ICS) are the most effective treatment for long-term control of asthma in children (Adams 2005; Manning 2008; Adams 2008a; Chauhan 2012). They are recommended as first-line agents for the management of childhood asthma in all national and international consensus statements (NAEPP 2011; Lougheed 2012; BTS 2014; GINA 2015). When ICS alone are insufficient to achieve asthma control, various options may be considered, such as increasing the dose of ICS (Adams 2008b) or adding a second drug such as a long-acting beta$_2$-agonist (LABA) or a leukotriene receptor antagonist (LTRA) (Chauhan 2014).

Description of the intervention

In adults with unsatisfactory asthma control, international guidelines clearly favour the addition of LABA to low or moderate doses of ICS over other options such as increasing the dose of steroids or adding other agents (NAEPP 2011; BTS 2014; GINA 2015). In children five to 12 years of age with insufficient control on ICS, however, recommendations regarding the preferred step 3 strategy and the dose of ICS to which LABA should be added differ markedly across countries. The International Australian and Canadian guidelines recommend increasing the dose of ICS to medium dose (201 to 400 µg beclomethasone equivalent) rather than adding LABA or LTRA to low-dose ICS in children six to 11 years of age (Lougheed 2012; NAC Guidelines 2014). British Thoracic Society guidelines recommend combination therapy at a low dose (200 to 400 µg/d beclomethasone equivalent) (BTS 2014). Global Initiative for Asthma (GINA) and Australian guidelines recommend increasing the dose of ICS over adding LABA to a higher dose of ICS (400 µg/d) (NAC Guidelines 2014; GINA 2015). American guidelines reveal no clear preference for adding LABA to a low dose of ICS or increasing the dose of ICS for children five to 11 years of age with uncontrolled asthma and taking a low dose of ICS (NAEPP 2011). No formal recommendation is available for their use in preschool-age children.

How the intervention might work

Data from paediatric clinical trials have been included in few previous meta-analyses assessing the efficacy and safety of LABA in combination with ICS (Ducharme 2010; Ducharme 2010a). However, Bisgaard 2003 cautioned against routine use of LABA in children, as they did not offer protection against exacerbations and led to increased risk of hospital admission. Other outcomes such as adverse effects, lung function and symptoms were not examined.

Why it is important to do this review

The wide divergence of recommendations likely stems from lack of solid evidence in children to support international asthma guidelines and justifies a systematic review of the topic. In 2010, we published a Cochrane review conducted to compare LABA added to ICS of the same dose, or a higher dose, for adults and children with chronic persistent asthma, which demonstrated that LABA and ICS led to a significant reduction in risk of exacerbations requiring oral steroids (Ducharme 2010; Ducharme 2010a). The Cochrane Collaboration had published a separate paediatric systematic review on the same topic in the year 2009 (Ni Chroinin 2009). Since that time, additional published and unpublished paediatric trials have become available, enabling us to update the review to include newly available evidence and to shed more light on the role of LABA as adjunct therapy to ICS for children with partial control when taking ICS alone.

OBJECTIVES

To assess the safety and efficacy of adding a LABA to an ICS in children and adolescents with asthma. To determine whether the benefit of LABA was influenced by baseline severity of airway obstruction, the dose of ICS to which it was added or with which it was compared, the type of LABA used, the number of devices used to deliver combination therapy and trial duration.

METHODS

Criteria for considering studies for this review

Types of studies

Randomised controlled trials conducted in children for whom a LABA was added to an ICS were eligible.

Types of participants

Children and adolescents two to 18 years of age with persistent asthma who had received daily ICS therapy for at least four weeks before study entry.

Types of interventions

LABA (salmeterol or formoterol) versus placebo administered daily for at least four weeks. LABA added to ICS was compared:

- with the same ICS dose; or
- with an increased dose of ICS.

Studies in which maintenance ICS therapy was interrupted for the purposes of run-in were not eligible for the review. Other co-interventions such as xanthines, anticholinergics and other anti-asthmatic medications were permitted, provided that the dose remained unchanged throughout the study. Inhaled short-acting beta$_2$-agonists (SABA) and short courses of systemic steroids were allowed as rescue medications.

Types of outcome measures

Primary outcomes

- Number of asthma exacerbations of moderate intensity, that is, requiring a short course of systemic corticosteroids.

Secondary outcomes

- Admissions to hospital.
- Urgent care visits.
- Pulmonary function tests (morning and evening peak expiratory flow (PEF) or forced expiratory flow rate in one second (FEV_1)).
- Symptoms.
- Quality of life scores.
- Use of rescue SABA.
- Nighttime awakening.
- Changes in measures of inflammation such as serum eosinophil cationic protein and sputum eosinophils.
- Rates of clinical and biochemical adverse effects.

- Any adverse effects including growth suppression, adrenal suppression, bone mineral loss and others. A suite of related Cochrane reviews considered serious adverse effects related to LABA (Cates 2008a; Cates 2009a; Cates 2009b).

Search methods for identification of studies

Electronic searches

We carried out an electronic literature search of the Cochrane Airways Group Specialised Register of asthma trials, which is derived from systematic searches of bibliographic databases including the Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE, EMBASE and the Cumulative Index to Nursing and Allied Health Literature (CINAHL), and we handsearched respiratory journals and meeting abstracts (see Appendix 1 for additional details). This Register also includes a variety of studies published in foreign languages. We did not exclude trials on the basis of language. In Appendix 2, we have detailed search methods used in the previous version of this review. For this update, we searched the Register from May 2008 to January 2015, using the strategy presented in Appendix 3.

Searching other resources

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

We searched manufacturers' and clinical trial websites (Glaxo Smith Kline clinical trials website ; AstraZeneca clinical trials website; Novartis clinical trial results website; Clinical Study Results) to identify other published or unpublished study data.

Data collection and analysis

Selection of studies

From the title, abstract or descriptors, two of three review authors (BC, MNC, SM) independently reviewed the literature searches. We excluded all studies that were not randomised controlled trials or that clearly did not fit the inclusion criteria. Two review authors independently reviewed all other citations in full text to assess eligibility.

Data extraction and management

Two of four review authors (BC, MNC, CC, SM) independently extracted data from included trials onto Excel spreadsheets and entered data into the Cochrane software program, Review Manager 5.3 (Review Manager (RevMan)). When necessary, we expanded graphic reproductions and estimations from other data presented in the paper. We contacted primary authors or sponsors to request confirmation of methods and data extraction and to ask for additional information, when needed.

We recorded the following as a 'User defined order'.

- Mean daily dose of ICS in trials in which both intervention and control groups used the same dose of ICS.
- Dose difference between groups in studies that compared LABA added to ICS with an increased dose of ICS. Researchers reported both values in chlorofluorocarbon (CFC)-propelled beclomethasone-equivalents, where 1 µg of beclomethasone dipropionate equates to 1 µg of budesonide and 0.5 µg of fluticasone propionate (NAEPP 2011), and all doses of inhaled medications as ex-valve, rather than ex-inhaler, values.

Assessment of risk of bias in included studies

We assessed risk of bias according to the following domains.

- Random sequence generation.
- Allocation concealment.
- Blinding of participants and personnel.
- Blinding of outcome assessment.
- Incomplete outcome data.
- Selective outcome reporting.
- Other bias.

For each domain, we judged risk of bias as low, unclear or high, in line with recommendations provided in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). We judged the study to have high methodological quality when reported randomisation procedures and blinding were adequate and low and balanced group attrition was noted, supporting low risk of bias.

Measures of treatment effect

We calculated treatment effects for dichotomous variables as pooled risk ratios (RRs) with 95% confidence intervals (CI). For continuous outcomes, such as pulmonary function tests, we calculated pooled statistics as mean differences (MD) or standardised mean differences (SMD) if results were reported on different scales and were reported with 95% CIs. When standard deviations were not presented but could be estimated from an effect estimate and use of confidence intervals, standard error or P value, we combined the MD with the generic inverse variance function (GIV) in Review Manager.

Unit of analysis issues

We excluded cross-over studies from contributing data to dichotomous measurements of exacerbations, as we used analyses that assumed measurements were taken from independent samples.

Dealing with missing data

We directly contacted study investigators (or study sponsors when trials had pharmaceutical company sponsorship) to request confirmation of methods and to ask for data missing from the original trial report, if needed.

Assessment of heterogeneity

We examined homogeneity of effect sizes between pooled studies by using the I^2 statistic, with 50% or more as the cutoff for exploring possible causes of heterogeneity (Higgins 2003; Higgins 2011). In the absence of heterogeneity, we used the fixed-effect model; otherwise, we applied the Dersimonian and Laird random-effects model (DerSimonian 1986) to the summary estimates. We reported results of the fixed-effect model unless otherwise stated in the text.

Assessment of reporting biases

We planned to use funnel plots to check for indications of possible publication bias and small-study effects, if we had been able to pool data from 10 or more studies.

Data synthesis

We performed meta-analyses using the Cochrane statistical package RevMan 5 (Review Manager (RevMan)) and assumed

equivalence if the risk ratio estimate and its confidence interval were between 0.9 and 1.1.

We performed the analysis to examine two main comparisons, namely, the combination of LABA and ICS versus:

- a similar dose of ICS with placebo, representing step 2 of the BTS guidelines; or
- an increased dose of ICS with placebo, representing step 3 of the BTS guidelines.

When a trial included more than two arms, we considered additional control-intervention group comparisons for this review. If the same group was used twice as a comparator in a three-arm study, we halved the number of participants in the group used twice to avoid over-representation. For event rates, we halved the denominator in the control group (Verberne 1998a; Verberne 1998b; Zimmerman 2004a; Zimmerman 2004b; Pohunek 2006a; Pohunek 2006b; Morice 2008a; Morice 2008b; Eid 2010a; Eid 2010b; SAM40012a; SAM40012b).

Subgroup analysis and investigation of heterogeneity

We planned subgroup analyses to explore possible reasons for heterogeneity and, in the absence of heterogeneity, to identify potential effect modifiers when the magnitude of benefit may vary according to baseline characteristics. We examined the following a priori defined subgroups.

- Magnitude of airway obstruction at baseline as determined by the mean percent predicted FEV_1: classified as mild (80% of predicted or more), moderate (61% to 79% of predicted) or severe (60% of predicted or less) (GINA 2015).
- Mean dose (ex-valve) of ICS in comparison 1 when LABA + ICS was compared with placebo + ICS, and the dose difference in comparison 2 when LABA + ICS was compared with increased doses of ICS, both reported in CFC-propelled beclomethasone-equivalent doses (µg/d) and portrayed as the user-defined number.
- Usual versus higher than usual dose (reported as ex-valve in µg) of the LABA (salmeterol or formoterol).
- Type of LABA given (salmeterol vs formoterol).
- Use of one or two devices to deliver the combination of ICS and LABA.
- Trial duration with trials ≤ 16 weeks compared with those ≥ 24 weeks.

Sensitivity analysis

We performed sensitivity analyses to assess whether results for our primary outcome were sensitive to blinding, publication status and funding.

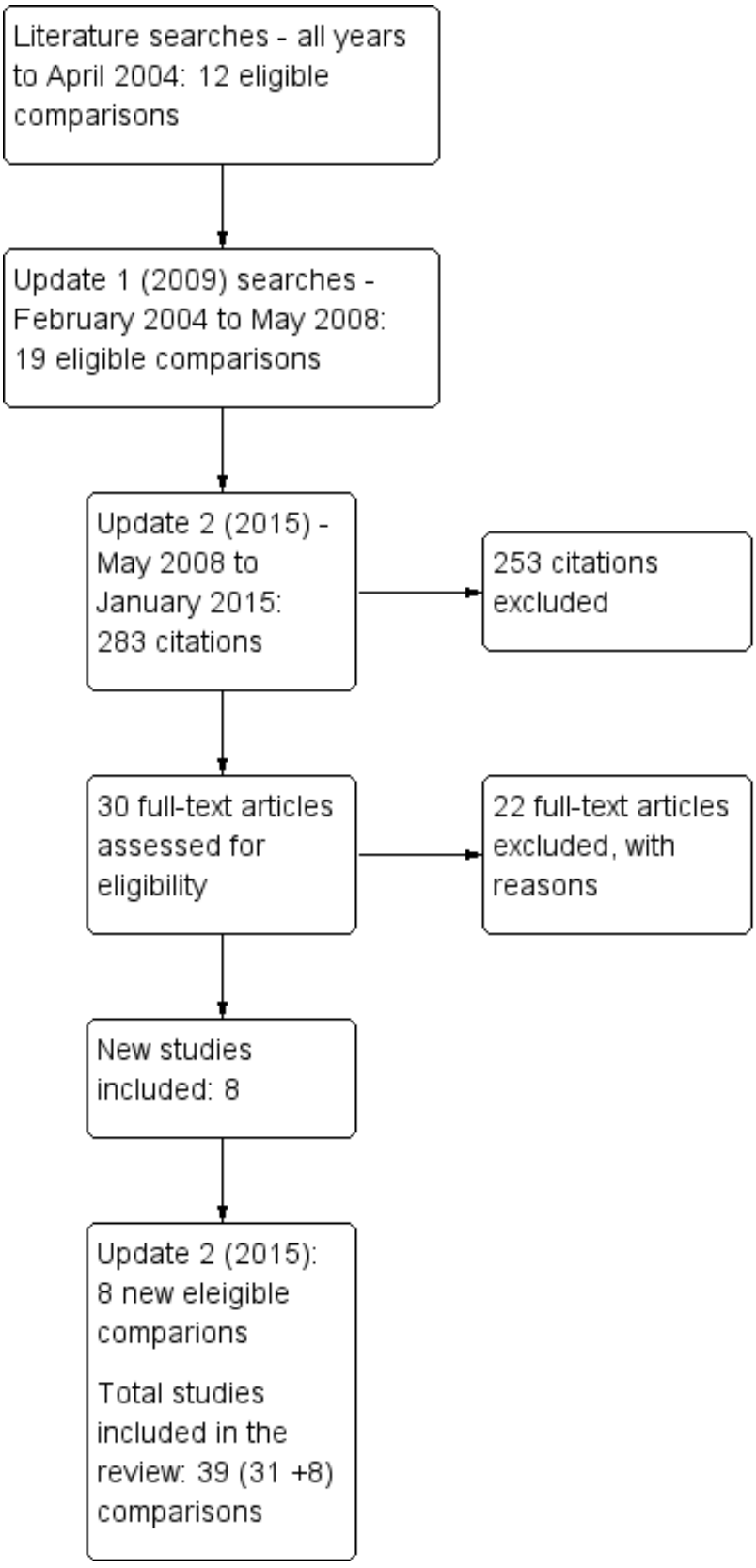
RESULTS

Description of studies

Results of the search

See Figure 1 for an overview of the literature search results, their assessment and inclusion of studies in the review. Updated electronic and additional handsearches from May 2008 to January 2015 yielded 283 additional citations. We included eight new trials, resulting in a total of 33 eligible trials representing 39 control-intervention comparisons.

Figure 1. Study flow diagram.



Please note that some of the study names have changed since the last published version to reflect the Cochrane study naming convention: SAM104926, SFA 100314, SD 039 0719, SD 039 0725a, SD 039 0725b, and SFA100316 and were replaced with De Blic 2009; Pearlman 2009; Berger 2010; Eid 2010a; Eid 2010band Murray 2011, respectively.

Six trials generated an additional control-intervention comparison. Three trials (representing six control-intervention comparisons) assessed two forms of additive therapy (ICS and LABA via one inhaler or via two inhaler devices against one dose of ICS): Pohunek 2006a; Pohunek 2006b; Morice 2008a; Morice 2008b; Eid 2010a; Eid 2010b. Three trials (representing six control-intervention comparisons) assessed one form of ICS and LABA versus two doses of ICS (Verberne 1998a; Verberne 1998b; Zimmerman 2004a; Zimmerman 2004b; SAM40012a; SAM40012b). The review therefore lists 39 control-intervention comparisons.

Included studies

A total of 33 trials randomly assigned 6381 children. Twenty-seven trials were available as full-text publications, and six trials were published as abstracts or were presented in unpublished reports of trials accessed through pharmaceutical company trial registries.

Most (69.7%) studies were funded by producers of both LABA and ICS inhalers: 13 were supported by GSK; nine by AstraZeneca; and one by Allen & Hanburys, a subsidiary of GSK in the United Kingdom (Russell 1995). Two were supported by grant agencies (Lemanske 2010; Lenney 2013), two were independently supported by a charitable organization (Langton Hewer 1995; Stelmach 2007) and five failed to identify the source of funding (Ortega-Cisneros 1998; Heuck 2000; Zimmerman 2004a; Zimmerman 2004b; Teper 2005; Stelmach 2008).

We classified studies into one of two comparisons according to the research question addressed. In accordance with therapeutic management as recommended by GINA 2015 and BTS 2014, we considered participants given low-dose ICS alone as receiving step 2 therapy. We referred to the comparison of LABA versus placebo added to the same ICS dose as step 3 versus step 2 comparison (28 control-intervention comparisons). Hereafter, we refer to comparisons testing the combination of LABA and ICS versus a double dose of ICS used before randomisation as a step 3 versus step 3 comparison (11 control-intervention comparisons). Bisgaard 2006 examined LABA added to a lower dose of ICS (BDP 100 µg) than has been advocated by international guidelines as step 3 and included this in the step 3/step 3 comparison.

We describe hereafter characteristics of studies that contributed outcome data to one or more comparisons in the review. For a full description of each eligible study, see Characteristics of included studies.

LABA + ICS versus same dose of ICS as used before randomisation (step 3 vs step 2)

Twenty-eight control-intervention comparisons randomly assigned 4753 children to assessLABA versus placebo added to the same dose of ICS in both groups (Langton Hewer 1995; Meijer 1995; Russell 1995; Simons 1997; Verberne 1998a; Akpinarli 1999; Tal 2002; Zimmerman 2004a; Zimmerman 2004b; Malone 2005; Teper 2005; Pohunek 2006a; Pohunek 2006b; Stelmach 2007; Morice 2008a; Morice 2008b; Stelmach 2008; Pearlman 2009; Rutkowski 2009; Berger 2010; Carroll 2010; Eid 2010a; Eid 2010b; Murray 2011; SAM40012a; Lenney 2013; SD 039 0714; SD 039 0718).

Participants

The mean age of participants was 11 years, and males accounted for 59% of study populations. Mean FEV_1 % predicted at baseline was ≥ 80% in 19 control-intervention comparisons: Morice 2008a; Morice 2008b; Langton Hewer 1995; Meijer 1995; Simons 1997; Verberne 1998a; Verberne 1998b; Malone 2005; Teper 2005; Pohunek 2006a; Pohunek 2006b; Stelmach 2007; Stelmach 2008; Pearlman 2009; Berger 2010; Carroll 2010; Murray 2011; Lenney 2013; SD 039 0718); 61% to 79% of predicted in six control-intervention comparisons (Russell 1995; Akpinarli 1999; Tal 2002; Zimmerman 2004a; Zimmerman 2004b; SD 039 0714) and unreported in the remaining studies. Participants were inadequately controlled before randomisation in all but four studies in which they were described as well controlled (Meijer 1995; Simons 1997; Pohunek 2006a; Pohunek 2006b), or when control was not reported (Teper 2005; Stelmach 2008; Rutkowski 2009; Berger 2010; Eid 2010a; Eid 2010b).

Interventions

Salmeterol was assessed in 12, and formoterol in 16, control-intervention comparisons. All but one comparison tested the usual recommended dose of the LABA (i.e. salmeterol 50 µg twice daily, formoterol 4.5, 6 or 12 µg twice daily); Langton Hewer 1995 used salmeterol 100 µg twice daily. The dose of ICS (beclomethasone-equivalent) was 200 µg/d in five studies (Stelmach 2007; Stelmach 2008; Eid 2010a; Eid 2010b; SD 039 0718); 400 µg/d in 13 control-intervention comparisons (Verberne 1998a; Tal 2002; Malone 2005; Pohunek 2006a; Pohunek 2006b; Morice 2008a; Morice 2008b; Pearlman 2009; Carroll 2010; Murray 2011; SAM40012a; Lenney 2013; SD 039 0714), 500 µg/d in two studies (Meijer 1995; Teper 2005), 800 µg/d in two studies (Rutkowski 2009; Berger 2010) and unspecified or varied in six studies (Langton Hewer 1995; Russell 1995; Simons 1997; Akpinarli 1999; Zimmerman 2004a; Zimmerman 2004b). Eighteen (46%) control-intervention comparisons assessed the combination of LABA and ICS in a single device; the remainder assessed the efficacy and safety of a LABA administered separately from an ICS.

Trial duration ranged from eight weeks or less in nine studies (Langton Hewer 1995; Simons 1997; Akpinarli 1999; Stelmach 2007; Stelmach 2008; Rutkowski 2009; Pearlman 2009; Carroll 2010; Murray 2011), to 12 to 16 weeks in 14 control-intervention comparisons (Meijer 1995; Russell 1995; Tal 2002; Zimmerman 2004a; Zimmerman 2004b; Malone 2005; Pohunek 2006a; Pohunek 2006b; Morice 2008a; Morice 2008b; Eid 2010a; Eid 2010b; SD 039 0718; SD 039 0714), to 24 to 26 weeks in two studies (Berger 2010; SAM40012a) to 48 to 52 weeks in three studies (Verberne 1998a; Teper 2005; Lenney 2013).

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

medications such as inhaled SABA and systemic steroids were permitted in all studies.

Outcomes

The primary outcome - the number of children with at least one exacerbation requiring systemic steroids - was reported by 12 studies. When data were not reported, or were described only in a format we could not use directly, we asked study sponsors to provide further information, if possible. Our requests for data on exacerbations requiring rescue oral steroids for Pohunek 2006a; Pohunek 2006b; Stelmach 2007; Morice 2008a; Morice 2008b; SD 039 0718 and SD 039 0714 yielded no response.

Hospital admission data were available for seven studies. Measurement of lung function was reported in most studies. Many studies reported other secondary outcomes. Withdrawals were reported in all but five studies (Meijer 1995; Akpinarli 1999; Teper 2005; Stelmach 2008; Rutkowski 2009). Adverse events were reported in all studies except Stelmach 2008; Rutkowski 2009; Berger 2010; Carroll 2010; Lemanske 2010 and Lenney 2013.

LABA + ICS versus increased dose of ICS (step 3/step3)

A total of 11 studies, representing 1628 children, assessed the addition of LABA versus placebo to ICS therapy with increased dose of ICS in the control group (Ortega-Cisneros 1998; Verberne 1998b; Heuck 2000; Bisgaard 2006; De Blic 2009; Gappa 2009; Lemanske 2010; Murray 2010; Vaessen-Verberne 2010; SAM40100; SAM40012b). Three studies did not contribute data (Ortega-Cisneros 1998; Heuck 2000; Lemanske 2010).

Participants

The mean age of participants was 10 years and 64% were male. Baseline airway obstruction was reported in seven of the 11 studies (Verberne 1998b; Heuck 2000; Bisgaard 2006: Gappa 2009; Lemanske 2010; Murray 2010; Vaessen-Verberne 2010). Mean FEV_1 % predicted at baseline was ≥ 80% in five control-intervention comparisons (Verberne 1998b; Gappa 2009; Lemanske 2010; Murray 2010; Vaessen-Verberne 2010).

Interventions

Salmeterol and formoterol were evaluated in eight and three studies, respectively. All comparisons tested the usual recommended dose of the LABA (i.e. salmeterol 50 µg twice daily, formoterol 6 or 12 µg twice daily). Intervention groups in eight studies received BDP equivalent doses of 400 µg/d (Verberne 1998b; De Blic 2009; Gappa 2009; Lemanske 2010; Murray 2010; Vaessen-Verberne 2010; SAM40100; SAM40012b). BDP at 100 µg/d was used in Bisgaard 2006, and 200 µg/d was used in Heuck 2000. Respective control groups received twice the dose of ICS administered to the intervention group. Four studies assessed LABA and ICS as a single inhaler administration (Bisgaard 2006; De Blic 2009; SAM40100; SAM40012b).

Study duration was six to eight weeks in three studies (Gappa 2009; Murray 2010; SAM40100), 12 to 16 weeks in four studies (Heuck 2000; Bisgaard 2006; De Blic 2009; Lemanske 2010), 26 weeks in two comparisons (Vaessen-Verberne 2010; SAM40012b), and one year in one study (Verberne 1998b).

All studies recruited children who were taking an ICS at baseline. Rescue medications such as inhaled SABA and systemic steroids were permitted in all trials.

Outcome data (obtaining data from trial authors)

Data on the primary outcome were available from three studies (Verberne 1998b; De Blic 2009; Vaessen-Verberne 2010). When data were not reported, or were described for an undefined exacerbation or composite of types of exacerbations, we requested study sponsors to provide further information. Our requests for data on exacerbations requiring rescue oral corticosteroids (OCS) from study sponsors for Bisgaard 2006, SAM40012b and SAM40100 have not been successful.

Hospital admission data were available for four studies. Lung function outcomes were available for all studies. Most studies provided data on symptoms, SABA use, adverse events and withdrawals. Two studies provided data on linear growth (Verberne 1998b; Bisgaard 2006).

Excluded studies

Details of 85 excluded studies, for which full-text articles were examined to judge eligibility, are listed in Characteristics of excluded studies along with reasons for their exclusion (this number is drawn from searches over all years January 2015 across this review).

Risk of bias in included studies

We have provided an overview of judgements on domains related to risk of bias in Figure 2. We have summarised our findings below.

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

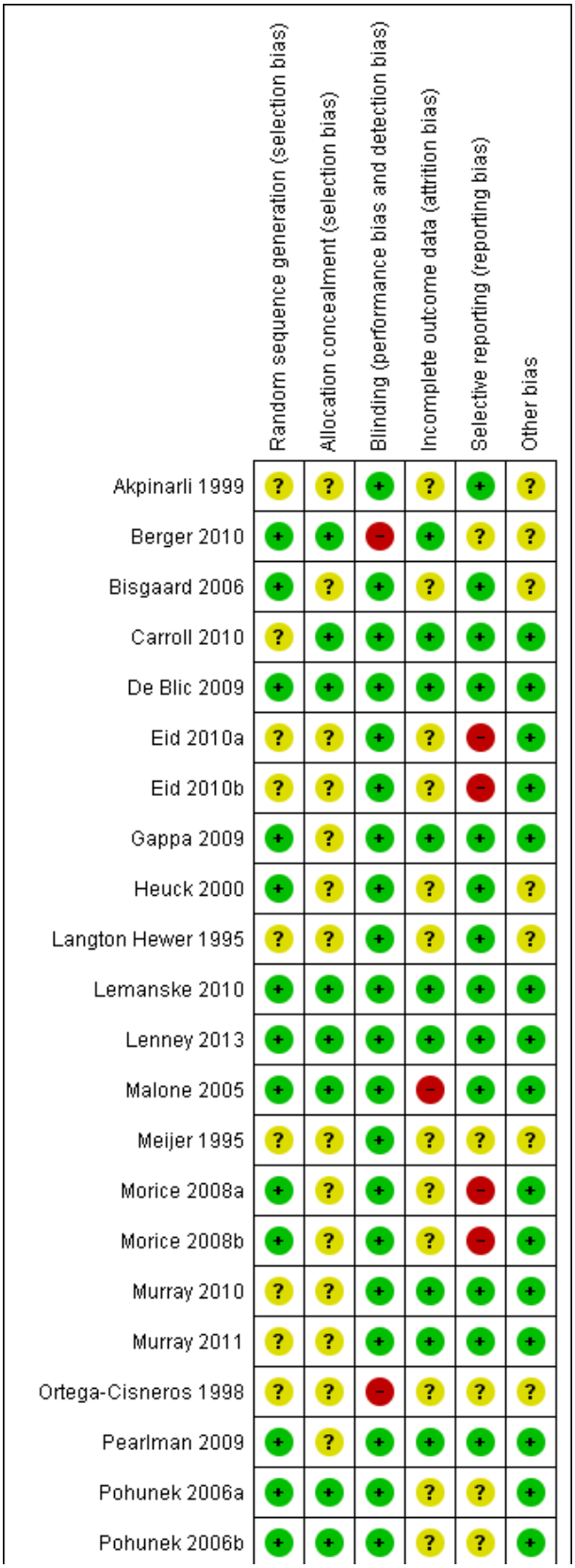
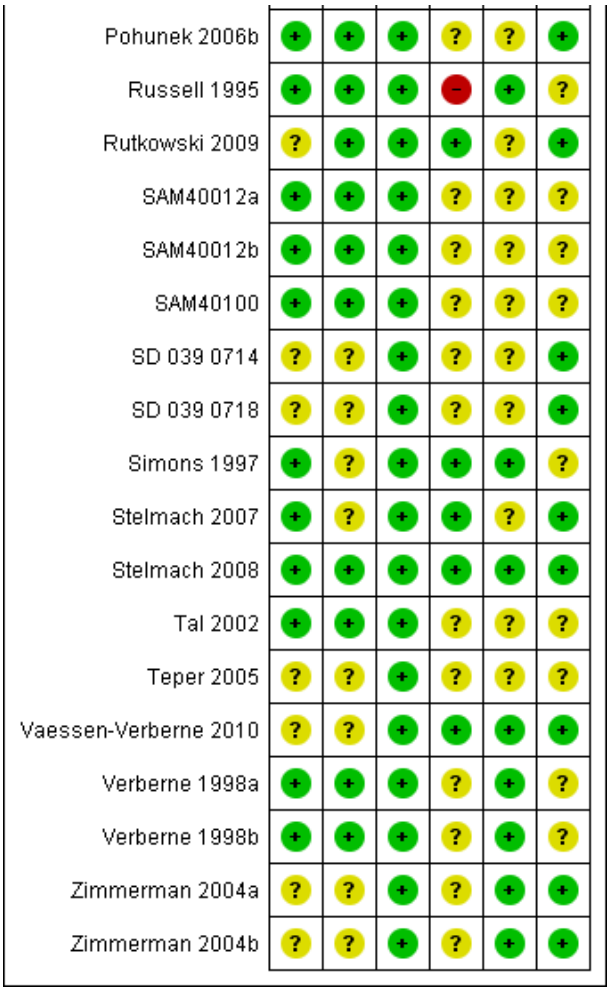


Figure 2. (Continued)



We verified with study authors study details for six control-intervention comparisons (Russell 1995; Simons 1997; Verberne 1998a; Verberne 1998b; Pohunek 2006a; Pohunek 2006b). Information on the design of GSK-sponsored studies was provided in correspondence (Appendix 4). A total of 23 comparisons reported the randomisation technique in adequate detail, and we assessed remaining studies as unclear on the basis of inadequate reporting of the randomisation technique.

Allocation

Seventeen studies reported adequate details on allocation concealment of intervention treatment, and 22 provided unclear information.

Blinding

Double-dummy designs or use of identical inhaler devices in 37 comparisons maintained blinding of the intervention. Two studies had an open-label design (Ortega-Cisneros 1998; Berger 2010).

Incomplete outcome data

Information on the definition of intention-to-treat principle used across studies was insufficient. Our judgement of this aspect of the studies reflects uncertainty over the reliability of stated methods. However, on the basis of our judgements, we designated 14 comparisons as high-quality trials reporting complete outcomes, 23 as unclear and two as having high risk of bias (Russell 1995; Eid 2010a; Eid 2010b).

Selective reporting

We did not find major selective reporting bias in included studies. Availability of our prespecified primary outcome - participants with exacerbations requiring rescue systemic steroids - from trial reports was limited. This can be explained in part by the different definitions of exacerbation used by investigators across studies. Despite extensive efforts to obtain data for our primary outcome, we obtained a limited quantity of available data for analysis. We remain uncertain as to whether data for this endpoint were collected in nine studies (Langton Hewer 1995; Meijer 1995; Ortega-Cisneros 1998; Tal 2002; Pohunek 2006a; Pohunek 2006b; Teper 2005; Stelmach 2007; SAM40100); 21 were at low risk, 14 at unclear risk and four at high risk.

Other potential sources of bias

In all, 23 studies were at low risk and 16 were at unclear risk.

Effects of interventions

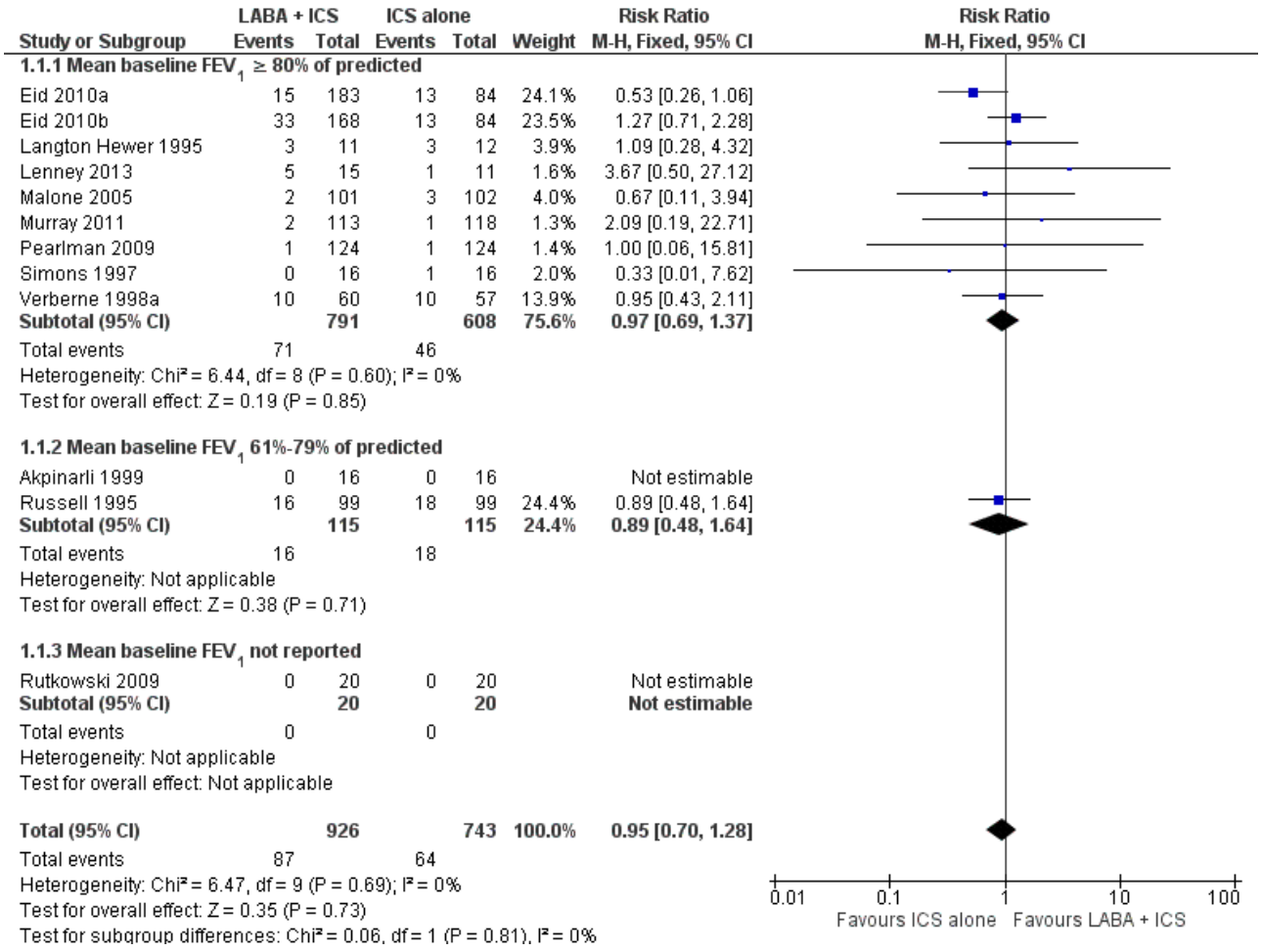
See: **Summary of findings for the main comparison**; **Summary of findings 2**

LABA + ICS versus same dose of ICS (step 3 vs step 2)

Primary outcome: participants with at least one exacerbation requiring systemic steroids

Investigators reported no statistically significant differences between treatments in the number of participants with exacerbations requiring systemic corticosteroids (12 studies; RR 0.95, 95% CI 0.70 to 1.28, N = 1669; Analysis 1.1; Figure 3).

Figure 3. Forest plot of comparison: 1 LABA versus placebo: both groups receiving similar dose ICS, outcome: 1.1 # participants with exacerbations requiring systemic steroids.



Subgroup analysis

We performed subgroup analysis based on characteristics of participants and interventions to evaluate their influence on the magnitude of the primary outcome. Airway obstruction as determined by baseline mean FEV_1 (Analysis 1.1), dose of ICS (Analysis 3.1), dose of LABA (Analysis 3.2), type of LABA (Analysis 3.3), use of single versus separate inhaler(s) to deliver LABA and ICS (Analysis 3.4) and trial duration (Analysis 3.5) did not influence the magnitude of response.

Sensitivity analysis

We performed a sensitivity analysis on the primary outcome. The primary outcome was robust and was not influenced by the funding source (Analysis 3.6) or by publication status (Analysis 3.7). All studies contributing data to the primary outcome were double-blinded, thus preventing exclusion of unblinded trials.

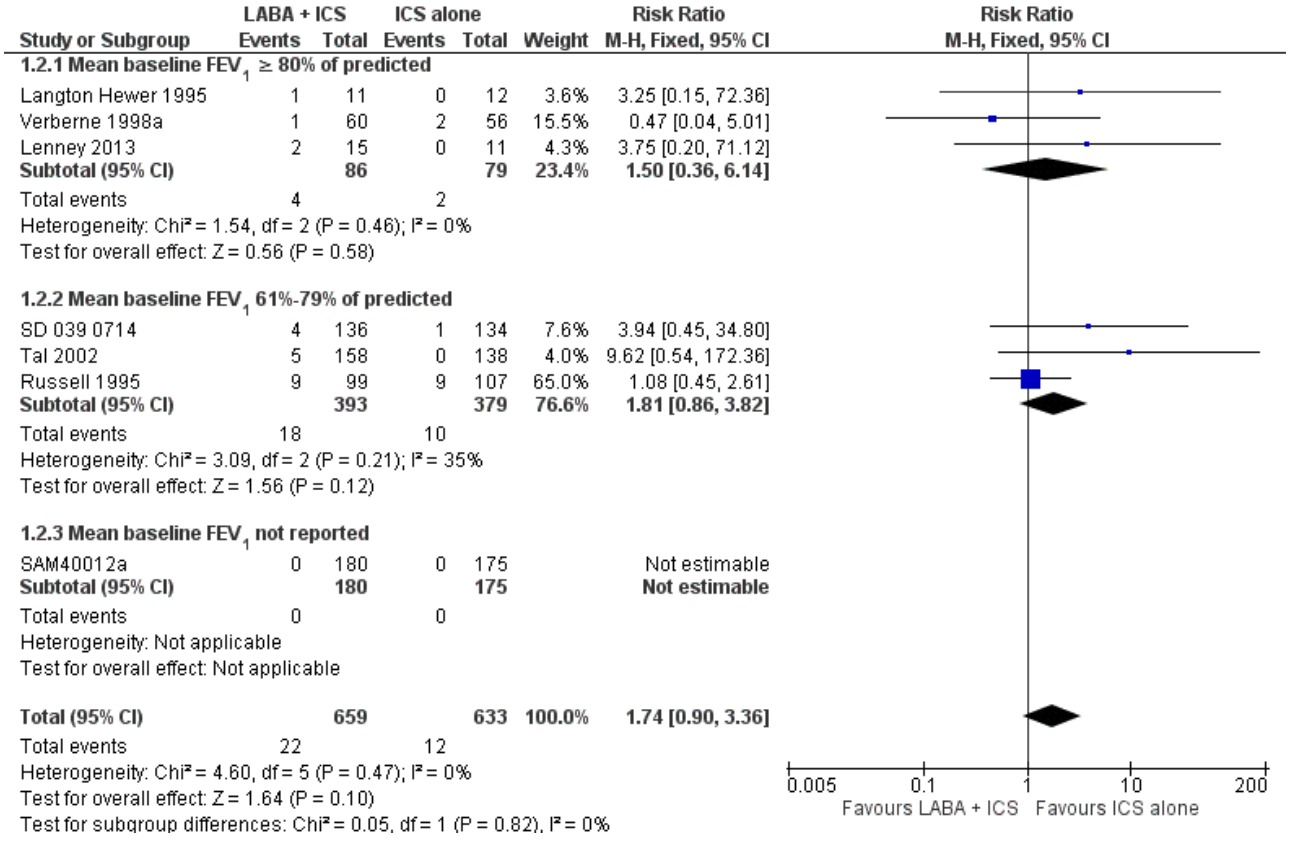
Secondary outcomes

Hospital admission, urgent care visit, withdrawal

Researchers found no statistically significant differences in numbers of participants with exacerbations requiring hospital admission (seven studies, RR 1.74, 95% CI 0.90 to 3.36, N = 1292; Analysis 1.2; Figure 4), numbers of participants with exacerbations requiring urgent care visit (one study, RR 0.29, 95% CI 0.09 to 0.96, N = 186; Analysis 1.3), withdrawals due to poor asthma control (14 studies, RR 0.81, 95% CI 0.57 to 1.16, N = 2255; Analysis 1.6), withdrawals due to adverse events (18 studies, RR 0.79, 95% CI 0.52 to 1.21, N = 4117; Analysis 1.7) or withdrawals due to serious non-

respiratory events (two studies, RR 4.66, 95% CI 0.23 to 96.30; N = 318; Analysis 1.8). Withdrawals for any reason were significantly fewer with LABA than with placebo (23 studies, RR 0.80, 95% CI 0.67 to 0.94, N = 4374; Analysis 1.5).

Figure 4. Forest plot of comparison: 1 LABA versus placebo: both groups receiving similar dose ICS, outcome: 1.2 # participants with exacerbations requiring hospitalisation.



Lung function

LABA added to ICS provided significantly greater improvement in lung function from baseline compared with the same dose of ICS. This was true, irrespective of whether group differences were reported for FEV_1 as change in litres (inverse variance (IV) 0.08 L, 95% CI 0.06 to 0.10, nine studies, N = 1942; Analysis 1.9), change in % predicted (MD 2.99%, 95% CI 0.86 to 5.11; seven studies, N = 534; Analysis 1.10) or change in morning PEF (MD 10.20 L/min, 95% CI 8.14 to 12.26, 16 studies, N = 3934; Analysis 1.12; and one study, MD 3.77%, 95% CI 1.84 to 5.70, N = 286; Analysis 1.13) or evening PEF (MD 9.30 L/min, 95% CI 6.96 to 11.65, 12 studies, N = 3140; Analysis 1.14; and MD 3.40%, 95% CI 1.54 to 5.26, one study, N = 286; Analysis 1.15). The change in clinic PEF (Analysis 1.16) and the variability in PEF (Analysis 1.17) could not be aggregated, as they were reported by a single trial. Studies contributing data to lung function endpoints recruited children with mild to moderate airway obstruction, with a range of lung function at baseline; they examined the effects of both salmeterol and formoterol, given in conjunction with a range of doses of ICS. The % fall in FEV_1 % predicted due to exercise showed no significant group difference (three studies, MD 0.46%, 95% CI -1.00 to 1.93, N = 517; Analysis 1.11).

Symptoms, rescue SABA use and quality of life

LABA added to ICS resulted in significant group differences for the following outcomes: change in daytime use of rescue SABA (MD -0.07 puffs/d, 95% CI -0.11 to -0.02, seven studies, N = 1798; Analysis 1.23) and change in nighttime use of rescue SABA (MD -0.08 puffs/d, 95% CI -0.13 to -0.03, three studies, N = 672; Analysis 1.24).

The addition of LABA did not result in significant group differences for the following outcomes: change in mean symptom scores (SMD -0.07, 95% CI -0.17 to 0.04, six studies, N = 1653; Analysis 1.18), change in nighttime symptom scores (two studies, MD -0.03, 95% CI -0.07 to 0.02, N = 534; Analysis 1.19), change in % symptom-free days at endpoint (MD 0.96, 95% CI -1.91 to 3.84, seven studies, N = 1831; Analysis 1.20), % symptom-free days (MD -0.04, 95% CI -0.20 to 0.12, four studies, N = 623; Analysis 1.21), % symptom-free nights (MD 0.00, 95% CI -2.38 to 2.38, one study, N = 82; Analysis 1.22), % days without bronchodilator use (MD 2.07, 95% CI -1.03 to 5.16, seven studies, N = 1710, random-effects model; Analysis 1.25), change in nighttime awakening (number of nights) (MD 0.20, 95% CI -2.21 to 2.61, one study, N = 286; Analysis 1.26), % nights with awakening (MD -1.10, 95% CI -3.51 to 1.31, one study, N = 286; Analysis 1.27), % change in awakening-free nights (MD 0.60, 95% CI -1.05 to 2.26, N = 519; Analysis 1.28), change in rescue medication-free days (two studies, MD -2.20, 95% CI -12.15 to 7.75, two studies, N = 231; Analysis 1.29), % change in asthma control days (MD 4.30, 95% CI -5.56 to 9.16, two studies, N = 519; Analysis 1.30), change in

paediatric asthma quality of life (MD -0.02, 95% CI -0.14 to 0.10, four studies, N = 668; Analysis 1.31), absolute paediatric asthma quality of life (MD 0.03, 95% CI -0.04 to 0.11, 10 studies, N = 2333; Analysis 1.32) and change in paediatric asthma caregiver quality of life (MD 0.07, 95% CI -0.05 to 0.18; four studies, N = 669; Analysis 1.33).

Adverse events

There was no statistically significant differences in risk of overall adverse effects (RR 1.04, 95% 0.98 to 1.10, 15 studies, N = 3284; Analysis 1.34), reaching our a priori defined criterion for equivalence. However, for specific adverse effects, confidence intervals are wide, so we cannot rule out differences in any of these specific events. Specifically, there was no significant group differences in risk of oral candidiasis (RR 3.41, 95% CI 0.73 to 15.87, six studies, N = 1341; Analysis 1.35), tremor (RR 3.07, 95% CI 0.38 to 25.05, six studies, N = 1467; Analysis 1.36), palpitations (RR 0.44, 95% CI 0.08 to 2.31, six studies, N = 1238; Analysis 1.37), headache (RR 1.10, 95% CI 0.90 to 1.33, 14 studies, N = 2966; Analysis 1.38), vomiting (RR 0.74, 95% CI 0.34 to 1.62, three studies, N = 707; Analysis 1.39), otitis media (RR 0.70, 95% CI 0.30 to 1.63, three studies, N = 707; Analysis 1.40), upper respiratory tract infection (RR 0.86, 95% CI 0.58 to 1.27, five studies, N = 1186; Analysis 1.41), urticaria (RR 0.11, 95% CI 0.01 to 2.04, one study, N = 248; Analysis 1.42), cardiovascular adverse events (RR 0.31, 95% CI 0.01 to 7.49, two studies, N = 148; Analysis 1.43) and serious adverse events (RR 1.17, 95% CI 0.75 to 1.85, 17 studies, N = 4021; Analysis 1.4), Although effects on growth could not be aggregated because only one study documented this outcome (Verberne 1998a), data show no statistically significant group differences in growth velocity over 52 weeks among prepubertal children (mean age 10 to 11 years) when beclomethasone 400 µg with salmeterol was compared with beclomethasone 400 µg alone (5.1 cm vs 4.5 cm, respectively; Analysis 1.47). In three studies that recorded mortality, no deaths were mentioned (Analysis 1.44).

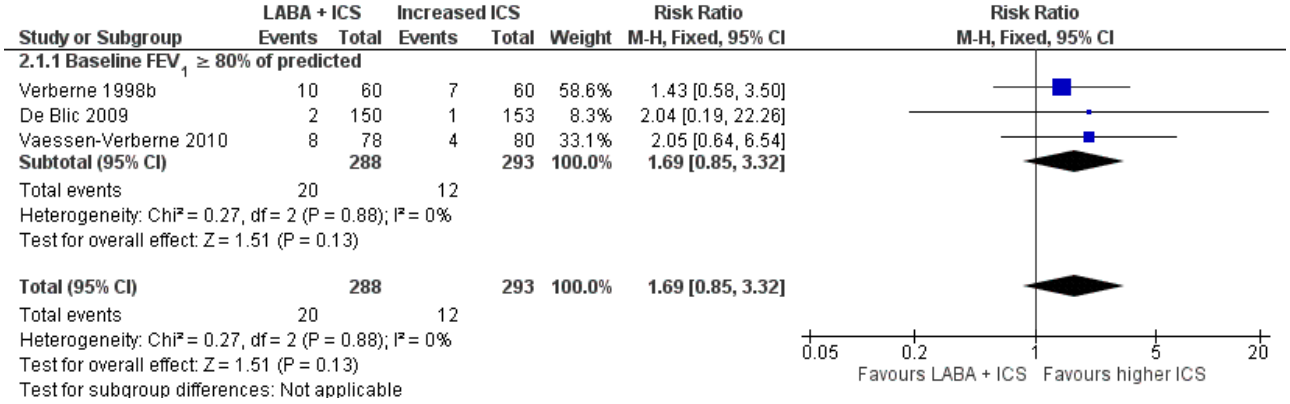
LABA and ICS versus increased dose of ICS (step 3 vs step 3)

Eight studies on 1520 participants contributed data to outcomes under this comparison (Verberne 1998b; Bisgaard 2006; De Blic 2009; Gappa 2009; Vaessen-Verberne 2010; Murray 2010; SAM40100; SAM40012b).

Primary outcome: participants with at least one exacerbation requiring systemic steroids

Despite correspondence with study sponsors to obtain data on exacerbations requiring rescue oral steroids, we obtained data from only three studies (Verberne 1998b; De Blic 2009; Vaessen-Verberne 2010). There was no significant group differences in the number of participants with exacerbations requiring OCS (RR 1.69, 95% CI 0.85 to 3.32, three studies, N = 581; Analysis 2.1; Figure 5). All trials contributing data to the primary outcome recruited participants with mild airway obstruction (FEV_1 % predicted ≥ 80%).

Figure 5. Forest plot of comparison: 2 LABA + ICS versus placebo + higher dose of ICS, outcome: 2.1 # participants with exacerbations requiring oral steroids.



Subgroup analysis

We performed subgroup analysis to evaluate the potential influence of characteristics of participants and interventions on the magnitude of the primary outcome. Dose of ICS (Analysis 4.1), dose of LABA (Analysis 4.2), type of LABA (Analysis 4.3), use of single versus separate inhaler(s) to deliver LABA and ICS (Analysis 4.4) and trial duration (Analysis 4.5) did not influence the magnitude of response.

Sensitivity analysis

We performed sensitivity analysis by including data from Lemanske 2010, which was a cross-over study that reported data on the number of participants with exacerbations requiring oral corticosteroids and contributed the greatest weight by including the largest number of participants. There was no significant group difference in numbers of participants with exacerbations requiring OCS (RR 0.93, 95% CI 0.64 to 1.33, four studies, N = 895; Analysis 5.1). We were not able to perform the other sensitivity analysis, as all trials contributing data on the primary outcome were funded by producers of LABA and ICS, were published as full-text articles and were double-blinded.

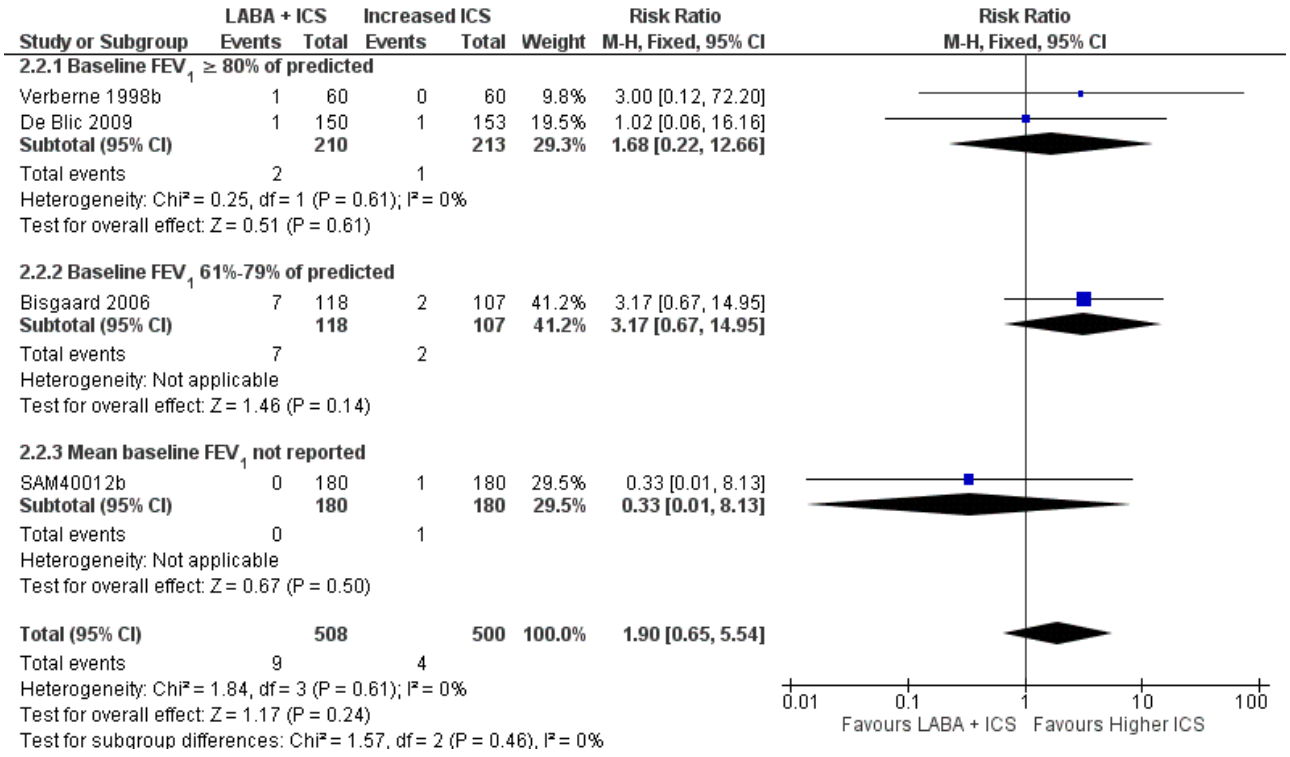
Secondary outcomes

Hospital admission, urgent care visit, withdrawal

There was no significant group difference in the number of participants with exacerbations requiring hospital admission (RR 1.90, 95% CI 0.65 to 5.54, four studies, N = 1008; Analysis 2.2; Figure 6) or an urgent care visit (RR 5.13, 95% CI 0.25 to 105.10, one study, N = 158; Analysis 2.3). Data also showed no statistically significant group differences in overall risk of all-cause withdrawals (RR 0.96, 95% CI 0.67 to 1.37, eight studies, N = 1491; Analysis 2.5), withdrawals due to poor asthma control (RR 0.34, 95% CI 0.05 to

2.13, four studies, N = 862; Analysis 2.6) and withdrawals due to adverse events (RR 0.76, 95% CI 0.19 to 3.07, five studies, N = 951; Analysis 2.7). Only one trial reported withdrawals due to a serious non-respiratory event, none of which occurred (Analysis 2.8), thus preventing aggregation.

Figure 6. Forest plot of comparison: 2 LABA + ICS versus placebo + higher dose of ICS, outcome: 2.2 # participants with exacerbations requiring hospitalisation.



Lung function

LABA added to ICS led to greater improvement from baseline in the change in morning PEF (MD 8.73 L/min, 95% CI 5.15 to 12.31, five studies, N = 1283; Analysis 2.11) and evening PEF (MD 6.5 L/min, 95% CI 2.64 to 10.37, four studies, N = 1163; Analysis 2.12). Similarly, data showed a significant group difference in change in PEF recorded at clinic visit at the end point (MD 8.33 L/min, 95% CI 2.12 to 14.54, two studies, N = 637; Analysis 2.13). Changes from baseline in FEV_1 between treatment options were not statistically significant (MD 0.01 L, 95% CI -0.03 to 0.05, two trials, N = 526; Analysis 2.9; and MD 0.38%, 95% CI -0.39 to 1.15, two trials, N = 682; Analysis 2.10). Data were insufficient for pooling of other lung function data.

Symptoms and SABA

There was no statistically significant group difference in change in daytime asthma symptom score (MD 0.01 L, 95% CI -0.20 to 0.23, three studies, N = 329; Analysis 2.17) and change in nighttime asthma symptom score (MD 0.01 L, 95% CI -0.20 to 0.23, three studies, N = 329; Analysis 2.18). Studies were insufficient for aggregation of other data related to markers of symptoms and use of rescue SABA.

Adverse events

There was no statistically significant difference in risk of overall adverse effects (RR 1.01, 95% CI 0.92 to 1.10, seven studies, N = 1254; Analysis 2.28), meeting our a priori criteria for equivalence. However, the specific adverse events have wide confidence intervals, so we cannot rule out a difference in any of these specific events. Data show no significant group difference in risk of oral candidiasis (RR 0.76, 95% CI 0.17 to 3.30, three studies, N = 182; Analysis 2.29), headache (RR 1.13, 95% CI 0.85 to 1.50, five studies, N = 1230; Analysis 2.30) and serious adverse events (RR 1.54, 95% CI 0.81 to 2.94, seven studies, N = 1343; Analysis 2.4). Other adverse events including vomiting, cold, upper respiratory tract infection and death could not be aggregated because trials reporting data are lacking. Two studies measured linear growth over one year (Verberne 1998b; Bisgaard 2006); findings favoured LABA treatment for children by an average of 1.21 cm/y (95% CI 0.72 to 1.7; Analysis 2.34).

DISCUSSION

Summary of main results

Exacerbations requiring systemic steroids in school-aged children with inadequately controlled asthma despite the use of daily low-dose ICS were not significantly reduced by adding LABA to ICS compared with using the same, or an increased, dose of ICS. A priori defined subgroup analysis indicates that characteristics of participants or of the intervention did not influence outcomes.

Although not statistically significant, a trend towards increased risk of exacerbations requiring hospital admissions was noted in children treated with combination therapy. This trend towards increased risk of hospital admission with the addition of LABA

compared with the same dose of ICS (step 2) or an increased dose of ICS (step 3) is a matter of concern, particularly as combination therapy failed to show any benefit in reducing severity markers including the primary outcome, that is, exacerbation requiring systemic steroids.

