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Long-acting beta2-agonists for chronic asthma in adults and children where background therapy contains varied or no inhaled corticosteroid (Review)

Walters EH, Gibson PG, Lasserson TJ, Walters JAE

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[Intervention Review]

Long-acting beta2-agonists for chronic asthma in adults and children where background therapy contains varied or no inhaled corticosteroid

E. Haydn Walters[1], Peter G Gibson[2], Toby J Lasserson[3], Julia AE Walters[4]

[1]NHMRC CRE for Chronic Respiratory Disease, School of Medicine, University of Tasmania, Hobart, Australia. [2]Department of Respiratory and Sleep Medicine, John Hunter Hospital, New Lambton, Australia. [3]Cochrane Editorial Unit, The Cochrane Collaboration, London, UK. [4]School of Medicine, University of Tasmania, Hobart, Australia

Contact: E. Haydn Walters, NHMRC CRE for Chronic Respiratory Disease, School of Medicine, University of Tasmania, Hobart, Tasmania, Australia. Haydn.Walters@utas.edu.au.

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ABSTRACT

Background

Asthma is a common respiratory disease among both adults and children and short acting inhaled beta-2 agonists are used widely for 'reliever' bronchodilator therapy. Long acting beta-2 agonists (LABA) were introduced as prospective 'symptom controllers' in addition to inhaled corticosteroid 'preventer' therapy (ICS).

We originally analysed studies comparing the use of LABA with placebo in mixed populations in which only some were taking ICS and in populations not using ICS therapy. However international guidelines no longer recommend the use of LABA in people who are not taking ICS for their asthma. We are therefore no longer updating this review.

Objectives

This review aimed to determine the benefit or detriment on the primary outcome of asthma control with the regular use of LABA compared with placebo, in mixed populations in which only some were taking ICS and in populations not using ICS therapy.

Search methods

We carried out searches using the Cochrane Airways Group trial register, most recently in October 2005. We searched bibliographies of identified RCTs for additional relevant RCTs and contacted authors of identified RCTs for other published and unpublished studies.

Selection criteria

All randomised studies of at least four weeks duration, comparing a LABA given twice daily with a placebo, in chronic asthma. Selection criteria to this updated review have been altered to accommodate recently published Cochrane reviews on combination and addition of LABA to ICS therapy. Studies in which all individuals were uniformly taking ICS were excluded from this review.

Data collection and analysis

Two review authors performed data extraction and study quality assessment independently. We contacted authors of studies for missing data.

Main results

Sixty-seven studies (representing 68 experimental comparisons) randomising 42,333 participants met the inclusion criteria. Salmeterol was used as long-acting agent in 50 studies and formoterol fumarate in 17. The treatment period was four to nine weeks in 29 studies, and 12 to 52 weeks in 38 studies. Twenty-four studies did not permit the use of ICS, and forty permitted either inhaled corticosteroid or cromones (in three studies this was unclear). In these studies between 22% and 92% were taking ICS, with a median of 62%. There were significant advantages to LABA treatment compared to placebo for a variety of measurements of airway calibre including morning peak expiratory flow (PEF), evening PEF and FEV1. They were associated with significantly fewer symptoms, less use of rescue medication and higher quality of life scores. This was true whether patients were taking LABA in combination with ICS or not. Findings from SMART (a recently published surveillance study) indicated significant increases in asthma related deaths, respiratory related deaths and combined asthma related deaths and life threatening experiences. The absolute increase in asthma-related mortality was consistent with an increase of around one per 1250 patients treated with LABA for six months, but the confidence intervals are wide (from 700 to 10,000). Post-hoc exploratory subgroups suggested that African-Americans and those not on inhaled corticosteroids were at particular risk for the primary end-point of death or life-threatening asthma event. There was also a suggestion of an increase in exacerbation rate in children. Pharmacologically predicted side effects such as headache, throat irritation, tremor and nervousness were more frequent with LABA treatment.

Authors' conclusions

LABA are effective in the control of chronic asthma in the "real-life" subject groups included. However there are potential safety issues which call into question the safety of LABA, particularly people with asthma who are not taking ICS, and it is not clear why African-Americans were found to have significant differences in comparison to Caucasians for combined respiratory-related death and life threatening experiences, but not for asthma-related death.

Since the original version of this review, the US Food and Drug Agency (FDA) has added a warning that LABA should not be used to treat asthma without concurrent ICS. International guidelines only recommend the use of LABA in conjunction with ICS. Readers should consult the overviews which summarise the results of Cochrane reviews on the safety of LABAs in adults and children (Cates 2012; Cates 2014).

PLAIN LANGUAGE SUMMARY

Long-acting beta2-agonists for chronic asthma in adults and children where background therapy contains varied or no inhaled corticosteroid

Note added in July 2014: Since the original version of this review, guidance around LABA has changed. International asthma guidelines now only recommend the use of LABA in conjunction with ICS. The US Food and Drug Agency (FDA) has issued a warning that LABA should not be used to treat asthma without concurrent ICS. The review will continue to be available for people to read on the Cochrane Library, but we will not update the review again. It is no longer considered safe to take LABA on their own without taking inhaled steroids due to harms which can occur.

Plain language summary published in 2006: In this review of studies in which patients were either not on inhaled corticosteroids, or in which some patients but not all were on inhaled corticosteroids, treatment with regular long-acting beta-2 agonists such as salmeterol (Serevent) or formoterol (Foradil, Oxis) in chronic asthma resulted in fewer asthma symptoms by day or night, less relief bronchodilator medication requirement, better lung function, a lower risk of acute worsening of asthma and better quality of life, but most of the evidence comes from groups in which at least some used inhaled corticosteroid therapy. There is less information on asthma control in patients who did not use a regular 'preventer medication' or in children under twelve years, but the same generally positive effects on symptoms and lung function seem to apply. We have also been particularly focused on serious adverse events, given previous concerns about potential risks, especially of death, from regular beta-2 agonist use. A significant increase in asthma related deaths or life threatening experiences has been found in a recently published surveillance study, with an increased risk of around one event over 6 months for every thousand patients treated. This increase was mainly in African-Americans and those not on inhaled corticosteroids, although these observations were drawn from analyses conducted after the event (post-hoc) and as such lack the validity of pre-defined distinctions.

BACKGROUND

Asthma is a common respiratory disease among both adults and children (Pearce 2000), though there are large geographical differences in the prevalence of asthma (Janson 2001). The prevalence is increasing in many countries; estimates for asthma prevalence for adults in 1990 varied from 8.5% in Australia to 4% in the USA and 3% in the United Kingdom (Sullivan 1996) and repeat estimates in Australia in 1999 (Woods 2001) gave rates for physician diagnosed asthma of 18% while 10% had used asthma medications in the past year. As a chronic illness, asthma is responsible for significant economic costs, both direct medical costs and indirect costs. Measurements in Australia (population approximately 20 million) range from direct costs of US$250 million to US$3.6 billion for total costs. Costs per patient have been estimated at US$326 per year in Australia and US$1,043 per year in the United Kingdom (Sullivan 1996).

Pathophysiological studies over the past two decades have increasingly recognised asthma as an inflammatory airway disease. National treatment guidelines for asthma have been published in several countries including Britain, USA and Australia (BTS 1993; BTS 1995; GINA 1995 and NAC 2002). They recommend the use of ICS as 'preventer' maintenance therapy for all but mildest grades of asthma severity. In addition, bronchodilator therapy is an essential component of treatment, traditionally used for relief of symptoms as needed. The most widely used bronchodilators in asthma are inhaled beta-2 agonists which can be divided into two groups: those with a short duration of action (2-6 hours) which are used in a reactive 'relief' mode and those, introduced more recently, with a longer duration of action (>12 hours). The latter were introduced as prospective 'symptom controllers'. The major representatives of the short acting beta-2 agonist agents in clinical use are salbutamol (known in North America as albuterol), terbutaline and orciprenaline, while the LABA in use are salmeterol and formoterol.

There has been controversy over the regular use of beta-2 agonists (AAACI 1993). It was proposed that excessive use of short acting beta-2 agonists might have contributed directly or indirectly to peaks in asthma mortality seen in the 1960's and late 1970's (Sears 1986). A study by Campbell (Campbell 1976) showed that in four Australian states there was a high correlation between the sales of adrenergic bronchodilator aerosols and the corresponding asthma mortality rates for the periods 1961-1963 and 1964-1966. Later, in 1989, a case control study in New Zealand linked the use of inhaled fenoterol with increased risk of death from asthma (Crane 1989). This was followed soon after by a similar study in Saskatchewan that also showed an association between excessive use of beta-2 agonists and the risk of death or near death from asthma (Spitzer 1992).

Excessive use of beta-2 agonists and high blood levels of beta-2 agonists in poorly controlled asthma may contribute to deaths (Abramson 2001). This study also showed significantly less use of asthma management plans and less use of inhaled corticosteroids in fatal cases.

The development of beta-2- agonists with long-acting properties, such as salmeterol (Adkins 1997) and (e)formoterol (Bartow 1998) has provided potential pharmacological advantages over short-acting beta-agonists, such as prolonged bronchodilatation and protection against induced bronchospasm. However, there remain concerns about adverse effects of regular use of LABA (Devoy 1995), especially on enhancing bronchial hyper responsiveness (Cockcroft 1993), the development of tolerance to bronchodilatation (Newnham 1995), progressively reduced protection against provoking stimuli (Taylor 1997) and masking of deteriorating asthma pathology (McIvor 1998). These concerns have influenced national and international guidelines for asthma management, which stipulate that short-acting beta-2 agonists should be used only as needed, and not on a regular basis. LABA are in contrast generally only recommended to be taken on a regular basis.

The initial version of this review aimed to determine the benefit or detriment on the primary outcome of asthma control with the regular use of LABA compared with placebo. The review concluded that LABAs conferred benefits when given in addition to ICS therapy, and that they were safe. Several Cochrane reviews have since been published which confirm the benefit of LABA when given in addition to inhaled steroid therapy (Greenstone 2005; Ni Chroinin 2004; Ni Chroinin 2005), and so we have narrowed the focus of this update. In addition to these reviews, the publication of a large study that suggested that there was an increase in the risk of asthma related mortality, (SMART), prompted us to re-assess the evidence base supporting the safety of LABA in chronic asthma.

OBJECTIVES

The objective of this new updated review was to compare the effects of regular inhaled LABA versus placebo in chronic asthma. The specific purpose of the review was to assess whether there are any beneficial or harmful effects from the regular use of inhaled LABA compared with placebo on the primary outcome of asthma control, assessed through measurements of airway calibre, symptoms and exacerbations of asthma. Secondary outcomes included assessment of quality of life, airway hyper-reactivity, adverse events and the tolerance (tachyphylaxis) to bronchodilatation and bronchoprotection. Following the publication of SMART, we have also updated the review to include an estimate of the risk of death in participants given a LABA to control their asthma. Studies in which all subjects were given LABA consistently with ICS were excluded.

METHODS

Criteria for considering studies for this review

Types of studies

We considered all randomised studies, both open and blinded, though double blind studies were preferable. The scoring system gave a lower score to open studies, and was used to assess the contribution of open studies, or if necessary to exclude them from analyses. Studies could be either of parallel group or crossover design.

Types of participants

We included studies in which participants had a clinical diagnosis of asthma, present for at least three months but excluded the studies already included in currently published Cochrane reviews i.e. in which all patients were on ICS (see below). Participants belonged to populations with either variable ICS rates of use, or were uniformly not on ICS.

We included both adults and children. We looked specifically for evidence of reversibility of airway obstruction to short acting inhaled beta-2 agonists as a basic diagnostic criterion. We sought to document the severity of participants' asthma at inclusion and the proportion of participants using other asthma therapies, most notably disease-modifying agents such as ICS. Studies that included some or all participants with other pulmonary diseases, and especially smoking-related Chronic Obstructive Pulmonary Disease (COPD) were excluded unless the results for those with asthma alone were available or could be extracted separately.

Types of interventions

Participants in one treatment arm used a LABA either salmeterol or formoterol (also known as eformoterol), administered twice daily via any inhalation device. The second treatment arm consisted of regular doses of placebo, administered in the same way. The dose, inhalational device and frequency of administration were recorded. The minimum period of treatment was changed from the two weeks in our original review to four weeks in this update, to fit with the aim of assessing regular use in a relatively chronic setting. Since the initial publication of this review, a number of reviews have been published assessing the effects of addition of ICS or combination of LABA with ICS in chronic asthma (Greenstone 2005; Ni Chroinin 2004; Ni Chroinin 2005). We have therefore modified the criteria of this review in order to address a more focused question than the one we sought to answer previously. Thus, for the 2006 update of this review, we have included studies only where a LABA was administered without a standardised co-intervention with ICS (e.g. without standardised fixed combination therapy, where use of ICS therapy was an inclusion criterion or was uniformly provided by the study investigator). This means that we have included studies where a LABA was administered on top of usual therapy, such that a subset of participants only were using a regular ICS, provided that the regimen of maintenance ICS was not altered prior to the study. There was also a subgroup not using ICS or other disease - modifying agents at all. We have combined these studies, with subdivisions into subgroups, and recorded the number of participants on "preventer" inhaled therapy where this is available (Table 1).

Types of outcome measures

Outcome measures chosen were those generally accepted as reflecting the primary outcome of asthma control. Thus the planned outcome measures were: daytime and night-time asthma symptom scores, bronchodilator use for symptom relief, daily peak flow measurement (PEF) and its variability, clinic measurements of lung function and asthma exacerbation rates. Secondary outcomes used were: adverse events (with a particular interest in mortality and life threatening asthma events), airway hyper-reactivity, quality of life score, global assessment of efficacy by patient and investigator, reduction in use of other asthma medication including ICS, development of tolerance to the effects of beta-2 agonists and effects on exercise-induced asthma.

Search methods for identification of studies

Electronic searches

The Cochrane Airways Review Group (ARG) has developed an "Asthma and Wheeze RCT" register, derived from a comprehensive search of EMBASE, MEDLINE, CINAHL. In addition hand searching of the 20 most productive respiratory care journals has been completed and relevant RCTs have been added to the register, including those published in a language other than English. Search of this database was completed using the following search strategy:

(beta and agonist*) or beta-agonist* or bronchodilat* or salbutamol or albuterol or terbutalin* or isoproterenol or reproterol or reproterenol or rimiterol or fenoterol or ventolin or orciprenaline or metaproterenol or pirbuterol or salmeterol or eformoterol or formoterol

Searching other resources

Reference lists of all available primary studies and review articles were screened to identify potentially relevant citations. Researchers known to have an interest in the field were contacted to identify other relevant past or current studies.

Data collection and analysis

Selection of studies

From the abstracts or titles, two reviewers (JW and FR) independently reviewed literature searches to identify potentially relevant trials for full review. Searches of bibliographies and texts were carried out to identify additional studies. Using the specified criteria, inclusion of studies in the review was decided by agreement between the reviewers (JW, EHW and FR).

Data extraction and management

Methods-study design, location and setting, method of randomisation and blinding, withdrawals/drop outs, compliance, confounders and quality score.

Participants- total number of subjects (N), numbers of males and females, the mean age and range, baseline severity of asthma, inclusion and exclusion criteria, ICS (or other "preventer") or not, and dose if relevant.

Interventions- the long-acting beta-2 agonist used, with dose and frequency of dosing, use of placebo drug and whether matched, the device used to administer drugs, the treatment period, the additional rescue agent used if any, any co-intervention used during study by participants, with its dose and whether dose remained stable.
Outcomes- which outcomes were measured, which reported, in what form and whether they were complete, the standard deviation or other measure of variability.
Studies could use a variety of measures of asthma control and we specifically extracted results for the following outcomes where available:
Peak expiratory flow (PEF): morning
PEF: evening
% Predicted PEF: morning
% Predicted PEF: evening
Change in PEF: morning
Change in PEF: evening
Amplitude of diurnal variation in PEF
Forced expiratory flow in 1 second (FEV1)
% Predicted FEV1
Change in FEV1
Forced Vital Capacity (FVC)
Forced expiratory flow between 25-75% of ventilatory capacity (FEF25-75)
Symptom score: whole day (24 hours)

Symptom score: day time
Symptom score: night time
%days without asthma symptoms
% nights without asthma awakenings
Rescue bronchodilator use: whole day (number of doses, normally 2 puffs or 1 inhalation dry powder)
Rescue bronchodilator use: day time number of doses
Rescue bronchodilator use: night time number of doses
Quality of life score: overall
Quality of life score: symptoms
Quality of life score: emotions
Quality of life score: exposure to environmental stimuli
Quality of life score: activity limitations
Bronchial hyper reactivity
Adverse events: mortality and life-threatening events
Adverse events: palpitations
Adverse events: headache
Adverse events: tremor
Adverse events: cramps
Exacerbations of asthma
Overall efficacy of treatment
Weaning from ICS medication or non-steroidal 'preventer' asthma medication
Tolerance to bronchodilator effects of beta-2 agonists
Tolerance to bronchoprotective effects of beta-2 agonists on direct/indirect airway challenge
Measures of airway inflammation, obtained by bronchoscopy, sputum, exhaled breath/condensate analysis

Assessment of risk of bias in included studies

The trials were scored using the Cochrane approach to assessment of allocation concealment:
Grade A: Adequate concealment.
Grade B: Unclear concealment.
Grade C: Obviously not adequate concealment.

Each study was also assessed for validity using the method of Jadad (Jadad 1996), on a 0-5 scale as follows:
1. Was the study described as randomised? (1=yes, 0=no)
2. Was the study described as double-blind?(1=yes, 0=no)
3. Was there a description of withdrawals and drop outs? (1=yes, 0=no)
4. Was the method of randomisation well described and appropriate? (1=yes, 0=no)
5. Was the method of double-blinding well described and appropriate? (1=yes, 0=no)
6. Deduct 1 point if methods of randomisation or blinding were inappropriate.
Differences were resolved by discussion between the reviewers.

Dealing with missing data

Where possible we have attempted to extract and verify raw data for continuous variable endpoints for all of the studies where these are reported. However, we have come across a number of studies where means, or mean differences are reported without an associated estimate of variance (e.g. standard deviation, standard error or 95% CI). We have therefore calculated a weighted estimate of the variation for each study where this is reported, and applied this to studies where such data are missing. This is calculated based from the ratio of the sample size for each study to the pooled sample size, generating a fraction. We have multiplied the standard deviation by the fraction, and then we have summed these to generate an average standard deviation.

Data synthesis

All included trials were combined using the Review Manager. Data from parallel group and crossover studies were analysed separately.

For continuous outcomes, individual and pooled statistics were calculated as mean differences (MD) with 95% Confidence Intervals (CI), routinely using fixed effects models. However if heterogeneity was found in analyses (I square >20%, Higgins 2003), use of the random effects model was included in its investigation. Results are reported as fixed effect unless otherwise stated. Where different scales had been used to measure the outcome, the pooled standardised mean differences (SMD), with 95% Confidence Intervals (CI) were calculated. The SMD is a statistic that expresses the difference in means between the two treatment groups in units of the pooled standard deviation. This applied particularly to measures of bronchial reactivity, symptom scores and diurnal variation in PEF.

For dichotomous outcomes, individual and pooled statistics were calculated as Odds Ratios (OR) with 95% Confidence Intervals (CI), using a fixed-effect model, with random-effects model being used in the investigation of any heterogeneity, as above.

For pooled effects a Breslow-Day test of heterogeneity was carried out, and a P value <0.05 was considered significant, indicating possible differences between studies. Investigation of heterogeneity included performing analyses using the domains:
1. Fixed-effect versus random-effects modelling.
2. Methodological quality - Cochrane criteria A and B versus C ; Jadad score 3-5 versus 1-2.
3. Use of funnel plots to examine the effects, and investigate publication bias and look for asymmetry of effect sizes.

With regular use for at least two weeks there does not seem to be a significant difference between eformoterol used twice daily at either 6, 12 or 24 mcg dose on the development of tachyphylaxis to their bronchoprotective effects (Lipworth 1998). The effects on lung function and asthma symptom scores after 12 weeks treatment are similar for formoterol at doses of 12 and 24 mcg twice daily (Bensch 2001). Schreurs 1996 found that the lowest effective dose of eformoterol was 6 mcg twice daily on outcomes such as daily PEF, lung function, daily asthma symptoms scores and use of rescue medication. Higher doses induced a greater effect in absolute numbers for some outcomes such as PEF in the morning, with a significant difference between the 6 mcg and 24 mcg doses. Bensch 2001 showed a slightly greater frequency of adverse events with the higher dose of 24 mcg compared to 12 mcg twice daily.

The four week Dahl 1991a study showed that the lowest effective dose of salmeterol on outcomes such as PEF, asthma symptom scores, rescue bronchodilator use and nocturnal awakenings was 12.5 mcg twice daily, with dose related increases occurring with salmeterol 50 and 100 mcg twice daily. The incidence of pharmacologically predictable adverse events was greater with a dose of 100 mcg twice daily.

Fitzpatrick 1990 showed improvement in overnight PEF and sleep quality using salmeterol 50 mcg twice daily, while the 100 mcg dose also improved PEF and reduced the need for rescue bronchodilator

use but did not improve sleep quality. When 100 mcg was used once daily at night (Faurschou 1994a) it was shown that there was a similar effect on nocturnal asthma symptoms compared to 50 mcg given twice daily.

Because of these differences in likely outcomes dependent on dose of LABA used, sensitivity analyses were performed for dose variations in the meta-analysis.

Subgroup analysis and investigation of heterogeneity

Subgroup analyses were planned to assess the effect of treatment in different populations of asthmatics and the following subgroup analyses were carried out:

1. Asthmatics not using regular inhaled corticosteroids
2. Asthmatics using a variety of mixed co-interventions
3. Children
4. Severity of asthma (mild, mild-moderate, moderate-severe, persistent, unclear)

Differences between subgroups were tested with an interaction test (Altman 2003).

RESULTS

Description of studies

Results of the search

Search history is provided in Table 2. From update searches conducted between October 2002 and October 2005, 29 studies were retrieved for scrutiny. Of these 17 met the entry criteria of the review (Busse 2004; Creticos 1999; LaForce 2005; Lazarus 2001; Levy 2005; Lindqvist 2003; Pleskow 2003; SAS30003; SAS30004; SLGA2004; SLGA3014 1994; SLGL82; SLMP03; SMART; SMS40221; von Berg 2003; Wolfe 2000b). Additional data were available from the GSK clinical trials website for Kavuru 2000a; Shapiro 2000b; Dahl 1991a; Wolfe 2000a; Wolfe 2000b; Leblanc 1996; Zarkovic 1998. Data from individual studies previously published and reported as pooled data from two clinical trials were made available from the GSK website (Wolfe 2000a; Wolfe 2000b: studies: SLGA3010 and SLGA3011). Following revision of the review entry criteria, 38 studies were excluded which had previously met the entry criteria (see Table 3).

Included studies

Sixty-seven published and unpublished studies representing 68 different experimental groups which contribute to the data analyses in this review (see table Characteristics of included studies).

The studies for inclusion were independently assessed and scored by at least two reviewers using the full text of the paper. Agreement on grading of quality was good. Kappa statistics showed 96% agreement on Cochrane grades and 86% on Jadad grades. After discussion between the reviewers (EHW and JAEW) and following reception of further details directly from authors or sponsors, there was full agreement on grading. A total of 159 studies were excluded for the following reasons (see table of excluded studies):

- absence of a placebo group (63);
- 100% use of ICS throughout the study (32);
- period of treatment less than 4 weeks (47);
- not an RCT (five): reviews (two);
- only published as an abstract without any further details available or obtainable (three);
- Combination therapy versus ICS (four), or versus placebo (one);
- Treatment administered at one-off clinic visits (two).

Sixty-three references gave additional information on the background to the review or further details on experimental designs of the included studies.

Author verification

An attempt was made to contact authors for studies with data missing on relevant outcomes. A total of 24 principal authors of eligible studies were contacted. Nine authors or sponsors of studies replied with data (Busse 1998; D'Alonzo 1994; Bensch 2001; Leblanc 1996; Meijer 1995; Pauwels 1997; Pearlman 1992; Self 1998 and von Berg 1998) and fifteen have not provided any data to date or failed to reply.

Study design

Fifty-four studies were of parallel group design and 13 of cross over design.

Intervention

Agents

The LABA agent was salmeterol xinafoate in 49 studies and formoterol fumarate in 18 studies. Salmeterol 50 mcg given twice daily at 12 hourly intervals was used in 49 studies. Two studies compared different doses with placebo: 12.5, 50 and 100 mcg in Dahl 1991a, and 25 with 50mcg BID in SLGA3014 1994.

Formoterol fumarate was the LABA agent used in 17 studies. The dose was 24 mcg twice daily in four studies, 12 mcg twice daily in nine studies and 6 mcg twice daily in three studies. Four studies using a 24 mcg dosage had a comparison group using a different dose: Bensch 2001 and Bensch 2002 using 12 mcg, Schreurs 1996 using 6 mcg and 12 mcg,

Where data from studies were combined, the dose of LABA used was the same or equivalent i.e. salmeterol 50 mcg, formoterol 12 mcg or 24 mcg (Campbell 1999). As mentioned, sensitivity analyses were performed to assess the effect of variations in doses on the result.

The bronchodilator rescue agent used in 54 studies was a short-acting beta-2 agonist agent; salbutamol (albuterol) in 48 studies at doses of 200 or 400 mcg or terbutaline in 4 studies at doses of 250 or 500 mcg. In one study fenoterol was used and in additional trial the agent used was either salbutamol or terbutaline. One study permitted the use of either salbutamol or fenoterol. In one study a combination short-acting beta-agonist and anticholinergic was used. In three studies the rescue agent was ipratropium bromide (an anticholinergic agent), and in eight studies the agent was not stated.

Treatment period

Any treatment period of four weeks or greater was specified in the revised review protocol and of the included studies the treatment periods were: four weeks (20 studies); six weeks (four studies); eight weeks (four studies); nine weeks (one study); 12 weeks (25 studies); 16 weeks (three studies); 24 weeks (three studies); 26 weeks (two studies); 36 weeks (one study); 52 weeks (five studies).

Participants

Age

Fifty-six studies included adult or adolescent participants over the age of 12 and eleven included children younger than 12 years of age.

Asthma severity

Information on the severity of participants' asthma at entry to the study was sought from each paper. Few authors specified how the classification of participants' asthma was arrived at and consistent use of guidelines to assess severity, such as those described in the Global Strategy for Asthma Management and Prevention (GINA 1995) was used or not evident. Where authors of the included studies stated that the participants had asthma of specific grades of severity this was recorded under the categories: mild, mild - moderate, moderate - severe or "persistent" if asthma was described as "persistent or symptomatic". Those studies in which no details were available on the participants' asthma severity were classified as "unknown severity".

Of the 67 included studies, 28 included participants with mild - moderate asthma, nine included subjects with mild asthma only and one included participants with moderate - severe asthma. Eleven studies included participants with persistent or symptomatic asthma and for 18 studies the severity of participants' asthma was unknown.

Co-interventions

Studies were assessed according to the co-intervention treatment for asthma used by subjects during the course of the study. The information was available for all but three unpublished studies (SLGA2004; SLGL82; SLMP03), and in most cases the authors specified that the dose was kept constant during the course of the study treatment period.

The majority of studies permitted a mixture of co-intervention treatments (40 out of 67 studies). The most frequently used were ICS or cromones, but some of these studies also permitted oral steroids at low dose and theophyllines (see table 'Characteristics of included studies').

Twenty-four studies did not permit ICS.

Table 1 details the studies in terms of their severity and concomitant steroid use.

Outcomes

Not all the 68 experimental groups contributed to the analyses in the review because of lack of data. Seven studies did not contribute any data, either because none could be obtained in a suitable form from the papers or on request from the authors or sponsors, or because the outcomes in the studies could not be combined.

The results from the parallel group studies, with subjects of any age, were combined and analysed together, stratified on the basis of age (participants under 12) and maintenance therapy usage (ICS at any dose versus no ICS used). For the crossover studies, results for first period of treatment alone were not available for combination with the parallel group studies analyses. Therefore, the crossover studies were separately combined and then the two data sets compared. The results discussed below refer to studies of parallel group design, unless otherwise specified in the text.

Excluded studies

See Characteristics of excluded studies.

Risk of bias in included studies

The methodological quality of the majority of trials was good and on the Jadad scoring method, seven scored 5 while thirty-three scored 4 and twenty-three scored 3. Four studies were given the lower score of 2 as they were not blinded by intervention. Lack of information in publications on the methods of randomisation used, meant that allocation concealment could not be confirmed in many cases (although they probably were adequate), so only eight studies were graded as confirmed adequate (A), fifty-eight were unclear (B) with one graded as obviously inadequately concealed (C).

Effects of interventions

OVERVIEW OF OUTCOMES

Measures of airway calibre showed consistent benefit from LABA treatment on morning and evening peak expiratory flow and FEV1. There were also benefits in asthma symptoms, quality of life and rescue bronchodilator usage. Major exacerbations were reduced in adults but not in children. A recently published surveillance study SMART has found a statistically significant increase in asthma-related deaths in LABA in comparison with placebo, respiratory related deaths and the combined outcome of asthma related deaths or life threatening experiences. The increase in all cause mortality and the primary outcome of the study (combined respiratory related deaths or life threatening experiences) did not show statistical significance. The absolute increase in all of these events with LABA was in the region of one extra per thousand patients treated over 6 months, but the confidence intervals around these estimate are wide. For asthma related deaths NNT(H) is 1250 (95% CI 700 to 10,000). Serious adverse events were significantly higher with LABA when the results of three studies in children were combined.

PRIMARY OUTCOMES

AIRWAY CALIBRE ASSESSMENTS

There were statistically significant advantages to LABA treatment compared to placebo for all indices of airway calibre.

PEAK EXPIRATORY FLOW (PEF)

Morning PEF was greater in the LABA group by around 15 L/min (95% CI 11 to 19.4; 20 studies, 3682 participants), but with high levels of heterogeneity (I square 69.5%). The result remained significant with random effects modelling (23 L/min (95% CI 13.3 to 32.5). In six studies with 235 participants not using any ICS the MD was 23.08 L/min (95%CI 4.74 to 41.41). There was a comparable result from three crossover studies (38.2 L/min (95% CI 3.1 to 73.29). The majority of these studies were conducted in participants with mild and mild-moderate asthma (4 studies (140 participants), 11 studies, (1410 participants) respectively). In the mild studies the effect of LABA was not significant with either random effects or fixed effect modelling but they included only small numbers and may be examples of Type II statistical errors. In the mild-moderate and persistent/symptomatic studies the effect of LABA was significant with both models (mild-moderate: FE: 16.12 L/min (95% CI 11.17 to 21.07); RE: 28.82 L/min (95% CI 14.06 to 43.59); persistent/symptomatic studies: FE/RE: 15.04 L/min (95% CI 1.95 to 28.13)).

For evening PEF the advantage to the LABA group across all studies was 12.43 L/min (95%CI 7.61 to 17.24; 14 studies, 2590 participants). In the subgroup analyses, for studies with mixed co-interventions, the difference in favour of LABA-treated participants was 23.81 L/min (95%CI 14.81 to 32.81). For non-ICS users the difference was significant, but the finding was less precise (18.32 (95% CI 2.25 to 34.38), six studies, 245 participants). There was a moderate level of statistical variation in this subgroup (I square 48.1%), and when applying a random effects model the result became non-significant (29.22 L/min (95% CI -9.31 to 67.74). Subgroup analyses by severity of asthma gave similar results for mild-moderate studies (13.29 L/min (95%CI 8.12 to 18.46)). There was a significant difference in studies recruiting children less than 12 years old (change in am PEF: 12 L/min (95% CI 2 to 22), but an advantage was not evident in three studies in mild asthma with 79 participants.

When all of the studies were combined there were significantly greater changes from baseline in PEF during treatment, measured both in the morning and the evening, in the LABA group. The differences in those treated with and without ICS were similar.

Change scores also indicated that LABA treatment led to significant differences compared with placebo (change in am PEF: 24.7 L/min (95% CI 22.62 to 26.79; 25 studies, 5512 participants); change in pm PEF: 15.09 L/min (95%CI 12.98 to 17.2; 22 studies, 5350 participants)). The findings remained significant when random effects modelling was applied (change in am PEF: 24.84 L/min (95%CI 20.41 to 29.27); change in pm PEF: 15.09 L/min (95%CI 12.98 to 17.2)). In studies where LABA was added to usual 'preventer' therapies, the change in am PEF was 29 L/min (95% CI 23 to 35.4; random effects model). In studies where participants were not using ICS the difference was 24 (95% CI 15 to 33; random effects model). Among the studies contributing to this result Nathan 1999; Pearlman 1999a and Rosenthal 1999 only included participants who had not used ICS for at least three months. The result from these studies alone did not show heterogeneity, MD 22.30 L/min (95%CI 16.70 to 27.89) (chi-squared 2.26 df 2).

There was significant heterogeneity in the subgroup analyses for the change in evening PEF. In participants where LABA was added to usual therapies the subgroup effect was 17 L/min (95%CI 14 to 20) (2980 participants, 12 studies; I square 71.2%). Funnel plots and selective omission of individual studies did not fully explain the causes of heterogeneity, although omitting Jones 1994 reduced the I square statistic to 57%). This study did not provide an estimate of the variance for the published trial and so we applied an imputed standard deviation.

Subgroup analyses of change in PEF by severity of asthma confirmed advantages of similar magnitude, though in the two largest groups those with asthma of mild-moderate and persistent/symptomatic asthma severity there was significant heterogeneity, probably related to the wide variety of co-interventions used by participants. The random effects WMD for change in morning PEF was 25.31 L/min (95%CI 16.25 to 34.38, I square 79.9%) and for persistent/symptomatic asthma was 26.31 L/min (95%CI 17.56 to 35.06, I square 86.1%). There was a high level of statistical heterogeneity of effect size of LABAs on change in evening in mild-moderate asthma (I square 77.6%), although random effects modelling did not alter the direction of the fixed effect (16.75 L/min (95% CI 12.03 to 21.47). For both morning and evening PEF changes there was only one study contributing to the analysis in mild asthmatics and in only two studies for moderate-severe asthmatics, where the difference failed to achieve statistical significance.

Studies conducted in children

There was a significant advantage in treatment with LABAs in children less than 12 years old with a larger improvement seen for both change in morning PEF (MD 16 L/min (95%CI 12 to 20); four studies, 1065 children) and for change in evening PEF (15 L/min (95%CI 12 to 19); four studies, 1063 children).

FEV1

For laboratory measures of lung function, the most frequently reported measure was the forced expiratory volume in 1 second (FEV1). Overall FEV1 was higher in LABA treated participants by around 0.24 litres (95%CI 0.21 to 0.28) with a moderate level of heterogeneity (I square 45.9%). In studies where LABA was added to background therapy the effect was 0.25 L (0.21 to 0.28). Two small studies on participants not using ICS were underpowered to detect significant differences between treatment groups (MD 0.1 litres (95%CI -0.3 to 0.5).

Small numbers of studies in the extremes of mild or severe asthmatics, limited subgroup analyses by severity of asthma. In seven studies with 1932 participants with mild-moderate asthma the MD was 0.22 litres (95%CI 0.16 to 0.29).

Similar results were seen in five studies of crossover design with a MD at the end of treatment of 0.13 litres (95%CI 0.01 to 0.25). In one parallel group study with 354 children under 12 years the difference was 0.19 litres (95%CI 0.06 to 0.32).

LABA led to a significantly greater increase in FEV1 from baseline over that on placebo by 0.17 litres (95%CI 0.14 to 0.2); 17 studies, 3295 participants. The difference between the subgroups of studies where background therapy was used and studies with no ICS use was not significant (P = 0.269).

Two subgroups had two or more studies in them. In persistent/symptomatic asthma the mean difference was 0.2 (95 % CI 0.15 to 0.26, four studies with 1336 participants), and in moderate asthma the MD was 0.15 litres (95%CI 0.06 to 0.24, two studies with 274 participants). There was only one study each with data including subjects with either mild or severe asthma, though both gave significant results of similar magnitude to the overall outcome data.

Data on FEV_1 change for children were available as % predicted FEV1 from three trials (693 children), indicating a significant difference in favour of LABA of 4% (95% CI 2 to 6).

FEV1 AUC

There was a significant difference in favour of LABA of around L-h 2.23 L-h (95% CI 1.71 to 2.75), seven studies, 1312 participants.

FVC, FEF 25-75%

Results for forced vital capacity (FVC) or maximum mid expiratory flow (FEF25-75%) were only reported in two studies using 302 subjects with asthma of mild-moderate severity and taking a variety of co-interventions. The differences favoured the LABA treatment group but were not statistically significant.

SYMPTOM SCORES

There were significantly fewer symptoms in the LABA group across the board on a variety of measures at the end of treatment. Scales used to measure asthma symptoms varied from 3 to 6 points and scores were generally derived as a composite based on a number of symptoms, e.g. cough, wheezing, shortness of breath and chest tightness assessed during the day and/or overnight and whether sleep was broken by asthma symptoms. The proportion of days with symptom scores of zero and nights without awakenings due to asthma were also assessed. All measures showed significant advantages in the LABA compared with placebo. All findings reported below pertain to SMDs because of the different metrics used to assess this series of outcomes.

Daytime symptoms were significantly better in LABA treated participants (-0.34 95% CI -0.44 to -0.25; 14 studies, 1836 participants). Nocturnal symptoms were also better in LABA treated participants: SMD -0.54 (95% CI -0.64 to -0.45 in eight studies with 1758 participants). There was no significant difference between the subgroups analysed on the basis of including background ICS use.

Subgroup analysis of symptom score data indicated that the effect of LABAs was consistent across the groups of trials based on the classifications of severity in the review.

Symptoms fell from baseline by a greater amount during treatment with LABAs compared to placebo. The difference overall was -0.49 (95%CI -0.58 to -0.41) for day time symptoms in eleven studies with data reported on 2629 participants, and -0.54 (95%CI -0.87 to -0.22, random-effects modelling) for night time symptoms in three studies with 823 participants. The nocturnal symptom results showed significant heterogeneity that may be due to the variations in severity of asthma and different doses of preventer drugs being used.

LABA treated participants had significantly fewer days affected by asthma (16%, 95% CI 14 to 19; nine studies, 2060 participants), and also fewer night symptoms expressed as both % nights without symptoms (10.79%, 95% CI 6.48 to 15.1; nine studies, 2093 participants), and the % nights without awakenings (15.81%, 95% CI 14.22 to 17.41; 13 studies, 3925 participants). The high level of statistical heterogeneity observed for % nights without symptoms may be partly explained by the difference between non-ICS users and participants where LABA was added to variable usual therapies (P = 0.047). Two possible effects could explain this difference. One possibility is that in the usual therapy trials, the addition of LABA improves asthma control in the participants on stable doses of ICS whose relief from symptoms is more pronounced than it is in the participants who are given LABA alone, who do not benefit from an effective concomitant maintenance treatment. The second possibility is that since this difference is of only borderline statistical significance, it is an artefact of the numerous analyses based on multiple outcomes and subgroups identified in this review. Only one study in children was reported with the percentage of nights affected by asthma awakenings with LABA in 210 children being fewer with the MD being 6.40% (95%CI 2.11 to 10.69).

RESCUE BRONCHODILATOR USE

LABA treated participants used significantly less rescue medication than the placebo group. The rescue agent used in all studies contributing data to the analyses was a short-acting beta-2 agonist. LABA reduced the requirement for rescue short-acting beta-agonist when expressed as absolute and change scores for 24-hour and also day and night periods. In spite of high levels of statistical heterogeneity in these outcomes the results were significant with both fixed-effect and random-effects modelling (difference in SABA usage for 24 hours: -0.9 puffs/d, 95% CI -1 to -0.7; eight studies, 1885 participants; mean change in SABA usage over 24 hours: -1.2 puffs/d, 95% CI -1.4 to -1; 12 studies, 2197 participants; SABA use (day): -1 puffs/d, (95% CI -1.3 to -0.8; three studies, 691 participants; change in SABA use (night): -0.54, 95% CI -0.7 to -0.4; two studies, 633 participants).

There was significant heterogeneity found in the pooled analysis of rescue therapy use. A contributing factor in addition to variation in asthma severity and treatment may have been the different short acting beta-2 agonist agents used, the different doses and varying inhalational devices. Heterogeneity persisted in the subgroup analyses.

Results of a similar magnitude and direction were seen for the change in rescue medication use both during the day time and at night time across the severity range. The limited data from mild and severe asthma mean that a larger evidence base in these patients is required before more reliable statistical investigation of the effects of LABA on rescue medication usage based upon disease severity can be undertaken.

EXACERBATIONS OF ASTHMA: MAJOR EXACERBATIONS

Twenty-three studies (5995 participants) reported data on exacerbations of asthma. There was a large reduction in the odds of experiencing at least one major exacerbation during the study in the LABA group compared with placebo, OR 0.73 (95%CI 0.64 to 0.84). The definition of a major exacerbation was stated for the majority of studies. In 10 studies with 2547 adult participants a major exacerbation of asthma was defined as worsening of asthma symptoms requiring treatment in addition to the study drug and usual rescue short acting inhaled beta-2 agonist agent. When the analysis was confined to these studies the OR was 0.64 (95%CI 0.52 to 0.79). In 10 studies with 2468 adult participants where a definition was not given or was less precise the result was similar, OR 0.59 (95%CI 0.46 to 0.76). 5 cross over studies (n=337) showed a similar but non-significant result, OR 0.80 (95%CI 0.42 to1.54).

Paradoxically, three studies on children reported data on exacerbations and the pooled analysis actually suggested an increased risk of exacerbation, OR 1.22 (95%CI 0.92 to 1.62) though the result was not statistically significant. Based on a test of interaction, the difference between the adult and children subgroups was highly significant (P = 0.000045).

Subgroup analyses - Inhaled corticosteroid (ICS) use

In 17 studies with 4439 participants with varying rates of use of 'preventer' therapy, there was a significant reduction in exacerbations in the active treatment group, OR 0.64 (95%CI 0.54 to 0.76). In six studies with 1500 participants not using ICS, the reduction in the odds of an exacerbation was similar and also significant, OR 0.71 (95%CI 0.53 to 0.96).

Subgroup analyses -Asthma severity

The LABA treatment group had a significantly lower risk of a major exacerbation in mild - moderate asthma and persistent/ symptomatic asthma, which characterised the majority of the

study populations in this outcome (mild - moderate asthma: OR 0.68, 95%CI 0.55 to 0.83; 10 studies with 3106 participants; persistent/symptomatic asthma: OR 0.76, 95% CI 0.63 to 0.93; eight studies, 2408 participants). The findings were re-examined with sensitivity analysis restricted to adult studies since the paediatric data highlighted the possibility of an increase in the odds of an exacerbation in children. The resultant OR in the mild - moderate subgroup of studies was lower (OR 0.46 (95% CI 0.35 to 0.6)).
A single crossover study (Taylor 1998) reported a difference for the corrected rate of major exacerbations of -0.18 exacerbations per patient per year (95%CI -0.38 to 0.02) with LABA.

MINOR EXACERBATIONS OF ASTHMA

Taylor 1998 applied a somewhat onerous definition for a minor exacerbation based on fall in morning PEF, increasing symptoms and increasing use of rescue bronchodilator in a crossover study. The difference was significant (-0.68 exacerbations per patient per year, 95%CI -0.95 to-0.41).