With regard to secondary outcomes, lung function endpoints consistently favoured the addition of LABA to ICS therapy, whether compared with the same or an increased dose of ICS. A modest reduction in the use of rescue SABA was evident with the addition of LABA to ICS when compared with the same dose of ICS; however, data were insufficient to pool for comparison with an increased ICS dose. In contrast, LABA added to ICS did not result in significantly greater improvement in asthma symptoms compared with the same or an increased dose of ICS. With the exception of growth, data show no statistically significant group differences in reported adverse events; overall adverse events met our definition of equivalence. The combination of LABA and ICS led to greater gain in linear growth than was seen with an increased dose of ICS; this is consistent with recent findings of a dose-response effect of ICS on growth in children (Pruteanu 2014).

In this paediatric review, LABA added to ICS did not result in improvement in most other clinical indicators of asthma control and future risk of exacerbations. We recognised that absence of a significant group difference in other clinical indicators of asthma control may be due to mild asthma severity among most participants. Yet, aggregation of the best available evidence to date provides little data to support the addition of LABA to ICS in children insufficiently controlled by ICS monotherapy.

Overall completeness and applicability of evidence

Although we identified several unpublished studies, we had only limited success in obtaining useable data for our primary outcome. We successfully obtained data for exacerbations requiring rescue systemic steroids and for hospital admissions for a small number of trials from a recent meta-analysis of GSK-sponsored trials (Bateman 2008). Few data in study reports are available as downloads from pharmaceutical company trial results registries.

Quality of the evidence

Overall we judged the quality of evidence to be moderate. Most outcomes showed wide confidence intervals, which led to downgrading of evidence quality to moderate. In a few outcomes for which open-label studies contributed data, we further downgraded evidence quality to low.

Potential biases in the review process

These findings are consistent with findings of Bisgaard 2003. Of note, about half of the trials in our review were conducted in school-aged children treated predominantly with ICS and LABA delivered in separate (rather than single) devices. Although adherence to ICS may have been suboptimal, we cannot speculate whether different results would have been obtained if most trials had used a single device to deliver LABA and ICS. Is it possible that ongoing inflammation associated with use of a lower dose of ICS or tachyphylaxis associated with prolonged use of LABA may be associated with more severe exacerbations with combination therapy. In light of the prevailing uncertainty and an FDA mandate, a large six-month study, to evaluate safety and benefit of LABA and ICS (salmeterol and fluticasone), is ongoing in children of four to 11 years of age. Outcomes of the study will shed more light on the safety and benefits of this combination (NCT01462344).

Agreements and disagreements with other studies or reviews

Our findings contrast with some of the estimates derived from the systematic review of adult trials performing the same comparisons (Ducharme 2010). Indeed, when compared with a similar dose of ICS, LABA added to ICS reduces by 20% the risk for adults with exacerbations requiring systemic steroids (RR 0.77, 95% CI 0.68 to 0.88; Ducharme 2010). This was accompanied by notably greater improvement in lung function (170 mL in FEV_1) and symptom-free days (+ 17%) and a modest reduction in use of rescue SABA (-0.7 puffs/d). Given the smaller lung volumes in children, the observed 80 mL greater improvement in FEV_1 associated with LABA added to ICS in children may be of clinical importance. However, observed improvement in lung function was expected, given that LABA is a bronchodilator, and children were selected primarily on the basis of significant reversibility with SABA to confirm the diagnosis of asthma. This apparent discordance between outcomes may be due to a more rapid effect of LABA on lung function, which is more easily detectable in studies of short duration, whereas a longer period of follow-up may be required to detect an effect on exacerbations, particularly among children with normal or near normal lung function.

With regard to the second comparison - LABA and ICS versus a higher dose of ICS - findings also differ from a Cochrane Review of studies in adults (Ducharme 2010a), which demonstrates a significant reduction associated with LABA in the risk of patients with exacerbations requiring rescue systemic steroids (RR 0.88, 95% CI 0.78 to 0.98). Despite identification of 11 studies, only four provided data for the primary outcome. A modest improvement (< 9 L/min) in morning and evening PEF, but not in FEV_1, was associated with use of LABA compared with a higher ICS dose. Insufficient reporting prevented aggregation of most outcomes. However, the trend towards a higher proportion of exacerbations requiring hospital admission and serious adverse events in children using LABA in combination with ICS, compared with a high dose of ICS, is a matter of concern. Findings are consistent with an overview of Cochrane Reviews evaluating the safety of formoterol or salmeterol in children with asthma (Cates 2012), in which review authors reported an additional three children per 1000 who suffered a non-fatal serious adverse event with combination therapy in comparison with ICS over three months. Meanwhile, available data are also insufficient to allow firm recommendations regarding the preference of increasing the ICS dose versus adding LABA to ICS as a step 3 strategy. One must weigh the greater linear growth (reported in only two trials with beclomethasone and budesonide - molecules known to be associated with growth suppression) (Skoner 2000; CAMP Research Group 2012) and the improvement in PEF against the possible, but unproven, increased risk of greater severity of exacerbations associated with combination therapy.

Data show no group differences in adverse effects or withdrawals due to adverse effects when the combination of LABA and ICS was compared with the step 2 or step 3 strategy. Of note, side effects were scarcely reported in short-term trials, and long-term studies were lacking. Moreover, although an increased dose of ICS calls for assessment of growth, adrenal function and bone mineralisation in children, no trial reported data on adrenal

function and bone mineralisation that could be aggregated. Only two studies reporting the addition of LABA to 400 versus 800 µg of beclomethasone (Verberne 1998b) and to 100 versus 400 µg of budesonide (Bisgaard 2006) examined growth, for a differential of 300 to 400 µg of BDP-equivalent. The observed reduction in growth averaging 1.2 cm/y is consistent with the documented decrease in linear growth associated with 400 µg/d of BDP (Sharek 1999; Pruteanu 2014) and the documented dose-response relationship between growth impairment and ICS dose (Pruteanu 2014). Any apparent benefit of doubling the dose of ICS should be weighed against the possible impact on growth compared with other therapeutic regimens; it deserves careful evaluation (Pruteanu 2014).

AUTHORS' CONCLUSIONS

Implications for practice

Evidence is insufficient at present to firmly support use of LABA as an adjunct therapy to ICS as a step 3 strategy to reduce risk of asthma exacerbations requiring steroids, as compared with using the usual dose of ICS (step 2) or an increased dose of ICS (step 3). The wide confidence intervals do not rule out a superior effect of either treatment. Stepping up therapy with the addition of LABA to the usual dose of ICS improves lung function beyond that observed when remaining on ICS as step 2 strategy, but with no apparent benefits of asthma symptom control and use of rescue SABA. Similarly, significant improvements in morning PEF observed with the combination of LABA and usual ICS dose versus an increased dose of ICS have not been associated with improvement in other indicators of lung function and asthma control. The apparent reduction in growth associated with use of 400 to 800 µg/d of BDP-equivalent raises concern when high-dose beclomethasone or budesonide is considered as increased ICS (step 3 therapy). Of note, the trend towards increased hospital admission with LABA, irrespective of the dose of ICS, and toward serious adverse health events compared with an increased dose of ICS is a matter of some concern and calls for larger, longer-term trials in children with substantial morbidity, to clarify this issue.

Implications for research

Future trials should have the following characteristics.

Population

A large study is urgently needed in children with moderate and severe airway obstruction and with higher asthma morbidity (e.g. prior hospital admission, requirement for OCS) at baseline than those recruited to trials aggregated in this review. Stratification according to degree of airway obstruction (i.e. baseline FEV_1) and inclusion of younger, preschool-aged children should feature in the design of such trials. Use of diagnostic criteria for asthma that do not require a positive bronchodilator response for enrolment would allow the study to be more generalisable to the general paediatric asthma population and would reduce the potential overestimation of effect on lung function (by preselecting responders to SABA).

Interventions

Future interventions should test the combination therapy delivered by a single inhaler (combining LABA and ICS) to ensure no use of LABA as monotherapy. Interventions may include head-to-head comparisons of salmeterol versus formoterol, combined with low or moderate doses of ICS. The control intervention should focus on increased doses of ICS (step 3), so that two step 3 treatment strategies are compared.

Design

- Double-blinding, adequate randomisation and complete reporting of withdrawals and dropouts with an explicit definition of the intention-to-treat population analysed.
- Intervention period of 24 to 52 weeks or longer, to properly assess the impact on exacerbations requiring systemic corticosteroids and those resulting in hospital admission, as well as adverse health events (growth, adrenal function, bone mineralisation, serious adverse health events).
- Clear reporting of the percentage of (and reasons for) non-eligibility of approached participants and of those enrolled in the run-in period is required, as inadequate reporting of the selected population results in difficulty identifying to whom the results can be generalised.
- Complete reporting of continuous (denominators, mean change and mean standard deviation of change) and dichotomous (denominators and rate) data in the units used in this systematic review would allow aggregation of data.

Outcomes of particular importance to assess include the following.

- Exacerbations requiring rescue systemic corticosteroids.
- Asthma-related hospital admission or acute care visit.
- Compliance with either intervention both before (for ICS) and after randomisation (for both ICS and combination therapy). The impact of compliance with combination therapy versus placebo and ICS on the magnitude of the effect size should be examined.
- Cost-effectiveness of use of combination inhalers as compared with ICS alone.
- Serious or overall adverse events associated with LABA or ICS especially growth, adrenal function, bone mineralisation.
- Functional measures including quality of life.

An ongoing large six-month study on safety and benefit of LABA and ICS (salmeterol and fluticasone) in children four to 11 years of age may provide further evidence to support our preliminary outcomes (NCT01462344).

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studies Verberne 1998b, De Blic 2009, Lemanske 2010 and Vaessen-Verberne 2010.

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

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

Akpinarli 1999

Methods	Parallel-group multi-centre study
Participants	Symptomatic asthmatic children % ELIGIBLE OF SCREENED POPULATION: not reported % RUN-IN PARTICIPANTS RANDOMLY ASSIGNED: not reported RANDOMLY ASSIGNED: 32 (ICS + F12 (twice daily): 16; ICS: 16) WITHDRAWALS: not described

Akpinarli 1999 *(Continued)*

	AGE, mean (range) or mean (SD): 6 to 14 years
	GENDER (% male): 47
	SEVERITY: not reported
	BASELINE % PRED FEV_1: not described
	BASELINE DOSE OF ICS: 400 to 800 µg
	ASTHMA DURATION: not described
	ATOPY (%): 68
	ELIGIBILITY CRITERIA: met ATS criteria for asthma; ≥ 15% increase in FEV_1 within previous year
	EXCLUSION CRITERIA: asthma exacerbation or respiratory infection within last month
	ELIGIBILITY CRITERIA DURING RUN-IN: Only participants requiring salbutamol more than once a week were randomly assigned
Interventions	LABA + ICS vs SAME dose of ICS
	OUTCOMES reported at 6 weeks
	RUN-IN PERIOD: 2 weeks with ICS 400 to 800 µg/d to document symptoms and $beta_2$-use
	DOSE OPTIMISATION PERIOD: none
	INTERVENTION PERIOD: 6 weeks
	TEST GROUP: (ICS + F12) ICS 400 to 800 µg/d + F 12 µg twice daily
	CONTROL GROUP: (ICS) ICS (400 to 800 µg/d) + placebo twice daily
	DEVICE: MDI + large volume spacer (Volumatic)
	NUMBER OF DEVICES: 2
	COMPLIANCE: assessed by weighing canisters
	CO-TREATMENT: SABA as needed
Outcomes	PULMONARY FUNCTION TEST: FEV_1 predicted; am PEF; pm PEF; PEF variability (%); PC 20
	SYMPTOM SCORES: score of 0 to 3 (max 9); nighttime symptom score; symptom-free days or nights
	FUNCTIONAL STATUS: rescue medication use; exacerbations requiring systemic steroids; exacerbations requiring admission
	INFLAMMATORY MARKERS: not described
	ADVERSE EFFECTS: described
	WITHDRAWALS: not described
	PRIMARY OUTCOME MEASURE; not reported
Notes	Full-text publication
	Funded by AstraZeneca
	Study author contacted and unable to confirm methods or data
	User-defined number: 600 (mean ICS dose in LAB2 group in µg/d of BDP-equivalent: 400 to 800)

Akpinarli 1999 *(Continued)*

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Described as randomised; no other information presented
Allocation concealment (selection bias)	Unclear risk	Information not available
Blinding (performance bias and detection bias) All outcomes	Low risk	Double-blind; identical placebo used
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	No information available on statistical handling of missing data
Selective reporting (reporting bias)	Low risk	Data on OCS-treated exacerbations available
Other bias	Unclear risk	No data provided on % participants meeting eligibility criteria from screening nor on run-in populations

Berger 2010

Methods	Randomised open-label tolerability study (SD-039-0719)
Participants	Inadequately controlled on other asthma controller medication % ELIGIBLE OF SCREENED POPULATION: 74 % RUN-IN PARTICIPANTS RANDOMLY ASSIGNED: not reported RANDOMLY ASSIGNED: 187 (ICS + F (twice daily): 124; ICS: 63) WITHDRAWALS: ICS + F: 13 ICS: 10 AGE, mean (SD): 9 (1.6) years GENDER (% male): 64 SEVERITY: not reported BASELINE % PRED FEV_1: 83.5 BASELINE DOSE OF ICS, mean (SD) µg/d: ICS + F: 306 (214.1) ICS: 309 (212.6) ASTHMA DURATION: not reported ATOPY (%): not reported

Berger 2010 *(Continued)*

	ELIGIBILITY CRITERIA • 6 to 11 years of age • Documented diagnosis of asthma for 6 months, as defined by the American Thoracic Society; 23 eligible to participate • Must have received daily ICS treatment (as monotherapy or in combination with other controller medications) at any consistent dose for 4 weeks before screening and to have a forced expiratory volume in 1 second (FEV_1) of 50% of predicted normal 6 hours after the last dose of a short-acting $beta_2$-adrenergic agonist and 24 hours after the last dose of LABA • Documented history of reversibility of 12% in FEV_1 or of 15% in PEF within 15 to 30 minutes after albuterol inhalation EXCLUSION CRITERIA • Required treatment with any non-inhaled corticosteroids within previous 4 weeks, sensitivity to drugs specified in the protocol or need for treatment with beta-blockers • Cancer in the previous 5 years or with significant disease. ELIGIBILITY CRITERIA DURING RUN-IN • Only participants not adequately controlled on other asthma controller medication
Interventions	LABA + ICS vs SAME dose of ICS OUTCOMES reported at 12 weeks RUN-IN PERIOD: 1 week with existing ICS to document inadequate asthma control DOSE OPTIMISATION PERIOD: none INTERVENTION PERIOD: 12 weeks TEST GROUP: BUD 320 µg/d + F 9 µg twice daily CONTROL GROUP: budesonide 400 µg/d DEVICE: single device • Test group: MDI • Control: dry powder inhaler COMPLIANCE: not reported. CO-TREATMENT: Albuterol pMDI was permitted as rescue medication throughout the study but was to be withheld for 6 hours before scheduled spirometry. If the participant experienced uncontrolled asthma or increased symptoms after 2 weeks of randomly assigned treatment, leukotriene receptor antagonists, inhaled non-steroidal anti-inflammatory agents, methylxanthines and alternative SABA were permitted as needed. OCS bursts were allowed for treatment of asthma exacerbations
Outcomes	PULMONARY FUNCTION TEST: morning predose forced vital capacity (FVC [L]), FEV_1 (L) and forced expiratory flow expired during middle half of exhalation (FEF25–75% [L/s]) SYMPTOM SCORES: FUNCTIONAL STATUS: physician and caregiver global assessments, Quality of Life Questionnaire (PAQLQ[S]) and caregiver quality of life INFLAMMATORY MARKERS: not described ADVERSE EFFECTS: adverse effects, clinical laboratory data (including serum glucose, serum potassium and 24-hour urinary cortisol), vital signs, 12-lead ECGs and physical examinations

Berger 2010 *(Continued)*

	WITHDRAWALS: described
	Blood chemistry, haematology tests and urinary free cortisol were evaluated
	Validated standardised paediatric asthma
	PRIMARY OUTCOME MEASURE: Safety evaluation was the primary aim of the study. However, specific primary outcome was not specified
Notes	Full-text publication
	Funded by AstraZeneca
	Dose of ICS: Intervention: 800 µg/d of BDP-equivalent; control: 800 µg/d of BDP-equivalent

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated allocation schedule was used
Allocation concealment (selection bias)	Low risk	Interactive voice response system was used to assign randomisation numbers and treatment assignments to eligible participants to avoid selection bias
Blinding (performance bias and detection bias) All outcomes	High risk	Open-label study
Incomplete outcome data (attrition bias) All outcomes	Low risk	Withdrawal rate is imbalance. Reasons for withdrawals were reported
Selective reporting (reporting bias)	Unclear risk	Primary or secondary outcomes were not distinguished. Not clear
Other bias	Unclear risk	Inadequate information was reported

Bisgaard 2006

Methods	Parallel-group multi-centre study
Participants	Steroid-using asthmatic children
	% ELIGIBLE OF SCREENED POPULATION: not reported
	% RUN-IN PARTICIPANTS RANDOMLY ASSIGNED: not reported
	RANDOMLY ASSIGNED: 223 (Bud/F: 117; Bud: 106)
	WITHDRAWALS: not reported
	AGE, mean (range): 8 (4 to 11) years
	GENDER (% male): 68
	ASTHMA SEVERITY: moderate
	BASELINE % PRED FEV_1 mean: 76

Bisgaard 2006 *(Continued)*

	BASELINE DOSE OF ICS (start of run-in): 200 to 500 µg/d
	ASTHMA DURATION: not reported
	ATOPY (%): not reported
	ELIGIBILITY CRITERIA: ICS 200 to 500 µg BDP-equivalent (≥ 3 months before run-in); FEV_1 60% to 100% of predicted normal; ≥ 1 severe exacerbation ≤ 12 months before run-in
	EXCLUSION CRITERIA: not reported
	CRITERIA FOR RANDOMISATION DURING RUN-IN: 8 puffs over last 10 days of run-in
Interventions	LABA + ICS vs INCREASED dose of ICS
	OUTCOMES: reported at 12 months
	RUN-IN PERIOD: 2 weeks to document stability
	DOSE OF ICS DURING RUN-IN: not clear
	DOSE OPTIMISATION PERIOD: none reported
	INTERVENTION PERIOD: 12 months
	TEST GROUP: combination F 4.5/BUD 80 µg qd
	CONTROL GROUP: BUD 320 µg qd
	DEVICE: Turbuhaler
	NUMBER OF DEVICES: 1
	COMPLIANCE: not reported
	CO-TREATMENT: SABA as needed
Outcomes	PULMONARY FUNCTION TEST: recorded but not reported
	SYMPTOM SCORES: recorded but not reported
	FUNCTIONAL STATUS: night awakenings; rescue medication use; exacerbations* (hospitalisation/need for OCS or other medication, increase in ICS, PEF ≤ 70% baseline on 2 consecutive days)
	INFLAMMATORY MARKERS: not reported
	ADVERSE EFFFECTS: reported
	WITHDRAWALS: not reported
	*Primary outcome
Notes	Full-text article
	Additional data downloaded from AZ website (www.astrazenecaclinicaltrials.com)
	Funded by AstraZeneca
	User-defined number: 320

Risk of bias

Bias	Authors' judgement	Support for judgement

Bisgaard 2006 *(Continued)*

Random sequence generation (selection bias)	Low risk	Computer generated randomisation scheme
Allocation concealment (selection bias)	Unclear risk	Eligible patients were randomised in balanced blocks by allocating patient numbers in consecutive order
Blinding (performance bias and detection bias) All outcomes	Low risk	Double-blind; identical inhaler devices used.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	'All analyses were performed on an intention-to-treat basis.' Additional information on the composition of the ITT population was not provided.
Selective reporting (reporting bias)	Low risk	Data on OCS-treated exacerbations reported as composite with ED visits/hospitalisations, PEF falls and requirement for medical intervention. Request for separate data on OCS-treated exacerbations from study sponsors has not been successful
Other bias	Unclear risk	No data provided on % participants meeting eligibility criteria from screening or run-in populations

Carroll 2010

Methods	Randomised double-blind placebo-controlled
Participants	Children with persistent asthma symptoms despite treatment with low-dose ICS % ELIGIBLE OF SCREENED POPULATION: 84 % RUN-IN PARTICIPANTS RANDOMLY ASSIGNED: 93 RANDOMLY ASSIGNED: 39 Fluticasone/salmeterol: not reported. Fluticasone: not reported. WITHDRAWALS: 2 • Fluticasone/salmeterol: 0 • Fluticasone: 2 AGE, mean (range): 10.6 (7 to 18) years GENDER (% male): 59 ASTHMA SEVERITY: not reported BASELINE % PRED FEV_1 mean: 95.8% BASELINE DOSE OF ICS (start of run-in): 400 µg/d of BDP, BUD or 200 µg/d of fluticasone propionate ASTHMA DURATION: not reported ATOPY (%): not reported ELIGIBILITY CRITERIA:

Carroll 2010 *(Continued)*

	• Children between 7 and 18 years of age with physician-confirmed diagnosis of asthma and persistent symptoms despite treatment with low-dose ICS EXCLUSION CRITERIA: • Unable to perform spirometry; unable to demonstrate satisfactory inhaler technique • Respiratory disorders other than asthma CRITERIA FOR RANDOMISATION DURING RUN-IN: not adequately reported
Interventions	LABA + ICS vs SAME dose of ICS OUTCOMES: reported at 4 and 8 weeks RUN-IN PERIOD: 4 weeks DOSE OF ICS DURING RUN-IN: FP 100 µg twice daily DOSE OPTIMISATION PERIOD: none reported INTERVENTION PERIOD: 8 weeks TEST GROUP: combination fluticasone and salmeterol 100/50 twice daily CONTROL GROUP: fluticasone 100 µg twice daily DEVICE: Diskus inhaler NUMBER OF DEVICES: 1 COMPLIANCE: estimated at each visit by reading the number of doses left in each inhaler device CO-TREATMENT: not reported
Outcomes	PULMONARY FUNCTION TEST: changes in mean basal FEV_1 (% predicted), fall in mean basal FEV_1 (% predicted) due to cold air*, salbutamol reversibility SYMPTOM SCORES: reported FUNCTIONAL STATUS: not reported INFLAMMATORY MARKERS: not reported ADVERSE EFFECTS: reported WITHDRAWALS: reported *Primary outcome
Notes	Full-text article Funded by GlaxoSmithKline Dose of ICS: intervention: 400 µg/d of BDP-equivalent; control: 400 µg/d of BDP-equivalent

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Trail was randomised but no information was provided on how the randomisation was generated.
Allocation concealment (selection bias)	Low risk	Devices were masked to make them identical in external physical appearance.

Carroll 2010 *(Continued)*

Blinding (performance bias and detection bias) All outcomes	Low risk	Dobule-blind study.
Incomplete outcome data (attrition bias) All outcomes	Low risk	12% withdrawal from control vs no withdrawal in the treatment group. Reasons for withdrawals were mentioned.
Selective reporting (reporting bias)	Low risk	Study protocol was not available. All outcomes were presented.
Other bias	Low risk	No apparent source of bias was noted.

De Blic 2009

Methods	Randomised double-blind double-dummy parallel-group non-inferiority study (SAM104926)
Participants	Not controlled asthmatic children % ELIGIBLE OF SCREENED POPULATION: 55 % RUN-IN PARTICIPANTS RANDOMLY ASSIGNED: not reported RANDOMLY ASSIGNED: 321 Fluticasone/salmeterol: 160 Fluticasone: 161 WITHDRAWALS: • Fluticasone/salmeterol: 3 • Fluticasone: 6 AGE, mean (range): 8.1 (4 to 11) years GENDER (% male): 65 ASTHMA SEVERITY: not reported BASELINE % PRED FEV_1 mean: not reported BASELINE DOSE OF ICS (start of run-in): BDP 400 µg/d or equivalent ASTHMA DURATION: not reported ATOPY (%): 88 ELIGIBILITY CRITERIA: • Children, 4 to 11 years of age with clinical history of asthma for ≥ 6 months, documented reversibility in FEV_1 or PEF of ‡15%, who were currently receiving ICS (BDP, 400 µg/d or equivalent) EXCLUSION CRITERIA: • Respiratory tract infection or acute asthma exacerbation requiring emergency room treatment within previous 4 weeks, or hospitalisation due to asthma or use of systemic corticosteroids in previous 12 weeks

De Blic 2009 *(Continued)*

	CRITERIA FOR RANDOMISATION DURING RUN-IN: Asthma had been assessed as 'Not controlled' for ≥ 2 of the 4 weeks of the run-in period
Interventions	LABA + ICS vs INCREASED dose of ICS OUTCOMES: reported at 12 months RUN-IN PERIOD: 4 weeks to document asthma control DOSE OF ICS DURING RUN-IN: FP 100 µg twice daily DOSE OPTIMISATION PERIOD: none reported INTERVENTION PERIOD: 12 weeks TEST GROUP: combination fluticasone and salmeterol 100/50 twice daily CONTROL GROUP: fluticasone 200 µg twice daily DEVICE: Diskus inhaler NUMBER OF DEVICES: 1 COMPLIANCE: checked by counting the number of remaining doses in the Diskus inhalers CO-TREATMENT: not reported
Outcomes	PULMONARY FUNCTION TEST: clinic morning PEF, home morning and evening, before taking any study medication, FEV_1, MEF50, reversibility in PEF/FEV_1 SYMPTOM SCORES: symptoms, exacerbations* (deterioration in asthma requiring administration of OCS and/or deterioration in asthma requiring emergency room visit and/or admission to hospital); exacerbation requiring OCS FUNCTIONAL STATUS: number of night-time awakenings, amount of rescue use, asthma control INFLAMMATORY MARKERS: not reported ADVERSE EFFECTS: reported WITHDRAWALS: reported *Primary outcome
Notes	Full-text article Funded by GlaxoSmithKline Dose of ICS: intervention: 400 µg/d of BDP-equivalent; control: 800 µg/d of BDP-equivalent

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomisation was generated by centralised RANDALL system
Allocation concealment (selection bias)	Low risk	All study inhalers were identical in appearance, and use of dummy inhalers ensured that both participants and site personnel remained blinded to an individual's treatment
Blinding (performance bias and detection bias)	Low risk	Double-blind, double-dummy study

De Blic 2009 *(Continued)*

All outcomes		
Incomplete outcome data (attrition bias) All outcomes	Low risk	Well-balanced withdrawal in both groups; intention-to-treat analysis
Selective reporting (reporting bias)	Low risk	Study protocol is available, and primary and secondary outcomes are predefined
Other bias	Low risk	No apparent source of bias was noted

Eid 2010a

Methods	Parallel-group multi-centre study
Participants	% ELIGIBLE OF SCREENED POPULATION: 35 % RUN-IN PARTICIPANTS RANDOMLY ASSIGNED: 79 RANDOMLY ASSIGNED: 521 (BUD/F twice daily: 184; BUD/F QD: 168; BUD: 169) WITHDRAWALS: BUD/F twice daily: 21; BUD/F QD: 37; BUD: 33 AGE, mean (range) or mean (SD): 10.3 (2.5) years SEVERITY: not stated BASELINE % PRED FEV_1: 78.3 (8.56) BASELINE DOSE OF ICS: 245.3 ASTHMA DURATION: 6.8 ATOPY (%): not reported ELIGIBILITY CRITERIA: 6 to 15 years; diagnosis of asthma for ≥ 6 months; maintenance ICS treatment for ≥ 4 weeks before screening; FEV_1 predicted 60%-90% predicted; reversibility of FEV_1 ≥ 12% and > 0.20 L from baseline; children > 11 years were required to demonstrate reversibility > 12% only EXCLUSION CRITERIA: not stated ELIGIBILITY CRITERIA DURING RUN-IN: stable asthma symptoms
Interventions	LABA and ICS vs SAME DOSE ICS OUTCOMES: 12 weeks RUN-IN PERIOD: 4 to 5 weeks DOSE OPTIMISATION PERIOD: not reported INTERVENTION PERIOD: 12 weeks TEST GROUP: combination BUD and F 80/9 µg twice daily via MDI CONTROL GROUP: BUD 160 µg QD via MDI NUMBER OF DEVICES: 1 COMPLIANCE: not assessed

Eid 2010a *(Continued)*

	CO-TREATMENT: SABA as needed
Outcomes	PULMONARY FUNCTION TEST: FEV_1; am PEF; pm PEF* SYMPTOM SCORES: day and nocturnal symptoms FUNCTIONAL STATUS: AQLQ INFLAMMATORY MARKERS: not reported ADVERSE EFFECTS: reported WITHDRAWALS: reported by treatment group
Notes	Full-text article Funding source: AZ Confirmation of methods and data obtained from AZ in April 2008 Unpublished data downloaded from http://www.astrazenecaclinicaltrials.com Dose of ICS: intervention: 200 µg/d of BDP-equivalent; control: 200 µg/d of BDP-equivalent

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Described as randomised; no other information presented. Age-based strata to ensure balance in ages between groups (6-11 years & 12-15 years)
Allocation concealment (selection bias)	Unclear risk	Information not available
Blinding (performance bias and detection bias) All outcomes	Low risk	Double-blind; double dummy
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Efficacy analysis does not explicitly describe whether missing data imputed or drawn from follow-up: 'all randomised subjects who took at least 1 dose of double-blind treatment, and who contributed at least 1 evening PEF diary entry after receiving double-blind medication, was used in the primary analysis.'
Selective reporting (reporting bias)	High risk	OCS-treated exacerbations were not reported in the study publication. Data request has been made to study sponsors for this information.
Other bias	Low risk	37% screening population eligible for randomisation

Eid 2010b

Methods	See Eid 2010b
Participants	See Eid 2010b
Interventions	See Eid 2010b TEST GROUP:

Eid 2010b *(Continued)*

	• Combination BUD and F 160/9 µg QD via MDI
Outcomes	See Eid 2010b
Notes	See Eid 2010b

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Information not available
Allocation concealment (selection bias)	Unclear risk	Information not available
Blinding (performance bias and detection bias) All outcomes	Low risk	Double-blind; double-dummy
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Efficacy analysis does not explicitly describe whether missing data imputed or drawn from follow-up: 'all randomised subjects who took at least 1 dose of double-blind treatment, and who contributed at least 1 evening PEF diary entry after receiving double-blind medication, were used in the primary analysis'
Selective reporting (reporting bias)	High risk	OCS-treated exacerbations were not reported in the study publication. Data request has been made to study sponsors for this information.
Other bias	Low risk	37% screening population eligible for randomisation

Gappa 2009

Methods	Multi-center prospective randomised double-blind double-dummy parallel-group study
Participants	Children with uncontrolled asthma % ELIGIBLE OF SCREENED POPULATION: not reported % RUN-IN PARTICIPANTS RANDOMLY ASSIGNED: 64.2 RANDOMLY ASSIGNED: 283 • Fluticasone/salmeterol: 145 • Fluticasone: 138 WITHDRAWALS: 8 • Fluticasone/salmeterol: 5 • Fluticasone: 3 MEAN AGE, mean age (range): 9.5 (4 to 16) years GENDER (% male): 81 SEVERITY: not reported. BASELINE FEV_1 % predicted: 91.6

Gappa 2009 *(Continued)*

	BASELINE DOSE OF ICS: mean: (200 to 400 µg/d BDP-equivalent)
	
	ASTHMA DURATION (range in years): not reported.
	
	ATOPY (%): not reported
	
	ELIGIBILITY CRITERIA:
	
	• Children and adolescents 4 to 16 years of age with symptomatic persistent seasonal or perennial asthma according to current guidelines and prior treatment with ICS were eligible for the study. Participants were included if:
	  • continuous treatment with ICS (200 to 400 µg/d BDP-equivalent) during at least the previous 4 weeks;
	  • consent to change ICS treatment to twice-daily inhalation of fluticasone 100 µg via a Diskus inhaler; or
	  • consent to not use SABA or anticholinergic drugs on a regular basis.
	
	EXCLUSION CRITERIA: Participants were excluded if they had experienced 1 of the following events during the 4 weeks preceding the study: pneumonia, bronchitis, respiratory infection requiring antibiotic treatment or an asthma-related hospitalisation. Asthma medications
	during the 4 weeks before visit 1, which precluded the child from being admitted to the trial, were oral or parenteral corticosteroids, and included oral or inhaled LABA

Interventions	LABA + ICS vs increased dose of ICS OUTCOMES: reported weekly RUN-IN: none DOSE OF ICS DURING RUN-IN: N/A INTERVENTION PERIOD: 12 weeks TEST GROUP: F 12 µg twice daily + BUD 100 twice daily CONTROL GROUP: placebo + ICS BUD 200 twice daily DEVICE: Diskus inhalers NUMBER OF DEVICES: 1 COMPLIANCE: not reported CO-TREATMENT: Participants were not allowed to take any other drugs for the long-term treatment of asthma. Medications for concomitant illnesses could be continued during the study, if the dose was kept constant and the drug had no influence on asthma
Outcomes	PULMONARY FUNCTION TEST: FVC, FEV_1 and morning and evening PEF SYMPTOM SCORE: asthma Symptom Score (ASS) on a scale of 0 to 4 FUNCTIONAL STATUS: number of days (24 hours) without asthma symptoms, use of salbutamol as rescue medication, number of weeks with successful asthma control INFLAMMATORY MARKERS: ADVERSE EFFECTS: reported WITHDRAWALS: reported PRIMARY OUTCOME MEASURE: change in mean morning expiratory PEF (L/min)
Notes	Full-text publication

Gappa 2009 *(Continued)*

	Source of funding: GlaxoSmithKline
	Confirmation of methods and data not obtained
	Dose of ICS: intervention: 400 µg/d of BDP-equivalent; control: 800 µg/d of BDP-equivalent

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated code produced in the centralised facility
Allocation concealment (selection bias)	Unclear risk	Inadequate details were reported on allocation concealment
Blinding (performance bias and detection bias) All outcomes	Low risk	Double-blind, double-dummy study
Incomplete outcome data (attrition bias) All outcomes	Low risk	Well-balanced withdrawals in groups compared; intention-to-treat analysis
Selective reporting (reporting bias)	Low risk	Study protocol is available. Primary and secondary outcomes were prespecified
Other bias	Low risk	No apparent source of bias was noted

Heuck 2000

Methods	Cross-over study; single centre (outpatient referral centre)
Participants	Asthmatic children
	% ELIGIBLE OF SCREENED POPULATION: not reported
	% RUN-IN PARTICIPANTS RANDOMLY ASSIGNED: not reported
	RANDOMLY ASSIGNED: 27
	WITHDRAWALS: 2 participants were withdrawn during treatment with BUD alone; 1 withdrawal - unclear which period
	AGE, mean (range): 9.6 (6.1 to 13.5) years
	GENDER (% male): 52
	SEVERITY: mild to moderate
	BASELINE FEV_1: not reported
	BASELINE PEF L/min: 280 L/min
	BASELINE DOSE OF ICS: mean - BUD 200 twice daily or equivalent
	ASTHMA DURATION (range in years): 4.5 (1.4 to 9.5)
	ATOPY (%): not reported

Heuck 2000 *(Continued)*

	ELIGIBILITY CRITERIA: treatment with inhaled BUD 200 µg twice daily (or equipotent doses of other ICS) for 1 month before study entry; children were prepubertal EXCLUSION CRITERIA: not described
Interventions	LABA + ICS vs INCREASED DOSE ICS OUTCOMES: reported weekly RUN-IN: none DOSE OF ICS DURING RUN-IN: N/A INTERVENTION PERIOD: 12 weeks TEST GROUP: F 12 µg twice daily + BUD 100 µg twice daily CONTROL GROUP: placebo + ICS BUD 200 µg twice daily DEVICE: Turbuhaler (ICS) and Aerolizer (F) NUMBER OF DEVICES: 2 COMPLIANCE: Turbuhalers weighed and number of F capsules counted CO-TREATMENT: SABA as needed
Outcomes	PULMONARY FUNCTION TEST: FEV_1; am PEF; pm PEF SYMPTOM SCORE: daytime and nighttime score (score of 0 to 4) FUNCTIONAL STATUS: exacerbations; rescue medication use; lower leg growth; serum and urinary markers of type I and III collagen turnover INFLAMMATORY MARKERS: inflammatory markers in serum ADVERSE EFFECTS: reported WITHDRAWALS: reported PRIMARY OUTCOME MEASURES: not reported
Notes	Full-text publication Source of funding not stated Confirmation of methods and data not obtained User-defined number: 400

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	'Treatment order was allocated by a computerised randomisation scheme prepared in balanced blocks'
Allocation concealment (selection bias)	Unclear risk	Information on concealment of allocation not provided
Blinding (performance bias and detection bias) All outcomes	Low risk	Double-blind; double-dummy

Heuck 2000 *(Continued)*

Incomplete outcome data (attrition bias) All outcomes	Unclear risk	No information available
Selective reporting (reporting bias)	Low risk	Data on OCS-treated exacerbations available
Other bias	Unclear risk	No data provided on % participants meeting eligibility criteria from screening or run-in populations

Langton Hewer 1995

Methods	Parallel-group single-centre double-blind placebo-controlled study
Participants	Symptomatic children % ELIGIBLE OF SCREENED POPULATION: not reported % RUN-IN PARTICIPANTS RANDOMLY ASSIGNED: not reported NUMBER RECRUITED NOT RANDOMLY ASSIGNED: not stated RANDOMLY ASSIGNED: 23 (usual ICS + salmeterol 100 twice daily: 11; usual ICS: 12) WITHDRAWALS: usual ICS + salmeterol: 0; usual ICS: 2 AGE, median (range): 15 (12 to 17) years GENDER (% male): 70 SEVERITY: severe BASELINE % PRED FEV_1: 82 BASELINE DOSE OF ICS (start of run-in): 400 ASTHMA DURATION: 13 years ATOPY (%): 100 ELIGIBILITY CRITERIA: severe asthma (not defined but severe enough to be attending residential school for asthma and persistent symptoms) EXCLUSION CRITERIA: already taking LABA CRITERIA FOR RANDOMISATION DURING RUN-IN: none specified
Interventions	LABA + ICS vs SAME DOSE (usual dose) of ICS OUTCOMES reported at 8 and 10 weeks RUN-IN PERIOD: 2 weeks DOSE OF ICS DURING RUN-IN: same as during study DOSE OPTIMISATION PERIOD: none INTERVENTION PERIOD: 8 weeks TEST GROUP: (usual ICS + salmeterol): salmeterol 100 µg twice daily CONTROL GROUP: usual ICS and placebo twice daily

Langton Hewer 1995 *(Continued)*

	DEVICE: Diskhaler NUMBER OF DEVICES: 2 COMPLIANCE: supervised in school taking medication by investigators CO-TREATMENT OCS: methylxanthines and anticholinergics taken by 20% of participants
Outcomes	PULMONARY FUNCTION TEST: FEV_1; am PEF; pm PEF SYMPTOM SCORES: morning and evening symptom scores FUNCTIONAL STATUS: SABA; symptom-free days/nights; exacerbation (requiring systemic steroids); quality of life score INFLAMMATORY MARKERS: none ADVERSE EFFECTS: described WITHDRAWALS: described PRIMARY OUTCOME MEASURES: not reported
Notes	Full-text publication Funded by Charity Confirmation of methods and data pending User-defined number: not reported

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Described as randomised; no other information presented
Allocation concealment (selection bias)	Unclear risk	Information not available
Blinding (performance bias and detection bias) All outcomes	Low risk	Identical placebo
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Data analysis described as intention to treat; methods applied not elaborated
Selective reporting (reporting bias)	Low risk	Data on OCS-treated exacerbations available
Other bias	Unclear risk	No data provided on % participants meeting eligibility criteria from screening or run-in populations (niche population sampled for residential school for children with particularly difficult to treat asthma)

Lemanske 2010

Methods	Randomised double-blind 3-treatment 3-period cross-over trial

Lemanske 2010 *(Continued)*

Participants	Symptomatic asthmatic children despite low-dose ICS therapy % ELIGIBLE OF SCREENED POPULATION: not reported % RUN-IN PARTICIPANTS RANDOMLY ASSIGNED: 38 RANDOMLY ASSIGNED: 182 WITHDRAWALS: 25 AGE, median ± SD years: 2 age strata 6 to 11 years (N = 126): 9.1 ± 1.5 12 to 17 years (N = 56): 14.7 ± 1.7 GENDER (% male): 65 SEVERITY: mild to moderate BASELINE % PRED FEV_1: 97 BASELINE DOSE OF ICS (start of run-in): 100 µg of fluticasone twice daily ASTHMA DURATION: not reported ATOPY (%): not reported ELIGIBILITY CRITERIA: children 6 to 17 years of age with mild to moderate asthma diagnosed by a physician on the basis of criteria recommended by the National Asthma Education and Prevention Program; ability to perform reproducible spirometry; FEV_1 ≥ 60% before bronchodilation; increase in FEV_1 ≥ 12% (bronchodilator reversibility) or methacholine PC_{20} in FEV_1 ≤ 12.5 mg/mL EXCLUSION CRITERIA: not reported. CRITERIA FOR RANDOMISATION DURING RUN-IN: after use of 100 µg of fluticasone twice daily during run-in period, documentation of uncontrolled asthma, which was defined as occurrence of ≥ 1 of the following more than 2 days per week on average during a 2-week period: diary-reported symptoms (coughing rated as moderate or severe, or wheezing rated as mild, moderate or severe); rescue use of an inhaled bronchodilator with ≥ 2 puffs per day; or PEF < 80% of predetermined reference value
Interventions	LABA + ICS vs INCREASED dose of ICS OUTCOMES: reported at 16 weeks RUN-IN PERIOD: 2 to 8 weeks DOSE OF ICS DURING RUN-IN: 100 µg of fluticasone twice daily INTERVENTION PERIOD: 16-weeks TEST GROUP: 100 µg of fluticasone + 50 µg of long-acting beta-agonist salmeterol (Advair Diskus, GlaxoSmithKline) twice daily CONTROL GROUP: 250 µg of fluticasone (Flovent Diskus, GlaxoSmithKline) twice daily DEVICE: Diskus NUMBER OF DEVICES: 1 COMPLIANCE: recorded

Lemanske 2010 *(Continued)*

	CO-TREATMENT: Participants received open-label metered-dose inhaler of albuterol (Ventolin HFA, GlaxoSmithKline). Standardised course of prednisone treatment was initiated for an asthma exacerbation if predetermined clinical criteria were met
Outcomes	PULMONARY FUNCTION TEST: FEV_1, PC20 SYMPTOM SCORES: symptom scores; symptom-free days FUNCTIONAL STATUS: An asthma-control day, as documented in each participant's diary, was a day with no use of albuterol rescue (excluding use of albuterol as pre-exercise treatment), no use of a non-study asthma medication, no daytime or nighttime asthma symptoms, no unscheduled visit to a healthcare provider for asthma and no PEF < 80% of predetermined reference value EXACERBATION: OCS-treated exacerbations; hospitalisations. INFLAMMATORY MARKERS: FeNO ADVERSE EFFECTS: reported WITHDRAWALS: stated PRIMARY OUTCOME MEASURES: differential response to each of the 3 step-up therapies on the basis of fixed threshold criteria for the following 3 asthma-control measures: need for treatment with oral prednisone for acute asthma exacerbations, number of asthma-control days and FEV_1
Notes	Full-text publication Funded by grant agencies but not by pharmaceutical companies Confirmation of data and methods not obtained Dose of ICS: intervention: 400 µg/d of BDP-equivalent; control: 1000 µg/d of BDP-equivalent

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	3 × 3 cross-over design based on complete set of orthogonal Latin squares; stratification based on clinical sites
Allocation concealment (selection bias)	Low risk	Drug assignments were masked with use of placebo tablets and dummy disk devices that discharged powder without active drug
Blinding (performance bias and detection bias) All outcomes	Low risk	Triple-blinded
Incomplete outcome data (attrition bias) All outcomes	Low risk	Few withdrawals; intention-to-treat analysis
Selective reporting (reporting bias)	Low risk	Study protocol is available; primary and secondary outcomes were prespecified
Other bias	Low risk	No apparent source of bias was noted

Lenney 2013

Methods	Randomised double-blind placebo-controlled trial

Participants	Children with uncontrolled asthma
	
	% ELIGIBLE OF SCREENED POPULATION: 7
	
	% RUN-IN PARTICIPANTS RANDOMLY ASSIGNED: not reported
	
	RANDOMLY ASSIGNED: 42
	
	• Fluticasone/salmeterol: 23
	• Fluticasone: 19
	
	WITHDRAWALS: 9
	
	• Fluticasone/salmeterol: 6
	• Fluticasone: 3
	
	AGE, mean (range): 10.5 (6 to 14) years
	
	GENDER (male%): 73
	
	ASTHMA SEVERITY: not reported
	
	BASELINE % PRED FEV_1 mean: 88.5
	
	BASELINE DOSE OF ICS (start of run-in): not reported
	
	ASTHMA DURATION: not reported
	
	ATOPY (%): not reported
	
	ELIGIBILITY CRITERIA:
	
	• Physician-diagnosed asthma in individuals 6 years to 14 years 11 months of age
	• Required frequent SABA relief therapy: ≥ 7 puffs in the past 7 days
	• Symptoms of asthma (i.e. wheeze, shortness of breath but not cough alone) that resulted in:
	  • nocturnal wakening in the last week; and/or
	  • interference with usual activities in the past week; and/or
	  • exacerbations, defined as short course of OCS, an unscheduled general practitioner or accident and emergency (A&E) department visit or a hospital admission within past 6 months
	• Fully informed written (proxy) consent and assent, when appropriate
	
	EXCLUSION CRITERIA:
	
	• Received LABA, LTRA, regular theophylline therapy or high-dose ICS (> 1000 µg) and unlicensed BDP or equivalent (at the discretion of the investigator)
	• Other respiratory diseases, cystic fibrosis, cardiac disease or immunological disorders
	
	CRITERIA FOR RANDOMISATION DURING RUN-IN: The following eligibility criteria were considered before randomisation
	
	INCLUSION CRITERIA:
	
	• Asthma in individuals 6 years to 14 years 11 months of age
	• Required frequent SABA relief therapy: ≥ 7 puffs in the past 7 days
	• Symptoms of asthma (i.e. wheeze, shortness of breath but not cough alone) resulting in:
	  ○ nocturnal wakening in the last week; and/or
	  ○ interference with usual activities in the past week.
	• Continuing consent/assent (when appropriate)
	
	EXCLUSION CRITERIA:

Lenny 2013 *(Continued)*

	• Asthma controlled after 4-week run-in, in which control was defined as absence of any symptoms of asthma (except cough alone) or cases in which symptoms of asthma had not interfered with usual activities in the past week • Receiving LABA, LTRA, regular theophylline therapy or high-dose ICS (> 1000 µg) and unlicensed BDP or equivalent (at the discretion of the investigator) • Other respiratory diseases, cystic fibrosis, cardiac disease or immunological disorders
Interventions	LABA + ICS vs same dose of ICS OUTCOMES: reported at 48 weeks RUN-IN PERIOD: 4 weeks DOSE OF ICS DURING RUN-IN: usual maintenance dose INTERVENTION PERIOD: 48 weeks TEST GROUP: combination fluticasone propionate 100 µg and salmeterol 50 µg twice daily CONTROL GROUP: fluticasone propionate 100 µg twice daily DEVICE: Accuhaler NUMBER OF DEVICES: 1 COMPLIANCE: reported CO-TREATMENT: SABA as needed
Outcomes	PULMONARY FUNCTION TEST: FEV_1, FVC SYMPTOM SCORES: not reported FUNCTIONAL STATUS: quality of life of children as measured by the Paediatric Asthma Quality of Life Questionnaire, quality of life of caregivers as measured by the Paediatric Asthma Caregiver's Quality of Life Questionnaire, number of schooldays missed because of respiratory problems, amount of rescue SABA therapy prescribed for asthma symptoms, time from randomisation to treatment withdrawal (because of lack of efficacy or side effects) EXACERBATIONS: number of asthma exacerbations requiring treatment with OCS*; time from randomisation to first exacerbation requiring treatment with a short course of OCS; number of hospital admissions due to respiratory problems INFLAMMATORY MARKERS: not reported ADVERSE EFFECTS: reported WITHDRAWALS: stated *Primary outcome
Notes	Full-text publication Funded by the Health Technology Assessment programme (HTA) of the Department of Health Confirmation of data and methods not obtained Dose of ICS: intervention: 400 µg/d of BDP-equivalent; control: 400 µg/d of BDP-equivalent

Risk of bias

Bias	Authors' judgement	Support for judgement

Lenney 2013 *(Continued)*

Random sequence generation (selection bias)	Low risk	Block randomisation with variable block length, stratified by secondary care centre, with allocation to 3 treatment arms in the ratio of 1 : 1 : 1
Allocation concealment (selection bias)	Low risk	Study drugs were identical in appearance and were identically packaged, with all participants, clinicians and trial personnel blinded to treatment allocation throughout
Blinding (performance bias and detection bias) All outcomes	Low risk	Double-blind study
Incomplete outcome data (attrition bias) All outcomes	Low risk	Reasons for withdrawals reported
Selective reporting (reporting bias)	Low risk	Full protocol is available. Primary and secondary outcomes were prespecified.
Other bias	Low risk	Study was prematurely terminated due to lack of funds. However, no apparent source of bias was noticed.

Malone 2005

Methods	Parallel-group multi-centre (66 centres in North America)
Participants	Steroid-using asthmatic children % ELIGIBLE OF SCREENED POPULATION: not reported % RUN-IN PARTICIPANTS RANDOMLY ASSIGNED: 48 RANDOMLY ASSIGNED: 203 (fluticasone/salmeterol: 101; fluticasone: 102) WITHDRAWALS: fluticasone/salmeterol: 19; fluticasone: 16 AGE, mean: 8 years GENDER (male %): 64 ASTHMA SEVERITY: mild to moderate BASELINE % PRED FEV_1 mean: 80% BASELINE DOSE OF ICS (start of run-in): 166 µg fluticasone ASTHMA DURATION: not reported ATOPY (%): not reported ELIGIBILITY CRITERIA: 4 to 11 years of age; ATS defined asthma ≥ 2 months; ICS therapy (BDP-equivalent 252 to 336 µg/d) for 1 month before entry; participants 6 to 11 years of age required to have FEV_1% predicted; participants 4 to 5 years of age required to have am PEF 50% to 95% of predicted; ≥ 12% response to $beta_2$-agonist at screening visit or within 1 year of screening visit EXCLUSION CRITERIA: history of life-threatening asthma; hospitalisation with asthma twice or more in previous year; significant concurrent disease; oral or parenteral use of steroids during month before study entry

Malone 2005 *(Continued)*

	CRITERIA FOR RANDOMISATION DURING RUN-IN: am FEV_1 50% to 95% of predicted; daytime asthma (score ≥ 1); use of SABA on 3+ days of last 7 days of run-in; ≥ 70% diary card entry
Interventions	LABA + ICS vs SAME dose of ICS OUTCOMES: reported at 3 months RUN-IN PERIOD: 2 weeks DOSE OF ICS DURING RUN-IN: usual maintenance dose INTERVENTION PERIOD: 3 months TEST GROUP: combination salmeterol 50/fluticasone 100 µg twice daily CONTROL GROUP: fluticasone 100 µg twice daily DEVICE: Diskus NUMBER OF DEVICES: 1 COMPLIANCE: not reported CO-TREATMENT: SABA as needed
Outcomes	PULMONARY FUNCTION TEST: FEV_1; clinic PEF; am PEF; pm PEF SYMPTOM SCORES: symptom scores; symptom-free days FUNCTIONAL STATUS: OCS-treated exacerbations; hospitalisations; use of reliever medication; SABA-free days INFLAMMATORY MARKERS: not reported ADVERSE EFFECTS: reported WITHDRAWALS: stated *Primary outcome: not identified (safety study)
Notes	Full-text publication Funded by GSK User-defined number: 400 Confirmation of data and methods obtained

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	See Appendix 4
Allocation concealment (selection bias)	Low risk	See Appendix 4
Blinding (performance bias and detection bias) All outcomes	Low risk	Double-blind; identical inhaler devices

Malone 2005 *(Continued)*

Incomplete outcome data (attrition bias) All outcomes	High risk	'For patients who withdrew from the study prematurely, all available data up to the time of discontinuation were included in the intent-to-treat population'
Selective reporting (reporting bias)	Low risk	Full protocol is available. Primary and secondary outcomes were prespecified.
Other bias	Low risk	Study was prematurely terminated due to lack of funds. However, no apparent source of bias was noticed.

Meijer 1995

Methods	Parallel-group single-centre study
Participants	Asymptomatic asthmatic children % ELIGIBLE OF SCREENED POPULATION: not reported % RUN-IN PARTICIPANTS RANDOMLY ASSIGNED: not reported RANDOMLY ASSIGNED: 40 (salmeterol 50 µg twice daily + ICS: 20; ICS + placebo: 20) WITHDRAWALS: salmeterol 50 µg twice daily + ICS: 0; ICS + placebo: 1 (5%) AGE, mean (SD): 11.4 (2.6) years GENDER (% male): 58 SEVERITY: mild BASELINE % PRED FEV_1: 94 BASELINE DOSE OF ICS: twice-daily 200 or 400 µg BDP rotadisk ASTHMA DURATION: 8.4 years ATOPY (%): 100 ELIGIBILITY CRITERIA: none reported EXCLUSION CRITERIA: none reported CRITERIA FOR RANDOMISATION DURING RUN-IN: N/A
Interventions	LABA + ICS vs SAME dose of ICS OUTCOMES: reported at 1, 8, 16 weeks RUN-IN PERIOD: none DOSE OPTIMISATION PERIOD: none INTERVENTION PERIOD: 16 weeks TEST GROUP: salmeterol 50 µg twice daily + BDP 250 µg twice daily CONTROL GROUP: BDP 250 µg twice daily + placebo DEVICE: dry powder inhaler (Diskhaler) NUMBER OF DEVICES: 2

Meijer 1995 *(Continued)*

	COMPLIANCE: returned powder disks counted
	CO-TREATMENT: SABA as needed
Outcomes	PULMONARY FUNCTION TEST: FEV_1 predicted; PC20 doubling doses (DD); circadian variation (day-night differences in FEV_1)
	SYMPTOM SCORES: only individual symptoms reported (yes/no)
	FUNCTIONAL STATUS: rescue medication use
	INFLAMMATORY MARKERS: not reported
	ADVERSE EFFECTS: not reported
	WITHDRAWALS: reported
	PRIMARY OUTCOME MEASURE: not specified
Notes	Full-text publication
	Funded by Glaxo
	User-defined number: 500
	Confirmation of data and methods not obtained

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Described as randomised; no other information presented
Allocation concealment (selection bias)	Unclear risk	Information not available
Blinding (performance bias and detection bias) All outcomes	Low risk	Double-blind; double-dummy
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Not enough information presented to determine this
Selective reporting (reporting bias)	Unclear risk	Unclear whether data on OCS-treated exacerbations were collected in the study
Other bias	Unclear risk	No data presented on % screening population eligible for randomisation

Morice 2008a

Methods	Parallel-group multi-centre study (53 centres in South America, Europe, Hong Kong and Taiwan)
Participants	% ELIGIBLE OF SCREENED POPULATION: not reported
	% RUN-IN PARTICIPANTS RANDOMLY ASSIGNED: 77
	RANDOMLY ASSIGNED: 622 (BUD: 207; BUD/F (DPI): 203; BUD/F (MDI): 212)

Morice 2008a *(Continued)*

	WITHDRAWALS: BUD: 14 BUD/F (DPI): 11; BUD/F (MDI): 14 AGE, mean (range): 9 (6 to 11) years GENDER (% male): 66 SEVERITY: not specified BASELINE % PRED FEV_1: 89 BASELINE DOSE OF ICS: (start of run-in): 470 µg ASTHMA DURATION: not reported ATOPY (%): not reported ELIGIBILITY CRITERIA: age 6 to 11 years; diagnosis of asthma for ≥ 6 months; PEF > 50% of predicted normal; history daily ICS use (stable dose of 375 to 1000 µg 30 days before enrolment); clinically important exercise-induced bronchoconstriction for 3 months before enrolment; ability to use DPI, pMDI and peak flow meter EXCLUSION CRITERIA: not reported CRITERIA FOR RANDOMISATION DURING RUN-IN: symptom score 1 to 4; mean morning PEF 50% to 85% post SABA
Interventions	LABA + ICS vs SAME dose of ICS OUTCOMES: 12 weeks RUN-IN PERIOD: 2 weeks DOSE OF ICS DURING RUN-IN: 470 DOSE OPTIMISATION PERIOD: not reported INTERVENTION PERIOD: 12 weeks TEST GROUP: combination BUD and F (160/9 µg) twice daily via dry powder inhaler + placebo metered-dose inhaler CONTROL GROUP: BUD 200 µg twice daily DEVICE: MDI and DPI NUMBER OF DEVICES: 1 COMPLIANCE: not reported CO-TREATMENT: SABA as needed
Outcomes	PULMONARY FUNCTION TEST: am PEF*; pm PEF; FEV_1 SYMPTOM SCORES: day/night scores FUNCTIONAL STATUS: paediatric AQLQ INFLAMMATORY MARKERS: NA ADVERSE EFFECTS: stated WITHDRAWALS: stated *Primary outcome
Notes	Full-text publication

Morice 2008a *(Continued)*

	AZ funded User-defined number: 200 Confirmation of data and methods not obtained

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated schedule
Allocation concealment (selection bias)	Unclear risk	Information not provided
Blinding (performance bias and detection bias) All outcomes	Low risk	Double-blind; double-dummy
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	'...all randomised patients with post-randomisation data'
Selective reporting (reporting bias)	High risk	Data on OCS-treated exacerbations were not reported in the trial publication. Study sponsors have indicated that the data from this study are not available
Other bias	Low risk	77% of screening population eligible for randomisation

Morice 2008b

Methods	See Morice 2008a
Participants	See Morice 2008a
Interventions	See Morice 2008a, except for: TEST GROUP: • Combination BUD and F (160/9 µg) twice daily via metered-dose inhaler + placebo dry powder inhaler
Outcomes	See Morice 2008a
Notes	See Morice 2008a

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	See Morice 2008a
Allocation concealment (selection bias)	Unclear risk	See Morice 2008a
Blinding (performance bias and detection bias)	Low risk	See Morice 2008a

Morice 2008b *(Continued)*

All outcomes		
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	See Morice 2008a
Selective reporting (reporting bias)	High risk	See Morice 2008a
Other bias	Low risk	See Morice 2008a

Murray 2010

Methods	Two-centre randomised double-blind double-dummy study (SAM40100)
Participants	Children with moderate/severe persistent asthma % ELIGIBLE OF SCREENED POPULATION: 40 % RUN-IN PARTICIPANTS RANDOMLY ASSIGNED: 69 RANDOMLY ASSIGNED: 24 • Fluticasone\salmeterol: 12 • Fluticasone: 12 WITHDRAWALS: 2 • Fluticasone\salmeterol: 1 • Fluticasone: 1 AGE, mean (SD): 7.3 (2.2) years GENDER (% male): 50 SEVERITY: moderate to severe BASELINE % PRED FEV_1 mean (SD): 84.5 ASTHMA DURATION: reported as strata of 1 to 5 years and > 5 years ATOPY (%): not reported ELIGIBILITY CRITERIA: children 4 to 11 years of age, physician-diagnosed asthma, daily 200 to 800 µg BDP-equivalent ICS use EXCLUSION CRITERIA: participants with oral, parenteral or nebulized corticosteroids 4 weeks before run-in; ≥ 3 courses of oral prednisolone in previous year; intensive care admission in previous 3 months; regular use of SABA; use of LTRA; cromoglycates and/or theophyllines; known serious, uncontrolled systemic disease and asthma exacerbation requiring change of asthma medication during run-in CRITERIA FOR RANDOMISATION DURING RUN-IN: Randomisation included sRaw ≥ 1.3 kPa.s; correct completion of diary; symptom score ≥ 2 or required use of salbutamol on ≥ 2 occasions per day for ≥ 3 days of previous 7 days of run-in period
Interventions	LABA + ICS vs HIGH HIGH dose ICS RUN-IN PERIOD: 2 weeks OUTCOMES: reported at 6 weeks

Murray 2010 *(Continued)*

	DOSE OF ICS DURING RUN-IN: FP 100 µg twice daily DOSE OPTIMISATION PERIOD: none INTERVENTION PERIOD: 6 weeks TEST GROUP: fluticasone 100 µg and salmeterol 50 µg twice daily CONTROL GROUP: fluticasone 200 µg twice daily DEVICE: Accuhaler/Diskus NUMBER OF DEVICES: 1 COMPLIANCE: reported CO-TREATMENT: albuterol as needed
Outcomes	PULMONARY FUNCTION TEST: predose sRaw at end of 6 weeks of treatment*, FEV_1 SYMPTOM SCORES: symptom score recorded FUNCTIONAL STATUS: salbutamol rescue use, percent of rescue-free days and nights, percent of symptom-free days INFLAMMATORY MARKERS: not reported ADVERSE EFFECTS: reported WITHDRAWALS: reported *Primary outcome
Notes	Full-text publication Funded by GlaxoSmithKline Confirmation of methods and data not obtained Dose of ICS: intervention: 400 µg/d of BDP-equivalent; control: 800 µg/d of BDP-equivalent

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Insufficient information on sequence generation reported
Allocation concealment (selection bias)	Unclear risk	Insufficient information on allocation concealment reported
Blinding (performance bias and detection bias) All outcomes	Low risk	Double-blind study
Incomplete outcome data (attrition bias) All outcomes	Low risk	Low and balanced withdrawals. Intention to treat analysis.
Selective reporting (reporting bias)	Low risk	Primary and secondary outcomes prespecified. All outcomes were reported.