ADVERSE EVENTS

Asthma-related Death

Findings from SMART indicated that in participants using mixed co-interventions (including ICS) at baseline there was a significant increase in the odds of asthma-related death occurring in the LABA treated group (13 versus 3; RR 4.4, 1.25 to 15.3; N = 26355). This represents an absolute increase of one extra death over six months for every 1250 patients treated with LABA, but the confidence interval is wide (95% CI 700 to 10,000). The size of this difference was consistent across all the mortality and life threatening experience outcomes measured in this study, and was statistically significant for asthma related death, respiratory related death and the combined outcome of asthma-related death and life threatening experiences, but not for all cause mortality (with or without life-threatening experiences or the combined endpoint of respiratory-related death or life-threatening experiences). In those not using ICS at baseline, the number of participants suffering asthma-related death was higher in LABA than placebo treated groups (9 versus 0, N = 14090). The published trial report did not provide an estimate of the risk ratio as the authors decided that Relative Risk should not be calculated when there were no event rates in the control group. However, we used RevMan 4.2 to calculate the Relative Risk of asthma-related death for both the subgroups with and without ICS at baseline (using the normal adjustment of adding 0.5 to each cell when there are no events in one cell); for those taking ICS at baseline the Relative Risk is 1.34 (95% CI 0.30 to 5.97), whilst for those not taking ICS at baseline the Relative Risk is 18.98 (95% CI 1.1 to 326). The test for interaction between these subgroups does not reach significance (P= 0.08). Caution should be exercised in the interpretation of subgroup differences as patients were not randomised to ICS in this study, and data on ICS use was collected at baseline only.

A post-hoc within study subgroup analysis by ethnicity, indicated that African-Americans were more likely to experience a composite endpoint of respiratory -related death and life threatening adverse events (intubation and mechanical ventilation) than Caucasians, Relative Risk Increase 3.9 (95% CI 1.29 to 11.84). There was, however, no significant difference found in asthma-related deaths between African-Americans and Caucasians; results from life table analyses for African-Americans 7 versus 1; RR 7.26(95% CI 0.89 to 58.94: N = 4685), whilst for Caucasians 6 versus 1; RR 5.82 (95% CI 0.70 to 48.37; N=18,642).

When the endpoint was broadened to incorporate respiratory-related death there was a just significant difference in the Relative Risk of death between LABA and placebo for the total population of 2.18 (95% CI 1.07 to 4.05), N = 26355. There was no significant difference between the subgroups using ICS at baseline and those not using ICS at baseline (test for interaction P = 0.84). The increase in all-cause mortality yielded non-significant results (RR 1.33, 95% CI 0.76 to 2.35; three studies using the non-ICS subgroup from SMART, N = 14534 and RR 1.37, 95% CI 0.87 to 2.14 using all participants from SMART, N = 26799).

Serious adverse events

There was a significant increase in the odds of asthma-related serious adverse events on LABA treatment (OR 7.46, 95% CI 2.21 to 25.16; three studies, N = 895). However, the odds ratios of life-threatening adverse events from SMART for both mixed (i.e. total) and ICS - treated populations were not significantly different. LABA treatment led to a significant increase in the odds of serious adverse events where this was reported for 'total events' in three paediatric studies (OR 2.11, 1.03 to 4.31; N = 973).

Total and drug-related adverse events

There was no significant difference between LABA and placebo in total adverse events, although the lower limit of the 95% CI only just crossed unity (OR 1.15, 95% CI 0.99 to 1.33; 18 studies, N = 3447). There was a higher instance of drug-related adverse events occurring in LABA treated participants in mixed co-intervention groups (OR 1.37, 95%CI 1.01 to 1.87; seven studies, N = 2130), and "nervousness" (OR 5.11, 95% CI 1.72 to 15.22;, two studies, N = 546). There were also significant differences in favour of placebo in mixed co-intervention studies for tremor (OR 3.86, 95% CI 1.91 to 7.78; eight studies, 2257 participants), and across total populations for headache (OR 1.28, 95%CI 1.04 to 1.57; 23 studies with 5667 participants) and throat irritation (OR 1.68, 95% CI 1.10 to 2.56; eight studies, N = 1170). There was no significant different in the odds for pharyngitis, cough, cramps, myalgia/fatigue, insomnia, upper respiratory tract infection, of asthma, musculoskeletal pain or palpitations.
Withdrawals
All-cause study withdrawal was less likely on LABA than on placebo treatment (OR 0.91, 95% CI 0.86 to 0.96; 19 studies, N = 30599). There was no significant difference in the likelihood of withdrawal due to adverse events between placebo and LABA (OR 1.11, 95% CI 0.93 to 1.32; 21 studies, N = 30943). Withdrawals due to lack of efficacy were significantly less frequent on LABA than on placebo (OR 0.60, 95% CI 0.53 to 0.68; 14 studies, N = 29466). There was no significant difference in withdrawal due to exacerbations of asthma (OR 0.82, 95% CI 0.46 to 1.46; seven studies, N = 1658).

SECONDARY OUTCOMES

QUALITY OF LIFE

In addition to instruments to measure general quality of life, asthma-specific measurement of the impact of asthma on patients' quality of life is now possible, using purpose - designed instruments, which are of proven reliability, validity and responsiveness. These provide a robust and reliable measurement of this aspect of treatment efficacy. The asthma specific measures most often used in the studies included in this review were the

Living with Asthma Questionnaire (LWAQ) by Hyland 1991 and Asthma Quality Of Life Score (AQOL) based on Juniper 1992.

Six parallel group studies (1608 participants) measured quality of life changes with treatment and reported results that could be combined for analyses. They each used the AQOL, which contains 32 questions in four domains; activity limitation, symptoms, emotional function and environmental stimuli. For the global score, there was a clinically and statistically significant advantage to the LABA treatment group compared with placebo, though on inspection there were high levels of statistical heterogeneity across the trials (I square 73.1%). The random effects MD for the improvement in global score during treatment was 0.51 (95%CI 0.42 to 0.6)).

Results for improvements in the separate QOL domains for a subset of these studies were: for activity limitations: 0.4 (95%CI 0.3 to 0.50; three trials), for symptoms: 0.73 (95%CI 0.58 to 0.87; two trials), for emotional function: 0.66 (95%CI 0.48 to 0.83; two trials) and for exposure to environmental stimuli: 0.56 (95%CI 0.42 to 0.7; two trials). There were no studies on participants not using ICS.

One crossover study (Juniper 1995) used the same instrument to assess quality of life in 140 participants on a variety of mixed co-interventions with asthma of unclassified severity, and reported the results as differences between active and placebo treatment. There were significant advantages, similar to the combined parallel group studies results above, for the LABA group overall in the global score of 0.55 (95%CI 0.48 to 0.83) and in the four individual domains:, activity limitation 0.43 (95%CI 0.28 to 0.58); symptoms 0.65 (95%CI 0.48 to 0.83); emotional function 0.65 (95%CI 0.43 to 0.86); and exposure to environmental stimuli 0.45 (95%CI 0.29 to 0.61).

REDUCTION IN USE OF CO-INTERVENTIONS: ANTI-INFLAMMATORY NON-STEROIDAL MEDICATIONS

One study (Adinoff 1998) attempted to wean subjects in both active and placebo groups from non-steroidal asthma medications. A higher proportion of subjects (62%) treated with LABA was weaned from at least one other non steroidal medication compared to placebo (54%) but the difference was not statistically significant (OR 1.43, 95%CI 0.85 to 2.40)

GLOBAL ASSESSMENT OF EFFICACY

Four studies reported on results of the assessment of efficacy of study treatment, using scales offering the patient a range from very good or very effective to poor or poorly effective. LABA treatment was associated with significantly better assessment of efficacy by participants (OR 2.83,95% CI 2.15 to 3.74;, N = 879) There were similar results for the investigators' assessment of efficacy of study treatment (OR 8.04, 95% CI 4.63 to 13.94; two studies, N = 268).

BRONCHIAL HYPERREACTIVITY

Seven studies assessed bronchial hyperreactivity which involved inhalational challenge to the airways with solutions of methacholine or histamine, carried out 8-12 hours after the last dose of study medication, and measured changes in "underlying" airway reactivity from baseline during treatment periods from 4-52 weeks. There was a greater increase in PD/PC 20 i.e. a larger fall in airway reactivity in the LABA group relative to baseline, than during treatment with placebo. There was a consistent and significant difference in favour of LABA over placebo of 0.56 doubling-doses of inhalational bronchoconstrictor (95% CI 0.30 to 0.82).

BRONCHOPROTECTION AGAINST AIRWAY CHALLENGE

Measurement of airway reactivity one hour after a dose of a beta-2 agonist measures the bronchoprotection that it confers, presumably mainly due to physiological antagonism of the induced airway smooth muscle contraction. This was investigated in four studies for the first dose of a LABA and repeated after regular doses over periods from 2 to 8 weeks, to assess the development of "tachyphylaxis" to bronchoprotection. The degree of protection fell from the initial dose effect after regular LABA treatment. In one parallel group study with 23 participants (Cheung 1992) the difference in first dose bronchoprotection for LABA treatment compared to placebo was MD 3.94 doubling doses methacholine (95%CI 3.21 to 4.67). Similarly, in one study of crossover design (Boulet 1998b), the MD was 1.76 doubling doses (95%CI 0.81 to 2.71).

BRONCHODILATOR TOLERANCE OR TACHYPHYLAXIS ON REGULAR LABA TREATMENT

Newnham 1995 investigated tachyphylaxis to airway response to formoterol with regular treatment over 4 weeks in two crossover studies in subjects on a variety of asthma co-interventions. The peak FEV1 increase from the dose response curve to LABA was significantly attenuated with regular use; the difference in one study was -0.26 litres (95%CI -0.43 to -0.09) and in the other study the results were given as 0.84 litres for active treatment compared to 1.00 litres for placebo, but the standard deviation was not available. Investigation of tachyphylaxis after regular LABA treatment to salbutamol-induced bronchodilatation in two studies did not produce results suitable for combining in an analysis. Nelson 1999b found no significant differences in the salbutamol dose-response curves for changes in FEV1 after treatment with salmeterol whether participants were treated with or without ICS.

EXERCISE-INDUCED ASTHMA

Data were reported in one parallel group study (Garcia 2001) and in two crossover studies (Simons 1997b and Ramage 1994) for exercise induced asthma in subjects treated with formoterol (Garcia 2001) or salmeterol (Ramage 1994 and Simons 1997b). Regular treatment with LABAs gave protection against exercise-induced bronchoconstriction. There was a significantly smaller fall in FEV1 (measured in litres or as a percentage) with exercise in a standard exercise test , performed 6 to 12 hours after study drug dosing, in the active treatment group compared to placebo, SMD -0.61 (95%CI -1.15 to -0.07) in crossover studies (n=28) and WMD -11.12% (95%CI -21.04 to -1.20) in one parallel group study (n=19).

DISCUSSION

As a chronic disease, with no known cure, the accepted goals of management in chronic asthma are to minimise the adverse impact of the disease on the patient's physical and mental well being and to try, through good control, to minimise long term damage to the airways and prevent undue fixed airway obstruction thought to be due to structural "remodelling" of the airway wall. Treatment is therefore directed at improving physiological endpoints, patient-perceived physical and mental health, and overall minimisation of disease activity and risk to health.

There have now been a number of systematic reviews on LABA use published in the Cochrane Library on asthma subjects uniformly receiving ICS. This review has attempted to summarise the remaining studies, which have included patients receiving

either a variety of background disease modifying agents (usually ICS) or none. We have focused on disease control, but have also emphasised severe adverse events, and especially mortality; drug related death being the worse outcome of all. For the primary outcome of interest in this review, that of asthma control as assessed by airway calibre, asthma symptoms with rescue medication use and exacerbations of asthma, we have demonstrated that there were significant and clinically meaningful advantages to regular treatment with inhaled LABA agents compared to placebo in both adults and children, generally across the board in the subjects of interest: both those on a variable regime of preventer medication and those taking no preventer (ICS).

There were consistent advantages for FEV1, morning and evening peak expiratory flows, in patient-assessed symptoms and in the amount of additional bronchodilator agent used in overall pooled analyses. Subgroup analyses indicated the most consistent effects to be in studies with participants using ICS or other co-interventions regularly. Evidence from analyses on studies of asthmatics not using inhaled corticosteroids generally similar but was less consistent, though there were fewer studies in this category

The heterogeneity found in some of our analyses, especially when all studies were combined, may be explained by differences in the population of asthmatics from which participants were recruited, reflecting a large natural variation within the disease spectrum. Heterogeneity was markedly less in the analyses of studies classified by participants' use of ICS or severity of asthma. For the most part we have accepted the study authors' categorisation of "severity" of disease. This is likely to reflect a mixture of asthma features: past severe disease episodes, need for ICS at whatever dose, and current level of symptoms and lung function in spite of that dose on ICS. The concept of asthma severity is always somewhat circular and tautological, but in a robust way is helpful clinically and as a general descriptor. Although the precise definitions used might have differed in specific circumstances, it is likely that the definitions here would not have been much different to those used by national and international guidelines (BTS 1995; GINA 1995; NAC 2002) because they all arise from similar clinical concepts and shared clinical cultures and experiences. Where exactly to fit into a "severity" spectrum those described as "symptomatic" or "persistent" is perhaps rather more difficult, because it depends on context, and how aggressively their caring physician had attempted to ameliorate the symptoms with preventer therapy i.e. ICS. It is likely that they would have fitted best with the moderate - severe group, and their outcomes as a group would suggest that, but we made a prospective decision to analyse them separately which was undertaken. However, overall the consistency of the results across the board and their clinically important levels make the positive results for LABA use compelling.

Evidence of deterioration in asthma control was sought in assessing occurrence of exacerbations of asthma during treatment, particularly in the light of historical concerns about regular use of beta-2 agonist agents potentially making asthma control worse. In the event, there was a significantly decreased risk of experiencing an exacerbation of asthma in the total adult LABA treatment group, and this result was robust with differing definitions of an exacerbation. When defined precisely as worsening of asthma symptoms that required treatment in addition to the study drug and rescue bronchodilator, the OR for an exacerbation was 0.7 (95%CI 0.6 to 0.8). Although the outcome was generally consistent, it was not significant in those studies not using ICS at all or in those with either mild asthma alone or moderate - severe asthma alone. A paradoxical result was obtained in studies with children alone. There was a non-significant increase in risk of exacerbation of asthma found in five studies in which all paediatric participants used regular preventer, the majority using ICS, with cromones being used by the remainder. Why children might be different from adults needs further investigations as it could be of major concern and clinical relevance.

The lower risk of asthma exacerbations in adults is in contrast to the fears expressed in the debate over regular beta-2 agonist use and its possible harmful effects. The finding is of interest in terms of the pathological data found in studies of airway biopsies and lavage fluid from airways taken during treatment with LABA, which have consistently shown either no change or an improvement in underlying airway inflammation on LABA treatment (Gardiner 1994, Li 1999 and Wallin 1999). LABA may enhance the effects of corticosteroid at a gene level by increasing translocation of the CS-CS Receptor complex to the nucleus (Johnson 2004), but LABA may have independent anti-inflammatory effects especially on the Innate Immune System (Reid 2003).

Deaths

We were especially interested in the most severe potential negative outcome from LABA therapy, namely asthma-related death and life-threatening asthma events. Most of the data contributing to these analyses came from SMART (Nelson 2006), which recruited over 26,000 adult subjects between 1996 and 2003, 47% on ICS, before being concluded prematurely because of excess asthma deaths on LABA (Salmeterol) and difficulties in recruiting. The all-cause deaths were low (72 in total in a 28 week study i.e. about 0.2%), and not significantly different between LABA and placebo groups. The asthma-related death rate was lower overall than expected, by about 50%, but significantly different between groups: 13 to 3 in LABA versus placebo groups. There was a significant excess of the primary outcome of combined asthma-related death or life threatening experience on LABA, 37 to 22 (relative risk 1.7, 95% CI 1 to 2.9), with a significant difference found between African-Americans (who constituted 18% of this study population) and Caucasians (71%), test for interaction P = 0.02. The former as a group had more symptomatic asthma and worse lung function, but less use of ICS (38% versus 49% for Caucasians). No significant differences were found for the outcomes asthma-related deaths or respiratory-related deaths when African-Americans were compared with Caucasians. Furthermore, all the excess in deaths occurred in the first three year phase of recruitment, and in particular in 1998, when recruitment was by community advertisement, rather than through the subsequent method of recruitment through doctors' clinics. The excess of deaths was also predominantly in those not on ICS. Although the finger of doubt is undoubtedly pointed at LABA for "causing" excess deaths from SMART, it may be that the excess mortality relates to poorly controlled, non-ICS treated patients. It is possible that there could be a genetic polymorphism common in African-Americans that makes them more pre-disposed to severe asthma events on LABA (Hawkins 2006), but given the other features and peculiarities in this study's outcomes, it seems even more likely that danger arises if LABA is prescribed without ICS in poorly controlled subjects who should definitely be on ICS by standard guideline definitions.

For the secondary outcomes assessed, results from Quality of Life measures showed that treatment with LABA conferred clinically significant advantages at or above the minimally important level in overall score and in the separate domains of asthma symptoms, emotional function, and exposure to environmental stimuli. For activity limitation the change was just less than that defined as of minimal clinical importance, a mean difference of >= 0.5 representing the minimally clinically important change, with 1.0 and 1.5 representing moderate and maximal changes respectively (Juniper 1994).

The evidence for an effect of regular treatment with LABA in permitting weaning from non-steroidal anti-inflammatory asthma medication was not conclusive, but there was a significantly greater odds ratio for at least a 50% reduction in ICS dose in one study (Nielsen 1999) and a non-significant reduction in daily ICS dose in two other studies. This was supported by a similar difference in ICS dose after weaning in a crossover study, -18% (95%CI -38 to 2) (McIvor 1998). The possibility of a reduction in need for anti-inflammatory medication on treatment with LABA again suggests some inherent anti-inflammatory or disease modifying effects. This may be independent of ICS use, or may be through enhancing the efficacy of ICS (Johnson 2004)

The results confirm the acceptability of treatment with LABA as assessed by both patients and investigators. Results for assessment of control of asthma as 'good' or 'very good' by patients gave significantly higher odds ratio in those using LABA compared to those using placebo. Investigators also rated efficacy with LABA as superior, though most studies did not quote the actual results.

This review specifically assessed possible pharmacologically - predictable adverse effects of regular use of inhaled LABA. If beta-2 agonists are absorbed into the systemic circulation, then stimulation of beta-adrenergic receptors in non-respiratory tissues will occur, in a dose-related way i.e. dependent upon blood levels of drug achieved. These effects include a positive cardiac chronotropic (increased heart rate) and inotropic (increased force of heart contraction) effect, which may be experienced as palpitations. Skeletal muscle receptor activation will cause fine tremor of the hands, and contribute to metabolic effects including hypokalaemia, hyperglycaemia, metabolic acidosis, elevation of free fatty acids and ketones. Direct vascular effects cause systemic peripheral vasodilatation, which may precipitate headaches and cause a fall in blood pressure. For those studies that reported adverse events data, there was a small increase in the odds ratio for some for these predictable trial medication-related adverse event occurring in the LABA group compared with the placebo group, but this was mainly for the occurrence of headache. There was no significantly increased risk found for the occurrence of palpitations, tremor or muscle cramps.

Underlying airway responsiveness was assessed to directly acting bronchoconstrictor agents such as methacholine or histamine, at a time when most of the bronchodilator effects would have dissipated, with a significant improvement in BHR during treatment, WMD 0.5 doubling doses (95%CI 0.3 to 0.7) when all studies were combined. This was similar whether participants were using ICS or not. This is reassuring in that underlying airway responsiveness is not worsened, as had been hypothesised in the "ß-agonist debate" of the late 1980's and early 1990's. Even so the residual improvement in this late phase may not be clinically meaningful, being still less than one doubling dose, which is usually taken as the minimally significant and measurable change in PD 20 in a group.

There is ongoing debate over tachyphylaxis to LABA protection against direct airway challenge agents and against indirect agents acting through mast cell de-granulation. The analyses confirmed that tachyphylaxis develops to the initial bronchoprotective effect of LABA on direct airway challenge with regular treatment. Even so, there was continuing clinically significant protection against direct airway challenge conferred by LABA even after regular periods of treatment.

Overall, this review gives reassuring evidence for the effectiveness of LABA used regularly in chronic asthma, and does not show any evidence that underlying control of asthma deteriorates with regular use. The evidence is based on a broad range of studies across the asthma spectrum, but is strongest for mild - moderate severity and when concurrent treatment with inhaled corticosteroids is given. There was a relative paucity of studies on children with contributing data and in children a possible increase in exacerbations requires further investigation.

A lack of consistency in outcomes chosen for measurement and reported in individual studies reduced the data available for the analyses. However, the conclusions for the main clinical outcomes were based on large numbers of subjects, whereas for secondary outcomes in studies investigating the mechanisms of action of LABA the conclusions were based on smaller numbers and may thus have less weight. Heterogeneity was quite large in the analyses of some outcomes, but do not confound the conclusions.

AUTHORS' CONCLUSIONS

Implications for practice

Long acting beta-2 agonists (LABA) are highly effective in chronic asthma, and the evidence particularly supports their use in ICS treated asthmatics, as emphasised in current guidelines. These suggest that LABA should be used in patients who remain symptomatic in spite of the use of reasonable doses of ICS. The short acting beta-2 agonist debate, centred mainly on epidemiological data, suggests that regular short acting beta-2 agonist use might have risks and lead to deterioration of underlying disease. This review indicates that the overall risk of asthma-related deaths may be increased with LABA, but the size of this increase in uncertain with a confidence interval ranging from one extra death for every 700 to 10,000 given LABA for six months.

The US Food and Drug Agency (FDA) has added a warning that LABA should not be used to treat asthma without concurrent ICS. Therefore we have decided not to carry out any further updates to this review.

Implications for research

Future research is needed on whether LABA modify the long term accelerated decline in FEV1 in chronic asthma, especially if used in addition to ICS. Studies in children using preventer medication and adults with mild asthma not using ICS over longer periods are needed to investigate exacerbation rates and safety. LABA given regularly would seem to have disease modifying effects that cannot be explained merely by long-acting bronchodilatation and this needs further exploration to gain insights into what pathophysiological changes occur in the airways during their

use. More evidence is needed on effects of LABA on chronic inflammation and especially on airway wall remodelling, where there is a particularly marked paucity of information in such an important area.

The implications for research have been revised to reflect current evidence regarding the known benefits and harms of LABAs from other Cochrane Reviews. Readers should consult the overviews which summarise the results of Cochrane reviews on the safety of LABAs in adults and children (Cates 2012; Cates 2014).

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

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

Adinoff 1998

Methods	STUDY DESIGN: Parallel group 4 groups, multicentre, 27 in USA (majority primary care). 4-6 weeks initially, 2 groups weaned from non steroidal asthma medications, then 36 weeks treatment RANDOMISATION: Yes, randomised in blocks 5:5:5:1 BLINDING: double blind, double dummy, matching devices WITHDRAWALS/DROP OUTS:75 withdrawals in total, 61 protocol violations, 5 lack efficacy COMPLIANCE: Not assessed CONFOUNDERS: Groups well balanced by characteristics QUALITY: Jadad 4. Cochrane B
Participants	N= RANDOMISED 386 /COMPLETED 311, adult/adolescents, M=203 F=183 Mean age36.5 (range 12-85) BASELINE SEVERITY: stable asthma, severity not stated INCLUSION : Diagnosis asthma by ATS criteria, Baseline FEV1 50-80% predicted, >15% FEV1 reversibility to SABA.

Adinoff 1998 *(Continued)*

	EXCLUSION: non smoker >1yr, history life threatening asthma, requiring > 2 canisters SABA/month, oral steroids or RTI < 1 month
Interventions	LONG ACTING BETA AGONIST: Salmeterol 42 mcg BD PLACEBO: BD DEVICE: MDI TREATMENT PERIOD: 2-6 weeks weaning, 36 weeks maintenance RESCUE: Albuterol prn CO-INTERVENTIONS: ICS 64%, cromones 20%, theophylline 77%
Outcomes	OUTCOMES: FEV1, PEF, Rescue use, asthma symptom score, adverse events . Exacerbations, % days with no symptoms ,% nights with no asthma awakenings
Notes	Patients weaned from non steroidal asthma therapy during initial treatment period, asthma symptoms score=6 pt scale for chest tightness, wheezing, shortness of breath, coughing, exacerbation= events requiring treatment in addition to current asthma therapy

Bensch 2001

Methods	STUDY DESIGN: Parallel group. Multi centre, 26 in USA. 12 week treatment period. RANDOMISATION: Yes, no method stated. BLINDING: double blind, double dummy, placebo controlled. Matching capsules and devices. WITHDRAWALS/DROP OUTS: 83described, 35 due to adverse events. COMPLIANCE: Assessed by counting capsules and weighing canisters, >80% in all groups. CONFOUNDERS: Baseline characteristics similar for all groups. QUALITY: Jadad 4. Cochrane B
Participants	N= 541 randomised, 535 ITT M=224, F=317 ADULT Mean age 35.5 yrs (SD14.6) BASELINE SEVERITY: Mild-moderate persistent asthma. INCLUSION : Diagnosis of asthma, requiring daily use of inhaled SABA. Baseline FEV1 40-80% predicted, >15% reversibility to inhaled SABA EXCLUSION: URTI, hospitalization/asthma exacerbation < 4 weeks, serious illness.
Interventions	LONG ACTING BETA AGONIST: Formoterol 12/ 24 mcg BD SHORT ACTING BETA AGONIST: Albuterol 180 mcg QDS PLACEBO: Placebo QDS DEVICE: LABA Aerolizer DP device & SABA MDI TREATMENT PERIOD: 12weeks RESCUE: Short acting beta2 agonist- albuterol 90 mcg inhalation PRN CO-INTERVENTIONS: ICS 51%, Slow release theophylline 17%.
Outcomes	OUTCOMES: FEV1, FVC, FEV25-75%, PEF, Rescue albuterol, asthma symptom score, asthma exacerbations, adverse events.
Notes	Symptom Score- breathlessness, chest tightness, wheezing, cough; scaled 0-4.

Bensch 2002

Methods	STUDY DESIGN: Parallel group, international paediatric multicentre (42). 2 week run-in/ 52 week treatment period. RANDOMISATION: Randomised, no method given. BLINDING double blind, placebo controlled, no details. WITHDRAWALS/DROP OUTS: 111 post randomisation. COMPLIANCE: no details. CONFOUNDERS: groups balanced by baseline characteristics.

Bensch 2002 *(Continued)*

	QUALITY: Jadad 3 Cochrane B
Participants	N = 601 enrolled, 518 randomised (ITT analysis population), M=342, F=194 Mean age 9 yrs (SD2) BASELINE SEVERITY: Persistent asthma on preventer. INCLUSION : Diagnosis asthma by ATS criteria, ICS or cromone treatment for 4 weeks. Baseline FEV150-85% predicted, >15% FEV1 reversibility to SABA. EXCLUSION : Unstable asthma, URTI, OS course or exacerbation asthma within 4 weeks, QT interval on ECG >0.46sec.
Interventions	LONG ACTING BETA AGONIST: Formoterol 12 mcg or 24 mcg BD PLACEBO: BD DEVICE: Aerolizer RESCUE: salbutamol PRN TREATMENT PERIOD: Part 1: 4 weeks . Part 2 : 26 weeks. CO-INTERVENTIONS: 70% on ICS, 30% on cromones (all stable dosage)
Outcomes	OUTCOMES: Part 1: Primary= AUC for FEV1 over 12 hours after morning study drug dose Secondary= PEF, FEV1, FVC, day and night ASS, rescue use, exacerbations asthma. Adverse events.
Notes	Exacerbation defined as increase symptoms asthma, >4 x200mcg SABA /day, requiring OS and nebulized SABA. Data published as adjusted mean, requested actual data from authors.

Booth 1993

Methods	STUDY DESIGN: Parallel group single centre, UK, hospital setting, 2-12 days run in/ 8 weeks treatment/ 2 weeks run out RANDOMISATION: Yes, no method stated. BLINDING: double blind, placebo controlled, matching devices WITHDRAWALS/DROP OUTS: 4 withdrawals, 3 LABA, 1 placebo COMPLIANCE: Not assessed CONFOUNDERS: Baseline characteristics similar, study performed out of pollen season, salbutamol withheld 8 hrs prior to BHR measurement QUALITY: Jadad 4. Cochrane B
Participants	N= RANDOMISED 26 , M=15 F=17, adults, Mean age 40 (range 20-64) BASELINE SEVERITY: Mild-moderate asthma INCLUSION : Diagnosis clinically stable ,>15% FEV1 reversibility to SABA. EXCLUSION: OS within 3 months
Interventions	LONG ACTING BETA AGONIST: Salmeterol 50 mcg BD PLACEBO: BD DEVICE: MDI TREATMENT PERIOD: 8 weeks RESCUE: Salbutamol 100 mcg prn CO-INTERVENTIONS: ICS <1000mcg BDP daily in 19/26, 73%
Outcomes	OUTCOMES: FEV1, PD20 methacholine,
Notes	

Boulet 1997

Methods	STUDY DESIGN: Parallel group, single centre, Canada, hospital setting, 2 weeks run in/ 8 weeks treatment RANDOMISATION: Randomised treatment , code used.

Boulet 1997 *(Continued)*

	BLINDING: double blind, placebo controlled WITHDRAWALS/DROP OUTS: 3 withdrawals. COMPLIANCE: not stated CONFOUNDERS : Groups well balanced by characteristics, study avoided allergen season QUALITY: Jadad 4. Cochrane B
Participants	N= RANDOMISED 16, 1 completed. & analysed M=5 F=8, adults, Mean age 25 (range 20-37) BASELINE SEVERITY: mild asthma INCLUSION : Diagnosis asthma by ATS criteria, Baseline FEV1 >70% predicted. Dual response to allergen, EAR >20% fall FEV1, LAR >15% fall FEV1, atopic. EXCLUSION: URTI/ LRTI/allergen exposure <4 weeks, ICS/OS < 4 weeks, smokers
Interventions	LONG ACTING BETA AGONIST: Salmeterol 50 mcg BD PLACEBO: BD DEVICE: MDI TREATMENT PERIOD: 8 weeks RESCUE: Salbutamol 100 mcg prn CO-INTERVENTIONS: none permitted
Outcomes	OUTCOMES: PEF, Rescue use, asthma symptom scores, allergen challenges, BAL, EBB, BHR
Notes	PEF -SD for result in paper 2l/min, probable typographic error, queried with authors. Symptom Score- respiratory symptoms graded 11 pt scale on waking and at bed time- 0= nothing to 10= maximum bearable,

Boulet 1998b

Methods	STUDY DESIGN: 2 way cross over, single centre, Canada, hospital setting, 2 weeks run in/ 4 weeks treatment/ 2 weeks crossover & run out RANDOMISATION: Randomised treatment order, no method stated. BLINDING: double blind, placebo controlled WITHDRAWALS/DROP OUTS: 2 withdrawals. COMPLIANCE: checked by weighing canisters- result not given CONFOUNDERS : Study drug stopped 48 hrs prior to BHR measurement QUALITY: Jadad 3. Cochrane B
Participants	N= RANDOMISED 16, 15 completed. & analysed M=5 F=10, adults, Mean age 31.0 (range 18-59) BASELINE SEVERITY: moderate asthma INCLUSION : Diagnosis asthma by ATS criteria, requiring treatment for >6months. Baseline FEV1 >60% predicted. PC20 methacholine < 8mg/ml. Not using ICS regularly. EXCLUSION: URTI/ LRTI/hospitalisation <4 weeks, use of theophylline, OS, ipratropium< 4 weeks, smoking <2mths. Serious uncontrolled systemic disease or pregnancy.
Interventions	LONG ACTING BETA AGONIST: Salmeterol 50 mcg BD PLACEBO: BD DEVICE: MDI TREATMENT PERIOD: 4 weeks RESCUE: Salbutamol 100 mcg prn CO-INTERVENTIONS: none permitted
Outcomes	OUTCOMES: FEV1, FVC , PEF, PC20 methacholine, Rescue use, asthma symptom scores.
Notes	Symptom Score- respiratory symptoms graded on 6 pt scale- o= nothing, 1= very light, 2=light, 3= moderate, 4= severe, 5= very severe

Busse 1998

Methods	STUDY DESIGN: Parallel group, multicentre (55), USA, 2 weeks run in/ 12 weeks treatment RANDOMISATION: Randomised treatment , no method given BLINDING: double blind, double dummy, matching devices. WITHDRAWALS/DROP OUTS: 95 withdrawals, 47 active, 48 placebo. COMPLIANCE: not stated CONFOUNDERS : baseline characteristics- both groups similar, except morning PEF lower in active group QUALITY: Jadad 3. Cochrane B
Participants	N= Randomised 538, Completed 443. M=51 F=68, adults, Mean age 36 (range 12-80) BASELINE SEVERITY: Moderate persistent asthma. INCLUSION : Diagnosis asthma by ATS criteria, used SABA daily during 6mths. Baseline FEV1 40-80% predicted. >15% FEV1 reversibility to SABA. Symptomatic in run in ASS>=2 EXCLUSION: URTI/ LRTI/<4 weeks, COPD, CF, unstable asthma, pregnancy, lactation, Use of OS <1mth
Interventions	LONG ACTING BETA AGONIST: Salmeterol 42 mcg BD PLACEBO: BD DEVICE: MDI TREATMENT PERIOD: 12 weeks RESCUE: Salbutamol 100 mcg prn CO-INTERVENTIONS: ICS 65%, cromones 7%, theophyllines 30%- all fixed doses
Outcomes	OUTCOMES: FEV1, FVC, PEF, Asthma QOL score, Rescue use, asthma symptom score, % days with no symptoms ,% nights with no asthma awakenings
Notes	Symptom Score- Night-time 0-3 (none - so severe that no sleep possible). Day-time 0-3 (no symptoms - symptoms so severe normal activities not possible). AQOL based on Juniper.

Busse 2004

Methods	STUDY DESIGN: Parallel group LOCATION, NUMBER OF CENTRES: USA 18 centres DURATION OF STUDY: run in= 2 weeks single blind placebo, 12 weeks treatment CONCEALMENT OF ALLOCATION: COCHRANE QUALITY SCORE: A DESCRIBED AS RANDOMISED: Yes DESCRIBED AS DOUBLE BLIND: Yes METHOD OF RANDOMISATION WELL DESCRIBED/APPROPRIATE: Yes, 1:1:1 ratio using computer generated list of random numbers METHOD OF BLINDING WELL DESCRIBED/APPROPRIATE: Yes, double dummy matched devices DESCRIPTION OF WITHDRAWALS/DROPOUTS: 30 withdrawals (10 formoterol, 3 albuterol, 13 placebo, reasons described. JADAD SCORE (5-1): TYPE OF ANALYSIS (AVAILABLE CASE/TREATMENT RECEIVED/ ITT): ITT and per protocol COMPLIANCE: Not assessed CONFOUNDERS: Comparable baseline characteristics
Participants	N SCREENED: Not reported N RANDOMISED: 239 N COMPLETED:219 M= 147 F= 92 MEAN AGE: Formoterol 39.1, placebo 36.8, albuterol 38.4 (13-85) SEVERITY OF ASTHMA: unknown

Busse 2004 *(Continued)*

	BASELINE DETAILS: duration asthma mean 22.2- 25.9 yrs, % pred FEV1 formoterol 63.4%, placebo 66%, albuterol 64.6%, daily rescue use: formoterol 2.52, placebo 2.55, albuterol 2.75 puffs/24hr, ICS use formoterol 65%, placebo 63%, albuterol 64%., no significant differences in symptom score or QOL score. INCLUSION CRITERIA : Persistent asthma, requiring regular or PRN bronchodilators, F EV1 % predicted = 40%, BDR = 15% or = 12% and =200ml 30 minutes after SABA 400mcg. EXCLUSION: RT infection, use of OCS, parenteral CS or hospitalisation for asthma due to exacerbation < 1 month, use of unstable anti-inflammatory regime, corrected QT interval > 460ms, current smoker, ex-smoker >10 PHY, serious medical condition, pregnancy, lactation, Use of oral beta blocker, non- potassium sparing diuretic, anti arrhythmic, tricyclic antidepressant, MAOI, NSAIDS.
Interventions	1. Formoterol 10mcg BD 2. Placebo BD 3. Albuterol 180 mcg QDS DELIVERY: DPI multidose COMBINATION INHALER FOR LABA: NO TREATMENT PERIOD: 12 weeks RESCUE: Albuterol MDI PRN (<720 mcg daily) CO-INTERVENTIONS PERMITTED: ICS, cromolyn, montelukast, theophyllines, intra nasal ICS % on ICS: FORM group 65%, PLA group 63%
Outcomes	OUTCOMES MEASURED: 12 hour AUC formoterol, Asthma QOL (mini asthma QOL questionnaire) , vital signs, blood biochemistry, ECGs, clinic spirometry, daily PEF am/pm, asthma symptoms scores, rescue use, adverse events, asthma exacerbations. FOLLOW-UP ASSESSMENT POINTS: OUTCOMES INCLUDED IN ANALYSES SUB-GROUPS INDENTIFIED:
Notes	Mini asthma QOL- 4 domains of symptoms, activity limitation, emotional function, environmental stimuli. 15 Item score 1 maximum-7 minimum, Exacerbation -definition asthma symptoms that did not resolve with use of study medications and thus needed additional medical treatment

Cheung 1992

Methods	STUDY DESIGN: Parallel group, single centre Netherlands, 1 week run in / 8 weeks treatment/1 weeks follow up RANDOMISATION: Randomised treatment , method not stated BLINDING: double blind, placebo controlled, identical devices. WITHDRAWALS/DROP OUTS:1 withdrawal, COMPLIANCE: measured by weighing inhaler, no difference between groups CONFOUNDERS : baseline characteristics of both groups similar, stopped study drug 36 hours prior to BHR measurement QUALITY: Jadad 4. Cochrane B
Participants	N= Randomised 24, completed 23. M=11 F=13, adults, Mean age 25.1 (range 19-36) BASELINE SEVERITY: mild asthma. INCLUSION : Diagnosis asthma by ATS criteria, atopy . Baseline FEV1 >75% predicted. >15% FEV1 reversibility to SABA. PC20 methacholine < 8mg/ml EXCLUSION: URTI/ LRTI/<2 weeks, smoking history, use of ICS/OS , theophylline/antihistamine < 6mths
Interventions	LONG ACTING BETA AGONIST: Salmeterol 50 mcg BD PLACEBO: BD DEVICE: MDI via aerosol chamber TREATMENT PERIOD:8 weeks RESCUE: Albuterol 100 mcg prn up to 400 mcg/day CO-INTERVENTIONS: none permitted

Cheung 1992 *(Continued)*

Outcomes	OUTCOMES: FEV1, BHR PC20 methacholine
Notes	

Cloostermann2001

Methods	STUDY DESIGN: Parallel group, single tertiary centre, Netherlands. RANDOMISATION: randomised treatment allocation, no details of method BLINDING: double blind, double dummy WITHDRAWALS/DROP OUTS: 42 during wash out stopping ICS, 17 post randomisation to study drug COMPLIANCE: assessed by weighing medication canisters CONFOUNDERS: ICS withdrawal lead to selection of milder subjects able to tolerate no ICS QUALITY: Jadad 4. Cochrane B
Participants	N=258 enrolled, 204 entered run in, 162 randomised (48 SABA, 50 LABA, 47 placebo), 145 completed M= 77, F= 68 Mean age 34 yrs (SD 10) BASELINE SEVERITY: Mild allergic asthma INCLUSION : Atopic positive SPT to HDM, , clinical diagnosis asthma, baseline FEV1 > 50% predicted, FEV1 post SABA > 65% predicted, >15% reversibility to SABA, PC20 histamine < 8mg/ml EXCLUSION: Need for ICS, positive SPT to a pet still in household
Interventions	SHORT ACTING BETA AGONIST: Salbutamol 200 mcg QDS PLACEBO: QDS LONG ACTING BETA AGONIST: Formoterol 12 mcg BD DEVICE: MDI TREATMENT PERIOD: 12 weeks RESCUE: combination short acting beta2 agonist/anticholinergic-fenoterol 100 mcg/ ipratropium 40 mcg per puff PRN CO-INTERVENTIONS: none permitted
Outcomes	OUTCOMES: FEV1, BHR, PEF am /pm, ASS, rescue use, exacerbations
Notes	Exacerbation= asthma deterioration treated with OS by GP, ASS= cough, wheeze, SOB, sputum, sleep disturbance, Scale 1= none -10 = severe

Creticos 1999

Methods	STUDY DESIGN: Parallel group LOCATION, NUMBER OF CENTRES: single in USA DURATION OF STUDY: 2 week run in, 6 months treatment CONCEALMENT OF ALLOCATION: COCHRANE QUALITY SCORE: B DESCRIBED AS RANDOMISED: Yes DESCRIBED AS DOUBLE BLIND: Yes METHOD OF RANDOMISATION WELL DESCRIBED/APPROPRIATE: no details METHOD OF BLINDING WELL DESCRIBED/APPROPRIATE: not reported DESCRIPTION OF WITHDRAWALS/DROPOUTS: not reported JADAD SCORE (5-1): 2 TYPE OF ANALYSIS (AVAILABLE CASE/TREATMENT RECEIVED/ ITT): not reported COMPLIANCE: not reported CONFOUNDERS: no details
Participants	N SCREENED: not reported N RANDOMISED: 46 N COMPLETED: 221

Creticos 1999 *(Continued)*

	M= 20 F= 26 MEAN AGE: 37 (13) BASELINE DETAILS: mild-moderate asthma. INCLUSION CRITERIA : FEV1 >65% predicted; FEV1 reversibility =12% post-SABA; requiring rescue = 4days weekly. EXCLUSION: not reported
Interventions	1. SALMETEROL 50 mcg BD 2. Placebo BD 3. TRIAMCINOLONE 400 mcg BD 4. TRI/SALM FSC 400/50 BD DELIVERY: MDI TREATMENT PERIOD: 6 months RESCUE: Salbutamol CO-INTERVENTIONS PERMITTED: None during treatment CO-INTERVENTIONS : % on ICS: 0% in SALM and PLAC groups
Outcomes	OUTCOMES MEASURED: airway hyper-reactivity, rescue use, FEV1 FOLLOW-UP ASSESSMENT POINTS: 2 monthly OUTCOMES INCLUDED IN ANALYSES: SUB-GROUPS INDENTIFIED: None
Notes	Numbers in treatment groups not given. FEV1 results only (no SD), AHR measurements not given

D'Alonzo 1994

Methods	STUDY DESIGN:Three treatment parallel group, multicentre (11) study in USA, 1-2 weeks run in/12 weeks treatment RANDOMISATION: Yes, method not given. BLINDING:Double blind, double dummy, with 2 matching inhalers. WITHDRAWALS:42/322 , by groups- 15 in salmeterol , 16 in albuterol, 11in placebo CONFOUNDERS:differential rates of ICS and cromone use in regular and prn group, use of theophyllines in run in period QUALITY:Jadad=4, Cochrane B
Participants	N=322 Albuterol =108, placebo=108, salmeterol =106 AGE- means -albuterol 31(14), placebo 28(12), salmeterol 29(12) SEVERITY OF ASTHMA: unknown INCLUSION: Diagnosis asthma by ATS criteria, requiring daily drug treatment for > 6 months. Baseline FEV1 50-70% predicted, >15% FEV1 reversibility to SABA. EXCLUSION:Smokers
Interventions	LONG ACTING BETA AGONIST: Salmeterol 42 mcg BD SHORT ACTING B ETA AGONIST: Albuterol 180mcg QDS PLACEBO:placebo QDS DEVICE: MDI PERIOD:12 weeks RESCUE:albuterol 90mcg prn COINTERVENTIONS: ICS -used by 20% on placebo , 24% on albuterol, 21% on salmeterol ORAL STEROIDS- not at randomisation CROMONES-used by 9% on placebo , 6% on albuterol, 10% on salmeterol THEOPHYLIINES- used only during run in by 46% on placebo ,50% on albuterol, 43% on salmeterol ORAL BETA AGONISTS- not permitted

D'Alonzo 1994 *(Continued)*

Outcomes	OUTCOMES: FEV1, FVC, FEV25-75%, PEF, Rescue use, asthma symptom score, symptom free days & nights, adverse events .
Notes	Exacerbations defined as worsening of asthma symptoms that required treatment in addition to the study drug and rescue SABA. Symtom Score- composite based on individual scores for breathlessness, chest tightness, wheezing, cough. Scale : 0=none to 5= severe, activities cancelled.

Dahl 1991a

Methods	STUDY DESIGN: Parallel group multicentre (76) in 12 European countries, 3 active groups, differing doses Salmeterol. 1 week run in /4 weeks treatment/1 weeks follow up RANDOMISATION: Randomised treatment , blocks of 12 BLINDING: double blind, placebo controlled, identical devices. WITHDRAWALS/DROP OUTS:78 withdrawals COMPLIANCE: rescue inhaler MDI counter CONFOUNDERS : baseline characteristics of both groups similar, QUALITY: Jadad 5 Cochrane A
Participants	N=Enrolled 1086, Randomised 692, completed 614. M=360 F=332, adults, Mean age 42 BASELINE SEVERITY: Mild-moderate asthma INCLUSION : Diagnosis asthma clinically. Baseline FEV1 60-90% predicted. >15% FEV1 reversibility to SABA. Symptom score >2 , diurnal variation PEF >15% on 4/7 days run in EXCLUSION: URTI/ LRTI/hospitalisation with asthma<4 weeks, use of OS >20mg/day , theophylline/antihistamine < 6mths
Interventions	LONG ACTING BETA AGONIST: Salmeterol 12.5, 50, 100 mcg mcg BD PLACEBO: BD DEVICE: MDI TREATMENT PERIOD:4 weeks RESCUE: Albuterol 100 mcg prn up to 400 mcg/day CO-INTERVENTIONS: ICS, 75%, OS <20mg/day, cromones
Outcomes	OUTCOMES: FEV1, FVC, PEF, Rescue use, asthma symptom score, % days with no symptoms ,% nights with no asthma awakenings, Efficacy score-patient and investigator rated
Notes	ASS Day-time 0-5 (no symptoms - symptoms so severe normal activities not possible)

Dahl 1991b

Methods	STUDY DESIGN: Cross over, single centre Denmark. 4 weeks treatment RANDOMISATION: Randomised treatment, method not stated BLINDING: double blind, placebo controlled WITHDRAWALS/DROP OUTS: no details COMPLIANCE: no details CONFOUNDERS : no details QUALITY: Jadad 2 Cochrane B
Participants	N= Randomised 12, M= F=, adults, Mean age 32 BASELINE SEVERITY: Mild-moderate asthma INCLUSION : Diagnosis asthma clinically. Mean Baseline FEV1 85% predicted. >15% FEV1 reversibility to SABA EXCLUSION: no details

Dahl 1991b *(Continued)*

Interventions	LONG ACTING BETA AGONIST: Salmeterol 50 mcg mcg BD PLACEBO: BD DEVICE: TREATMENT PERIOD:4 weeks RESCUE: SABA CO-INTERVENTIONS: none used
Outcomes	OUTCOMES: BHR, BAL
Notes	

Ekstrom 1998a

Methods	STUDY DESIGN: Parallel group, 3 treatment arms; multicentre, 25 centres Norway, Sweden, Spain, Italy. 12 weeks. RANDOMISATION: Yes, method not given. BLINDING: double blind, double dummy, matching devices. WITHDRAWALS/DROP OUTS: 38 described. 27 to asthma, 11 to adverse events. COMPLIANCE: Not assessed/ reported. CONFOUNDERS: Groups well balanced by characteristics. Excess withdrawals from SABA group, 10 subjects did not fully meet inclusion criteria. QUALITY: Jadad 4. Cochrane B
Participants	N= 397 Adults, M=232 F=179 Mean age 47 (RANGE 18-79) BASELINE SEVERITY: mild - moderate asthma. INCLUSION : Diagnosis asthma by ATS criteria. Baseline FEV1 50-80% predicted, >15% FEV1 reversibility to SABA.. EXCLUSION: none stated in paper.
Interventions	LONG ACTING BETA AGONIST: Formoterol 6 mcg BD SHORT ACTING BETA AGONIST: Terbutaline 500mcg QDS PLACEBO: Placebo QDS DEVICE: Dry powder device. TEATMENT PERIOD: 12 weeks RESCUE: Terbutaline 250 mcg via turbuhaler PRN CO-INTERVENTIONS: ICS 80%, cromones 5% - stable d
Outcomes	OUTCOMES: FEV1, PEF, Rescue use, asthma symptom score, adverse events. asthma deterioration
Notes	Symptom Score- breathlessness, chest tightness, wheezing, cough. Scale :0 - 3. Asthma deterioration leading to withdrawal reported.

Ekstrom 1998b

Methods	STUDY DESIGN: Parallel group, 3 treatment arms; multicentre, 28 centres Scaninavia. 12 weeks. RANDOMISATION: Yes, computer generated random order, balanced blocks.. BLINDING: double blind, double dummy, matching devices. WITHDRAWALS/DROP OUTS: 32 described, due to asthma. COMPLIANCE: Not assessed/ reported. CONFOUNDERS: Groups well balanced by characteristics. QUALITY: Jadad 5. Cochrane A
Participants	N= 343 Adults, M=164 F=179 Mean age 48 (RANGE 18-82) BASELINE SEVERITY: moderate stable asthma.

Ekstrom 1998b *(Continued)*

	INCLUSION : Diagnosis asthma by ATS criteria. Baseline FEV1 40-80% predicted, >15% FEV1 reversibility to SABA.. EXCLUSION: none stated in paper.
Interventions	LONG ACTING BETA AGONIST: Formoterol 12 mcg BD SHORT ACTING BETA AGONIST: Terbutaline 500mcg QDS PLACEBO: Placebo QDS DEVICE: Dry powder device- turbuhaler. TEATMENT PERIOD: 12 weeks RESCUE: Terbutaline 250 mcg via turbuhaler PRN CO-INTERVENTIONS: ICS 89%, cromones 2% - stable doses OS 2 subjects
Outcomes	OUTCOMES: FEV1, PEF, Rescue use, asthma symptom score, adverse events
Notes	Symptom Score- breathlessness, chest tightness, wheezing, cough. Scale :0 - 3

Garcia 2001

Methods	STUDY DESIGN: Parallel group single centre study, Spain, specialist hospital. 4 week treatment period after a pre-study visit to prove exercise-induced asthma RANDOMISATION: Randomised, no method given. BLINDING double blind, placebo controlled, masked identical devices. WITHDRAWALS/DROP OUTS: all randomised participant completed study. COMPLIANCE: no details CONFOUNDERS: groups balanced by baseline characteristics. QUALITY: Jadad 4 Cochrane B
Participants	N = 104 screened, 23 enrolled, 19 randomised, 19 completed. M=8, F=11 Mean age 24.1 yrs (SD 5.6) SEVERITY OF ASTHMA: unknown INCLUSION : Clinical history of exercise induced asthma, >15% fall in FEV1 within 30 minutes exercise. EXCLUSION : Change asthma medication within 4 weeks. Use of > 2 puffs per week SABA as rescue.
Interventions	LONG ACTING BETA AGONIST: Formoterol 12 mcg BD PLACEBO: BD DEVICE: MDI RESCUE: Salbutamol or terbutaline PRN via MDI TREATMENT PERIOD: 4 weeks CO-INTERVENTIONS: Cromones, ipratropium, % on ICS 32% (6/19) - stable doses
Outcomes	OUTCOMES: Primary= change in bronchoprotection index (BI). Secondary= PEF
Notes	BI= % FEV1 fall in challenge2 minus % FEV1 fall in challenge 2 x 100/ % FEV1 fall in challenge 1 (performed on the same day) after inhaling formoterol

Hyland 1994

Methods	STUDY DESIGN: Parallel group, multicentre, S Africa. 2 weeks run in/ 6 weeks treatment/ 2 weeks follow up RANDOMISATION: Randomised treatment, method not stated BLINDING: double blind, placebo controlled, matching devices WITHDRAWALS/DROP OUTS: 3 COMPLIANCE: no details CONFOUNDERS : no details

Hyland 1994 *(Continued)*

	QUALITY: Jadad 4 Cochrane B
Participants	N= Randomised , completed 79, analysed 76. M=36 F=40, adults, Mean age 38.5 (range 17-75) SEVERITY OF ASTHMA: unknown INCLUSION : Symptoms asthma and use SABA 8/14 run in days, Baseline FEV1 <75% predicted, >15% FEV1 reversibility to SABA. EXCLUSION: OS, ICS >400mcg/day,
Interventions	LONG ACTING BETA AGONIST: Salmeterol 50 mcg mcg BD PLACEBO: BD DEVICE: MDI or diskhaler TREATMENT PERIOD: 4 weeks RESCUE: not stated CO-INTERVENTIONS: ICS <400 mcg/day
Outcomes	OUTCOMES: Asthma QOL score
Notes	Asthma QOL score= LWAQ by Hyland

Jones 1994

Methods	STUDY DESIGN: Parallel group , multicentre UK, primary care 146 GPs, 2weeks run-in/ 6 weeks treatment/ 2 weeks follow up. RANDOMISATION: Randomised treatment 2:1 salmeterol, method not stated BLINDING: double blind, placebo controlled, matching devices WITHDRAWALS/DROP OUTS: 85, 34 adverse events COMPLIANCE: no details CONFOUNDERS : no details. QUALITY: Jadad 3 Cochrane B
Participants	N= Enrolled 669, Randomised 427, M=207 F=220, adults, Mean age 38.3 (range 18-79) BASELINE SEVERITY: Mild asthma INCLUSION : Clinical diagnosis asthma , prescription SABA 1-4 in past 4 months. Baseline FEV1 >75% predicted, >15% FEV1 reversibility to SABA. 8/14 run in symptoms, PEF variability or rescue use. EXCLUSION: none stated
Interventions	LONG ACTING BETA AGONIST: Salmeterol 50 mcg mcg BD PLACEBO: BD DEVICE: DP diskhaler TREATMENT PERIOD: 6 weeks RESCUE: salbutamol 400mcg prn CO-INTERVENTIONS: ICS <400 mcg/day 180/427, no ICS 247/427 % on ICS= 42%
Outcomes	OUTCOMES: PEF, Rescue use, asthma symptom score Efficacy score-patient and investigator rated
Notes	Some subgroup results for ICS /noICS groups. Symptom Score- cough/wheeze/SOB. Night-time 0-3 (none - so severe that no sleep possible). Daytime 0-3 (no symptoms - symptoms so severe normal activities not possible)

Juniper 1995

Methods	STUDY DESIGN: 3 way cross over, multicentre, 14 centres Canada, 4 weeks. RANDOMISATION: Yes, no method stated. BLINDING: Double blind, double dummy, matching inhalers.

Juniper 1995 *(Continued)*

	WITHDRAWALS/DROP OUTS: 21 described after randomization. COMPLIANCE: >70% reported for all but 7 subjects. CONFOUNDERS: QUALITY: Jadad 4. Cochrane B
Participants	N= 140 RANDOMISED. Adults, M=66 F=74 Mean age 37.5 (sd 14.5) BASELINE SEVERITY: mild - moderate asthma. INCLUSION : Baseline FEV1 >60% predicted, >15% FEV1 reversibility to SABA. Symptom score >2 on 4/7 days run in EXCLUSION: Exacerbation asthma within 1 month, emergency room visit >3 months, uncontrolled illness, pregnancy. OS within 1mth. Theophylline .
Interventions	LONG ACTING BETA AGONIST: Salmeterol 50 mcg BD SHORT ACTING BETA AGONIST: Salbutamol 200 mcg QDS PLACEBO: placebo QDS DEVICE: MDI. TEATMENT PERIOD: 4 weeks RESCUE:Salbutamol 100 mcg PRN CO-INTERVENTIONS: ICS 77% . Cromones 15%, 30% none.
Outcomes	OUTCOMES: FEV1, FVC, FEV25-75%, PEF, Rescue use, asthma symptom score, symptom free days & nights, adverse events, AQOL scores.
Notes	AQOL score by Juniper, measures-symptoms, emotions, activity limitation, environment-overall scores + individual domains

Kavuru 2000a

Methods	STUDY DESIGN: Parallel group , multicentre (42) USA, 2weeks run in/ 12 weeks treatment RANDOMISATION: Randomised treatment, method not stated BLINDING: double blind, placebo controlled, matching devices WITHDRAWALS/DROP OUTS: 80 for worsening asthma COMPLIANCE: dose counter on devices, 93-100% adherence CONFOUNDERS : Groups well balanced by baseline characteristics QUALITY: Jadad 4 Cochrane B
Participants	N= Screened 527, Randomised 356, M=190, F=166, Adolescent/ adults. Mean age 37 (range 12-70) BASELINE SEVERITY: persistent/ symptomatic INCLUSION : Diagnosis asthma by ATS criteria >6mths, Baseline FEV1 40-80% predicted, >15% FEV1 reversibility to SABA. EXCLUSION: Serious uncontrolled systemic disease, pregnancy, life threatening asthma, course OS <4weeks, regular OS < 6nths, smokers, ICS
Interventions	LONG ACTING BETA AGONIST: Salmeterol 50 mcg mcg BD PLACEBO: BD DEVICE: DP diskhaler TREATMENT PERIOD: 12 weeks RESCUE: albuterol 100mcg prn CO-INTERVENTIONS: none permitted
Outcomes	OUTCOMES: FEV1, FVC, PEF, Rescue use, asthma symptom score, % days with no symptoms , % nights with no asthma awakenings, adverse events, Exacerbations.
Notes	Symptom Score- cough/wheeze/SOB -6 pt Scale :0= none to 5= very severe Exacerbations defined as acute episode requiring emergency medical attention or hospitalization or treatment not allowed by protocol.

Kemp 1998a

Methods	STUDY DESIGN: Parallel group, multicentre, 15 centres USA, 12 weeks. RANDOMISATION: Yes, no method stated. BLINDING: Double blind, double dummy, matching inhalers. WITHDRAWALS/DROP OUTS: 41 described after randomization. COMPLIANCE: >70% reported for all but 7 subjects. CONFOUNDERS: QUALITY: Jadad 4. Cochrane B
Participants	N= 451 RANDOMISED. Adults, M=262 F=189 Mean age 31 (sd 14) BASELINE SEVERITY: persistent/ symptomatic INCLUSION : Diagnosis asthma by ATS criteria. Baseline FEV1 50-80% predicted, >15% FEV1 reversibility to SABA. Requiring daily drug treatment for > 6 months. EXCLUSION: smoking.
Interventions	LONG ACTING BETA AGONIST: Salmeterol 50 mcg BD SHORT ACTING BETA AGONIST: Albuterol 180 mcg QDS PLACEBO: placebo QDS DEVICE: MDI & dry powder device. TEATMENT PERIOD: 12 weeks RESCUE:Albuterol 100 mcg PRN CO-INTERVENTIONS: ICS 55-70 % . Cromones 7-12 %
Outcomes	OUTCOMES: FEV1, FVC, FEV25-75%, PEF, Rescue use, asthma symptom score, symptom free days & nights, adverse events, exacerbations.
Notes	Symptom Score- breathlessness, chest tightness, wheezing, cough. Scale : 0-3 Exacerbations defined as worsening of asthma symptoms that required treatment in addition to the study drug and rescue SABA.

Kemp 1999

Methods	STUDY DESIGN: Parallel group , multicentre (18) USA, 2-4 weeks run in/ 52 weeks treatment/ 2 weeks run out RANDOMISATION: Randomised treatment, method not stated BLINDING: double blind, placebo controlled WITHDRAWALS/DROP OUTS: 87 COMPLIANCE: count unused blisters, rate > 90% both groups CONFOUNDERS : Groups well balanced by baseline characteristics QUALITY: Jadad 3 Cochrane B
Participants	N= Randomised 352, M=179, F=173, Adolescent/ adults. Mean age 28.5 (range 12-67) BASELINE SEVERITY: Mild-moderate asthma INCLUSION : clinical diagnosis asthma > 6mths, Baseline FEV1 70-90% predicted, >15% FEV1 reversibility to SABA. PC20 methacholine < 7.5mg/ml EXCLUSION: URTI/ LRTI <6 WKS , smoking < 12mths ,
Interventions	LONG ACTING BETA AGONIST: Salmeterol 50 mcg mcg BD PLACEBO: BD DEVICE: DP diskhaler TREATMENT PERIOD: 52 weeks RESCUE: albuterol 100mcg prn CO-INTERVENTIONS: ICS ,52% active group, 40% placebo
Outcomes	OUTCOMES: FEV1, FVC, PEF, asthma symptom score , Rescue use, BHR

Kemp 1999 *(Continued)*

Notes	Symptom Score- cough/wheeze/SOB -6 pt Scale :0= none to 5= severe

Kraft 1997

Methods	STUDY DESIGN: 2 way cross over single centre, 6 weeks treatment/ 1 weeks wash out RANDOMISATION: Randomised treatment order, method not stated BLINDING: double blind, placebo controlled WITHDRAWALS/DROP OUTS: none occurred but 3 subjects unable to have BAL due to low FEV1 COMPLIANCE: Not assessed CONFOUNDERS : No details QUALITY: Jadad 3 Cochrane B
Participants	N= Randomised 10, M=8, F=2, adults. Mean age 29.95 (SEM 1.9) BASELINE SEVERITY: Moderate to severe asthma. INCLUSION : Diagnosis asthma by ATS criteria, nocturnal symptoms. Overnight fall in PEF >20% on 4/7nights EXCLUSION: URTI/ LRTI/antibiotics <6 WKS , smoking <12mths, smoking history <5 pack years , Serious uncontrolled systemic disease, pregnancy. OS/ ICS/ cromones/ methotrexate
Interventions	LONG ACTING BETA AGONIST: Salmeterol 50 mcg mcg BD PLACEBO: BD DEVICE: MDI TREATMENT PERIOD: 6 weeks RESCUE: albuterol 100mcg prn CO-INTERVENTIONS: none permitted
Outcomes	OUTCOMES: PEF, asthma symptom score , BHR, BAL
Notes	Symptom Score- cough/wheeze/SOB -5 pt Scale :0= none to 4= severe

LaForce 2005

Methods	STUDY DESIGN: Parallel group LOCATION, NUMBER OF CENTRES: USA, 22 centres. DURATION OF STUDY: 12 weeks (preceded by two week run-in). CONCEALMENT OF ALLOCATION: COCHRANE QUALITY SCORE: A DESCRIBED AS RANDOMISED: YES DESCRIBED AS DOUBLE BLIND: YES METHOD OF RANDOMISATION WELL DESCRIBED/APPROPRIATE: Computer generated sequence METHOD OF BLINDING WELL DESCRIBED/APPROPRIATE: Double-dummy DESCRIPTION OF WITHDRAWALS/DROPOUTS: Reported (30/265: adverse events: 7; lack of efficacy: 7; withdrawal of consent: 11; others not specified) JADAD SCORE (5-1):5 TYPE OF ANALYSIS (AVAILABLE CASE/TREATMENT RECEIVED/ ITT): ITT (LOCF) COMPLIANCE: Not assessed. CONFOUNDERS: Slightly higher number of participants taking ICS in the placebo group (65 versus 56%)
Participants	N SCREENED: Not reported. N RANDOMISED: 265 N COMPLETED: 235 M= 113 F= 152 MEAN AGE: 37 SEVERITY OF ASTHMA: unknown

LaForce 2005 *(Continued)*

	BASELINE DETAILS: Mean FEV1 % predicted: 68; SABA usage: 2 puffs/d. INCLUSION CRITERIA: FEV1 >40% predicted; Reversibility >15% (12% if >/=200mL over baseline) EXCLUSION: Pregnant/lactating women; smoking history >10 pack years; history of malignancy; RTI or hospitalisation with exacerbation in previous month; treatment with systemic steroids.
Interventions	1. Formoterol 10mcg BID 2. Placebo 3. Salbutamol 180mcg QID DELIVERY: DPI (pMDI for salbutamol) TREATMENT PERIOD: 12 weeks RESCUE: Salbutamol (dose not specified) CO-INTERVENTIONS PERMITTED: ICS; cromolyns; leukotriene modifiers and xanthines. CO-INTERVENTIONS : % on ICS: LABA: 56; SABA: 56; PLA: 65
Outcomes	OUTCOMES MEASURED: AUC FEV1; am PEF; pm PEF; adverse events; symptoms; rescue beta-agonist use; quality of life (AQLQ) FOLLOW-UP ASSESSMENT POINTS: weeks 4 & 12 OUTCOMES INCLUDED IN ANALYSES AUC FEV1; adverse events SUB-GROUPS INDENTIFIED: None reported
Notes	Nocturnal asthma symptoms- 5 point scale, day time asthma symptoms: dyspnoea, chest discomfort, wheezing , cough each on 4 point scale (0-12 total)

Lazarus 2001

Methods	STUDY DESIGN: Parallel group LOCATION, NUMBER OF CENTRES: USA, 6 ambulatory care centres (university based NIH sponsored centres) DURATION OF STUDY: 28 weeks 1997-1999 -6 weeks pre-treatment with triamcinolone, 16 weeks treatment, 6 weeks run out. CONCEALMENT OF ALLOCATION: COCHRANE QUALITY SCORE: A DESCRIBED AS RANDOMISED: Yes DESCRIBED AS DOUBLE BLIND: Yes METHOD OF RANDOMISATION WELL DESCRIBED/APPROPRIATE: stratified, internet to data centre off site. METHOD OF BLINDING WELL DESCRIBED/APPROPRIATE: triple, patients identical inhalers, clinical personnel, data entry DESCRIPTION OF WITHDRAWALS/DROPOUTS: 34 (7PLA, 13 SALM, 14 ICS) 12 in treatment period, reasons listed JADAD SCORE (5-1): 5 TYPE OF ANALYSIS (AVAILABLE CASE/TREATMENT RECEIVED/ ITT): ITT for primary outcomes, survival data on last outcome entry COMPLIANCE: 81.1% medication CONFOUNDERS: Groups well balanced at baseline
Participants	N SCREENED: 422, 361 completed run in on ICS N RANDOMISED: 339 eligible, 175 entered into LABA+ICS trial if not well controlled, 164 randomised- 56 placebo, 54 SALM, 54 ICS N COMPLETED: active treatment 151 (51 PLA, 48 SALM, 53 ICS) run out phase 130 (49 PLA, 41 SALM, 40 ICS) M= 39 (36%) F= 69 (64%) MEAN AGE: 31.5 (10.6) SEVERITY OF ASTHMA: persistent/ symptomatic BASELINE DETAILS: Previous ICS use 93%, rescue SABA use 0.5-1.1p/day, ASS 0.2, AQOL median 2. INCLUSION CRITERIA : Age 12-65, persistent asthma, FEV1 % predicted <85%, BDR = 12% increase in FEV1 after SABA if not on ICS, or FEV1 >40% predicted /FEV1 40-80% predicted + BDR >12 % if on ICS, or

Lazarus 2001 *(Continued)*

	if FEV1 >80% predicted PC20 < 8mg/ml methacholine. Lifetime smoking exposure < 10PH, not smoker currently, all subjects completed 6 weeks on ICS 400mcg BD prior to randomisation into PLA/SALM EXCLUSION: Pregnancy, lactation, no RTI/exacerbation <6 weeks, no regular medication except oral contraceptives or nasal beclomethasone, no serious medical illness other than asthma.
Interventions	1.SALMETEROL 50 mcg BD 2. TRIAMCINOLONE 40mcg BD 3. Placebo BD DELIVERY: MDI TREATMENT PERIOD: 16 weeks RESCUE: SABA CO-INTERVENTIONS PERMITTED: none CO-INTERVENTIONS : nasal ICS
Outcomes	OUTCOMES MEASURED: treatment failure, asthma exacerbation, am PEF, pm PEF, FEV1, PC20, QOL, ASS, rescue, sputum markers inflammation FOLLOW-UP ASSESSMENT POINTS: every 2-4 weeks OUTCOMES INCLUDED IN ANALYSES: SUB-GROUPS INDENTIFIED: None
Notes	Asthma exacerbation definition-increase cough, chest tightness, or wheezing associated with 1 or more or : change of =8 puffs/day SABA for 48 hours, =16 puffs/day SABA for 48 hours, PEF <65% reference level despite 60 minutes rescue, Symptoms despite 60 minutes treatment, requirement for OCS. Treatment failure status definition- requirement OCS course for exacerbation, ED visit or urgent care for asthma , hospitalisation for exacerbation, physician safety judgement

Leblanc 1996

Methods	STUDY DESIGN: 3 way cross over, multicentre 15 Canada. 12 weeks. RANDOMISATION: Yes, no method stated. BLINDING: double blind, double dummy, matching devices. WITHDRAWALS/DROP OUTS: 67 described after randomization. COMPLIANCE: 93% assessed by diary card. CONFOUNDERS: Smokers included QUALITY: Jadad 4. Cochrane B
Participants	N= 367 RANDOMISED. Adults, M=164 F=203 Mean age:39 (SD 13.9) BASELINE SEVERITY: mild-moderate asthma. INCLUSION : Baseline FEV1 >60% predicted, >15% FEV1 reversibility to SABA. Symptoms on 4/7 days run in, EXCLUSION: methylxanthines, anticholinergic, OS
Interventions	LONG ACTING BETA AGONIST: Salmeterol 50 mcg BD SHORT ACTING BETA AGONIST: Salbutamol 200 mcg QDS PLACEBO: placebo QDS DEVICE: MDI. TEATMENT PERIOD: 12 weeks RESCUE: Salbutamol 100 mcg PRN CO-INTERVENTIONS: ICS >80%, cromones 7%
Outcomes	OUTCOMES: FEV1, FVC, PEF, Rescue use, asthma symptom free days & nights, adverse events .
Notes	

Levy 2005

Methods	STUDY DESIGN: Parallel group LOCATION, NUMBER OF CENTRES: 22 in USA DURATION OF STUDY: 2 week run in, 12 weeks treatment CONCEALMENT OF ALLOCATION: COCHRANE QUALITY SCORE: B DESCRIBED AS RANDOMISED: Yes DESCRIBED AS DOUBLE BLIND: Yes METHOD OF RANDOMISATION WELL DESCRIBED/APPROPRIATE: not reported METHOD OF BLINDING WELL DESCRIBED/APPROPRIATE: matched placebo DESCRIPTION OF WITHDRAWALS/DROPOUTS: 22/249 reasons given JADAD SCORE (5-1): 4 TYPE OF ANALYSIS (AVAILABLE CASE/TREATMENT RECEIVED/ ITT): ITT for efficacy variables. COMPLIANCE: not reported CONFOUNDERS: Baseline characteristics similar except higher % males in FORM group and BDR higher in PLAC group
Participants	Children <13 years. N SCREENED: N/A, N RANDOMISED: 249, N COMPLETED: 227 M= 167 F= 60 MEAN AGE: 9.4 (2) BASELINE DETAILS: mild-moderate persistent asthma, FEV1 75% predicted, asthma history 6.5 years INCLUSION CRITERIA:aged 5-13 years, FEV1 % predicted = 50%, BDR = 15% 30 minutes after SABA 200mcg, requiring PRN bronchodilators, EXCLUSION: Change in co-intervention or URTI or use of OCS within 1 month, significant medical condition, smoking.
Interventions	1. FORMOTEROL 10mcg BD 2. Placebo BD DELIVERY: DPI TREATMENT PERIOD: 12 weeks RESCUE: SABA albuterol PRN CO-INTERVENTIONS PERMITTED: cromones, ICS CO-INTERVENTIONS : % on ICS 74.8% FORM group 68.9% PLAC group
Outcomes	OUTCOMES MEASURED: FEV1, exacerbations, PEF am/pm, asthma symptom scores, rescue use, AEs FOLLOW-UP ASSESSMENT POINTS: 4 weekly OUTCOMES INCLUDED IN ANALYSES: SUB-GROUPS INDENTIFIED: none
Notes	Asthma exacerbation definition: asthma symptoms not resolving with study medication but requiring use of additional medication

Lindqvist 2003

Methods	STUDY DESIGN: Parallel group LOCATION, NUMBER OF CENTRES: single centre, Finland DURATION OF STUDY: 16 weeks with 2 week run in and 2 week follow up CONCEALMENT OF ALLOCATION: COCHRANE QUALITY SCORE: B DESCRIBED AS RANDOMISED: Yes DESCRIBED AS DOUBLE BLIND: Yes METHOD OF RANDOMISATION WELL DESCRIBED/APPROPRIATE: not reported METHOD OF BLINDING WELL DESCRIBED/APPROPRIATE: double dummy placebo controlled DESCRIPTION OF WITHDRAWALS/DROPOUTS: 2/80 reasons given JADAD SCORE (5-1): 4 TYPE OF ANALYSIS (AVAILABLE CASE/TREATMENT RECEIVED/ ITT): efficacy population COMPLIANCE: not reported

Lindqvist 2003 *(Continued)*

	CONFOUNDERS: baseline groups similar characteristics
Participants	N SCREENED: 83 N RANDOMISED: 80 N COMPLETED: 78 M= 34 F= 46 MEAN AGE: 39 SALM, 34 PLAC SEVERITY OF ASTHMA: persistent/ symptomatic BASELINE DETAILS: Asthma duration mean 4 months, FEV1 % predicted mean 80% INCLUSION CRITERIA : Asthma diagnosed within 2 years, symptomatic at enrolment, FEV1 60-100% predicted, PD15FEV1 <0.4mg, non smokers (minimum 2 years) EXCLUSION: no ICS/ OCS within 8 WEEKS, No URTI/exacerbation use LABA or cromones within 4 weeks, no antihistamines within 2 weeks.
Interventions	1. Salmeterol 50 mcg BD 2. Placebo BD 3. Fluticasone 250 BD 4. disodium cromoglycate 5 mg QID DELIVERY: DPI TREATMENT PERIOD: 16 weeks RESCUE: SABA PRN CO-INTERVENTIONS PERMITTED: None % on ICS 0% in SALM and PLAC groups
Outcomes	OUTCOMES MEASURED: PEF am/pm, symptoms (0-5 daytime, 0-4 night),rescue use, FEV1, BDR, bronchoscopy inflammatory cell analysis. FOLLOW-UP ASSESSMENT POINTS: 2 week period middle and end of treatment. OUTCOMES INCLUDED IN ANALYSES SUB-GROUPS INDENTIFIED: none
Notes	

Lockey 1999

Methods	STUDY DESIGN: Parallel group multicentre (49) USA, run as two identical studies. 2weeks run in/ 12 weeks treatment RANDOMISATION: Randomised treatment allocation, no details BLINDING: double blind, placebo controlled, matching devices WITHDRAWALS/DROP OUTS: 90 described, 54 placebo group, 36 active group COMPLIANCE: assessed from patient recordings CONFOUNDERS : Groups balanced by baseline characteristics, except active group more females, fewer ICS users, higher % predicted FEV1 QUALITY: Jadad 4 Cochrane B
Participants	N= Randomised 474. M=217 F=257, adult/adolescents Mean age 39 (range 12-76) BASELINE SEVERITY: Moderate persistent asthma. INCLUSION : Diagnosis asthma by ATS criteria >6mths, Baseline FEV1 40-80% predicted, >15% FEV1 reversibility to SABA. Nocturnal symptoms run in 10/14 EXCLUSION: Serious uncontrolled systemic disease, pregnancy, OS change in co interventions <6wks ,
Interventions	LONG ACTING BETA AGONIST: Salmeterol 42 mcg BD PLACEBO: BD DEVICE: MDI TREATMENT PERIOD: 12 weeks RESCUE: albuterol 100 mcg prn CO-INTERVENTIONS: ICS >62%, theophylline >23%

Lockey 1999 *(Continued)*

Outcomes	OUTCOMES: FEV1, FVC, PEF, Asthma QOL score, Rescue use, asthma symptom score, % days with no symptoms ,% nights with no asthma awakenings, adverse events, exacerbations
Notes	Exacerbations defined as worsening of asthma symptoms that required treatment in addition to the study drug and rescue SABA. Symptom Score- cough/wheeze/SOB. Night-time 0-3 (none - so severe that no sleep possible). Day-time 0-3 (no symptoms - symptoms so severe normal activities not possible

Mahajan 1998

Methods	STUDY DESIGN: Parallel group multicentre (11) USA, 12 weeks treatment RANDOMISATION: Randomised treatment allocation, no details BLINDING: double blind, placebo controlled, WITHDRAWALS/DROP OUTS: no details COMPLIANCE: no details CONFOUNDERS : Groups balanced by baseline characteristics QUALITY: Jadad 2 Cochrane B
Participants	N= Randomised 207. M=142 F=65, children Mean age 8.4 (SD 2.4) BASELINE SEVERITY: Mild-moderate asthma INCLUSION : Diagnosis asthma by ATS criteria >6mths, Baseline FEV1 60-80% predicted, >15% FEV1 reversibility to SABA. EXCLUSION: none detailed,
Interventions	LONG ACTING BETA AGONIST: Salmeterol 50 mcg BD PLACEBO: BD DEVICE: DP TREATMENT PERIOD: 12 weeks RESCUE: albuterol 100 mcg prn CO-INTERVENTIONS: stable doses ICS >58%, cromones, theophylline,
Outcomes	OUTCOMES: Asthma QOL scores -using FSII-R, SLR-C, parent activity limitation questionnaire.
Notes	Functional Status II-R, Sleep scale-children (SLP-C)

Nathan 1999

Methods	STUDY DESIGN: Parallel group 3 groups, multicentre (25) USA, 2 week run in/ 26 weeks treatment / 2 week run out RANDOMISATION: Randomised treatment allocation, no details BLINDING: double blind, double dummy, placebo controlled WITHDRAWALS/DROP OUTS: 81, 30 salmeterol, 23 BDP, 28 placebo COMPLIANCE: no details CONFOUNDERS : Groups well balanced by baseline characteristics QUALITY: Jadad 3 Cochrane B
Participants	N= Randomised 386, M=179 F=207 adult/adolescents Mean age 30 (SD 21) SEVERITY OF ASTHMA: persistent/symptomatic INCLUSION : Diagnosis asthma by ATS criteria > 3/12, Baseline FEV1: 65-90 % predicted. >15% FEV1 reversibility to SABA EXCLUSION: exacerbation asthma ,1mth, use of ICS/OS < 6mths, smoker, requiring > 12 puffs/day rescue SABA in run in 4/7

Nathan 1999 *(Continued)*

Interventions	LONG ACTING BETA AGONIST: Salmeterol 42 mcg BD PLACEBO: BD DEVICE: MDI, no spacer allowed TREATMENT PERIOD:26 weeks CO-INTERVENTIONS: none permitted
Outcomes	OUTCOMES: PEF ,FEV1, Rescue use, asthma symptom score, BHR , % days with no symptoms ,% nights with no asthma awakenings, Exacerbations
Notes	Exacerbations defined as worsening of asthma symptoms that required treatment in addition to the study drug and rescue SABA.

Nelson 1998

Methods	STUDY DESIGN: 2 way cross over single centre USA, 1 week run in and cross over / 4 weeks treatment RANDOMISATION: Randomised treatment order allocation, no details BLINDING: double blind, placebo controlled , identical inhalers WITHDRAWALS/DROP OUTS: none occurred COMPLIANCE: no details CONFOUNDERS : subjects examined at cross over point to establish similarity of exercise response, no treatment order effect seen. QUALITY: Jadad 4 Cochrane B
Participants	N= Randomised 20, M=9 F=11 adult Mean age 29 (SD 9) BASELINE SEVERITY: not described INCLUSION : Diagnosis exercise induced asthma by > 15 fall in FEV1 with exercise EXCLUSION: URTI/ LRTI/ OS 6 WKS
Interventions	LONG ACTING BETA AGONIST: Salmeterol 42 mcg BD PLACEBO: BD DEVICE: MDI RESCUE: albuterol PRN TREATMENT PERIOD:4 weeks CO-INTERVENTIONS: ICS (6/20), theophyllines: stable doses % ICS= 30%
Outcomes	OUTCOMES: FEV1, FEV1 response to exercise
Notes	

Nelson 1999b

Methods	STUDY DESIGN: 2 way cross over 2 centres USA, 2 week run in and 1 week cross over / 4 weeks treatment RANDOMISATION: Randomised treatment order allocation, no details BLINDING: double blind, placebo controlled , WITHDRAWALS/DROP OUTS: 6 COMPLIANCE: no details CONFOUNDERS : 14 day wash out for all beta2 agonists, none permitted during study. QUALITY: Jadad 3 Cochrane B
Participants	N= Randomised 27, M=14 F=13 adult Mean age 32 (range 20-56) BASELINE SEVERITY: Mild asthma

Nelson 1999b *(Continued)*

	INCLUSION : Diagnosis asthma by ATS criteria, Baseline FEV1 50-80% predicted, >12% FEV1 reversibility to SABA. EXCLUSION: oral /inhaled beta2 agonist, use ICS/ OS
Interventions	LONG ACTING BETA AGONIST: Salmeterol 42 mcg BD PLACEBO: BD DEVICE: MDI RESCUE: Ipratropium bromide PRN TREATMENT PERIOD:4 weeks CO-INTERVENTIONS: none permitted
Outcomes	OUTCOMES: FEV1, FVC, FEF 25-75%, DRC to albuterol
Notes	DRC=max FEV1 response to doubling doses inhaled albuterol

Newnham 1994

Methods	STUDY DESIGN: 2 way cross over single centre UK, 2 week run in / 4 weeks treatment RANDOMISATION: Randomised treatment order allocation, no details BLINDING: double blind, placebo controlled , matching devices WITHDRAWALS/DROP OUTS: none occurred COMPLIANCE: assessed by patient records CONFOUNDERS : No wash out at cross over. 12 hour wash-out after study drug dose prior to DRC QUALITY: Jadad 4 Cochrane B
Participants	N= Randomised 7, M=3 F= 4 adult. Mean age 34 (range 21-52) BASELINE SEVERITY: Mild-moderate asthma INCLUSION : Diagnosis asthma by ATS criteria, Baseline FEV1 44-77% predicted, EXCLUSION: OS < 3mths, recent exacerbation. smokers
Interventions	LONG ACTING BETA AGONIST: Formoterol 24 mcg BD PLACEBO: BD DEVICE: MDI RESCUE: Ipratropium bromide PRN TREATMENT PERIOD:4 weeks CO-INTERVENTIONS: ICS 5/7 100-2000mcg/day, nedocromil 1/7, theophylline % ICS=70%
Outcomes	OUTCOMES: FEV1, FVC, FEF 25-75%, DRC to albuterol, HR tremor, BP ECG
Notes	

Newnham 1995

Methods	STUDY DESIGN: 2 way cross over single centre UK, 2 week run in / 4 weeks treatment RANDOMISATION: Randomised treatment order allocation, no details BLINDING: double blind, placebo controlled , matching capsules WITHDRAWALS/DROP OUTS: 2 COMPLIANCE: assessed by patient records and capsule count CONFOUNDERS : No wash out at cross over. 24 hour wash out after study drug dose prior to DRC QUALITY: Jadad 4 Cochrane B
Participants	N= Randomised 18, completed 16, M=10 F= 6 adult. Mean age 33 (range 18-53) BASELINE SEVERITY: Mild-moderate stable asthma

Newnham 1995 *(Continued)*

	INCLUSION : Clinical diagnosis asthma, Baseline FEV1 40-80% predicted, >15% FEV1 reversibility to SA-BA. EXCLUSION: OS/ recent exacerbation < 3mths. Smokers. Requiring > 600mcg salbutamol /day
Interventions	LONG ACTING BETA AGONIST: Formoterol 24 mcg BD PLACEBO: BD DEVICE: DP capsules RESCUE: Ipratropium bromide 40mcg PRN TREATMENT PERIOD:4 weeks CO-INTERVENTIONS: ICS 13/16 200-2000mcg/day, theophylline 3/16- at constant % ICS=81%
Outcomes	OUTCOMES: PEF , FEV1, FVC, FEF 25-75%, DRC to albuterol, tremor,
Notes	

Pearlman 1992

Methods	STUDY DESIGN: parallel-group(3), multicentre (8) in USA RANDOMIISATION: Randomised- means and methods not described. BLINDING: double-blind, placebo controlled using 2 identical inhalers WITHDRAWALS: 33 DESCRIBED COMPLIANCE : Not reported in paper. CONFOUNDERS: Groups well balanced by characteristics QUALITY: Jadad score=4. COCHRANE= B
Participants	N= Randomised 20, M=9 F=11 adults, Mean age 29 (SD 9) SEVERITY OF ASTHMA: unknown INCLUSION : Diagnosis exercise induced asthma by > 15 fall in FEV1 with exercise EXCLUSION: URTI/ LRTI/ OS 6 WKS
Interventions	LONG ACTING BETA AGONIST : Salmeterol 42 mcg bd SHORT ACTING BETA AGONIST :Albuterol 180 mcg qds PLACEBO: placebo qds DEVICE:MDI PERIOD TREATMENT: 12 weeks RESCUE: Albuterol 90 mcg PRN COINTERVENTIONS: ICS 40%, cromones 7%,
Outcomes	OUTCOMES: FEV1, FVC, PEF, Rescue use, asthma symptom score, adverse events . exacerbations
Notes	Symtom Score- composite based on individual scores for breathlessness, chest tightness, wheezing, cough. Scale : 0=none to 5= severe, activities cancelled. Exacerbations defined as worsening of asthma symptoms that required treatment in addition to the study drug and rescue SABA.