Murray 2010 *(Continued)*

Other bias	Low risk	No apparent source of bias was noticed.

Murray 2011

Methods	Stratified multi-centre randomised double-blind parallel-group study (SFA100316)
Participants	Children with persistent asthma treated with daily ICS for ≥ 4 weeks % ELIGIBLE OF SCREENED POPULATION: 33 % RUN-IN PARTICIPANTS RANDOMLY ASSIGNED: not reported RANDOMLY ASSIGNED: 231 • Fluticasone/salmeterol: 113 • Fluticasone: 118 WITHDRAWALS: 17 • Fluticasone/salmeterol: 7 • Fluticasone: 10 AGE, mean (range): 11.6 (4 to 17) years GENDER (% male): 57 SEVERITY: not reported BASELINE % PRED FEV_1 mean (SD): 83.5 ASTHMA DURATION: not reported ATOPY (%): not reported ELIGIBILITY CRITERIA: • 4 to 17 years of age • Diagnosis of persistent asthma treated with daily ICS for ≥ 4 weeks • FEV_1 of 70% to 95% of predicted based on Polgar predicted normal values [10] • Decrease in FEV_1 ≥ 15% after exercise challenge EXCLUSION CRITERIA: • History of life-threatening asthma; asthma hospitalisation within 6 months of screening • Significant concurrent disease, including recent respiratory tract infection (within 4 weeks before screening) • Pregnancy and/or lactation • Use of oral or parenteral corticosteroids within 4 weeks of screening or 2 courses of oral or parenteral corticosteroids within 6 months of screening • Use of the following medications within 2 weeks before screening and throughout the study: inhaled cromolyn, nedocromil, leukotriene modifiers, LABA, theophylline products and inhaled anticholinergics CRITERIA FOR RANDOMISATION DURING RUN-IN: • Participants had to maintain their FEV_1 at 70% to 95%. To be randomly assigned to treatment, participants were required to have documented albuterol use and/or asthma symptoms during the 7 days

Murray 2011 *(Continued)*

	immediately before the study visit, while receiving FP 100 µg twice daily. A minimum 20% fall in baseline FEV_1 following exercise challenge was also required at the end of the run-in period
Interventions	LABA + ICS vs SAME dose ICS RUN-IN PERIOD: 2 to 5 weeks OUTCOMES: reported at 4 weeks DOSE OF ICS DURING RUN-IN: FP 100 µg twice daily (Flovent DISKUS, GlaxoSmithKline, Research Triangle Park, North Carolina) DOSE OPTIMISATION PERIOD: none INTERVENTION PERIOD: 4 weeks TEST GROUP: fluticasone 100 µg and salmeterol 50 µg twice daily CONTROL GROUP: fluticasone 100 µg twice daily DEVICE: Diskus NUMBER OF DEVICES: 1 COMPLIANCE: reported CO-TREATMENT: albuterol as needed
Outcomes	PULMONARY FUNCTION TEST: maximal percent fall in FEV_1 following exercise challenge*, 4-hour serial post-dose FEV_1 AUC on Treatment Day 1, morning PEF, evening PEF FUNCTIONAL STATUS: percent of rescue-free days, percent of symptom free days INFLAMMATORY MARKERS: not reported ADVERSE EFFECTS: reported WITHDRAWALS: reported *Primary outcome
Notes	Full-text publication Funded by GlaxoSmithKline Confirmation of methods and data not obtained Dose of ICS: intervention: 400 µg/d of BDP-equivalent; control: 400 µg/d of BDP-equivalent

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Insufficient information on sequence generation reported.
Allocation concealment (selection bias)	Unclear risk	Insufficient information on allocation concealment reported.
Blinding (performance bias and detection bias) All outcomes	Low risk	Double-blind study.

Murray 2011 *(Continued)*

Incomplete outcome data (attrition bias) All outcomes	Low risk	Low and balanced withdrawals. Intention to treat analysis.
Selective reporting (reporting bias)	Low risk	Primary and secondary outcomes prespecified. All outcomes were reported.
Other bias	Low risk	No apparent source of bias was noticed.

Ortega-Cisneros 1998

Methods	Parallel-group single-centre
Participants	Symptomatic asthmatic children % ELIGIBLE OF SCREENED POPULATION: not reported % RUN-IN PARTICAPNTS RANDOMLY ASSIGNED: not reported RANDOMLY ASSIGNED: 20 • Salmeterol + BDP: 10 • BDP: 10 WITHDRAWALS: not described AGE (range): 6 to 19 years GENDER (% male): not described SEVERITY: moderate BASELINE % PRED FEV_1 mean (SD): not reported ASTHMA DURATION: not reported ATOPY (%): not reported ELIGIBILITY CRITERIA: still symptomatic despite maintenance treatment with 200 µg twice daily of BDP EXCLUSION CRITERIA: not described
Interventions	LABA + ICS vs INCREASED dose ICS RUN-IN PERIOD: 2 weeks OUTCOMES: reported at 8, 12 weeks DOSE OF ICS DURING RUN-IN: BDP 200 µg twice daily DOSE OPTIMISATION PERIOD: none INTERVENTION PERIOD: 12 weeks TEST GROUP: salmeterol 50 µg twice daily + BDP 200 µg twice daily CONTROL GROUP: BDP 400 µg twice daily DEVICE: not specified NUMBER OF DEVICES: 2

Ortega-Cisneros 1998 *(Continued)*

	COMPLIANCE: not reported CO-TREATMENT: not specified
Outcomes	PULMONARY FUNCTION TEST: FEV_1; PEF; FEF 25% to 75% SYMPTOM SCORES: symptoms FUNCTIONAL STATUS: not reported INFLAMMATORY MARKERS: not reported ADVERSE EFFECTS: not reported WITHDRAWALS: not reported
Notes	Abstract Funding not reported Confirmation of methods 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; no other information presented
Allocation concealment (selection bias)	Unclear risk	Information not provided
Blinding (performance bias and detection bias) All outcomes	High risk	Open-label
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	No information provided
Selective reporting (reporting bias)	Unclear risk	Unclear whether data on OCS-treated exacerbations were collected in the study
Other bias	Unclear risk	No information provided

Pearlman 2009

Methods	Multi-centre stratified randomised double-blind parallel-group study (Protocol SFA100314)
Participants	Children with persistent asthma with a minimum decrease in FEV_1 of 15% after exercise challenge % ELIGIBLE OF SCREENED POPULATION: 31 % RUN-IN PARTICIPANTS RANDOMLY ASSIGNED: not reported RANDOMLY ASSIGNED: 248

Pearlman 2009 *(Continued)*

- Fluticasone/salmeterol: 124
- Fluticasone: 124

WITHDRAWALS: 35

- Fluticasone/salmeterol: 13
- Fluticasone: 22

AGE, mean (range) 11.1 (4 to 17) years

GENDER (male %): 60

ASTHMA SEVERITY: not reported

BASELINE % PRED FEV_1 mean: 83.6

BASELINE DOSE OF ICS (start of run-in): 237 µg/d

ASTHMA DURATION: not reported

ATOPY (%): not reported

ELIGIBILITY CRITERIA:

- Eligible participants had to demonstrate a minimum decrease in FEV_1 of 15% after exercise challenge at the

first visit, approximately 8 hours after taking their prestudy ICS

EXCLUSION CRITERIA:

POST-RUN-IN: Participants were required to have documented use of albuterol and/or asthma symptoms in the 7 days immediately before randomisation. In addition, at the end of the run-in period, each participant was required to demonstrate a ≥ 20% decrease from baseline in FEV_1 following the exercise challenge

Interventions	LABA + ICS vs SAME dose ICS OUTCOMES: 4 weeks RUN-IN PERIOD: 1 to 2 weeks DOSE OF ICS DURING RUN-IN: fluticasone 100 µg twice daily INTERVENTION PERIOD: 4 weeks TEST GROUP: combination fluticasone/salmeterol 100/50 µg twice daily CONTROL GROUP: fluticasone 100 µg twice daily DEVICE: Diskus NUMBER OF DEVICES: 1 COMPLIANCE: reported CO-TREATMENT: albuterol as needed
Outcomes	PULMONARY FUNCTION TEST: maximal % fall in FEV_1 following exercise challenge*, 4-hour serial post-dose FEV_1 AUC on Treatment Day 1, FEV_1 (L), am PEF (L/min), pm PEF (L/min) SYMPTOM SCORES: not reported FUNCTIONAL STATUS: % symptom-free days, % albuterol-free days

Pearlman 2009 *(Continued)*

	INFLAMMATORY MARKERS: not reported
	ADVERSE EFFECTS: reported
	WITHDRAWALS: reported
	*Primary outcome: defined
Notes	Full-text publication
	Funded by GlaxoSmithKline
	Confirmation of methods and data not obtained
	Dose of ICS: intervention: 400 µg/d of BDP-equivalent; control: 400 µg/d of BDP-equivalent

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Assignment to blinded study drug was stratified on the basis of age
Allocation concealment (selection bias)	Unclear risk	Inadequate information was reported on allocation concealment
Blinding (performance bias and detection bias) All outcomes	Low risk	Double-blind study
Incomplete outcome data (attrition bias) All outcomes	Low risk	Well-balanced withdrawals in comparison groups; reasons for withdrawals were reported; intention-to-treat analysis
Selective reporting (reporting bias)	Low risk	Study protocol is available; primary and secondary outcomes were prespecified
Other bias	Low risk	No apparent source of bias was noted

Pohunek 2006a

Methods	Parallel-group multi-centre study (80 centres in Europe); 3 treatment groups
Participants	Steroid-using asthmatic children
	% ELIGIBLE OF SCREENED POPULATION: not reported
	% RUN-IN PARTICIPANTS RANDOMLY ASSIGNED: 77
	RANDOMLY ASSIGNED: 429 (BUD/F: 216; BUD: 213)
	WITHDRAWALS: BUD/F: 14 BUD: 13
	AGE, mean (range): 8 (4 to 11) years
	GENDER (male %): 67
	ASTHMA SEVERITY: mild to moderate
	BASELINE % PRED FEV_1 mean: 92

Pohunek 2006a *(Continued)*

	BASELINE DOSE OF ICS (start of run-in): 454 µg/d ASTHMA DURATION: 3 ATOPY (%): not reported ELIGIBILITY CRITERIA: • 4 to 11 years of age • Diagnosis of asthma (ATS) for ≥ 6 months • Pre-SABA PEF ≥ 50% of predicted • ICS treatment ≥ 12 weeks before entry into the study, at a constant dose of 375 to 1000 µg/d during the 30 days before enrolment • History of an average of ≥1 clinically important exercise-induced bronchoconstriction per week during 12 weeks leading up to the study • Ability to use Turbuhaler device and peak flow meter EXCLUSION CRITERIA: • Oral, parenteral or rectal corticosteroids within 30 days • Respiratory infection affecting asthma control within 30 days • Any significant co-existing disease/disorder • Known/suspected hypersensitivity to study medication or inhaled lactose • Inhaled anticholinergics, beta-blockers (including eye drops), xanthines and other anti-asthma agents not permitted during the study POST-RUN-IN: total asthma symptom score ≥ 1 on ≥ 4 of last 7 days of run-in period; during last 7 days of run-in, participants had to have a mean morning PEF of 50% to 85% of post-SABA PEF
Interventions	LABA + ICS vs SAME dose ICS OUTCOMES: 12 weeks RUN-IN PERIOD: 10 to 14 days DOSE OF ICS DURING RUN-IN: usual dose of ICS INTERVENTION PERIOD: 12 weeks TEST GROUP: combination BUD/F 200/6 µg twice daily CONTROL GROUP: BUD 200 µg twice daily DEVICE: Turbuhaler NUMBER OF DEVICES: 1 (Symbicort; double-dummy) COMPLIANCE: not reported CO-TREATMENT: SABA as needed
Outcomes	PULMONARY FUNCTION TEST: am PEF; pm PEF; FEV_1 SYMPTOM SCORES: not reported FUNCTIONAL STATUS: not reported INFLAMMATORY MARKERS: not reported ADVERSE EFFECTS: reported WITHDRAWALS: not reported

Pohunek 2006a *(Continued)*

	PRIMARY OUTCOME MEASURE: not reported
Notes	Full-text publication Funded by AstraZeneca Confirmation of methods and data not obtained User-defined number: 400

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Schedule generated using a computer programme (AstraZeneca, UK)
Allocation concealment (selection bias)	Low risk	Person not involved in the study team generated the randomisation schedule
Blinding (performance bias and detection bias) All outcomes	Low risk	Double-blind; double-dummy
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	'Intent to treat analysis was performed using data from all randomised patients' No additional data were provided on the composition of the ITT population
Selective reporting (reporting bias)	Unclear risk	Unclear whether OCS-treated exacerbations were collected in the study; correspondence with trialist has failed to clarify this
Other bias	Low risk	78% screening population eligible for randomisation

Pohunek 2006b

Methods	See Pohunek 2006a
Participants	See Pohunek 2006a, except for RANDOMLY ASSIGNED: 414 (F + BUD: 201; BUD: 213)
Interventions	See Pohunek 2006a, except for TEST GROUP: separate F 6 and BUD 200 µg twice daily NUMBER OF DEVICES: 2
Outcomes	See Pohunek 2006a
Notes	See Pohunek 2006a

Risk of bias

Bias	Authors' judgement	Support for judgement

Pohunek 2006b *(Continued)*

Random sequence generation (selection bias)	Low risk	See Pohunek 2006a
Allocation concealment (selection bias)	Low risk	See Pohunek 2006a
Blinding (performance bias and detection bias) All outcomes	Low risk	See Pohunek 2006a
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	See Pohunek 2006a
Selective reporting (reporting bias)	Unclear risk	See Pohunek 2006a
Other bias	Low risk	See Pohunek 2006a

Russell 1995

Methods	Parallel-group multi-centre study (78 centres)
Participants	Symptomatic asthmatic children % ELIGIBLE OF SCREENED POPULATION: not reported % RUN-IN PARTICIPANTS RANDOMLY ASSIGNED: not reported RANDOMLY ASSIGNED: 208 (salmeterol 50 + ICS: 99; placebo + ICS: 109) WITHDRAWALS: salmeterol 50 + ICS: 22%; placebo + ICS: 16.8% AGE, mean (SD): 10.2 (2.7) years GENDER (% male): 60 SEVERITY: moderate BASELINE MEAN % PRED FEV_1: 78 BASELINE DOSE OF ICS: 750 µg ASTHMA DURATION (%): < 1 year: 3; 1 to 5 years: 20; > 5 years: 77 ATOPY (%): 77 ELIGIBILITY CRITERIA DURING RUN-IN: • Morning PEF-PP (percent predicted) ≤ 90 on ≥ 4 days of the last 10 days of the baseline period • Recorded symptoms on ≥ 7 of 14 days of the baseline period for which patients used ≥ 1 salbutamol blister per episode • Recorded diurnal variation in PEF ≥ 15% on ≥ 7 occasions during baseline period EXCLUSION CRITERIA: received a course of OCS; change in prophylactic therapy during previous 2 weeks
Interventions	LABA + ICS vs SAME dose of ICS

Russell 1995 *(Continued)*

	OUTCOMES: reported at 4, 8 and 12 weeks RUN-IN PERIOD: 2 weeks DOSE OF ICS DURING RUN-IN: continued on usual ICS of ≥ 400 µg/d BDP DOSE OPTIMISATION PERIOD: none INTERVENTION PERIOD: 12 weeks TEST GROUP: (salmeterol 50 + ICS) salmeterol 50 µg twice daily + ICS 400 to 2400 µg/d (average: 750 µg/d) CONTROL GROUP: (placebo + ICS) placebo + ICS 400 to 2400 µg/d (average 750 µg/d) DEVICE: Diskhaler NUMBER OF DEVICES: 2 COMPLIANCE: evaluated using participant-kept record booklets CO-TREATMENT: salbutamol as needed and any other prophylactic asthma medication via Diskhaler
Outcomes	PULMONARY FUNCTION TEST: am PEF percent predicted*; pm PEF percent predicted SYMTPOM SCORES: Symptoms were recorded daily as present or absent wheeze or cough during day or night FUNCTIONAL STATUS: proportion symptom-free days; proportion symptom-free nights; rescue medication use INFLAMMATORY MARKERS: not described ADVERSE EFFECTS: described WITHDRAWALS: described *Primary outcome
Notes	Full-text publication Funded by Allen & Hanburys Confirmation of methods and data obtained User-defined number: 750 (750 µg/d)

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	Numbered coded envelopes supplied by pharmacy
Blinding (performance bias and detection bias) All outcomes	Low risk	Double-blind; identical placebo
Incomplete outcome data (attrition bias) All outcomes	High risk	'Total population used, this comprised all subjects who received at least one puff of medication and recorded at least one day of valid diary or clinic data

Russell 1995 *(Continued)*

		during the treatment period. Where a subject withdrew before completion of the study, data recorded after this withdrawal data was excluded'
Selective reporting (reporting bias)	Low risk	OCS-treated exacerbation data available
Other bias	Unclear risk	Information on % screening population eligible not available

Rutkowski 2009

Methods	Randomised double-blind placebo-controlled study
Participants	Children with mild to moderate asthma % ELIGIBLE OF SCREENED POPULATION: not reported % RUN-IN PARTICIPANTS RANDOMLY ASSIGNED: not reported RANDOMLY ASSIGNED: 40 • BUD/F: 20 • BUD: 20 WITHDRAWALS: 0 • BUD/F: 0 • BUD: 0 AGE (range): 10 to 18 years GENDER (male %): 45 ASTHMA SEVERITY: mild to moderate asthma BASELINE % PRED FEV_1 mean: not reported BASELINE DOSE OF ICS (start of run-in): not reported ASTHMA DURATION: 4.8 years ATOPY (%): not reported ELIGIBILITY CRITERIA: children with diagnosed mild to moderate asthma as per GINA 2008, with FEV_1 > 60% of predicted values, positive reversibility test to salbutamol and no symptoms of respiratory tract infection EXCLUSION CRITERIA: children with positive skin prick tests with common airborne allergens (house dust mites, trees, grasses, weeds, cat, *Alternaria, Cladosporium*) ELIGIBILITY CRITERIA DURING RUN-IN: not reported
Interventions	ICS and LABA vs SAME dose ICS OUTCOMES: 6 weeks RUN-IN PERIOD: 1 week DOSE OPTIMISATION PERIOD: NA INTERVENTION PERIOD: 6 weeks

Rutkowski 2009 *(Continued)*

	TEST GROUP: 400 µg BUD with 12 µg F fumarate twice daily CONTROL GROUP: 400 µg BUD twice daily NUMBER OF DEVICES: 2 COMPLIANCE: not reported CO-TREATMENT: not reported
Outcomes	PULMONARY FUNCTION TEST: FEV_1 and FEF25% to 75%, adenosine provocative test SYMPTOM SCORES: dyspnoea severity score FUNCTIONAL STATUS: asthma exacerbation INFLAMMATORY MARKERS: NA ADVERSE EFFECTS: not reported WITHDRAWALS: reported
Notes	Full-text publication Funded by: not reported Confirmation of methods and data not obtained Dose of ICS: intervention: 800 µg/d of BDP-equivalent; control: 800 µg/d of BDP-equivalent

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Inadequate information on randomisation technique is reported.
Allocation concealment (selection bias)	Low risk	Placebo capsules were identical in appearance, coded and inhaled via identical aerosoliser.
Blinding (performance bias and detection bias) All outcomes	Low risk	Double-blind study.
Incomplete outcome data (attrition bias) All outcomes	Low risk	All data presented. No withdrawals in the study.
Selective reporting (reporting bias)	Unclear risk	Primary and secondary outcomes were not clearly defined. Study protocol is not available.
Other bias	Low risk	No apparent source of bias was noticed.

SAM40012a

Methods	Parallel-group multi-centre study in Europe and Middle East
Participants	Steroid-using asthmatic children

SAM40012a *(Continued)*

	% ELIGIBLE OF SCREENED POPULATION: not reported
	% RUN-IN PARTICIPANTS RANDOMLY ASSIGNED: not reported
	RANDOMLY ASSIGNED: 362 (fluticasone/salmeterol: 181; fluticasone: 181)
	WITHDRAWALS: fluticasone/salmeterol: 3; fluticasone: 10
	AGE, mean: 8 years
	GENDER (male %): 68
	ASTHMA SEVERITY: moderate
	BASELINE % PRED FEV_1 mean: not reported
	BASELINE DOSE OF ICS (start of run-in): not reported
	ASTHMA DURATION: not reported
	ATOPY (%): not reported
	ELIGIBILITY CRITERIA: 4 to 500 µg BDP-equivalent; documented history of asthma
	EXCLUSION CRITERIA: not reported
	ELIGIBILITY CRITERIA DURING RUN-IN: symptom score ≥ 2 on 3 of last 7 days of run-in
Interventions	LABA + ICS vs SAME dose of ICS
	OUTCOMES: reported at 6 months
	RUN-IN PERIOD: 2 weeks
	DOSE OF ICS DURING RUN-IN: not clear
	DOSE OPTIMISATION PERIOD: none reported
	INTERVENTION PERIOD: 6 months
	TEST GROUP: combination salmeterol 50/fluticasone 100 µg twice daily
	CONTROL GROUP: fluticasone 100 µg twice daily
	DEVICE: Diskus
	NUMBER OF DEVICES: 1
	COMPLIANCE: not reported
	CO-TREATMENT: SABA as needed
Outcomes	OUTCOMES: reported at 6 months
	PULMONARY FUNCTION TEST: am PEF; pm PEF; FEV_1
	SYMPTOM SCORES: symptom-free days
	FUNCTIONAL STATUS: use of reliever medication; exacerbations (undefined)
	INFLAMMATORY MARKERS: not reported
	ADVERSE EFFECTS: reported
	WITHDRAWALS: reported

SAM40012a *(Continued)*

	*Primary outcome
Notes	Full unpublished data set available from http://www.ctr.gsk.co.uk Source of funding: GSK Confirmation of methods 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 4
Allocation concealment (selection bias)	Low risk	See Appendix 4
Blinding (performance bias and detection bias) All outcomes	Low risk	Identical inhaler devices
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	'To be evaluable, subjects had to meet the entry and randomisation criteria, receive at least one dose of study medication and have completed at least one day's post-randomisation diary information.'
Selective reporting (reporting bias)	Unclear risk	Exacerbations described in trial report available; OCS-treated exacerbations could not be identified from the data available
Other bias	Unclear risk	Information not available

SAM40012b

Methods	See SAM40012a
Participants	See SAM40012a, except for RANDOMLY ASSIGNED: fluticasone/salmeterol: 181; FP: 186 WITHDRAWALS: fluticasone/salmeterol: 3; FP: 5
Interventions	LABA + ICS vs HIGH dose of ICS See SAM40012a
Outcomes	See SAM40012a
Notes	See SAM40012a

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	See Appendix 4

SAM40012b *(Continued)*

Allocation concealment (selection bias)	Low risk	See Appendix 4
Blinding (performance bias and detection bias) All outcomes	Low risk	See SAM40012a
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	See SAM40012a
Selective reporting (reporting bias)	Unclear risk	See SAM40012a
Other bias	Unclear risk	See SAM40012a

SAM40100

Methods	Parallel-group multi-centre study
Participants	% ELIGIBLE OF SCREENED POPULATION: not reported % RUN-IN PARTICIPANTS RANDOMLY ASSIGNED: not reported RANDOMLY ASSIGNED: 24 (fluticasone/salmeterol: 12; FP: 12) WITHDRAWALS: fluticasone/salmeterol: 1; FP: 1 AGE, mean: 7.3 years SEVERITY: not stated. BASELINE % PRED FEV_1: not reported BASELINE DOSE OF ICS: not stated ASTHMA DURATION: not reported ATOPY (%): not reported ELIGIBILITY CRITERIA: • 4 to 8 years of age • History of asthma ≥ 3 months • Maintenance ICS dose of 200 to 800 µg/d BDP or equivalent for ≥ 4 weeks • Sufficiently stable to receive FP 200 µg/d during 2-week run-in • sRAW value of 1.3 kPa.s for entry into screening and treatment periods EXCLUSION CRITERIA: • Use of systemic steroids in 4 weeks before study entry • Required ≥ 3 courses of OCS in 12 months before study entry • Admitted to intensive care for asthma within 3 months before study entry ELIGIBILITY CRITERIA DURING RUN-IN: Participants who had a change in medication following an exacerbation during run-in were excluded
Interventions	LABA + ICS vs INCREASED DOSE ICS

SAM40100 *(Continued)*

	OUTCOMES: 6 weeks RUN-IN PERIOD: 2 weeks DOSE OPTIMISATION PERIOD: 2 weeks INTERVENTION PERIOD: 6 weeks TEST GROUP: combination fluticasone and salmeterol 100/50 µg twice daily via DPI CONTROL GROUP: fluticasone 200 µg twice daily via DPI NUMBER OF DEVICES: 1 COMPLIANCE: not assessed CO-TREATMENT: SABA as needed
Outcomes	PULMONARY FUNCTION TEST: FEV_1 SYMPTOM SCORES: day and nocturnal scores FUNCTIONAL STATUS: rescue medication use INFLAMMATORY MARKERS: sRAW* ADVERSE EFFECTS: reported WITHDRAWALS: reported
Notes	Unpublished data source from http://ctr.gsk.co.uk Funding source: GSK Confirmation of methods 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 4
Allocation concealment (selection bias)	Low risk	See Appendix 4
Blinding (performance bias and detection bias) All outcomes	Low risk	Double-blind; identical devices used
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	No detailed information on how intention-to-treat population was composed
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
Other bias	Unclear risk	Information on % screening/run-in population eligible not reported

SD 039 0714

Methods	Parallel-group multi-centre study
Participants	Steroid-using symptomatic asthmatic adolescents % ELIGIBLE OF SCREENED POPULATION: not reported % RUN-IN PARTICIPANTS RANDOMLY ASSIGNED: 60 RANDOMLY ASSIGNED: 271 (F6/Bud 200 µg twice daily: 136; Bud 200 µg twice daily: 135) WITHDRAWALS: F/BUD 200 µg twice daily: 25; BUD 200 µg twice daily: 27 AGE, mean (range): 14 (11 to 17) years GENDER (male %): 42 ASTHMA SEVERITY: moderate BASELINE % PRED FEV_1 mean: 75 BASELINE DOSE OF ICS (start of run-in): not reported ASTHMA DURATION: not reported ATOPY (%): not reported ELIGIBILITY CRITERIA: ICS 375 to 1000 µg BDP equivalent; FEV_1 40% to 90% of predicted normal; ≥ 12% improvement following inhalation of 1 mg of terbutaline EXCLUSION CRITERIA: not reported CRITERIA FOR RANDOMISATION DURING RUN-IN: symptomatic
Interventions	LABA + ICS vs SAME dose of ICS OUTCOMES: reported at 1, 2 and 3 months RUN-IN PERIOD: 2 weeks to document stability DOSE OF ICS DURING RUN-IN: not clear DOSE OPTIMISATION PERIOD: none reported INTERVENTION PERIOD: 3 months TEST GROUP: combination BUD and F 200/6 µg twice daily CONTROL GROUP: BUD 200 µg twice daily DEVICE: Turbuhaler NUMBER OF DEVICES: 1 COMPLIANCE: not reported CO-TREATMENT: SABA as needed
Outcomes	PULMONARY FUNCTION TEST: FEV_1; am PEF*; pm PEF SYMPTOM SCORES: recorded but not reported FUNCTIONAL STATUS: rescue medication use (recorded but not reported); nocturnal awakening (recorded but not reported); episode-free days (recorded but not reported)

SD 039 0714 *(Continued)*

	INFLAMMATORY MARKERS: not reported
	ADVERSE EFFECTS: reported
	WITHDRAWALS: reported
	*Primary outcome
Notes	Unpublished data downloaded from AZ website (www.astrazenecaclinicaltrials.com)
	Funded by AstraZeneca
	Confirmation of data and methods obtained
	User-defined number: 400

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Information not available
Allocation concealment (selection bias)	Unclear risk	Information not available
Blinding (performance bias and detection bias) All outcomes	Low risk	Double-blind; double-dummy
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	No detailed information on how intention-to-treat population was composed
Selective reporting (reporting bias)	Unclear risk	OCS-treated exacerbations were not reported in the study publication; data request was made to study sponsors to ask for this information
Other bias	Low risk	59% run-in population eligible

SD 039 0718

Methods	Parallel-group multi-centre study (52 centres in USA)
Participants	% ELIGIBLE OF SCREENED POPULATION: not reported
	% RUN-IN PARTICIPANTS RANDOMLY ASSIGNED: 60
	RANDOMLY ASSIGNED: 273 (BUD/F: 128; BUD: 145)
	WITHDRAWALS: BUD/F: 36; BUD: 51
	AGE, mean (range) or mean (SD): 10.4 (2.6) years
	SEVERITY: not stated
	BASELINE % PRED FEV_1: 82
	BASELINE DOSE OF ICS: 235 µg/d
	ASTHMA DURATION: 7 years

SD 039 0718 *(Continued)*

	ATOPY (%): not stated
	ELIGIBILITY CRITERIA: 6 to 15 years; low to medium dose of ICS; FEV_1 predicted > 50%; reversibility criteria age dependent: > 12 years 14% and 0.2 L; < 12 years: 12%
	EXCLUSION CRITERIA: not reported
	ELIGIBILITY CRITERIA DURING RUN-IN: symptoms and lung function not otherwise described
Interventions	LABA + ICS vs SAME DOSE ICS
	OUTCOMES: 12 weeks
	RUN-IN PERIOD: 1 to 2 weeks
	DOSE OPTIMISATION PERIOD: not applicable
	INTERVENTION PERIOD: 12 weeks
	TEST GROUP: combination BUD/F (100/9 µg) twice daily via metered-dose inhaler
	CONTROL GROUP: BUD 100 µg twice daily via metered-dose inhaler
	NUMBER OF DEVICES: 1
	COMPLIANCE: not assessed
	CO-TREATMENT: SABA as needed
Outcomes	PULMONARY FUNCTION TEST: am PEF; pm PEF; FEV_1
	SYMPTOM SCORES: NA
	FUNCTIONAL STATUS: NA
	INFLAMMATORY MARKERS: NA
	ADVERSE EFFECTS: stated
	WITHDRAWALS: stated
Notes	Unpublished data from AZ clinical trials website
	Funded by AstraZeneca
	Confirmation of data and methods obtained
	User-defined number: 200

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Described as randomised; no other information presented
Allocation concealment (selection bias)	Unclear risk	Information not available
Blinding (performance bias and detection bias) All outcomes	Low risk	Double-blind; double-dummy

SD 039 0718 *(Continued)*

Incomplete outcome data (attrition bias) All outcomes	Unclear risk	'The efficacy analysis set (EAS) was defined as all randomised subjects who took at least 1 dose of study medication and contributed at least 1 PEF value to the primary endpoint' No information given on whether EAS population included last observation
Selective reporting (reporting bias)	Unclear risk	OCS-treated exacerbations were not reported in the study publication. Data request has been made to study sponsors for this information.
Other bias	Low risk	59% screening population eligible

Simons 1997

Methods	Randomised double-blind cross-over single-centre study
Participants	Asymptomatic children % ELIGIBLE OF SCREENED POPULATION: not reported % RUN-IN PARTICIPANTS RANDOMLY ASSIGNED: not reported RANDOMLY ASSIGNED: 16 WITHDRAWALS: 2 (13%) AGE, mean (range): 13.1 (12 to 16) years GENDER (% male): 44 SEVERITY: not described BASELINE % PRED FEV_1: 93.4 BASELINE DOSE OF ICS: 100 to 200 µg BDP twice daily ASTHMA DURATION: 5.9 ± 3.4 years ATOPY (%): 100 ELIGIBILITY CRITERIA: • 12 to 18 years old • Well-controlled chronic asthma; diagnosed according to American Thoracic Society criteria • Able to perform treadmill running tests • Perform pulmonary function tests satisfactorily • Use a Nebulizer Chronolog correctly EXCLUSION CRITERIA: • Any significant medical conditions other than mild asthma, allergic rhinitis or eczema • Respiratory tract infection, or an acute asthma exacerbation within the previous month • Prednisone treatment and emergency department visit or hospitalisations within 3 months • Life-threatening asthma episode or an adverse reaction to any $beta_2$-adrenergic agonist, or used salmeterol previously CRITERIA FOR RANDOMISATION DURING RUN-IN: N/A
Interventions	LABA + ICS vs SAME dose of ICS

Simons 1997 *(Continued)*

	OUTCOMES measured at: days 1 and 28 RUN-IN PERIOD: not specified DOSE OF ICS DURING RUN-IN: not reported DOSE OPTIMISATION PERIOD: none INTERVENTION PERIOD: 28 days WASHOUT PERIOD: 14 days TEST GROUP: salmeterol 50 µg once daily + BDP 100 to 200 µg twice daily CONTROL GROUP: BDP 100 to 200 µg twice daily + placebo DEVICE: metered-dose inhaler and Nebulizer Chronolog device NUMBER OF DEVICES: 2 COMPLIANCE: medication usage recorded in participant diary. Device inserted into MDI recorded date, hour and minute of each inhalation CO-TREATMENT: SABA as needed (200 µg up to 3 times daily), except that albuterol was not permitted 8 hours before each exercise test. If participants had allergic rhinitis, they were permitted to use pseudoephedrine (Sudafed) 1 to 3 times daily as needed, except on the days when exercise tests were scheduled
Outcomes	PULMONARY FUNCTION TEST: exercise challenge (max % fall in FEV_1 from pre-exercise baseline) SYMPTOM SCORES: symptoms FUNCTIONAL STATUS: rescue medication use; exacerbations requiring systemic steroids INFLAMMATORY MARKERS: not reported ADVERSE EFFECTS: reported WITHDRAWALS: described PRIMARY OUTCOME MEASURE: not specified
Notes	Full-text publication Funded by GSK Confirmation of data and methods obtained User-defined number: 300 (1/2 with BDP 100 twice daily; 1/2 with BDP 200 twice daily)

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated random numbers
Allocation concealment (selection bias)	Unclear risk	Information not available
Blinding (performance bias and detection bias) All outcomes	Low risk	Double-blind; double-dummy

Simons 1997 *(Continued)*

Incomplete outcome data (attrition bias) All outcomes	Low risk	All participants completed the study
Selective reporting (reporting bias)	Low risk	Data on OCS-treated exacerbations available
Other bias	Unclear risk	Information on % screening population eligible not available

Stelmach 2007

Methods	Parallel-group single-centre study in Poland
Participants	% ELIGIBLE OF SCREENED POPULATION: 97 % RUN-IN PARTICIPANTS RANDOMLY ASSIGNED: not reported RANDOMLY ASSIGNED: 58 (BUD/F: 29; BUD: 29) WITHDRAWALS: 0 AGE, mean (range) or mean (SD): 10 years SEVERITY: moderate BASELINE % PRED FEV_1: 94 BASELINE DOSE OF ICS: 400 µg/d BDP-equivalent ASTHMA DURATION: 4 years ATOPY (%): 100 ELIGIBILITY CRITERIA: 6 to 18 years; history of asthma requiring treatment with ICS EXCLUSION CRITERIA: upper RTI in previous 3 weeks; sinus disease requiring antibiotics within 4 weeks; oral steroids within 4 weeks of study entry; immunotherapy ELIGIBILITY CRITERIA DURING RUN-IN: not reported
Interventions	ICS and LABA vs SAME DOSE ICS OUTCOMES: 8 weeks RUN-IN PERIOD: 4 weeks DOSE OPTIMISATION PERIOD: INTERVENTION PERIOD: 8 weeks TEST GROUP: BUD 200 µg + F 9 µg via Turbuhaler CONTROL GROUP: BUD 200 µg/d via Turbuhaler NUMBER OF DEVICES: 2 COMPLIANCE: not assessed CO-TREATMENT: SABA as needed
Outcomes	PULMONARY FUNCTION TEST: FEV_1 predicted; FEF25% to 75%; SRaw

Stelmach 2007 *(Continued)*

	SYMPTOM SCORES: not reported FUNCTIONAL STATUS: not reported INFLAMMATORY MARKERS: not reported ADVERSE EFFECTS: not reported WITHDRAWALS: reported
Notes	Full-text article Funded by grant from Lodz University, Poland Confirmation of data and methods not obtained User-defined number: 200

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated randomisation schedule
Allocation concealment (selection bias)	Unclear risk	Information not available
Blinding (performance bias and detection bias) All outcomes	Low risk	Double-blind; double dummy
Incomplete outcome data (attrition bias) All outcomes	Low risk	All completed
Selective reporting (reporting bias)	Unclear risk	Unclear whether data on OCS-treated exacerbations were collected. Request for this information from study investigator has not been successful.
Other bias	Low risk	97% screening population eligible for study

Stelmach 2008

Methods	Randomised double-blind placebo-controlled study
Participants	Children with atopic asthma with confirmed fall ≥ 20% in FEV_1 post exercise % ELIGIBLE OF SCREENED POPULATION: 67 % RUN-IN PARTICIPANTS RANDOMLY ASSIGNED: not applicable RANDOMLY ASSIGNED: 40 • BUD/F: 20 • BUD: 20 WITHDRAWALS: 2 • BUD/F: 2

Stelmach 2008 *(Continued)*

	• BUD: 0 AGE, mean: 11.6 years GENDER (% male): not reported SEVERITY: not reported BASELINE % PRED FEV_1: 91.7 BASELINE DOSE OF ICS: not reported ASTHMA DURATION: not reported ATOPY (%): not reported ELIGIBILITY CRITERIA: Male and female outpatients 6 to 18 years of age with a clinical diagnosis of bronchial asthma lasting ≥ 6 months before the first visit were enrolled. To be included in the study, participants had to have a resting FEV_1 ≥ 70% and a documented decrease in FEV_1 ≥ 20% after a standard exercise challenge test EXCLUSION CRITERIA: Participants were excluded if they had an active upper respiratory tract infection within 3 weeks before the study and acute sinus disease requiring antibiotic treatment within 1 month before the study, previous intubation or asthma hospitalisation during the 3 months before the prestudy visit. Additional criteria were other clinically significant pulmonary, haematological, hepatic, gastrointestinal, renal, endocrine, neurological, cardiovascular and/or psychiatric disease or malignancy that put the patient at risk when participating in the study or could influence study results or the patient's ability to participate in the study as judged by the investigator. Medications that resulted in patient exclusion included beta-blockers (eye drops included) or OCS within 1 month before the first visit. Participants receiving immunotherapy were also excluded CRITERIA FOR RANDOMISATION DURING RUN-IN: ICS (BUD; average dose, 400 µg/d) and montelukast sodium (5 mg or 10 mg, according to age) or LABA
Interventions	LABA + ICS vs SAME dose of ICS OUTCOMES measured at: 4 weeks RUN-IN PERIOD: 4 weeks DOSE OF ICS DURING RUN-IN: not applicable. DOSE OPTIMISATION PERIOD: none INTERVENTION PERIOD: 4 weeks TEST GROUP: F 4.5 µg + BUD 100 µg twice daily CONTROL GROUP: BDP 100 µg twice daily and placebo DEVICE: Turbuhaler NUMBER OF DEVICES: 2 COMPLIANCE: not reported CO-TREATMENT: inhaled SABA as needed.
Outcomes	PULMONARY FUNCTION TEST: exercise-induced bronchoconstriction (AUC0-20min (% of predicted 3 minutes); maximum % fall in FEV_1) SYMPTOM SCORES: not reported FUNCTIONAL STATUS: not reported

Stelmach 2008 *(Continued)*

	INFLAMMATORY MARKERS: not reported
	ADVERSE EFFECTS: Standing height and weight were recorded
	WITHDRAWALS: described
Notes	Full-text publication
	Source of funding: not reported
	Confirmation of data and methods not obtained
	Dose of ICS: intervention: 200 µg/d of BDP-equivalent; control: 200 µg/d of BDP-equivalent

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer generated allocation schedule was used.
Allocation concealment (selection bias)	Low risk	Centralized hospital pharmacy prepared the drugs and placebos by breaking formulations open. The part of the turbuhaler containing a reservoir of powder with active ingredient was replaced with inert placebo powder.
Blinding (performance bias and detection bias) All outcomes	Low risk	Double-blind study.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Withdrawals were reported with reasons. All data presented.
Selective reporting (reporting bias)	Low risk	Although, the study protocol was not available, no selective reporting was noted.
Other bias	Low risk	No apparent source of bias was noticed.

Tal 2002

Methods	Parallel-group multi-centre study (48 centres in 7 countries)
Participants	Asymptomatic children
	% ELIGIBLE OF SCREENED POPULATION: not reported
	% RUN-IN PARTICIPANTS RANDOMLY ASSIGNED: not reported
	RANDOMLY ASSIGNED: 286 (F + BDP: 148; BDP: 138)
	WITHDRAWALS: F/BDP: 9; BDP: 9
	AGE, mean (range): 11 (4 to 17) years
	GENDER (% male): 62
	SEVERITY: mild
	BASELINE % PRED FEV_1: 75

Tal 2002 *(Continued)*

	BASELINE DOSE OF ICS: 548 ASTHMA DURATION: 6.8 years ATOPY (%): not reported ELIGIBILITY CRITERIA: • 4 to 17 years old • Asthma diagnosed minimum 6 months • FEV_1 40% to 90% of predicted and > 15% reversibility in FEV_1 within 15 minutes of bronchodilator • Constant dose ICS for prior 6 weeks (> 400 µg BUD turbuhaler, > 600 µg BUD via MDI, > 375 µg fluticasone propionate or > 600 µg CFC BDP) EXCLUSION CRITERIA: • Unstable asthma (defined as use of oral, parenteral or rectal corticosteroids within 30 days of study commencement) • Respiratory tract infection within previous 4 weeks • Known hypersensitivity to study medications or inhaled lactose • Use of ICS other than study medication not allowed CRITERIA FOR RANDOMISATION DURING RUN-IN: no other additional criteria
Interventions	LABA + ICS vs SAME dose of ICS OUTCOMES measured at: 4, 8 and 12 weeks RUN-IN PERIOD: 2 to 4 weeks DOSE OF ICS DURING RUN-IN: BUD 200 twice daily DOSE OPTIMISATION PERIOD: none INTERVENTION PERIOD: 12 weeks TEST GROUP: F 12 µg twice daily + BDP 200 µg twice daily CONTROL GROUP: BDP 200 µg twice daily and placebo DEVICE: Turbuhaler NUMBER OF DEVICES: 2 COMPLIANCE: not reported CO-TREATMENT: SABA as needed. If participants had allergic rhinitis, they were permitted to use nasal corticosteroids; treatment with other asthma medication not permitted
Outcomes	PULMONARY FUNCTION TEST: am PEF*; pm PEF; FEV_1 predicted SYMPTOM SCORES: daily and nocturnal on 4-point scale FUNCTIONAL STATUS: rescue medication use; nighttime awakening; symptom-free days INFLAMMATORY MARKERS: not reported ADVERSE EFFECTS: reported WITHDRAWALS: described *Primary outcome
Notes	Full-text publication

Tal 2002 *(Continued)*

	Source of funding: AstraZeneca Confirmation of data and methods obtained

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	'Individual treatment code envelopes were provided for each subject'
Blinding (performance bias and detection bias) All outcomes	Low risk	Double-blind; double-dummy
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Explicit description of how ITT population was composed was not presented: 'An intention-to-treat analysis was used with all available data'
Selective reporting (reporting bias)	Unclear risk	Unclear whether data on OCS-treated exacerbations were collected in the study; correspondence with study investigators has not clarified this
Other bias	Unclear risk	No information available on % screening/run-in populations eligible for the study

Teper 2005

Methods	Parallel-group single-centre study
Participants	Children with mild to moderate asthma % ELIGIBLE OF SCREENED POPULATION: not reported % RUN-IN PARTICIPANTS RANDOMLY ASSIGNED: not reported RANDOMLY ASSIGNED: 82 (fluticasone/salmeterol: 43; FP: 39) WITHDRAWALS: not reported AGE, mean: 10 years GENDER (male %): 59 ASTHMA SEVERITY: mild to moderate BASELINE % PRED FEV_1: 95 BASELINE DOSE OF ICS (start of run-in): not reported ASTHMA DURATION: not reported ATOPY (%): not reported ELIGIBILITY CRITERIA: ATS diagnosed mild or moderate asthma; age 6 to 14 years of participants; FEV_1 > 70% of predicted; methacholine PC20 < 2 µg/mL EXCLUSION CRITERIA: not reported

Teper 2005 *(Continued)*

	CRITERIA FOR RANDOMISATION DURING RUN-IN: not reported
Interventions	LABA + ICS vs SAME dose ICS OUTCOMES: 12 months RUN-IN PERIOD: unclear DOSE OF ICS DURING RUN-IN: not reported DOSE OPTIMISATION PERIOD: none reported INTERVENTION PERIOD: 12 months TEST GROUP: combination fluticasone and salmeterol 125/25 twice daily CONTROL GROUP: fluticasone 125 µg twice daily DEVICE: MDI (with aerochamber) NUMBER OF DEVICES: 1 COMPLIANCE: not reported CO-TREATMENT: SABA as needed
Outcomes	PULMONARY FUNCTION TEST: FEV_1 % predicted SYMPTOM SCORES: % symptom-free days; % symptom-free nights FUNCTIONAL STATUS: % SABA-free days INFLAMMATORY MARKERS: PC20 ADVERSE EFFECTS: reported WITHDRAWALS: not reported PRIMARY OUTCOME MEASURES: not clear
Notes	Unpublished conference abstract Source of funding: not reported Confirmation of data and methods not obtained User-defined number: 500

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	Low risk	Double-blind; means by which assignment to treatment group is masked is not available
Incomplete outcome data (attrition bias)	Unclear risk	No information provided on ITT population

Teper 2005 *(Continued)*
All outcomes

Selective reporting (reporting bias)	Unclear risk	Unclear whether data on OCS-treated exacerbations were collected
Other bias	Unclear risk	No information available on % screening/run-in populations eligible for the study

Vaessen-Verberne 2010

Methods	Multi-centre randomised parallel-group double-blind study
Participants	Children with moderate asthma % ELIGIBLE OF SCREENED POPULATION: 62 % RUN-IN PARTICIPANTS RANDOMLY ASSIGNED: not reported RANDOMLY ASSIGNED: 158 • Fluticasone/salmeterol: 78 • Fluticasone: 80 WITHDRAWALS: 7 • Fluticasone/salmeterol: 6 • Fluticasone: 1 AGE, mean: 9.4 years GENDER (male %): 58 ASTHMA SEVERITY: moderate BASELINE % PRED FEV_1: 100 BASELINE DOSE OF ICS (start of run-in): maximum 250 µg fluticasone or equivalent ASTHMA DURATION: 5.6 years ATOPY (%): 59 ELIGIBILITY CRITERIA: all children with moderate asthma; history of bronchial hyperresponsiveness; used ICS (maximum 250 µg fluticasone or equivalent) EXCLUSION CRITERIA: not reported CRITERIA FOR RANDOMISATION DURING RUN-IN: children still symptomatic despite regular use of FP, 100 µg twice a day
Interventions	LABA + ICS vs INCREASED dose ICS OUTCOMES: evaluated at 1, 6, 16 and 26 weeks RUN-IN PERIOD: 4 weeks DOSE OF ICS DURING RUN-IN: INTERVENTION PERIOD: 26 weeks DOSE OPTIMISATION PERIOD: none

Vaessen-Verberne 2010 *(Continued)*

	Test group: salmeterol/fluticasone 50/100 µg twice a day Control group: fluticasone 200 µg twice a day DEVICE: Diskhaler NUMBER OF DEVICES: 1 COMPLIANCE: reported CO-TREATMENT: salbutamol 200 µg Diskus
Outcomes	PULMONARY FUNCTION TEST: FEV_1, FVC, FEV_1/FVC, MEF50 and PEF rate, PD20 methacholine test SYMPTOM SCORES: symptom-free days after 26 weeks* FUNCTIONAL STATUS: oropharyngeal examination, height by stadiometry (including height history), 12-hour urine cortisol, weekly % of participants with 'good controlled weeks', 'maximal controlled weeks', cumulative number of symptom-free weeks until end of treatment, time to asthma control defined as time to first 'good controlled week' or 'maximum controlled week' INFLAMMATORY MARKERS: exhaled nitric oxide (in selected centres) ADVERSE EFFECTS: adverse events and serious adverse events reported WITHDRAWALS: reported *Primary outcome
Notes	Full-text publication Funded by GSK Confirmation of methods and data not obtained Dose of ICS: intervention: 400 µg/d of BDP-equivalent; control: 400 µg/d of BDP-equivalent

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not reported the technique of randomisation.
Allocation concealment (selection bias)	Unclear risk	Not reported the allocation technique.
Blinding (performance bias and detection bias) All outcomes	Low risk	Double-blind
Incomplete outcome data (attrition bias) All outcomes	Low risk	Intention to treat analysis. All outcomes were reported. Imbalanced withdrawals but reasons for withdrawals clearly reported.
Selective reporting (reporting bias)	Low risk	Primary and secondary outcomes were reported.
Other bias	Low risk	No apparent bias was noticed.