Pearlman 1999a

Methods	STUDY DESIGN: Parallel group 6 groups, multicentre (11 centres) USA, 2 week run in / 4 weeks treatment RANDOMISATION: Randomised treatment allocation, no details BLINDING: double blind, placebo controlled , matching devices WITHDRAWALS/DROP OUTS: 7 COMPLIANCE: assessed during run in CONFOUNDERS: Groups well balanced by baseline characteristics

Pearlman 1999a *(Continued)*

	QUALITY: Jadad 3 Cochrane B
Participants	N= Randomised 44, M=24 F= 20 adult/adolescent . Mean age 32 (range 12-62) SEVERITY OF ASTHMA: unknown INCLUSION : Diagnosis asthma by ATS criteria, stable, Baseline FEV1 50-80% predicted,, >15% FEV1 reversibility to SABA , EXCLUSION: use of ICS/OS within 6mths, life threatening asthma, smoker, smoking history < 10pack years.
Interventions	LONG ACTING BETA AGONIST: Salmeterol 42 mcg BD PLACEBO: BD DEVICE: MDI no spacer RESCUE: Albuterol prn TREATMENT PERIOD: 4 weeks CO-INTERVENTIONS: 3 groups B= no ICS,
Outcomes	OUTCOMES: PEF, FEV1, FVC, Rescue use, asthma symptom score, % days with no symptoms ,% nights with no asthma awakenings, adverse events, plasma cortisol
Notes	Symptom Score- cough/wheeze/SOB -4 pt Scale :0= none to 3= severe

Pleskow 2003

Methods	STUDY DESIGN: Parallel group LOCATION, NUMBER OF CENTRES: Not clear DURATION OF STUDY: 12 weeks preceded by two week run-in CONCEALMENT OF ALLOCATION: COCHRANE QUALITY SCORE: B DESCRIBED AS RANDOMISED: Yes DESCRIBED AS DOUBLE BLIND: Yes METHOD OF RANDOMISATION WELL DESCRIBED/APPROPRIATE: Unclear METHOD OF BLINDING WELL DESCRIBED/APPROPRIATE: Placebo inhaler devices matched to active treatments for double-dummy technique. DESCRIPTION OF WITHDRAWALS/DROPOUTS: 484/554 completed the study (reasons for withdrawal not stated) JADAD SCORE (5-1): 4 TYPE OF ANALYSIS (AVAILABLE CASE/TREATMENT RECEIVED/ ITT): ITT for primary outcome (FEV1 & % change in FEV1); symptoms, adverse events. Non-ITT for remaining outcomes. COMPLIANCE: Not assessed CONFOUNDERS: Groups balanced for age, duration of asthma, height and ethnic background.
Participants	Adults, N SCREENED: 707 (entered run-in phase), N RANDOMISED: 554 , N COMPLETED: 484 M= 273 F= 281 MEAN AGE: 33.1 BASELINE DETAILS: Duration of asthma: 18 years; mild to moderate asthma INCLUSION CRITERIA: 12-75 years; inhaled SABA daily for previous two months; FEV1 between 40-80% predicted; =15% increase in FEV1 post-SABA; CXR consistent with asthma prior to visit 1 EXCLUSION: Pregnant women/women child-bearing potential who did not have reliable form of contraception; significant coronary heart disease; prior MI; uncontrolled hypertension; diabetes; convulsive disorder; intolerance of beta-agonists; URTI within one month of study entry; hospitalisation for acute asthma within one month of study entry or during run-in; non-compliance to medical regimes; parenteral/oral steroids in month prior to visit 1; newly instituted/modified ICS therapy (including discontinuation); disodium cromoglycate; oral/inhaled anticholinergics; desensitization therapy; recent use of astemizole; use of theophylline in month prior to visit 1; use of antiarrhythmics; use of Prozac; vaccination with live virus in month prior to visit 1; weight 35% above or 25% predicted; significant smoking history; malignancy

Pleskow 2003 *(Continued)*

Interventions	1. Formoterol 12mcg BD 2. Formoterol 24mcg BD 3. Short-acting beta-agonist four times daily 4. Placebo DELIVERY: MDI TREATMENT PERIOD: 12 weeks RESCUE: Salbutamol 90mcg prn CO-INTERVENTIONS PERMITTED: ICS, theophylline SR. CO-INTERVENTIONS: SABA prn % on ICS: Review by Gunkel gives pooled % with study 40 as 47.3%, Pleskow 44% ICS (45% FORM 12, 43% FORM 24, 49% PLA
Outcomes	OUTCOMES MEASURED: % change in FEV1 L; FEV1 AUC; exacerbations (Defined as requirement for nebulised SABA); symptoms; FEV1 AUC; am PEF; deaths; ECG FOLLOW-UP ASSESSMENT POINTS: 0, 2, 4, 8 & 12weeks OUTCOMES INCLUDED IN ANALYSES: combined asthma score; exacerbations; adverse events; withdrawal due to adverse events; deaths; ECG (number of category 4 abnormal counts) SUB-GROUPS INDENTIFIED: Not reported.
Notes	FORNDA 20831_41 published as Pleskow 2003

Prieto 2002

Methods	STUDY DESIGN: Parallel group single centre study, Spain outpatient allergy clinic. 5-7 day run in / 6 week treatment period RANDOMISATION: Randomised, no details BLINDING double blind, placebo controlled, no details WITHDRAWALS/DROP OUTS: 3 described. COMPLIANCE: weighing used canisters, result 83% active group, 90% placebo. CONFOUNDERS: participants not sensitized to other perennial allergens. QUALITY: Jadad 3 Cochrane B
Participants	N = 30 randomised, 27 completed. M= 7, F= 20 Mean age 39.5 yrs range 17-55. BASELINE SEVERITY: Seasonal mild asthma only. INCLUSION : Clinical diagnosis seasonal asthma, Baseline FEV1 >80% predicted, positive skin prick test to pollen allergen and negative to perennial allergens. EXCLUSION : Ever smoker, perennial asthma, COPD, URTI within 4 weeks, regular use of asthma therapy.
Interventions	LONG ACTING BETA AGONIST: Salmeterol 50mcg BD PLACEBO: BD DEVICE: MDI via spacer RESCUE: Albuterol via MDI TREATMENT PERIOD: 6 weeks CO-INTERVENTIONS: none permitted
Outcomes	OUTCOMES: BHR PC20 methacholine, PC20 AMP, exhaled nitric oxide level, FEV1
Notes	

Ramage 1994

Methods	STUDY DESIGN: 2 way cross over single centre UK, 1 week run in / 4 weeks treatment/ 1 week wash out at cross over

Ramage 1994 *(Continued)*

	RANDOMISATION: Randomised treatment allocation, randomisation blocks balanced BLINDING: double blind, placebo controlled , WITHDRAWALS/DROP OUTS: none occurred COMPLIANCE: No details CONFOUNDERS: No details QUALITY: Jadad 4 Cochrane A
Participants	N= Randomised 12, M=8 F= 4 adult. Mean age 25.8 (range 18-50) SEVERITY OF ASTHMA: unknown INCLUSION : Clinical diagnosis asthma, Baseline FEV1 > 65% predicted; >20% fall in FEV1 with exercise , EXCLUSION: exacerbation/ change in asthma medication < 4wks, smoker URTI/ LRTI/hospitalisation/ OCS < 4 WKS , unstable asthma, smoking
Interventions	LONG ACTING BETA AGONIST: Salmeterol 50 mcg BD PLACEBO: BD DEVICE: MDI RESCUE: Salbutamol 100 mcg prn TREATMENT PERIOD: 4 weeks CO-INTERVENTIONS: ICS 11/12, cromone 1/12, theophylline %ICS 91%
Outcomes	OUTCOMES: Max fall in FEV1 with exercise
Notes	

Roberts 1999

Methods	STUDY DESIGN: Parallel group single centre UK, 2 week run in / 6 weeks treatment RANDOMISATION: Randomised treatment allocation, no details BLINDING: double blind, placebo controlled , matching devices. WITHDRAWALS/DROP OUTS: none occurred COMPLIANCE: No details CONFOUNDERS: Groups well balanced by baseline characteristics QUALITY: Jadad 4 Cochrane B
Participants	N= Randomised 26, M=14 F= 12 adult. Mean age 31 (range 18-55) BASELINE SEVERITY: symptomatic/persistent INCLUSION : Clinical diagnosis asthma, atopic, requiring SABA as sole treatment. Diurnal variation PEF >15% or ASS >2 or using SABA 7/14 days run in EXCLUSION:ICS / OCS < 4 week, methylxanthines, cromones, anticholinergic, antihistamines
Interventions	LONG ACTING BETA AGONIST: Salmeterol 50 mcg BD PLACEBO: BD DEVICE: MDI RESCUE: Salbutamol 100 mcg prn TREATMENT PERIOD: 6 weeks CO-INTERVENTIONS: none permitted
Outcomes	OUTCOMES: PEF, Rescue use, asthma symptom score, EBB. BAL. BHR
Notes	Symptom Score- cough/wheeze/SOB. Night-time 5 pt: 0-4 (none - so severe that no sleep possible). Day-time 5 pt: 0-4 (no symptoms - symptoms so severe normal activities not possible)

Rosenthal 1999

Methods	STUDY DESIGN: 2 Parallel group studies, multi-centre (31)USA, 2 week run in / 24 weeks treatment/ 4 weeks run out RANDOMISATION: Randomised treatment allocation, no details BLINDING: double blind, placebo controlled , blinded devices. WITHDRAWALS/DROP OUTS: 87 after randomisation COMPLIANCE: No details CONFOUNDERS: Groups well balanced by baseline characteristics QUALITY: Jadad 4 Cochrane B
Participants	N= Randomised 408, M=241 F= 167 adult/adolescent. Mean age 28 (range 12-65) BASELINE SEVERITY: Mild asthma INCLUSION : Clinical diagnosis asthma, Baseline FEV1 >70% predicted, >15% FEV1 reversibility to SA-BA.BHR PD20 <512mcg or 7.5mg/ml methacholine EXCLUSION: URTI/ LRTI < 6 WKS hospitalisation < 12wks Serious uncontrolled systemic disease
Interventions	LONG ACTING BETA AGONIST: Salmeterol 42 mcg BD PLACEBO: BD DEVICE: MDI RESCUE: Albuterol 100 mcg prn TREATMENT PERIOD: 24 weeks CO-INTERVENTIONS: none permitted
Outcomes	OUTCOMES: PEF, FEV1, FVC, Rescue use, asthma symptom score. BHR. . Exacerbations
Notes	Symptom Score- cough/wheeze/SOB. Night-time 4 pt: 0-3 (none - so severe that no sleep possible). Day-time 5 pt: 0-4 (no symptoms - symptoms so severe normal activities not possible) Exacerbations defined as worsening of asthma symptoms that required treatment in addition to the study drug and rescue SABA. If ICS/OS required subject withdrawn

SAS30003

Methods	STUDY DESIGN: Parallel group LOCATION, NUMBER OF CENTRES: 37 centres in North and Central America DURATION OF STUDY: 12 weeks CONCEALMENT OF ALLOCATION: COCHRANE QUALITY SCORE: B DESCRIBED AS RANDOMISED: Yes DESCRIBED AS DOUBLE BLIND: Yes METHOD OF RANDOMISATION WELL DESCRIBED/APPROPRIATE: Not reported METHOD OF BLINDING WELL DESCRIBED/APPROPRIATE: Not reported DESCRIPTION OF WITHDRAWALS/DROPOUTS: 81/360 JADAD SCORE (5-1): 3 TYPE OF ANALYSIS (AVAILABLE CASE/TREATMENT RECEIVED/ ITT): ITT COMPLIANCE: Not reported. CONFOUNDERS: Baseline characteristics similar.
Participants	N SCREENED: Not reported. N RANDOMISED: 360 N COMPLETED: 279 M= 159 F= 201 MEAN AGE: 33 years BASELINE DETAILS: FEV1 2.3L; SEVERITY OF ASTHMA: unknown, severity of asthma not described INCLUSION CRITERIA: =12 years of age; ATS defined asthma; FEV1 40-85% predicted; FEV1 reversibility =15% post-SABA; participants not treated with ICS were to have required SABA prn for one week prior to visit 1, and those with 7 day total symptom score =7 for 7 days prior to visit 2; participants previously treated with salmeterol were required to have been treated for one week prior to visit 1.

SAS30003 *(Continued)*

	EXCLUSION: ICS treatment which had been altered or initiated within previous three months.
Interventions	1. Salmeterol 42mcg BID 2. Placebo 3. Fluticasone/salmeterol combination 88/42mcg BID 4. Fluticasone 88mcg BID DELIVERY: MDI TREATMENT PERIOD: 12 weeks RESCUE: Salbutamol dose unspecified prn CO-INTERVENTIONS PERMITTED: ICS; SABA prn CO-INTERVENTIONS: as above % on ICS: 0% in PLA and SALM
Outcomes	OUTCOMES MEASURED: Withdrawals; Change in am FEV1; change in am PEF; change in pm PEF; Change in rescue medication usage; change in nighttime awakenings; change in daily asthma symptom score; change in AQLQ FOLLOW-UP ASSESSMENT POINTS: 12 weeks OUTCOMES INCLUDED IN ANALYSES: Withdrawals; change in am PEF; change in pm PEF; Change in rescue medication usage; change in nighttime awakenings; change in daily asthma symptom score SUB-GROUPS INDENTIFIED: Participants using ICS; participants not using ICS (stratified data not reported)
Notes	

SAS30004

Methods	STUDY DESIGN: Parallel group LOCATION, NUMBER OF CENTRES: 45 centres in USA DURATION OF STUDY: 12 weeks CONCEALMENT OF ALLOCATION: COCHRANE QUALITY SCORE: B DESCRIBED AS RANDOMISED: Yes DESCRIBED AS DOUBLE BLIND: Yes METHOD OF RANDOMISATION WELL DESCRIBED/APPROPRIATE: Not reported METHOD OF BLINDING WELL DESCRIBED/APPROPRIATE: Not reported DESCRIPTION OF WITHDRAWALS/DROPOUTS: 122/365 JADAD SCORE (5-1): 3 TYPE OF ANALYSIS (AVAILABLE CASE/TREATMENT RECEIVED/ ITT): ITT COMPLIANCE: Not assessed CONFOUNDERS: Baseline characteristics similar
Participants	N SCREENED: Not reported N RANDOMISED: 365 N COMPLETED: 243 M= 145 F= 220 MEAN AGE: 39 BASELINE DETAILS: Baseline FEV1 2.2L; SEVERITY OF ASTHMA: unknown INCLUSION CRITERIA: =12 years of age; ATS defined asthma; asthma inadequately controlled with ICS; FEV1 40-85% predicted; FEV1 =15% reversibility; treatment with ICS prior to visit 1 EXCLUSION: None reported
Interventions	1. Salmeterol 42mcg BID 2. Placebo 3. Fluticasone 220mcg BID 4. Fluticasone/salmeterol combination 220/42mcg BID DELIVERY: MDI TREATMENT PERIOD: 12 weeks

SAS30004 *(Continued)*

	RESCUE: SABA prn CO-INTERVENTIONS PERMITTED: SABA prn CO-INTERVENTIONS: SABA prn % on ICS: 0
Outcomes	OUTCOMES MEASURED: Withdrawal due to worsening asthma; change in FEV1 L; Change in am PEF; Change in pm PEF; Change in SABA usage; Change in % days with no SABA; Change in % nights with no awakening; Change in symptom scores; % change in symptom scores; Change in AQLQ; withdrawals; adverse events FOLLOW-UP ASSESSMENT POINTS: 12 weeks OUTCOMES INCLUDED IN ANALYSES: Withdrawal due to worsening asthma; withdrawals; adverse events SUB-GROUPS INDENTIFIED: Not reported
Notes	

Schreurs 1996

Methods	STUDY DESIGN: Parallel group, 4 groups, multi-centre (15) Netherlands, hospital setting, 1 week run in / 4 weeks treatment RANDOMISATION: Randomised treatment allocation, no details BLINDING: double blind, placebo controlled , WITHDRAWALS/DROP OUTS: 28 COMPLIANCE: No details CONFOUNDERS: Groups well balanced by baseline characteristics QUALITY: Jadad 3 Cochrane B
Participants	N=Enrolled 236 Randomised 220 completed 194. M=134 F= 60 adults. Mean age 47 (SD 15) BASELINE SEVERITY: Moderate asthma. INCLUSION : Diagnosis asthma by ATS criteria 6 months. Baseline FEV1 40-70% predicted, >15% FEV1 reversibility to SABA. EXCLUSION: URTI/ LRTI < 4 WKS, pronounced seasonal allergy, Serious uncontrolled systemic disease, OS, theophyllines, anticholinergics
Interventions	LONG ACTING BETA AGONIST: Formoterol 6mcg, 12 mcg or 24 mcg BD PLACEBO: BD DEVICE: DP turbuhaler RESCUE: terbutaline 50 mcg prn TREATMENT PERIOD: 4 weeks CO-INTERVENTIONS: ICS 90%, cromones; at stable dose
Outcomes	OUTCOMES: PEF, FEV1, Rescue use, asthma symptom score, diurnal variation PEF,
Notes	Symptom Score- cough/wheeze/SOB -4 pt Scale :0= none to 3= severe

Shapiro 2000b

Methods	STUDY DESIGN: Parallel group, multi- centre (42) study in USA, 2 week run in / 12 weeks treatment RANDOMISATION: Randomised treatment allocation, no details BLINDING: double blind, placebo controlled , WITHDRAWALS/DROP OUTS: 13 active = FP, 22 placebo + FP COMPLIANCE: by medication count .>91% all groups CONFOUNDERS: Groups well balanced by baseline characteristics QUALITY: Jadad 3 Cochrane B

Shapiro 2000b *(Continued)*

Participants	N=screened 484 Randomised 181 M=78 F= 103 adults/adolescents. Mean age 38 (range 12-69) BASELINE SEVERITY: moderate stable asthma on regular ICS INCLUSION : Diagnosis asthma by ATS criteria > 6mths Using ICS regularly for >3mths pre study . Baseline FEV1 >75% predicted, >15% FEV1 reversibility to SABA. EXCLUSION: unstable asthma- requiring > 12 puffs /day albuterol, OCS for exacerbation < 4 WKS, regular OS within 6mths, nocturnal asthma > 3/week, smoker, smoking history > 10 pack years
Interventions	LONG ACTING BETA AGONIST: Salmeterol 50 mcg BD PLACEBO: BD DEVICE: DP diskhaler RESCUE: albuterol 100 mcg prn TREATMENT PERIOD: 12 weeks CO-INTERVENTIONS: none permitted
Outcomes	OUTCOMES: Exacerbation of asthma leading to withdrawal, PEF, FEV1, Rescue use, asthma symptom score, 12 hr serial FEV1, nocturnal asthma awakenings
Notes	Exacerbations defined as clinical worsening of asthma symptoms that require Emergency room treatment, hospitalization or treatment in addition to the study drug and rescue SABA. Symptom Score- cough/wheeze/SOB. 5 pt: 0-4 (no symptoms - symptoms so severe normal activities not possible)

Simons 1997a

Methods	STUDY DESIGN: Parallel group, 3 treatment groups, multicentre Canada, 2 week run in/ 52 weeks treatment / 2 week run out RANDOMISATION: Randomised treatment allocation, no details BLINDING: double blind, placebo controlled , WITHDRAWALS/DROP OUTS: 60 COMPLIANCE: by counting unused blisters. 99% all subjects had compliance >75% CONFOUNDERS: Groups well balanced by baseline characteristics QUALITY: Jadad 3 Cochrane B
Participants	N enrolled= 315 Randomised 241 M=140 F= 101 children. Mean age 9.3 (range 6-14) BASELINE SEVERITY: Mild-moderate persistent asthma INCLUSION : Clinical stable asthma, atopic, well controlled, Baseline FEV1 >70% predicted, >10% FEV1 reversibility to SABA. PC20 methacholine < 8mg/ml EXCLUSION use ICS/ OS for >4 weeks previously, OS/ICS within 3mths. exacerbation < 12 WKS,
Interventions	LONG ACTING BETA AGONIST: Salmeterol 50 mcg BD PLACEBO: BD DEVICE: DP diskus RESCUE: albuterol 200 mcg prn TREATMENT PERIOD: 4 weeks CO-INTERVENTIONS: ICS not permitted (3rd group given BDP 400mcg/day)
Outcomes	OUTCOMES: FEV1, FVC, FEV25-75%, PEF, Rescue use, days missing school due to asthma , BHR, % days with no rescue use ,% nights with no asthma awakenings, adverse events
Notes	Exacerbations defined as worsening of asthma symptoms that required treatment in addition to the study drug and rescue SABA.

SLGA2004

Methods	STUDY DESIGN: Parallel group LOCATION, NUMBER OF CENTRES: 12 in USA DURATION OF STUDY: 4 weeks CONCEALMENT OF ALLOCATION: COCHRANE QUALITY SCORE: B DESCRIBED AS RANDOMISED: Yes DESCRIBED AS DOUBLE BLIND: Yes METHOD OF RANDOMISATION WELL DESCRIBED/APPROPRIATE: not reported METHOD OF BLINDING WELL DESCRIBED/APPROPRIATE: not reported DESCRIPTION OF WITHDRAWALS/DROPOUTS: 15/210 JADAD SCORE (5-1): 3 TYPE OF ANALYSIS (AVAILABLE CASE/TREATMENT RECEIVED/ ITT): ITT for safety data, efficacy population excluded WD prior to visit 3 and protocol deviations COMPLIANCE: Not reported CONFOUNDERS: Baseline characteristics similar
Participants	N SCREENED: not reported N RANDOMISED: 210 N COMPLETED: 195 M= 135 F= 75 MEAN AGE: 32 (14) BASELINE DETAILS: Mild-moderate asthma requiring therapy during previous 6 months INCLUSION CRITERIA: =12 years of age; ATS defined asthma; FEV1 50-85% predicted; FEV1 reversibility =15% post-SABA EXCLUSION: serious uncontrolled illness, current smokers, > 10 pack year history smoking
Interventions	1.Salmeterol 50mcg BD MDPI 2.Salmeterol 50 mcg BD Diskhaler 3.Placebo BD TREATMENT PERIOD: 4 weeks RESCUE: SABA PRN CO-INTERVENTIONS PERMITTED: not specified CO-INTERVENTIONS : not reported % on ICS not reported
Outcomes	OUTCOMES MEASURED: 12 hour serial FEV1, 12 hour serial FEF 25-75%, am/pm PEF, rescue use, awakenings, symptoms, QOL using SF36, ALQL, sleep scale FOLLOW-UP ASSESSMENT POINTS: 4 weeks OUTCOMES INCLUDED IN ANALYSES SUB-GROUPS INDENTIFIED: none
Notes	

SLGA3014 1994

Methods	STUDY DESIGN: Parallel group LOCATION, NUMBER OF CENTRES: 36 centres in USA. DURATION OF STUDY: CONCEALMENT OF ALLOCATION: COCHRANE QUALITY SCORE: B DESCRIBED AS RANDOMISED: Yes DESCRIBED AS DOUBLE BLIND: Yes METHOD OF RANDOMISATION WELL DESCRIBED/APPROPRIATE: Not reported METHOD OF BLINDING WELL DESCRIBED/APPROPRIATE: Yes (double-dummy) DESCRIPTION OF WITHDRAWALS/DROPOUTS: 59/449 (lack of efficacy: 11; adverse event: 8; failure to return: 7; other: 33). JADAD SCORE (5-1): 4.

SLGA3014 1994 *(Continued)*

	TYPE OF ANALYSIS (AVAILABLE CASE/TREATMENT RECEIVED/ ITT): Non-ITT for efficacy outcomes; ITT for safety outcomes. COMPLIANCE: Not assessed. CONFOUNDERS: Baseline characteristics not adequately presented.
Participants	N SCREENED: 756 N RANDOMISED: 449 N COMPLETED: 390 M= 61% F= 39% MEAN AGE: 8 years (range 4-11) BASELINE DETAILS: Caucasian 78%, Black 12%, Mean PEFR 80% predicted; mean FEV1 70% predicted; 65% report nocturnal symptoms; 80% report that symptoms interfere with activities one day per week SEVERITY OF ASTHMA: persistent INCLUSION CRITERIA: PEFR (4-5 years)/FEV1 (6-11 years 45-80% predicted) EXCLUSION: Not reported.
Interventions	1. Salmeterol 25mcg BID 2. Salmeterol 50mcg BID 3. Placebo DELIVERY: DPI TREATMENT PERIOD: 12 weeks (no run-in described) RESCUE: SABA prn CO-INTERVENTIONS PERMITTED: ICS, cromolyn, nedocromil CO-INTERVENTIONS: cromolyn/nedocromil: 25% % on ICS: approx 50%
Outcomes	OUTCOMES MEASURED: Serial PEFR % predicted; PEFR AUC; serial FEV1 % predicted; FEV1 AUC; change in post-dose PEFR % predicted; change in post-dose FEV1 % predicted; mean change in am PEFR; change in daily asthma symptom score; change in % nights with no awakenings; withdrawals; adverse events; FOLLOW-UP ASSESSMENT POINTS: Day 1, weeks 6 & 12 OUTCOMES INCLUDED IN ANALYSES: Withdrawals; adverse events SUB-GROUPS INDENTIFIED: <9 years versus >9 years.
Notes	Symptom score 1= no symptoms at all, 2= symptoms with little or no discomfort, unrestricted activity, 3=symptoms occurred, were sometimes annoying or affected routine activity, 4= symptoms occurring even at rest, were annoying or affected activity

SLGL82

Methods	STUDY DESIGN: Parallel group LOCATION, NUMBER OF CENTRES: Thailand, 4 centres DURATION OF STUDY: 4 weeks CONCEALMENT OF ALLOCATION: COCHRANE QUALITY SCORE: B DESCRIBED AS RANDOMISED: Yes DESCRIBED AS DOUBLE BLIND: Yes METHOD OF RANDOMISATION WELL DESCRIBED/APPROPRIATE: Not reported METHOD OF BLINDING WELL DESCRIBED/APPROPRIATE: Not reported. DESCRIPTION OF WITHDRAWALS/DROPOUTS: 7/90 (Adverse events: 5; other reasons: 2) JADAD SCORE (5-1): 3 TYPE OF ANALYSIS (AVAILABLE CASE/TREATMENT RECEIVED/ ITT): Available case for am & pm PEFR; ITT for other outcomes COMPLIANCE: Not assessed. CONFOUNDERS: Symptom scores higher in placebo group for night symptoms;
Participants	Adults, SCREENED: Not reported , N RANDOMISED: 90 , N COMPLETED: 82 M= 30 F= 52 MEAN AGE: 43

SLGL82 *(Continued)*

	BASELINE DETAILS: Mild asthma: 21; moderate asthma: 67 (criteria unspecified); FEV1: 1.73L INCLUSION CRITERIA: FEV1 >50% predicted; PEFR during last 7 days of run-in >50% predicted; FEV1 15% reversibility post-SABA; day/night symptom score =2 EXCLUSION: <12 years; serious uncontrolled disease; lower RTI; hospitalisation due to airways disease; maintenance dose of prednisolone <20mcg/d; intolerance of beta-agonist; current treatment with beta-agonist.
Interventions	1. Salmeterol 50mcg BID 2. Placebo DELIVERY: MDI TREATMENT PERIOD: 4 weeks RESCUE: Salbutamol (dose not specified) CO-INTERVENTIONS PERMITTED: oral steroids up to 20mcg/d CO-INTERVENTIONS: Not stated. % on ICS: Not reported.
Outcomes	OUTCOMES MEASURED: Symptoms; rescue medication usage; FEV1; PEFR; adverse events FOLLOW-UP ASSESSMENT POINTS: 2 & 4 weeks. OUTCOMES INCLUDED IN ANALYSES: Symptoms; rescue medication usage; FEV1; PEFR; adverse events SUB-GROUPS INDENTIFIED: Not reported.
Notes	

SLMP03

Methods	STUDY DESIGN: Parallel group LOCATION, NUMBER OF CENTRES: Italy, one centre. DURATION OF STUDY: 8 weeks CONCEALMENT OF ALLOCATION: COCHRANE QUALITY SCORE: B DESCRIBED AS RANDOMISED: Yes DESCRIBED AS DOUBLE BLIND: Yes METHOD OF RANDOMISATION WELL DESCRIBED/APPROPRIATE: Not reported METHOD OF BLINDING WELL DESCRIBED/APPROPRIATE: Same inhaler device use for both treatments. DESCRIPTION OF WITHDRAWALS/DROPOUTS: 15/24 (reasons not specified) JADAD SCORE (5-1): 4 TYPE OF ANALYSIS (AVAILABLE CASE/TREATMENT RECEIVED/ ITT): ITT COMPLIANCE: Not assessed CONFOUNDERS: Characteristics similar.
Participants	N SCREENED: Not reported. N RANDOMISED: 24 N COMPLETED: 9 M= 16 F= 8 MEAN AGE: 9.6 years (SD 2.7) BASELINE DETAILS: am PEFR: 325L/min; pm PEFR 334L/min; median % nights free from asthma: 100; median % days free from asthma: 90. INCLUSION CRITERIA: 6-14 years; mild to moderate asthma (criteria not specified); recent asthma attacks despite treatment with beta-agonists; sensitivity to methacholine. EXCLUSION: Seasonal allergic asthma; treatment with topical steroids, theophylline, salmeterol, anticholinergic agents, beta-blockers or cromones.
Interventions	1. Salmeterol 50mcg BID 2. Placebo DELIVERY: DPI TREATMENT PERIOD: 8 weeks RESCUE: Salbutamol (dose not specified). CO-INTERVENTIONS PERMITTED: Rescue medication (SABA prn)

SLMP03 *(Continued)*

	CO-INTERVENTIONS: Not reported. % on ICS:0%
Outcomes	OUTCOMES MEASURED: PD20; am PEFR; pm PEFR; symptoms & rescue medication usage. FOLLOW-UP ASSESSMENT POINTS: 8 weeks OUTCOMES INCLUDED IN ANALYSES: PD20; am PEFR; pm PEFR; symptoms & rescue medication usage SUB-GROUPS INDENTIFIED: Not reported.
Notes	

SMART

Methods	STUDY DESIGN: Parallel group LOCATION, NUMBER OF CENTRES: USA, 6163 centres DURATION OF STUDY: 28 weeks CONCEALMENT OF ALLOCATION: COCHRANE QUALITY SCORE: B DESCRIBED AS RANDOMISED: Yes DESCRIBED AS DOUBLE BLIND: Yes METHOD OF RANDOMISATION WELL DESCRIBED/APPROPRIATE: Not reported. METHOD OF BLINDING WELL DESCRIBED/APPROPRIATE: Treatments administered through same delivery device. DESCRIPTION OF WITHDRAWALS/DROPOUTS: 6102/26355 (adverse events: 244; lack of efficacy: 878; other reasons: 4974) JADAD SCORE (5-1): 4 TYPE OF ANALYSIS (AVAILABLE CASE/TREATMENT RECEIVED/ ITT): ITT COMPLIANCE: VAS measured (0-10, 10=most doses taken): 7.9 CONFOUNDERS: Baseline characteristics similar.
Participants	N SCREENED: Not reported. N RANDOMISED: 26,355 N COMPLETED: 19128 M= 9389 F= 16671 MEAN AGE: 39 BASELINE DETAILS: Mean PEFR: 355L/min; PEFR predicted: 84%; duration of asthma: 16.3 years SEVERITY OF ASTHMA: unknown INCLUSION CRITERIA: =12 years of age; diagnosis of asthma (clinical investigator); receiving current prescription of asthma medication. EXCLUSION: Prior use of LABA; pregnancy or lactation; concurrent disease that may pose a risk to the participant; sensitivity to long-acting beta-agonists; current ß-blocker use.
Interventions	1. Salmeterol 42mcg BID 2. Placebo DELIVERY: MDI TREATMENT PERIOD: 52 weeks RESCUE: Salbutamol (dose not reported). CO-INTERVENTIONS PERMITTED: usual asthma therapy CO-INTERVENTIONS: ICS, methylxanthines, leukotriene agents % on ICS: 47%
Outcomes	OUTCOMES MEASURED: Mortality; adverse events. FOLLOW-UP ASSESSMENT POINTS: 28 weeks. OUTCOMES INCLUDED IN ANALYSES: Mortality; adverse events. SUB-GROUPS INDENTIFIED: Caucasian/African American participants; ICS at baseline/no ICS at baseline.

SMART *(Continued)*

Notes	Exacerbations defined as worsening of asthma symptoms that required treatment in addition to the study drug and rescue SABA. Symptom Score- cough/wheeze/SOB. Night-time 0-3 (none - so severe that no sleep possible). Day-time 0-3 (no symptoms - symptoms so severe normal activities not possible

SMS40221

Methods	STUDY DESIGN: Parallel group LOCATION, NUMBER OF CENTRES: Taiwan, one centre. DURATION OF STUDY: 4 weeks CONCEALMENT OF ALLOCATION: COCHRANE QUALITY SCORE: B DESCRIBED AS RANDOMISED: Yes DESCRIBED AS DOUBLE BLIND: Yes METHOD OF RANDOMISATION WELL DESCRIBED/APPROPRIATE: Not reported METHOD OF BLINDING WELL DESCRIBED/APPROPRIATE: Both treatments delivered by the same device. DESCRIPTION OF WITHDRAWALS/DROPOUTS: 13/64 (adverse events: 3; lack of efficacy: 6; other reasons: 4) JADAD SCORE (5-1): 4 TYPE OF ANALYSIS (AVAILABLE CASE/TREATMENT RECEIVED/ ITT): ITT COMPLIANCE: Not assessed. CONFOUNDERS: Baseline data not available (all data reported as change).
Participants	N SCREENED: Not reported N RANDOMISED: 64 N COMPLETED: 51 M= 21 F= 43 MEAN AGE: 48 BASELINE DETAILS: Not reported. SEVERITY OF ASTHMA: unknown INCLUSION CRITERIA: >18 years; FEV1 % predicted >50; increase in FEV1 >15% predicted post 400mcg fenoterol or >20% post 800mcg fenoterol; symptom score of at least 2 on three of last 7 days of run-in period. EXCLUSION: Serious uncontrolled disease; lower RTI; hospitalisation with acute exacerbation of airways disease in previous two weeks; OCS in excess of 20mcg/d.
Interventions	1. Salmeterol 50mcg BID 2. Placebo DELIVERY: DPI TREATMENT PERIOD: 4 weeks preceded by run-in (duration not specified). RESCUE: Fenoterol (dose not specified). CO-INTERVENTIONS PERMITTED: Fenoterol; OCS up to 20mcg/d CO-INTERVENTIONS: SABA prn % on ICS: Not reported.
Outcomes	OUTCOMES MEASURED: Change in am PEFR (L/min); change in pm PEFR (L/min); change in FEV1 (L); change in FVC (L); change in symptoms; physician rated assessment; participant rated assessment; adverse events. FOLLOW-UP ASSESSMENT POINTS: 4 weeks. OUTCOMES INCLUDED IN ANALYSES: Change in am PEFR (L/min); change in pm PEFR (L/min); change in FEV1 (L); change in FVC (L); change in symptoms; physician rated assessment; participant rated assessment; adverse events. SUB-GROUPS INDENTIFIED: Not reported.
Notes	

Starke 1996

Methods	STUDY DESIGN: 2 way cross over single centre UK, 2 week run in/ 4 week treatment period/ 7-10 day run out RANDOMISATION: Randomised treatment allocation, no details BLINDING: double blind, placebo controlled ,matching devices WITHDRAWALS/DROP OUTS: 6 COMPLIANCE: no details CONFOUNDERS: data from weeks 2-4 treatment analysed QUALITY: Jadad 4 Cochrane B
Participants	N Randomised 28 M=15 F= 13 older adults Median age 74 (range 64-88) BASELINE SEVERITY: not specified INCLUSION : over 64 years age. >15% diurnal variation PEF or symptoms of airflow limitation > 4/7 run in days, able to use MDI with or without a spacer/adapter. EXCLUSION: LRTI/hospitalisation asthma with 4 weeks, use of methylxanthines, Serious uncontrolled systemic disease
Interventions	LONG ACTING BETA AGONIST: Salmeterol 50 mcg BD PLACEBO: BD DEVICE: MDI +/- spacer RESCUE: Salbutamol 100 mcg prn TREATMENT PERIOD: 4 weeks CO-INTERVENTIONS: ICS , OS, cromones, ketotifen, anticholinergics- all at stable dose
Outcomes	OUTCOMES: FEV1, PEF, Rescue use, asthma symptom score. Efficacy score-patient and investigator rated, adverse events
Notes	Symptom Score- cough/wheeze/SOB. 6 pt: 0-5 (no symptoms - symptoms so severe normal activities not possible)

Steffensen 1995

Methods	STUDY DESIGN: Parallel group (3 treatment groups)-multicentre , 20 Scandinavia. 2 week run in/ 12 weeks. RANDOMISATION: Yes, no method stated. BLINDING: double blind, double dummy, matching devices. WITHDRAWALS/DROP OUTS: 42 described after randomization. COMPLIANCE:. Not assessed CONFOUNDERS: Groups well balanced by characteristics QUALITY: Jadad 4. Cochrane B
Participants	N= 362 ENROLLED, 304 RANDOMISED 204 to LABA or placebo). ADULT , M=98 F=106 Mean age: 48.5 (SD 14) BASELINE SEVERITY: not specified, clinically stable. INCLUSION : Baseline FEV1 >40% predicted, >15% FEV1 reversibility to SABA. Requiring SABA. EXCLUSION: unstable asthma, altered dose medication.
Interventions	LONG ACTING BETA AGONIST: Formoterol 12 mcg BD SHORT ACTING BETA AGONIST: Salbutamol 400 mcg QDS PLACEBO: placebo QDS DEVICE: Dry powder device. TEATMENT PERIOD: 12 weeks RESCUE: Salbutamol 100 mcg PRN CO-INTERVENTIONS: ICS 84%, OS 6%, cromones stable dose

Steffensen 1995 *(Continued)*

Outcomes	OUTCOMES: FEV1, FVC, PEF, Rescue use, asthma symptom score. adverse events, including asthma exacerbations. Eficacy rating
Notes	Symptom Score- Day: 0=none, to 3=very severe symptoms. night: 0=none to 3=almost no sleep due to asthma. No definition of asthma exacerbation recorded as an adverse event given.

Stelmach 2002

Methods	STUDY DESIGN: Parallel group single centre study, Poland, university centre. 4 week run in (off all treatment except Ipratropium) / 4 week treatment period RANDOMISATION: Randomised, computer generated schedule. BLINDING double blind, placebo controlled, matching capsules. WITHDRAWALS/DROP OUTS: 2 in placebo group with exacerbations. COMPLIANCE: no details CONFOUNDERS: groups balanced by baseline characteristics. QUALITY: Jadad 5 Cochrane A
Participants	N = 34 randomised, 32 completed. M=19, F= 13 Mean age 11.9 yrs (SD 1.5) BASELINE SEVERITY: Moderate persistent asthma GINA guidelines. INCLUSION : Clinical diagnosis asthma > 6 months, , >15% FEV1 reversibility to SABA. Atopic EXCLUSION : Exacerbation or hospitalisation for asthma or change asthma medication or URTI within 4 weeks. Serious medical illness.
Interventions	LONG ACTING BETA AGONIST: Formoterol 12 mcg BD PLACEBO: BD DEVICE: DP capsules RESCUE: Salbutamol PRN via MDI TREATMENT PERIOD: 6 weeks CO-INTERVENTIONS: none permitted
Outcomes	OUTCOMES: Primary= serum levels of inflammatory markers, ECP, sIL-2R, IL-4, ICAM-1, IgE. Secondary= BHR PC20 histamine, FEV1, ASS.
Notes	

Sussman 1995

Methods	STUDY DESIGN: 2 way cross over single centre UK, 2-4 week run in/ 4-6 week treatment period RANDOMISATION: Randomised treatment allocation, no details BLINDING: double blind, placebo controlled , WITHDRAWALS/DROP OUTS: 2 COMPLIANCE: no details CONFOUNDERS: no details QUALITY: Jadad 3 Cochrane B
Participants	N Randomised 18 M=12 F= 6 adults Mean age not stated (range 18-60) BASELINE SEVERITY: moderate INCLUSION : over 18 years age. v Baseline FEV1 >60% predicted, >15% FEV1 reversibility to SABA >15% diurnal variation EXCLUSION: no details
Interventions	LONG ACTING BETA AGONIST: Eformoterol 24 mcg BD PLACEBO: BD

Sussman 1995 *(Continued)*

	DEVICE: DP capsules RESCUE: Ipratropium 80 mcg prn TREATMENT PERIOD: 4-6 weeks CO-INTERVENTIONS: ICS , salbutamol, theophylline
Outcomes	OUTCOMES: DRC to formoterol, PEF, Rescue use,tremor, serum potassium
Notes	

Taylor 1998

Methods	STUDY DESIGN:3 way cross over, 2 centre, New Zealand. 4 week run in/ 24 weeks treatment/ 4 week run out. RANDOMISATION: Yes, no method stated. BLINDING: double blind, double dummy, matching devices. WITHDRAWALS/DROP OUTS: 35 described after randomization and 8 protocol violators. COMPLIANCE:. Assessed by counting blisters, >87% CONFOUNDERS: Not analysed by ITT, Efficacy analysis similar. QUALITY: Jadad 4. Cochrane B
Participants	N= ENROLLED189, RANDOMISED 165, completed/analysed 157 . ADULT , M=73 F=92 Mean age: 38 (range 18-64) BASELINE SEVERITY: Mild-moderate asthma INCLUSION : >15% FEV1 reversibility to SABA. PC20 methacholine <8mg/ml. EXCLUSION: current smokers, requiring OS or theophyllines, SABA requirement > 10 puffs/day, significant illness.
Interventions	LONG ACTING BETA AGONIST: Salmeterol 50 mcg BD SHORT ACTING BETA AGONIST: Salbutamol 400 mcg QDS PLACEBO: placebo QDS DEVICE: Dry powder device- diskhaler. TEATMENT PERIOD: 24 weeks RESCUE: Salbutamol 100 mcg PRN CO-INTERVENTIONS: None 8%, ICS 92%, cromones stable dose
Outcomes	OUTCOMES: FEV1, FVC, PEF, Rescue use, exacerbations, daily asthma score.
Notes	Exacerbations- Major = daily asthma score 3, PEF 40-60% predicted, requiring OS. Minor- Daily asthma score 2, PEF 61-75% predicted, increased rescue use.

von Berg 1998

Methods	STUDY DESIGN: Parallel group, multicentre (57) in 11 .countries, 2 week run in on / 52 week treatment with 2 week period off treatment at 6mths to assess BHR RANDOMISATION: Randomised treatment allocation, method not stated BLINDING: double blind, placebo controlled , WITHDRAWALS/DROP OUTS: 66 COMPLIANCE: checked verbally CONFOUNDERS: Groups well balanced by baseline characteristics QUALITY: Jadad 3 Cochrane B
Participants	N Enrolled 627, Randomised 426, completed 360, M=262 F= 164 children Mean age 10 (range 5-15) BASELINE SEVERITY: Mild-moderate asthma

von Berg 1998 *(Continued)*

	INCLUSION : Clinical diagnosis asthma, >15% FEV1 reversibility to SABA or diurnal variation PEF > 15%, am PEF<85% best in run in. EXCLUSION : URTI/ LRTI/hospitalisation / changed asthma medication <4 weeks, requiring OS/ anticholinergics/ methylxanthines at entry
Interventions	LONG ACTING BETA AGONIST: Salmeterol 50 mcg BD PLACEBO: BD DEVICE: DP diskhaler RESCUE: Salbutamol 100 mcg prn TREATMENT PERIOD: 52 weeks CO-INTERVENTIONS: ICS 50%, cromones 22%
Outcomes	OUTCOMES: PEF, FEV1, Rescue use, asthma symptoms, Exacerbations, BHR, % days with no symptoms ,% nights with no asthma awakenings
Notes	Exacerbations defined as worsening of asthma symptoms that required treatment in addition to the study drug and rescue SABA. no details on symptom score.

von Berg 2003

Methods	STUDY DESIGN: Parallel group, LOCATION, NUMBER OF CENTRES: multi centre (32) in Europe DURATION OF STUDY: 2 weeks run in, 12 weeks treatment CONCEALMENT OF ALLOCATION: COCHRANE QUALITY SCORE: A DESCRIBED AS RANDOMISED: Yes DESCRIBED AS DOUBLE BLIND: Yes METHOD OF RANDOMISATION WELL DESCRIBED/APPROPRIATE: computer generated schedule by consecutive patient number, ratio 1:1:1 METHOD OF BLINDING WELL DESCRIBED/APPROPRIATE: Yes, identical devices DESCRIPTION OF WITHDRAWALS/DROPOUTS: 23 mainly due to asthma deterioration (7 placebo, 5 FM 4.5mcg, 2 FM 9mcg) JADAD SCORE (5-1): 5 TYPE OF ANALYSIS (AVAILABLE CASE/TREATMENT RECEIVED/ ITT): ITT COMPLIANCE: no details CONFOUNDERS: 3 treatment groups well balanced for baseline characteristics and asthma histories
Participants	N SCREENED: 331 N RANDOMISED: 248 N COMPLETED: 225 M= 161 F= 87 MEAN AGE: 11 (6-17) SEVERITY OF ASTHMA: unknown BASELINE DETAILS: mean duration asthma 6 yrs (1-16), FEV1 % predicted 80%, BRD 15%, ICS use in run in 82%. INCLUSION CRITERIA : 6-17 years, diagnosis asthma ATS guidelines = 6 months, FEV1 % predicted =40%, receiving anti-inflammatory agents (ICS, OCS, nedocromil, cromones) at stable dose for 30 days, able to use turbuhaler, BDR either increase in FEV1 =15%, or in % predicted FEV1 =9%, or am PEF =15% 4/8 days run in. EXCLUSION: Use of astemizole = 60days, regular nasal ICS or antihistamines = 30 days, immunotherapy =90 days, significant seasonal asthma or allergy, significant medical condition.
Interventions	1. Formoterol 9 mcg BD 2. Formoterol 4.5 mcg BD 3. placebo DELIVERY: turbuhaler COMBINATION INHALER FOR LABA: No TREATMENT PERIOD: 12 weeks

von Berg 2003 *(Continued)*

	RESCUE: terbutaline 250 mcg PRN CO-INTERVENTIONS PERMITTED: ICS, cromones, nedocromil CO-INTERVENTIONS : ICS 82%
Outcomes	OUTCOMES MEASURED: PEF am/pm, FEV1, ASS. sleep disturbance, AEs, blood biochemistry FOLLOW-UP ASSESSMENT POINTS: baseline, 4,8,12 weeks OUTCOMES INCLUDED IN ANALYSES: SUB-GROUPS INDENTIFIED: None
Notes	ASS: symptoms 4 pt scale 0 none -3 affecting daily activities or affecting sleep

Wallin 1999

Methods	STUDY DESIGN: Parallel group, 3 treatment groups 2 active 1 placebo, multicentre (3) in Sweden, 2 -4 week run in / 9 week treatment RANDOMISATION: Randomised treatment allocation, method not stated BLINDING: double blind, double dummy, placebo controlled , matched devices WITHDRAWALS/DROP OUTS: 4 COMPLIANCE: no details CONFOUNDERS: study conducted outside pollen season, same investigator performed broncho-scopies. QUALITY: Jadad 4 Cochrane B
Participants	N Randomised 64, completed 360, M=36 F= 28 adults Mean age not given (range 18-48) BASELINE SEVERITY: Mild intermittent persistent asthma INCLUSION : Clinical diagnosis asthma using SABA PRN as maintenance treatment, atopic, Baseline FEV1 >70% predicted, PC20 methacholine 0.1-6 mg/ml EXCLUSION : URTI <4 weeks, smoking within 5 years
Interventions	LONG ACTING BETA AGONIST: Formoterol 24 mcg BD PLACEBO: BD ICS GROUP: budesonide 400mcg BD DEVICE: DP Aerolizer or MDI RESCUE: Salbutamol 100 mcg prn TREATMENT PERIOD: 9 weeks CO-INTERVENTIONS: none permitted
Outcomes	OUTCOMES: PEF, FEV1, Rescue use, asthma symptom score, BHR, EBB, BAL
Notes	Symptom Score- 4 pt, day or night time - Scale :0= none to 3= severe.