Verberne 1998a

Methods	Parallel-group multi-centre study (9 centres); 3 groups, of which 2 are considered in this review
Participants	Asthmatic children % ELIGIBLE OF SCREENED POPULATION: not reported % RUN-IN PARTICIPANTS RANDOMLY ASSIGNED: not reported RANDOMLY ASSIGNED: 117 (BDP 400 + salmeterol: 60; BDP 400: 57) WITHDRAWALS: BDP 400 + salmeterol: 5; BDP 400: 4 AGE, mean (SD): 11 (2.6) years GENDER (% male): 65 SEVERITY: mild BASELINE % PRED FEV_1: 88 BASELINE DOSE OF ICS (SD): 489 (153) ASTHMA DURATION mean (SD): 8.1 (3.2) ATOPY (%): 88 ELIGIBILITY CRITERIA: • FEV_1 between 55% and 90% of predicted or FEV_1/FVC ratio of 50% to 75% • ≥ 10% improvement in FEV_1 after inhalation of salbutamol • Airway hyper-responsiveness to methacholine (PD20) • Ability to reproduce lung function test • History of stable asthma ≥ 1 month without exacerbation or respiratory tract infection • Use of ICS between 200 and 800 µg/d for ≥ 3 months before the beginning of the study EXCLUSION CRITERIA: • Operations for congenital heart disease, oesophageal atresia, congenital or acquired anatomical malformation of the lungs or airways, dyskinetic cilia syndrome • Bronchiectasis • Bronchopulmonary dysplasia • Diabetes • Renal disease • Other serious conditions that may influence the possibility of continuation of the study • Using OCS continuously or ICS at a dose > 800 µg daily • Using beta-blocking agents or used cromoglycate or nedocromil sodium within previous 2 weeks • Allergic to SABA, pregnant or lactating or females of childbearing age who in the opinion of the supervising physician were not taking adequate contraceptive precautions • Ongoing hyposensitising programme • Inability to follow therapy instructions, inability to inhale medications adequately or inability to use peak flow meter • During study: non-compliance with respect to study medication, completing diary cards, clinic visits; withdrawal at own or investigator's discretion; total number of courses of OCS more than allowed in the study CRITERIA FOR RANDOMISATION DURING RUN-IN: no additional criteria
Interventions	LABA + ICS vs SAME dose ICS

Verberne 1998a *(Continued)*

	OUTCOMES: reported at 6, 12, 18, 24, 30, 36, 42, 48 and 54 weeks RUN-IN PERIOD: 6 weeks DOSE OF ICS DURING RUN-IN: BDP 200 µg twice daily INTERVENTION PERIOD: 54 weeks DOSE OPTIMISATION PERIOD: none TEST GROUP: (salmeterol 50 µg + BDP 200 µg) salmeterol 50 µg twice daily and BDP 200 µg twice daily CONTROL GROUP: (BDP 200 + placebo) BDP 200 µg twice daily + placebo DEVICE: Rotadisks in combination with a Diskhaler NUMBER OF DEVICES: 2 COMPLIANCE: not reported CO-TREATMENT: SABA as needed
Outcomes	PULMONARY FUNCTION TEST: FEV_1; am PEF; pm PEF; FVC SYMPTOM SCORES: Asthma symptoms like wheezing, dyspnoea, exercise-induced asthma and cough were scored in the morning and evening on a scale from 1 to 3 FUNCTIONAL STATUS: Rescue medication use; exacerbation (requiring systemic steroids); height, body weight, heart rate and systolic and diastolic blood pressures were measured INFLAMMATORY MARKERS: total IgE ADVERSE EFFECTS: reported WITHDRAWALS: reported *Primary outcome: airway calibre measured as FEV_1 and airway responsiveness to methacholine
Notes	Full-text publication Funded by GSK Confirmation of methods and data obtained User-defined number: 400

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	Telephone notification of assignment by coordinating centre
Blinding (performance bias and detection bias) All outcomes	Low risk	Double-blind; identical placebo used
Incomplete outcome data (attrition bias)	Unclear risk	Not clear how population was identified for primary outcome Incomplete diary card data not included in analysis:

Verberne 1998a *(Continued)*

All outcomes		'Where patients failed to complete their daily record cards for more than 7 d in any 14-d period such assessments were not included in the analysis. Otherwise, when there were missing days in the record, pro rata adjustment was made to give a 2-wk assessment'
Selective reporting (reporting bias)	Low risk	OCS-treated exacerbation data available
Other bias	Unclear risk	No information available on % screening/run-in populations eligible for the study

Verberne 1998b

Methods	See Verberne 1998a
Participants	As for Verberne 1998a, except for RANDOMLY ASSIGNED: 120 WITHDRAWALS: BDP 400 + salmeterol: 5; BDP 800: 6
Interventions	LABA + ICS vs INCREASED dose ICS OUTCOMES: reported at 6, 12, 18, 24, 30, 36, 42, 48 and 54 RUN-IN PERIOD: 6 weeks DOSE OF ICS DURING RUN-IN: BDP 200 twice daily DOSE OPTIMISATION PERIOD: none INTERVENTION PERIOD: 54 weeks TEST GROUP: (salmeterol 50 + BDP200): salmeterol 50 µg twice daily + BDP 200 µg twice daily CONTROL GROUP: (BDP 400 + placebo): BDP 400 µg/d + placebo DEVICE: Rotadisks in combination with a Diskhaler NUMBER OF DEVICES: 2 COMPLIANCE: not reported CO-TREATMENT: SABA as needed
Outcomes	PULMONARY FUNCTION TEST: FEV_1; am PEF; pm PEF; FVC SYMPTOM SCORES: Asthma symptoms like wheezing, dyspnoea, exercise-induced asthma and cough were scored in the morning and evening on a scale from 1 to 3 FUNCTIONAL STATUS: Rescue medication use; exacerbation (requiring systemic steroids); height, body weight, heart rate and systolic and diastolic blood pressures were measured INFLAMMATORY MARKERS: total IgE ADVERSE EFFECTS: reported WITHDRAWALS: reported *Primary outcome: airway calibre measured as FEV_1 and airway responsiveness to methacholine

Verberne 1998b *(Continued)*

Notes	Full-text publication Funded by GSK Confirmation of methods and data obtained User-defined number: 400

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	See Verberne 1998a
Allocation concealment (selection bias)	Low risk	See Verberne 1998a
Blinding (performance bias and detection bias) All outcomes	Low risk	See Verberne 1998a
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	See Verberne 1998a
Selective reporting (reporting bias)	Low risk	See Verberne 1998a
Other bias	Unclear risk	See Verberne 1998a

Zimmerman 2004a

Methods	Parallel-group multi-centre study (27 centres in Canada). Three treatment arms comparing LABA/ICS with 2 doses of LABA and ICS alone. Two groups will be considered here, and as the same control group is used for both comparisons, half the control group will be applied to each
Participants	Children ≥ 6 to 11 years of age % ELIGIBLE OF SCREENED POPULATION: not reported % RUN-IN PARTICIPANTS RANDOMLY ASSIGNED: 68 RANDOMLY ASSIGNED: 196 (F + usual ICS twice daily: 95; usual ICS: 101) WITHDRAWALS: F + usual ICS: 7; usual ICS: 16 AGE, mean (range): 9 (6 to 11) years GENDER (% male): 63 SEVERITY: moderate BASELINE FEV_1 % Pred: 77.4 BASELINE DOSE OF ICS: 445 ASTHMA DURATION (years): 5.7

Zimmerman 2004a *(Continued)*

ATOPY (%): not reported

ELIGIBILITY CRITERIA:

- ≥ 12 years of age
- Clinical diagnosis of asthma according to ATS criteria for ≥ 12 months
- Treated with ICS for ≥ 3 months before entry
- FEV_1 between 50% and 90% of predicted normal
- ≥ 15% reversibility after bronchodilator
- Asthma symptoms suggestive that additional therapy might be needed
- Able to use peak flow meter and Turbuhaler, answer questions from the Paediatric Asthma Quality of Life Questionnaire and parent or guardian had to complete a daily diary card

EXCLUSION CRITERIA:

- Systemic corticosteroids or anti-leukotrienes within 30 days of study entry, astemizole within 120 days, sodium cromoglycate or ketotifen within 7 days, salmeterol or F within 72 hours or xanthines or antihistamines within 48 hours
- Nasal corticosteroids and immunotherapy permitted provided dose had been constant ≥ 30 days and 90 days, respectively, before study entry
- Smoking history

RANDOMISATION CRITERIA FOLLOWING RUN-IN:

- Postbronchodilator reversibility ≥ 12% of prebronchodilator value or ≥ 9% of predicted normal or diurnal variability or ≥ 15% on any 5 of the last 10 days of run-in
- 75% to 124% compliance with prescribed dose as assessed by diary card
- Symptoms during past 10 days of run-in (defined as having ≥ 1 of the following: ≥ 4 inhalations of rescue medication; daytime symptoms ≥ 4 days or night time awakening ≥ 1 night)

Interventions	LABA + ICS vs usual dose of ICS OUTCOMES: measured at trial entry and after 4, 8 and 12 weeks RUN-IN PERIOD: 2 weeks DOSE OF ICS DURING RUN-IN: usual ICS DOSE OPTIMISATION PERIOD: none INTERVENTION PERIOD: 12 weeks TEST GROUP: usual dose ICS + F 4.5 µg twice daily CONTROL GROUP: usual dose ICS + placebo twice daily DEVICE: Turbuhaler NUMBER OF DEVICES: 2 COMPLIANCE: measured during run-in CO-TREATMENT: SABA as needed
Outcomes	PULMONARY FUNCTION TEST: am PEF*; pm PEF; FEV_1 (Note: Mean value during treatment for 12 weeks reported rather than value at endpoint) SYMPTOM SCORES: total asthma symptom score FUNCTIONAL STATUS: rescue medication use; paediatric asthma quality of life score INFLAMMATORY MARKERS: not described

Zimmerman 2004a *(Continued)*

	ADVERSE EFFECTS: described WITHDRAWALS: described *Primary outcome measure
Notes	Full-text publication Supported by: not stated Confirmation of methods and data not obtained User-defined number (mean ICS dose in LABA group in µg/d of BDP-equivalent): 444

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Described as randomised; no other information presented
Allocation concealment (selection bias)	Unclear risk	Information not available
Blinding (performance bias and detection bias) All outcomes	Low risk	Double-blind; double-dummy
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Intention-to-treat population presented in study publication, but handling of missing data not described
Selective reporting (reporting bias)	Low risk	Exacerbations described as those requiring OCS-treatment and those requiring increased ICS. Separate OCS-treated exacerbation data could not be extracted
Other bias	Low risk	68% of screening population randomised

Zimmerman 2004b

Methods	See Zimmerman 2004a
Participants	See Zimmerman 2004a, except for TEST GROUP: usual dose ICS + F 9 µg twice daily CONTROL GROUP: usual dose ICS + placebo twice daily RANDOMLY ASSIGNED: 196 (F + usual ICS: 95; usual ICS: 101) WITHDRAWALS: F + usual ICS: 7; usual ICS: 16
Interventions	As for Zimmerman 2004a, except for: TEST GROUP: usual dose ICS + F 6 µg twice daily
Outcomes	See Zimmerman 2004a

Zimmerman 2004b *(Continued)*

Notes	See Zimmerman 2004a

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	See Zimmerman 2004a
Allocation concealment (selection bias)	Unclear risk	See Zimmerman 2004a
Blinding (performance bias and detection bias) All outcomes	Low risk	See Zimmerman 2004a
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	See Zimmerman 2004a
Selective reporting (reporting bias)	Low risk	See Zimmerman 2004a
Other bias	Low risk	See Zimmerman 2004a

AQLQ: Asthma Quality of Life Questionnaire; AUC: Area under the curve; BDP: Beclomethasone dipropionate; BUD: Budesonide; BUD/F: Budesonide and formoterol; DPI: Dry powder inhaler; F: Formoterol; FEF: Forced expiratory flow; FeNO: Exhaled nitric oxide; FEV_1: Forced expiratory volume in one second; FP: Fluticasone; FVC: Forced vital capacity; GINA: Global Initiative for Asthma; ICS: Inhaled corticosteroid; IgE: Immunoglobulin E; ITT: Intention-to-treat; LABA: Long-acting beta$_2$-agonist (salmeterol or formoterol); LTRA: Leukotriene receptor antagonist; MDI: Metered-dose inhaler; MEF50: Maximal expiratory flow at 50% vital capacity; OCS: Oral corticosteroids; PAQLQ: Paediatric Quality of Life Questionnaire; PC_{20}: Provocative concentrations that caused a 20% fall in FEV_1; PEF: Peak expiratory flow; QD: Once per day; RTI: Respiratory tract infection; SABA: Short-acting beta$_2$-agonist; sRAW: Specific airway resistance; SD: Standard deviation.

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

Study	Reason for exclusion
Aldington 2006	Inadequate duration
Aubier 1999	Study conducted in adults
Bateman 2008 Jul	Dose of ICS was not stable (dose tapering study)
Bergmann 2004	Not exclusively children
Bernstein 2011	Control was not ICS
Borker 2005	No LABA alone
Boulet 2003	Adult study
Bousquet 2005	No LABA alone
Bracamonte 2005	Comparison of devices

Study	Reason for exclusion
Bruce 2005	Review article
Bruggenjurgen 2005	Not exclusively paediatric
Buchvald 2002	No ICS alone
Buhl 2004	Adjustable dosing in adults
Caffey 2005	No LABA alone
Chen 2010	Not an RCT
Chopra 2005	No ICS alone
Chuchalin 2005	No ICS alone
Corren 2013	Adult study
Covar 2008 Oct	Duplication of Sorkness 2007
Cowan 2004	Not an RCT
Daviskas 2005	No ICS alone
Delaronde 2005	No assessment of asthma control
Drummond 2011	Duplication of LOCCS study
Dubus 2003	No LABA
Emeryk 2003	Comparison of devices
Everden 2004	Not placebo-controlled
Fardon 2005	No LABA
Grady 1995	Not exclusively children
Holgate 2004	Study of Xolair
Holt 2005	Not exclusively children
Ilowite 2004	Adult study
Jenkins 2005	Adult study
Karaman 2007	No prior ICS exposure
Katial 2011 Mar	Adult study
Kerwin 2008 Apr	Adult study
Lara-Perez 2005	No ICS alone

Study	Reason for exclusion
Levy 2005	Co-treatment with ICS in only 3/4 participants. Study primarily interested in efficacy of formoterol on top of usual therapy. ICS dosing not standardised
Li 2010	No asthma control
Lipworth 2013	Control group was not given ICS
LOCCS	Adult study
Lundbäck 2009 Mar	Adult study
Makela 2012	Steroid-naive patients enrolled in the study
Matthys 2004	Open study
Miraglia 2007	No prior exposure to ICS
Mitchell 2005	No LABA
Mitra 2003	No concurrent ICS
Morice 2005	Not exclusively children
Morice 2005a	Not exclusively children
Morice 2008	Compared the same medication
Murray 2004	Not exclusively children
Nathan 2005	Not exclusively children
Nelson 2006	Not exclusively children
Nguyen 2005	Not an RCT
Noyes 2013	Not an RCT
O'Byrne 2001	Adolescents and adults
Pearlman 2004	Study in adults
Peroni 2005	No ICS alone
Peters 2008 Sep-Oct	Adult study
Pijnenburg 2005	No LABA
Prates 2009	Not an RCT
Price 2011 May	Adult study
Prieto 2005	Not exclusively children
Quirce 2011 Oct	Adult study

Study	Reason for exclusion
Reddel 2010 Aug	Adult study
Renzi 2005	Not exclusively children
Renzi 2010 Apr	Steroid-naive patients enrolled in the study
SAM30002	Not exclusively children
SAM40101	Inadequate duration
SAS30021	Steroid-naive children
Schauer 2003	No ICS alone
Scicchitano 2004a	Study in adults
Selroos 2004	No LABA
SFCF3001	Different devices used
SFCF3002	Different devices used
Sienra-Monge 2004	Not an RCT
Soes-Petersen 2011 Jul	Adult study
Sorkness 2007	Mixed population at baseline
Spector 2012	Adult study
Stelmach 2008a	Steroids were stopped for 4 weeks before study visit
Storms 2004	Study in adults
van den Toorn 2005	No ICS alone
Vogelmeier 2005	No ICS alone
Von Berg 2003	No concurrent ICS
Weiler 2005	Study in adults
You-Ning 2005	Study in adults; no ICS alone

EIB: Exercise-induced bronchoconstriction; ICS: Inhaled corticosteroid; LABA: Long-acting beta$_2$-agonist; RCT: Randomised controlled trial.

DATA AND ANALYSES

Comparison 1. LABA versus placebo: both groups receiving similar dose of ICS

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 # participants with exacerbations requiring systemic steroids	12	1669	Risk Ratio (M-H, Fixed, 95% CI)	0.95 [0.70, 1.28]
1.1 Mean baseline FEV_1 ≥ 80% of predicted	9	1399	Risk Ratio (M-H, Fixed, 95% CI)	0.97 [0.69, 1.37]
1.2 Mean baseline FEV_1 61%-79% of predicted	2	230	Risk Ratio (M-H, Fixed, 95% CI)	0.89 [0.48, 1.64]
1.3 Mean baseline FEV_1 not reported	1	40	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
2 # participants with exacerbations requiring hospitalisation	7	1292	Risk Ratio (M-H, Fixed, 95% CI)	1.74 [0.90, 3.36]
2.1 Mean baseline FEV_1 ≥ 80% of predicted	3	165	Risk Ratio (M-H, Fixed, 95% CI)	1.50 [0.36, 6.14]
2.2 Mean baseline FEV_1 61%-79% of predicted	3	772	Risk Ratio (M-H, Fixed, 95% CI)	1.81 [0.86, 3.82]
2.3 Mean baseline FEV_1 not reported	1	355	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
3 # participants with exacerbations requiring urgent care visit	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
3.1 Mean baseline FEV_1 ≥ 80% of predicted	1		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
4 Serious adverse events	17	4021	Risk Ratio (M-H, Fixed, 95% CI)	1.17 [0.75, 1.85]
4.1 Mean baseline FEV_1 ≥ 80% of predicted	13	2897	Risk Ratio (M-H, Fixed, 95% CI)	1.01 [0.53, 1.92]
4.2 Mean baseline FEV_1 61%-79% of predicted	3	762	Risk Ratio (M-H, Fixed, 95% CI)	1.33 [0.68, 2.59]
4.3 Mean baseline FEV_1 not reported	1	362	Risk Ratio (M-H, Fixed, 95% CI)	2.0 [0.18, 21.86]
5 Total # withdrawals	23	4374	Risk Ratio (M-H, Fixed, 95% CI)	0.80 [0.67, 0.94]
5.1 Mean baseline FEV_1 ≥ 80% of predicted	17	3205	Risk Ratio (M-H, Fixed, 95% CI)	0.79 [0.66, 0.96]
5.2 Mean baseline FEV_1 61%-79% of predicted	4	794	Risk Ratio (M-H, Fixed, 95% CI)	0.91 [0.63, 1.32]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
5.3 Mean baseline FEV_1 not reported	2	375	Risk Ratio (M-H, Fixed, 95% CI)	0.36 [0.12, 1.11]
6 # withdrawals due to poor asthma control or exacerbation	14	2255	Risk Ratio (M-H, Fixed, 95% CI)	0.81 [0.57, 1.16]
6.1 Mean baseline FEV_1 ≥ 80% of predicted	10	1461	Risk Ratio (M-H, Fixed, 95% CI)	0.82 [0.55, 1.21]
6.2 Mean baseline FEV_1 61%-79% of predicted	4	794	Risk Ratio (M-H, Fixed, 95% CI)	0.78 [0.34, 1.81]
7 # withdrawals due to adverse events	18	4117	Risk Ratio (M-H, Fixed, 95% CI)	0.79 [0.52, 1.21]
7.1 Mean baseline FEV_1 ≥ 80% of predicted	13	3053	Risk Ratio (M-H, Fixed, 95% CI)	0.69 [0.42, 1.13]
7.2 Mean baseline FEV_1 61%-79% of predicted	5	1064	Risk Ratio (M-H, Fixed, 95% CI)	1.12 [0.51, 2.44]
8 # withdrawals due to serious non-respiratory event	2	318	Risk Ratio (M-H, Random, 95% CI)	4.66 [0.23, 96.30]
8.1 Mean baseline FEV_1 61%-79% of predicted	2	318	Risk Ratio (M-H, Random, 95% CI)	4.66 [0.23, 96.30]
9 Change in FEV_1 (L) at endpoint	9	1942	Litres (Fixed, 95% CI)	0.08 [0.06, 0.10]
9.1 Mean baseline FEV_1 ≥ 80% of predicted	7	1515	Litres (Fixed, 95% CI)	0.08 [0.05, 0.10]
9.2 Mean baseline FEV_1 61%-79% of predicted	2	427	Litres (Fixed, 95% CI)	0.12 [0.04, 0.19]
10 Change in FEV_1 at endpoint (% predicted) stratifying on baseline FEV_1	7	534	Mean Difference (IV, Fixed, 95% CI)	2.99 [0.86, 5.11]
10.1 Mean baseline FEV_1 ≥ 80% of predicted	4	214	Mean Difference (IV, Fixed, 95% CI)	4.06 [1.32, 6.80]
10.2 Mean baseline FEV_1 61%-79% of predicted	2	238	Mean Difference (IV, Fixed, 95% CI)	3.35 [-1.50, 8.20]
10.3 Mean baseline FEV_1 not reported	1	82	Mean Difference (IV, Fixed, 95% CI)	-0.40 [-5.03, 4.23]
11 % fall in FEV_1 % predicted due to exercise	3	517	Mean Difference (IV, Fixed, 95% CI)	0.46 [1.00, 1.93]
11.1 Mean baseline FEV_1 ≥ 80% of predicted	3	517	Mean Difference (IV, Fixed, 95% CI)	0.46 [1.00, 1.93]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
12 Change in morning PEF (L/min) at endpoint	16	3934	L/min (Fixed, 95% CI)	10.20 [8.14, 12.26]
12.1 Mean baseline FEV_1 ≥ 80% of predicted	12	2870	L/min (Fixed, 95% CI)	10.79 [8.43, 13.16]
12.2 Mean baseline FEV_1 61%-79% of predicted	3	713	L/min (Fixed, 95% CI)	9.26 [4.42, 14.10]
12.3 Mean baseline FEV_1 not reported	1	351	L/min (Fixed, 95% CI)	5.7 [-2.62, 14.02]
13 Change in morning PEF (% predicted)	1		% (Fixed, 95% CI)	Totals not selected
13.1 Mean baseline FEV_1 61%-79% of predicted	1		% (Fixed, 95% CI)	0.0 [0.0, 0.0]
14 Change in evening PEF (L/min) at endpoint	12	3140	L/min (Fixed, 95% CI)	9.30 [6.96, 11.65]
14.1 Mean baseline FEV_1 ≥ 80% of predicted	10	2503	L/min (Fixed, 95% CI)	9.31 [6.67, 11.94]
14.2 Mean baseline FEV_1 61%-79% of predicted	1	286	L/min (Fixed, 95% CI)	11.7 [5.29, 18.11]
14.3 Mean baseline FEV_1 not reported	1	351	L/min (Fixed, 95% CI)	5.0 [-3.58, 13.58]
15 Change in evening PEF (% of predicted)	1		% (Fixed, 95% CI)	Totals not selected
15.1 Mean baseline FEV_1 61%-79% of predicted	1		% (Fixed, 95% CI)	0.0 [0.0, 0.0]
16 Change in clinic PEF (L/min)	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
16.1 Mean baseline FEV_1 not reported	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
17 Change in PEF variability at endpoint	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
17.1 Mean baseline FEV_1 61%-79% of predicted	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
18 Mean change in asthma symptom score	6	1653	Std. Mean Difference (IV, Fixed, 95% CI)	-0.07 [-0.17, 0.04]
18.1 Mean baseline FEV_1 ≥ 80% of predicted	6	1653	Std. Mean Difference (IV, Fixed, 95% CI)	-0.07 [-0.17, 0.04]
19 Change in nighttime symptom score	2	534	Mean Difference (IV, Fixed, 95% CI)	-0.03 [-0.07, 0.02]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
19.1 Mean baseline FEV_1 ≥ 80% of predicted	2	534	Mean Difference (IV, Fixed, 95% CI)	-0.03 [-0.07, 0.02]
20 Change in % symptom-free days at endpoint	7	1831	Mean Difference (IV, Fixed, 95% CI)	0.96 [-1.91, 3.84]
20.1 Mean baseline FEV_1 ≥ 80% of predicted	7	1831	Mean Difference (IV, Fixed, 95% CI)	0.96 [-1.91, 3.84]
21 % symptom-free days	4	623	Std. Mean Difference (IV, Fixed, 95% CI)	-0.04 [-0.20, 0.12]
21.1 Mean baseline FEV_1 ≥ 80% of predicted	1	231	Std. Mean Difference (IV, Fixed, 95% CI)	-0.21 [-0.47, 0.05]
21.2 Mean baseline FEV_1 61%-79% of predicted	1	286	Std. Mean Difference (IV, Fixed, 95% CI)	0.12 [-0.11, 0.35]
21.3 Unclear baseline FEV_1	2	106	Std. Mean Difference (IV, Fixed, 95% CI)	-0.12 [-0.56, 0.31]
22 % symptom-free nights at 52 ± 4 weeks	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
22.1 Mean baseline FEV_1 not reported	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
23 Change in # daytime rescue inhalations (puffs per day) at endpoint	7	1798	Mean Difference (IV, Fixed, 95% CI)	-0.07 [-0.11, -0.02]
23.1 Mean baseline FEV_1 61%-79% of predicted	7	1798	Mean Difference (IV, Fixed, 95% CI)	-0.07 [-0.11, -0.02]
24 Change in # nighttime rescue inhalations at endpoint	3	672	Mean Difference (IV, Random, 95% CI)	-0.08 [-0.13, -0.03]
24.1 Mean baseline FEV_1 61%-79% of predicted	3	672	Mean Difference (IV, Random, 95% CI)	-0.08 [-0.13, -0.03]
25 % days without bronchodilator usage	7	1710	Mean Difference (IV, Random, 95% CI)	2.07 [-1.03, 5.16]
25.1 Mean baseline FEV_1 ≥ 80% of predicted	6	1628	Mean Difference (IV, Random, 95% CI)	2.87 [-0.44, 6.18]
25.2 Mean baseline FEV_1 not reported	1	82	Mean Difference (IV, Random, 95% CI)	-1.0 [-4.04, 2.04]
26 Change in nighttime awakening (number of nights) at endpoint	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
26.1 Mean baseline FEV_1 61%-79% of 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
27 % nights with awakening	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
27.1 Mean baseline FEV_1 61%-79% of predicted	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
28 % change in awakening-free nights	2	519	Mean Difference (IV, Fixed, 95% CI)	0.60 [-1.05, 2.26]
28.1 Mean baseline FEV_1 ≥ 80% of predicted	2	519	Mean Difference (IV, Fixed, 95% CI)	0.60 [-1.05, 2.26]
29 Change in rescue-free days (%)	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
29.1 Mean baseline FEV_1 ≥ 80% of predicted	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
30 Change in % asthma-control days at endpoint	2	519	Mean Difference (IV, Fixed, 95% CI)	4.30 [-0.56, 9.16]
30.1 Mean baseline FEV_1 ≥ 80% of predicted	2	519	Mean Difference (IV, Fixed, 95% CI)	4.30 [-0.56, 9.16]
31 Change in quality of life (P-AQLQ)	4	668	Mean Difference (IV, Fixed, 95% CI)	-0.02 [-0.14, 0.10]
31.1 Mean baseline FEV_1 ≥ 80% of predicted	4	668	Mean Difference (IV, Fixed, 95% CI)	-0.02 [-0.14, 0.10]
32 Quality of life (P-AQLQ)	10	2333	Mean Difference (IV, Fixed, 95% CI)	0.03 [-0.04, 0.11]
32.1 Mean baseline FEV_1 ≥ 80% of predicted	6	1586	Mean Difference (IV, Fixed, 95% CI)	0.07 [-0.01, 0.16]
32.2 Mean baseline FEV_1 61%-79% of predicted	4	747	Mean Difference (IV, Fixed, 95% CI)	-0.12 [-0.28, 0.03]
33 Change in paediatric asthma caregiver quality of life (P-AQLQ)	4	669	Mean Difference (IV, Fixed, 95% CI)	0.07 [-0.05, 0.18]
33.1 Mean baseline FEV_1 ≥ 80% of predicted	4	669	Mean Difference (IV, Fixed, 95% CI)	0.07 [-0.05, 0.18]
34 Total # adverse events	15	3284	Risk Ratio (M-H, Fixed, 95% CI)	1.04 [0.98, 1.10]
34.1 Mean baseline FEV_1 ≥ 80% of predicted	11	2424	Risk Ratio (M-H, Fixed, 95% CI)	1.08 [1.00, 1.16]
34.2 Mean baseline FEV_1 61%-79% of predicted	2	474	Risk Ratio (M-H, Fixed, 95% CI)	0.97 [0.86, 1.09]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
34.3 Mean baseline FEV_1 not reported	2	386	Risk Ratio (M-H, Fixed, 95% CI)	0.92 [0.78, 1.09]
35 # participants with oral candidiasis	6	1341	Risk Ratio (M-H, Fixed, 95% CI)	3.41 [0.73, 15.87]
35.1 $FEV_1 \geq 80\%$ of predicted	5	1135	Risk Ratio (M-H, Fixed, 95% CI)	3.46 [0.60, 19.99]
35.2 Mean baseline FEV_1 61%-79% of predicted	1	206	Risk Ratio (M-H, Fixed, 95% CI)	3.24 [0.13, 78.62]
36 # participants with tremor	6	1467	Risk Ratio (M-H, Fixed, 95% CI)	3.07 [0.38, 25.05]
36.1 Mean baseline $FEV_1 \geq 80\%$ of predicted	3	959	Risk Ratio (M-H, Fixed, 95% CI)	5.30 [0.26, 109.66]
36.2 Mean baseline FEV_1 61%-79% of predicted	3	508	Risk Ratio (M-H, Fixed, 95% CI)	1.46 [0.06, 35.18]
37 # participants with tachycardia or palpitations	6	1238	Risk Ratio (M-H, Fixed, 95% CI)	0.44 [0.08, 2.31]
37.1 Mean baseline $FEV_1 \geq 80\%$ of predicted	3	731	Risk Ratio (M-H, Fixed, 95% CI)	0.41 [0.05, 3.33]
37.2 Mean baseline FEV_1 61%-79% of predicted	3	507	Risk Ratio (M-H, Fixed, 95% CI)	0.49 [0.03, 7.61]
38 # participants with headache	14	2966	Risk Ratio (M-H, Fixed, 95% CI)	1.10 [0.90, 1.33]
38.1 Mean baseline $FEV_1 \geq 80\%$ of predicted	8	1779	Risk Ratio (M-H, Fixed, 95% CI)	1.00 [0.79, 1.26]
38.2 Mean baseline FEV_1 61%-79% of predicted	5	825	Risk Ratio (M-H, Fixed, 95% CI)	1.34 [0.88, 2.04]
38.3 Mean baseline FEV_1 not reported	1	362	Risk Ratio (M-H, Fixed, 95% CI)	1.4 [0.64, 3.07]
39 # participants with vomiting	3	707	Risk Ratio (M-H, Fixed, 95% CI)	0.74 [0.34, 1.62]
39.1 Mean baseline $FEV_1 \geq 80\%$ of predicted	3	707	Risk Ratio (M-H, Fixed, 95% CI)	0.74 [0.34, 1.62]
40 # participants with otitis media	3	707	Risk Ratio (M-H, Fixed, 95% CI)	0.70 [0.30, 1.63]
40.1 Mean baseline $FEV_1 \geq 80\%$ of predicted	3	707	Risk Ratio (M-H, Fixed, 95% CI)	0.70 [0.30, 1.63]

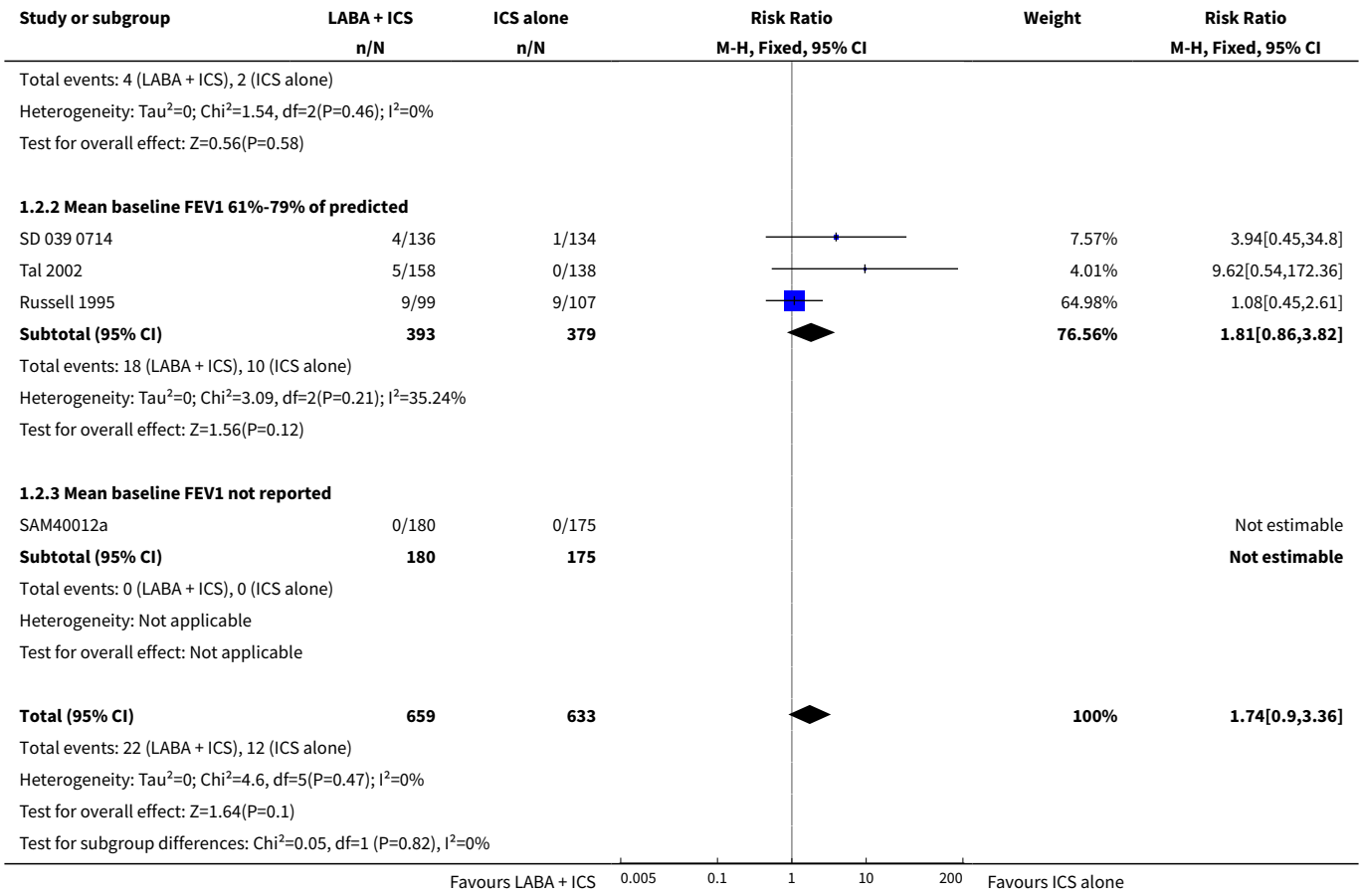
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
41 # participants with upper respiratory tract infection	5	1186	Risk Ratio (M-H, Fixed, 95% CI)	0.86 [0.58, 1.27]
41.1 Mean baseline FEV_1 ≥ 80% of predicted	5	1186	Risk Ratio (M-H, Fixed, 95% CI)	0.86 [0.58, 1.27]
42 # participants with urticaria	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
42.1 Mean baseline FEV_1 ≥ 80% of predicted	1		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
43 # participants with adverse cardiovascular events	2	148	Risk Ratio (M-H, Fixed, 95% CI)	0.31 [0.01, 7.49]
43.1 Mean baseline FEV_1 ≥ 80% of predicted	1	116	Risk Ratio (M-H, Fixed, 95% CI)	0.31 [0.01, 7.49]
43.2 Mean baseline FEV_1 61%-79% of predicted	1	32	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
44 Deaths	3	690	Risk Difference (M-H, Fixed, 95% CI)	0.0 [-0.01, 0.01]
44.1 Baseline FEV_1 ≥ 80% of predicted	3	690	Risk Difference (M-H, Fixed, 95% CI)	0.0 [-0.01, 0.01]
45 # participants with exacerbations requiring hospitalisation	7	1292	Risk Ratio (M-H, Fixed, 95% CI)	1.74 [0.90, 3.36]
45.1 Mean baseline FEV_1 ≥ 80% of predicted	3	165	Risk Ratio (M-H, Fixed, 95% CI)	1.50 [0.36, 6.14]
45.2 Mean baseline FEV_1 61%-79% of predicted	3	772	Risk Ratio (M-H, Fixed, 95% CI)	1.81 [0.86, 3.82]
45.3 Mean baseline FEV_1 not reported	1	355	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
46 Change in height (cm) as SD scores at 24 ± 4 weeks	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
46.1 Mean baseline FEV_1 ≥ 80% of predicted	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
47 Change in height at 1 year	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected

Analysis 1.1. Comparison 1 LABA versus placebo: both groups receiving similar dose of ICS, Outcome 1 # participants with exacerbations requiring systemic steroids.

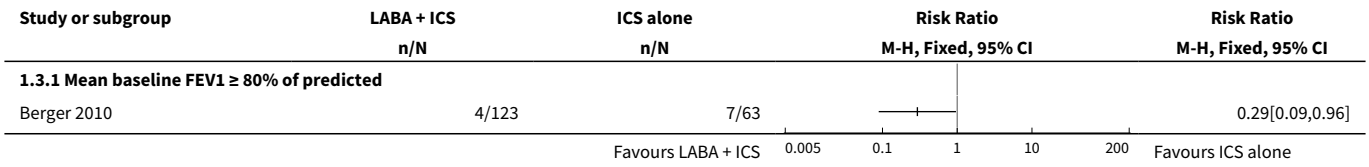
Study or subgroup	LABA + ICS n/N	ICS alone n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
1.1.1 Mean baseline FEV1 ≥ 80% of predicted					
Eid 2010a	15/183	13/84		24.11%	0.53[0.26,1.06]
Eid 2010b	33/168	13/84		23.46%	1.27[0.71,2.28]
Langton Hewer 1995	3/11	3/12		3.88%	1.09[0.28,4.32]
Lenney 2013	5/15	1/11		1.56%	3.67[0.5,27.12]
Malone 2005	2/101	3/102		4.04%	0.67[0.11,3.94]
Murray 2011	2/113	1/118		1.32%	2.09[0.19,22.71]
Pearlman 2009	1/124	1/124		1.35%	1[0.06,15.81]
Simons 1997	0/16	1/16		2.03%	0.33[0.01,7.62]
Verberne 1998a	10/60	10/57		13.88%	0.95[0.43,2.11]
Subtotal (95% CI)	**791**	**608**		**75.64%**	**0.97[0.69,1.37]**
Total events: 71 (LABA + ICS), 46 (ICS alone)					
Heterogeneity: Tau^2=0; Chi^2=6.44, df=8(P=0.6); I^2=0%					
Test for overall effect: Z=0.19(P=0.85)					
1.1.2 Mean baseline FEV1 61%-79% of predicted					
Akpinarli 1999	0/16	0/16			Not estimable
Russell 1995	16/99	18/99		24.36%	0.89[0.48,1.64]
Subtotal (95% CI)	**115**	**115**		**24.36%**	**0.89[0.48,1.64]**
Total events: 16 (LABA + ICS), 18 (ICS alone)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.38(P=0.71)					
1.1.3 Mean baseline FEV1 not reported					
Rutkowski 2009	0/20	0/20			Not estimable
Subtotal (95% CI)	**20**	**20**			**Not estimable**
Total events: 0 (LABA + ICS), 0 (ICS alone)					
Heterogeneity: Not applicable					
Test for overall effect: Not applicable					
Total (95% CI)	**926**	**743**		**100%**	**0.95[0.7,1.28]**
Total events: 87 (LABA + ICS), 64 (ICS alone)					
Heterogeneity: Tau^2=0; Chi^2=6.47, df=9(P=0.69); I^2=0%					
Test for overall effect: Z=0.35(P=0.73)					
Test for subgroup differences: Chi^2=0.06, df=1 (P=0.81), I^2=0%					

Analysis 1.2. Comparison 1 LABA versus placebo: both groups receiving similar dose of ICS, Outcome 2 # participants with exacerbations requiring hospitalisation.

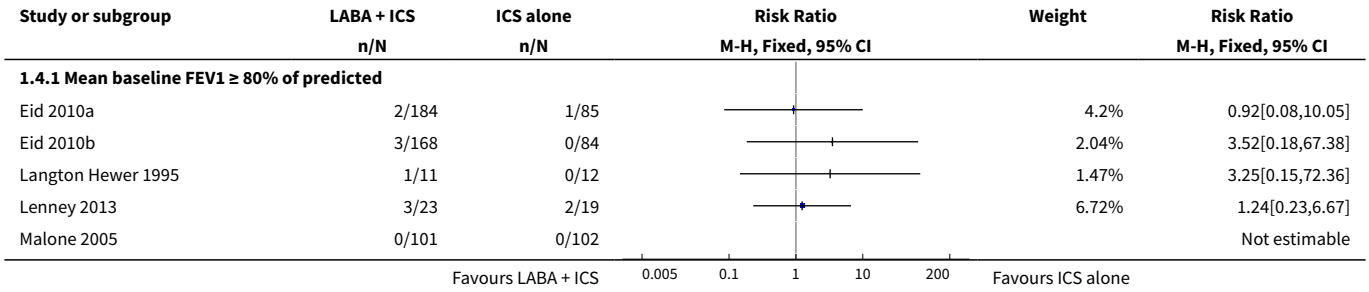
Study or subgroup	LABA + ICS n/N	ICS alone n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
1.2.1 Mean baseline FEV1 ≥ 80% of predicted					
Langton Hewer 1995	1/11	0/12		3.61%	3.25[0.15,72.36]
Verberne 1998a	1/60	2/56		15.54%	0.47[0.04,5.01]
Lenney 2013	2/15	0/11		4.29%	3.75[0.2,71.12]
Subtotal (95% CI)	**86**	**79**		**23.44%**	**1.5[0.36,6.14]**

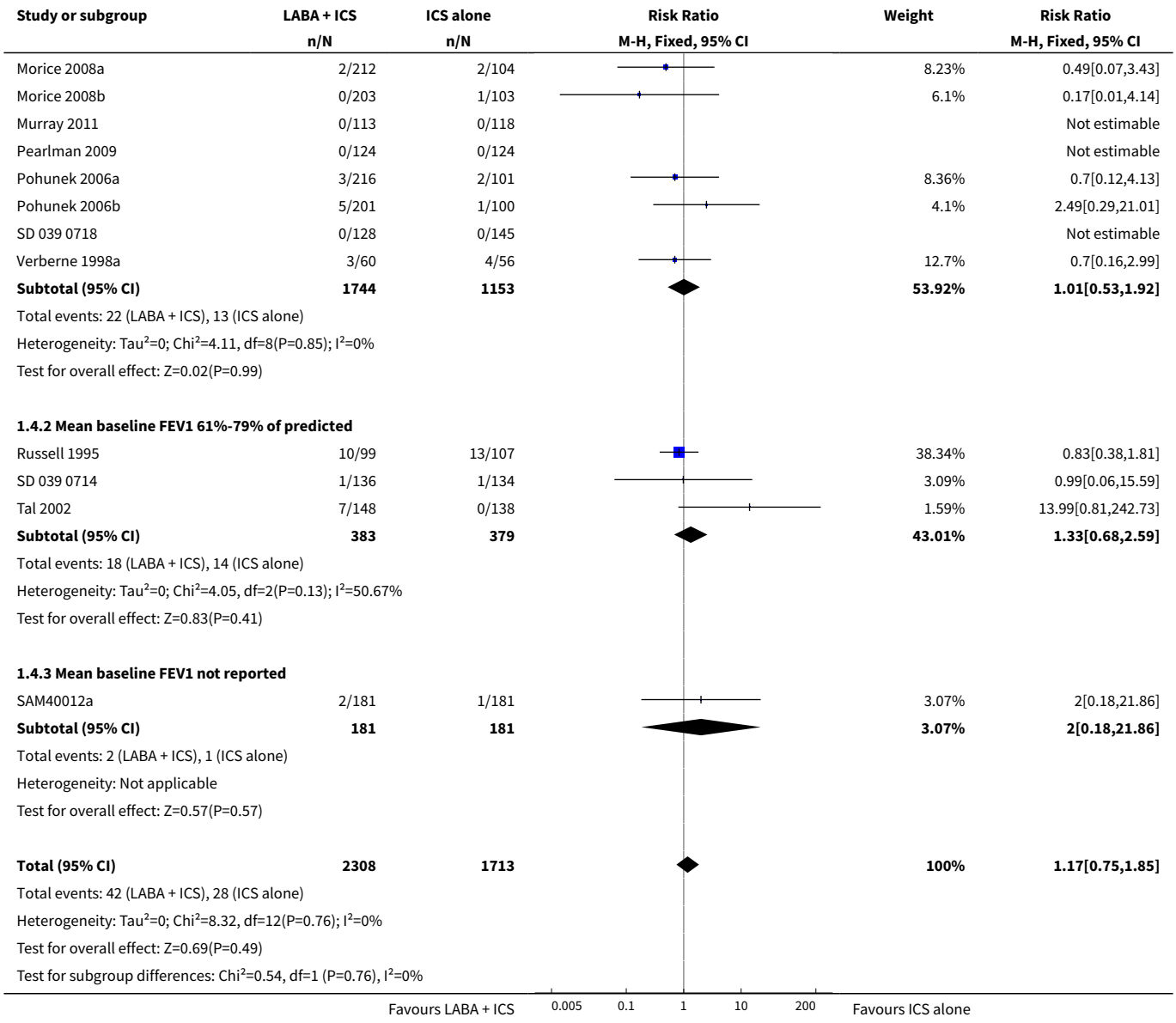


Analysis 1.3. Comparison 1 LABA versus placebo: both groups receiving similar dose of ICS, Outcome 3 # participants with exacerbations requiring urgent care visit.

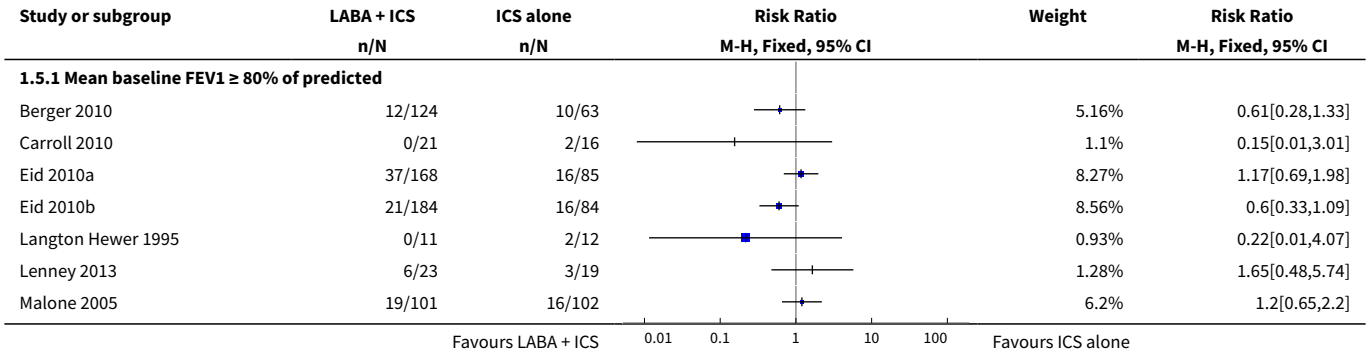


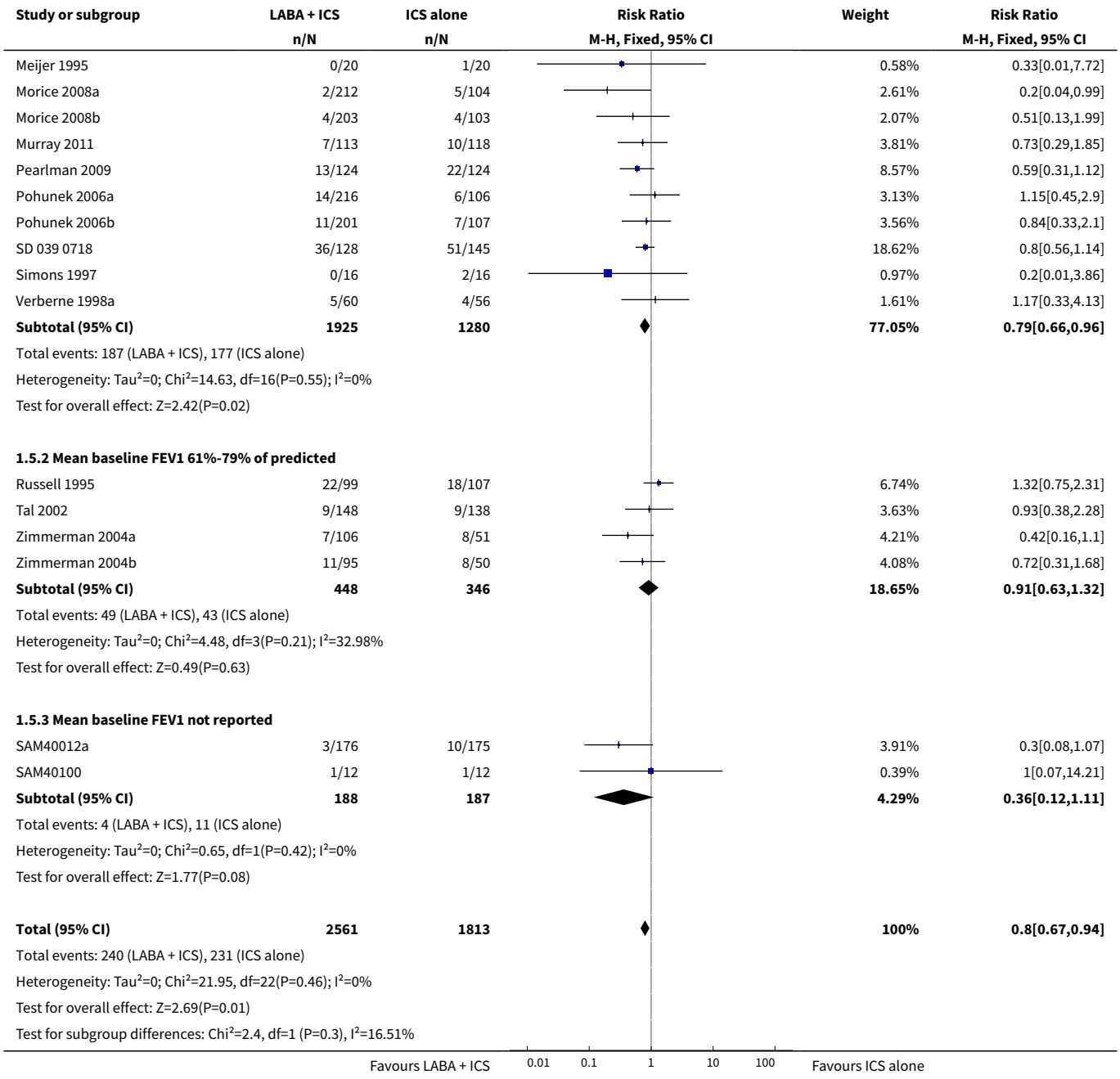
Analysis 1.4. Comparison 1 LABA versus placebo: both groups receiving similar dose of ICS, Outcome 4 Serious adverse events.



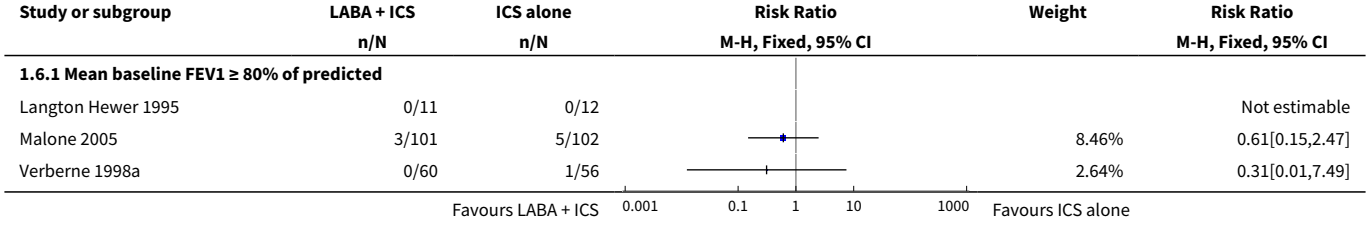


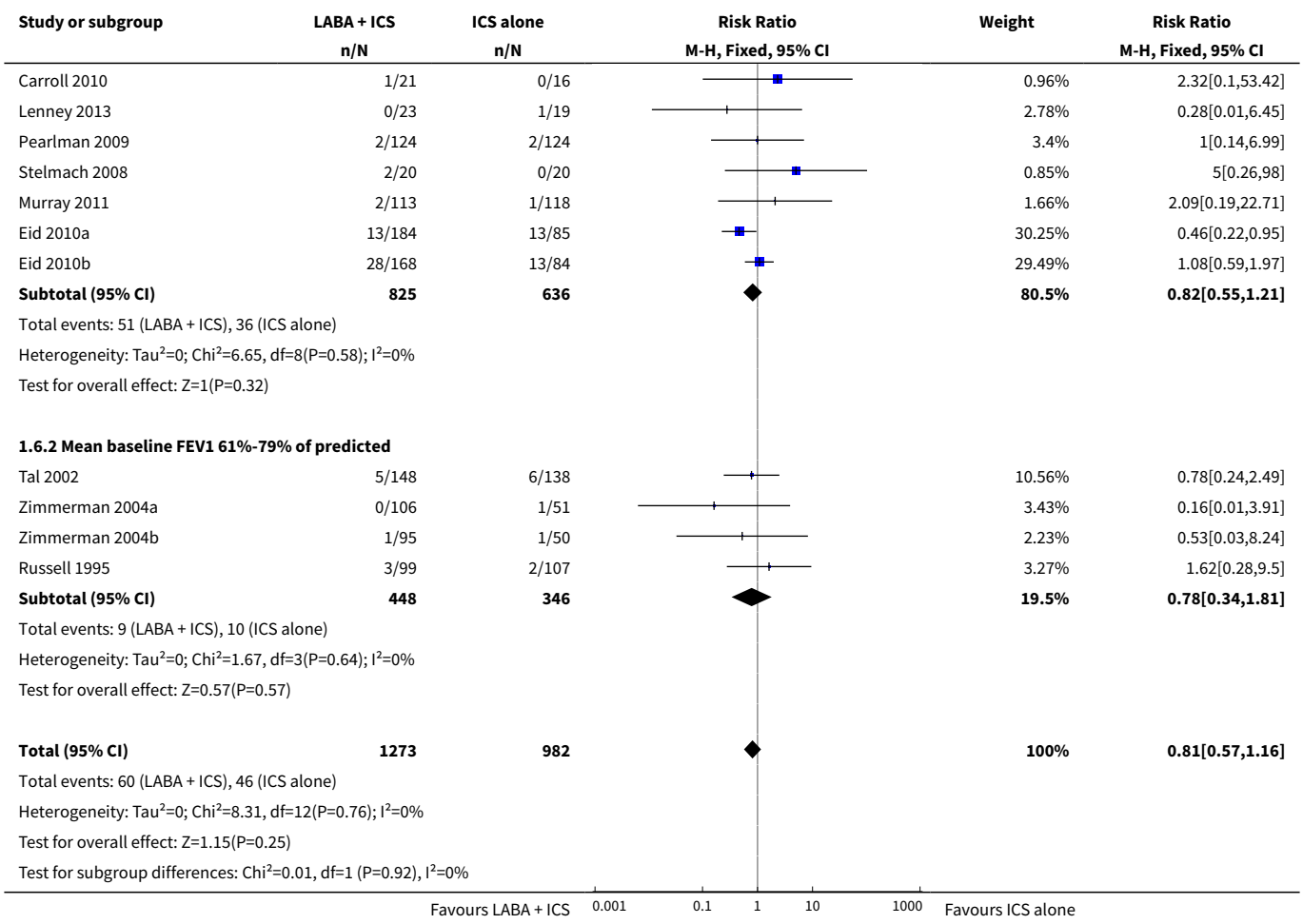
Analysis 1.5. Comparison 1 LABA versus placebo: both groups receiving similar dose of ICS, Outcome 5 Total # withdrawals.



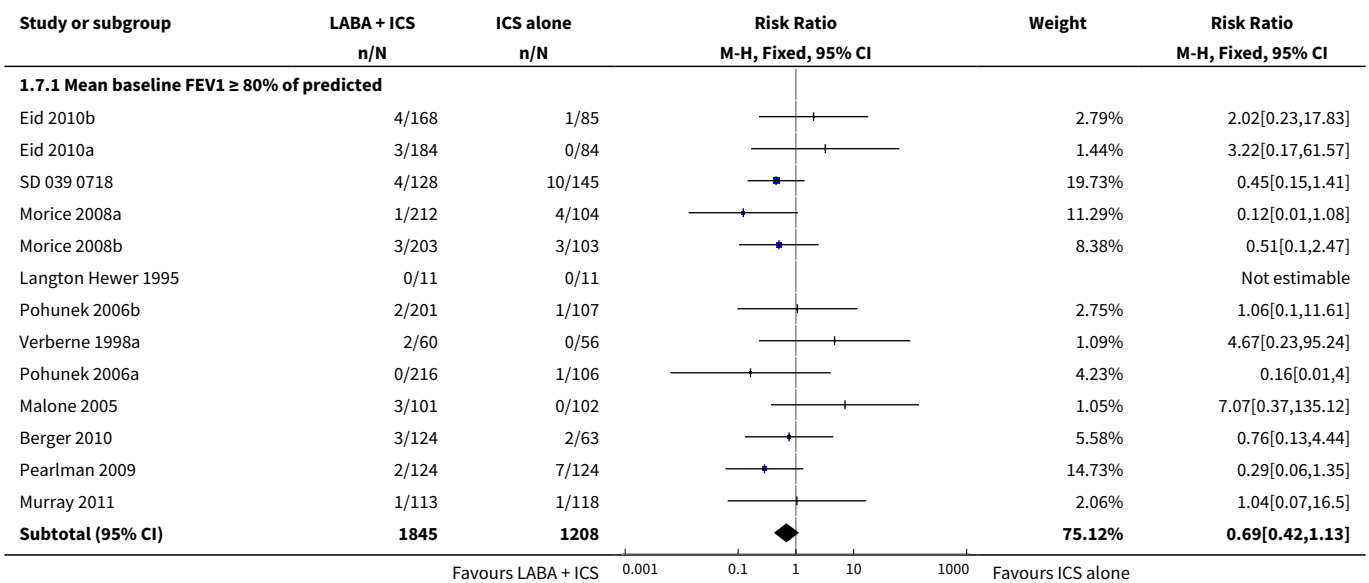


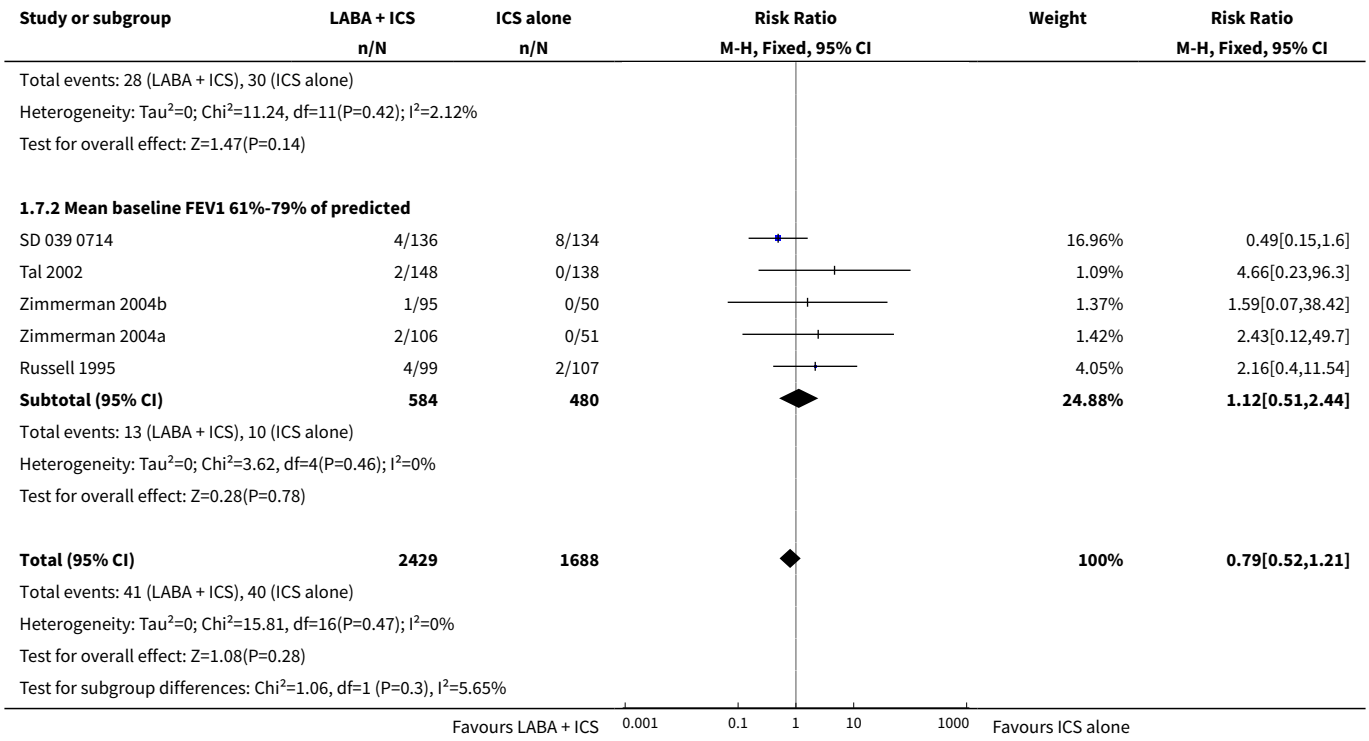
Analysis 1.6. Comparison 1 LABA versus placebo: both groups receiving similar dose of ICS, Outcome 6 # withdrawals due to poor asthma control or exacerbation.