Weinstein 1998

Methods	STUDY DESIGN: Parallel group, multicentre (11) USA, 1-2 week run in on single blind placebo / 12 week treatment RANDOMISATION: Randomised treatment allocation, method not stated BLINDING: double blind, double dummy, placebo controlled , WITHDRAWALS/DROP OUTS: 20, 4 lack efficacy, 6 adverse events, 2 exacerbations COMPLIANCE: no details CONFOUNDERS: Groups well balanced by baseline characteristics QUALITY: Jadad 3 Cochrane B
Participants	N SCREENED: 240 N Randomised 207, M=142 F= 65 children Mean age 8.4 (range 4-11) BASELINE SEVERITY: persistent asthma, severity not stated

Weinstein 1998 *(Continued)*

	INCLUSION : Diagnosis asthma by ATS criteria, Baseline FEV150-80% predicted, >15% FEV1 reversibility to SABA. EXCLUSION : URTI/ LRTI/hospitalisation <4 weeks, OS, anticholinergics, theophyllines, antihistamines, tobacco exposure, Serious uncontrolled systemic disease
Interventions	LONG ACTING BETA AGONIST: Salmeterol 50 mcg BD PLACEBO: BD DEVICE: DP Rotadiscs RESCUE: albuterol 100 mcg prn TREATMENT PERIOD: 12 weeks CO-INTERVENTIONS: ICS 57%, cromones 32% , immunotherapy continued at same dose
Outcomes	OUTCOMES: PEF, FEV1, Rescue use, asthma symptoms, night asthma awakenings, Exacerbations, adverse events
Notes	Exacerbations defined as worsening of asthma symptoms that required treatment in addition to the study drug and rescue SABA.

Wolfe 2000a

Methods	STUDY DESIGN: Parallel group 3, 2 forms of salmeterol, powder and aerosol and placebo, multicentre (27) USA 2 week run in period / 12 week treatment period RANDOMISATION: Randomised treatment allocation, computer generated BLINDING: double blind, double dummy, placebo controlled WITHDRAWALS/DROP OUTS: 103 COMPLIANCE: no details CONFOUNDERS: Groups well balanced by baseline characteristics QUALITY: Jadad 3 Cochrane B
Participants	N Randomised 498, M=235 F= 263 adults/ adolescents Mean age 33 (range 12-79) BASELINE SEVERITY: Mild-moderate asthma INCLUSION : Diagnosis asthma by ATS criteria 6 months requiring pharmacotherapy. Baseline FEV1>85% predicted, >15% FEV1 reversibility to SABA. EXCLUSION : URTI/ LRTI/exacerbation <6 weeks, smoker or >10 year pack history
Interventions	LONG ACTING BETA AGONIST: Salmeterol 50 mcg BD either accuhaler or 42 mcg aerosol PLACEBO: BD aerosol or accuhaler DEVICE: MDI or accuhaler RESCUE: albuterol 100 mcg prn TREATMENT PERIOD: 12 weeks CO-INTERVENTIONS: ICS >30% all groups, cromones continued at same dose
Outcomes	OUTCOMES: PEF, FEV1, Rescue use, asthma symptom score, frequency nocturnal asthma, % days with no symptoms, adverse events,
Notes	ASS- no details in paper

Wolfe 2000b

Methods	As for Wolfe 2000a
Participants	As for Wolfe 2000a

Wolfe 2000b *(Continued)*

Interventions	As for Wolfe 2000a
Outcomes	As for Wolfe 2000a
Notes	Study data available as SLGA3011. Entered as Wolfe 2000b as the published paper reported pooled data from two clinical trials (SLGA3010/SLGA3011)

Wolfe 2006

Methods	STUDY DESIGN: Parallel group LOCATION, NUMBER OF CENTRES: 194 cited for screening. DURATION OF STUDY: 16 weeks (preceded by two week run-in) CONCEALMENT OF ALLOCATION: COCHRANE QUALITY SCORE: B DESCRIBED AS RANDOMISED: YES. DESCRIBED AS DOUBLE BLIND: YES - an open label arm was also included as a parallel group to the blinded assessments. METHOD OF RANDOMISATION WELL DESCRIBED/APPROPRIATE: Not reported. METHOD OF BLINDING WELL DESCRIBED/APPROPRIATE: Double-blind. Devices not described as identical. DESCRIPTION OF WITHDRAWALS/DROPOUTS: 294/2083 (Adverse events: 104; data missing: 8; lack of efficacy: 52; protocol violation: 43; withdrawn consent: 114; loss to follow-up: 43; admin problem: 17) JADAD SCORE (5-1): 3. TYPE OF ANALYSIS (AVAILABLE CASE/TREATMENT RECEIVED/ ITT): ITT. COMPLIANCE: Not reported. CONFOUNDERS: Similar characteristics at baseline.
Participants	Adults, SCREENED: 3820, N RANDOMISED: 2085 , N COMPLETED: 1791 M= 936 F= 1149 MEAN AGE: 38.11 SEVERITY OF ASTHMA: unknown BASELINE DETAILS: Moderate asthma (68-70% predicted) INCLUSION CRITERIA: Use of inhaled beta-agonist for two months prior to study entry; FEV1 reversibility >/=12% predicted post-SABA; CXR consistent with asthma in 18 months prior to study entry (including run-in) EXCLUSION: Hospitalisation within one month/treatment of exacerbation of asthma in month prior to study entry; evidence/ array of other systemic diseases; pregnancy/failure to use of reliable contraception; change to ongoing medication used to treat chronic asthma
Interventions	1. Formoterol 12mcg BID 2. Placebo 3. Formoterol 24mcg BID 4. Open label formoterol 12mcg BID (with up to two uses prn per day) DELIVERY: DPI (Aerolizer) TREATMENT PERIOD: 16 weeks RESCUE: SABA prn CO-INTERVENTIONS PERMITTED: ICS; leukotriene antagonists; disodium cromoglycate. CO-INTERVENTIONS: None as standard % on ICS: 57.8
Outcomes	OUTCOMES MEASURED: Post-dose FEV1; adverse events; exacerbations (use of oral steroids) FOLLOW-UP ASSESSMENT POINTS: 4, 8, 12 & 16 weeks. OUTCOMES INCLUDED IN ANALYSES: Absolute FEV1; adverse events SUB-GROUPS INDENTIFIED: Regular ICS throughout the study; Regular ICS added after baseline; no regular ICS during the study; regular anti-inflammatory medication throughout the study; regular an-

Wolfe 2006 *(Continued)*

	ti-inflammatory medication added after the study; no regular anti-inflammatory medication during the study.
Notes	

Wronska 1998

Methods	STUDY DESIGN: Parallel group single centre Poland, 1 week run in period / 4 week treatment period RANDOMISATION: Randomised treatment allocation, no details BLINDING: double blind, no details WITHDRAWALS/DROP OUTS: no details COMPLIANCE: no details CONFOUNDERS: significant difference in baseline BHR, salmeterol group more responsive QUALITY: Jadad 2 Cochrane C
Participants	N Randomised 22, M=9 F= 13 adults Mean age 34 (SD 12) BASELINE SEVERITY: No details on severity of asthma INCLUSION : Clinical diagnosis asthma . EXCLUSION : use ICS <4 weeks,
Interventions	LONG ACTING BETA AGONIST: Salmeterol 50 mcg BD PLACEBO: BD DEVICE: no details RESCUE: Salbutamol or fenoterol prn TREATMENT PERIOD: 4 weeks CO-INTERVENTIONS: none on ICS
Outcomes	OUTCOMES: PEF, FEV1, asthma symptom score, BHR
Notes	Symptom Score- 6 pt, day 5 pt night time - Scale :0= none to 4/5= most severe.

Zarkovic 1998

Methods	STUDY DESIGN: 2 way cross over multicentre (14) UK and Austria 2 week run in period / 26 week treatment period/ 2 week wash out at crossover RANDOMISATION: Randomised treatment allocation, no details BLINDING: double blind, double dummy , no details WITHDRAWALS/DROP OUTS:23 COMPLIANCE: no details CONFOUNDERS: no details QUALITY: Jadad 3 Cochrane B
Participants	N Enrolled 153 Randomised 91, M=59 F= 32 children Mean age 11 (range 6-15) BASELINE SEVERITY: Mild-moderate asthma INCLUSION : Clinical diagnosis asthma 12mths requiring SABA, Baseline PEF>85% predicted, >15% FEV1 reversibility to SABA. EXCLUSION : URTI/ LRTI/exacerbation <4 weeks, unstable asthma, OS, theophyllines, anticholinergics
Interventions	LONG ACTING BETA AGONIST: Salmeterol 50 mcg BD PLACEBO: BD DEVICE: DP diskhaler RESCUE: Salbutamol 200 mcg prn TREATMENT PERIOD26 weeks CO-INTERVENTIONS: ICS >80%, cromones 4%

Zarkovic 1998 *(Continued)*

Outcomes	OUTCOMES: PEF, FEV1, Rescue use, asthma symptom score, % days with no symptoms, ,% nights with no asthma awakenings. Exacerbations, BHR
Notes	Exacerbations defined as worsening of asthma symptoms that required treatment in addition to the study drug and rescue SABA. ASS- no details on scale

ITT= Intention to treat population (number of participants in analyses of results in a study). ATS= American Thoracic Society, BTS= British Thoracic Society, GINA= Global Initiative for Asthma, ASS=asthma symptom score. OS= oral corticosteroids. ICS= Inhaled corticosteroids. LABA= long-acting beta-2 agonist. SABA= Short-acting beta-2 agonist. Short-acting beta-2 agonist salbutamol known in USA as albuterol-dose measured at mouthpiece 90 mcg = 100mcg from inhaler . Minimum acceptable dose ICS =(MAD). COAD= chronic obstructive airways disease.
Bronchial hyperreactivity = BHR (measured as PD20 or PC20 of direct agents methacholine and histamine or indirect agents AMP). BAL= bronchoalveolar lavage, EBB= endobronchial biopsy,
BDP = beclomethasone dipropionate, BUD= budesonide , FP= fluticasone propionate. Cromones = sodium cromoglycate, nedocromil sodium .
MDI= metered dose inhaler. DP= dry powder.
AQOL score = Asthma quality of life score, based on Juniper 1992 (Juniper EF, Guyatt GH. Evaluation of impairment of health related quality of life in asthma: development of a questionnaire for use in clinical trials. Thorax 1992;47:76-83) value of 1 =maximum impairment, value 7= no impairment. Results 0.5=small change, 1.0= moderate change, 1.5= large change.
LWAQ= Living with asthma questionnaire (Hyland M. The living with asthma questionnaire. Respir Med 1991;85 supp:13-16.), lower score indicates better quality of life.
CAQC= Childhood Asthma Questionnaire Form C, produces 5 sub scale scores, including self reported severity (the frequency of 5 symptoms of severity of asthma), distress (feelings about these symptoms) , active quality of living (frequency and enjoyment of activities including swimming, sports, outdoor play). Christie M, French D, Sowden A, West A. The development of child centred, disease specific questionnaires for living with asthma. Psychosomatic Medicine 1993;55:541-8.
SF-36= Generic Health related quality of life questionnaire
FS II-R : Stein R, Jessup D. Functional status II(R): a measure of child health status. Med Care 1990;28:1041-55.
SLR-C: Boyer G, Aaronson G, Meltzer E, LaForce C, Grossman J, Yancey S. Enhancement of a general quality of life scale: validation of a sleep scale. J Allergy Clin Immunol 1992;89:186.
ECP= eosinophilic cationic protein, sIL-2R= soluble receptor of interlukin-4, ICAM-1= level of soluble intercellular adhesion molecule-1, immunoglobulin E= IgE

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

Study	Reason for exclusion
Akpinarli 1999	100% on ICS at baseline
Arvidsson 1989	No placebo group
Arvidsson 1991	No placebo group
Aziz 1999	Treatment period < 4 weeks
Aziz 1998	Treatment period < 4 weeks
Aziz 1998a	Treatment period < 4 weeks
Baki 1998	Treatment period < 4 weeks
Baumgarten 2002	Not RCT, No placebo group
Beach 1993	No placebo group
Becker 1989	Treatment period < 4 weeks

Study	Reason for exclusion
Becker 1993	No placebo group
Bhagat 1995	Treatment period < 4 weeks
Bishop 1994	Treatment period < 4 weeks
Blake 1992	Treatment period < 4 weeks
Boner 1992	No placebo group
Booth 1996	100% on ICS at baseline
Boulet Laviol 1997	No placebo group
Boulet 1998a	ICS in all treatment groups
Boulet 2001	Treatment period < 4 weeks
Bowers 1997	Review
Boyd 1995	100% on ICS at baseline
Brambilla 1994	No placebo group
Brambilla 2003	No placebo group
Britton 1992	No placebo group
Byrnes 1996	No placebo group
Byrnes 2000	No placebo group
Campbell 1999	No placebo group
Campbell 2000	No placebo group
Carlsen 1995	Treatment period < 4 weeks
Castle 1993	No placebo group
Charpin 1992	No placebo group
Chuchalin 2002	Combination therapy versus placebo
Clark 1993	Not RCT- case reports
Clauzel 1998	No placebo group
Cockcroft 1997	Treatment period < 4 weeks
Cox 1996	No placebo group
D'Urzo 2001	100% on ICS at baseline
D5125C00344	100% on ICS at baseline

Study	Reason for exclusion
De Carli 1995	No placebo group
De Oliveira 1998	No placebo group
Derom 1992	Treatment period < 4 weeks
Di Lorenzo 1995	No placebo group
Droszcz 1999	No placebo group, subjects COPD and Asthma
Faurschou 1992	No placebo group
Faurschou 1994a	Treatment period < 4 weeks
Faurschou 1996	No placebo group
Faurschou 1997	Abstract only, full details not available
FitzGerald 1999	100% on ICS at baseline
Fitzpatrick 1990	Treatment period < 4 weeks
Fuglsang 1998	Treatment period < 4 weeks
Fuller 1993	No placebo group
Gardiner 1994	100% on ICS at baseline
Giannini 1995	Treatment period < 4 weeks
Giannini 1999	Treatment period < 4 weeks
Gong 1996	Treatment period < 4 weeks
Goodwin 1996	No placebo group
Green 1002	Treatment period < 4 weeks
Greening 1994	No placebo group
Grove 1995	100% on ICS at baseline
Grove 1996	Treatment period < 4 weeks
Hacki 1993	No placebo group
Hekking 1990	No placebo group
Hermansson 1995	No placebo group
Jartti 1998	100% on ICS at baseline
Jenkins 1991	letter- not RCT
Kalra 1996	Treatment period < 4 weeks

Study	Reason for exclusion
Kavuru 2000b	Combination therapy versus ICS
Kemp 1993	Treatment period < 4 weeks
Kemp 1994	Treatment period < 4 weeks
Kemp 1998b	100% on ICS at baseline
Kesten 1991	No placebo group
Kesten 1992	No placebo group
Kozlik-Feldmann 1996	No placebo group
Lai 1995	No placebo group
Langley 1998	100% on ICS at baseline
Langton Hewer 1995	100% on ICS at baseline
Lenney 1995	No placebo group
Li 1999	100% on ICS at baseline
Lipworth 1998	100% on ICS at baseline
Lipworth 1999	Treatment period < 4 weeks
Lipworth 2000a	100% on ICS at baseline
Lipworth 2000b	Treatment period < 4 weeks
Lotvall 1992	No placebo group
Lundback 1993	No placebo group
Malo 1992	Cohort study- not RCT
Mann 1996	No placebo group
Martin 1999	No placebo group
McIvor 1998	100% on ICS at baseline
Meijer 1995	100% on ICS at baseline
Midgren 1992	No placebo group
Molimard 2001	No placebo group
Nelson 1999a	100% on ICS at baseline
Newnham 1993	Treatment period < 4 weeks
Nichol 1990	Treatment period < 4 weeks

Study	Reason for exclusion
Nielsen 1999	100% on ICS at baseline
Nightingale 2002	100% on ICS at baseline
Nix 1990	Treatment period < 4 weeks
Norhaya 1999	100% on ICS at baseline
Nowak 1992	Treatment period < 4 weeks
O'Byrne 2001	Combination therapy versus ICS
Palmer 1992	No placebo group
Pauwels 1997	100% on ICS at baseline
Pearlman 1999	Combination therapy versus ICS.
Pederson 1993	Treatment period < 4 weeks
Price 2002	100% on ICS at baseline
Quebe-Fehling 1996	Treatment period < 4 weeks
Rabe 1993	Treatment period < 4 weeks
Ramsdale 1991	Treatment period < 4 weeks
Rhee 1997	No placebo group
Ringbaek 1996	No placebo group
Rosenhall 1990	No placebo group
Russell 1995	100% on ICS at baseline
Ruttenvan Molken1995	No placebo group
Schaaning 1996	No placebo group
Scherner 2004	Treatment period < 4 weeks
Self 1998	100% on ICS at baseline
Shapiro 2000a	Combination therapy versus ICS
Shepherd 1991	Letter - not RCT
Sichletidis 1993	No placebo group
Siergiejko 1998	No placebo group
Simons 1992	Treatment period < 4 weeks
Simons 1997b	100% on ICS at baseline

Study	Reason for exclusion
SLGA2016	Treatment administered as one-offs at clinic visits
SLGB4011R	Treatment period < 4 weeks
SMO30003	Treatment administered as one-offs at clinic visits
SMS30035	Treatment period < 4 weeks
Smyth 1993	Treatment period < 4 weeks
Sprogoe-Jakobsen1992	No placebo group
Staehr 1995	No placebo group
Steffensen 1996	No placebo group
Tan 1997	100% on ICS at baseline
Tattersfield 2001	No placebo group, not regular use of LABA
Taylor 1992	No placebo group
Taylor Jensen 1997	Treatment period < 4 weeks
Thomson 1998	No placebo group
Totterman 1998	No placebo group
Turner 1998	Treatment period < 4 weeks
Twentyman 1990	Treatment period < 4 weeks
Ullman 1988	No placebo group
Van der Molen 1996	100% on ICS at baseline
van der Woude 2001	Treatment period < 4 weeks
Venables 1992	No placebo group
Verberne 1991	Abstract only- details not available
Verberne 1996	No placebo group
Verberne 1997	No placebo group
Verberne 1998	100% on ICS at baseline
Verberne 2000	Review- not RCT
Verini 1998	Treatment period < 4 weeks
Wallaert 1999	No placebo group
Walters 1992	Abstract only- details not available

Study	Reason for exclusion
Weinstein 1997	Treatment period < 4 weeks
Wenzel 1998	No placebo group
Wilding 1997	100% on ICS at baseline
Wolfe 1995	No placebo group
Wong 1997	Treatment period < 4 weeks
Woolcock 1996	No placebo group
Yates 1995	Treatment period < 4 weeks
Yates 1997	Treatment period < 4 weeks
Zellweger 1994	No placebo group, Treatment period < 4 weeks
Zimmerman 2004	100% on ICS at baseline

DATA AND ANALYSES

Comparison 1. Studies with parallel group design: efficacy outcomes

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Peak expiratory flow: morning	20	3682	L/min (Fixed, 95% CI)	12.64 [8.37, 16.92]
1.1 Participants using mixed cointerventions	11	2826	L/min (Fixed, 95% CI)	21.81 [14.07, 29.55]
1.2 Participants not using ICS	6	235	L/min (Fixed, 95% CI)	19.23 [0.62, 37.84]
1.3 Children <12 years	3	621	L/min (Fixed, 95% CI)	7.73 [2.39, 13.07]
2 Peak expiratory flow: evening	14	2586	L/min (Fixed, 95% CI)	9.68 [4.79, 14.57]
2.1 Participants mixed cointerventions	8	2027	L/min (Fixed, 95% CI)	15.73 [6.28, 25.17]
2.2 Subjects not using ICS (PG design)	4	103	L/min (Fixed, 95% CI)	15.42 [-0.82, 31.67]
2.3 Children <12 years	2	456	L/min (Fixed, 95% CI)	6.35 [0.26, 12.45]
3 Change in PEF morning	25	4773	L/min (Random, 95% CI)	25.70 [20.30, 31.09]
3.1 Participants using mixed cointerventions	12	2503	L/min (Random, 95% CI)	29.14 [21.57, 36.70]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
3.2 Participants not using ICS (PG design)	8	1582	L/min (Random, 95% CI)	24.24 [14.23, 34.25]
3.3 Children <12 years	4	562	L/min (Random, 95% CI)	14.33 [8.64, 20.01]
3.4 Unclear	1	126	L/min (Random, 95% CI)	30.00 [15.87, 44.13]
4 Change in PEF morning (%)	1		Mean Difference (IV, Random, 95% CI)	Totals not selected
4.1 Participants using mixed cointerventions	1		Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]
4.2 Participants not using ICS	0		Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]
4.3 Children <12 years	0		Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]
5 Change in PEF evening	22	4611	L/min (Random, 95% CI)	17.66 [12.93, 22.39]
5.1 Participants using mixed cointerventions	12	2744	L/min (Random, 95% CI)	21.32 [14.70, 27.94]
5.2 Participants not using ICS	5	1181	L/min (Random, 95% CI)	10.68 [6.38, 14.98]
5.3 Children <12 years	4	560	L/min (Random, 95% CI)	23.04 [-3.54, 49.61]
5.4 Unclear	1	126	L/min (Random, 95% CI)	17.0 [5.02, 28.98]
6 N with >/=15% increase in FEV1	1		Odds Ratio (M-H, Fixed, 95% CI)	Totals not selected
6.1 Participants using mixed cointerventions	0		Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
6.2 Participants not using ICS	0		Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
6.3 Children <12 years	0		Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
6.4 Unclear	1		Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
7 Change in PEF morning -percent predicted	2		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
7.1 Participants using mixed cointerventions	0		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
7.2 Participants not using ICS	0		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
7.3 Children <12 years	2		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
8 Change in PEF evening-percent predicted	2		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
8.1 Participants using mixed cointerventions	0		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
8.2 Participants not using ICS	0		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
8.3 Children <12 years	2		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
9 Amplitude PEF: diurnal variation (l/min or %)	1		Std. Mean Difference (IV, Fixed, 95% CI)	Totals not selected
9.1 Participants using mixed cointerventions	1		Std. Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
9.2 Participants not using ICS	0		Std. Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
9.3 Children <12 years	0		Std. Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
10 N with >/=15% increase in PEF	1		Odds Ratio (M-H, Fixed, 95% CI)	Totals not selected
10.1 Participants using mixed cointerventions	0		Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
10.2 Participants not using ICS	0		Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
10.3 Children <12 years	1		Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
11 Change in peak expiratory flow: % predicted	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
11.1 Participants using mixed cointerventions	0		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
11.2 Participants not using ICS	0		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
11.3 Children <12 years	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
12 Peak expiratory flow: % predicted	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
12.1 Subjects using mixed cointerventions	0		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
12.2 Participants not using ICS	0		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
12.3 Children <12 years	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
13 AUC- mean area under 12 hr serial PEF curve (% predicted)	2		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
13.1 Participants using mixed cointerventions	0		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
13.2 Subjects not on ICS >12 weeks treatment	0		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
13.3 Children <12 years	2		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
14 Change in Amplitude PEF: diurnal variation (l/min or %)	2	1001	Std. Mean Difference (IV, Fixed, 95% CI)	-0.43 [-0.55, -0.30]
14.1 Participants using mixed cointerventions	2	1001	Std. Mean Difference (IV, Fixed, 95% CI)	-0.43 [-0.55, -0.30]
14.2 Participants not using ICS	0	0	Std. Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
14.3 Children <12 years	0	0	Std. Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
15 FEV1	14	3882	Litres (Fixed, 95% CI)	0.24 [0.20, 0.28]
15.1 Participants using mixed cointerventions	11	3458	Litres (Fixed, 95% CI)	0.24 [0.20, 0.28]
15.2 Participants not using ICS (PG design)	2	70	Litres (Fixed, 95% CI)	0.12 [-0.24, 0.48]
15.3 Children <12 years	1	354	Litres (Fixed, 95% CI)	0.19 [0.06, 0.32]
16 FEV1 predicted	4	595	% (Fixed, 95% CI)	3.46 [0.20, 6.72]
16.1 Participants using mixed cointerventions	0	0	% (Fixed, 95% CI)	0.0 [0.0, 0.0]
16.2 Children <12 years	3	593	% (Fixed, 95% CI)	3.46 [0.20, 6.72]
16.3 Participants not using ICS	1	2	% (Fixed, 95% CI)	0.0 [0.0, 0.0]
17 Change in FEV (litres)	15	3295	Mean Difference (IV, Fixed, 95% CI)	0.17 [0.13, 0.21]
17.1 Participants using mixed cointerventions	7	1565	Mean Difference (IV, Fixed, 95% CI)	0.20 [0.14, 0.25]
17.2 Participants not using ICS	6	1225	Mean Difference (IV, Fixed, 95% CI)	0.18 [0.10, 0.25]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
17.3 Children <12 years	2	505	Mean Difference (IV, Fixed, 95% CI)	0.08 [-0.00, 0.16]
18 N with >/=15% increase in FEV1	2	344	Odds Ratio (M-H, Fixed, 95% CI)	1.90 [1.22, 2.95]
18.1 Participants using mixed cointerventions	0	0	Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
18.2 Children <12 years	2	344	Odds Ratio (M-H, Fixed, 95% CI)	1.90 [1.22, 2.95]
18.3 Participants not using ICS	0	0	Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
19 AUC- mean area under 12 hr serial FEV1 curve	7	1312	L-h (Fixed, 95% CI)	2.23 [1.71, 2.75]
19.1 Participants using mixed cointerventions	4	726	L-h (Fixed, 95% CI)	3.79 [2.98, 4.60]
19.2 Participants not on ICS	2	337	L-h (Fixed, 95% CI)	2.01 [0.21, 3.81]
19.3 Children <12 years	1	249	L-h (Fixed, 95% CI)	0.95 [0.21, 1.69]
20 Change in FEV1 %predicted	3	695	Mean Difference (IV, Fixed, 95% CI)	5.00 [1.95, 8.05]
20.1 Participants using mixed cointerventions	0	0	Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
20.2 Participants not using ICS	0	0	Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
20.3 Children <12 years	3	695	Mean Difference (IV, Fixed, 95% CI)	5.00 [1.95, 8.05]
21 AUC- mean area under 12 hr serial FEV1 curve (% predicted)	2		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
21.1 Participants using mixed cointerventions	0		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
21.2 Subjects not on ICS >12 weeks treatment	0		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
21.3 Children <12 years	2		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
22 AUC- mean change area under 12 hr serial FEV1 curve (L-h)	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
22.1 Participants using mixed cointerventions	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
22.2 Participants not on ICS	0		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
22.3 Children <12 years	0		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
23 Fall in FEV1 post exercise (12 hrs post study drug) %	1		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
23.1 Participants using mixed cointerventions	1	19	Mean Difference (IV, Fixed, 95% CI)	-11.12 [-21.04, -1.20]
23.2 Participants not on ICS	0	0	Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
23.3 Children <12 years	0	0	Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
24 Fall in FEV1 post exercise (premedication with formoterol) %	1		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
24.1 Participants using mixed cointerventions	1	19	Mean Difference (IV, Fixed, 95% CI)	5.19 [-1.23, 11.61]
24.2 Participants not on ICS	0	0	Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
24.3 Children <12 years	0	0	Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
25 FEV1 12hr post dose	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
25.1 Participants using mixed cointerventions	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
25.2 Participants not using ICS	0		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
25.3 Children <12 years	0		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
26 Change in FEV1 12hr post dose	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
26.1 Participants using mixed cointerventions	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
26.2 Participants not using ICS	0		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
26.3 Children <12 years	0		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
27 Forced Vital Capacity (litres)	2	302	Mean Difference (IV, Fixed, 95% CI)	0.09 [-0.14, 0.32]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
27.1 Participants using mixed cointerventions	2	302	Mean Difference (IV, Fixed, 95% CI)	0.09 [-0.14, 0.32]
27.2 Participants not using ICS	0	0	Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
27.3 Children <12 years	0	0	Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
28 Change in Forced Vital Capacity (litres)	5	626	Mean Difference (IV, Fixed, 95% CI)	0.13 [0.03, 0.22]
28.1 Participants using mixed cointerventions	4	466	Mean Difference (IV, Fixed, 95% CI)	0.13 [0.03, 0.22]
28.2 Participants not using ICS	0	0	Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
28.3 Children <12 years	1	160	Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
29 FEF25-75 (litres/sec)	3	462	Mean Difference (IV, Fixed, 95% CI)	0.17 [-0.06, 0.40]
29.1 Participants using mixed cointerventions	2	302	Mean Difference (IV, Fixed, 95% CI)	0.17 [-0.06, 0.40]
29.2 Participants not using ICS	0	0	Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
29.3 Children <12 years	1	160	Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
30 Symptom score - whole day	4	905	Std. Mean Difference (IV, Fixed, 95% CI)	-0.37 [-0.50, -0.24]
30.1 Participants using mixed cointerventions	3	873	Std. Mean Difference (IV, Fixed, 95% CI)	-0.35 [-0.49, -0.22]
30.2 Participants all using ICS	0	0	Std. Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
30.3 Children <12 years	1	32	Std. Mean Difference (IV, Fixed, 95% CI)	-0.93 [-1.67, -0.20]
31 Symptom score - day time	11	1995	Std. Mean Difference (IV, Fixed, 95% CI)	-0.33 [-0.41, -0.24]
31.1 Participants using mixed cointerventions	8	1916	Std. Mean Difference (IV, Fixed, 95% CI)	-0.32 [-0.41, -0.23]
31.2 Participants not using ICS (PG design)	3	79	Std. Mean Difference (IV, Fixed, 95% CI)	-0.39 [-0.84, 0.05]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
31.3 Children <12 years	0	0	Std. Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
32 Symptom score - night time	9	1917	Std. Mean Difference (IV, Fixed, 95% CI)	-0.51 [-0.60, -0.41]
32.1 Participants using mixed cointerventions	7	1851	Std. Mean Difference (IV, Fixed, 95% CI)	-0.51 [-0.60, -0.42]
32.2 Children <12 years	0	0	Std. Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
32.3 Participants not using ICS	2	66	Std. Mean Difference (IV, Fixed, 95% CI)	-0.39 [-0.88, 0.10]
33 Change in symptom score: whole day	2	333	Std. Mean Difference (IV, Random, 95% CI)	-0.27 [-0.60, 0.06]
33.1 Participants using mixed cointerventions	2	333	Std. Mean Difference (IV, Random, 95% CI)	-0.27 [-0.60, 0.06]
33.2 Participants not using ICS	0	0	Std. Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]
33.3 Children <12 years	0	0	Std. Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]
33.4 Unclear	0	0	Std. Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]
34 Change in symptom score: day time	13	2629	Std. Mean Difference (IV, Random, 95% CI)	-0.48 [-0.60, -0.37]
34.1 Participants using mixed cointerventions	5	1008	Std. Mean Difference (IV, Random, 95% CI)	-0.55 [-0.76, -0.33]
34.2 Participants not using ICS	6	1148	Std. Mean Difference (IV, Random, 95% CI)	-0.42 [-0.54, -0.29]
34.3 Children <12 years	1	347	Std. Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]
34.4 Unclear	1	126	Std. Mean Difference (IV, Random, 95% CI)	-0.38 [-0.73, -0.03]
35 Change in symptom score: night time	4	823	Std. Mean Difference (IV, Random, 95% CI)	-0.54 [-0.87, -0.22]
35.1 Participants using mixed cointerventions	3	697	Std. Mean Difference (IV, Random, 95% CI)	-0.59 [-1.03, -0.16]
35.2 Participants not using ICS	0	0	Std. Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
35.3 Children <12 years	0	0	Std. Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]
35.4 Unclear	1	126	Std. Mean Difference (IV, Random, 95% CI)	-0.38 [-0.73, -0.03]
36 Change in total symptom score	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
36.1 Participants using mixed cointerventions	0		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
36.2 Participants not using ICS	0		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
36.3 Children <12 years	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
37 % days without rescue medication	2	251	Mean Difference (IV, Random, 95% CI)	23.60 [12.86, 34.33]
37.1 Participants using mixed cointerventions	2	251	Mean Difference (IV, Random, 95% CI)	23.60 [12.86, 34.33]
37.2 Participants not using ICS	0	0	Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]
37.3 Children <12 years	0	0	Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]
38 N with <50% days free from rescue medication	1		Odds Ratio (M-H, Fixed, 95% CI)	Totals not selected
38.1 Participants using mixed cointerventions	0		Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
38.2 Participants not using ICS	1		Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
38.3 Children <12 years	0		Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
39 % days without asthma symptoms	7	2254	Mean Difference (IV, Random, 95% CI)	15.77 [9.75, 21.79]
39.1 Participants using mixed cointerventions	7	2254	Mean Difference (IV, Random, 95% CI)	15.77 [9.75, 21.79]
39.2 Participants not using ICS	0	0	Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]
39.3 Children <12 years	0	0	Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]
40 N with <50% symptom free days	1		Odds Ratio (M-H, Fixed, 95% CI)	Totals not selected

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
40.1 Participants using mixed cointerventions	0		Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
40.2 Participants not using ICS	1		Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
40.3 Subjects children <12 years	0		Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
41 % nighttime awakenings requiring no SABA	1		Mean Difference (IV, Random, 95% CI)	Totals not selected
41.1 Participants using mixed cointerventions	1		Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]
41.2 Participants not using ICS	0		Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]
41.3 Children <12 years	0		Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]
41.4 Unclear	0		Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]
42 Change in nighttime awakenings	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
42.1 Participants using mixed cointerventions	0		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
42.2 Participants not using ICS	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
42.3 Children <12 years	0		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
43 N with <50% symptom free nights	1		Odds Ratio (M-H, Fixed, 95% CI)	Totals not selected
43.1 Participants using mixed cointerventions	0		Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
43.2 Participants not using ICS	1		Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
43.3 Subjects children <12 years	0		Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
44 Change in % no nighttime awakenings	2	333	Mean Difference (IV, Random, 95% CI)	10.84 [-0.92, 22.59]
44.1 Participants using mixed cointerventions	2	333	Mean Difference (IV, Random, 95% CI)	10.84 [-0.92, 22.59]
44.2 Participants not using ICS	0	0	Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]
44.3 Children <12 years	0	0	Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
45 % nights without asthma awakenings	13	3925	Mean Difference (IV, Random, 95% CI)	14.76 [9.68, 19.84]
45.1 Participants using mixed cointerventions	12	3715	Mean Difference (IV, Random, 95% CI)	15.93 [10.84, 21.02]
45.2 Participants not using ICS	0	0	Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]
45.3 Children <12 years	1	210	Mean Difference (IV, Random, 95% CI)	6.40 [2.11, 10.69]
46 Change in % nighttime awakenings requiring no SABA	2		Mean Difference (IV, Random, 95% CI)	Totals not selected
46.1 Participants using mixed cointerventions	0		Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]
46.2 Participants not using ICS	1		Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]
46.3 Children <12 years	0		Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]
46.4 Unclear	1		Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]
47 N with <50% nights free from rescue medication	1		Odds Ratio (M-H, Fixed, 95% CI)	Totals not selected
47.1 Participants using mixed cointerventions	0		Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
47.2 Participants not using ICS	1		Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
47.3 Children <12 years	0		Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
48 Change in % days without asthma symptoms	13	2866	Mean Difference (IV, Random, 95% CI)	15.26 [10.51, 20.01]
48.1 Participants using mixed cointerventions	7	1514	Mean Difference (IV, Random, 95% CI)	16.33 [9.73, 22.92]
48.2 Participants not using ICS	6	1226	Mean Difference (IV, Random, 95% CI)	12.73 [8.61, 16.84]
48.3 Children <12 years	0	0	Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]
48.4 Unclear	1	126	Mean Difference (IV, Random, 95% CI)	16.4 [6.92, 25.88]
49 Change in % nights without asthma symptoms	10	2183	Mean Difference (IV, Random, 95% CI)	12.55 [5.53, 19.57]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
49.1 Participants using mixed cointerventions	4	930	Mean Difference (IV, Random, 95% CI)	19.94 [13.64, 26.25]
49.2 Participants not using ICS	5	1046	Mean Difference (IV, Random, 95% CI)	8.10 [4.88, 11.32]
49.3 Children <12 years	1	207	Mean Difference (IV, Random, 95% CI)	5.00 [-0.83, 10.83]
50 Rescue bronchodilator use: whole day	8	1885	Mean Difference (IV, Random, 95% CI)	-1.17 [-1.73, -0.61]
50.1 Participants using mixed cointerventions	6	1635	Mean Difference (IV, Random, 95% CI)	-1.53 [-1.92, -1.15]
50.2 Participants not using ICS	1	43	Mean Difference (IV, Random, 95% CI)	-0.30 [-0.53, -0.07]
50.3 Children <12 years	1	207	Mean Difference (IV, Random, 95% CI)	-0.4 [-0.84, 0.04]
51 Rescue bronchodilator use: day time	5	1172	Mean Difference (IV, Random, 95% CI)	-0.95 [-1.65, -0.25]
51.1 Participants using mixed cointerventions	4	1149	Mean Difference (IV, Random, 95% CI)	-1.02 [-1.81, -0.22]
51.2 Participants not using ICS	1	23	Mean Difference (IV, Random, 95% CI)	-0.56 [-1.67, 0.55]
51.3 Children <12 years	0	0	Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]
52 Rescue bronchodilator use: night time	5	1176	Mean Difference (IV, Random, 95% CI)	-0.56 [-0.87, -0.25]
52.1 Participants using mixed cointerventions	4	1153	Mean Difference (IV, Random, 95% CI)	-0.59 [-0.91, -0.27]
52.2 Participants not using ICS	1	23	Mean Difference (IV, Random, 95% CI)	0.14 [-1.30, 1.58]
52.3 Children <12 years	0	0	Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]
53 Change in use of rescue bronchodilator/day	3	691	Mean Difference (IV, Random, 95% CI)	-1.03 [-1.65, -0.41]
53.1 Participants using mixed cointerventions	3	691	Mean Difference (IV, Random, 95% CI)	-1.03 [-1.65, -0.41]
53.2 Children <12 years	0	0	Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
53.3 Participants not using ICS	0	0	Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]
54 Change in use of rescue bronchodilator/night	3	697	Mean Difference (IV, Random, 95% CI)	-0.46 [-0.67, -0.25]
54.1 Participants using mixed cointerventions	3	697	Mean Difference (IV, Random, 95% CI)	-0.46 [-0.67, -0.25]
54.2 Participants not using ICS	0	0	Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]
54.3 Children <12 years	0	0	Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]
55 Change in use of rescue bronchodilator/ whole day	12	2197	Mean Difference (IV, Random, 95% CI)	-1.16 [-1.47, -0.85]
55.1 Participants using mixed cointerventions	5	842	Mean Difference (IV, Random, 95% CI)	-1.35 [-1.86, -0.83]
55.2 Participants not using ICS	6	1148	Mean Difference (IV, Random, 95% CI)	-1.22 [-1.57, -0.86]
55.3 Children <12 years	1	207	Mean Difference (IV, Random, 95% CI)	-0.5 [-0.94, -0.06]
56 Change in % days without rescue medication	2	352	Mean Difference (IV, Random, 95% CI)	13.0 [4.27, 21.73]
56.1 Participants using mixed cointerventions	1	172	Mean Difference (IV, Random, 95% CI)	13.0 [4.27, 21.73]
56.2 Participants not using ICS	1	180	Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]
56.3 Children <12 years	0	0	Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]
57 AQOL- Change in Quality of life score: global	6	1608	Mean Difference (IV, Fixed, 95% CI)	0.54 [0.44, 0.64]
57.1 Participants using mixed cointerventions	4	1249	Mean Difference (IV, Fixed, 95% CI)	0.54 [0.44, 0.64]
57.2 Participants not using ICS	2	359	Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
57.3 Children <12 years	0	0	Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
58 Change in Quality of life score-symptoms	2	916	Mean Difference (IV, Fixed, 95% CI)	0.73 [0.58, 0.87]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
58.1 Participants using mixed cointerventions	2	916	Mean Difference (IV, Fixed, 95% CI)	0.73 [0.58, 0.87]
58.2 Participants not using ICS	0	0	Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
58.3 Children <12 years	0	0	Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
59 Change in Quality of life score: emotions	2	916	Mean Difference (IV, Fixed, 95% CI)	0.66 [0.48, 0.83]
59.1 Participants using mixed cointerventions	2	916	Mean Difference (IV, Fixed, 95% CI)	0.66 [0.48, 0.83]
59.2 Participants not using ICS	0	0	Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
59.3 Children <12 years	0	0	Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
60 Change in Quality of life score: exposure to environmental stimuli	2	916	Mean Difference (IV, Fixed, 95% CI)	0.56 [0.42, 0.70]
60.1 Participants using mixed cointerventions	2	916	Mean Difference (IV, Fixed, 95% CI)	0.56 [0.42, 0.70]
60.2 Participants not using ICS	0	0	Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
60.3 Children <12 years	0	0	Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
61 Change in Quality of life score: activity limitations	3	1086	Mean Difference (IV, Fixed, 95% CI)	0.40 [0.30, 0.50]
61.1 Participants using mixed cointerventions	2	916	Mean Difference (IV, Fixed, 95% CI)	0.41 [0.31, 0.51]
61.2 Participants not using ICS	1	170	Mean Difference (IV, Fixed, 95% CI)	0.19 [-0.18, 0.56]
61.3 Children <12 years	0	0	Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
62 Mini AQLQ (Total)	2		AQLQ (Fixed, 95% CI)	0.22 [0.02, 0.43]
62.1 Participants using mixed cointerventions	2		AQLQ (Fixed, 95% CI)	0.22 [0.02, 0.43]
62.2 Participants not using ICS (PG design)	0		AQLQ (Fixed, 95% CI)	0.0 [0.0, 0.0]
62.3 Children <12 years	0		AQLQ (Fixed, 95% CI)	0.0 [0.0, 0.0]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
63 Mini AQLQ (Symptoms)	1		AQLQ (Fixed, 95% CI)	Totals not selected
63.1 Participants using mixed cointerventions	1		AQLQ (Fixed, 95% CI)	0.0 [0.0, 0.0]
63.2 Participants not using ICS (PG design)	0		AQLQ (Fixed, 95% CI)	0.0 [0.0, 0.0]
63.3 Children <12 years	0		AQLQ (Fixed, 95% CI)	0.0 [0.0, 0.0]
64 Mini AQLQ (Activity limitation)	1		AQLQ (Fixed, 95% CI)	Totals not selected
64.1 Participants using mixed cointerventions	1		AQLQ (Fixed, 95% CI)	0.0 [0.0, 0.0]
64.2 Participants not using ICS (PG design)	0		AQLQ (Fixed, 95% CI)	0.0 [0.0, 0.0]
64.3 Children <12 years	0		AQLQ (Fixed, 95% CI)	0.0 [0.0, 0.0]
65 Mini AQLQ (Emotional function)	1		AQLQ (Fixed, 95% CI)	Totals not selected
65.1 Participants using mixed cointerventions	1		AQLQ (Fixed, 95% CI)	0.0 [0.0, 0.0]
65.2 Participants not using ICS	0		AQLQ (Fixed, 95% CI)	0.0 [0.0, 0.0]
65.3 Children <12 years	0		AQLQ (Fixed, 95% CI)	0.0 [0.0, 0.0]
66 Mini AQLQ (Environmental stimuli)	1		AQLQ (Fixed, 95% CI)	Totals not selected
66.1 Participants using mixed cointerventions	1		AQLQ (Fixed, 95% CI)	0.0 [0.0, 0.0]
66.2 Participants not using ICS	0		AQLQ (Fixed, 95% CI)	0.0 [0.0, 0.0]
66.3 Children <12 years	0		AQLQ (Fixed, 95% CI)	0.0 [0.0, 0.0]
67 Quality of life score: COMBINED ALL SCALES	2	286	Mean Difference (IV, Fixed, 95% CI)	-0.10 [-0.28, 0.08]
67.1 Participants using mixed cointerventions	1	79	Mean Difference (IV, Fixed, 95% CI)	-0.10 [-0.28, 0.08]
67.2 Subjects not using ICS	0	0	Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
67.3 Children <12 years	1	207	Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]