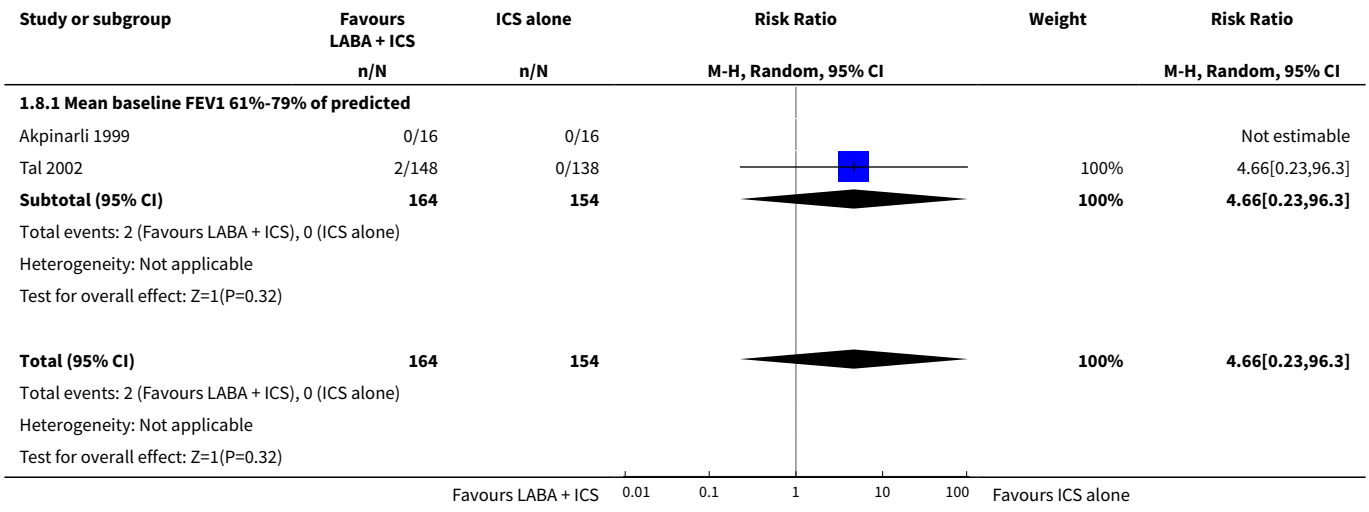


Analysis 1.7. Comparison 1 LABA versus placebo: both groups receiving similar dose of ICS, Outcome 7 # withdrawals due to adverse events.



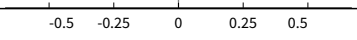


Analysis 1.8. Comparison 1 LABA versus placebo: both groups receiving similar dose of ICS, Outcome 8 # withdrawals due to serious non-respiratory event.



Analysis 1.9. Comparison 1 LABA versus placebo: both groups receiving similar dose of ICS, Outcome 9 Change in FEV_1 (L) at endpoint.

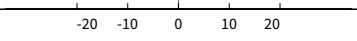
Study or subgroup	LABA + ICS N	ICS alone N	Litres (SE)	Litres IV, Fixed, 95% CI	Weight	Litres IV, Fixed, 95% CI
1.9.1 Mean baseline FEV1 ≥ 80% of predicted						
Berger 2010	123	63	0.1 (0.03)		14.29%	0.08[0.02,0.14]
Eid 2010a	184	85	0.1 (0.026)		19.78%	0.07[0.02,0.12]
Eid 2010b	168	84	0.1 (0.026)		19.78%	0.08[0.03,0.13]
Langton Hewer 1995	11	10	0.4 (0.107)		1.12%	0.42[0.21,0.63]
Malone 2005	79	81	0.1 (0.041)		7.73%	0.06[-0.02,0.14]
Pohunek 2006a	213	106	0.1 (0.031)		13.74%	0.07[0.01,0.13]
Pohunek 2006b	201	107	0.1 (0.031)		13.74%	0.07[0.01,0.13]
Subtotal (95% CI)					**90.19%**	**0.08[0.05,0.1]**
Heterogeneity: Tau^2=0; Chi^2=10.65, df=6(P=0.1); I^2=43.68%						
Test for overall effect: Z=6.47(P<0.0001)						
1.9.2 Mean baseline FEV1 61%-79% of predicted						
Russell 1995	76	87	0.1 (0.061)		3.46%	0.09[-0.03,0.21]
SD 039 0714	133	131	0.1 (0.045)		6.35%	0.13[0.04,0.22]
Subtotal (95% CI)					**9.81%**	**0.12[0.04,0.19]**
Heterogeneity: Tau^2=0; Chi^2=0.28, df=1(P=0.6); I^2=0%						
Test for overall effect: Z=3.2(P=0)						
Total (95% CI)					**100%**	**0.08[0.06,0.1]**
Heterogeneity: Tau^2=0; Chi^2=11.96, df=8(P=0.15); I^2=33.09%						
Test for overall effect: Z=7.15(P<0.0001)						
Test for subgroup differences: Chi^2=1.03, df=1 (P=0.31), I^2=2.52%						



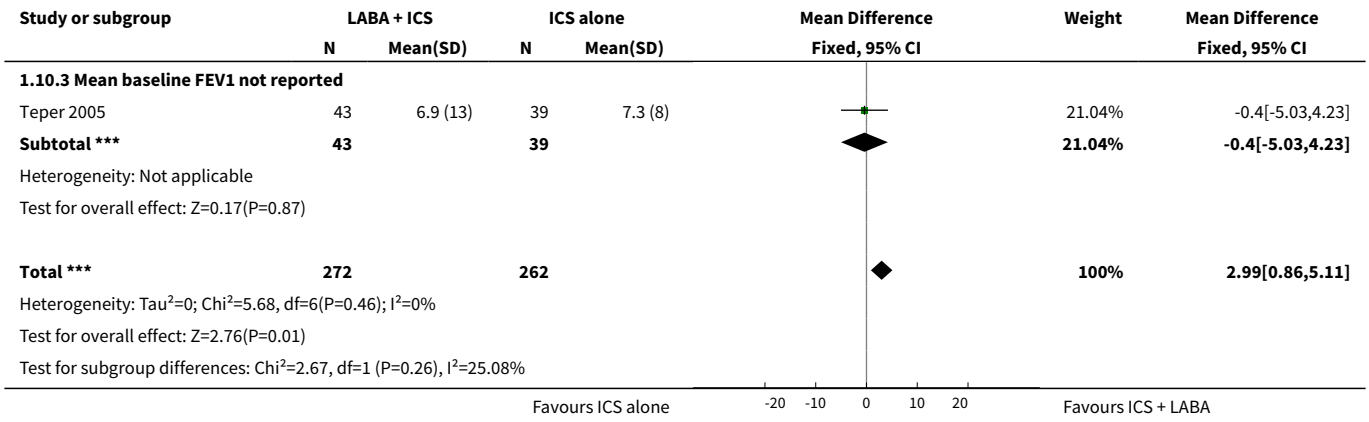
Favours treatment — Favours control

Analysis 1.10. Comparison 1 LABA versus placebo: both groups receiving similar dose of ICS, Outcome 10 Change in FEV_1 at endpoint (% predicted) stratifying on baseline FEV_1.

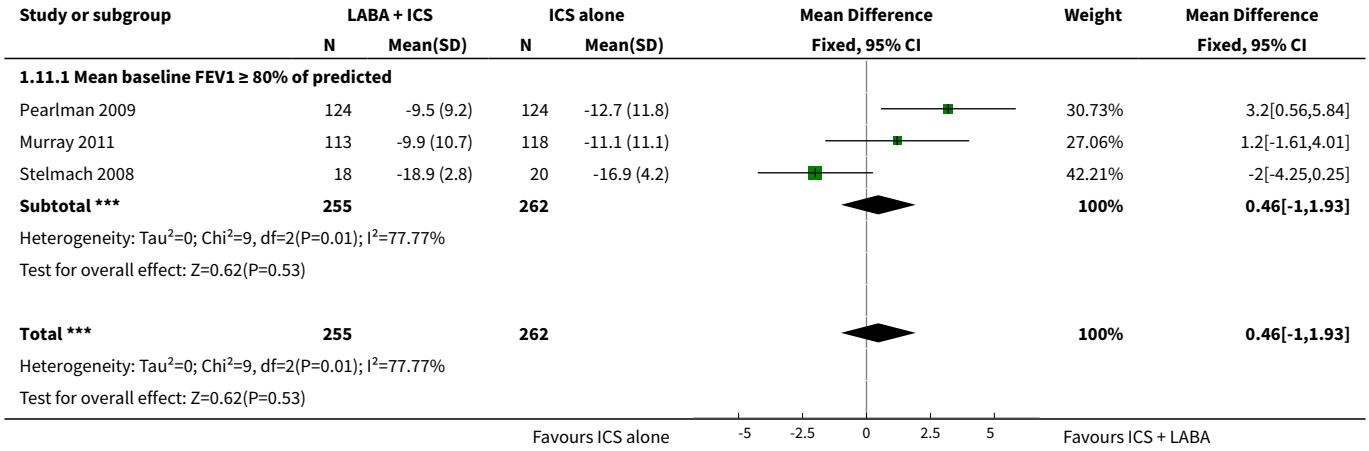
Study or subgroup	LABA + ICS N	Mean(SD)	ICS alone N	Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
1.10.1 Mean baseline FEV1 ≥ 80% of predicted							
Verberne 1998a	60	4.4 (10.5)	57	1.3 (9.1)		35.41%	3.08[-0.49,6.65]
Carroll 2010	21	6.4 (9.6)	16	1.2 (9.6)		11.55%	5.2[-1.04,11.44]
Lenney 2013	13	15.5 (19.8)	8	0.1 (12.7)		2.33%	15.42[1.51,29.33]
Meijer 1995	20	5.8 (11.6)	19	2.2 (9.2)		10.53%	3.6[-2.94,10.14]
Subtotal ***	**114**		**100**			**59.82%**	**4.06[1.32,6.8]**
Heterogeneity: Tau^2=0; Chi^2=3, df=3(P=0.39); I^2=0%							
Test for overall effect: Z=2.9(P=0)							
1.10.2 Mean baseline FEV1 61%-79% of predicted							
Akpinarli 1999	16	3 (42.8)	16	1 (31.6)		0.66%	2[-24.1,28.1]
Russell 1995	99	5.2 (20)	107	1.8 (15.7)		18.48%	3.4[-1.54,8.34]
Subtotal ***	**115**		**123**			**19.14%**	**3.35[-1.5,8.2]**
Heterogeneity: Tau^2=0; Chi^2=0.01, df=1(P=0.92); I^2=0%							
Test for overall effect: Z=1.35(P=0.18)							



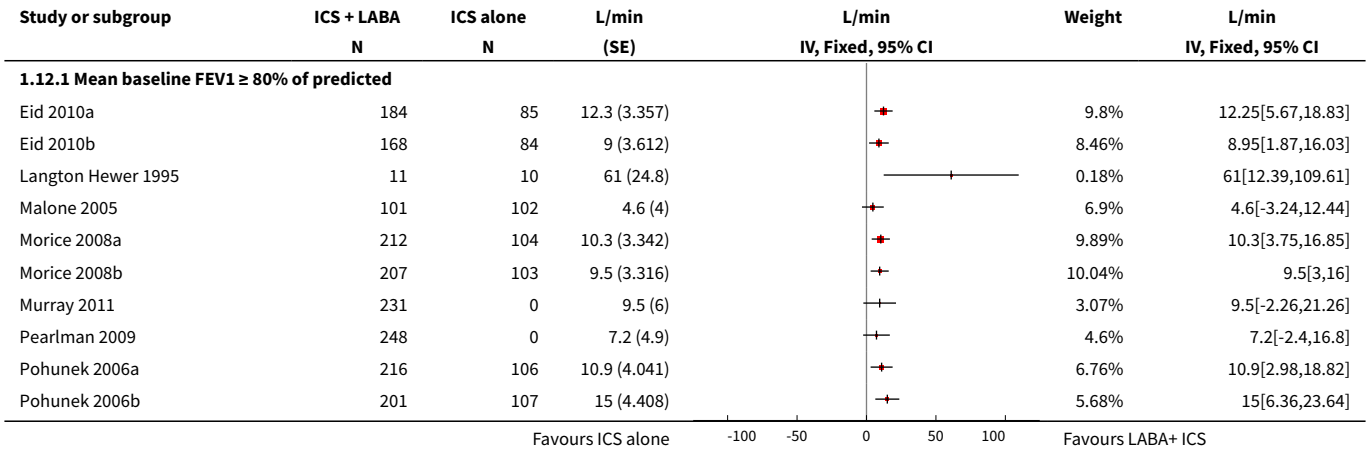
Favours ICS alone — Favours ICS + LABA

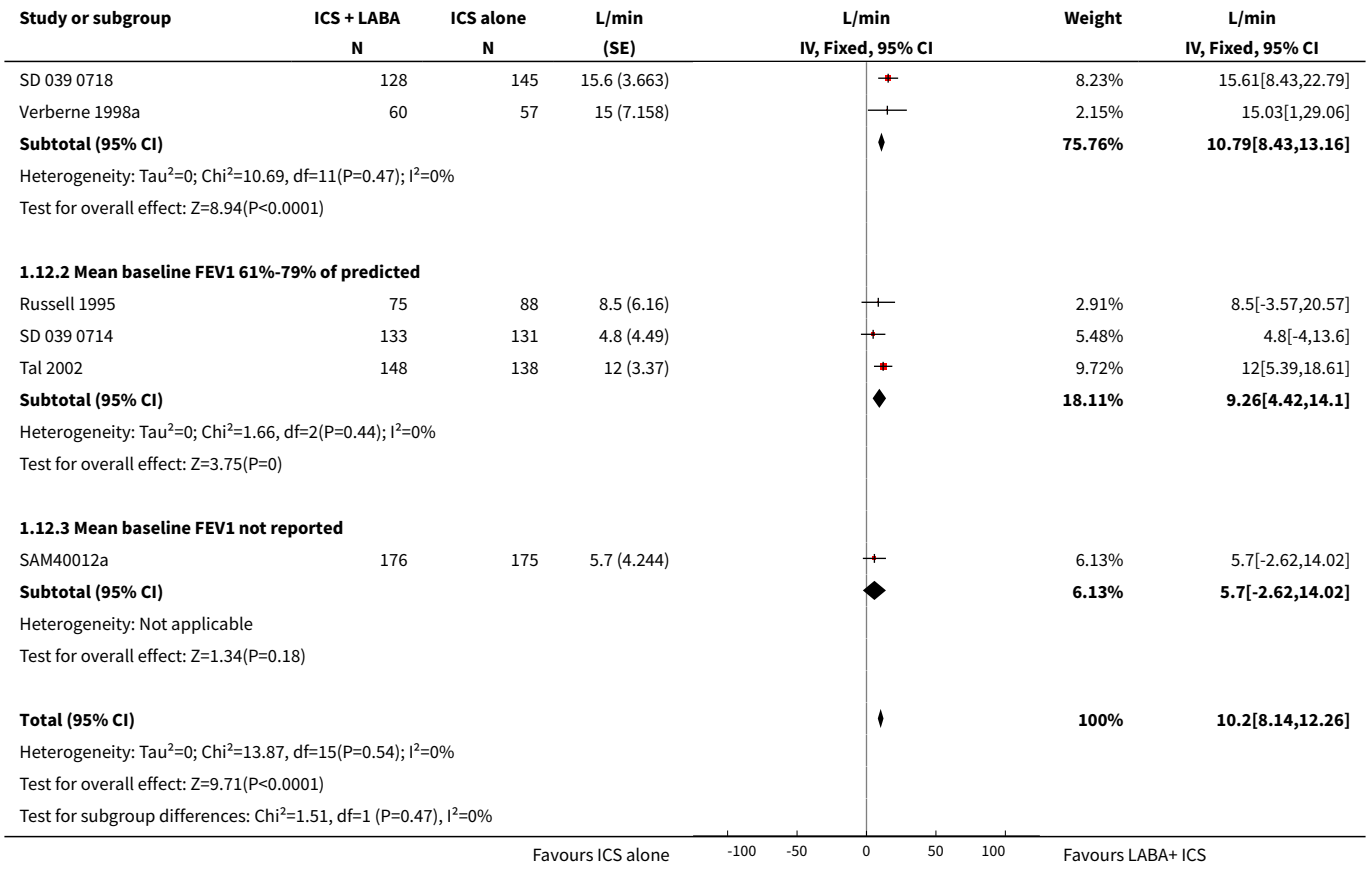


Analysis 1.11. Comparison 1 LABA versus placebo: both groups receiving similar dose of ICS, Outcome 11 % fall in FEV_1 % predicted due to exercise.

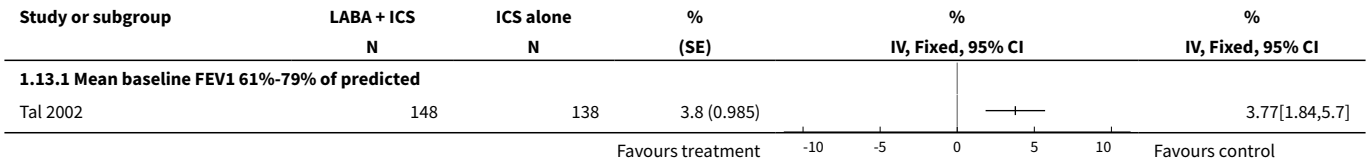


Analysis 1.12. Comparison 1 LABA versus placebo: both groups receiving similar dose of ICS, Outcome 12 Change in morning PEF (L/min) at endpoint.

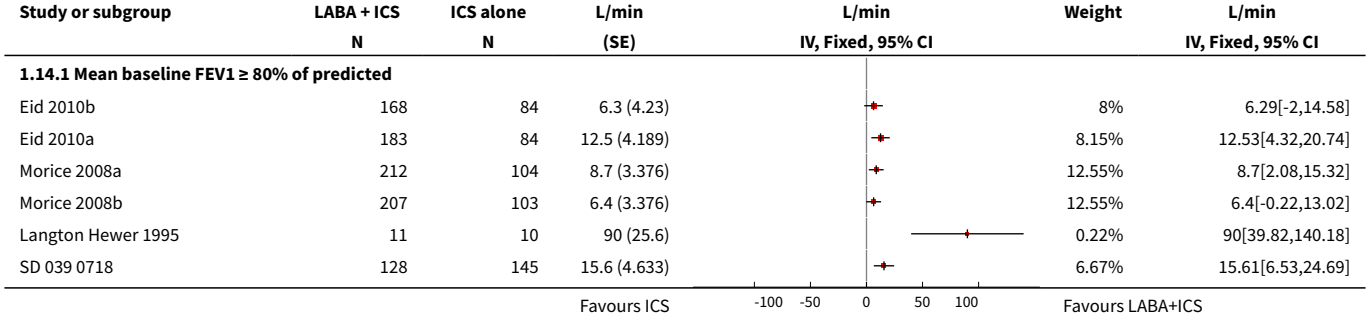




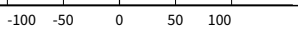
Analysis 1.13. Comparison 1 LABA versus placebo: both groups receiving similar dose of ICS, Outcome 13 Change in morning PEF (% predicted).



Analysis 1.14. Comparison 1 LABA versus placebo: both groups receiving similar dose of ICS, Outcome 14 Change in evening PEF (L/min) at endpoint.



Study or subgroup	LABA + ICS N	ICS alone N	L/min (SE)	L/min IV, Fixed, 95% CI	Weight	L/min IV, Fixed, 95% CI
Pohunek 2006a	216	106	9.2 (4.367)		7.5%	9.2[0.64,17.76]
Malone 2005	101	102	6.4 (3.69)		10.51%	6.4[-0.83,13.63]
Pohunek 2006b	201	107	12 (4.367)		7.5%	12[3.44,20.56]
Murray 2011	113	118	8.1 (5.1)		5.5%	8.1[-1.9,18.1]
Subtotal (95% CI)					**79.16%**	**9.31[6.67,11.94]**
Heterogeneity: Tau^2=0; Chi^2=14.72, df=9(P=0.1); I^2=38.85%						
Test for overall effect: Z=6.92(P<0.0001)						
1.14.2 Mean baseline FEV1 61%-79% of predicted						
Tal 2002	148	138	11.7 (3.27)		13.38%	11.7[5.29,18.11]
Subtotal (95% CI)					**13.38%**	**11.7[5.29,18.11]**
Heterogeneity: Not applicable						
Test for overall effect: Z=3.58(P=0)						
1.14.3 Mean baseline FEV1 not reported						
SAM40012a	176	175	5 (4.38)		7.46%	5[-3.58,13.58]
Subtotal (95% CI)					**7.46%**	**5[-3.58,13.58]**
Heterogeneity: Not applicable						
Test for overall effect: Z=1.14(P=0.25)						
Total (95% CI)					**100%**	**9.3[6.96,11.65]**
Heterogeneity: Tau^2=0; Chi^2=16.22, df=11(P=0.13); I^2=32.19%						
Test for overall effect: Z=7.78(P<0.0001)						
Test for subgroup differences: Chi^2=1.5, df=1 (P=0.47), I^2=0%						



Favours ICS | Favours LABA+ICS

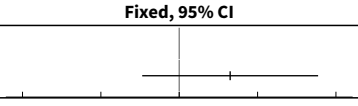
Analysis 1.15. Comparison 1 LABA versus placebo: both groups receiving similar dose of ICS, Outcome 15 Change in evening PEF (% of predicted).

Study or subgroup	LABA + ICS N	ICS alone N	% (SE)	% IV, Fixed, 95% CI	% IV, Fixed, 95% CI
1.15.1 Mean baseline FEV1 61%-79% of predicted					
Tal 2002	148	138	3.4 (0.95)		3.4[1.54,5.26]

Favours treatment | Favours control

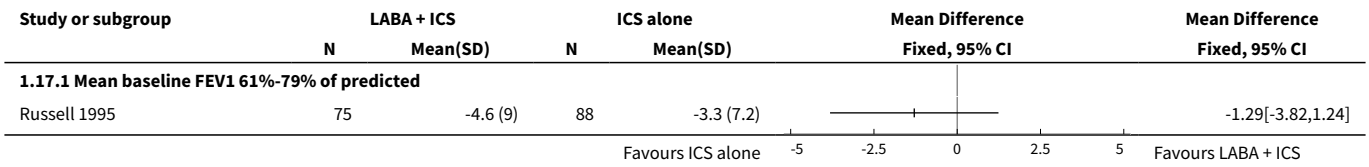
Analysis 1.16. Comparison 1 LABA versus placebo: both groups receiving similar dose of ICS, Outcome 16 Change in clinic PEF (L/min).

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
1.16.1 Mean baseline FEV1 not reported						
SAM40012a	176	52.7 (53.1)	175	46.2 (54.2)		6.5[-4.72,17.72]

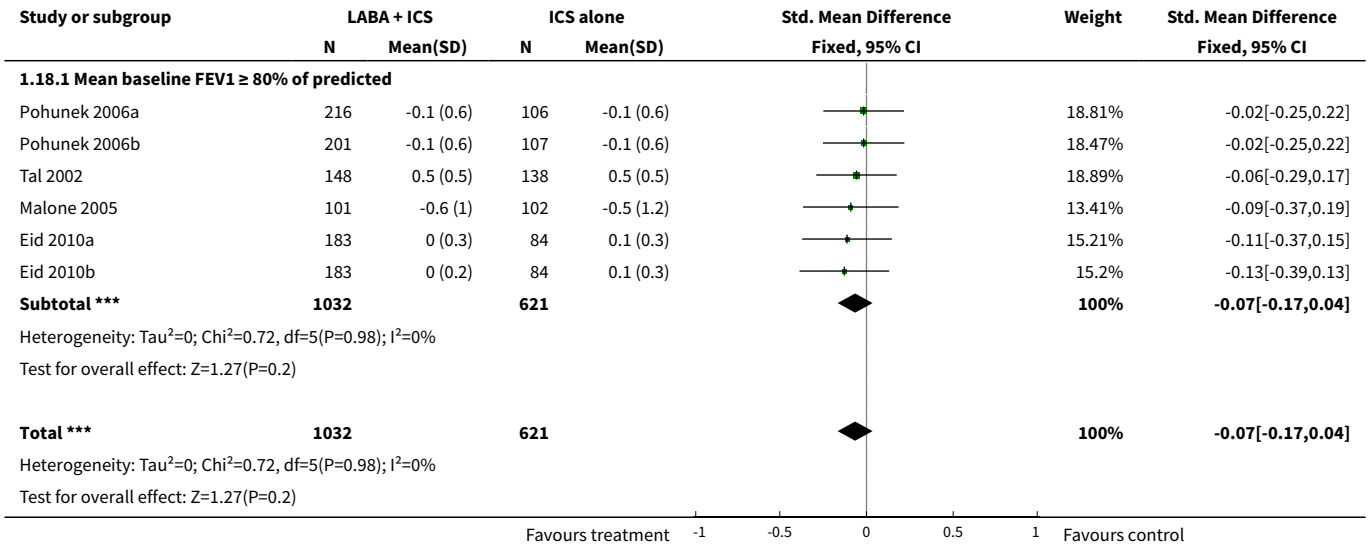


Favours ICS alone | Favours LABA + ICS

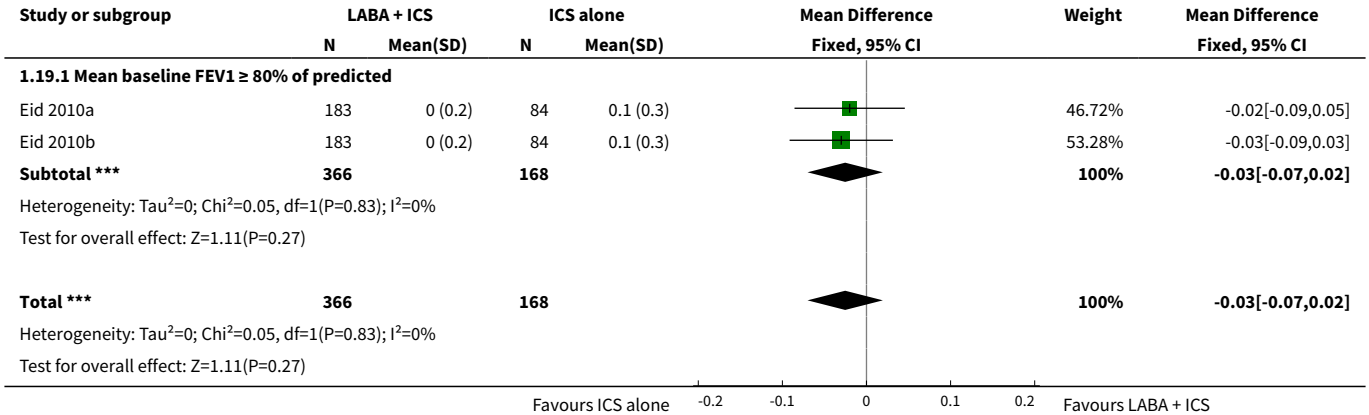
Analysis 1.17. Comparison 1 LABA versus placebo: both groups receiving similar dose of ICS, Outcome 17 Change in PEF variability at endpoint.



Analysis 1.18. Comparison 1 LABA versus placebo: both groups receiving similar dose of ICS, Outcome 18 Mean change in asthma symptom score.

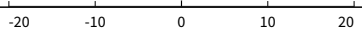


Analysis 1.19. Comparison 1 LABA versus placebo: both groups receiving similar dose of ICS, Outcome 19 Change in nighttime symptom score.



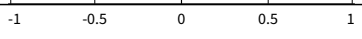
Analysis 1.20. Comparison 1 LABA versus placebo: both groups receiving similar dose of ICS, Outcome 20 Change in % symptom-free days at endpoint.

Study or subgroup	LABA + ICS N	LABA + ICS Mean(SD)	ICS alone N	ICS alone Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
1.20.1 Mean baseline FEV1 ≥ 80% of predicted							
Eid 2010a	168	-0.2 (24.6)	84	-3.7 (27.3)		17.29%	3.5[-3.42,10.42]
Eid 2010b	183	-0.9 (21.3)	84	-3.7 (27.3)		19%	2.8[-3.8,9.4]
Malone 2005	101	24.4 (41)	102	21.2 (41)		6.51%	3.2[-8.08,14.48]
Murray 2011	113	10.9 (33.9)	118	18.8 (44.6)		7.98%	-7.9[-18.09,2.29]
Pearlman 2009	124	11.5 (32.3)	124	12.2 (31.2)		13.26%	-0.7[-8.6,7.2]
Pohunek 2006a	216	33 (29.1)	106	32 (29.1)		18.14%	1[-5.76,7.76]
Pohunek 2006b	201	32.9 (29.1)	107	32 (29.1)		17.81%	0.9[-5.92,7.72]
Subtotal ***	**1106**		**725**			**100%**	**0.96[-1.91,3.84]**
Heterogeneity: Tau^2=0; Chi^2=4.04, df=6(P=0.67); I^2=0%							
Test for overall effect: Z=0.66(P=0.51)							
Total ***	**1106**		**725**			**100%**	**0.96[-1.91,3.84]**
Heterogeneity: Tau^2=0; Chi^2=4.04, df=6(P=0.67); I^2=0%							
Test for overall effect: Z=0.66(P=0.51)							



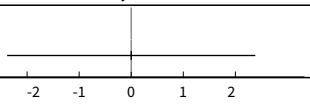
Analysis 1.21. Comparison 1 LABA versus placebo: both groups receiving similar dose of ICS, Outcome 21 % symptom-free days.

Study or subgroup	LABA + ICS N	LABA + ICS Mean(SD)	ICS alone N	ICS alone Mean(SD)	Std. Mean Difference Fixed, 95% CI	Weight	Std. Mean Difference Fixed, 95% CI
1.21.1 Mean baseline FEV1 ≥ 80% of predicted							
Murray 2011	113	27.2 (41.4)	118	36.2 (43.5)		38.5%	-0.21[-0.47,0.05]
Subtotal ***	**113**		**118**			**38.5%**	**-0.21[-0.47,0.05]**
Heterogeneity: Not applicable							
Test for overall effect: Z=1.6(P=0.11)							
1.21.2 Mean baseline FEV1 61%-79% of predicted							
Tal 2002	148	77.5 (20)	138	75.1 (20)		47.81%	0.12[-0.11,0.35]
Subtotal ***	**148**		**138**			**47.81%**	**0.12[-0.11,0.35]**
Heterogeneity: Tau^2=0; Chi^2=0, df=0(P<0.0001); I^2=100%							
Test for overall effect: Z=1.01(P=0.31)							
1.21.3 Unclear baseline FEV1							
SAM40100	12	0 (0)	12	0 (0)			Not estimable
Teper 2005	43	92 (9)	39	93 (7)		13.69%	-0.12[-0.56,0.31]
Subtotal ***	**55**		**51**			**13.69%**	**-0.12[-0.56,0.31]**
Heterogeneity: Not applicable							
Test for overall effect: Z=0.55(P=0.58)							
Total ***	**316**		**307**			**100%**	**-0.04[-0.2,0.12]**
Heterogeneity: Tau^2=0; Chi^2=3.64, df=2(P=0.16); I^2=45%							
Test for overall effect: Z=0.5(P=0.62)							
Test for subgroup differences: Chi^2=3.64, df=1 (P=0.16), I^2=45%							



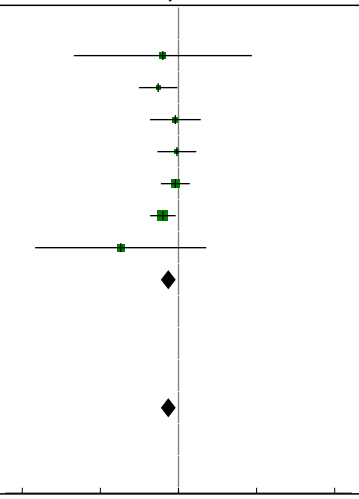
Analysis 1.22. Comparison 1 LABA versus placebo: both groups receiving similar dose of ICS, Outcome 22 % symptom-free nights at 52 ± 4 weeks.

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
1.22.1 Mean baseline FEV1 not reported						
Teper 2005	43	95 (6)	39	95 (5)		0[-2.38,2.38]



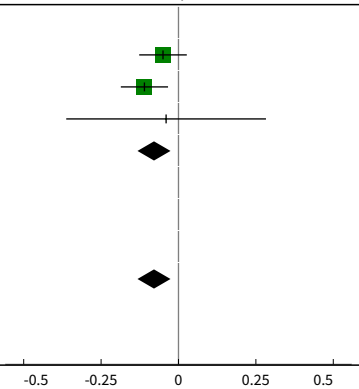
Analysis 1.23. Comparison 1 LABA versus placebo: both groups receiving similar dose of ICS, Outcome 23 Change in # daytime rescue inhalations (puffs per day) at endpoint.

Study or subgroup	LABA + ICS N	LABA + ICS Mean(SD)	ICS alone N	ICS alone Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
1.23.1 Mean baseline FEV1 61%-79% of predicted							
Malone 2005	101	-0.5 (2.2)	102	-0.4 (1.9)		0.7%	-0.1[-0.67,0.47]
Pohunek 2006a	216	-0.6 (0.5)	106	-0.5 (0.5)		14.93%	-0.13[-0.25,-0.01]
Tal 2002	148	-0.1 (0.7)	138	-0.1 (0.7)		8.6%	-0.02[-0.18,0.14]
Pohunek 2006b	201	-0.5 (0.5)	107	-0.5 (0.5)		14.66%	-0.01[-0.13,0.11]
Eid 2010a	168	0.1 (0.4)	85	0.1 (0.3)		26.44%	-0.02[-0.11,0.07]
Eid 2010b	183	0 (0.3)	84	0.1 (0.3)		33.92%	-0.1[-0.18,-0.02]
Russell 1995	73	-0.7 (1.8)	86	-0.4 (1.7)		0.75%	-0.37[-0.92,0.18]
Subtotal ***	**1090**		**708**			**100%**	**-0.07[-0.11,-0.02]**
Heterogeneity: Tau^2=0; Chi^2=4.93, df=6(P=0.55); I^2=0%							
Test for overall effect: Z=2.69(P=0.01)							
Total ***	**1090**		**708**			**100%**	**-0.07[-0.11,-0.02]**
Heterogeneity: Tau^2=0; Chi^2=4.93, df=6(P=0.55); I^2=0%							
Test for overall effect: Z=2.69(P=0.01)							

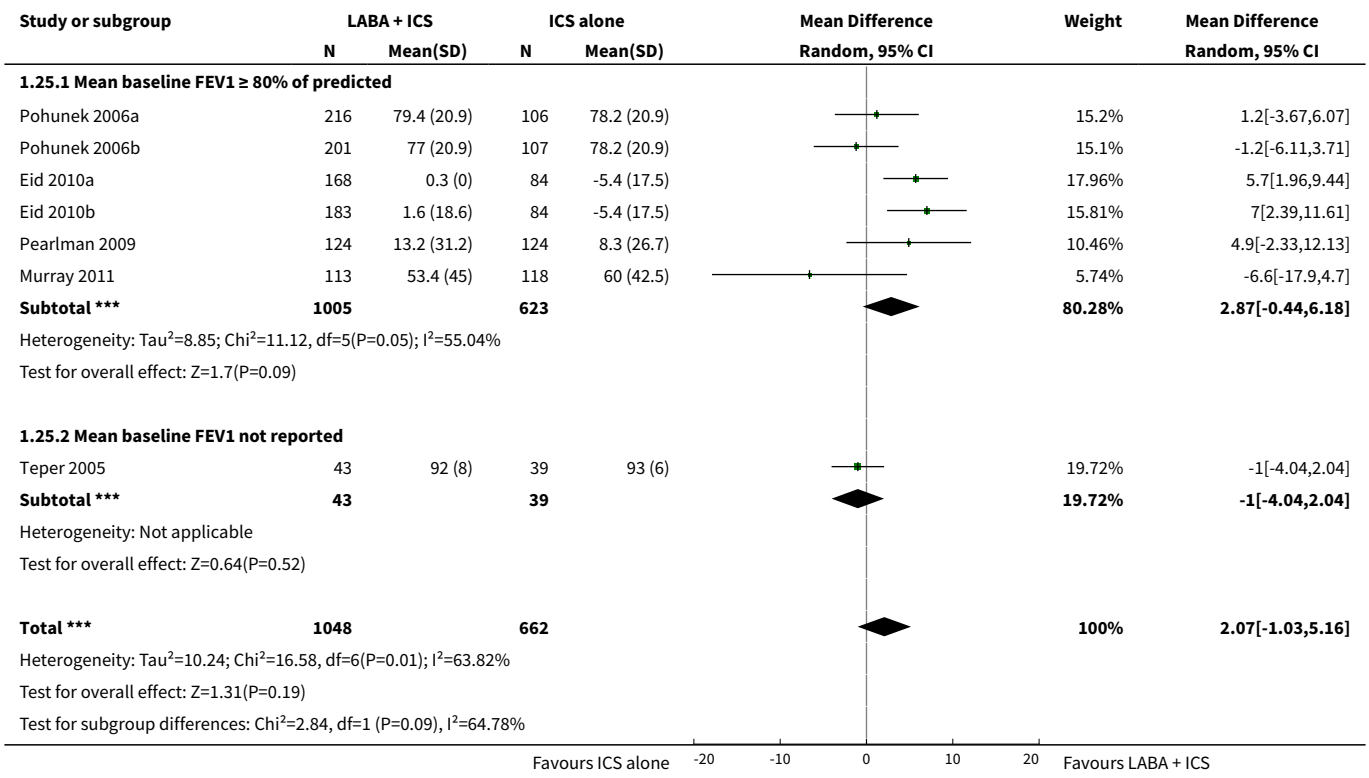


Analysis 1.24. Comparison 1 LABA versus placebo: both groups receiving similar dose of ICS, Outcome 24 Change in # nighttime rescue inhalations at endpoint.

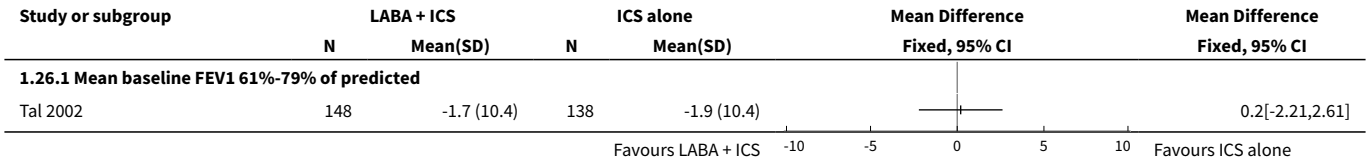
Study or subgroup	LABA + ICS N	LABA + ICS Mean(SD)	ICS alone N	ICS alone Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
1.24.1 Mean baseline FEV1 61%-79% of predicted							
Eid 2010a	168	0 (0.3)	84	0.1 (0.3)		48.26%	-0.05[-0.13,0.03]
Eid 2010b	183	-0 (0.3)	84	0.1 (0.3)		49%	-0.11[-0.19,-0.03]
Russell 1995	70	-0.1 (1.1)	83	-0.1 (1)		2.74%	-0.04[-0.36,0.28]
Subtotal ***	**421**		**251**			**100%**	**-0.08[-0.13,-0.03]**
Heterogeneity: Tau^2=0; Chi^2=1.24, df=2(P=0.54); I^2=0%							
Test for overall effect: Z=2.91(P=0)							
Total ***	**421**		**251**			**100%**	**-0.08[-0.13,-0.03]**
Heterogeneity: Tau^2=0; Chi^2=1.24, df=2(P=0.54); I^2=0%							
Test for overall effect: Z=2.91(P=0)							



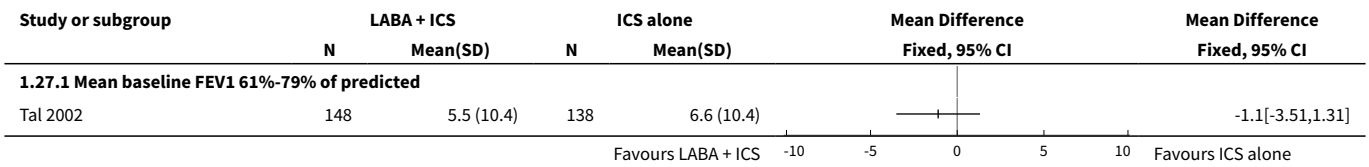
Analysis 1.25. Comparison 1 LABA versus placebo: both groups receiving similar dose of ICS, Outcome 25 % days without bronchodilator usage.



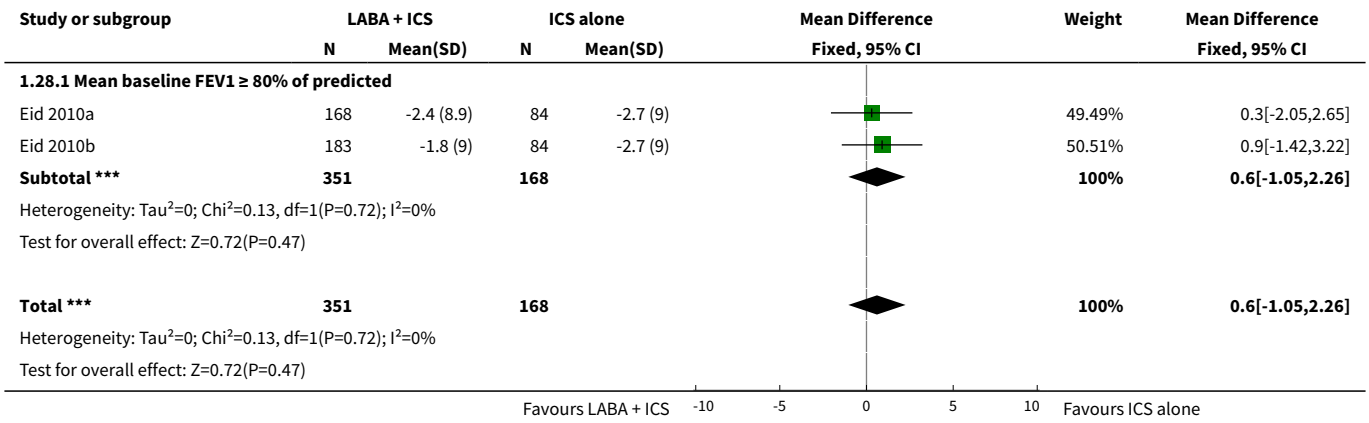
Analysis 1.26. Comparison 1 LABA versus placebo: both groups receiving similar dose of ICS, Outcome 26 Change in nighttime awakening (number of nights) at endpoint.



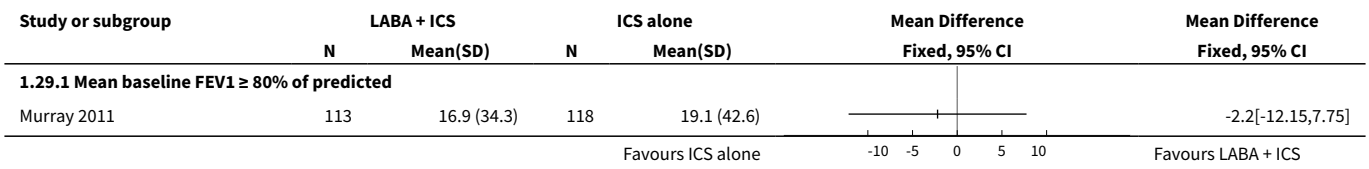
Analysis 1.27. Comparison 1 LABA versus placebo: both groups receiving similar dose of ICS, Outcome 27 % nights with awakening.



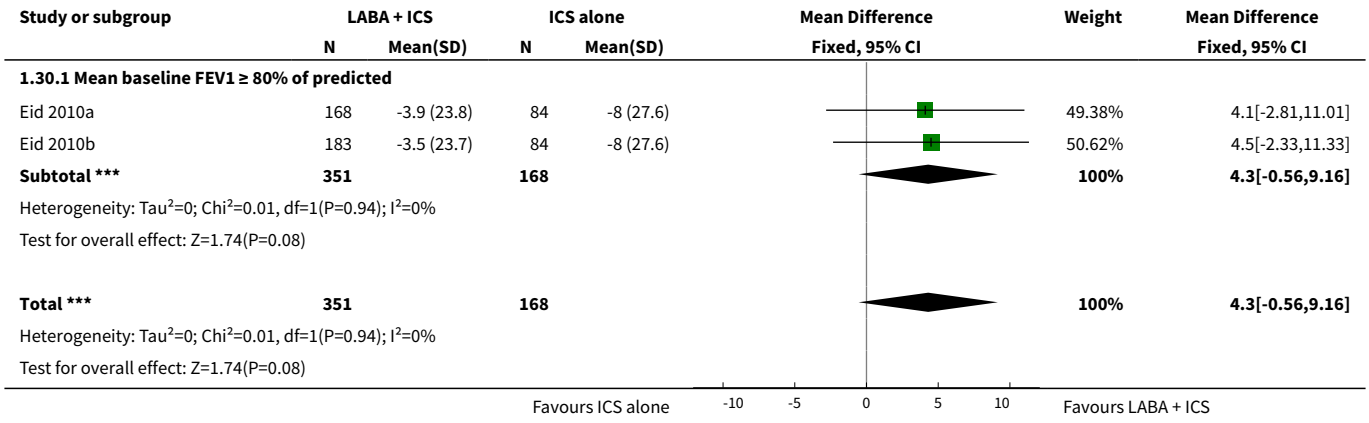
Analysis 1.28. Comparison 1 LABA versus placebo: both groups receiving similar dose of ICS, Outcome 28 % change in awakening-free nights.



Analysis 1.29. Comparison 1 LABA versus placebo: both groups receiving similar dose of ICS, Outcome 29 Change in rescue-free days (%).

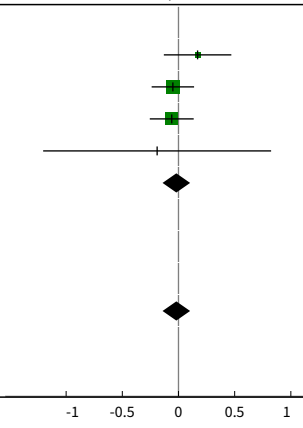


Analysis 1.30. Comparison 1 LABA versus placebo: both groups receiving similar dose of ICS, Outcome 30 Change in % asthma-control days at endpoint.



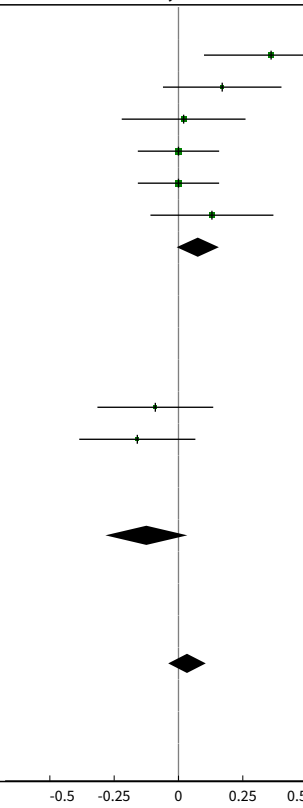
Analysis 1.31. Comparison 1 LABA versus placebo: both groups receiving similar dose of ICS, Outcome 31 Change in quality of life (P-AQLQ).

Study or subgroup	LABA+ICS N	LABA+ICS Mean(SD)	ICS N	ICS Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
1.31.1 Mean baseline FEV1 ≥ 80% of predicted							
Berger 2010	108	0.5 (0.8)	55	0.4 (1)		16.71%	0.17[-0.13,0.47]
Eid 2010a	151	-0.1 (0.8)	78	-0 (0.6)		42.3%	-0.05[-0.24,0.14]
Eid 2010b	173	-0.1 (0.9)	78	-0 (0.6)		39.52%	-0.06[-0.26,0.14]
Lenney 2013	15	1.1 (1.9)	10	1.3 (0.6)		1.47%	-0.19[-1.2,0.82]
Subtotal ***	**447**		**221**			**100%**	**-0.02[-0.14,0.1]**
Heterogeneity: Tau^2=0; Chi^2=1.9, df=3(P=0.59); I^2=0%							
Test for overall effect: Z=0.31(P=0.76)							
Total ***	**447**		**221**			**100%**	**-0.02[-0.14,0.1]**
Heterogeneity: Tau^2=0; Chi^2=1.9, df=3(P=0.59); I^2=0%							
Test for overall effect: Z=0.31(P=0.76)							

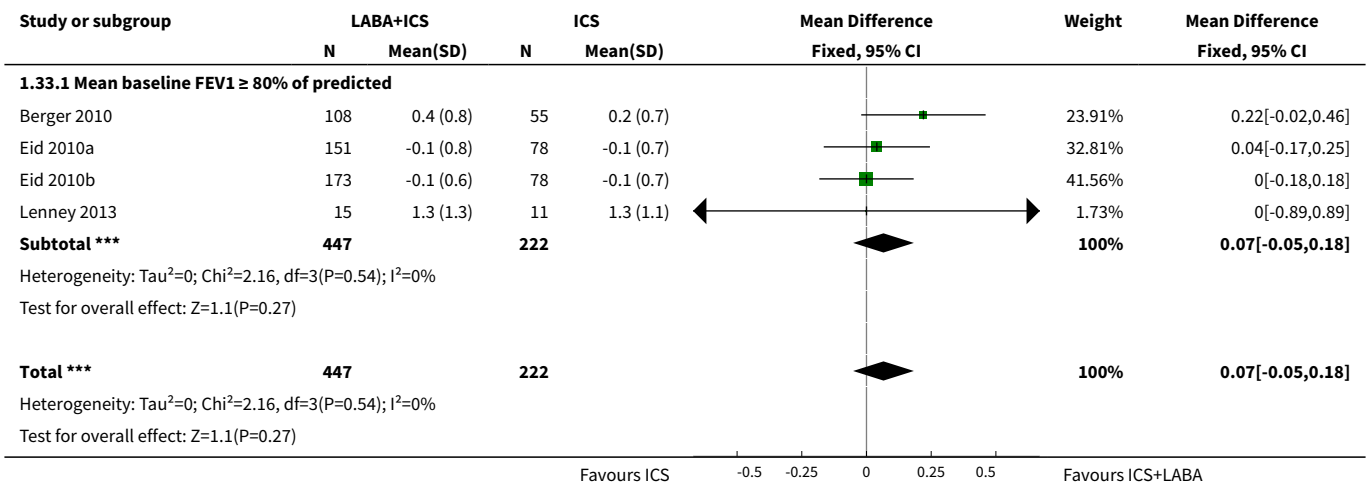


Analysis 1.32. Comparison 1 LABA versus placebo: both groups receiving similar dose of ICS, Outcome 32 Quality of life (P-AQLQ).

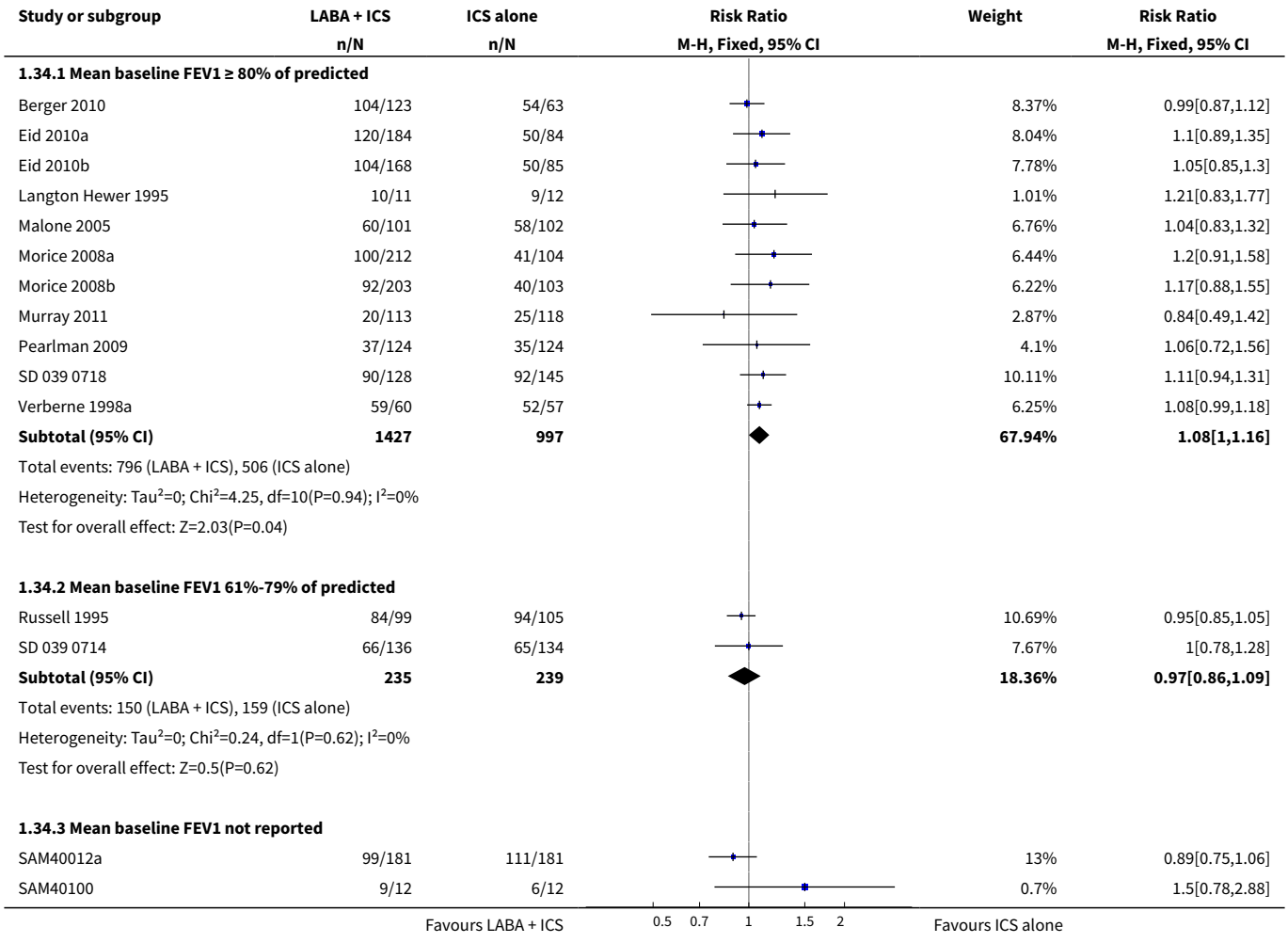
Study or subgroup	LABA+ICS N	LABA+ICS Mean(SD)	ICS N	ICS Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
1.32.1 Mean baseline FEV1 ≥ 80% of predicted							
Berger 2010	108	6.6 (0.5)	55	6.2 (0.9)		7.83%	0.36[0.1,0.62]
Morice 2008a	185	6.2 (0.9)	91	6 (0.9)		10.04%	0.17[-0.06,0.4]
Morice 2008b	172	6 (1)	90	6 (0.9)		9.2%	0.02[-0.22,0.26]
Pohunek 2006a	216	6.2 (0.7)	106	6.2 (0.7)		21.31%	0[-0.16,0.16]
Pohunek 2006b	213	6.2 (0.7)	107	6.2 (0.7)		21.34%	0[-0.16,0.16]
SD 039 0718	114	6.1 (0.9)	129	6 (1)		9.32%	0.13[-0.11,0.37]
Subtotal ***	**1008**		**578**			**79.04%**	**0.07[-0.01,0.16]**
Heterogeneity: Tau^2=0; Chi^2=7.38, df=5(P=0.19); I^2=32.23%							
Test for overall effect: Z=1.79(P=0.07)							
1.32.2 Mean baseline FEV1 61%-79% of predicted							
Eid 2010a	173	6.3 (1)	78	6.4 (0.8)		10.51%	-0.09[-0.32,0.14]
Eid 2010b	151	6.3 (0.9)	78	6.4 (0.8)		10.45%	-0.16[-0.39,0.07]
Zimmerman 2004a	99	5.8 (0)	43	5.8 (0)			Not estimable
Zimmerman 2004b	83	5.7 (0)	42	5.8 (0)			Not estimable
Subtotal ***	**506**		**241**			**20.96%**	**-0.12[-0.28,0.03]**
Heterogeneity: Tau^2=0; Chi^2=0.19, df=1(P=0.67); I^2=0%							
Test for overall effect: Z=1.54(P=0.12)							
Total ***	**1514**		**819**			**100%**	**0.03[-0.04,0.11]**
Heterogeneity: Tau^2=0; Chi^2=12.34, df=7(P=0.09); I^2=43.26%							
Test for overall effect: Z=0.89(P=0.38)							
Test for subgroup differences: Chi^2=4.77, df=1 (P=0.03), I^2=79.05%							

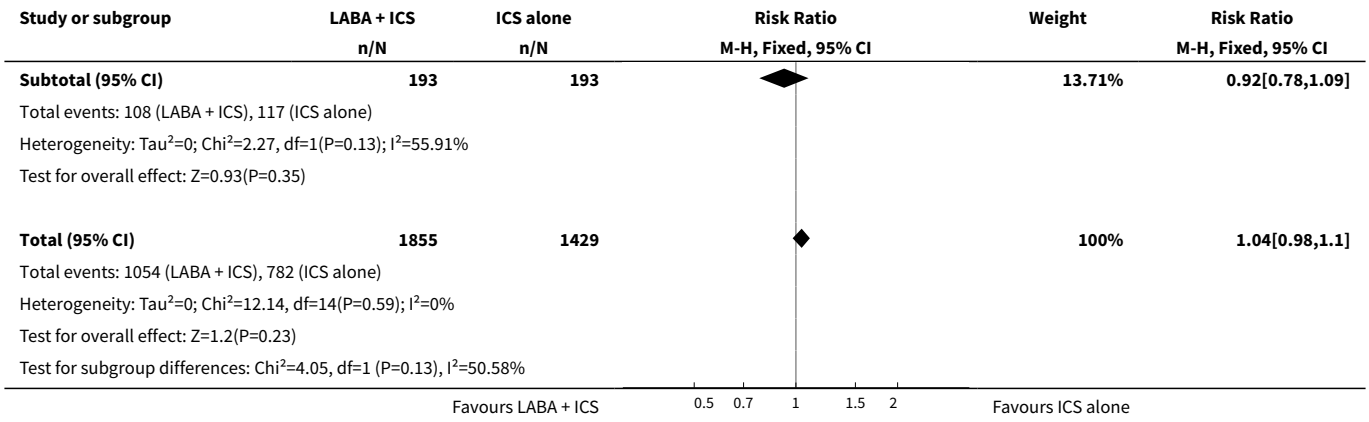


Analysis 1.33. Comparison 1 LABA versus placebo: both groups receiving similar dose of ICS, Outcome 33 Change in paediatric asthma caregiver quality of life (P-AQLQ).