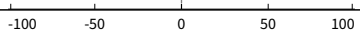
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
68 Bronchial hyperreactivity- log PD20/PC20 methacholine or histamine	8	689	Std. Mean Difference (IV, Fixed, 95% CI)	0.16 [-0.02, 0.33]
68.1 Participants using mixed cointerventions	2	269	Std. Mean Difference (IV, Fixed, 95% CI)	0.05 [-0.19, 0.29]
68.2 Children <12 years	3	332	Std. Mean Difference (IV, Fixed, 95% CI)	0.21 [-0.09, 0.51]
68.3 Participants not using ICS	3	88	Std. Mean Difference (IV, Fixed, 95% CI)	0.49 [-0.01, 0.98]
69 Bronchial hyperreactivity- log PD20/PC20 methacholine or histamine	1	24	Doubling doses (Fixed, 95% CI)	-0.01 [-0.21, 0.19]
69.1 Participants using mixed cointerventions	0	0	Doubling doses (Fixed, 95% CI)	0.0 [0.0, 0.0]
69.2 Participants not using ICS	1	24	Doubling doses (Fixed, 95% CI)	-0.01 [-0.21, 0.19]
69.3 Children <12 years	0	0	Doubling doses (Fixed, 95% CI)	0.0 [0.0, 0.0]
70 Change in BHR (end treatment vs. baseline)- doubling doses (DD)	7	1024	Mean Difference (IV, Fixed, 95% CI)	0.56 [0.30, 0.82]
70.1 Participants using mixed cointerventions	2	277	Mean Difference (IV, Fixed, 95% CI)	0.45 [-0.05, 0.95]
70.2 Children <12 years	1	42	Mean Difference (IV, Fixed, 95% CI)	0.45 [-0.37, 1.27]
70.3 Participants not using ICS	4	705	Mean Difference (IV, Fixed, 95% CI)	0.62 [0.30, 0.95]
71 Bronchoprotection to methacholine challenge(protection ratio end treatment vs. baseline)- doubling doses (DD)	1	23	Mean Difference (IV, Fixed, 95% CI)	1.91 [0.88, 2.94]
71.1 Participants using mixed cointerventions	0	0	Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
71.2 Participants not using ICS	1	23	Mean Difference (IV, Fixed, 95% CI)	1.91 [0.88, 2.94]
71.3 Children <12 years	0	0	Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
72 Bronchoprotection to methacholine challenge (protection ratio first dose treatment vs. baseline)- double dose	1	23	Mean Difference (IV, Fixed, 95% CI)	3.94 [3.21, 4.67]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
72.1 Participants using mixed cointerventions	0	0	Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
72.2 Participants not using ICS	1	23	Mean Difference (IV, Fixed, 95% CI)	3.94 [3.21, 4.67]
72.3 Children <12 years	0	0	Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
73 Exacerbations asthma - >1 major	25	7285	Odds Ratio (M-H, Fixed, 95% CI)	0.69 [0.61, 0.79]
73.1 Adults- Similar definition of exacerbation	11	3588	Odds Ratio (M-H, Fixed, 95% CI)	0.59 [0.49, 0.71]
73.2 Adults- Definition of exacerbation imprecise	10	2468	Odds Ratio (M-H, Fixed, 95% CI)	0.59 [0.46, 0.76]
73.3 Children <12 years	4	1229	Odds Ratio (M-H, Fixed, 95% CI)	1.15 [0.88, 1.49]
74 Exacerbations asthma - >1 major(sub-group by use of inhaled corticosteroid)	24		Odds Ratio (M-H, Fixed, 95% CI)	Subtotals only
74.1 Participants using mixed cointerventions	18	4688	Odds Ratio (M-H, Fixed, 95% CI)	0.65 [0.55, 0.77]
74.2 Participants not using ICS	6	1500	Odds Ratio (M-H, Fixed, 95% CI)	0.71 [0.53, 0.96]
75 Weaned from at least 1 non steroidal asthma medication	1		Odds Ratio (M-H, Fixed, 95% CI)	Subtotals only
75.1 Participants using mixed cointerventions	1	238	Odds Ratio (M-H, Fixed, 95% CI)	1.43 [0.85, 2.40]
75.2 Children <12 years	0	0	Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
76 Global assessment of efficacy by patient- very good/good	4	879	Odds Ratio (M-H, Fixed, 95% CI)	2.83 [2.15, 3.74]
76.1 Participants using mixed cointerventions	3	695	Odds Ratio (M-H, Fixed, 95% CI)	3.34 [2.43, 4.58]
76.2 Participants not using ICS	0	0	Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
76.3 Children <12 years	1	184	Odds Ratio (M-H, Fixed, 95% CI)	1.63 [0.91, 2.94]
77 Global assessment of efficacy by investigator- very good/good	2	268	Odds Ratio (M-H, Fixed, 95% CI)	8.04 [4.63, 13.94]
77.1 Participants using mixed cointerventions	2	268	Odds Ratio (M-H, Fixed, 95% CI)	8.04 [4.63, 13.94]
77.2 Participants not using ICS	0	0	Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]

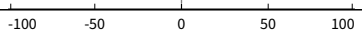
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
77.3 Children <12 years	0	0	Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
78 Global assessment of efficacy by patient - improved	1		Odds Ratio (M-H, Fixed, 95% CI)	Totals not selected
78.1 Participants using mixed cointerventions	1		Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
78.2 Participants all using ICS	0		Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
78.3 Children <12 years	0		Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
79 Global assessment of efficacy by patient - not improved	1		Odds Ratio (M-H, Fixed, 95% CI)	Totals not selected
79.1 Participants using mixed cointerventions	1		Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
79.2 Participants all using ICS	0		Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
79.3 Children <12 years	0		Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
80 Global assessment of efficacy by investigator - improved	1		Odds Ratio (M-H, Fixed, 95% CI)	Totals not selected
80.1 Participants using mixed cointerventions	1		Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
80.2 Participants all using ICS	0		Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
80.3 Children <12 years	0		Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
81 Global assessment of efficacy by investigator - not improved	1		Odds Ratio (M-H, Fixed, 95% CI)	Totals not selected
81.1 Participants using mixed cointerventions	1		Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
81.2 Participants all using ICS	0		Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
81.3 Children <12 years	0		Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]

Analysis 1.1. Comparison 1 Studies with parallel group design: efficacy outcomes, Outcome 1 Peak expiratory flow: morning.

Study or subgroup	LABA N	Placebo N	L/min (SE)	L/min IV, Fixed, 95% CI	Weight	L/min IV, Fixed, 95% CI
1.1.1 Participants using mixed cointerventions						
Bensch 2001	135	136	51 (12.724)		2.94%	51[26.06,75.94]
Busse 1998	261	231	18.8 (9.107)		5.75%	18.8[0.95,36.65]



Study or subgroup	LABA N	Placebo N	L/min (SE)	L/min IV, Fixed, 95% CI	Weight	L/min IV, Fixed, 95% CI
D'Alonzo 1994	87	90	14 (15.3)		2.04%	14[-15.99,43.99]
Dahl 1991a	171	172	70 (0)			Not estimable
Ekstrom 1998a	135	129	10 (13.153)		2.76%	10[-15.78,35.78]
Ekstrom 1998b	114	113	31 (12.566)		3.02%	31[6.37,55.63]
Kemp 1999	176	176	35 (10.627)		4.22%	35[14.17,55.83]
LaForce 2005	75	83	2 (15.214)		2.06%	2[-27.82,31.82]
Pearlman 1992	66	62	26 (16.393)		1.77%	26[-6.13,58.13]
SLGL82	41	41	6 (16.02)		1.86%	6[-25.4,37.4]
Wolfe 2000a	165	167	12 (10.699)		4.16%	12[-8.97,32.97]
Subtotal (95% CI)					**30.58%**	**21.81[14.07,29.55]**
Heterogeneity: Tau²=0; Chi²=12.09, df=9(P=0.21); I²=25.55%						
Test for overall effect: Z=5.52(P<0.0001)						
1.1.2 Participants not using ICS						
Boulet 1997	7	6	151 (0)			Not estimable
Lazarus 2001	54	56	0 (20.362)		1.15%	0[-39.91,39.91]
Roberts 1999	12	11	80 (47.01)		0.22%	80[-12.14,172.14]
SLMP03	11	13	16.8 (12.32)		3.14%	16.8[-7.35,40.95]
Wallin 1999	13	9	8 (31.566)		0.48%	8[-53.87,69.87]
Wronska 1998	21	22	92 (39.69)		0.3%	92[14.21,169.79]
Subtotal (95% CI)					**5.29%**	**19.23[0.62,37.84]**
Heterogeneity: Tau²=0; Chi²=6.09, df=4(P=0.19); I²=34.32%						
Test for overall effect: Z=2.03(P=0.04)						
1.1.3 Children <12 years						
Levy 2005	127	122	6.2 (3.21)		46.26%	6.2[-0.09,12.49]
von Berg 2003	81	84	11.1 (5.82)		14.07%	11.1[-0.31,22.51]
Weinstein 1998	102	105	13.9 (11.21)		3.79%	13.9[-8.07,35.87]
Subtotal (95% CI)					**64.13%**	**7.73[2.39,13.07]**
Heterogeneity: Tau²=0; Chi²=0.87, df=2(P=0.65); I²=0%						
Test for overall effect: Z=2.84(P=0)						
Total (95% CI)					**100%**	**12.64[8.37,16.92]**
Heterogeneity: Tau²=0; Chi²=28.16, df=17(P=0.04); I²=39.64%						
Test for overall effect: Z=5.79(P<0.0001)						
Test for subgroup differences: Chi²=9.12, df=1 (P=0.01), I²=78.07%						



Analysis 1.2. Comparison 1 Studies with parallel group design: efficacy outcomes, Outcome 2 Peak expiratory flow: evening.

Study or subgroup	LABA N	Placebo N	L/min (SE)	L/min IV, Fixed, 95% CI	Weight	L/min IV, Fixed, 95% CI
1.2.1 Participants mixed cointerventions						
Bensch 2001	135	136	45 (13.24)		3.54%	45[19.05,70.95]
Busse 1998	224	230	-1 (9.21)		7.32%	-1[-19.05,17.05]
D'Alonzo 1994	87	90	22 (14.65)		2.89%	22[-6.71,50.71]
Dahl 1991a	171	172	55 (0)			Not estimable
Ekstrom 1998a	135	129	6 (13.26)		3.53%	6[-19.99,31.99]

Study or subgroup	LABA N	Placebo N	L/min (SE)	L/min IV, Fixed, 95% CI	Weight	L/min IV, Fixed, 95% CI
Ekstrom 1998b	114	113	25 (11.714)		4.53%	25[2.04,47.96]
LaForce 2005	77	84	7 (15.061)		2.74%	7[-22.52,36.52]
Pearlman 1992	67	63	23.5 (16.87)		2.18%	23.48[-9.58,56.54]
Subtotal (95% CI)					**26.75%**	**15.73[6.28,25.17]**
Heterogeneity: Tau²=0; Chi²=10.08, df=6(P=0.12); I²=40.49%						
Test for overall effect: Z=3.26(P=0)						
1.2.2 Subjects not using ICS (PG design)						
Boulet 1997	7	6	146 (0)			Not estimable
Roberts 1999	12	11	30 (36.33)		0.47%	30[-41.21,101.21]
SLMP03	11	13	15.4 (8.85)		7.93%	15.4[-1.95,32.75]
Wallin 1999	21	22	5 (31.107)		0.64%	5[-55.97,65.97]
Subtotal (95% CI)					**9.05%**	**15.42[-0.82,31.67]**
Heterogeneity: Tau²=0; Chi²=0.27, df=2(P=0.87); I²=0%						
Test for overall effect: Z=1.86(P=0.06)						
1.2.3 Children <12 years						
Levy 2005	127	122	6 (3.24)		59.19%	6[-0.35,12.35]
Weinstein 1998	102	105	10.5 (11.122)		5.02%	10.5[-11.3,32.3]
Subtotal (95% CI)					**64.21%**	**6.35[0.26,12.45]**
Heterogeneity: Tau²=0; Chi²=0.15, df=1(P=0.7); I²=0%						
Test for overall effect: Z=2.04(P=0.04)						
Total (95% CI)					**100%**	**9.68[4.79,14.57]**
Heterogeneity: Tau²=0; Chi²=13.71, df=11(P=0.25); I²=19.74%						
Test for overall effect: Z=3.88(P=0)						
Test for subgroup differences: Chi²=3.2, df=1 (P=0.2), I²=37.49%						

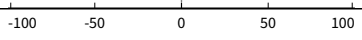
Favours placebo -100 -50 0 50 100 Favours LABA

Analysis 1.3. Comparison 1 Studies with parallel group design: efficacy outcomes, Outcome 3 Change in PEF morning.

Study or subgroup	LABA N	Placebo N	L/min (SE)	L/min IV, Random, 95% CI	Weight	L/min IV, Random, 95% CI
1.3.1 Participants using mixed cointerventions						
Adinoff 1998	1	1	0 (0)			Not estimable
Busse 1998	261	272	33.5 (4.133)		5.96%	33.5[25.4,41.6]
D'Alonzo 1994	87	90	27 (7.949)		4.37%	27[11.42,42.58]
Dahl 1991a	107	104	45 (6.12)		5.13%	45[33.01,56.99]
Kemp 1998a	149	152	28 (5.235)		5.51%	28[17.74,38.26]
Lockey 1999	240	234	45 (5.658)		5.33%	45[33.91,56.09]
Pearlman 1992	66	62	17 (8.76)		4.05%	17[-0.17,34.17]
SAS30004	91	89	0 (0)			Not estimable
Schreurs 1996	49	51	36 (7.209)		4.67%	36[21.87,50.13]
SMS40221	32	32	29.7 (10.878)		3.32%	29.65[8.33,50.97]
Wolfe 2000a	80	81	10 (5.658)		5.33%	10[-1.09,21.09]
Wolfe 2000b	86	86	18 (5.685)		5.32%	18[6.86,29.14]
Subtotal (95% CI)					**49%**	**29.14[21.57,36.7]**
Heterogeneity: Tau²=104.55; Chi²=33.85, df=9(P<0.0001); I²=73.41%						

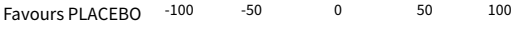
Favours placebo -100 -50 0 50 100 Favours LABA

Study or subgroup	LABA N	Placebo N	L/min (SE)	L/min IV, Random, 95% CI	Weight	L/min IV, Random, 95% CI
Test for overall effect: Z=7.55(P<0.0001)						
1.3.2 Participants not using ICS (PG design)						
Jones 1994	162	85	0 (0)			Not estimable
Kavuru 2000a	77	86	22 (6.653)		4.91%	22[8.96,35.04]
Lazarus 2001	54	56	39.7 (3.199)		6.3%	39.7[33.43,45.97]
Nathan 1999	128	129	24 (7.066)		4.73%	24[10.15,37.85]
Pearlman 1999a	21	23	42 (13.897)		2.5%	42[14.76,69.24]
Rosenthal 1999	202	206	20.9 (3.204)		6.29%	20.9[14.62,27.18]
SAS30003	92	87	24 (6.801)		4.85%	24[10.67,37.33]
Shapiro 2000b	84	90	2.5 (6.505)		4.97%	2.5[-10.25,15.25]
Subtotal (95% CI)					**34.55%**	**24.24[14.23,34.25]**
Heterogeneity: Tau^2=137.7; Chi^2=35.65, df=6(P<0.0001); I^2=83.17%						
Test for overall effect: Z=4.75(P<0.0001)						
1.3.3 Children <12 years						
Bensch 2002	1	1	0 (0)			Not estimable
Simons 1997a	1	1	0 (0)			Not estimable
von Berg 1998	180	171	13 (5)		5.61%	13[3.2,22.8]
Weinstein 1998	102	105	15 (3.561)		6.17%	15[8.02,21.98]
Subtotal (95% CI)					**11.78%**	**14.33[8.64,20.01]**
Heterogeneity: Tau^2=0; Chi^2=0.11, df=1(P=0.74); I^2=0%						
Test for overall effect: Z=4.94(P<0.0001)						
1.3.4 Unclear						
SLGA2004	63	63	30 (7.209)		4.67%	30[15.87,44.13]
Subtotal (95% CI)					**4.67%**	**30[15.87,44.13]**
Heterogeneity: Tau^2=0; Chi^2=0, df=0(P<0.0001); I^2=100%						
Test for overall effect: Z=4.16(P<0.0001)						
Total (95% CI)					**100%**	**25.7[20.3,31.09]**
Heterogeneity: Tau^2=110.13; Chi^2=89.8, df=19(P<0.0001); I^2=78.84%						
Test for overall effect: Z=9.34(P<0.0001)						
Test for subgroup differences: Chi^2=11.69, df=1 (P=0.01), I^2=74.34%						



Analysis 1.4. Comparison 1 Studies with parallel group design: efficacy outcomes, Outcome 4 Change in PEF morning (%).

Study or subgroup	LABA N	LABA Mean(SD)	PLACEBO N	PLACEBO Mean(SD)	Mean Difference Random, 95% CI	Mean Difference Random, 95% CI
1.4.1 Participants using mixed cointerventions						
SAS30004	91	4.4 (0)	89	-4.2 (0)		Not estimable
1.4.2 Participants not using ICS						
1.4.3 Children <12 years						

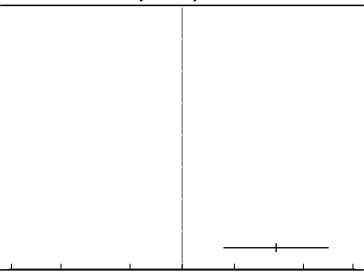


Analysis 1.5. Comparison 1 Studies with parallel group design: efficacy outcomes, Outcome 5 Change in PEF evening.

Study or subgroup	LABA N	Placebo N	L/min (SE)	L/min IV, Random, 95% CI	Weight	L/min IV, Random, 95% CI
1.5.1 Participants using mixed cointerventions						
Adinoff 1998	1	1	0 (0)			Not estimable
Busse 1998	258	269	15.9 (3.505)		7.75%	15.9[9.03,22.77]
D'Alonzo 1994	87	90	32 (7.066)		5.16%	32[18.15,45.85]
Dahl 1991a	101	100	18 (5.1)		6.55%	18[8,28]
Jones 1994	282	145	0 (0)			Not estimable
Kemp 1998a	149	152	14 (5.092)		6.56%	14[4.02,23.98]
Lockey 1999	240	234	28 (5.658)		6.14%	28[16.91,39.09]
Pearlman 1992	67	63	24 (8.337)		4.4%	24[7.66,40.34]
SAS30004	91	89	0 (0)			Not estimable
Schreurs 1996	49	51	39 (6.383)		5.62%	39[26.49,51.51]
SMS40221	32	32	20.8 (13.444)		2.39%	20.76[-5.59,47.11]
Wolfe 2000a	80	81	6 (5.658)		6.14%	6[-5.09,17.09]
Subtotal (95% CI)					**50.71%**	**21.32[14.7,27.94]**
Heterogeneity: Tau^2=62.34; Chi^2=23, df=8(P=0); I^2=65.21%						
Test for overall effect: Z=6.31(P<0.0001)						
1.5.2 Participants not using ICS						
Kavuru 2000a	77	86	5.9 (6.643)		5.44%	5.9[-7.12,18.92]
Nathan 1999	128	129	14 (7.219)		5.06%	14[-0.15,28.15]
Rosenthal 1999	202	206	12.3 (2.898)		8.17%	12.3[6.62,17.98]
SAS30003	92	87	13 (6.528)		5.52%	13[0.21,25.79]
Shapiro 2000b	84	90	2.1 (6.51)		5.53%	2.1[-10.66,14.86]
Subtotal (95% CI)					**29.74%**	**10.68[6.38,14.98]**
Heterogeneity: Tau^2=0; Chi^2=2.91, df=4(P=0.57); I^2=0%						
Test for overall effect: Z=4.87(P<0.0001)						
1.5.3 Children <12 years						
Bensch 2002	1	1	0 (0)			Not estimable
Simons 1997a	1	1	0 (0)			Not estimable
von Berg 1998	179	170	37 (5.831)		6.01%	37[25.57,48.43]
Weinstein 1998	102	105	9.9 (3.536)		7.73%	9.87[2.94,16.8]
Subtotal (95% CI)					**13.74%**	**23.04[-3.54,49.61]**
Heterogeneity: Tau^2=344.77; Chi^2=15.83, df=1(P<0.0001); I^2=93.68%						
Test for overall effect: Z=1.7(P=0.09)						
1.5.4 Unclear						
SLGA2004	63	63	17 (6.112)		5.81%	17[5.02,28.98]
Subtotal (95% CI)					**5.81%**	**17[5.02,28.98]**
Heterogeneity: Not applicable						
Test for overall effect: Z=2.78(P=0.01)						
Total (95% CI)					**100%**	**17.66[12.93,22.39]**
Heterogeneity: Tau^2=62.81; Chi^2=51.85, df=16(P<0.0001); I^2=69.14%						
Test for overall effect: Z=7.32(P<0.0001)						
Test for subgroup differences: Chi^2=7.65, df=1 (P=0.05), I^2=60.77%						

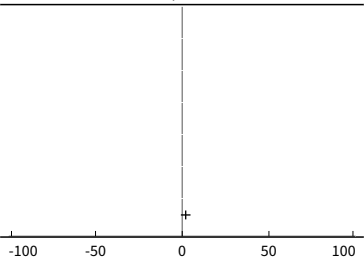
Analysis 1.6. Comparison 1 Studies with parallel group design: efficacy outcomes, Outcome 6 N with >/=15% increase in FEV1.

Study or subgroup	LABA n/N	PLACEBO n/N	Odds Ratio M-H, Fixed, 95% CI	Odds Ratio M-H, Fixed, 95% CI
1.6.1 Participants using mixed cointerventions				
1.6.2 Participants not using ICS				
1.6.3 Children <12 years				
1.6.4 Unclear				
SLGA2004	44/71	22/69		3.48[1.73,6.99]



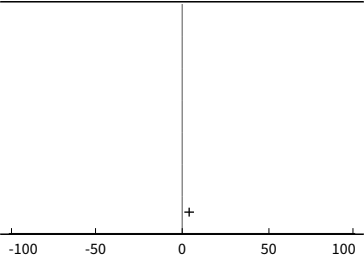
Analysis 1.7. Comparison 1 Studies with parallel group design: efficacy outcomes, Outcome 7 Change in PEF morning -percent predicted.

Study or subgroup	LABA N	LABA Mean(SD)	Placebo N	Placebo Mean(SD)	Mean Difference Fixed, 95% CI	Mean Difference Fixed, 95% CI
1.7.1 Participants using mixed cointerventions						
1.7.2 Participants not using ICS						
1.7.3 Children <12 years						
Bensch 2002	171	40 (0)	176	21 (0)		Not estimable
von Berg 1998	180	17 (13.4)	171	15 (13.1)		2[-0.77,4.77]



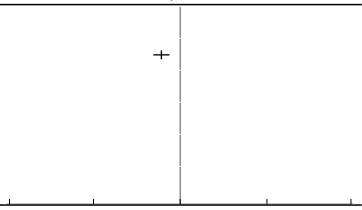
Analysis 1.8. Comparison 1 Studies with parallel group design: efficacy outcomes, Outcome 8 Change in PEF evening-percent predicted.

Study or subgroup	LABA N	LABA Mean(SD)	Placebo N	Placebo Mean(SD)	Mean Difference Fixed, 95% CI	Mean Difference Fixed, 95% CI
1.8.1 Participants using mixed cointerventions						
1.8.2 Participants not using ICS						
1.8.3 Children <12 years						
Bensch 2002	171	35 (0)	176	19 (0)		Not estimable
von Berg 1998	179	16 (13.4)	170	12 (13)		4[1.23,6.77]



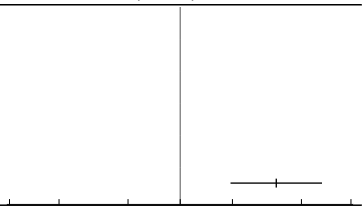
Analysis 1.9. Comparison 1 Studies with parallel group design: efficacy outcomes, Outcome 9 Amplitude PEF: diurnal variation (l/min or %).

Study or subgroup	LABA N	LABA Mean(SD)	Placebo N	Placebo Mean(SD)	Std. Mean Difference Fixed, 95% CI	Std. Mean Difference Fixed, 95% CI
1.9.1 Participants using mixed cointerventions						
Busse 1998	224	25.3 (40.6)	230	44.2 (46)		-0.43[-0.62,-0.25]
1.9.2 Participants not using ICS						
1.9.3 Children <12 years						



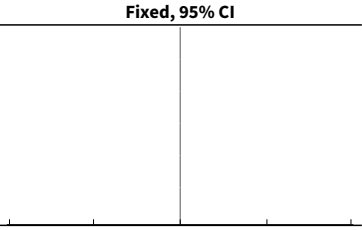
Analysis 1.10. Comparison 1 Studies with parallel group design: efficacy outcomes, Outcome 10 N with >/=15% increase in PEF.

Study or subgroup	LABA n/N	Placebo n/N	Odds Ratio M-H, Fixed, 95% CI	Odds Ratio M-H, Fixed, 95% CI
1.10.1 Participants using mixed cointerventions				
1.10.2 Participants not using ICS				
1.10.3 Children <12 years				
SLGA3014 1994	79/103	46/96		3.58[1.95,6.57]



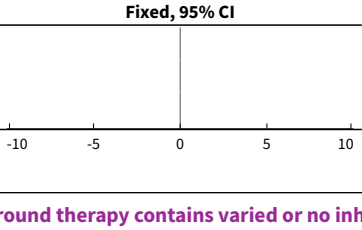
Analysis 1.11. Comparison 1 Studies with parallel group design: efficacy outcomes, Outcome 11 Change in peak expiratory flow: % predicted.

Study or subgroup	LABA N	LABA Mean(SD)	Placebo N	Placebo Mean(SD)	Mean Difference Fixed, 95% CI	Mean Difference Fixed, 95% CI
1.11.1 Participants using mixed cointerventions						
1.11.2 Participants not using ICS						
1.11.3 Children <12 years						
SLGA3014 1994	103	19.8 (0)	96	12.8 (0)		Not estimable



Analysis 1.12. Comparison 1 Studies with parallel group design: efficacy outcomes, Outcome 12 Peak expiratory flow: % predicted.

Study or subgroup	LABA N	LABA Mean(SD)	Placebo N	Placebo Mean(SD)	Mean Difference Fixed, 95% CI	Mean Difference Fixed, 95% CI
1.12.1 Subjects using mixed cointerventions						
1.12.2 Participants not using ICS						



Study or subgroup	LABA N	LABA Mean(SD)	Placebo N	Placebo Mean(SD)	Mean Difference Fixed, 95% CI	Mean Difference Fixed, 95% CI
1.12.3 Children <12 years						
SLGA3014 1994	103	78.4 (0)	86	80.6 (0)		Not estimable

Favours Placebo -10 -5 0 5 10 Favours LABA

Analysis 1.13. Comparison 1 Studies with parallel group design: efficacy outcomes, Outcome 13 AUC- mean area under 12 hr serial PEF curve (% predicted).

Study or subgroup	LABA N	LABA Mean(SD)	Placebo N	Placebo Mean(SD)	Mean Difference Fixed, 95% CI	Mean Difference Fixed, 95% CI
1.13.1 Participants using mixed cointerventions						
1.13.2 Subjects not on ICS >12 weeks treatment						
1.13.3 Children <12 years						
SLGA3014 1994	86	100 (0)	96	93.2 (0)		Not estimable
Weinstein 1998	91	104.2 (0)	93	97.7 (0)		Not estimable

Favours Placebo -4 -2 0 2 4 Favours LABA

Analysis 1.14. Comparison 1 Studies with parallel group design: efficacy outcomes, Outcome 14 Change in Amplitude PEF: diurnal variation (l/min or %).

Study or subgroup	LABA N	LABA Mean(SD)	Placebo N	Placebo Mean(SD)	Std. Mean Difference Fixed, 95% CI	Weight	Std. Mean Difference Fixed, 95% CI
1.14.1 Participants using mixed cointerventions							
Busse 1998	258	-42.7 (45.3)	269	-23.5 (41.7)		52.56%	-0.44[-0.61,-0.27]
Lockey 1999	240	-18 (46.5)	234	1 (45.9)		47.44%	-0.41[-0.59,-0.23]
Subtotal ***	**498**		**503**			**100%**	**-0.43[-0.55,-0.3]**
Heterogeneity: Tau²=0; Chi²=0.06, df=1(P=0.81); I²=0%							
Test for overall effect: Z=6.67(P<0.0001)							
1.14.2 Participants not using ICS							
Subtotal ***	**0**		**0**				**Not estimable**
Heterogeneity: Not applicable							
Test for overall effect: Not applicable							
1.14.3 Children <12 years							
Subtotal ***	**0**		**0**				**Not estimable**
Heterogeneity: Not applicable							
Test for overall effect: Not applicable							
Total ***	**498**		**503**			**100%**	**-0.43[-0.55,-0.3]**
Heterogeneity: Tau²=0; Chi²=0.06, df=1(P=0.81); I²=0%							
Test for overall effect: Z=6.67(P<0.0001)							
Test for subgroup differences: Not applicable							

Favours LABA -1 -0.5 0 0.5 1 Favours placebo

Analysis 1.15. Comparison 1 Studies with parallel group design: efficacy outcomes, Outcome 15 FEV1.

Study or subgroup	LABA N	Placebo N	Litres (SE)	Litres IV, Fixed, 95% CI	Weight	Litres IV, Fixed, 95% CI
1.15.1 Participants using mixed cointerventions						
Bensch 2001	134	134	0.3 (0.1)		3.94%	0.3[0.1,0.5]
Busse 1998	216	226	0.1 (0.077)		6.74%	0.12[-0.03,0.27]
D'Alonzo 1994	84	87	0.1 (0.112)		3.13%	0.07[-0.15,0.29]
Dahl 1991a	146	130	0.2 (0.06)		10.95%	0.2[0.08,0.32]
Ekstrom 1998a	135	129	0 (0.087)		5.24%	0.01[-0.16,0.18]
Kemp 1999	176	176	0.3 (0.087)		5.24%	0.33[0.16,0.5]
Pearlman 1992	68	63	0.2 (0.147)		1.82%	0.16[-0.13,0.45]
Pleskow 2003	139	139	0 (0)			Not estimable
SLGL82	41	41	0.1 (0.127)		2.44%	0.09[-0.16,0.34]
Wolfe 2000a	73	67	0.2 (0.663)		0.09%	0.19[-1.11,1.49]
Wolfe 2006	527	527	0.3 (0.028)		50.28%	0.3[0.25,0.35]
Subtotal (95% CI)					**89.89%**	**0.24[0.2,0.28]**
Heterogeneity: Tau^2=0; Chi^2=19.95, df=9(P=0.02); I^2=54.89%						
Test for overall effect: Z=11.58(P<0.0001)						
1.15.2 Participants not using ICS (PG design)						
Prieto 2002	14	13	0.2 (0.296)		0.45%	0.18[-0.4,0.76]
Wallin 1999	21	22	0.1 (0.239)		0.69%	0.08[-0.39,0.55]
Subtotal (95% CI)					**1.14%**	**0.12[-0.24,0.48]**
Heterogeneity: Tau^2=0; Chi^2=0.07, df=1(P=0.79); I^2=0%						
Test for overall effect: Z=0.64(P=0.52)						
1.15.3 Children <12 years						
von Berg 1998	183	171	0.2 (0.066)		8.97%	0.19[0.06,0.32]
Subtotal (95% CI)					**8.97%**	**0.19[0.06,0.32]**
Heterogeneity: Not applicable						
Test for overall effect: Z=2.87(P=0)						
Total (95% CI)					**100%**	**0.24[0.2,0.28]**
Heterogeneity: Tau^2=0; Chi^2=20.99, df=12(P=0.05); I^2=42.83%						
Test for overall effect: Z=11.91(P<0.0001)						
Test for subgroup differences: Chi^2=0.97, df=1 (P=0.62), I^2=0%						

Analysis 1.16. Comparison 1 Studies with parallel group design: efficacy outcomes, Outcome 16 FEV1 predicted.

Study or subgroup	LABA N	Placebo N	% (SE)	% IV, Fixed, 95% CI	Weight	% IV, Fixed, 95% CI
1.16.1 Participants using mixed cointerventions						
Subtotal (95% CI)						**Not estimable**
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						
1.16.2 Children <12 years						
Stelmach 2002	15	17	7.5 (5.173)		10.32%	7.45[-2.69,17.59]
von Berg 1998	183	171	3 (1.755)		89.68%	3[-0.44,6.44]

Study or subgroup	LABA N	Placebo N	% (SE)	% IV, Fixed, 95% CI	Weight	% IV, Fixed, 95% CI
Weinstein 1998	102	105	3.6 (0)			Not estimable
Subtotal (95% CI)					**100%**	**3.46[0.2,6.72]**
Heterogeneity: Tau²=0; Chi²=0.66, df=1(P=0.42); I²=0%						
Test for overall effect: Z=2.08(P=0.04)						
1.16.3 Participants not using ICS						
Wronska 1998	1	1	0 (0)			Not estimable
Subtotal (95% CI)						**Not estimable**
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						
Total (95% CI)					**100%**	**3.46[0.2,6.72]**
Heterogeneity: Tau²=0; Chi²=0.66, df=1(P=0.42); I²=0%						
Test for overall effect: Z=2.08(P=0.04)						
Test for subgroup differences: Not applicable						

Favours placebo -100 -50 0 50 100 Favours LABA

Analysis 1.17. Comparison 1 Studies with parallel group design: efficacy outcomes, Outcome 17 Change in FEV (litres).

Study or subgroup	LABA N	LABA Mean(SD)	Placebo N	Placebo Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
1.17.1 Participants using mixed cointerventions							
Busse 1998	215	0.4 (0.5)	227	0.1 (0.5)		16.72%	0.26[0.17,0.35]
D'Alonzo 1994	84	0.4 (0.6)	87	0.2 (0.6)		4.55%	0.13[-0.05,0.31]
Lockey 1999	240	0.4 (0.5)	234	0.2 (0.6)		15.07%	0.17[0.07,0.27]
Pearlman 1992	71	0.3 (0.6)	63	0.1 (0.5)		4.03%	0.17[-0.02,0.36]
SAS30004	91	0.2 (0)	89	-0.1 (0)			Not estimable
Schreurs 1996	49	0.2 (0.3)	51	0 (0.3)		10.67%	0.15[0.03,0.27]
SMS40221	32	0.3 (0.5)	32	-0 (0.5)		2.24%	0.31[0.06,0.56]
Subtotal ***	**782**		**783**			**53.28%**	**0.2[0.14,0.25]**
Heterogeneity: Tau²=0; Chi²=4.04, df=5(P=0.54); I²=0%							
Test for overall effect: Z=7.38(P<0.0001)							
1.17.2 Participants not using ICS							
Kavuru 2000a	77	0.1 (0.6)	86	0 (0.6)		4.51%	0.1[-0.08,0.28]
Nathan 1999	128	0.3 (0.5)	129	0.1 (0.5)		12.01%	0.2[0.09,0.31]
Pearlman 1999a	21	0.3 (0.6)	23	0 (0.4)		1.69%	0.29[-0,0.58]
Rosenthal 1999	202	0.3 (0)	206	0.1 (0)			Not estimable
SAS30003	92	0.3 (0)	87	0.1 (0)			Not estimable
Shapiro 2000b	84	0.1 (0.5)	90	-0.1 (0.5)		7.61%	0.16[0.02,0.3]
Subtotal ***	**604**		**621**			**25.81%**	**0.18[0.1,0.25]**
Heterogeneity: Tau²=0; Chi²=1.5, df=3(P=0.68); I²=0%							
Test for overall effect: Z=4.61(P<0.0001)							
1.17.3 Children <12 years							
Simons 1997a	80	0.2 (0)	80	0.1 (0)			Not estimable
von Berg 1998	176	0.3 (0.4)	169	0.2 (0.4)		20.92%	0.08[-0,0.16]
Subtotal ***	**256**		**249**			**20.92%**	**0.08[-0,0.16]**

Favours placebo -1 -0.5 0 0.5 1 Favours LABA

Study or subgroup	LABA N	LABA Mean(SD)	Placebo N	Placebo Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
Heterogeneity: Not applicable							
Test for overall effect: Z=1.88(P=0.06)							
Total ***	**1642**		**1653**		♦	**100%**	**0.17[0.13,0.21]**
Heterogeneity: Tau²=0; Chi²=11.03, df=10(P=0.36); I²=9.33%							
Test for overall effect: Z=8.59(P<0.0001)							
Test for subgroup differences: Chi²=5.49, df=1 (P=0.06), I²=63.57%							

Favours placebo -1 -0.5 0 0.5 1 Favours LABA

Analysis 1.18. Comparison 1 Studies with parallel group design: efficacy outcomes, Outcome 18 N with >/=15% increase in FEV1.