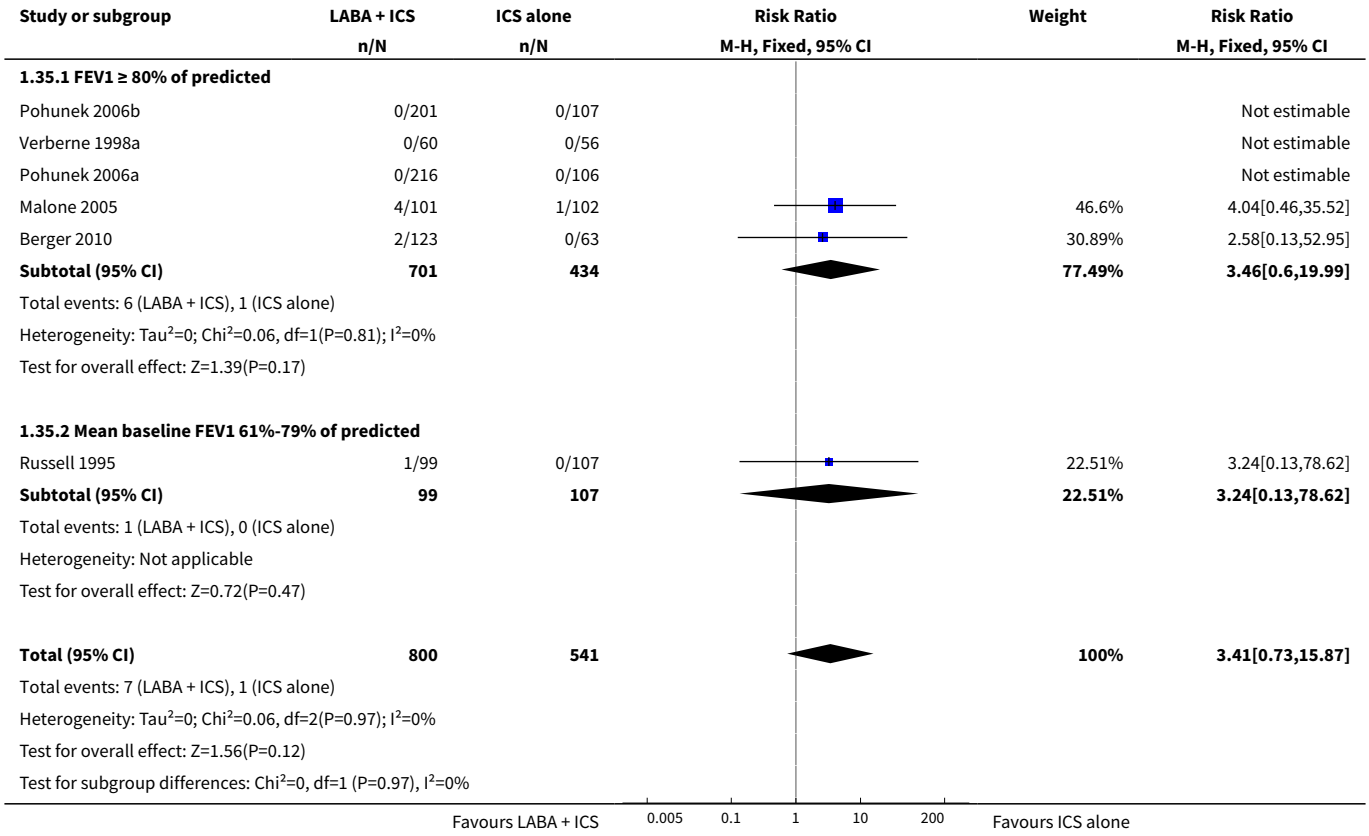


Analysis 1.34. Comparison 1 LABA versus placebo: both groups receiving similar dose of ICS, Outcome 34 Total # adverse events.



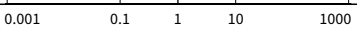


Analysis 1.35. Comparison 1 LABA versus placebo: both groups receiving similar dose of ICS, Outcome 35 # participants with oral candidiasis.



Analysis 1.36. Comparison 1 LABA versus placebo: both groups receiving similar dose of ICS, Outcome 36 # participants with tremor.

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
1.36.1 Mean baseline FEV1 ≥ 80% of predicted					
Pohunek 2006a	0/216	0/213			Not estimable
Pohunek 2006b	2/201	0/213		41.91%	5.3[0.26,109.66]
Verberne 1998a	0/60	0/56			Not estimable
Subtotal (95% CI)	**477**	**482**		**41.91%**	**5.3[0.26,109.66]**
Total events: 2 (LABA + ICS), 0 (ICS alone)					
Heterogeneity: Not applicable					
Test for overall effect: Z=1.08(P=0.28)					
1.36.2 Mean baseline FEV1 61%-79% of predicted					
Russell 1995	0/99	0/107			Not estimable
Zimmerman 2004a	1/106	0/51		58.09%	1.46[0.06,35.18]
Zimmerman 2004b	0/95	0/50			Not estimable
Subtotal (95% CI)	**300**	**208**		**58.09%**	**1.46[0.06,35.18]**
Total events: 1 (LABA + ICS), 0 (ICS alone)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.23(P=0.82)					
Total (95% CI)	**777**	**690**		**100%**	**3.07[0.38,25.05]**
Total events: 3 (LABA + ICS), 0 (ICS alone)					
Heterogeneity: Tau^2=0; Chi^2=0.33, df=1(P=0.56); I^2=0%					
Test for overall effect: Z=1.05(P=0.3)					
Test for subgroup differences: Chi^2=0.33, df=1 (P=0.57), I^2=0%					



Analysis 1.37. Comparison 1 LABA versus placebo: both groups receiving similar dose of ICS, Outcome 37 # participants 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
1.37.1 Mean baseline FEV1 ≥ 80% of predicted					
Berger 2010	1/123	1/63		31.65%	0.51[0.03,8.05]
Pohunek 2006a	0/216	1/213		36.14%	0.33[0.01,8.02]
Verberne 1998a	0/60	0/56			Not estimable
Subtotal (95% CI)	**399**	**332**		**67.79%**	**0.41[0.05,3.33]**
Total events: 1 (LABA + ICS), 2 (ICS alone)					
Heterogeneity: Tau^2=0; Chi^2=0.04, df=1(P=0.84); I^2=0%					
Test for overall effect: Z=0.83(P=0.41)					
1.37.2 Mean baseline FEV1 61%-79% of predicted					
Russell 1995	0/99	0/107			Not estimable
Zimmerman 2004a	1/105	1/51		32.21%	0.49[0.03,7.61]
Zimmerman 2004b	0/95	0/50			Not estimable
Subtotal (95% CI)	**299**	**208**		**32.21%**	**0.49[0.03,7.61]**
Total events: 1 (LABA + ICS), 1 (ICS alone)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.51(P=0.61)					

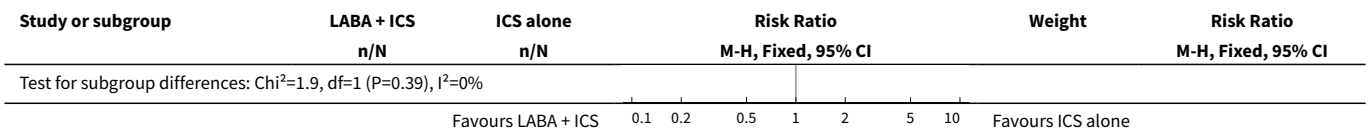
Study or subgroup	LABA + ICS n/N	ICS alone n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Total (95% CI)	**698**	**540**		**100%**	**0.44[0.08,2.31]**
Total events: 2 (LABA + ICS), 3 (ICS alone)					
Heterogeneity: Tau^2=0; Chi^2=0.05, df=2(P=0.98); I^2=0%					
Test for overall effect: Z=0.97(P=0.33)					
Test for subgroup differences: Chi^2=0.01, df=1 (P=0.93), I^2=0%					

Favours LABA + ICS — Favours ICS alone

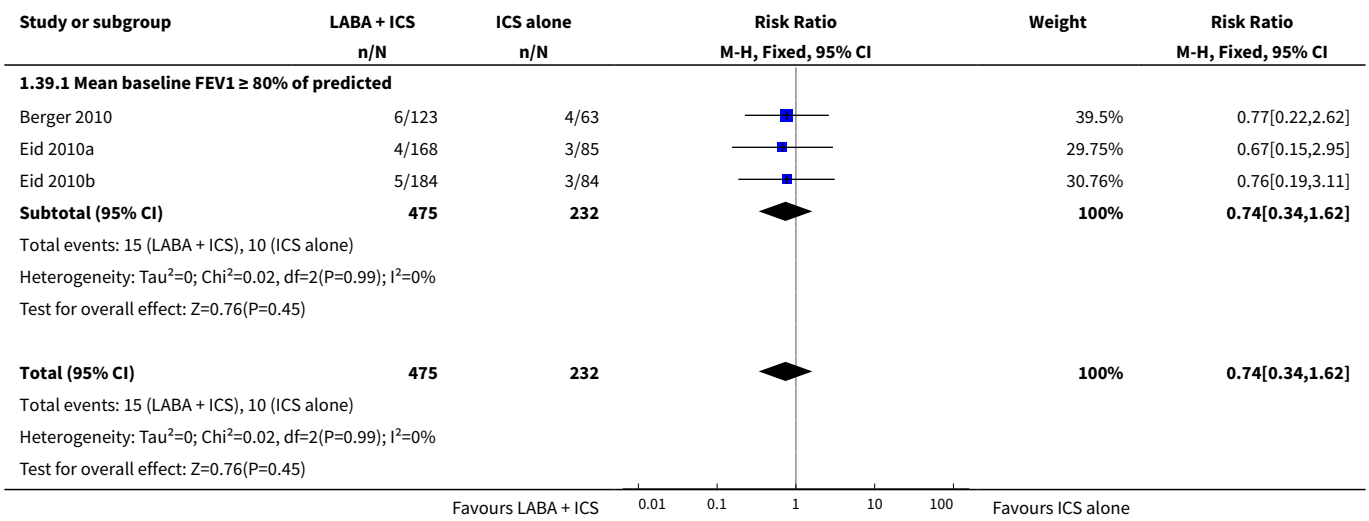
Analysis 1.38. Comparison 1 LABA versus placebo: both groups receiving similar dose of ICS, Outcome 38 # participants with headache.

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
1.38.1 Mean baseline FEV1 ≥ 80% of predicted					
Berger 2010	26/123	14/63		11.72%	0.95[0.54,1.69]
Eid 2010a	13/168	9/85		7.56%	0.73[0.33,1.64]
Eid 2010b	21/184	8/84		6.95%	1.2[0.55,2.59]
Malone 2005	20/101	20/102		12.59%	1.01[0.58,1.76]
Murray 2011	6/113	5/118		3.1%	1.25[0.39,3.99]
Pearlman 2009	4/124	6/124		3.8%	0.67[0.19,2.3]
SD 039 0718	19/128	20/145		11.87%	1.08[0.6,1.92]
Verberne 1998a	25/60	23/57		14.93%	1.03[0.67,1.6]
Subtotal (95% CI)	**1001**	**778**		**72.5%**	**1[0.79,1.26]**
Total events: 134 (LABA + ICS), 105 (ICS alone)					
Heterogeneity: Tau^2=0; Chi^2=1.46, df=7(P=0.98); I^2=0%					
Test for overall effect: Z=0.02(P=0.98)					
1.38.2 Mean baseline FEV1 61%-79% of predicted					
Akpinarli 1999	0/16	0/16			Not estimable
Russell 1995	20/99	9/107		5.47%	2.4[1.15,5.02]
Tal 2002	9/148	6/138		3.93%	1.4[0.51,3.83]
Zimmerman 2004a	13/105	7/51		5.96%	0.9[0.38,2.12]
Zimmerman 2004b	10/95	7/50		5.8%	0.75[0.3,1.86]
Subtotal (95% CI)	**463**	**362**		**21.17%**	**1.34[0.88,2.04]**
Total events: 52 (LABA + ICS), 29 (ICS alone)					
Heterogeneity: Tau^2=0; Chi^2=4.81, df=3(P=0.19); I^2=37.57%					
Test for overall effect: Z=1.37(P=0.17)					
1.38.3 Mean baseline FEV1 not reported					
SAM40012a	14/181	10/181		6.33%	1.4[0.64,3.07]
Subtotal (95% CI)	**181**	**181**		**6.33%**	**1.4[0.64,3.07]**
Total events: 14 (LABA + ICS), 10 (ICS alone)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.84(P=0.4)					
Total (95% CI)	**1645**	**1321**		**100%**	**1.1[0.9,1.33]**
Total events: 200 (LABA + ICS), 144 (ICS alone)					
Heterogeneity: Tau^2=0; Chi^2=7.89, df=12(P=0.79); I^2=0%					
Test for overall effect: Z=0.91(P=0.36)					

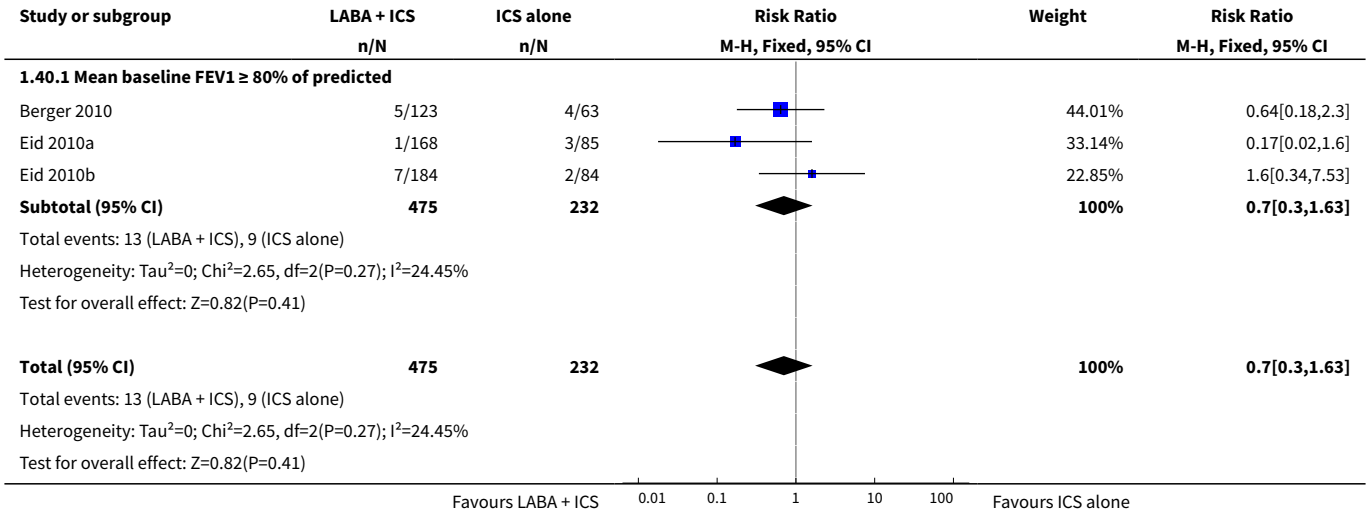
Favours LABA + ICS — Favours ICS alone



Analysis 1.39. Comparison 1 LABA versus placebo: both groups receiving similar dose of ICS, Outcome 39 # participants with vomiting.

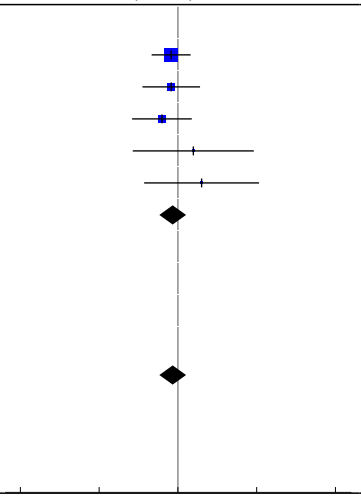


Analysis 1.40. Comparison 1 LABA versus placebo: both groups receiving similar dose of ICS, Outcome 40 # participants with otitis media.



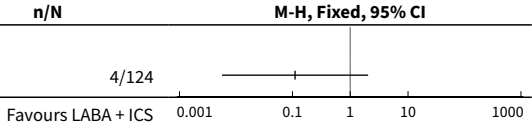
Analysis 1.41. Comparison 1 LABA versus placebo: both groups receiving similar dose of ICS, Outcome 41 # participants with upper respiratory tract infection.

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
1.41.1 Mean baseline FEV1 ≥ 80% of predicted					
Berger 2010	24/123	15/63		43.69%	0.82[0.46,1.45]
Eid 2010a	13/168	8/85		23.4%	0.82[0.35,1.91]
Eid 2010b	11/184	8/84		24.19%	0.63[0.26,1.5]
Murray 2011	3/113	2/118		4.31%	1.57[0.27,9.2]
Pearlman 2009	4/124	2/124		4.4%	2[0.37,10.72]
Subtotal (95% CI)	**712**	**474**		**100%**	**0.86[0.58,1.27]**
Total events: 55 (LABA + ICS), 35 (ICS alone)					
Heterogeneity: Tau²=0; Chi²=1.95, df=4(P=0.75); I²=0%					
Test for overall effect: Z=0.77(P=0.44)					
Total (95% CI)	**712**	**474**		**100%**	**0.86[0.58,1.27]**
Total events: 55 (LABA + ICS), 35 (ICS alone)					
Heterogeneity: Tau²=0; Chi²=1.95, df=4(P=0.75); I²=0%					
Test for overall effect: Z=0.77(P=0.44)					



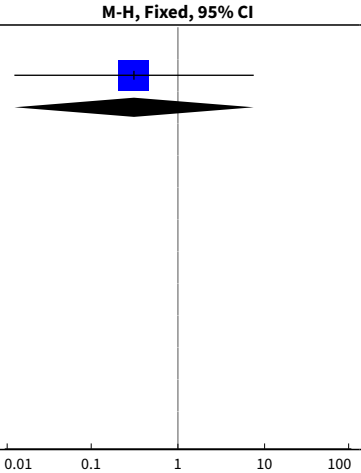
Analysis 1.42. Comparison 1 LABA versus placebo: both groups receiving similar dose of ICS, Outcome 42 # participants with urticaria.

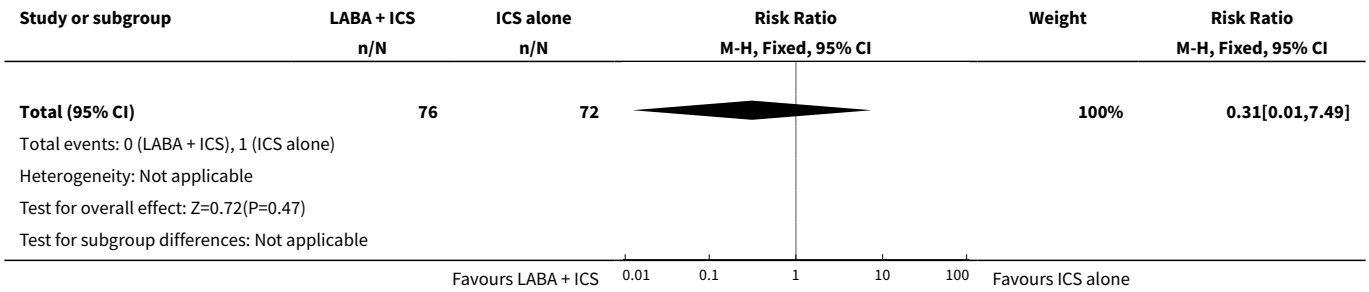
Study or subgroup	LABA + ICS n/N	ICS alone n/N	Risk Ratio M-H, Fixed, 95% CI	Risk Ratio M-H, Fixed, 95% CI
1.42.1 Mean baseline FEV1 ≥ 80% of predicted				
Pearlman 2009	0/124	4/124		0.11[0.01,2.04]



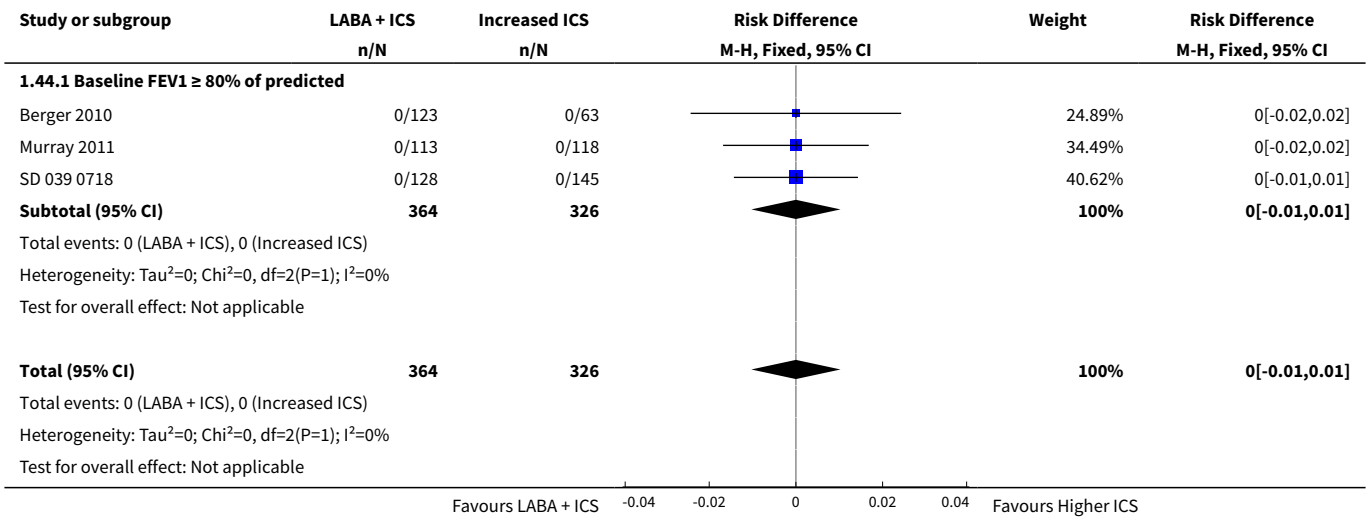
Analysis 1.43. Comparison 1 LABA versus placebo: both groups receiving similar dose of ICS, Outcome 43 # participants with adverse cardiovascular events.

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 Mean baseline FEV1 ≥ 80% of predicted					
Verberne 1998a	0/60	1/56		100%	0.31[0.01,7.49]
Subtotal (95% CI)	**60**	**56**		**100%**	**0.31[0.01,7.49]**
Total events: 0 (LABA + ICS), 1 (ICS alone)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.72(P=0.47)					
1.43.2 Mean baseline FEV1 61%-79% of predicted					
Akpinarli 1999	0/16	0/16			Not estimable
Subtotal (95% CI)	**16**	**16**			**Not estimable**
Total events: 0 (LABA + ICS), 0 (ICS alone)					
Heterogeneity: Not applicable					
Test for overall effect: Not applicable					

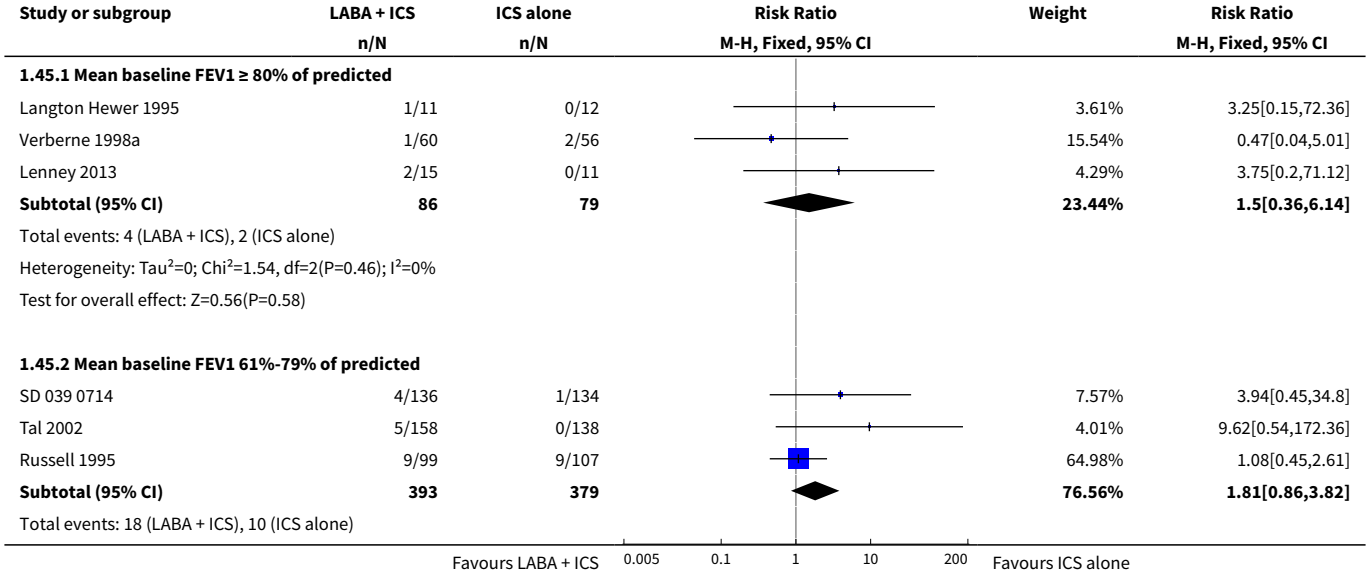


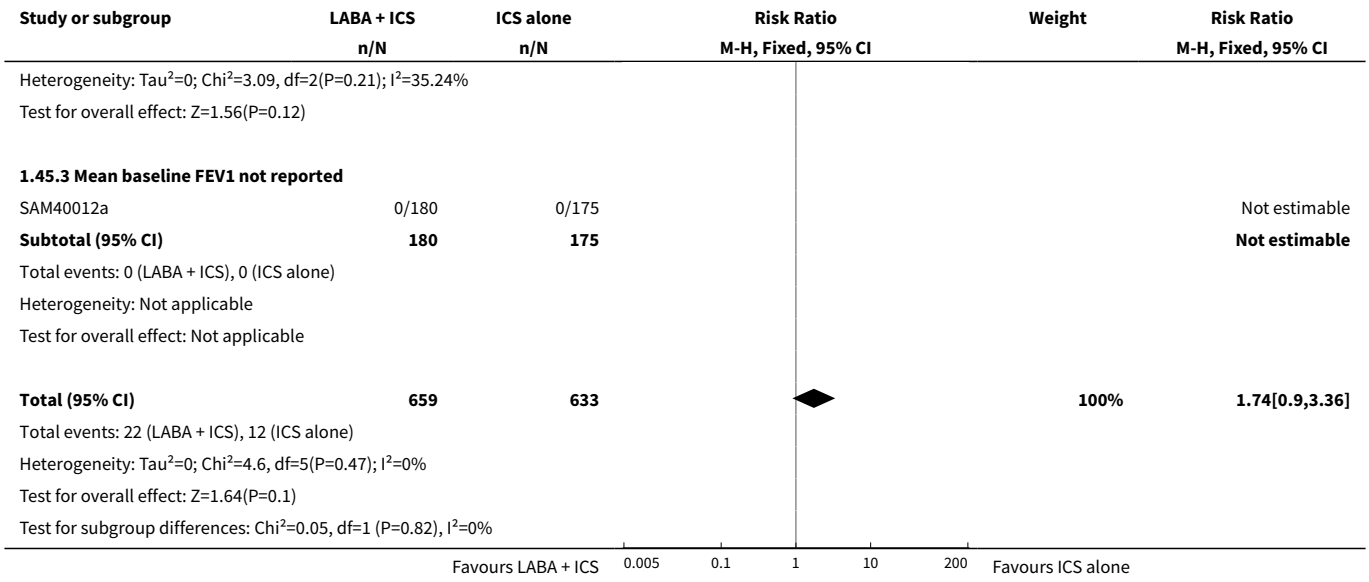


Analysis 1.44. Comparison 1 LABA versus placebo: both groups receiving similar dose of ICS, Outcome 44 Deaths.

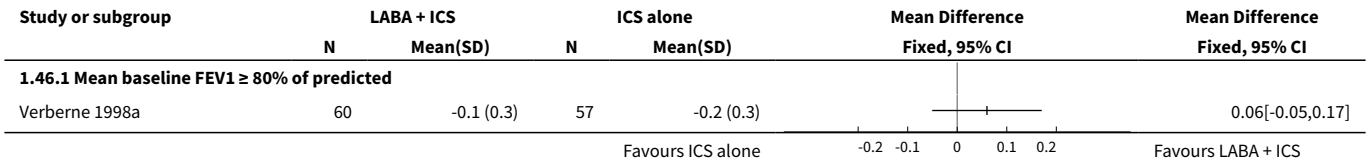


Analysis 1.45. Comparison 1 LABA versus placebo: both groups receiving similar dose of ICS, Outcome 45 # participants with exacerbations requiring hospitalisation.

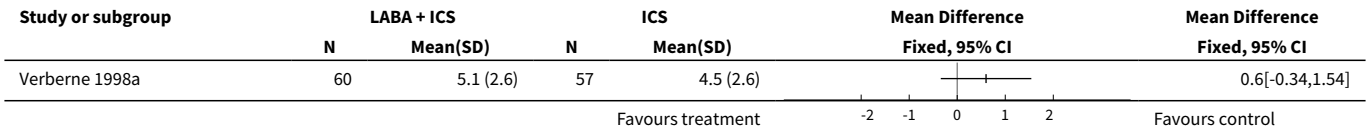




Analysis 1.46. Comparison 1 LABA versus placebo: both groups receiving similar dose of ICS, Outcome 46 Change in height (cm) as SD scores at 24 ± 4 weeks.



Analysis 1.47. Comparison 1 LABA versus placebo: both groups receiving similar dose of ICS, Outcome 47 Change in height at 1 year.



Comparison 2. LABA + ICS versus placebo + higher dose of ICS

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 # participants with exacerbations requiring oral steroids	3	581	Risk Ratio (M-H, Fixed, 95% CI)	1.69 [0.85, 3.32]
1.1 Baseline FEV_1 ≥ 80% of predicted	3	581	Risk Ratio (M-H, Fixed, 95% CI)	1.69 [0.85, 3.32]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
2 # participants with exacerbations requiring hospitalisation	4	1008	Risk Ratio (M-H, Fixed, 95% CI)	1.90 [0.65, 5.54]
2.1 Baseline FEV_1 ≥ 80% of predicted	2	423	Risk Ratio (M-H, Fixed, 95% CI)	1.68 [0.22, 12.66]
2.2 Baseline FEV_1 61%-79% of predicted	1	225	Risk Ratio (M-H, Fixed, 95% CI)	3.17 [0.67, 14.95]
2.3 Mean baseline FEV_1 not reported	1	360	Risk Ratio (M-H, Fixed, 95% CI)	0.33 [0.01, 8.13]
3 # participants with exacerbations requiring urgent care visit	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
3.1 Baseline FEV_1 ≥ 80% of predicted	1		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
4 Serious adverse events	7	1343	Risk Ratio (M-H, Random, 95% CI)	1.54 [0.81, 2.94]
4.1 Baseline FEV_1 ≥ 80% predicted	4	729	Risk Ratio (M-H, Random, 95% CI)	1.15 [0.42, 3.16]
4.2 Baseline FEV_1 61%-79% of predicted	1	223	Risk Ratio (M-H, Random, 95% CI)	2.90 [1.10, 7.64]
4.3 Mean baseline FEV_1 not reported	2	391	Risk Ratio (M-H, Random, 95% CI)	0.51 [0.10, 2.77]
5 Total # withdrawals	8	1491	Risk Ratio (M-H, Fixed, 95% CI)	0.96 [0.67, 1.37]
5.1 Baseline FEV_1 ≥ 80% of predicted	5	888	Risk Ratio (M-H, Fixed, 95% CI)	1.15 [0.75, 1.78]
5.2 Baseline FEV_1 61%-79% of predicted	1	223	Risk Ratio (M-H, Fixed, 95% CI)	0.65 [0.30, 1.39]
5.3 Mean baseline FEV_1 not reported	2	380	Risk Ratio (M-H, Fixed, 95% CI)	0.68 [0.20, 2.36]
6 # withdrawals due to poor asthma control or exacerbation	4	862	Risk Ratio (M-H, Fixed, 95% CI)	0.34 [0.05, 2.13]
6.1 Baseline FEV_1 ≥ 80% of predicted	4	862	Risk Ratio (M-H, Fixed, 95% CI)	0.34 [0.05, 2.13]
7 # withdrawals due to adverse events	5	951	Risk Ratio (M-H, Fixed, 95% CI)	0.76 [0.19, 3.07]
7.1 Baseline FEV_1 ≥ 80% of predicted	4	728	Risk Ratio (M-H, Fixed, 95% CI)	0.72 [0.14, 3.63]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
7.2 Baseline FEV_1 61%-79% of predicted	1	223	Risk Ratio (M-H, Fixed, 95% CI)	0.91 [0.06, 14.30]
8 # withdrawals due to serious non-respiratory event	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
8.1 Mean baseline $FEV_1 \geq 80\%$ of predicted	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
9 Change in FEV_1 (L) at endpoint	2	526	Mean Difference (Fixed, 95% CI)	0.01 [-0.03, 0.05]
9.1 Baseline $FEV_1 \geq 80\%$ of predicted	1	303	Mean Difference (Fixed, 95% CI)	0.0 [-0.05, 0.05]
9.2 Baseline FEV_1 61%-79% of predicted	1	223	Mean Difference (Fixed, 95% CI)	0.04 [-0.06, 0.14]
10 Change in FEV_1 % predicted at endpoint	2		% (Random, 95% CI)	0.38 [-0.39, 1.15]
10.1 Baseline $FEV_1 \geq 80\%$ of predicted	2		% (Random, 95% CI)	0.38 [-0.39, 1.15]
11 Change in morning PEF (L/min) at endpoint	5	1283	Mean Difference (IV, Fixed, 95% CI)	8.73 [5.15, 12.31]
11.1 Baseline $FEV_1 \geq 80\%$ of predicted	3	704	Mean Difference (IV, Fixed, 95% CI)	9.50 [5.07, 13.93]
11.2 Baseline FEV_1 61%-79% of predicted	1	223	Mean Difference (IV, Fixed, 95% CI)	9.0 [-0.07, 18.07]
11.3 Baseline FEV_1 not reported	1	356	Mean Difference (IV, Fixed, 95% CI)	5.90 [-2.28, 14.08]
12 Change in evening PEF (L/min) at endpoint	4	1163	Mean Difference (Fixed, 95% CI)	6.50 [2.64, 10.37]
12.1 Baseline FEV_1 predicted $\geq 80\%$	2	584	Mean Difference (Fixed, 95% CI)	7.08 [2.13, 12.02]
12.2 Baseline FEV_1 61%-79% of predicted	1	223	Mean Difference (Fixed, 95% CI)	7.0 [-2.07, 16.07]
12.3 Baseline FEV_1 not reported	1	356	Mean Difference (Fixed, 95% CI)	4.4 [-4.05, 12.85]
13 Change in clinic PEF (L/min)	2	637	Mean Difference (IV, Fixed, 95% CI)	8.33 [2.12, 14.54]
13.1 Baseline $FEV_1 \geq 80\%$ of predicted	1	281	Mean Difference (IV, Fixed, 95% CI)	11.3 [3.84, 18.76]

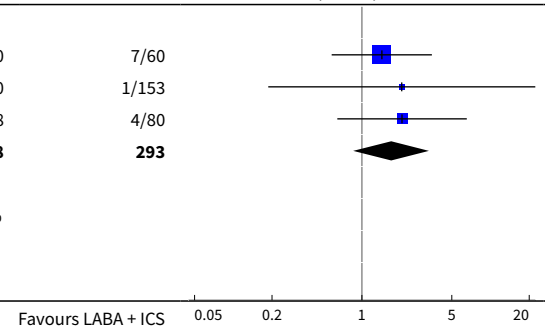
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
13.2 Baseline FEV_1 not reported	1	356	Mean Difference (IV, Fixed, 95% CI)	1.60 [-9.63, 12.83]
14 Change in morning PEF (% predicted) at endpoint	1		Mean Difference (IV, Random, 95% CI)	Totals not selected
14.1 Baseline FEV_1 ≥ 80% of predicted	1		Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]
15 Change in evening PEF (% predicted) at endpoint	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
15.1 Baseline FEV_1 ≥ 80% of predicted	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
16 Change in % of days with a peak flow variability ≥ 20%	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
16.1 Baseline FEV_1 ≥ 80% of predicted	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
17 Change in daytime asthma symptom score (mean over study period)	3	329	Std. Mean Difference (IV, Fixed, 95% CI)	0.01 [-0.20, 0.23]
17.1 Baseline FEV_1 ≥ 80% of predicted	2	305	Std. Mean Difference (IV, Fixed, 95% CI)	0.01 [-0.21, 0.24]
17.2 Baseline FEV_1 not reported	1	24	Std. Mean Difference (IV, Fixed, 95% CI)	0.03 [-0.77, 0.84]
18 Change in nighttime asthma symptom score (mean over study period)	3	329	Std. Mean Difference (IV, Fixed, 95% CI)	0.01 [-0.20, 0.23]
18.1 Baseline FEV_1 ≥ 80% of predicted	2	305	Std. Mean Difference (IV, Fixed, 95% CI)	0.01 [-0.21, 0.24]
18.2 Baseline FEV_1 not reported	1	24	Std. Mean Difference (IV, Fixed, 95% CI)	0.00 [-0.80, 0.80]
19 Change in % of days without asthma symptoms	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
19.1 Baseline FEV_1 ≥ 80% of predicted	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
20 # daytime rescue inhalations (puffs per day; mean over study period)	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
20.1 Baseline FEV_1 not reported	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
21 # nighttime rescue inhalations (puffs per day; mean over study period)	1		Mean Difference (IV, Random, 95% CI)	Totals not selected

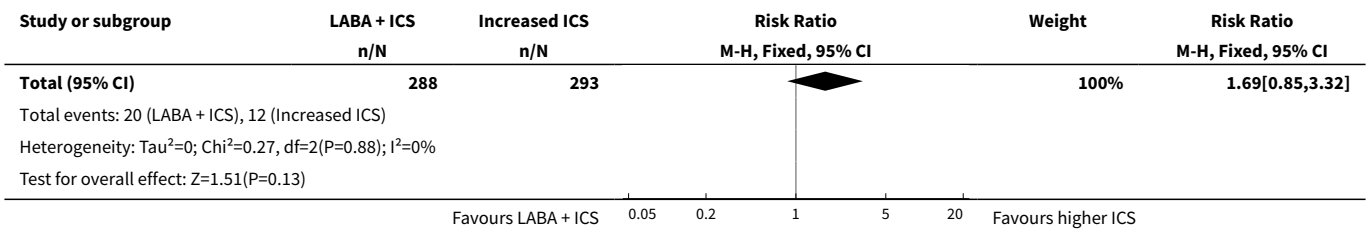
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
21.1 Baseline FEV_1 not reported	1		Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]
22 # daytime rescue inhalations at endpoint	1		puffs/d (Fixed, 95% CI)	Totals not selected
22.1 Baseline FEV_1 61%-79% of predicted	1		puffs/d (Fixed, 95% CI)	0.0 [0.0, 0.0]
23 Change in daytime rescue inhalations (puffs per day)	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
23.1 Baseline FEV_1 ≥ 80% of predicted	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
24 Change in nighttime rescue inhalations (puffs per day)	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
24.1 Baseline FEV_1 ≥ 80% of predicted	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
25 Change in number of weeks with successful asthma control	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
25.1 Baseline FEV_1 ≥ 80% of predicted	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
26 Change in % of days without salbutamol	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
26.1 Baseline FEV_1 ≥ 80% of predicted	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
27 Number of nighttime awakenings	1		Awakenings/yr (Fixed, 95% CI)	Totals not selected
27.1 Baseline FEV_1 61%-79% of predicted	1		Awakenings/yr (Fixed, 95% CI)	0.0 [0.0, 0.0]
28 Total # adverse events	6	1254	Risk Ratio (M-H, Fixed, 95% CI)	1.01 [0.92, 1.10]
28.1 Baseline FEV_1 ≥ 80% of predicted	4	863	Risk Ratio (M-H, Fixed, 95% CI)	1.04 [0.94, 1.15]
28.2 Mean baseline FEV_1 not reported	2	391	Risk Ratio (M-H, Fixed, 95% CI)	0.94 [0.79, 1.11]
29 # participants with oral candidiasis	2	182	Risk Ratio (M-H, Fixed, 95% CI)	1.01 [0.15, 6.85]
29.1 Mean baseline FEV_1 ≥ 80% of predicted	2	182	Risk Ratio (M-H, Fixed, 95% CI)	1.01 [0.15, 6.85]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
30 # participants with headache	5	1230	Risk Ratio (M-H, Fixed, 95% CI)	1.13 [0.85, 1.50]
30.1 Baseline FEV_1 ≥ 80% of predicted	4	863	Risk Ratio (M-H, Fixed, 95% CI)	1.08 [0.80, 1.46]
30.2 Mean baseline FEV_1 not reported	1	367	Risk Ratio (M-H, Fixed, 95% CI)	1.44 [0.66, 3.16]
31 # participants with vomiting	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
31.1 Baseline FEV_1 ≥ 80% of predicted	1		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
32 # participants with cold	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
32.1 Mean baseline FEV_1 ≥ 80% of predicted	1		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
33 # participants with upper respiratory tract infection	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
33.1 Baseline FEV_1 ≥ 80% of predicted	1		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
34 Linear growth	2		Mean Difference (Fixed, 95% CI)	1.21 [0.72, 1.70]
35 Deaths	1		Risk Difference (M-H, Fixed, 95% CI)	Totals not selected
35.1 Baseline FEV_1 ≥ 80% of predicted	1		Risk Difference (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]

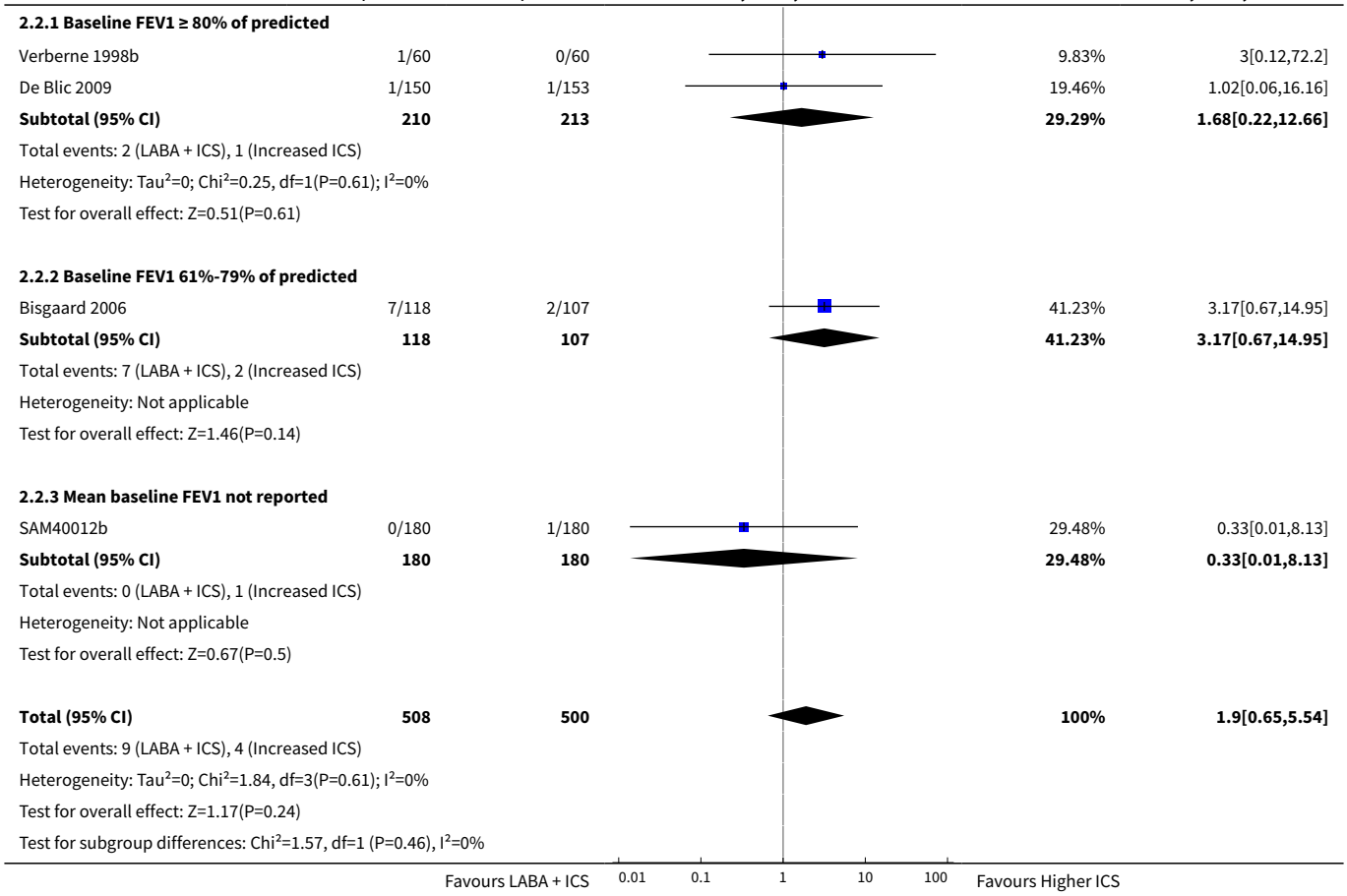
Analysis 2.1. Comparison 2 LABA + ICS versus placebo + higher dose of ICS, Outcome 1 # participants with exacerbations requiring oral steroids.

Study or subgroup	LABA + ICS n/N	Increased ICS n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
2.1.1 Baseline FEV1 ≥ 80% of predicted					
Verberne 1998b	10/60	7/60		58.63%	1.43[0.58,3.5]
De Blic 2009	2/150	1/153		8.29%	2.04[0.19,22.26]
Vaessen-Verberne 2010	8/78	4/80		33.08%	2.05[0.64,6.54]
Subtotal (95% CI)	**288**	**293**		**100%**	**1.69[0.85,3.32]**
Total events: 20 (LABA + ICS), 12 (Increased ICS)					
Heterogeneity: Tau^2=0; Chi^2=0.27, df=2(P=0.88); I^2=0%					
Test for overall effect: Z=1.51(P=0.13)					

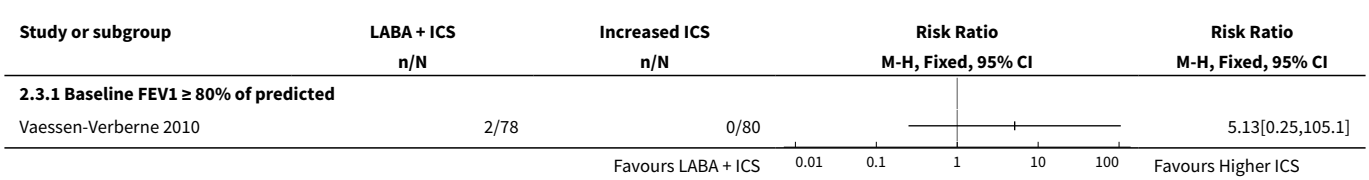




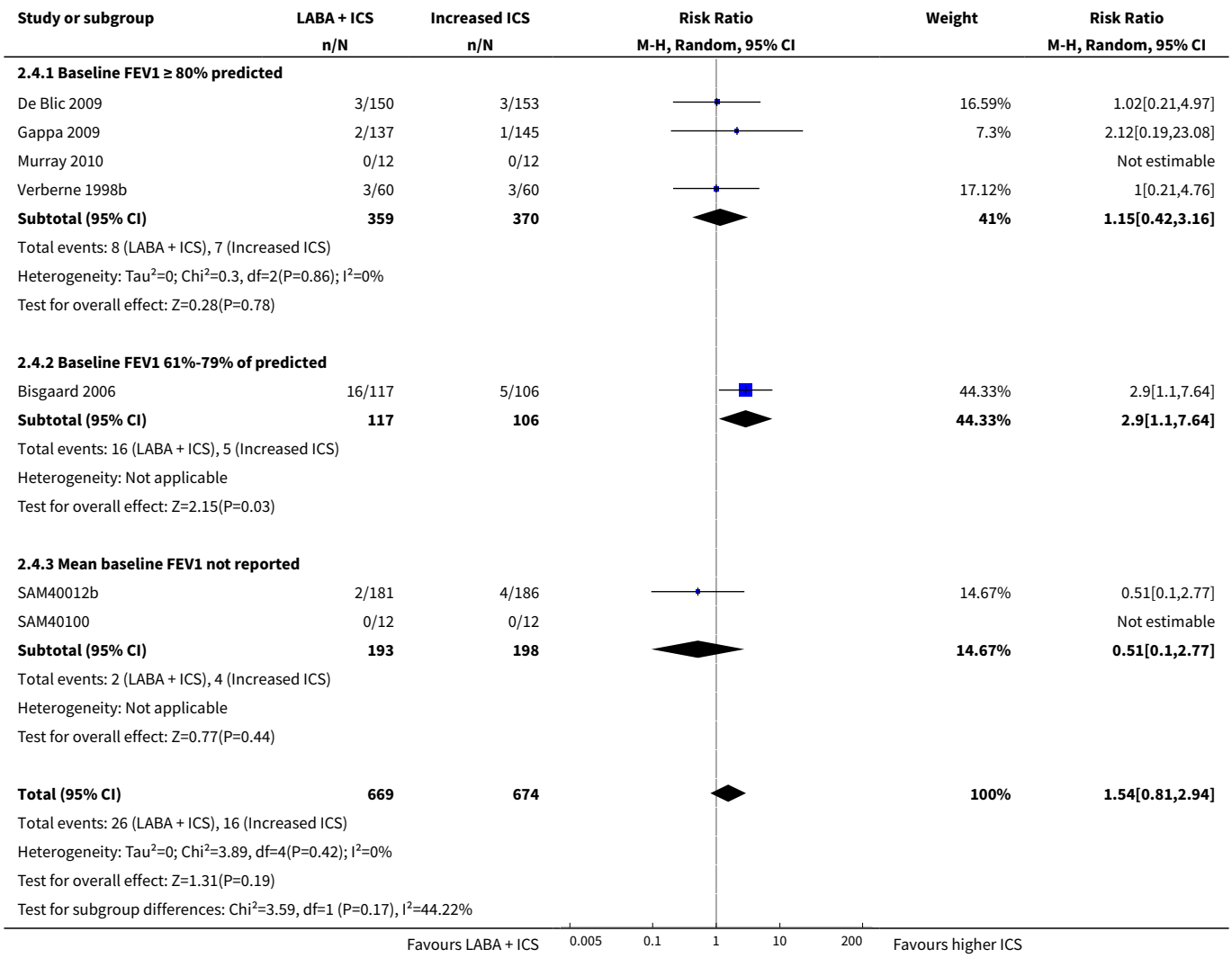
Analysis 2.2. Comparison 2 LABA + ICS versus placebo + higher dose of ICS, Outcome 2 # participants with exacerbations requiring hospitalisation.



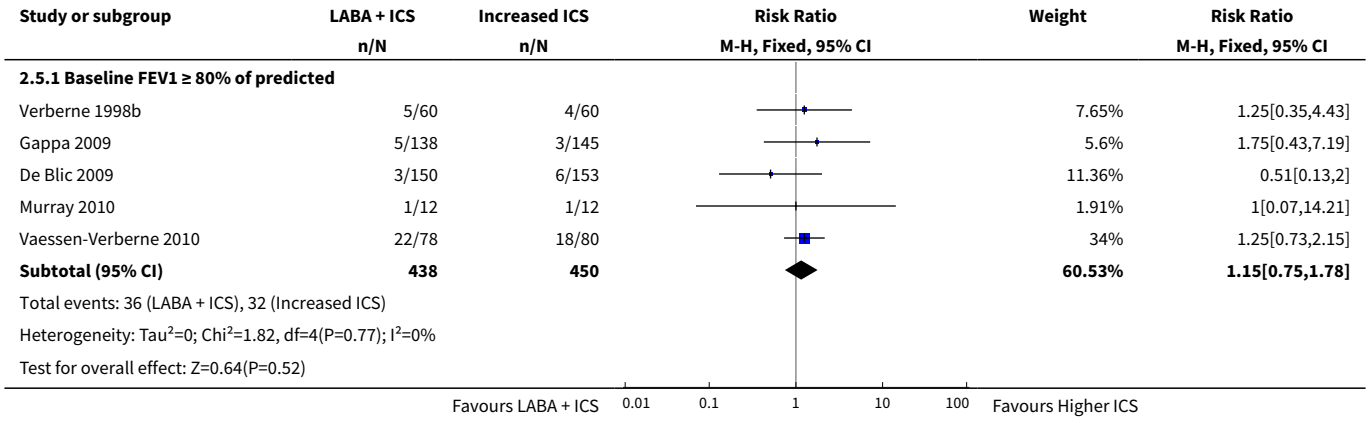
Analysis 2.3. Comparison 2 LABA + ICS versus placebo + higher dose of ICS, Outcome 3 # participants with exacerbations requiring urgent care visit.

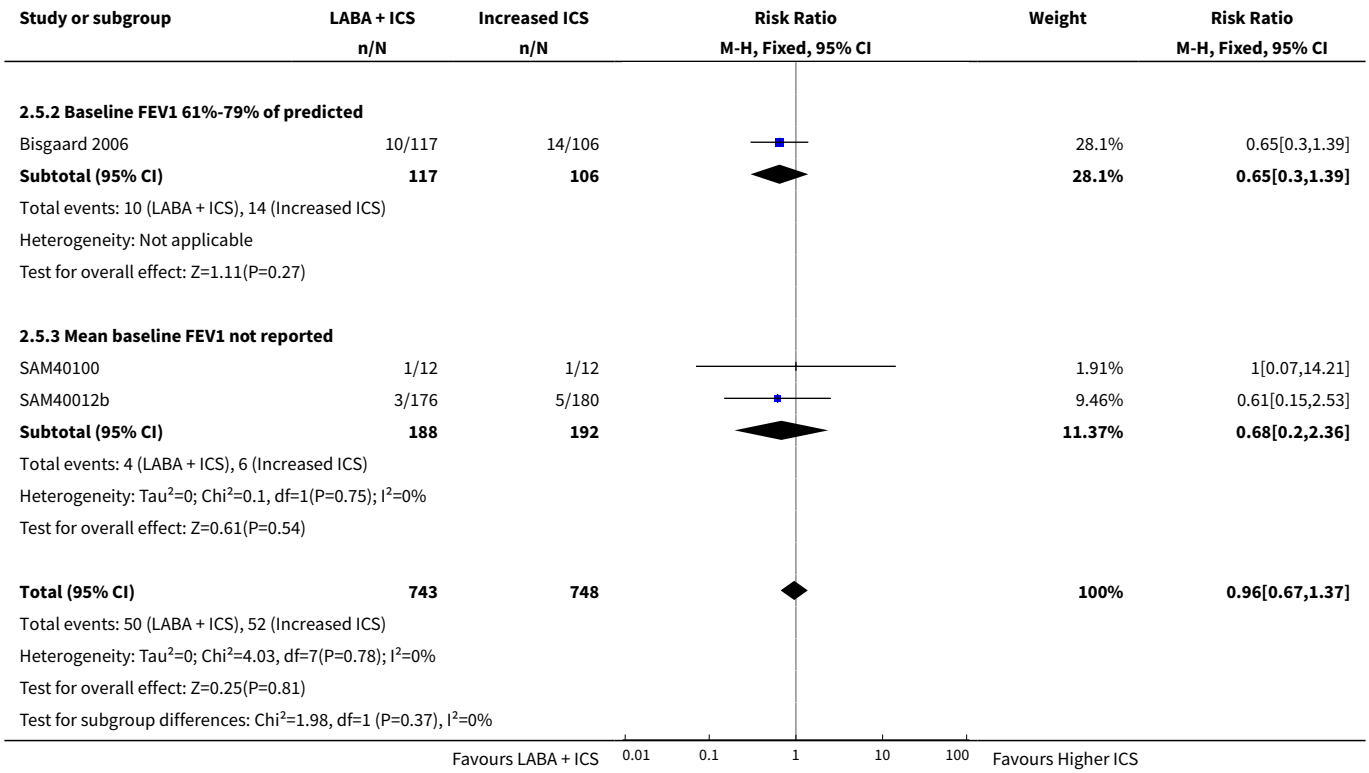


Analysis 2.4. Comparison 2 LABA + ICS versus placebo + higher dose of ICS, Outcome 4 Serious adverse events.

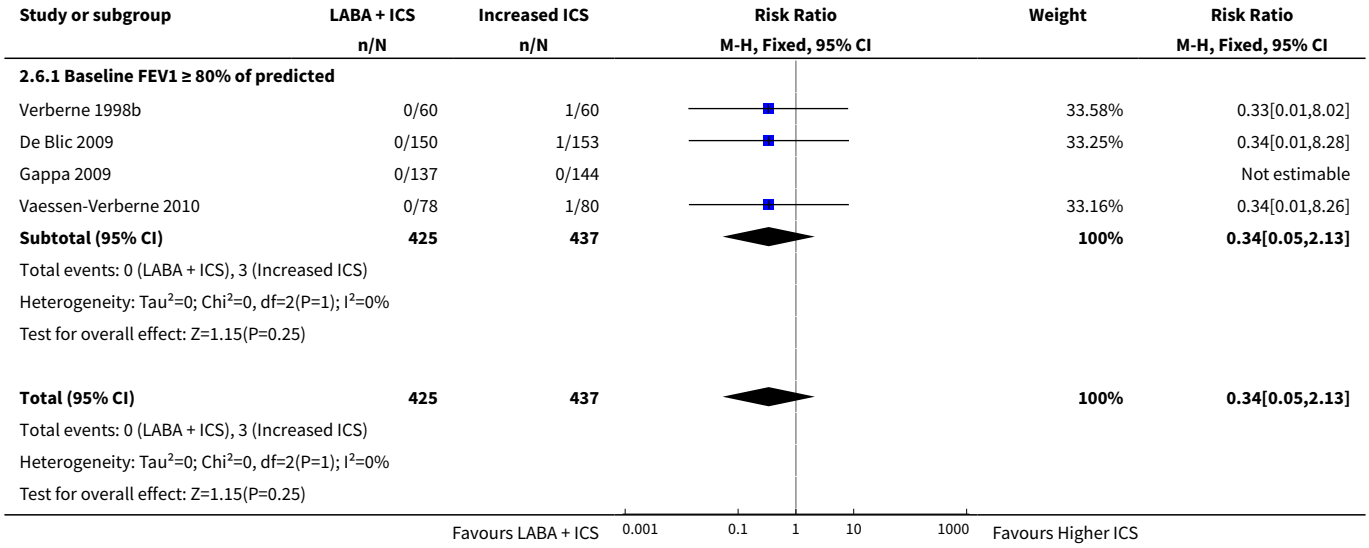


Analysis 2.5. Comparison 2 LABA + ICS versus placebo + higher dose of ICS, Outcome 5 Total # withdrawals.