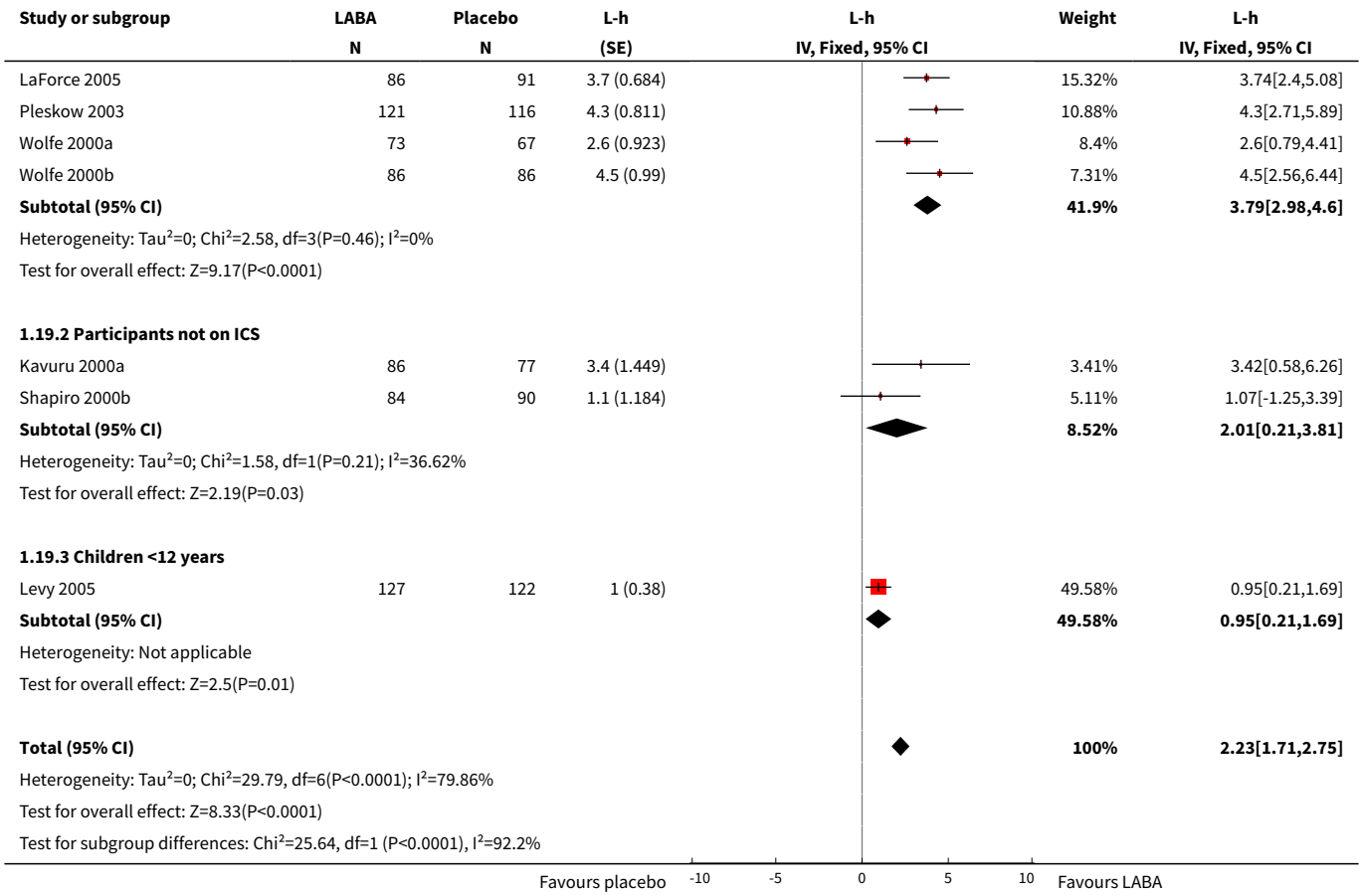
Study or subgroup	LABA n/N	Placebo n/N	Odds Ratio M-H, Fixed, 95% CI	Weight	Odds Ratio M-H, Fixed, 95% CI
1.18.1 Participants using mixed cointerventions					
Subtotal (95% CI)	**0**	**0**			**Not estimable**
Total events: 0 (LABA), 0 (Placebo)					
Heterogeneity: Not applicable					
Test for overall effect: Not applicable					
1.18.2 Children <12 years					
SLGA3014 1994	73/100	49/88		49.06%	2.15[1.17,3.96]
Weinstein 1998	51/81	38/75		50.94%	1.66[0.87,3.14]
Subtotal (95% CI)	**181**	**163**	◆	**100%**	**1.9[1.22,2.95]**
Total events: 124 (LABA), 87 (Placebo)					
Heterogeneity: Tau²=0; Chi²=0.34, df=1(P=0.56); I²=0%					
Test for overall effect: Z=2.85(P=0)					
1.18.3 Participants not using ICS					
Subtotal (95% CI)	**0**	**0**			**Not estimable**
Total events: 0 (LABA), 0 (Placebo)					
Heterogeneity: Not applicable					
Test for overall effect: Not applicable					
Total (95% CI)	**181**	**163**	◆	**100%**	**1.9[1.22,2.95]**
Total events: 124 (LABA), 87 (Placebo)					
Heterogeneity: Tau²=0; Chi²=0.34, df=1(P=0.56); I²=0%					
Test for overall effect: Z=2.85(P=0)					
Test for subgroup differences: Not applicable					

Favours placebo 0.1 0.2 0.5 1 2 5 10 Favours LABA

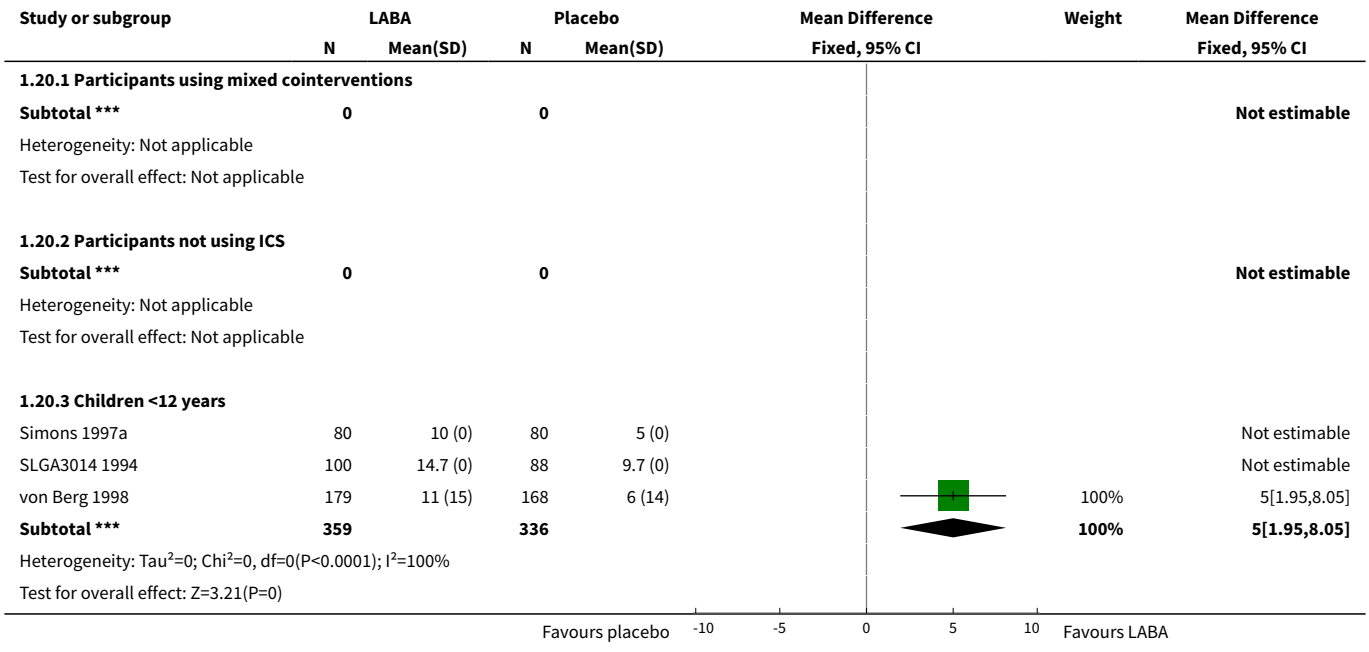
Analysis 1.19. Comparison 1 Studies with parallel group design: efficacy outcomes, Outcome 19 AUC- mean area under 12 hr serial FEV1 curve.

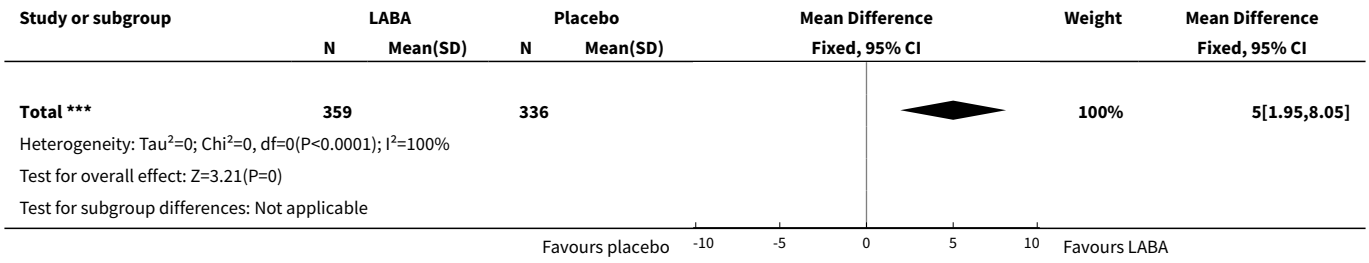
Study or subgroup	LABA N	Placebo N	L-h (SE)	L-h IV, Fixed, 95% CI	Weight	L-h IV, Fixed, 95% CI
1.19.1 Participants using mixed cointerventions						

Favours placebo -10 -5 0 5 10 Favours LABA

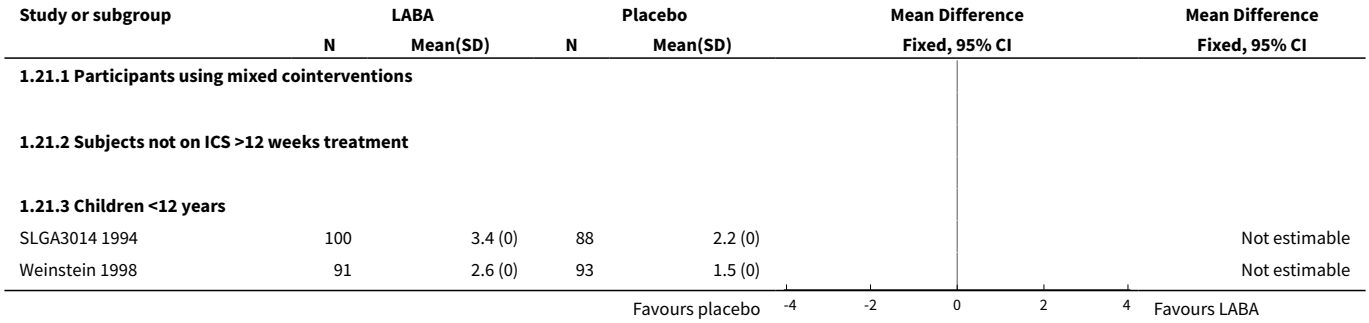


Analysis 1.20. Comparison 1 Studies with parallel group design: efficacy outcomes, Outcome 20 Change in FEV1 %predicted.

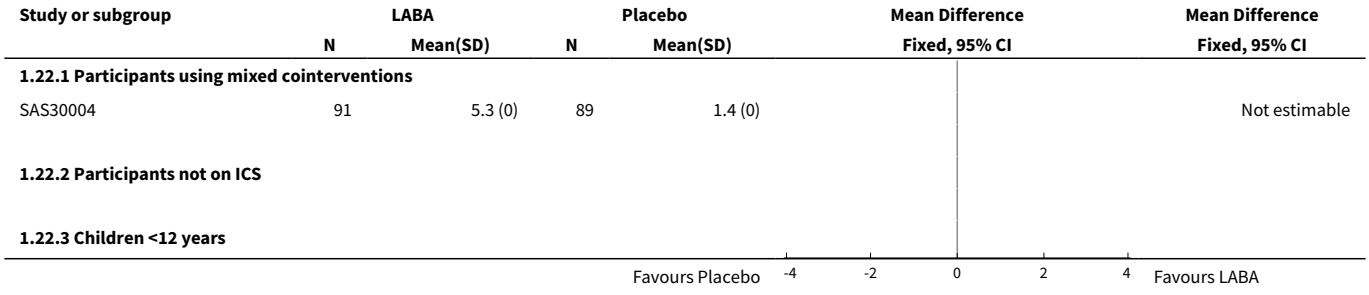




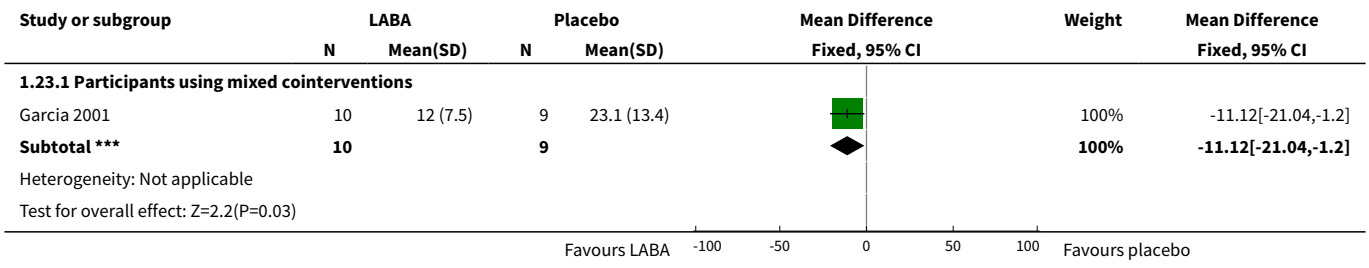
Analysis 1.21. Comparison 1 Studies with parallel group design: efficacy outcomes, Outcome 21 AUC- mean area under 12 hr serial FEV1 curve (% predicted).



Analysis 1.22. Comparison 1 Studies with parallel group design: efficacy outcomes, Outcome 22 AUC- mean change area under 12 hr serial FEV1 curve (L-h).



Analysis 1.23. Comparison 1 Studies with parallel group design: efficacy outcomes, Outcome 23 Fall in FEV1 post exercise (12 hrs post study drug) %.



Study or subgroup	LABA N	LABA Mean(SD)	Placebo N	Placebo Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
1.23.2 Participants not on ICS							
Subtotal ***	**0**		**0**				**Not estimable**
Heterogeneity: Not applicable							
Test for overall effect: Not applicable							
1.23.3 Children <12 years							
Subtotal ***	**0**		**0**				**Not estimable**
Heterogeneity: Not applicable							
Test for overall effect: Not applicable							
Test for subgroup differences: Not applicable							

Favours LABA -100 -50 0 50 100 Favours placebo

Analysis 1.24. Comparison 1 Studies with parallel group design: efficacy outcomes, Outcome 24 Fall in FEV1 post exercise (pre-medication with formoterol) %.

Study or subgroup	LABA N	LABA Mean(SD)	Placebo N	Placebo Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
1.24.1 Participants using mixed cointerventions							
Garcia 2001	10	10.2 (6.8)	9	5 (7.5)		100%	5.19[-1.23,11.61]
Subtotal ***	**10**		**9**			**100%**	**5.19[-1.23,11.61]**
Heterogeneity: Not applicable							
Test for overall effect: Z=1.58(P=0.11)							
1.24.2 Participants not on ICS							
Subtotal ***	**0**		**0**				**Not estimable**
Heterogeneity: Not applicable							
Test for overall effect: Not applicable							
1.24.3 Children <12 years							
Subtotal ***	**0**		**0**				**Not estimable**
Heterogeneity: Not applicable							
Test for overall effect: Not applicable							
Test for subgroup differences: Not applicable							

Favours LABA -100 -50 0 50 100 Favours placebo

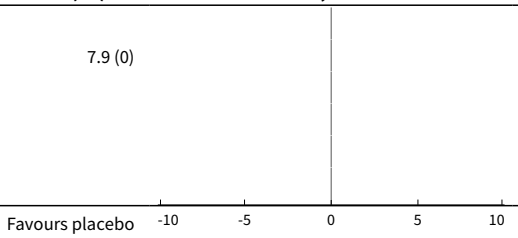
Analysis 1.25. Comparison 1 Studies with parallel group design: efficacy outcomes, Outcome 25 FEV1 12hr post dose.

Study or subgroup	LABA N	LABA Mean(SD)	Placebo N	Placebo Mean(SD)	Mean Difference Fixed, 95% CI	Mean Difference Fixed, 95% CI
1.25.1 Participants using mixed cointerventions						
Pleskow 2003	139	2.8 (0)	141	2.4 (0)		Not estimable
1.25.2 Participants not using ICS						
1.25.3 Children <12 years						

Favours placebo -10 -5 0 5 10 Favours LABA

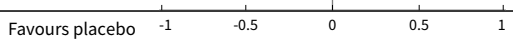
Analysis 1.26. Comparison 1 Studies with parallel group design: efficacy outcomes, Outcome 26 Change in FEV1 12hr post dose.

Study or subgroup	LABA N	LABA Mean(SD)	Placebo N	Placebo Mean(SD)	Mean Difference Fixed, 95% CI	Mean Difference Fixed, 95% CI
1.26.1 Participants using mixed cointerventions						
Bensch 2001	139	19.4 (0)	141	7.9 (0)		Not estimable
1.26.2 Participants not using ICS						
1.26.3 Children <12 years						



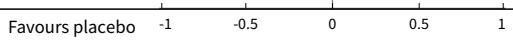
Analysis 1.27. Comparison 1 Studies with parallel group design: efficacy outcomes, Outcome 27 Forced Vital Capacity (litres).

Study or subgroup	LABA N	LABA Mean(SD)	Placebo N	Placebo Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
1.27.1 Participants using mixed cointerventions							
D'Alonzo 1994	84	4 (1.1)	87	3.9 (0.9)		59.1%	0.11[-0.19,0.41]
Pearlman 1992	68	3.8 (1.1)	63	3.7 (1)		40.9%	0.05[-0.31,0.41]
Subtotal ***	**152**		**150**			**100%**	**0.09[-0.14,0.32]**
Heterogeneity: Tau^2=0; Chi^2=0.06, df=1(P=0.8); I^2=0%							
Test for overall effect: Z=0.73(P=0.47)							
1.27.2 Participants not using ICS							
Subtotal ***	**0**		**0**				**Not estimable**
Heterogeneity: Not applicable							
Test for overall effect: Not applicable							
1.27.3 Children <12 years							
Subtotal ***	**0**		**0**				**Not estimable**
Heterogeneity: Not applicable							
Test for overall effect: Not applicable							
Total ***	**152**		**150**			**100%**	**0.09[-0.14,0.32]**
Heterogeneity: Tau^2=0; Chi^2=0.06, df=1(P=0.8); I^2=0%							
Test for overall effect: Z=0.73(P=0.47)							
Test for subgroup differences: Not applicable							

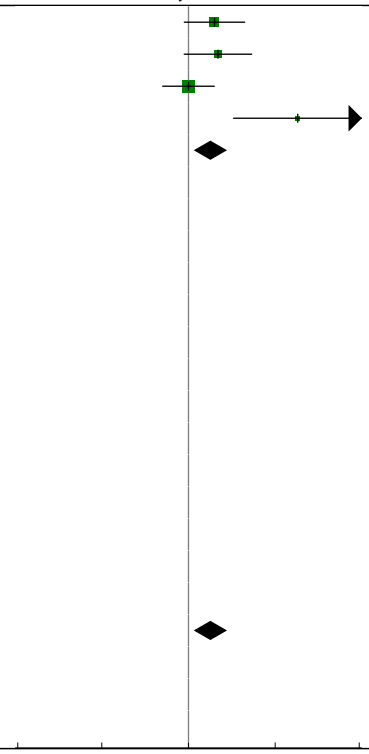


Analysis 1.28. Comparison 1 Studies with parallel group design: efficacy outcomes, Outcome 28 Change in Forced Vital Capacity (litres).

Study or subgroup	LABA N	LABA Mean(SD)	Placebo N	Placebo Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
1.28.1 Participants using mixed cointerventions							

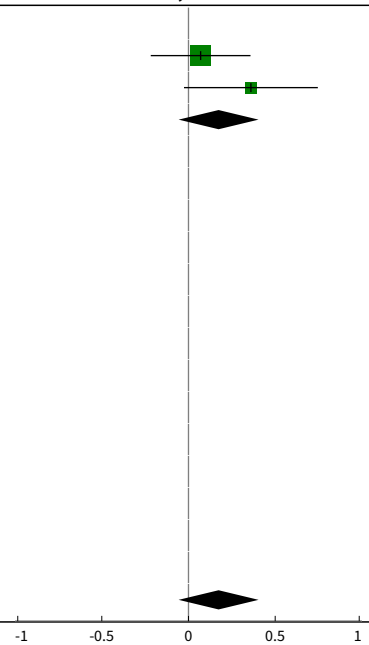


Study or subgroup	LABA N	LABA Mean(SD)	Placebo N	Placebo Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
D'Alonzo 1994	84	0.3 (0.6)	87	0.2 (0.6)		29.48%	0.15[-0.03,0.33]
Pearlman 1992	68	0.2 (0.6)	63	0.1 (0.5)		23.65%	0.17[-0.03,0.37]
Schreurs 1996	49	0.1 (0.4)	51	0.1 (0.4)		40.21%	0[-0.15,0.15]
SMS40221	32	0.4 (0.8)	32	-0.2 (0.8)		6.65%	0.63[0.26,1]
Subtotal * **	**233**		**233**			**100%**	**0.13[0.03,0.22]**
Heterogeneity: Tau^2=0; Chi^2=9.96, df=3(P=0.02); I^2=69.86%							
Test for overall effect: Z=2.58(P=0.01)							
1.28.2 Participants not using ICS							
Subtotal * **	**0**		**0**				**Not estimable**
Heterogeneity: Not applicable							
Test for overall effect: Not applicable							
1.28.3 Children <12 years							
Simons 1997a	80	0.2 (0)	80	0.1 (0)			Not estimable
Subtotal * **	**80**		**80**				**Not estimable**
Heterogeneity: Not applicable							
Test for overall effect: Not applicable							
Total * **	**313**		**313**			**100%**	**0.13[0.03,0.22]**
Heterogeneity: Tau^2=0; Chi^2=9.96, df=3(P=0.02); I^2=69.86%							
Test for overall effect: Z=2.58(P=0.01)							
Test for subgroup differences: Not applicable							



Analysis 1.29. Comparison 1 Studies with parallel group design: efficacy outcomes, Outcome 29 FEF25-75 (litres/sec).

Study or subgroup	LABA N	LABA Mean(SD)	Placebo N	Placebo Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
1.29.1 Participants using mixed cointerventions							
D'Alonzo 1994	84	2.3 (1)	87	2.2 (0.9)		64.29%	0.07[-0.22,0.36]
Pearlman 1992	68	2.7 (1.2)	63	2.3 (1)		35.71%	0.36[-0.03,0.75]
Subtotal * **	**152**		**150**			**100%**	**0.17[-0.06,0.4]**
Heterogeneity: Tau^2=0; Chi^2=1.39, df=1(P=0.24); I^2=28.31%							
Test for overall effect: Z=1.48(P=0.14)							
1.29.2 Participants not using ICS							
Subtotal * **	**0**		**0**				**Not estimable**
Heterogeneity: Not applicable							
Test for overall effect: Not applicable							
1.29.3 Children <12 years							
Simons 1997a	80	0.4 (0)	80	0.2 (0)			Not estimable
Subtotal * **	**80**		**80**				**Not estimable**
Heterogeneity: Not applicable							
Test for overall effect: Not applicable							
Total * **	**232**		**230**			**100%**	**0.17[-0.06,0.4]**



Study or subgroup	LABA N	LABA Mean(SD)	Placebo N	Placebo Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
Heterogeneity: Tau²=0; Chi²=1.39, df=1(P=0.24); I²=28.31%							
Test for overall effect: Z=1.48(P=0.14)							
Test for subgroup differences: Not applicable							

Favours placebo -1 -0.5 0 0.5 1 Favours LABA

Analysis 1.30. Comparison 1 Studies with parallel group design: efficacy outcomes, Outcome 30 Symptom score - whole day.

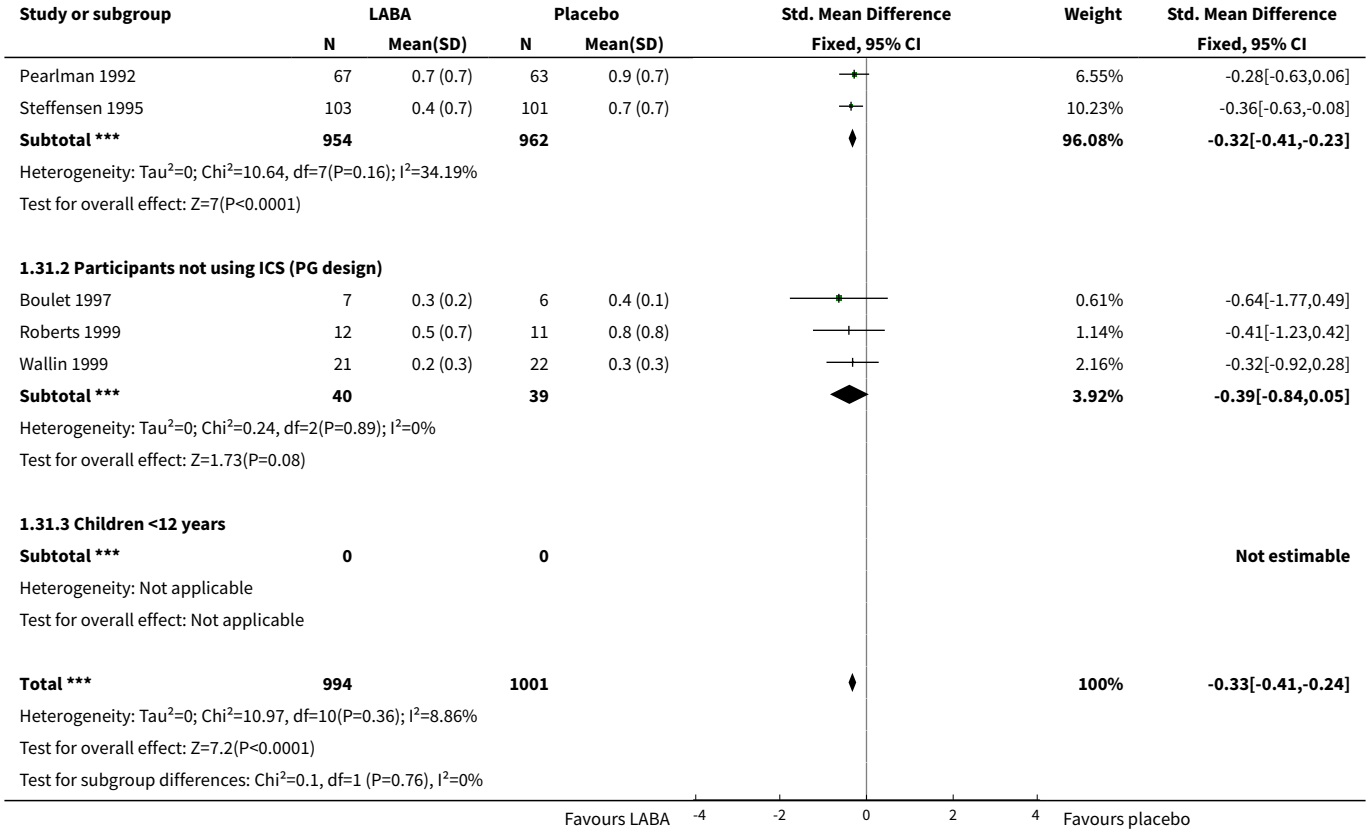
Study or subgroup	LABA N	LABA Mean(SD)	Placebo N	Placebo Mean(SD)	Std. Mean Difference Fixed, 95% CI	Weight	Std. Mean Difference Fixed, 95% CI
1.30.1 Participants using mixed cointerventions							
Bensch 2001	134	0.7 (0.6)	132	1 (0.6)		29.13%	-0.5[-0.74,-0.25]
Pleskow 2003	135	0.7 (0.6)	139	1 (0.7)		30.15%	-0.46[-0.7,-0.22]
Wolfe 2000a	166	1.8 (1.3)	167	2 (1.3)		37.51%	-0.15[-0.37,0.06]
Subtotal ***	**435**		**438**			**96.79%**	**-0.35[-0.49,-0.22]**
Heterogeneity: Tau²=0; Chi²=5.41, df=2(P=0.07); I²=63.04%							
Test for overall effect: Z=5.16(P<0.0001)							
1.30.2 Participants all using ICS							
Subtotal ***	**0**		**0**				**Not estimable**
Heterogeneity: Not applicable							
Test for overall effect: Not applicable							
1.30.3 Children <12 years							
Stelmach 2002	15	5.9 (1.2)	17	6.9 (0.9)		3.21%	-0.93[-1.67,-0.2]
Subtotal ***	**15**		**17**			**3.21%**	**-0.93[-1.67,-0.2]**
Heterogeneity: Not applicable							
Test for overall effect: Z=2.48(P=0.01)							
Total ***	**450**		**455**			**100%**	**-0.37[-0.5,-0.24]**
Heterogeneity: Tau²=0; Chi²=7.72, df=3(P=0.05); I²=61.14%							
Test for overall effect: Z=5.52(P<0.0001)							
Test for subgroup differences: Chi²=2.31, df=1 (P=0.13), I²=56.7%							

Favours LABA -4 -2 0 2 4 Favours placebo

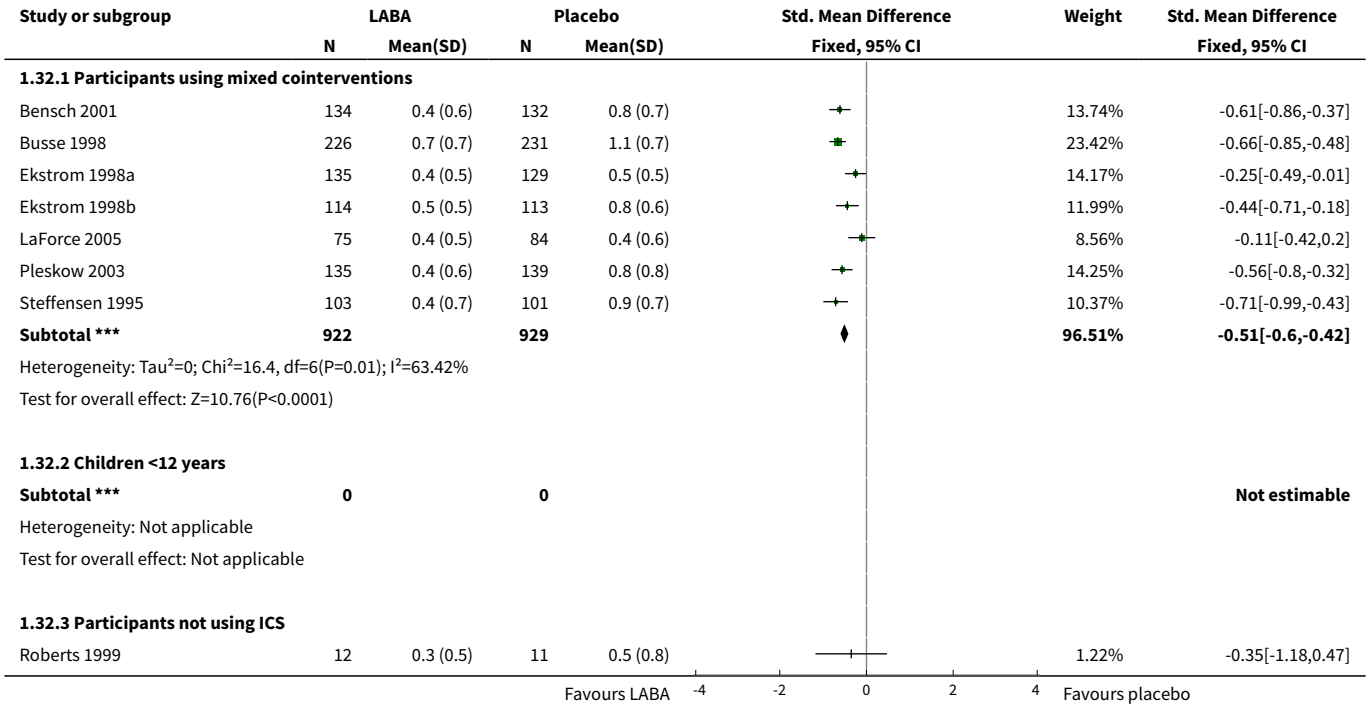
Analysis 1.31. Comparison 1 Studies with parallel group design: efficacy outcomes, Outcome 31 Symptom score - day time.

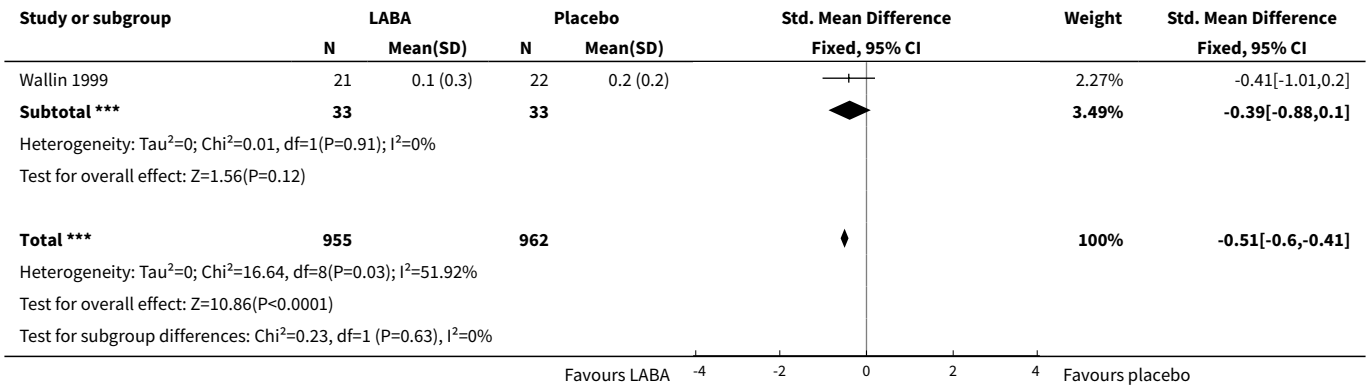
Study or subgroup	LABA N	LABA Mean(SD)	Placebo N	Placebo Mean(SD)	Std. Mean Difference Fixed, 95% CI	Weight	Std. Mean Difference Fixed, 95% CI
1.31.1 Participants using mixed cointerventions							
Busse 1998	224	0.8 (0.7)	230	1.1 (0.6)		22.31%	-0.54[-0.73,-0.35]
D'Alonzo 1994	87	0.7 (0.7)	90	1 (0.7)		8.82%	-0.43[-0.72,-0.13]
Ekstrom 1998a	135	0.5 (0.5)	129	0.6 (0.5)		13.32%	-0.28[-0.52,-0.04]
Ekstrom 1998b	114	0.6 (0.6)	113	0.8 (0.7)		11.48%	-0.26[-0.52,0]
Kemp 1998a	149	0.8 (0.7)	152	0.9 (0.7)		15.31%	-0.14[-0.36,0.09]
LaForce 2005	75	0.4 (0.5)	84	0.4 (0.6)		8.07%	-0.11[-0.42,0.2]

Favours LABA -4 -2 0 2 4 Favours placebo

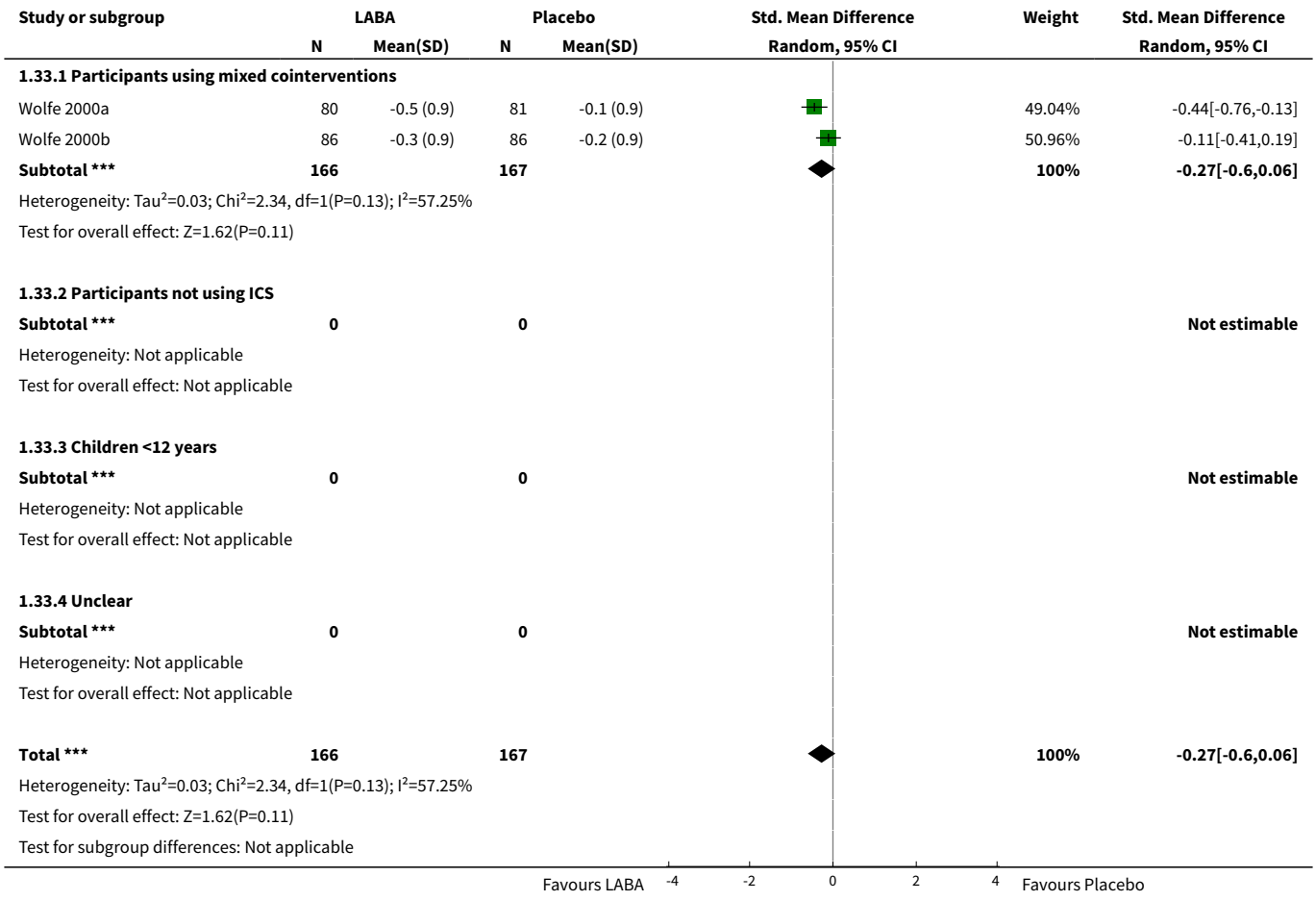


Analysis 1.32. Comparison 1 Studies with parallel group design: efficacy outcomes, Outcome 32 Symptom score - night time.



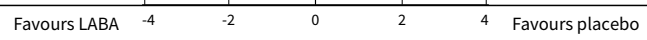


Analysis 1.33. Comparison 1 Studies with parallel group design: efficacy outcomes, Outcome 33 Change in symptom score: whole day.



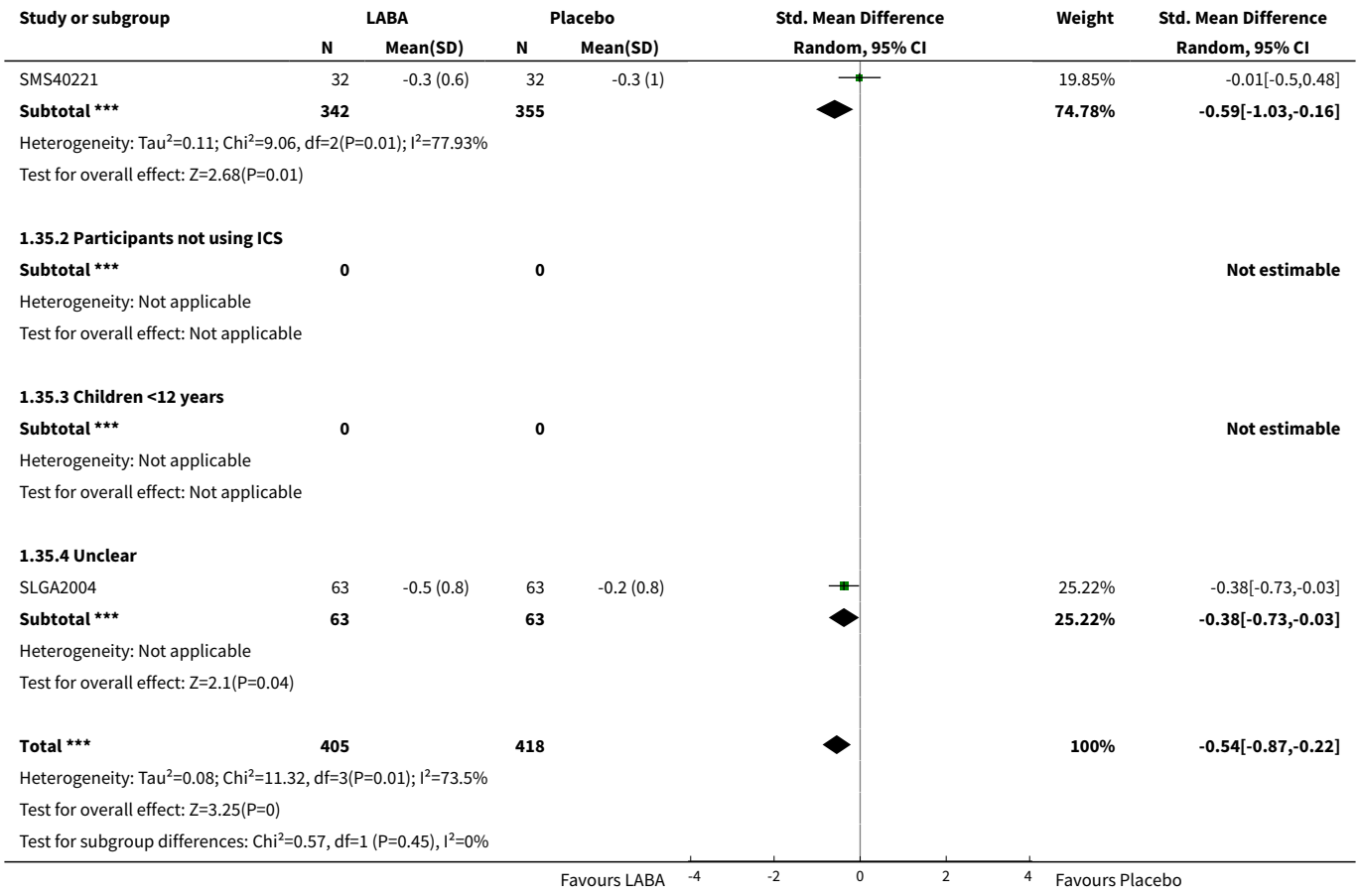
Analysis 1.34. Comparison 1 Studies with parallel group design: efficacy outcomes, Outcome 34 Change in symptom score: day time.

Study or subgroup	LABA N	LABA Mean(SD)	Placebo N	Placebo Mean(SD)	Std. Mean Difference Random, 95% CI	Weight	Std. Mean Difference Random, 95% CI
1.34.1 Participants using mixed cointerventions							
Busse 1998	258	-0.8 (0.6)	269	-0.4 (0.5)		17.18%	-0.68[-0.85,-0.5]
D'Alonzo 1994	93	-0.4 (0.6)	94	-0.1 (0.6)		9.95%	-0.5[-0.79,-0.21]
Pearlman 1992	67	-0.3 (0.8)	63	-0.1 (0.7)		7.84%	-0.26[-0.61,0.08]
Schreurs 1996	49	-0.3 (0.5)	51	0.2 (0.5)		5.94%	-0.94[-1.36,-0.53]
SMS40221	32	-0.7 (1)	32	-0.4 (0.9)		4.46%	-0.27[-0.77,0.22]
Subtotal ***	**499**		**509**			**45.37%**	**-0.55[-0.76,-0.33]**
Heterogeneity: Tau^2=0.03; Chi^2=9.12, df=4(P=0.06); I^2=56.12%							
Test for overall effect: Z=5(P<0.0001)							
1.34.2 Participants not using ICS							
Kavuru 2000a	77	-0.1 (0.9)	86	0.4 (0.8)		8.99%	-0.57[-0.88,-0.26]
Pearlman 1999a	21	-0.5 (0.5)	23	-0.2 (0.5)		3.1%	-0.63[-1.23,-0.02]
Rosenthal 1999	202	-0.3 (0.6)	206	-0.1 (0.4)		15.6%	-0.38[-0.57,-0.18]
SAS30003	92	-0.4 (1)	87	0 (1)		9.72%	-0.41[-0.71,-0.12]
SAS30004	91	-0.3 (0)	89	0.5 (0)			Not estimable
Shapiro 2000b	84	0.1 (0.9)	90	0.4 (1)		9.6%	-0.32[-0.62,-0.02]
Subtotal ***	**567**		**581**			**47.02%**	**-0.42[-0.54,-0.29]**
Heterogeneity: Tau^2=0; Chi^2=1.94, df=4(P=0.75); I^2=0%							
Test for overall effect: Z=6.39(P<0.0001)							
1.34.3 Children <12 years							
Bensch 2002	171	-0.3 (0)	176	-0.2 (0)			Not estimable
Subtotal ***	**171**		**176**				**Not estimable**
Heterogeneity: Not applicable							
Test for overall effect: Not applicable							
1.34.4 Unclear							
SLGA2004	63	-0.5 (0.8)	63	-0.2 (0.8)		7.61%	-0.38[-0.73,-0.03]
Subtotal ***	**63**		**63**			**7.61%**	**-0.38[-0.73,-0.03]**
Heterogeneity: Not applicable							
Test for overall effect: Z=2.1(P=0.04)							
Total ***	**1300**		**1329**			**100%**	**-0.48[-0.6,-0.37]**
Heterogeneity: Tau^2=0.01; Chi^2=14.95, df=10(P=0.13); I^2=33.1%							
Test for overall effect: Z=8.39(P<0.0001)							
Test for subgroup differences: Chi^2=1.23, df=1 (P=0.54), I^2=0%							

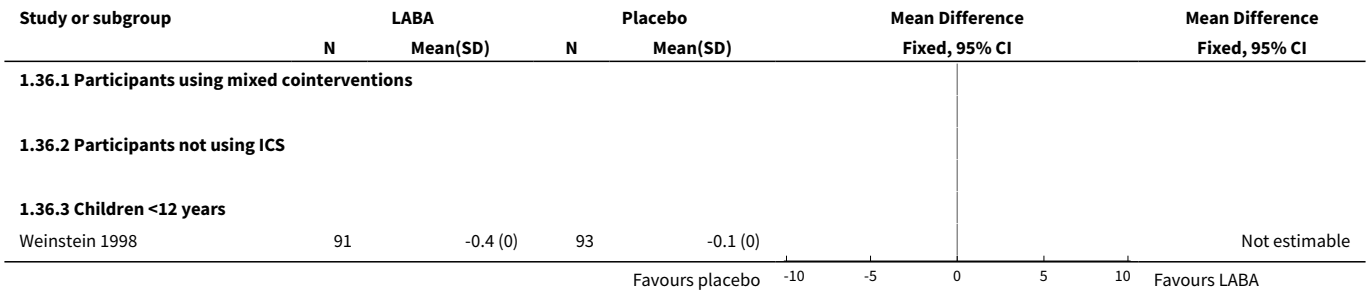


Analysis 1.35. Comparison 1 Studies with parallel group design: efficacy outcomes, Outcome 35 Change in symptom score: night time.