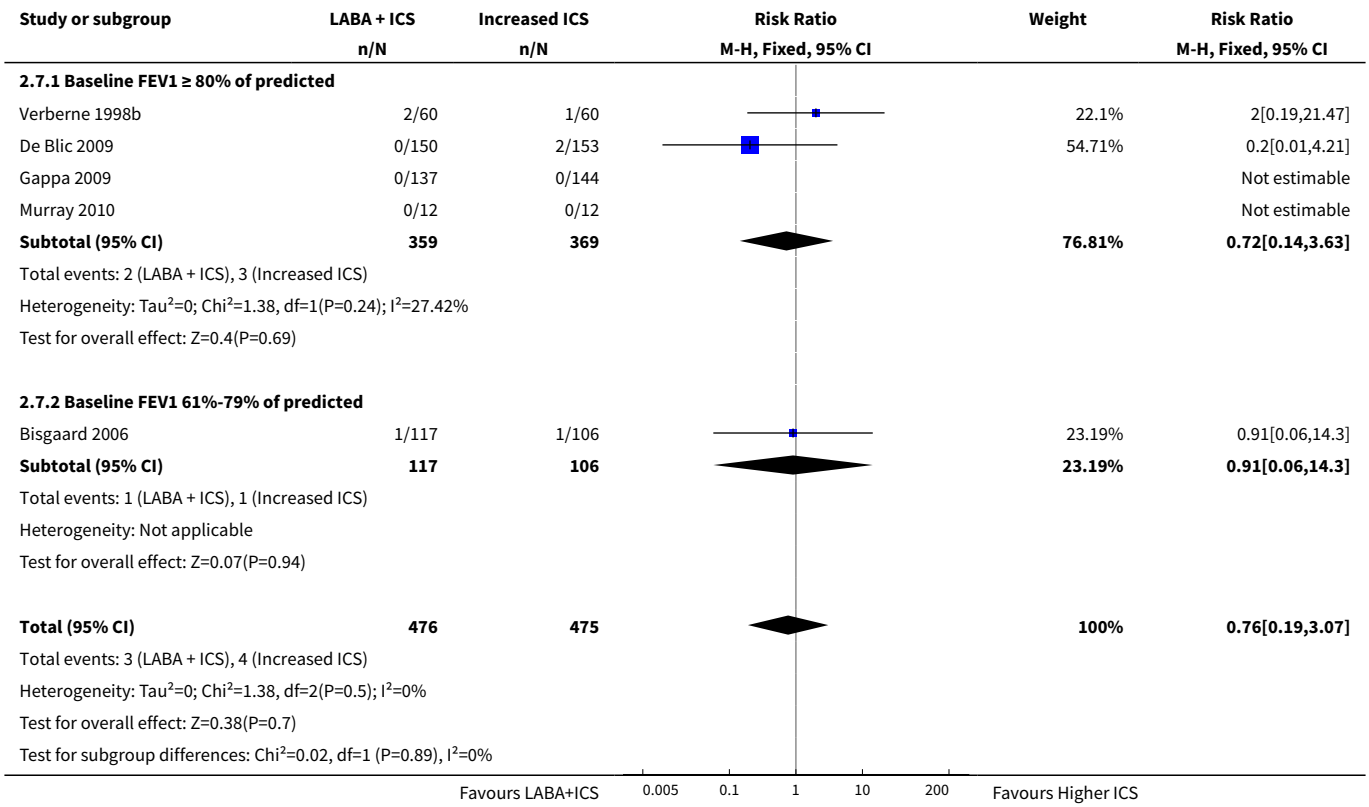




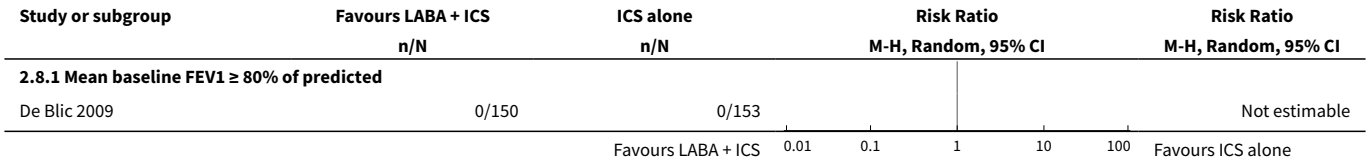
Analysis 2.6. Comparison 2 LABA + ICS versus placebo + higher dose of ICS, Outcome 6 # withdrawals due to poor asthma control or exacerbation.



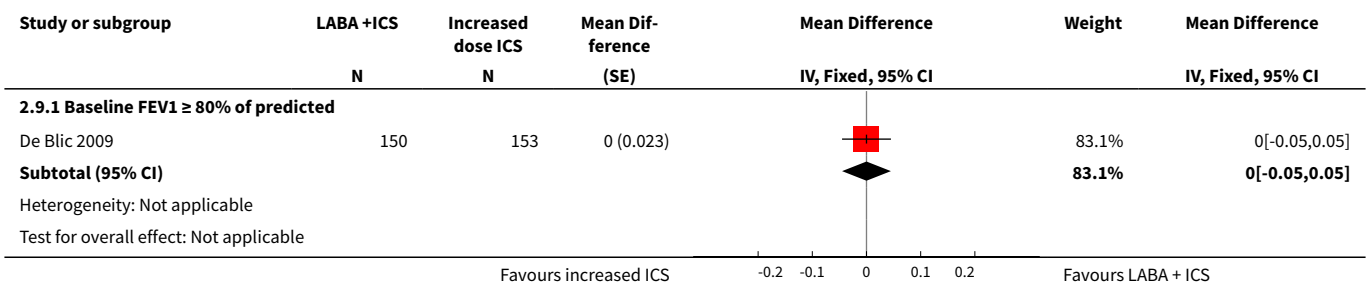
Analysis 2.7. Comparison 2 LABA + ICS versus placebo + higher dose of ICS, Outcome 7 # withdrawals due to adverse events.

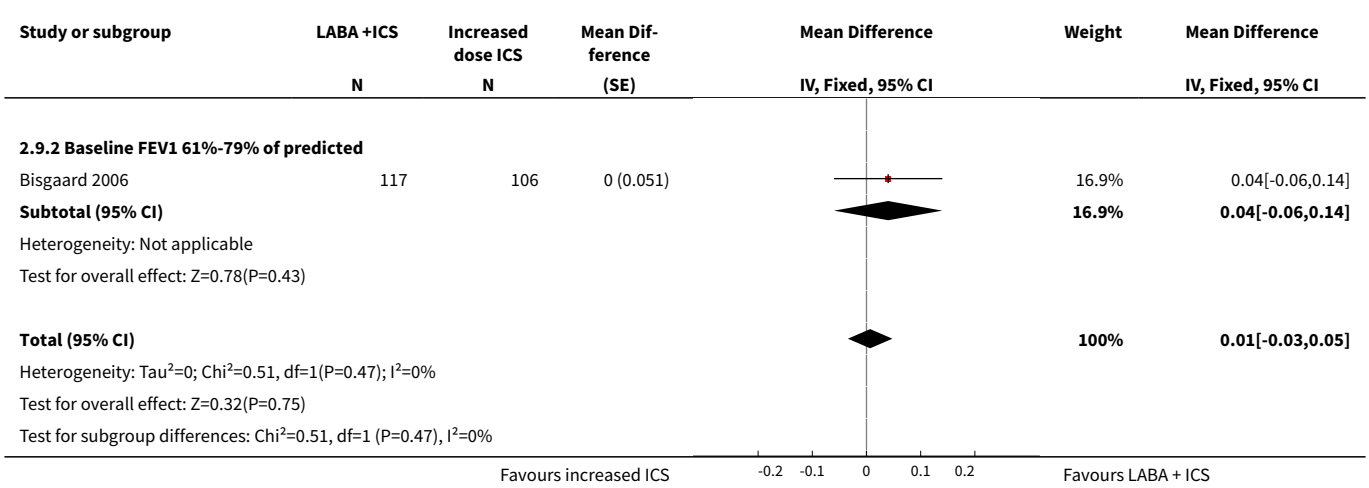


Analysis 2.8. Comparison 2 LABA + ICS versus placebo + higher dose of ICS, Outcome 8 # withdrawals due to serious non-respiratory event.

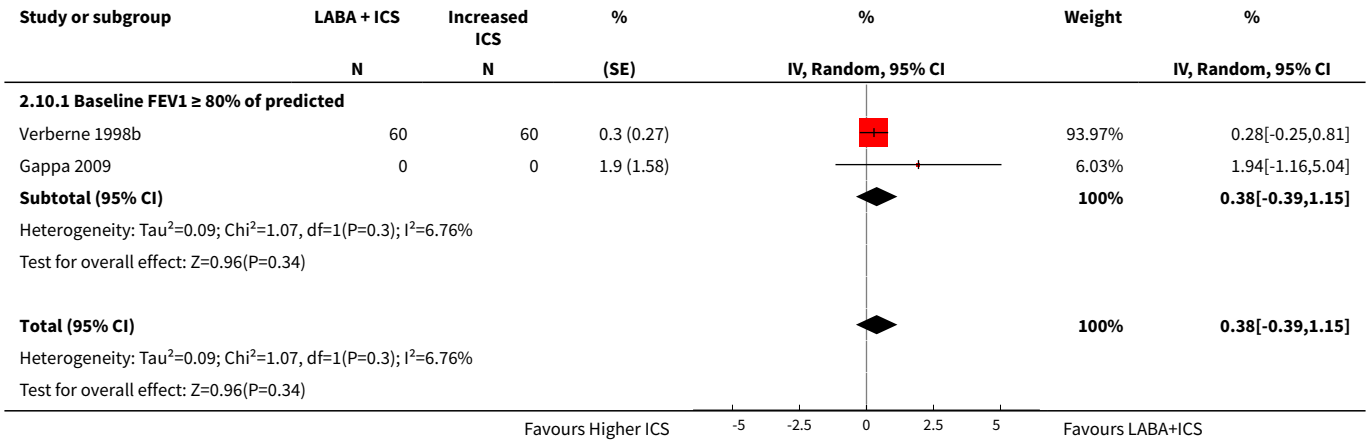


Analysis 2.9. Comparison 2 LABA + ICS versus placebo + higher dose of ICS, Outcome 9 Change in FEV_1 (L) at endpoint.

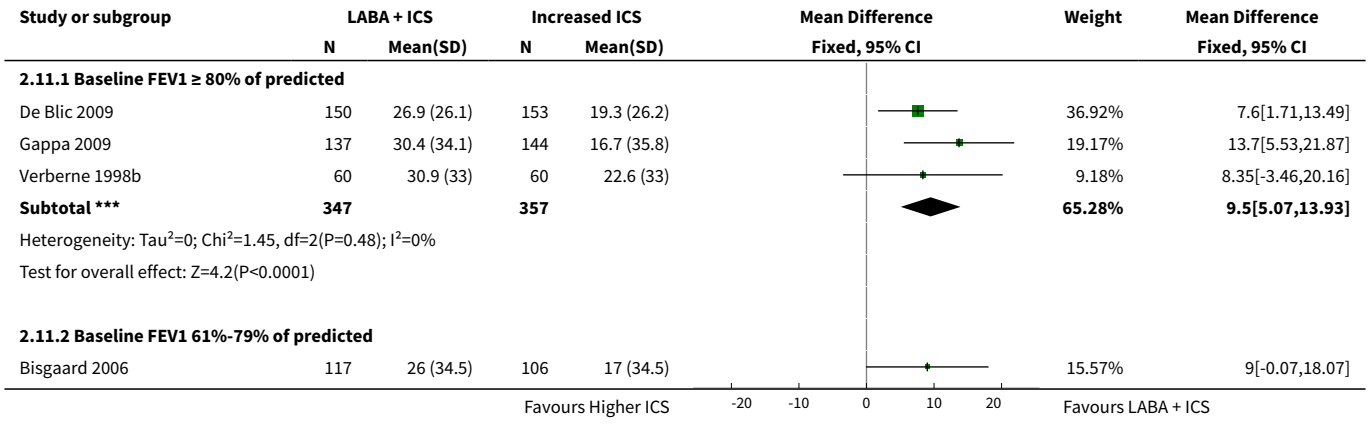


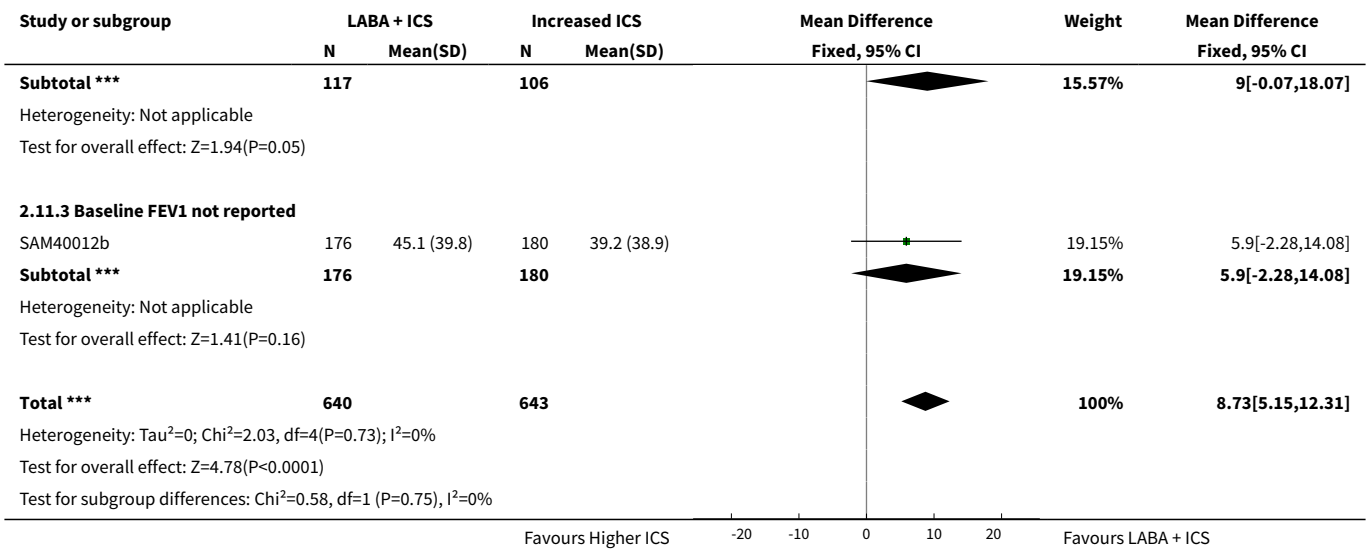


Analysis 2.10. Comparison 2 LABA + ICS versus placebo + higher dose of ICS, Outcome 10 Change in FEV_1 % predicted at endpoint.

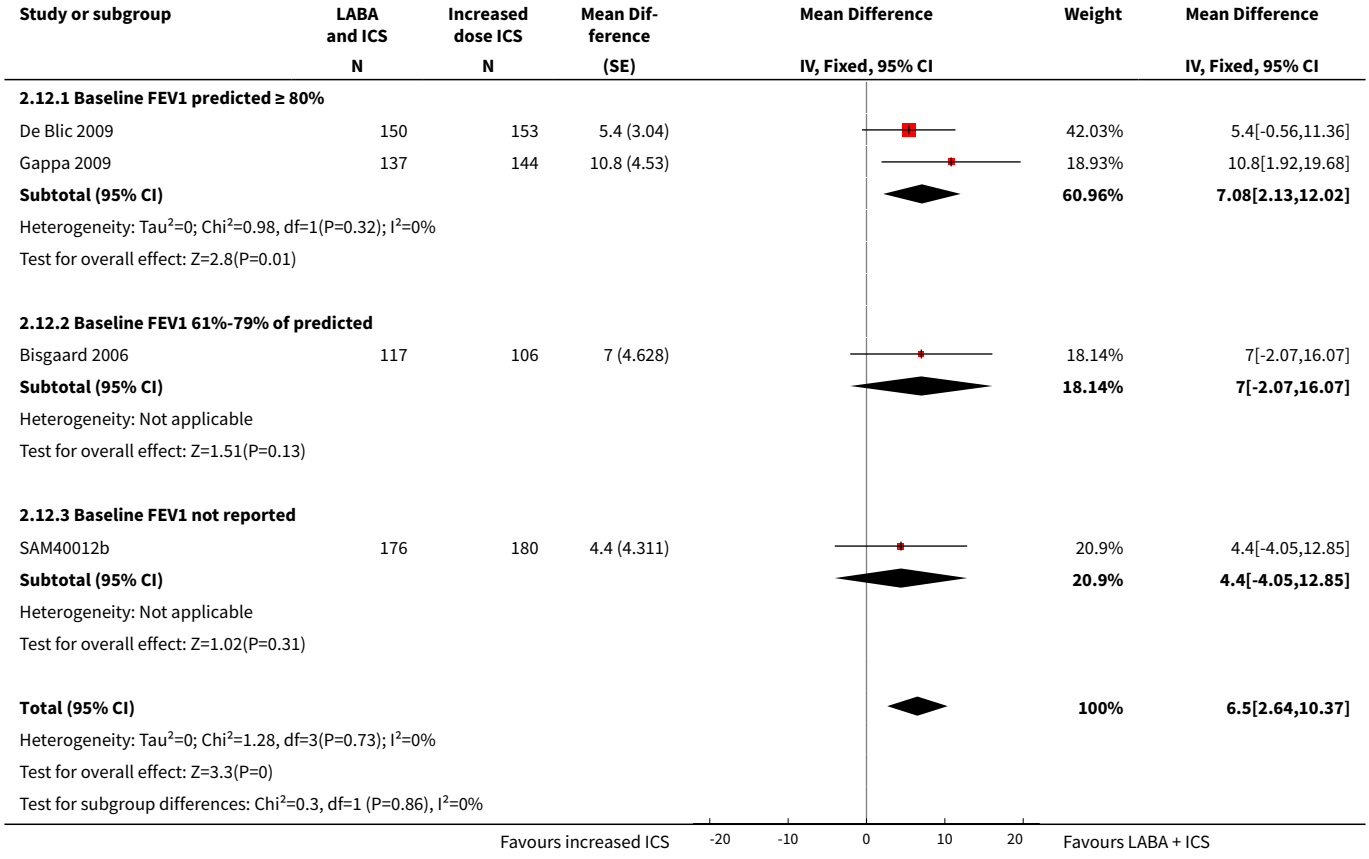


Analysis 2.11. Comparison 2 LABA + ICS versus placebo + higher dose of ICS, Outcome 11 Change in morning PEF (L/min) at endpoint.

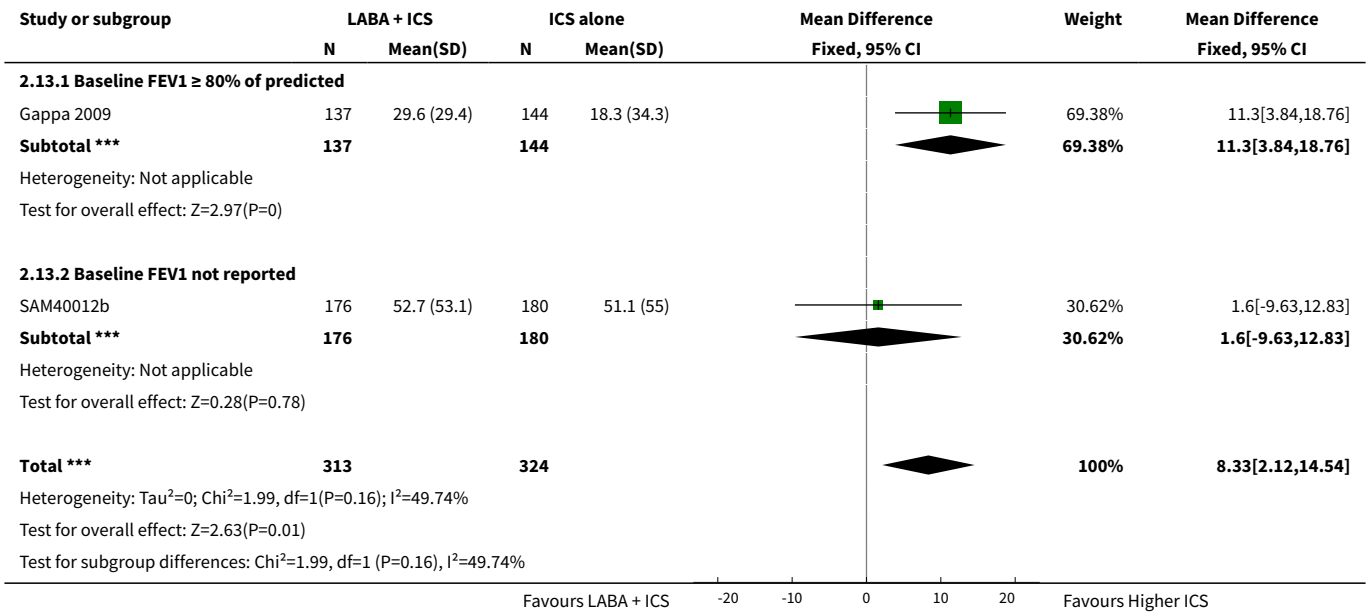




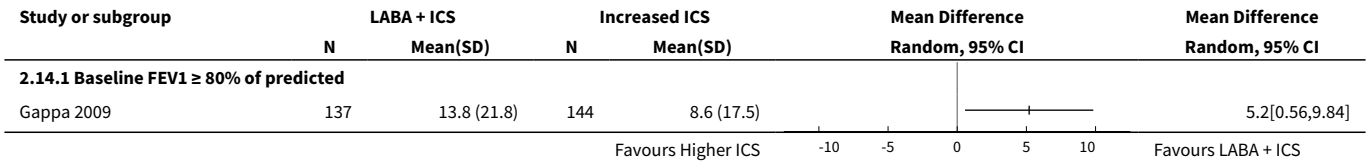
Analysis 2.12. Comparison 2 LABA + ICS versus placebo + higher dose of ICS, Outcome 12 Change in evening PEF (L/min) at endpoint.



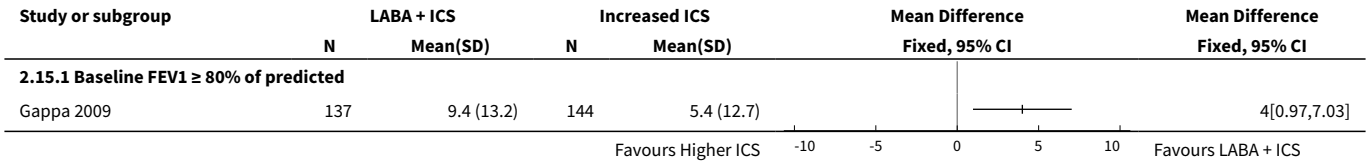
Analysis 2.13. Comparison 2 LABA + ICS versus placebo + higher dose of ICS, Outcome 13 Change in clinic PEF (L/min).



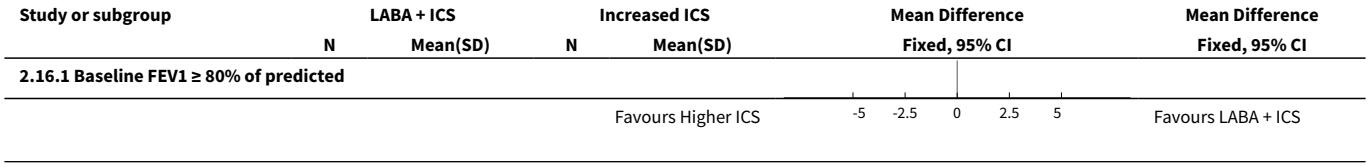
Analysis 2.14. Comparison 2 LABA + ICS versus placebo + higher dose of ICS, Outcome 14 Change in morning PEF (% predicted) at endpoint.



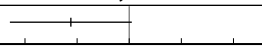
Analysis 2.15. Comparison 2 LABA + ICS versus placebo + higher dose of ICS, Outcome 15 Change in evening PEF (% predicted) at endpoint.



Analysis 2.16. Comparison 2 LABA + ICS versus placebo + higher dose of ICS, Outcome 16 Change in % of days with a peak flow variability ≥ 20%.



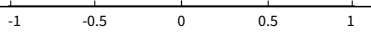
Study or subgroup	LABA + ICS N	LABA + ICS Mean(SD)	Increased ICS N	Increased ICS Mean(SD)	Mean Difference Fixed, 95% CI	Mean Difference Fixed, 95% CI
Gappa 2009	137	-4.7 (12.5)	144	-1.9 (12.5)		-2.8[-5.72,0.12]



Favours Higher ICS | Favours LABA + ICS

Analysis 2.17. Comparison 2 LABA + ICS versus placebo + higher dose of ICS, Outcome 17 Change in daytime asthma symptom score (mean over study period).

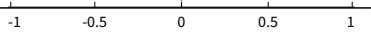
Study or subgroup	LABA + ICS N	LABA + ICS Mean(SD)	ICS alone N	ICS alone Mean(SD)	Std. Mean Difference Fixed, 95% CI	Weight	Std. Mean Difference Fixed, 95% CI
2.17.1 Baseline FEV1 ≥ 80% of predicted							
Gappa 2009	137	-0.8 (0.8)	144	-0.8 (0.8)		85.43%	0[-0.23,0.23]
Murray 2010	12	-0.3 (0.7)	12	-0.5 (0.6)		7.27%	0.17[-0.63,0.97]
Subtotal ***	**149**		**156**			**92.7%**	**0.01[-0.21,0.24]**
Heterogeneity: Tau^2=0; Chi^2=0.15, df=1(P=0.69); I^2=0%							
Test for overall effect: Z=0.11(P=0.91)							
2.17.2 Baseline FEV1 not reported							
SAM40100	12	0.5 (0.5)	12	0.4 (0.6)		7.3%	0.03[-0.77,0.84]
Subtotal ***	**12**		**12**			**7.3%**	**0.03[-0.77,0.84]**
Heterogeneity: Not applicable							
Test for overall effect: Z=0.09(P=0.93)							
Total ***	**161**		**168**			**100%**	**0.01[-0.2,0.23]**
Heterogeneity: Tau^2=0; Chi^2=0.16, df=2(P=0.92); I^2=0%							
Test for overall effect: Z=0.13(P=0.89)							
Test for subgroup differences: Chi^2=0, df=1 (P=0.96), I^2=0%							



Favours treatment | Favours control

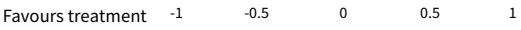
Analysis 2.18. Comparison 2 LABA + ICS versus placebo + higher dose of ICS, Outcome 18 Change in nighttime asthma symptom score (mean over study period).

Study or subgroup	LABA + ICS N	LABA + ICS Mean(SD)	ICS alone N	ICS alone Mean(SD)	Std. Mean Difference Fixed, 95% CI	Weight	Std. Mean Difference Fixed, 95% CI
2.18.1 Baseline FEV1 ≥ 80% of predicted							
Gappa 2009	137	-0.5 (0.6)	144	-0.5 (0.6)		85.43%	0[-0.23,0.23]
Murray 2010	12	-0.1 (0.3)	12	-0.1 (0.3)		7.27%	0.17[-0.63,0.97]
Subtotal ***	**149**		**156**			**92.7%**	**0.01[-0.21,0.24]**
Heterogeneity: Tau^2=0; Chi^2=0.16, df=1(P=0.69); I^2=0%							
Test for overall effect: Z=0.12(P=0.91)							
2.18.2 Baseline FEV1 not reported							
SAM40100	12	0.3 (35)	12	0.2 (0.5)		7.3%	0[-0.8,0.8]
Subtotal ***	**12**		**12**			**7.3%**	**0[-0.8,0.8]**
Heterogeneity: Tau^2=0; Chi^2=0, df=0(P<0.0001); I^2=100%							
Test for overall effect: Z=0(P=1)							
Total ***	**161**		**168**			**100%**	**0.01[-0.2,0.23]**
Heterogeneity: Tau^2=0; Chi^2=0.16, df=2(P=0.92); I^2=0%							



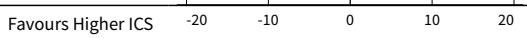
Favours treatment | Favours control

Study or subgroup	LABA + ICS N	LABA + ICS Mean(SD)	ICS alone N	ICS alone Mean(SD)	Std. Mean Difference Fixed, 95% CI	Weight	Std. Mean Difference Fixed, 95% CI
Test for overall effect: Z=0.11(P=0.91)							
Test for subgroup differences: Chi²=0, df=1 (P=0.98), I²=0%							



Analysis 2.19. Comparison 2 LABA + ICS versus placebo + higher dose of ICS, Outcome 19 Change in % of days without asthma symptoms.

Study or subgroup	LABA + ICS N	LABA + ICS Mean(SD)	Increased ICS N	Increased ICS Mean(SD)	Mean Difference Fixed, 95% CI	Mean Difference Fixed, 95% CI
2.19.1 Baseline FEV1 ≥ 80% of predicted						
Gappa 2009	137	41.5 (34.5)	144	33.3 (31.4)		8.2[0.47,15.93]



Analysis 2.20. Comparison 2 LABA + ICS versus placebo + higher dose of ICS, Outcome 20 # daytime rescue inhalations (puffs per day; mean over study period).

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
2.20.1 Baseline FEV1 not reported						
SAM40100	12	0.3 (0.5)	12	0.3 (0.3)		0.05[-0.27,0.37]

Analysis 2.21. Comparison 2 LABA + ICS versus placebo + higher dose of ICS, Outcome 21 # nighttime rescue inhalations (puffs per day; mean over study period).

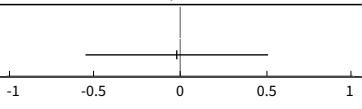
Study or subgroup	LABA + ICS N	LABA + ICS Mean(SD)	ICS alone N	ICS alone Mean(SD)	Mean Difference Random, 95% CI	Mean Difference Random, 95% CI
2.21.1 Baseline FEV1 not reported						
SAM40100	12	0.1 (0.1)	12	0.1 (0.2)		0[-0.1,0.1]

Analysis 2.22. Comparison 2 LABA + ICS versus placebo + higher dose of ICS, Outcome 22 # daytime rescue inhalations at endpoint.

Study or subgroup	LABA + ICS N	ICS alone N	puffs/d (SE)	puffs/d IV, Fixed, 95% CI	puffs/d IV, Fixed, 95% CI
2.22.1 Baseline FEV1 61%-79% of predicted					
Bisgaard 2006	117	106	0 (0.091)		0.02[-0.16,0.2]

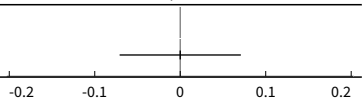
Analysis 2.23. Comparison 2 LABA + ICS versus placebo + higher dose of ICS, Outcome 23 Change in daytime rescue inhalations (puffs per day).

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
2.23.1 Baseline FEV1 ≥ 80% of predicted						
Murray 2010	12	-0.4 (0.8)	12	-0.4 (0.4)		-0.02[-0.55,0.51]



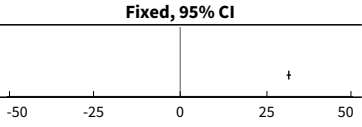
Analysis 2.24. Comparison 2 LABA + ICS versus placebo + higher dose of ICS, Outcome 24 Change in nighttime rescue inhalations (puffs per day).

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
2.24.1 Baseline FEV1 ≥ 80% of predicted						
Murray 2010	12	0.1 (0.1)	12	0.1 (0.1)		0[-0.07,0.07]



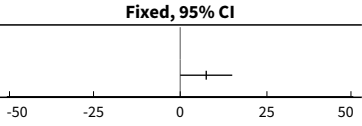
Analysis 2.25. Comparison 2 LABA + ICS versus placebo + higher dose of ICS, Outcome 25 Change in number of weeks with successful asthma control.

Study or subgroup	LABA + ICS N	LABA + ICS Mean(SD)	Increased ICS N	Increased ICS Mean(SD)	Mean Difference Fixed, 95% CI	Mean Difference Fixed, 95% CI
2.25.1 Baseline FEV1 ≥ 80% of predicted						
Gappa 2009	137	34 (2.7)	144	2.7 (2.7)		31.3[30.67,31.93]



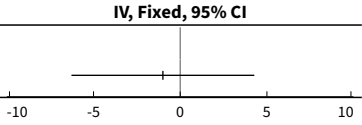
Analysis 2.26. Comparison 2 LABA + ICS versus placebo + higher dose of ICS, Outcome 26 Change in % of days without salbutamol.

Study or subgroup	LABA + ICS N	LABA + ICS Mean(SD)	Increased ICS N	Increased ICS Mean(SD)	Mean Difference Fixed, 95% CI	Mean Difference Fixed, 95% CI
2.26.1 Baseline FEV1 ≥ 80% of predicted						
Gappa 2009	137	39.9 (33.3)	144	32.4 (30.7)		7.5[0,15]

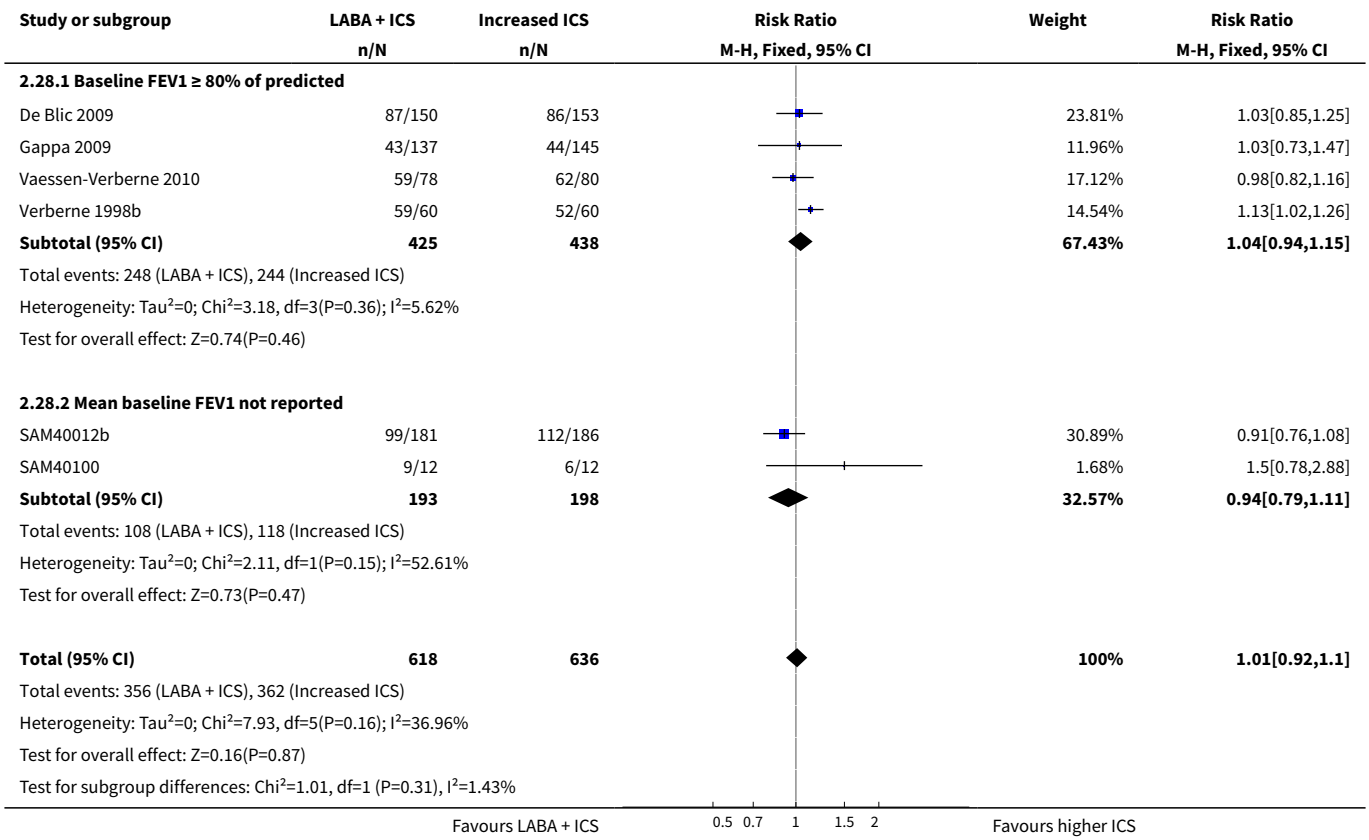


Analysis 2.27. Comparison 2 LABA + ICS versus placebo + higher dose of ICS, Outcome 27 Number of nighttime awakenings.

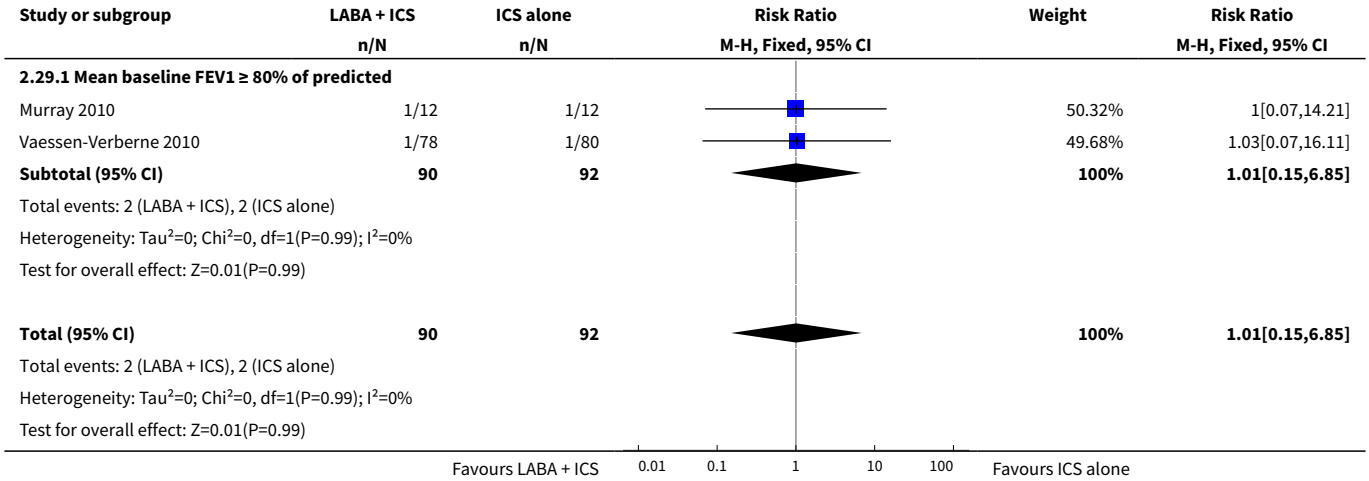
Study or subgroup	LABA + ICS N	ICS alone N	Awakenings/yr (SE)	Awakenings/yr IV, Fixed, 95% CI	Awakenings/yr IV, Fixed, 95% CI
2.27.1 Baseline FEV1 61%-79% of predicted					
Bisgaard 2006	117	106	-1 (2.69)		-1[-6.27,4.27]



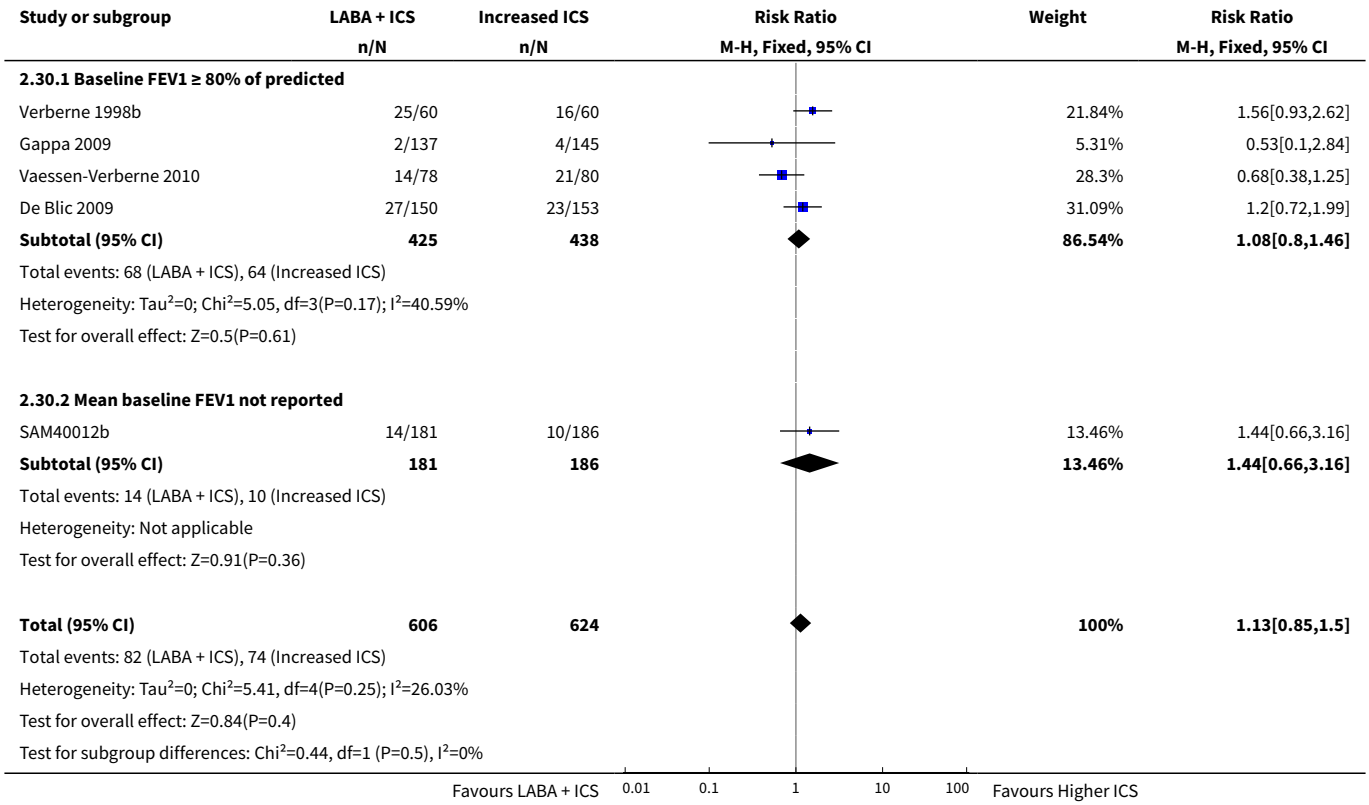
Analysis 2.28. Comparison 2 LABA + ICS versus placebo + higher dose of ICS, Outcome 28 Total # adverse events.



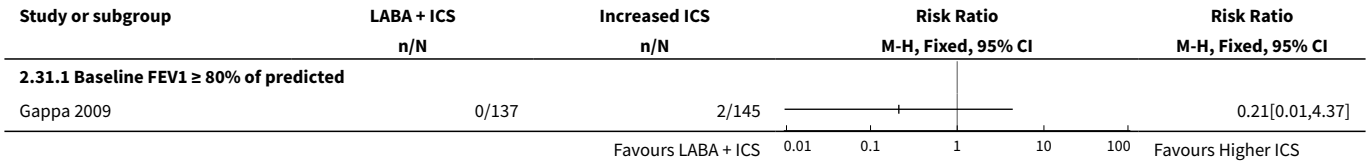
Analysis 2.29. Comparison 2 LABA + ICS versus placebo + higher dose of ICS, Outcome 29 # participants with oral candidiasis.



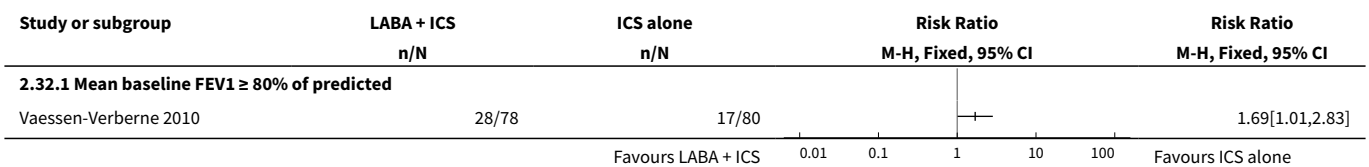
Analysis 2.30. Comparison 2 LABA + ICS versus placebo + higher dose of ICS, Outcome 30 # participants with headache.



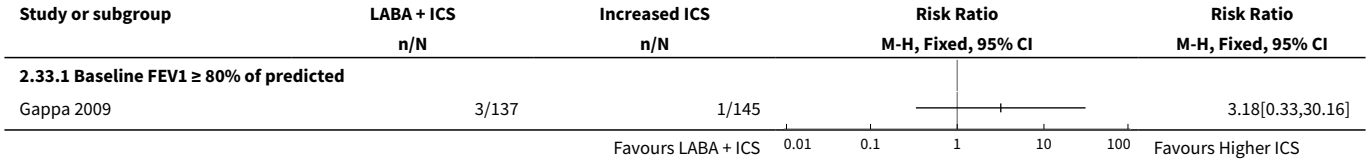
Analysis 2.31. Comparison 2 LABA + ICS versus placebo + higher dose of ICS, Outcome 31 # participants with vomiting.



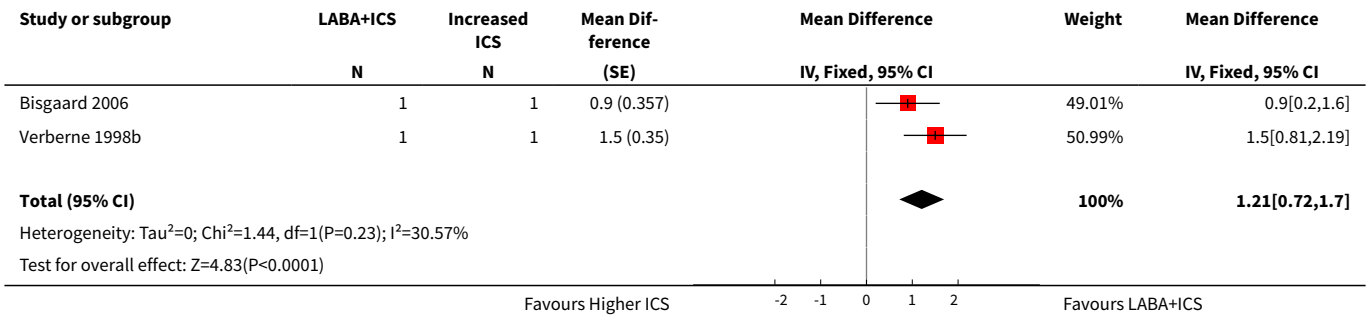
Analysis 2.32. Comparison 2 LABA + ICS versus placebo + higher dose of ICS, Outcome 32 # participants with cold.



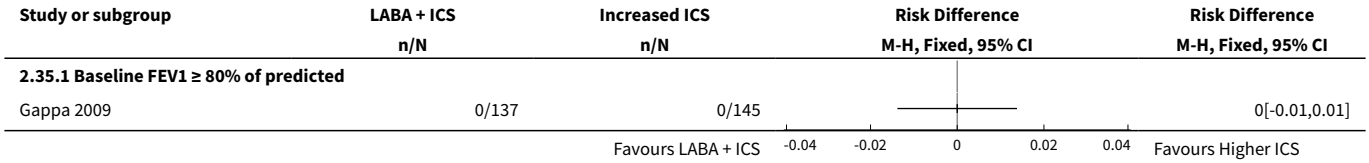
Analysis 2.33. Comparison 2 LABA + ICS versus placebo + higher dose of ICS, Outcome 33 # participants with upper respiratory tract infection.



Analysis 2.34. Comparison 2 LABA + ICS versus placebo + higher dose of ICS, Outcome 34 Linear growth.



Analysis 2.35. Comparison 2 LABA + ICS versus placebo + higher dose of ICS, Outcome 35 Deaths.



Comparison 3. Subgroup analyses (comparison 01: LABA + ICS vs same dose of ICS)

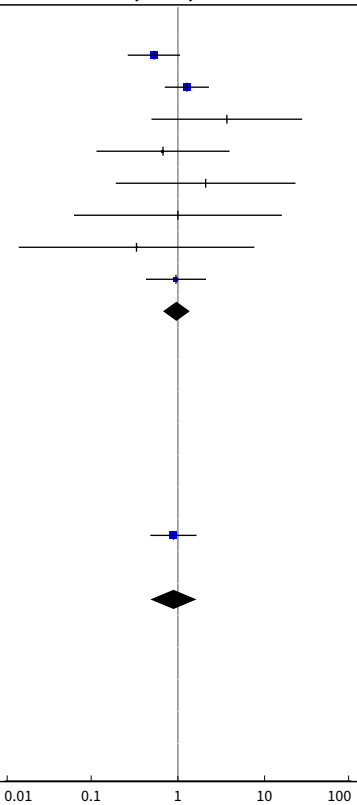
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 # participants with exacerbations requiring oral steroids by dose of ICS in both groups	12	1669	Risk Ratio (M-H, Fixed, 95% CI)	0.95 [0.70, 1.28]
1.1 Low dose of ICS (≤ 400 µg/d of BDP-eq)	8	1376	Risk Ratio (M-H, Fixed, 95% CI)	0.96 [0.67, 1.37]
1.2 Moderate dose of ICS (401 to 800 µg/d of BDP-eq)	3	270	Risk Ratio (M-H, Fixed, 95% CI)	0.89 [0.48, 1.64]
1.3 High dose of ICS (> 800 µg/d of BDP-eq)	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]

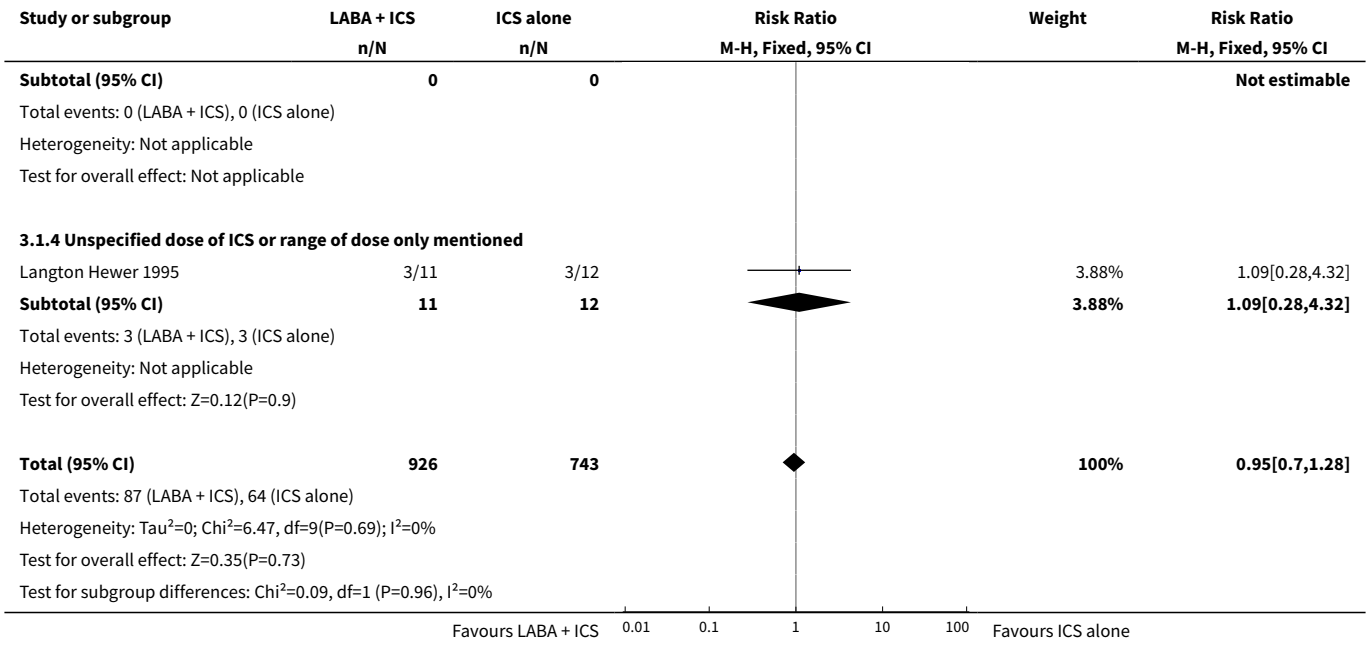
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.4 Unspecified dose of ICS or range of dose only mentioned	1	23	Risk Ratio (M-H, Fixed, 95% CI)	1.09 [0.28, 4.32]
2 # participants with exacerbations requiring oral steroids by whether LABA dose is usual or higher than usual	12	1669	Risk Ratio (M-H, Fixed, 95% CI)	0.95 [0.70, 1.28]
2.1 LABA at usual dose	11	1646	Risk Ratio (M-H, Fixed, 95% CI)	0.94 [0.69, 1.28]
2.2 LABA at higher than usual dose	1	23	Risk Ratio (M-H, Fixed, 95% CI)	1.09 [0.28, 4.32]
3 # participants with exacerbations requiring oral steroids by type of LABA	12	1669	Risk Ratio (M-H, Fixed, 95% CI)	0.95 [0.70, 1.28]
3.1 Formoterol	4	591	Risk Ratio (M-H, Fixed, 95% CI)	0.89 [0.58, 1.39]
3.2 Salmeterol	8	1078	Risk Ratio (M-H, Fixed, 95% CI)	1.00 [0.66, 1.51]
4 # participants with exacerbations requiring oral steroids by single inhaler or separate inhalers for LABA and ICS	12	1669	Risk Ratio (M-H, Fixed, 95% CI)	0.95 [0.70, 1.28]
4.1 Single inhaler	6	1227	Risk Ratio (M-H, Fixed, 95% CI)	0.99 [0.66, 1.47]
4.2 Separate inhaler	6	442	Risk Ratio (M-H, Fixed, 95% CI)	0.90 [0.57, 1.42]
5 # participants with exacerbations requiring oral steroids by trial duration	12	1669	Risk Ratio (M-H, Fixed, 95% CI)	0.95 [0.70, 1.28]
5.1 ≤ 16 weeks	10	1526	Risk Ratio (M-H, Fixed, 95% CI)	0.90 [0.65, 1.25]
5.2 ≥ 24 weeks	2	143	Risk Ratio (M-H, Fixed, 95% CI)	1.22 [0.59, 2.52]
6 # participants with exacerbations requiring oral steroids by whether funded by producers of LABA	12	1669	Risk Ratio (M-H, Fixed, 95% CI)	0.95 [0.70, 1.28]
6.1 Charity/grant agency funded	2	49	Risk Ratio (M-H, Fixed, 95% CI)	1.83 [0.60, 5.56]
6.2 Funded by manufacturers of LABA	9	1580	Risk Ratio (M-H, Fixed, 95% CI)	0.90 [0.66, 1.23]
6.3 Unknown funding source	1	40	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
7 # participants with exacerbations requiring systemic steroids by publication status	12	1669	Risk Ratio (M-H, Fixed, 95% CI)	0.95 [0.70, 1.28]
7.1 Published as full-text papers	10	1439	Risk Ratio (M-H, Fixed, 95% CI)	0.97 [0.69, 1.37]
7.2 Not published as full-text papers	2	230	Risk Ratio (M-H, Fixed, 95% CI)	0.89 [0.48, 1.64]
8 # participants with exacerbations requiring systemic steroids by blinding of study	12	1669	Risk Ratio (M-H, Fixed, 95% CI)	0.95 [0.70, 1.28]
8.1 Double-blinded studies	12	1669	Risk Ratio (M-H, Fixed, 95% CI)	0.95 [0.70, 1.28]
8.2 Open-label studies	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]

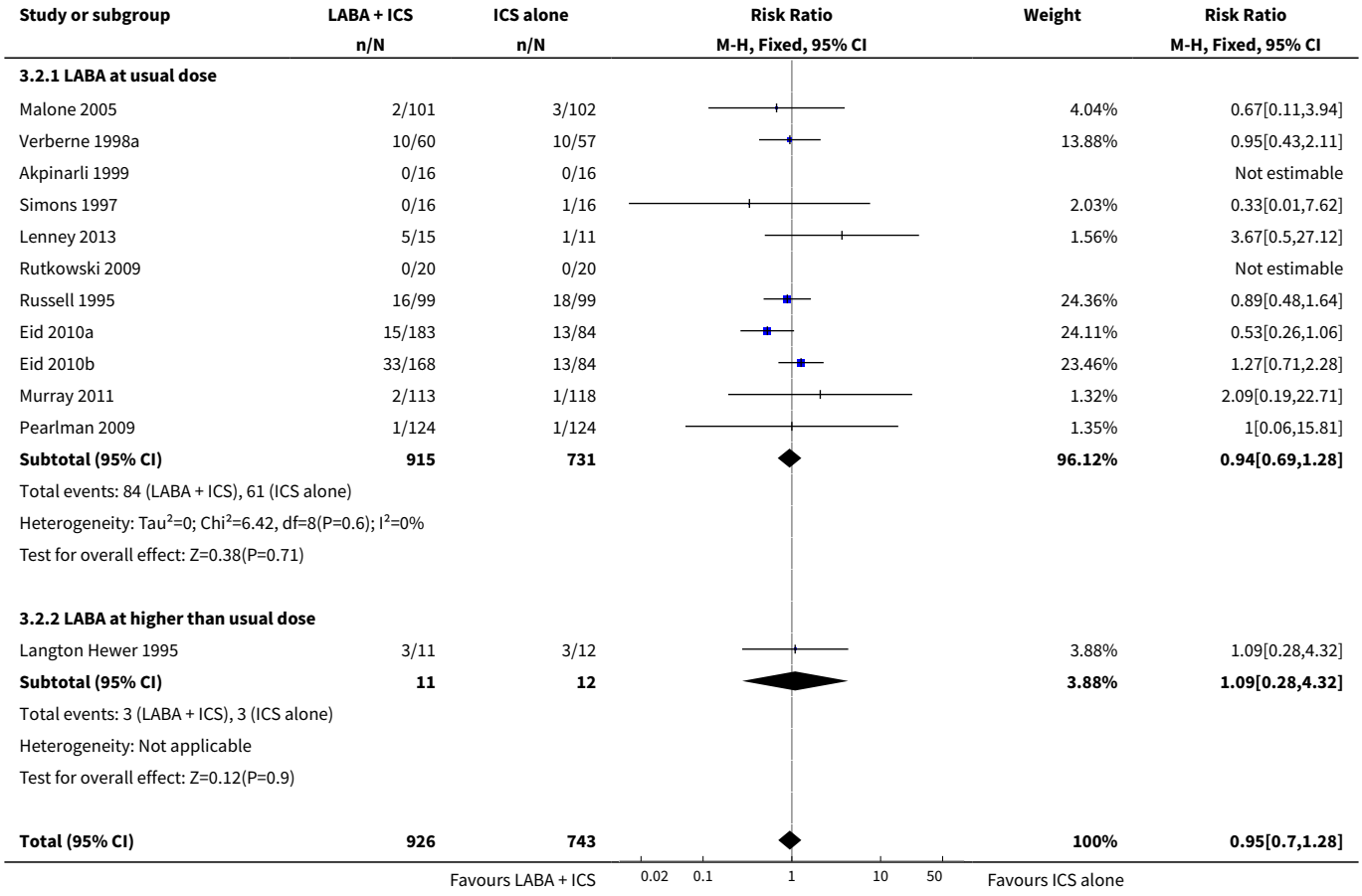
Analysis 3.1. Comparison 3 Subgroup analyses (comparison 01: LABA + ICS vs same dose of ICS), Outcome 1 # participants with exacerbations requiring oral steroids by dose of ICS in both groups.

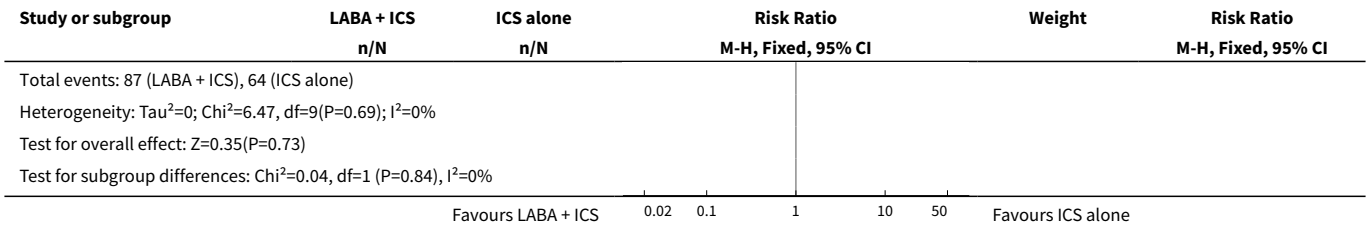
Study or subgroup	LABA + ICS n/N	ICS alone n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
3.1.1 Low dose of ICS (≤ 400 µg/d of BDP-eq)					
Eid 2010a	15/183	13/84		24.11%	0.53[0.26,1.06]
Eid 2010b	33/168	13/84		23.46%	1.27[0.71,2.28]
Lenney 2013	5/15	1/11		1.56%	3.67[0.5,27.12]
Malone 2005	2/101	3/102		4.04%	0.67[0.11,3.94]
Murray 2011	2/113	1/118		1.32%	2.09[0.19,22.71]
Pearlman 2009	1/124	1/124		1.35%	1[0.06,15.81]
Simons 1997	0/16	1/16		2.03%	0.33[0.01,7.62]
Verberne 1998a	10/60	10/57		13.88%	0.95[0.43,2.11]
Subtotal (95% CI)	**780**	**596**		**71.76%**	**0.96[0.67,1.37]**
Total events: 68 (LABA + ICS), 43 (ICS alone)					
Heterogeneity: Tau^2=0; Chi^2=6.4, df=7(P=0.49); I^2=0%					
Test for overall effect: Z=0.22(P=0.83)					
3.1.2 Moderate dose of ICS (401 to 800 µg/d of BDP-eq)					
Akpinarli 1999	0/16	0/16			Not estimable
Russell 1995	16/99	18/99		24.36%	0.89[0.48,1.64]
Rutkowski 2009	0/20	0/20			Not estimable
Subtotal (95% CI)	**135**	**135**		**24.36%**	**0.89[0.48,1.64]**
Total events: 16 (LABA + ICS), 18 (ICS alone)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.38(P=0.71)					
3.1.3 High dose of ICS (> 800 µg/d of BDP-eq)					



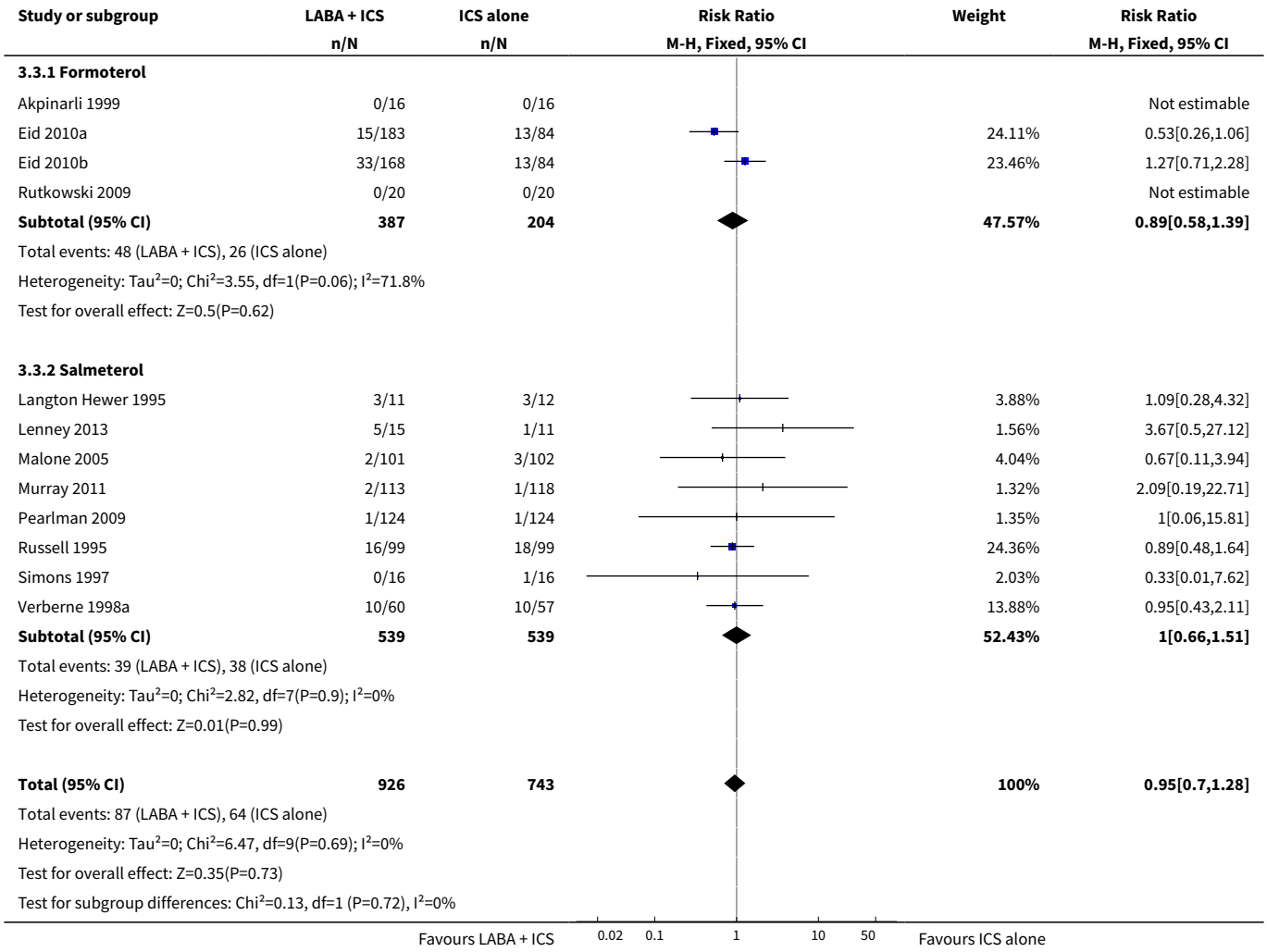


Analysis 3.2. Comparison 3 Subgroup analyses (comparison 01: LABA + ICS vs same dose of ICS), Outcome 2 # participants with exacerbations requiring oral steroids by whether LABA dose is usual or higher than usual.



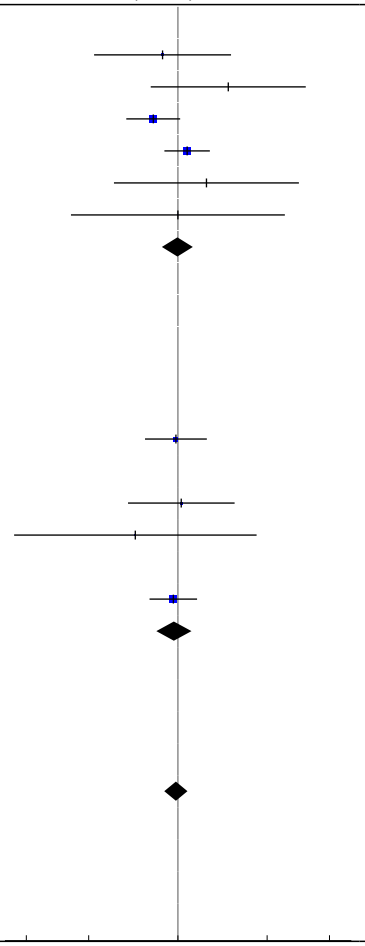


Analysis 3.3. Comparison 3 Subgroup analyses (comparison 01: LABA + ICS vs same dose of ICS), Outcome 3 # participants with exacerbations requiring oral steroids by type of LABA.



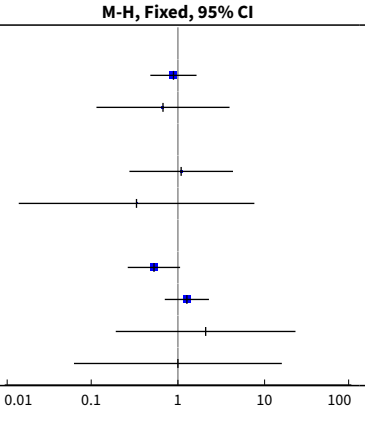
Analysis 3.4. Comparison 3 Subgroup analyses (comparison 01: LABA + ICS vs same dose of ICS), Outcome 4 # participants with exacerbations requiring oral steroids by single inhaler or separate inhalers for LABA and ICS.

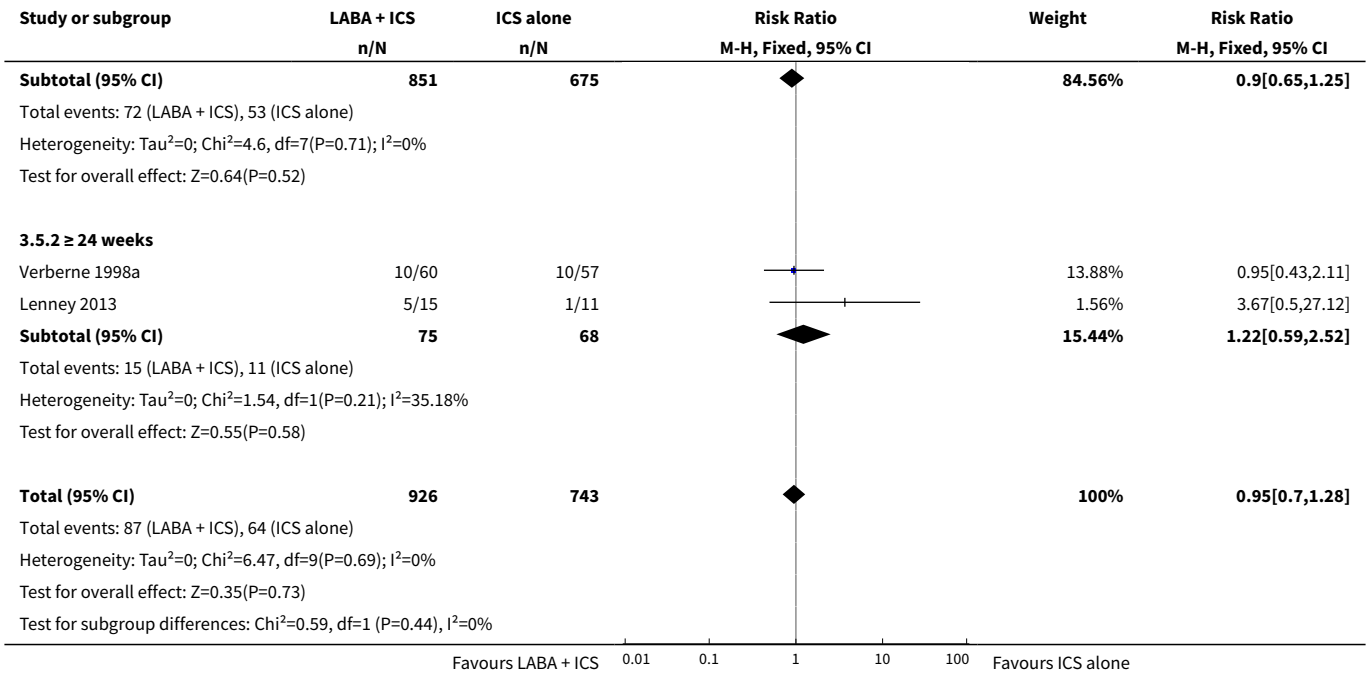
Study or subgroup	LABA + ICS n/N	ICS alone n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
3.4.1 Single inhaler					
Malone 2005	2/101	3/102		4.04%	0.67[0.11,3.94]
Lenney 2013	5/15	1/11		1.56%	3.67[0.5,27.12]
Eid 2010a	15/183	13/84		24.11%	0.53[0.26,1.06]
Eid 2010b	33/168	13/84		23.46%	1.27[0.71,2.28]
Murray 2011	2/113	1/118		1.32%	2.09[0.19,22.71]
Pearlman 2009	1/124	1/124		1.35%	1[0.06,15.81]
Subtotal (95% CI)	**704**	**523**		**55.85%**	**0.99[0.66,1.47]**
Total events: 58 (LABA + ICS), 32 (ICS alone)					
Heterogeneity: Tau^2=0; Chi^2=5.99, df=5(P=0.31); I^2=16.5%					
Test for overall effect: Z=0.07(P=0.95)					
3.4.2 Separate inhaler					
Verberne 1998a	10/60	10/57		13.88%	0.95[0.43,2.11]
Akpinarli 1999	0/16	0/16			Not estimable
Langton Hewer 1995	3/11	3/12		3.88%	1.09[0.28,4.32]
Simons 1997	0/16	1/16		2.03%	0.33[0.01,7.62]
Rutkowski 2009	0/20	0/20			Not estimable
Russell 1995	16/99	18/99		24.36%	0.89[0.48,1.64]
Subtotal (95% CI)	**222**	**220**		**44.15%**	**0.9[0.57,1.42]**
Total events: 29 (LABA + ICS), 32 (ICS alone)					
Heterogeneity: Tau^2=0; Chi^2=0.48, df=3(P=0.92); I^2=0%					
Test for overall effect: Z=0.45(P=0.65)					
Total (95% CI)	**926**	**743**		**100%**	**0.95[0.7,1.28]**
Total events: 87 (LABA + ICS), 64 (ICS alone)					
Heterogeneity: Tau^2=0; Chi^2=6.47, df=9(P=0.69); I^2=0%					
Test for overall effect: Z=0.35(P=0.73)					
Test for subgroup differences: Chi^2=0.09, df=1 (P=0.77), I^2=0%					



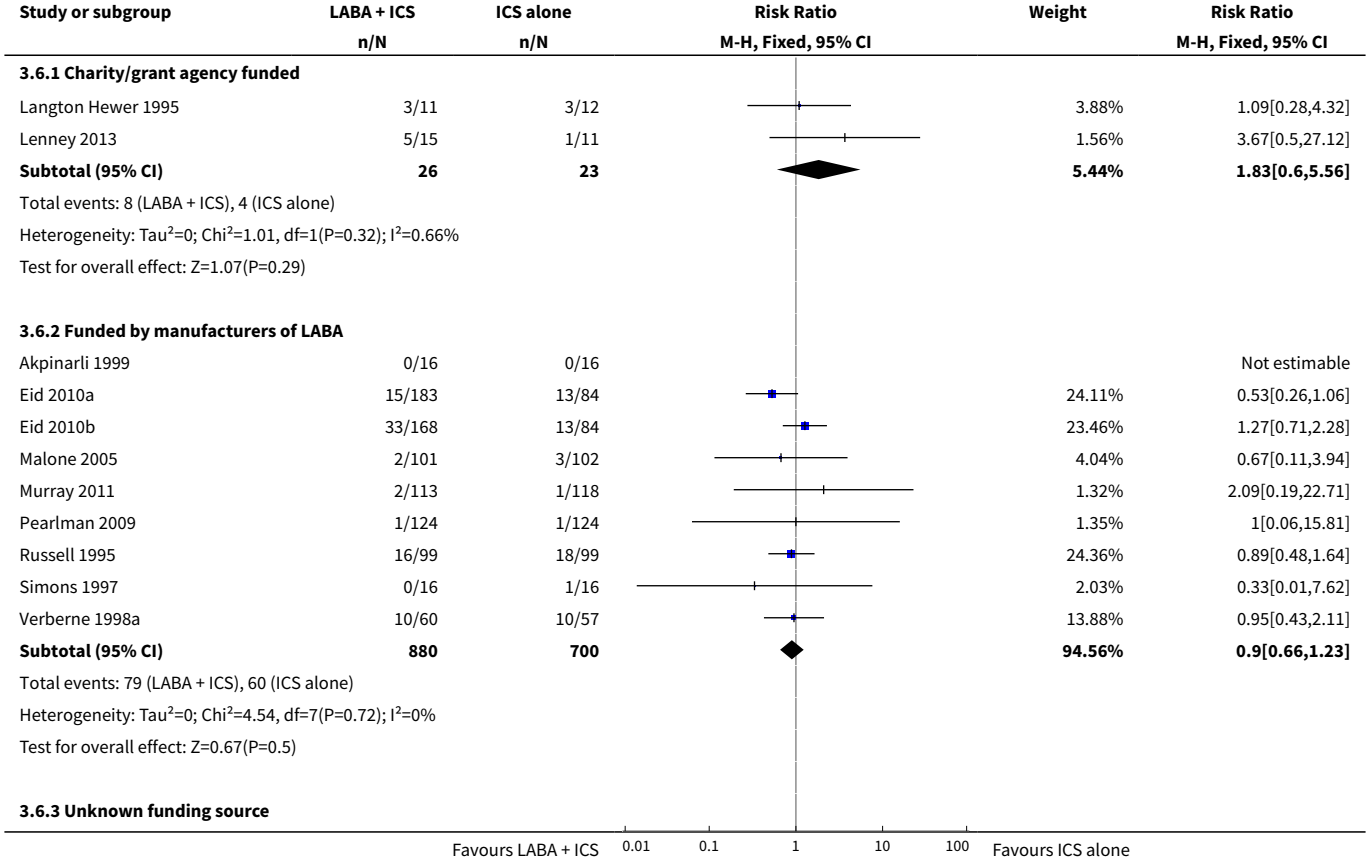
Analysis 3.5. Comparison 3 Subgroup analyses (comparison 01: LABA + ICS vs same dose of ICS), Outcome 5 # participants with exacerbations requiring oral steroids by trial duration.

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
3.5.1 ≤ 16 weeks					
Russell 1995	16/99	18/99		24.36%	0.89[0.48,1.64]
Malone 2005	2/101	3/102		4.04%	0.67[0.11,3.94]
Akpinarli 1999	0/16	0/16			Not estimable
Langton Hewer 1995	3/11	3/12		3.88%	1.09[0.28,4.32]
Simons 1997	0/16	1/16		2.03%	0.33[0.01,7.62]
Rutkowski 2009	0/20	0/20			Not estimable
Eid 2010a	15/183	13/84		24.11%	0.53[0.26,1.06]
Eid 2010b	33/168	13/84		23.46%	1.27[0.71,2.28]
Murray 2011	2/113	1/118		1.32%	2.09[0.19,22.71]
Pearlman 2009	1/124	1/124		1.35%	1[0.06,15.81]





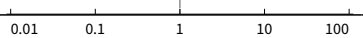
Analysis 3.6. Comparison 3 Subgroup analyses (comparison 01: LABA + ICS vs same dose of ICS), Outcome 6 # participants with exacerbations requiring oral steroids by whether funded by producers of LABA.



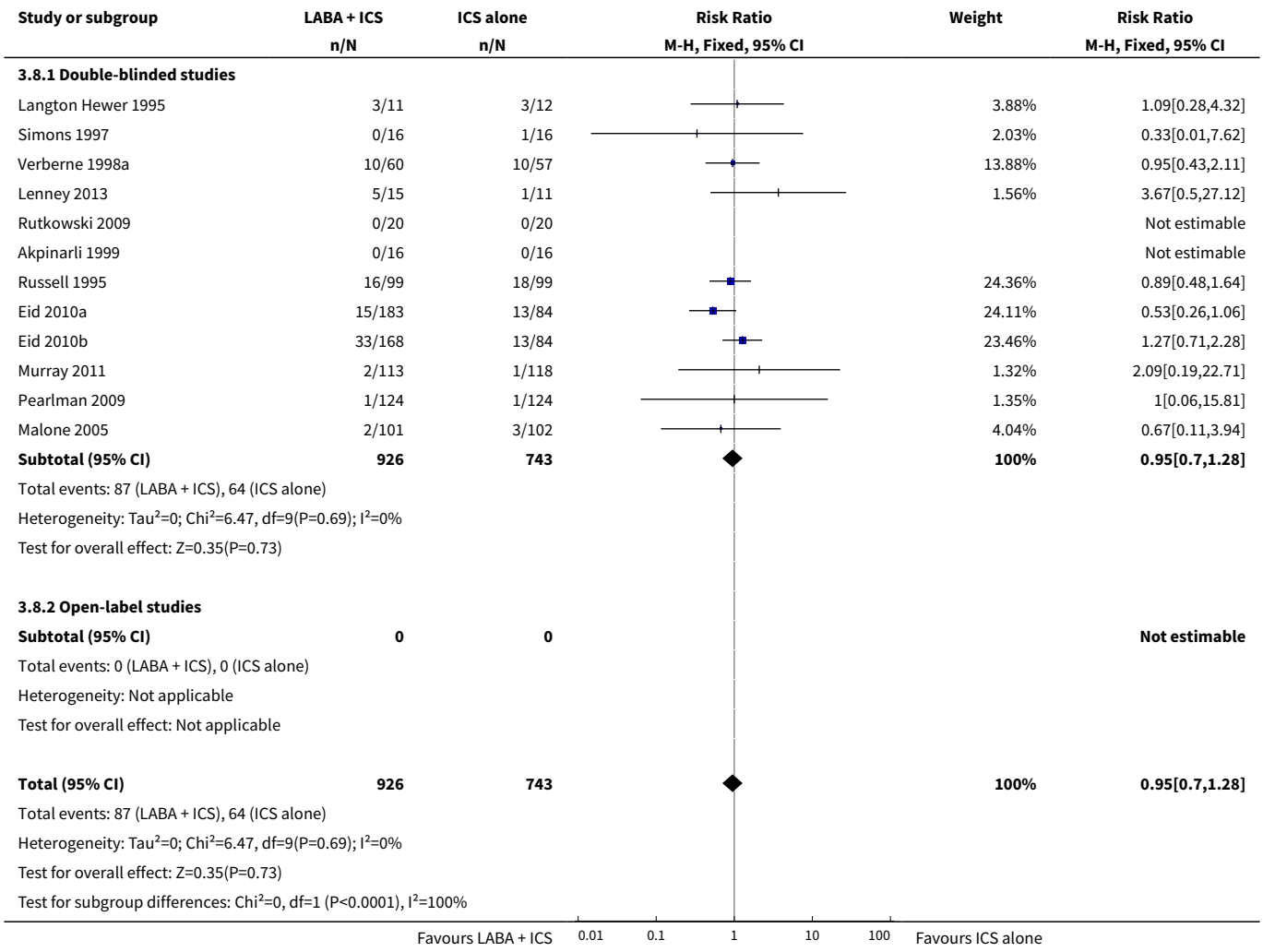
Study or subgroup	LABA + ICS n/N	ICS alone n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Rutkowski 2009	0/20	0/20			Not estimable
Subtotal (95% CI)	**20**	**20**			**Not estimable**
Total events: 0 (LABA + ICS), 0 (ICS alone)					
Heterogeneity: Not applicable					
Test for overall effect: Not applicable					
Total (95% CI)	**926**	**743**		**100%**	**0.95[0.7,1.28]**
Total events: 87 (LABA + ICS), 64 (ICS alone)					
Heterogeneity: Tau^2=0; Chi^2=6.47, df=9(P=0.69); I^2=0%					
Test for overall effect: Z=0.35(P=0.73)					
Test for subgroup differences: Chi^2=1.46, df=1 (P=0.23), I^2=31.59%					

Analysis 3.7. Comparison 3 Subgroup analyses (comparison 01: LABA + ICS vs same dose of ICS), Outcome 7 # participants with exacerbations requiring systemic steroids by publication status.

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
3.7.1 Published as full-text papers					
Langton Hewer 1995	3/11	3/12		3.88%	1.09[0.28,4.32]
Simons 1997	0/16	1/16		2.03%	0.33[0.01,7.62]
Verberne 1998a	10/60	10/57		13.88%	0.95[0.43,2.11]
Lenney 2013	5/15	1/11		1.56%	3.67[0.5,27.12]
Rutkowski 2009	0/20	0/20			Not estimable
Eid 2010a	15/183	13/84		24.11%	0.53[0.26,1.06]
Eid 2010b	33/168	13/84		23.46%	1.27[0.71,2.28]
Murray 2011	2/113	1/118		1.32%	2.09[0.19,22.71]
Pearlman 2009	1/124	1/124		1.35%	1[0.06,15.81]
Malone 2005	2/101	3/102		4.04%	0.67[0.11,3.94]
Subtotal (95% CI)	**811**	**628**		**75.64%**	**0.97[0.69,1.37]**
Total events: 71 (LABA + ICS), 46 (ICS alone)					
Heterogeneity: Tau^2=0; Chi^2=6.44, df=8(P=0.6); I^2=0%					
Test for overall effect: Z=0.19(P=0.85)					
3.7.2 Not published as full-text papers					
Akpinarli 1999	0/16	0/16			Not estimable
Russell 1995	16/99	18/99		24.36%	0.89[0.48,1.64]
Subtotal (95% CI)	**115**	**115**		**24.36%**	**0.89[0.48,1.64]**
Total events: 16 (LABA + ICS), 18 (ICS alone)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.38(P=0.71)					
Total (95% CI)	**926**	**743**		**100%**	**0.95[0.7,1.28]**
Total events: 87 (LABA + ICS), 64 (ICS alone)					
Heterogeneity: Tau^2=0; Chi^2=6.47, df=9(P=0.69); I^2=0%					
Test for overall effect: Z=0.35(P=0.73)					
Test for subgroup differences: Chi^2=0.06, df=1 (P=0.81), I^2=0%					



Analysis 3.8. Comparison 3 Subgroup analyses (comparison 01: LABA + ICS vs same dose of ICS), Outcome 8 # participants with exacerbations requiring systemic steroids by blinding of study.

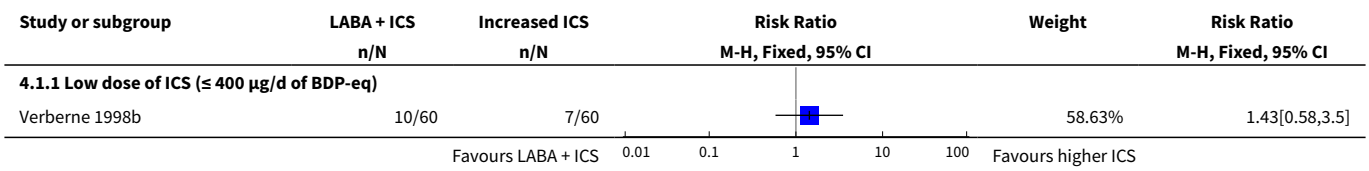


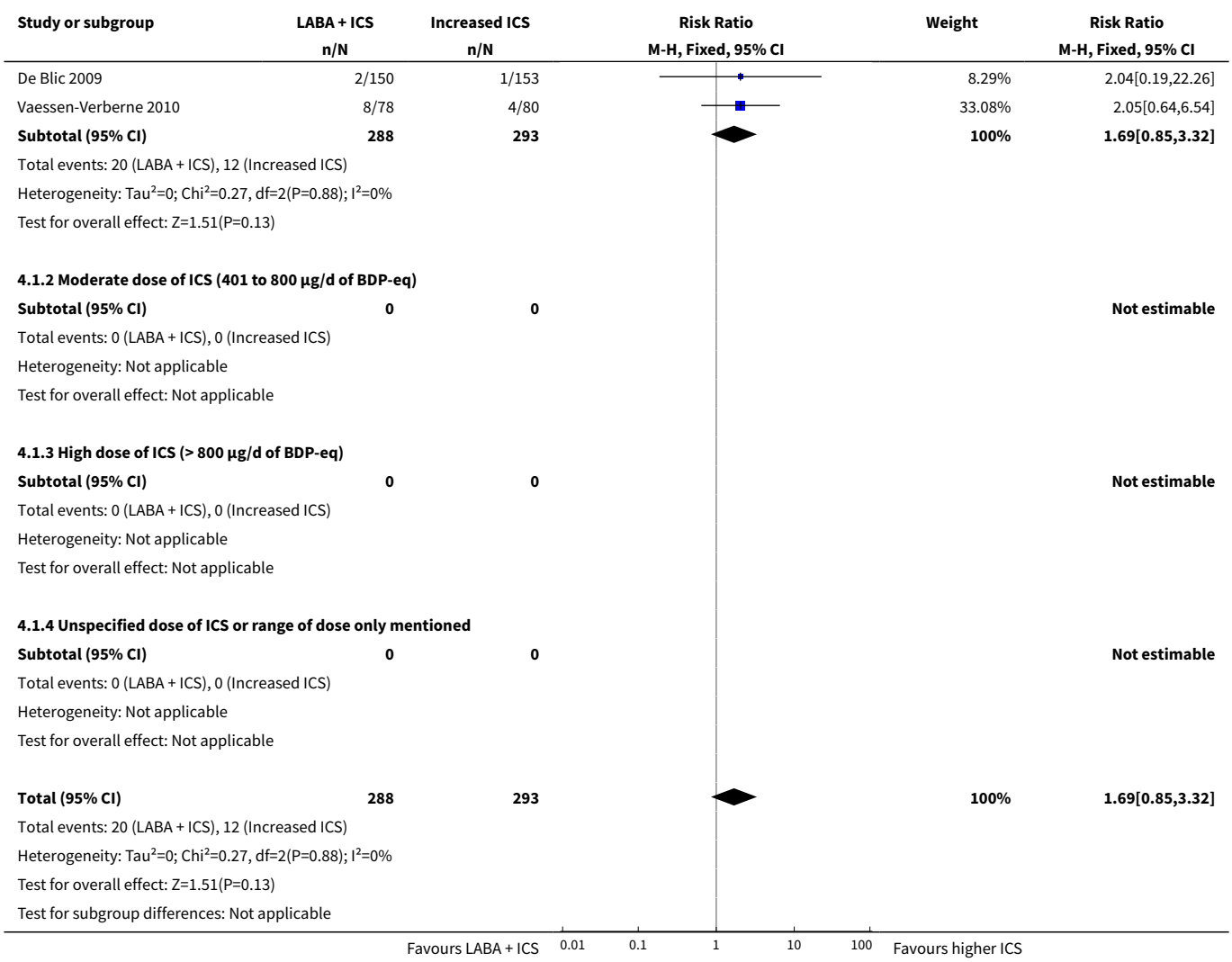
Comparison 4. Subgroup analyses (comparison 02: LABA + ICS vs higher dose of ICS)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 # participants with exacerbations requiring oral steroids by dose of ICS in control groups	3	581	Risk Ratio (M-H, Fixed, 95% CI)	1.69 [0.85, 3.32]
1.1 Low dose of ICS (≤ 400 µg/d of BDP-eq)	3	581	Risk Ratio (M-H, Fixed, 95% CI)	1.69 [0.85, 3.32]
1.2 Moderate dose of ICS (401 to 800 µg/d of BDP-eq)	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
1.3 High dose of ICS (> 800 µg/d of BDP-eq)	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]

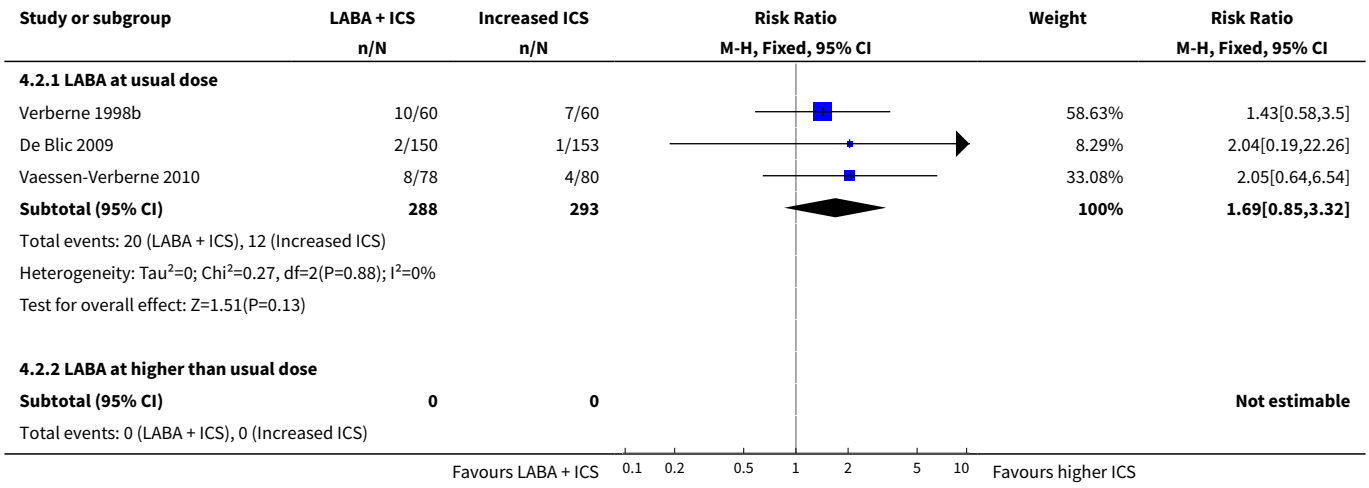
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.4 Unspecified dose of ICS or range of dose only mentioned	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
2 # participants with exacerbations requiring oral steroids by whether LABA dose is usual or higher than usual	3	581	Risk Ratio (M-H, Fixed, 95% CI)	1.69 [0.85, 3.32]
2.1 LABA at usual dose	3	581	Risk Ratio (M-H, Fixed, 95% CI)	1.69 [0.85, 3.32]
2.2 LABA at higher than usual dose	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
3 # participants with exacerbations requiring oral steroids by type of LABA	3	581	Risk Ratio (M-H, Fixed, 95% CI)	1.69 [0.85, 3.32]
3.1 Formoterol	2	461	Risk Ratio (M-H, Fixed, 95% CI)	2.05 [0.72, 5.82]
3.2 Salmeterol	1	120	Risk Ratio (M-H, Fixed, 95% CI)	1.43 [0.58, 3.50]
4 # participants with exacerbations requiring oral steroids by single inhaler or separate inhalers for LABA and ICS	3	581	Risk Ratio (M-H, Fixed, 95% CI)	1.69 [0.85, 3.32]
4.1 Combination inhaler	2	461	Risk Ratio (M-H, Fixed, 95% CI)	2.05 [0.72, 5.82]
4.2 Separate inhaler	1	120	Risk Ratio (M-H, Fixed, 95% CI)	1.43 [0.58, 3.50]
4.3 Not reported	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
5 # participants with exacerbations requiring oral steroids by trial duration	3	581	Risk Ratio (M-H, Fixed, 95% CI)	1.69 [0.85, 3.32]
5.1 ≤ 16 weeks	1	303	Risk Ratio (M-H, Fixed, 95% CI)	2.04 [0.19, 22.26]
5.2 ≥ 24 weeks	2	278	Risk Ratio (M-H, Fixed, 95% CI)	1.65 [0.81, 3.36]

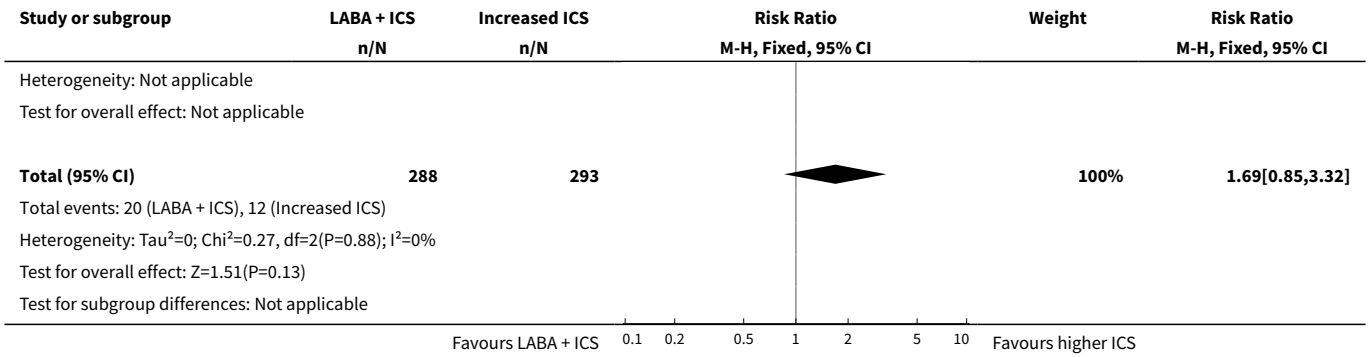
Analysis 4.1. Comparison 4 Subgroup analyses (comparison 02: LABA + ICS vs higher dose of ICS), Outcome 1 # participants with exacerbations requiring oral steroids by dose of ICS in control groups.



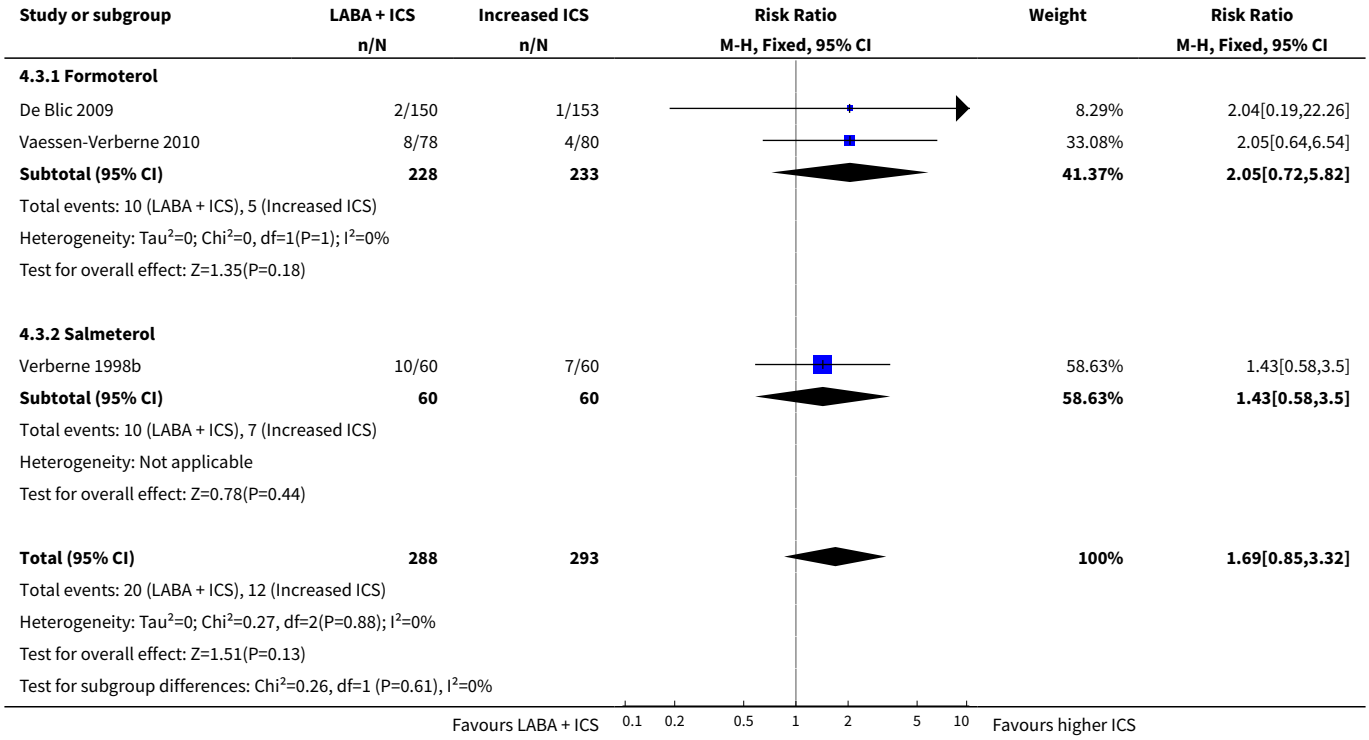


Analysis 4.2. Comparison 4 Subgroup analyses (comparison 02: LABA + ICS vs higher dose of ICS), Outcome 2 # participants with exacerbations requiring oral steroids by whether LABA dose is usual or higher than usual.

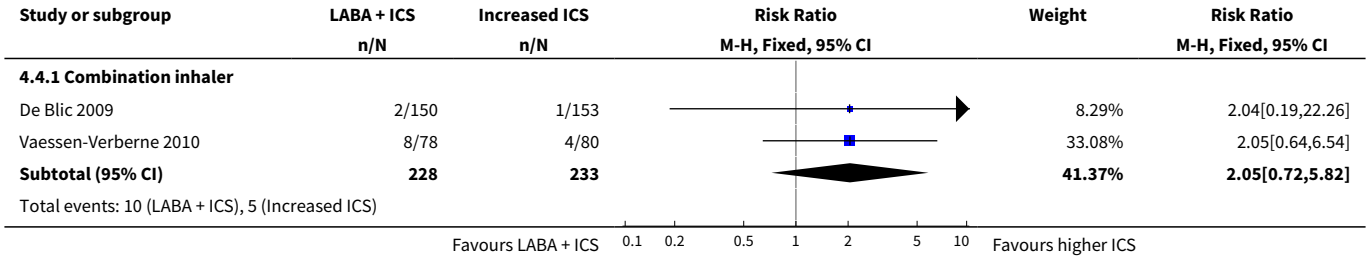


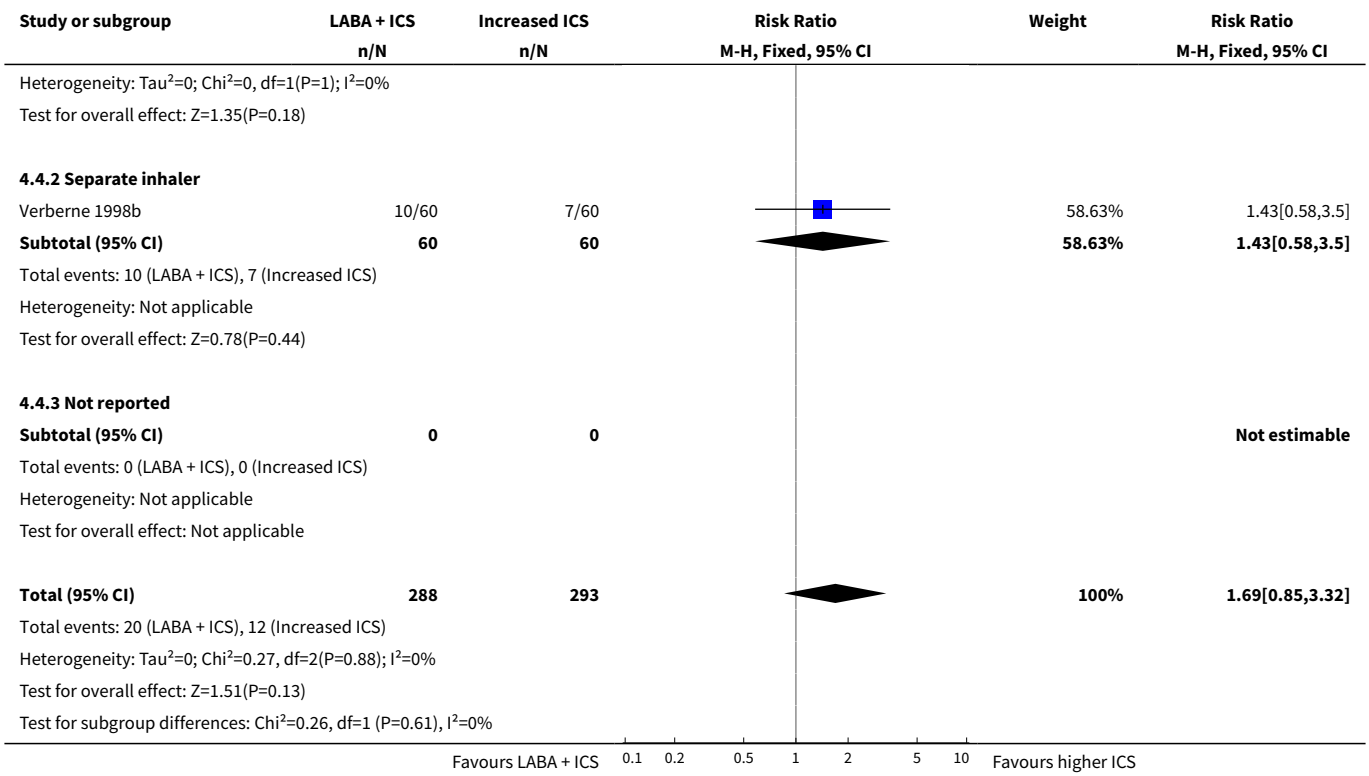


Analysis 4.3. Comparison 4 Subgroup analyses (comparison 02: LABA + ICS vs higher dose of ICS), Outcome 3 # participants with exacerbations requiring oral steroids by type of LABA.

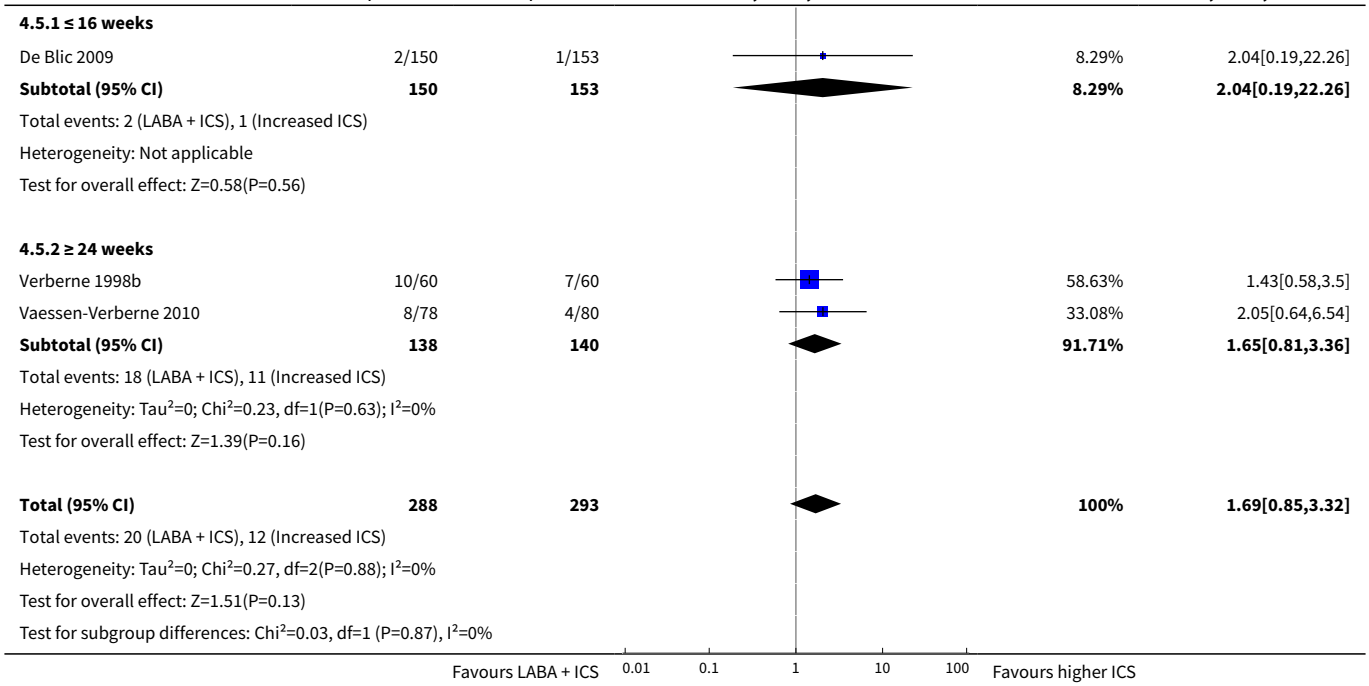


Analysis 4.4. Comparison 4 Subgroup analyses (comparison 02: LABA + ICS vs higher dose of ICS), Outcome 4 # participants with exacerbations requiring oral steroids by single inhaler or separate inhalers for LABA and ICS.





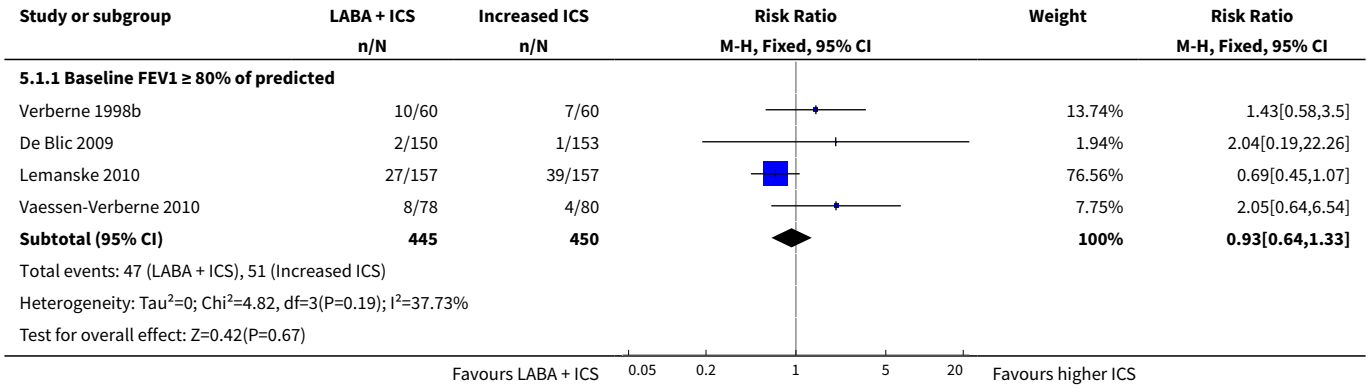
Analysis 4.5. Comparison 4 Subgroup analyses (comparison 02: LABA + ICS vs higher dose of ICS), Outcome 5 # participants with exacerbations requiring oral steroids by trial duration.



Comparison 5. Sensitivity analysis: LABA + ICS versus placebo + higher dose of ICS

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 # participants with exacerbations requiring oral steroids	4		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
1.1 Baseline FEV_1 ≥ 80% of predicted	4	895	Risk Ratio (M-H, Fixed, 95% CI)	0.93 [0.64, 1.33]

Analysis 5.1. Comparison 5 Sensitivity analysis: LABA + ICS versus placebo + higher dose of ICS, Outcome 1 # participants with exacerbations requiring oral steroids.



APPENDICES

Appendix 1. Sources and search methods for the Cochrane Airways Group Specialised Register (CAGR)

Electronic searches: core databases

Database	Frequency of search
CENTRAL (*The Cochrane Library*)	Monthly
MEDLINE (Ovid)	Weekly
EMBASE (Ovid)	Weekly
PsycINFO (Ovid)	Monthly
CINAHL (EBSCO)	Monthly
AMED (EBSCO)	Monthly

Handsearches: core respiratory conference abstracts

Conference	Years searched
American Academy of Allergy, Asthma and Immunology (AAAAI)	2001 onwards
American Thoracic Society (ATS)	2001 onwards
Asia Pacific Society of Respirology (APSR)	2004 onwards
British Thoracic Society Winter Meeting (BTS)	2000 onwards
Chest Meeting	2003 onwards
European Respiratory Society (ERS)	1992, 1994, 2000 onwards
International Primary Care Respiratory Group Congress (IPCRG)	2002 onwards
Thoracic Society of Australia and New Zealand (TSANZ)	1999 onwards

MEDLINE search strategy used to identify trials for the CAGR

Asthma search

1. exp Asthma/
2. asthma$.mp.
3. (antiasthma$ or anti-asthma$).mp.
4. Respiratory Sounds/
5. wheez$.mp.
6. Bronchial Spasm/
7. bronchospas$.mp.
8. (bronch$ adj3 spasm$).mp.
9. bronchoconstrict$.mp.
10. exp Bronchoconstriction/
11. (bronch$ adj3 constrict$).mp.
12. Bronchial Hyperreactivity/
13. Respiratory Hypersensitivity/
14. ((bronchial$ or respiratory or airway$ or lung$) adj3 (hypersensitiv$ or hyperreactiv$ or allerg$ or insufficiency)).mp.
15. ((dust or mite$) adj3 (allerg$ or hypersensitiv$)).mp.
16. or/1-15

Filter to identify RCTs

1. exp "clinical trial [publication type]"/
2. (randomized or randomised).ab,ti.

3. placebo.ab,ti.

4. dt.fs.

5. randomly.ab,ti.

6. trial.ab,ti.

7. groups.ab,ti.

8. or/1-7

9. Animals/

10. Humans/

11. 9 not (9 and 10)

12. 8 not 11

The MEDLINE strategy and RCT filter are adapted to identify trials in other electronic databases.

Appendix 2. Search methods up to May 2008

Electronic searches

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

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

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

Appendix 3. Search strategy to identify relevant trials from the CAGR

#1 AST:MISC1

#2 MeSH DESCRIPTOR Asthma Explode All

#3 asthma*:ti,ab

#4 #1 or #2 or #3

#5 MeSH DESCRIPTOR Adrenergic beta-2 Receptor Antagonists

#6 (beta* and agonist*) and (long-acting or "long acting")

#7 (beta* and adrenergic*) and (long-acting or "long acting")

#8 bronchodilat* and (long-acting or "long acting")

#9 salmeterol

#10 *formoterol

#11 #5 or #6 or #7 or #8 or #9 or #10

#12 MeSH DESCRIPTOR Glucocorticoids Explode All

#13 budesonide

#14 beclomethasone

#15 beclometasone

#16 fluticasone

#17 triamcinolone

#18 flunisolide

#19 ciclesonide

#20 #12 or #13 or #14 or #15 or #16 or #17 or #18 or #19

#21 #11 and #20

#22 Advair or symbicort or Viani or Seretide or Flutiform

#23 #21 or #22

#24 #4 and #23

#25 child* or paediat* or pediat* or adolesc* or infan* or toddler* or bab* or young* or preschool* or "pre school*" or pre-school* or newborn* or "new born*" or new-born* or neo-nat* or neonat*

#26 #24 and #25

[In search line #1, MISC1 denotes the field in which the reference has been coded for condition, in this case, asthma]

Appendix 4. Randomisation procedures for GSK-sponsored studies

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

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

WHAT'S NEW

Date	Event	Description
23 January 2015	New citation required but conclusions have not changed	8 studies added - conclusions similar Few new outcomes added - urgent care visits, nighttime awakenings - new lead author added Results and discussion redrafted. Summary of findings tables added
23 January 2015	New search has been performed	New literature search run

HISTORY

Review first published: Issue 3, 2009

Date	Event	Description
8 December 2009	Amended	We have revised the reporting of correspondence in relation to missing data Correspondence regarding data from Bisgaard 2006 was made directly with study sponsors, not with Hans Bisgaard. Sponsors

Date	Event	Description
		were not able to provide data on children in this study with exacerbations requiring oral corticosteroids
21 April 2008	Amended	Converted to new review format

CONTRIBUTIONS OF AUTHORS

BC: update of the review, screening of citations, data extraction, method assessment, write-up and correspondence with the editorial board of the Cochrane Airways Group.

CC: data extraction and method assessment.

MNC: protocol initiation and write-up, study assessment, characterisation extraction of data and write-up.

SJM: data extraction and proofreading of the manuscript.

FD: protocol development, review development, interpretation of results and review of final manuscript.

DECLARATIONS OF INTEREST

In the past five years, Francine Ducharme received some research funding from GSK, Merck and AstraZeneca, and gave CME conferences supported by Merck Frost, GSK and Takeda. Over the past five years, M Ni Chroinin has given CME lectures sponsored by AstraZeneca. Bhupendrasinh Chauhan, Caroline Chartrand and Stephen J Milan, as well as previous authors, namely, A. Danish, H. Magalinos, V. Masse, X. Zhang, Toby Lasserson and Ilana Greenstone, report no conflicts of interest.

SOURCES OF SUPPORT

Internal sources

- The authors declare that no such funding was received for this systematic review, Other.

External sources

- The authors declare that no such funding was received for this systematic review, Other.

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

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

In the current update, we have added two new secondary outcomes, numbers of participants with exacerbations requiring an urgent care visit and % nights with awakening. We have added a 'Summary of findings' table.

INDEX TERMS

Medical Subject Headings (MeSH)

Adrenal Cortex Hormones [*administration & dosage] [adverse effects]; Adrenergic beta-Agonists [*administration & dosage] [adverse effects]; Albuterol [administration & dosage] [analogs & derivatives]; Anti-Asthmatic Agents [*administration & dosage] [adverse effects]; Asthma [*drug therapy]; Beclomethasone [administration & dosage] [adverse effects]; Chronic Disease; Disease Progression; Drug Therapy, Combination; Ethanolamines [administration & dosage]; Formoterol Fumarate [administration & dosage] [adverse effects]; Randomized Controlled Trials as Topic; Salmeterol Xinafoate [administration & dosage] [adverse effects]

MeSH check words

Adolescent; Child; Female; Humans; Male