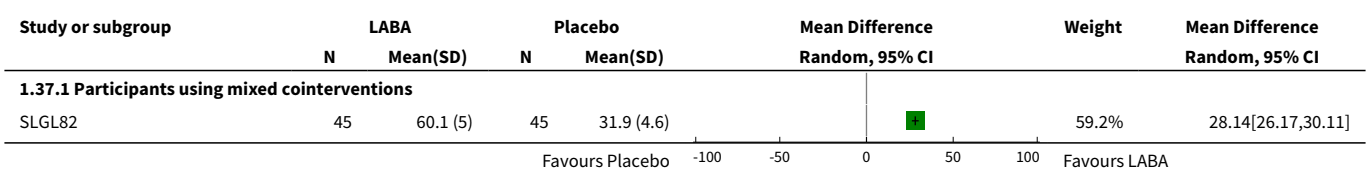
Study or subgroup	LABA N	LABA Mean(SD)	Placebo N	Placebo Mean(SD)	Std. Mean Difference Random, 95% CI	Weight	Std. Mean Difference Random, 95% CI
1.35.1 Participants using mixed cointerventions							
Busse 1998	261	-0.8 (0.7)	272	-0.3 (0.6)		32.26%	-0.7[-0.88,-0.53]
Schreurs 1996	49	-0.3 (0.5)	51	0.1 (0.5)		22.66%	-0.97[-1.39,-0.55]



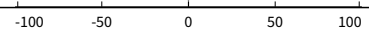
Analysis 1.36. Comparison 1 Studies with parallel group design: efficacy outcomes, Outcome 36 Change in total symptom score.



Analysis 1.37. Comparison 1 Studies with parallel group design: efficacy outcomes, Outcome 37 % days without rescue medication.

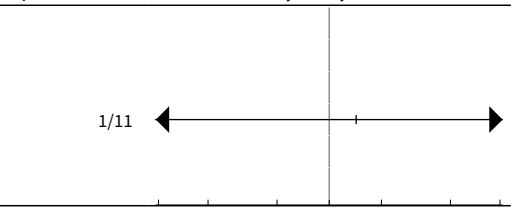


Study or subgroup	LABA N	LABA Mean(SD)	Placebo N	Placebo Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
Wolfe 2000a	80	29 (32.2)	81	12 (29.7)		40.8%	17[7.43,26.57]
Subtotal ***	**125**		**126**			**100%**	**23.6[12.86,34.33]**
Heterogeneity: Tau^2=49.62; Chi^2=4.99, df=1(P=0.03); I^2=79.97%							
Test for overall effect: Z=4.31(P<0.0001)							
1.37.2 Participants not using ICS							
Subtotal ***	**0**		**0**				**Not estimable**
Heterogeneity: Not applicable							
Test for overall effect: Not applicable							
1.37.3 Children <12 years							
Subtotal ***	**0**		**0**				**Not estimable**
Heterogeneity: Not applicable							
Test for overall effect: Not applicable							
Total ***	**125**		**126**			**100%**	**23.6[12.86,34.33]**
Heterogeneity: Tau^2=49.62; Chi^2=4.99, df=1(P=0.03); I^2=79.97%							
Test for overall effect: Z=4.31(P<0.0001)							
Test for subgroup differences: Not applicable							



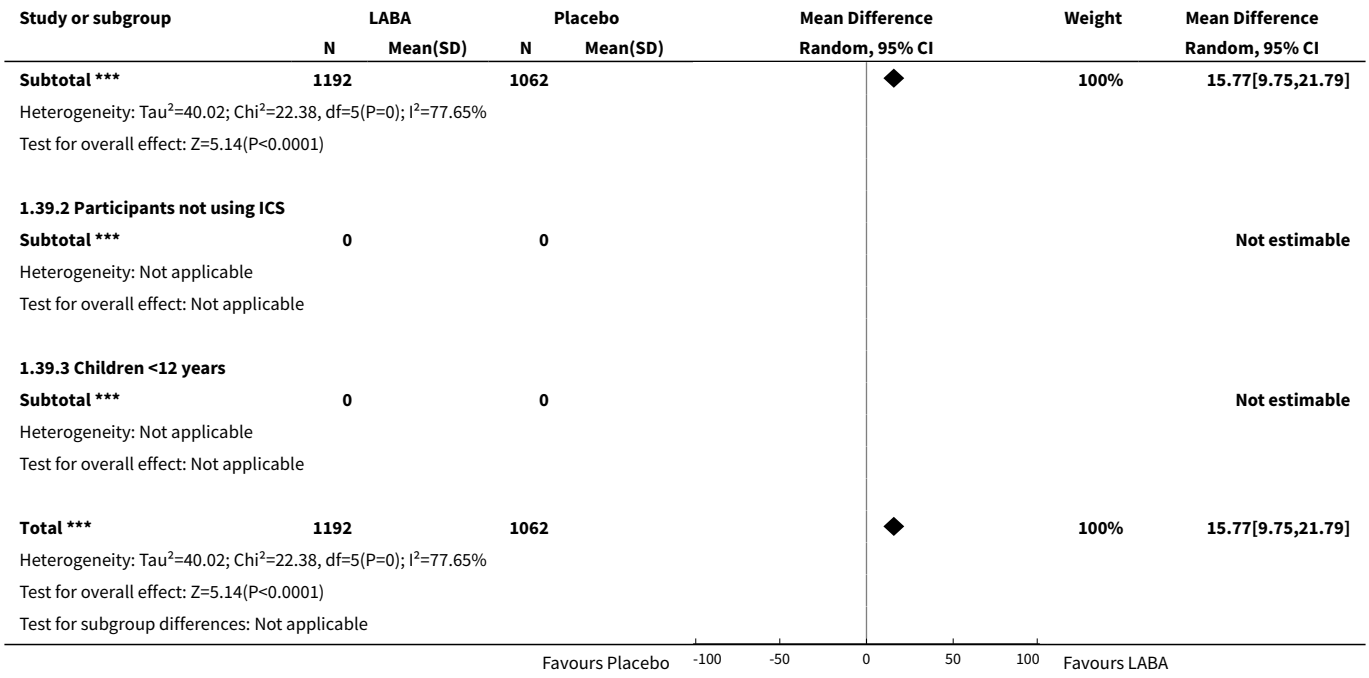
Analysis 1.38. Comparison 1 Studies with parallel group design: efficacy outcomes, Outcome 38 N with <50% days free from rescue medication.

Study or subgroup	LABA n/N	Placebo n/N	Odds Ratio M-H, Fixed, 95% CI	Odds Ratio M-H, Fixed, 95% CI
1.38.1 Participants using mixed cointerventions				
1.38.2 Participants not using ICS				
SLMP03	1/8	1/11		1.43[0.08,26.9]
1.38.3 Children <12 years				

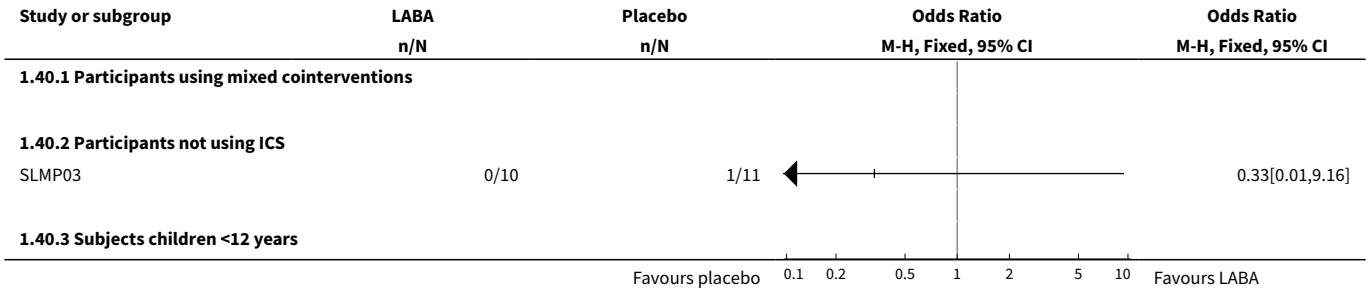


Analysis 1.39. Comparison 1 Studies with parallel group design: efficacy outcomes, Outcome 39 % days without asthma symptoms.

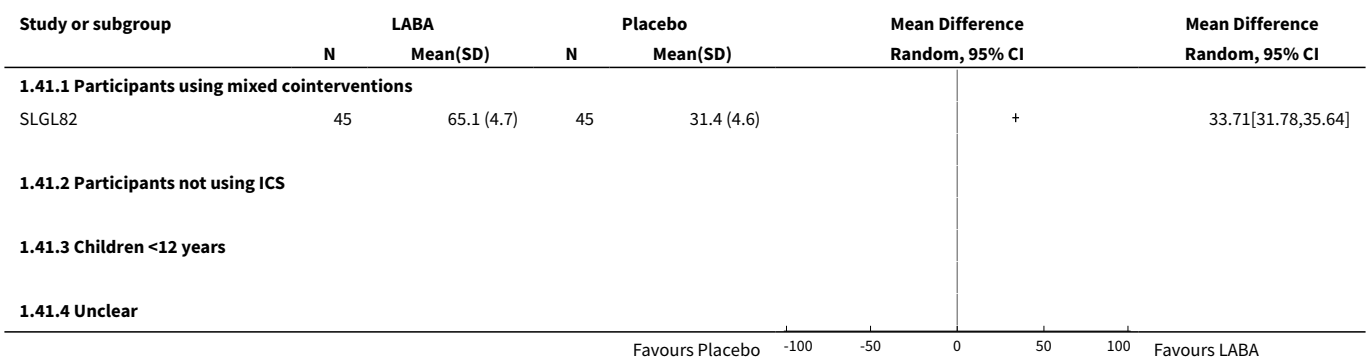
Study or subgroup	LABA N	LABA Mean(SD)	Placebo N	Placebo Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
1.39.1 Participants using mixed cointerventions							
Bensch 2001	135	53 (0)	136	33 (0)			Not estimable
Busse 1998	215	30.8 (40.7)	227	12.1 (25.1)		18.67%	18.7[12.35,25.05]
D'Alonzo 1994	87	35 (40)	90	18 (33)		13.37%	17[6.18,27.82]
Jones 1994	282	55 (37)	145	51 (37)		17.36%	4[-3.41,11.41]
Lockey 1999	240	48 (15.5)	234	26 (15.3)		22.44%	22[19.23,24.77]
Pearlman 1992	67	35 (40)	63	16 (31)		11.91%	19[6.74,31.26]
Wolfe 2000a	166	50 (38.6)	167	37 (38.8)		16.25%	13[4.69,21.31]



Analysis 1.40. Comparison 1 Studies with parallel group design: efficacy outcomes, Outcome 40 N with <50% symptom free days.

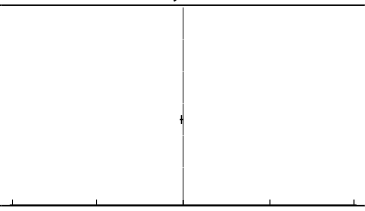


Analysis 1.41. Comparison 1 Studies with parallel group design: efficacy outcomes, Outcome 41 % nighttime awakenings requiring no SABA.



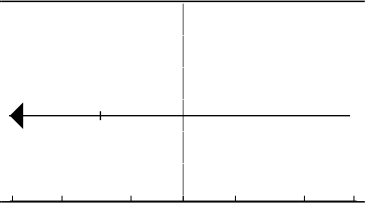
Analysis 1.42. Comparison 1 Studies with parallel group design: efficacy outcomes, Outcome 42 Change in nighttime awakenings.

Study or subgroup	LABA N	LABA Mean(SD)	Placebo N	Placebo Mean(SD)	Mean Difference Fixed, 95% CI	Mean Difference Fixed, 95% CI
1.42.1 Participants using mixed cointerventions						
1.42.2 Participants not using ICS						
SAS30003	92	-0 (0.3)	87	0.1 (0.4)		-0.1[-0.2,-0]
1.42.3 Children <12 years						



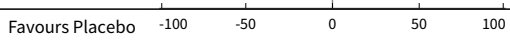
Analysis 1.43. Comparison 1 Studies with parallel group design: efficacy outcomes, Outcome 43 N with <50% symptom free nights.

Study or subgroup	LABA n/N	Placebo n/N	Odds Ratio M-H, Fixed, 95% CI	Odds Ratio M-H, Fixed, 95% CI
1.43.1 Participants using mixed cointerventions				
1.43.2 Participants not using ICS				
SLMP03	0/10	1/11		0.33[0.01,9.16]
1.43.3 Subjects children <12 years				



Analysis 1.44. Comparison 1 Studies with parallel group design: efficacy outcomes, Outcome 44 Change in % no nighttime awakenings.

Study or subgroup	LABA N	LABA Mean(SD)	Placebo N	Placebo Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
1.44.1 Participants using mixed cointerventions							
Wolfe 2000a	80	19 (28.6)	81	2 (19.8)		48.64%	17[9.39,24.61]
Wolfe 2000b	86	10 (24.1)	86	5 (19.5)		51.36%	5[-1.55,11.55]
Subtotal ***	**166**		**167**			**100%**	**10.84[-0.92,22.59]**
Heterogeneity: Tau^2=58.87; Chi^2=5.49, df=1(P=0.02); I^2=81.77%							
Test for overall effect: Z=1.81(P=0.07)							
1.44.2 Participants not using ICS							
Subtotal ***	**0**		**0**				**Not estimable**
Heterogeneity: Not applicable							
Test for overall effect: Not applicable							
1.44.3 Children <12 years							
Subtotal ***	**0**		**0**				**Not estimable**
Heterogeneity: Not applicable							
Test for overall effect: Not applicable							



Study or subgroup	LABA N	LABA Mean(SD)	Placebo N	Placebo Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
Total ***	**166**		**167**			**100%**	**10.84[-0.92,22.59]**
Heterogeneity: Tau²=58.87; Chi²=5.49, df=1(P=0.02); I²=81.77%							
Test for overall effect: Z=1.81(P=0.07)							
Test for subgroup differences: Not applicable							

Favours Placebo -100 -50 0 50 100 Favours LABA

Analysis 1.45. Comparison 1 Studies with parallel group design: efficacy outcomes, Outcome 45 % nights without asthma awakenings.

Study or subgroup	LABA N	LABA Mean(SD)	Placebo N	Placebo Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
1.45.1 Participants using mixed cointerventions							
Adinoff 1998	117	91.7 (0)	121	80.5 (0)			Not estimable
Bensch 2001	135	73 (0)	136	53 (0)			Not estimable
Busse 1998	215	70 (16.1)	227	49 (25.6)		12.32%	21[17.03,24.97]
D'Alonzo 1994	87	86 (25)	90	70 (34)		9.54%	16[7.23,24.77]
Dahl 1991a	171	100 (0)	172	70 (0)			Not estimable
Ekstrom 1998b	114	60 (0)	113	45 (0)			Not estimable
Jones 1994	282	36 (38)	145	21 (32)		10.73%	15[8.16,21.84]
Kemp 1998a	149	85 (23.2)	152	73 (28.4)		11.33%	12[6.15,17.85]
Kemp 1999	176	92.5 (22.2)	176	84 (22.2)		12%	8.5[3.87,13.13]
Lockey 1999	240	72 (27.1)	234	42 (38.2)		11.25%	30[24.02,35.98]
Pearlman 1992	67	89 (21)	63	78 (32)		9.17%	11[1.63,20.37]
Wolfe 2000a	166	84 (25.8)	167	71 (25.8)		11.5%	13[7.46,18.54]
Subtotal ***	**1919**		**1796**			**87.83%**	**15.93[10.84,21.02]**
Heterogeneity: Tau²=43.24; Chi²=41.28, df=7(P<0.0001); I²=83.04%							
Test for overall effect: Z=6.13(P<0.0001)							
1.45.2 Participants not using ICS							
Subtotal ***	**0**		**0**				**Not estimable**
Heterogeneity: Not applicable							
Test for overall effect: Not applicable							
1.45.3 Children <12 years							
Weinstein 1998	105	94.8 (11.1)	105	88.4 (19.5)		12.17%	6.4[2.11,10.69]
Subtotal ***	**105**		**105**			**12.17%**	**6.4[2.11,10.69]**
Heterogeneity: Not applicable							
Test for overall effect: Z=2.92(P=0)							
Total ***	**2024**		**1901**			**100%**	**14.76[9.68,19.84]**
Heterogeneity: Tau²=50.39; Chi²=57.93, df=8(P<0.0001); I²=86.19%							
Test for overall effect: Z=5.7(P<0.0001)							
Test for subgroup differences: Chi²=7.87, df=1 (P=0.01), I²=87.29%							

Favours Placebo -100 -50 0 50 100 Favours LABA

Analysis 1.46. Comparison 1 Studies with parallel group design: efficacy outcomes, Outcome 46 Change in % nighttime awakenings requiring no SABA.

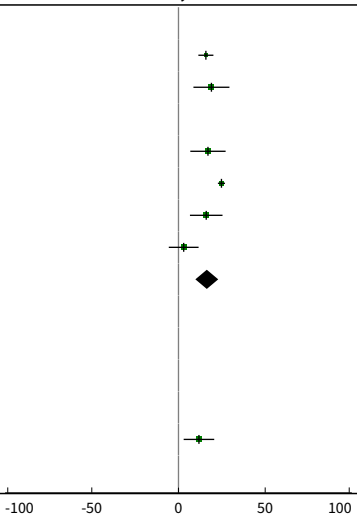
Study or subgroup	LABA N	LABA Mean(SD)	Placebo N	Placebo Mean(SD)	Mean Difference Random, 95% CI	Mean Difference Random, 95% CI
1.46.1 Participants using mixed cointerventions						
1.46.2 Participants not using ICS						
SAS30004	91	18.7 (0)	89	182 (0)		Not estimable
1.46.3 Children <12 years						
1.46.4 Unclear						
SLGA2004	63	14.4 (22.2)	63	9.2 (18.3)		5.2[-1.9,12.3]

Analysis 1.47. Comparison 1 Studies with parallel group design: efficacy outcomes, Outcome 47 N with <50% nights free from rescue medication.

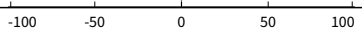
Study or subgroup	LABA n/N	Placebo n/N	Odds Ratio M-H, Fixed, 95% CI	Odds Ratio M-H, Fixed, 95% CI
1.47.1 Participants using mixed cointerventions				
1.47.2 Participants not using ICS				
SLMP03	1/7	0/11		5.31[0.19,150.08]
1.47.3 Children <12 years				

Analysis 1.48. Comparison 1 Studies with parallel group design: efficacy outcomes, Outcome 48 Change in % days without asthma symptoms.

Study or subgroup	LABA N	LABA Mean(SD)	Placebo N	Placebo Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
1.48.1 Participants using mixed cointerventions							
Busse 1998	258	24.3 (30.7)	269	8.5 (18.2)		11.75%	15.8[11.47,20.13]
D'Alonzo 1994	87	26 (41)	90	7 (28)		8.03%	19[8.62,29.38]
Nathan 1999	128	36 (0)	129	16 (0)			Not estimable
Pearlman 1992	67	21 (33)	63	4 (26)		8.15%	17[6.82,27.18]
SLGL82	45	63 (4.8)	45	38.2 (5.1)		12.71%	24.78[22.73,26.83]
Wolfe 2000a	80	22 (33.4)	81	6 (27)		8.63%	16[6.61,25.39]
Wolfe 2000b	86	15 (33.4)	86	12 (23.2)		9.14%	3[-5.59,11.59]
Subtotal ***	**751**		**763**			**58.42%**	**16.33[9.73,22.92]**
Heterogeneity: Tau^2=52.49; Chi^2=36.48, df=5(P<0.0001); I^2=86.29%							
Test for overall effect: Z=4.85(P<0.0001)							
1.48.2 Participants not using ICS							
Kavuru 2000a	77	8 (30.5)	86	-3.8 (26.4)		9%	11.8[2.99,20.61]
Nathan 1999	128	36 (0)	129	16 (0)			Not estimable

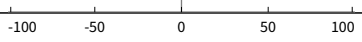


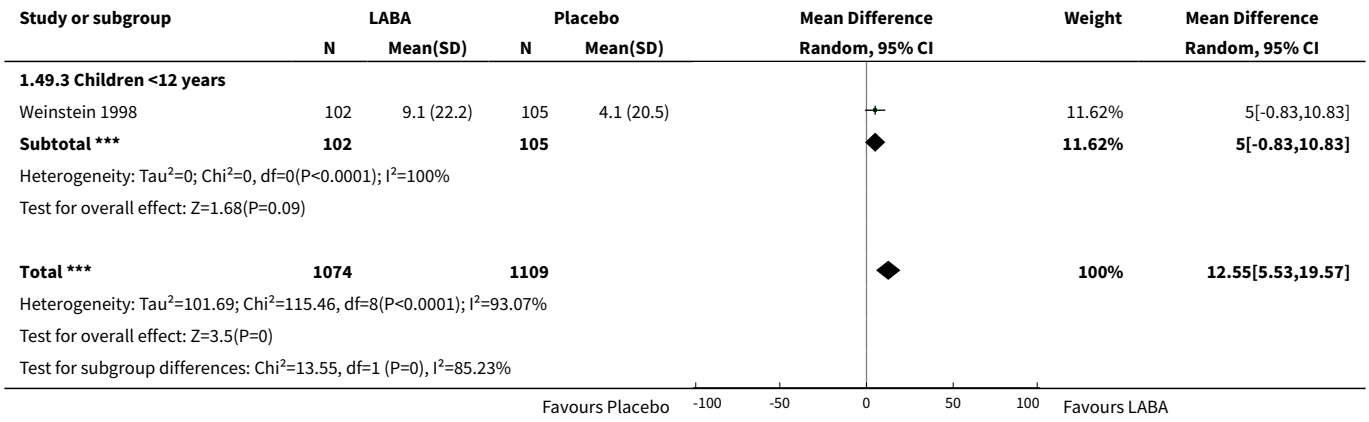
Study or subgroup	LABA N	LABA Mean(SD)	Placebo N	Placebo Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
Pearlman 1999a	21	22 (32.1)	23	2 (28.8)		4.51%	20[1.92,38.08]
Rosenthal 1999	202	20.9 (29.9)	206	7.6 (27.3)		11.06%	13.3[7.75,18.85]
SAS30004	91	14 (0)	89	-9.1 (0)			Not estimable
Shapiro 2000b	84	2.1 (33)	90	-7.9 (32.3)		8.43%	10[0.29,19.71]
Subtotal ***	**603**		**623**			**33%**	**12.73[8.61,16.84]**
Heterogeneity: Tau^2=0; Chi^2=1.01, df=3(P=0.8); I^2=0%							
Test for overall effect: Z=6.06(P<0.0001)							
1.48.3 Children <12 years							
Subtotal ***	**0**		**0**				**Not estimable**
Heterogeneity: Not applicable							
Test for overall effect: Not applicable							
1.48.4 Unclear							
SLGA2004	63	29.5 (33.3)	63	13.1 (19.1)		8.58%	16.4[6.92,25.88]
Subtotal ***	**63**		**63**			**8.58%**	**16.4[6.92,25.88]**
Heterogeneity: Not applicable							
Test for overall effect: Z=3.39(P=0)							
Total ***	**1417**		**1449**			**100%**	**15.26[10.51,20.01]**
Heterogeneity: Tau^2=45.15; Chi^2=53.99, df=10(P<0.0001); I^2=81.48%							
Test for overall effect: Z=6.29(P<0.0001)							
Test for subgroup differences: Chi^2=1.09, df=1 (P=0.58), I^2=0%							



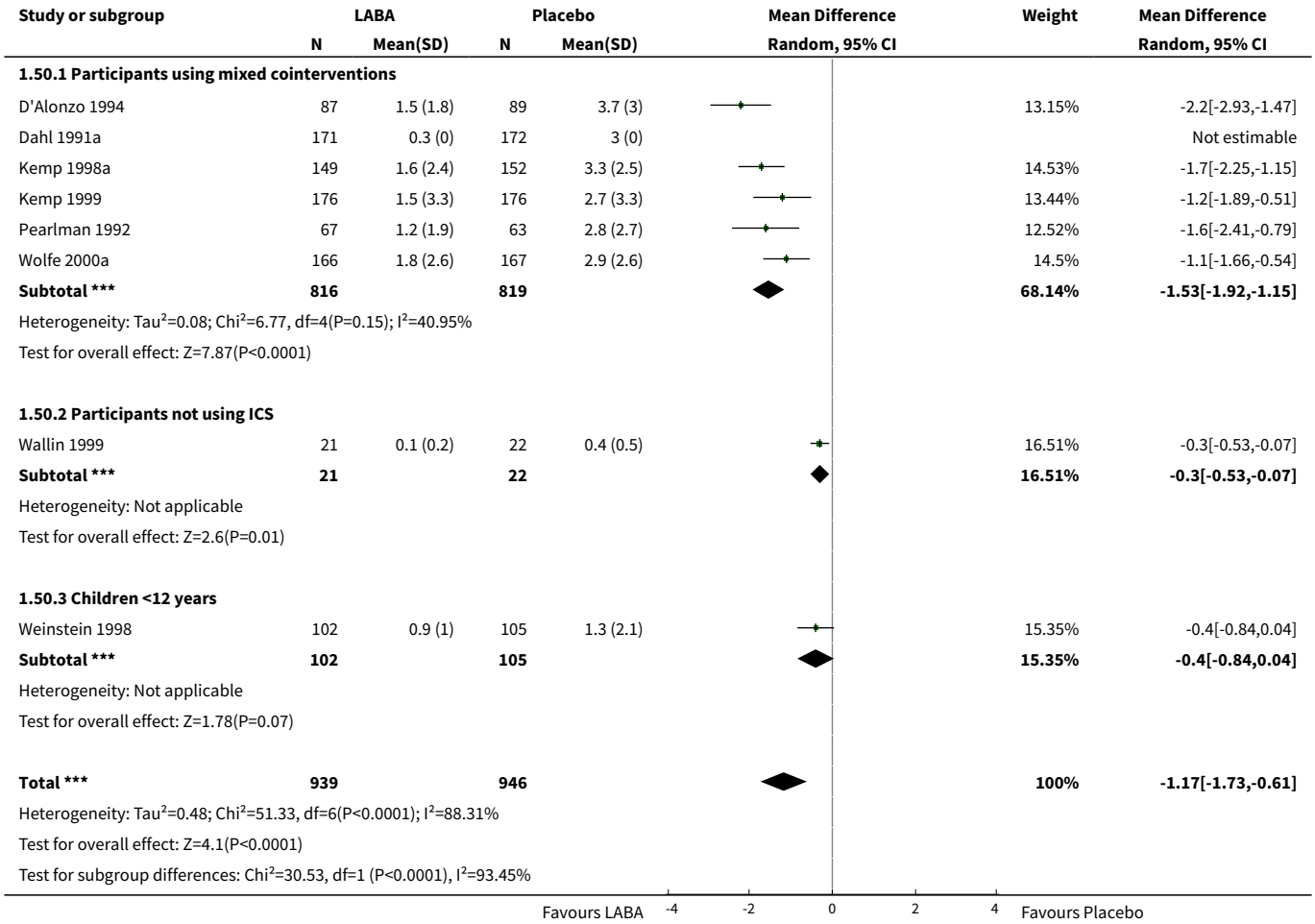
Analysis 1.49. Comparison 1 Studies with parallel group design: efficacy outcomes, Outcome 49 Change in % nights without asthma symptoms.

Study or subgroup	LABA N	LABA Mean(SD)	Placebo N	Placebo Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
1.49.1 Participants using mixed cointerventions							
Busse 1998	261	28.1 (33.5)	272	6.6 (26.7)		11.83%	21.5[16.35,26.65]
D'Alonzo 1994	87	24 (32)	90	5 (32)		10.29%	19[9.57,28.43]
Pearlman 1992	67	14 (27)	63	6 (31)		10.05%	8[-2.02,18.02]
SLGL82	45	63.5 (4.7)	45	37.7 (5.1)		12.5%	25.77[23.74,27.8]
Subtotal ***	**460**		**470**			**44.66%**	**19.94[13.64,26.25]**
Heterogeneity: Tau^2=29.73; Chi^2=14.52, df=3(P=0); I^2=79.34%							
Test for overall effect: Z=6.2(P<0.0001)							
1.49.2 Participants not using ICS							
Kavuru 2000a	77	-5.3 (23.8)	86	-16.5 (30)		10.74%	11.2[2.92,19.48]
Nathan 1999	128	15 (0)	129	4 (0)			Not estimable
Pearlman 1999a	21	10 (13.8)	23	2 (14.4)		10.72%	8[-0.33,16.33]
Rosenthal 1999	202	11.2 (24.2)	206	3.1 (18.7)		12.08%	8.1[3.91,12.29]
Shapiro 2000b	84	-8 (33)	90	-12 (32.3)		10.17%	4[-5.71,13.71]
Subtotal ***	**512**		**534**			**43.72%**	**8.1[4.88,11.32]**
Heterogeneity: Tau^2=0; Chi^2=1.22, df=3(P=0.75); I^2=0%							
Test for overall effect: Z=4.93(P<0.0001)							



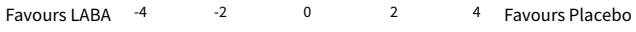


Analysis 1.50. Comparison 1 Studies with parallel group design: efficacy outcomes, Outcome 50 Rescue bronchodilator use: whole day.



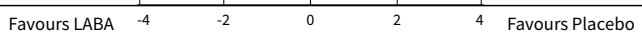
Analysis 1.51. Comparison 1 Studies with parallel group design: efficacy outcomes, Outcome 51 Rescue bronchodilator use: day time.

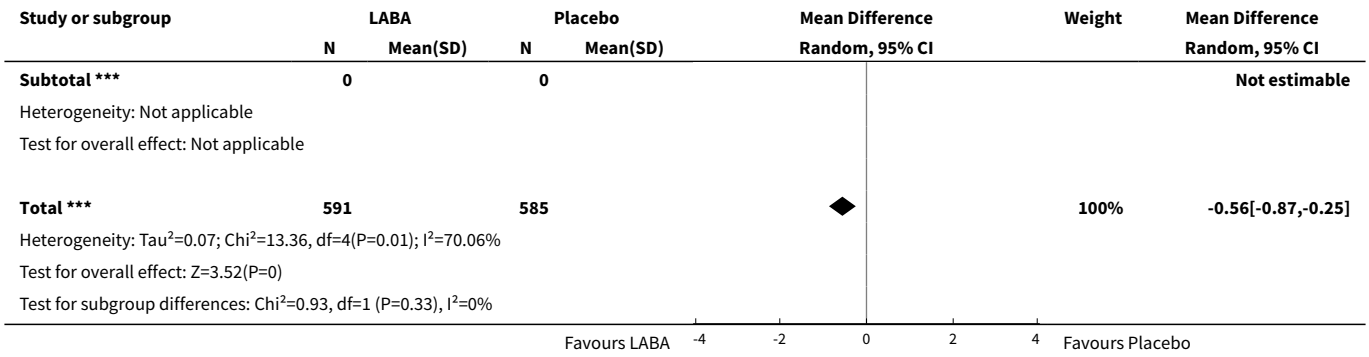
Study or subgroup	LABA N	LABA Mean(SD)	Placebo N	Placebo Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
1.51.1 Participants using mixed cointerventions							
Busse 1998	224	2.6 (2.5)	230	3.8 (2.5)		21.35%	-1.25[-1.71,-0.79]
Ekstrom 1998a	135	0.8 (1.2)	129	1 (1.3)		22.52%	-0.21[-0.51,0.09]
Ekstrom 1998b	114	1.2 (1.8)	113	1.9 (2.3)		20.65%	-0.66[-1.2,-0.12]
Steffensen 1995	103	0.8 (1.5)	101	2.8 (2.3)		20.68%	-2[-2.53,-1.47]
Subtotal ***	**576**		**573**			**85.21%**	**-1.02[-1.81,-0.22]**
Heterogeneity: Tau^2=0.59; Chi^2=37.96, df=3(P<0.0001); I^2=92.1%							
Test for overall effect: Z=2.52(P=0.01)							
1.51.2 Participants not using ICS							
Roberts 1999	12	0.5 (0.9)	11	1 (1.7)		14.79%	-0.56[-1.67,0.55]
Subtotal ***	**12**		**11**			**14.79%**	**-0.56[-1.67,0.55]**
Heterogeneity: Not applicable							
Test for overall effect: Z=0.99(P=0.32)							
1.51.3 Children <12 years							
Subtotal ***	**0**		**0**				**Not estimable**
Heterogeneity: Not applicable							
Test for overall effect: Not applicable							
Total ***	**588**		**584**			**100%**	**-0.95[-1.65,-0.25]**
Heterogeneity: Tau^2=0.54; Chi^2=38.1, df=4(P<0.0001); I^2=89.5%							
Test for overall effect: Z=2.65(P=0.01)							
Test for subgroup differences: Chi^2=0.43, df=1 (P=0.51), I^2=0%							



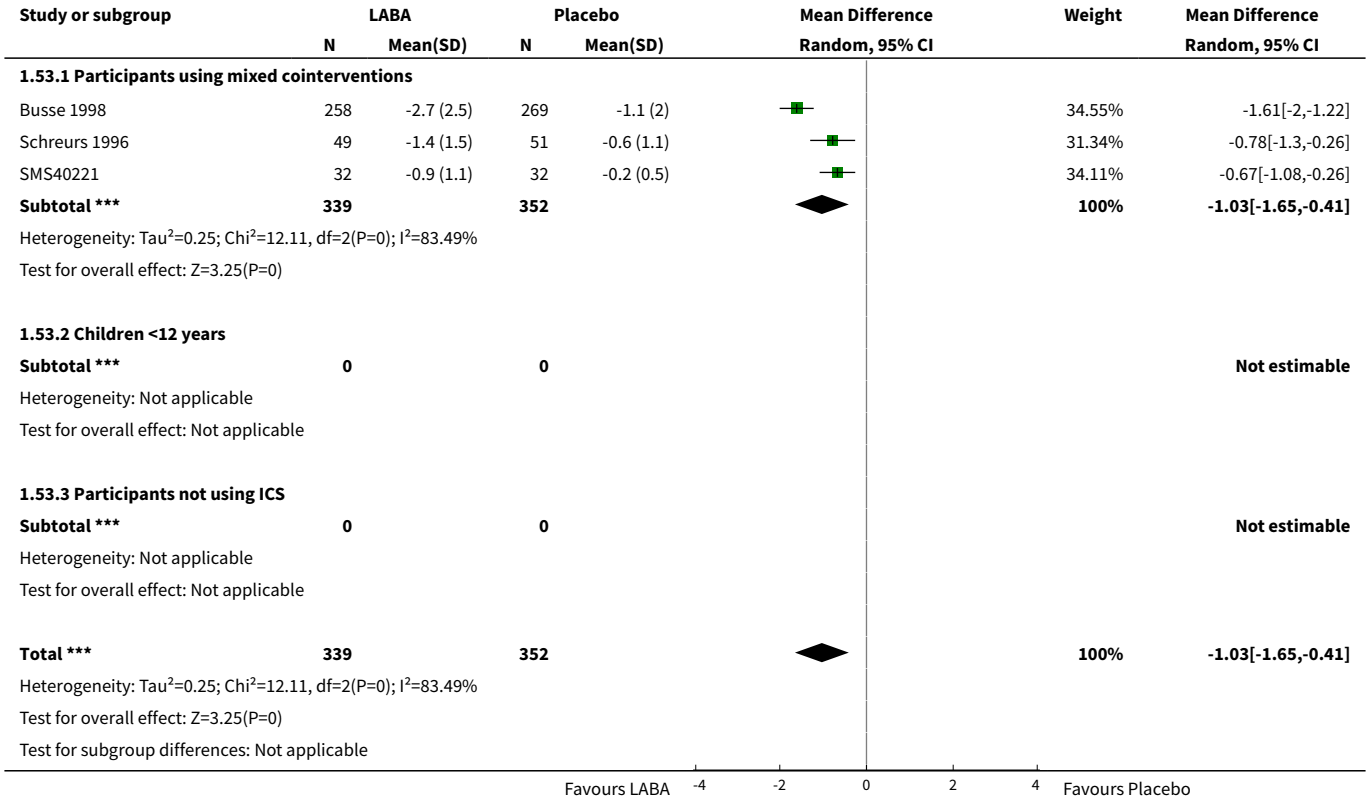
Analysis 1.52. Comparison 1 Studies with parallel group design: efficacy outcomes, Outcome 52 Rescue bronchodilator use: night time.

Study or subgroup	LABA N	LABA Mean(SD)	Placebo N	Placebo Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
1.52.1 Participants using mixed cointerventions							
Busse 1998	227	0.5 (0.9)	231	1.2 (1.3)		30.44%	-0.64[-0.84,-0.44]
Ekstrom 1998a	135	0.4 (0.7)	129	0.6 (1)		30.05%	-0.22[-0.43,-0.01]
Ekstrom 1998b	114	1 (1.8)	113	1.7 (2.1)		17.98%	-0.7[-1.21,-0.19]
Steffensen 1995	103	0.4 (1)	101	1.4 (2.5)		17.46%	-1[-1.52,-0.48]
Subtotal ***	**579**		**574**			**95.92%**	**-0.59[-0.91,-0.27]**
Heterogeneity: Tau^2=0.07; Chi^2=12.62, df=3(P=0.01); I^2=76.22%							
Test for overall effect: Z=3.58(P=0)							
1.52.2 Participants not using ICS							
Roberts 1999	12	1 (1.7)	11	0.9 (1.8)		4.08%	0.14[-1.3,1.58]
Subtotal ***	**12**		**11**			**4.08%**	**0.14[-1.3,1.58]**
Heterogeneity: Not applicable							
Test for overall effect: Z=0.19(P=0.85)							
1.52.3 Children <12 years							

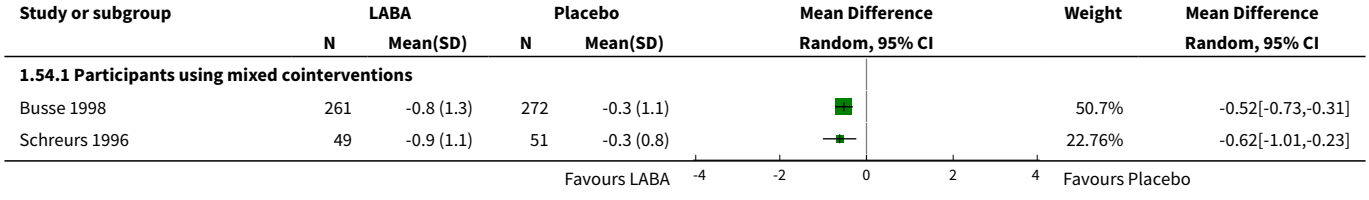




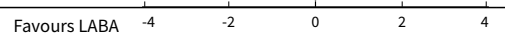
Analysis 1.53. Comparison 1 Studies with parallel group design: efficacy outcomes, Outcome 53 Change in use of rescue bronchodilator/day.



Analysis 1.54. Comparison 1 Studies with parallel group design: efficacy outcomes, Outcome 54 Change in use of rescue bronchodilator/night.

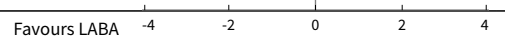


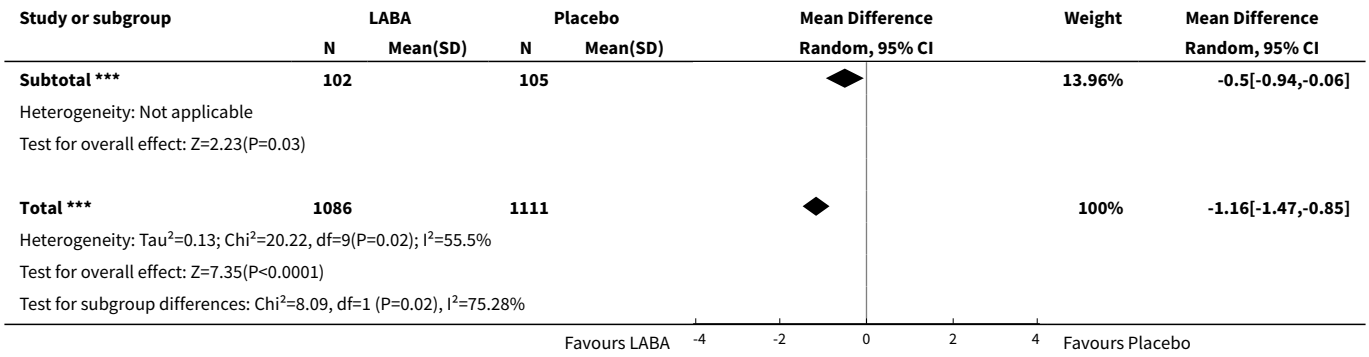
Study or subgroup	LABA N	LABA Mean(SD)	Placebo N	Placebo Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
SMS40221	32	-0.5 (0.7)	32	-0.3 (0.7)		26.54%	-0.21[-0.56,0.14]
Subtotal ***	**342**		**355**			**100%**	**-0.46[-0.67,-0.25]**
Heterogeneity: Tau²=0.01; Chi²=2.95, df=2(P=0.23); I²=32.2%							
Test for overall effect: Z=4.3(P<0.0001)							
1.54.2 Participants not using ICS							
Subtotal ***	**0**		**0**				**Not estimable**
Heterogeneity: Not applicable							
Test for overall effect: Not applicable							
1.54.3 Children <12 years							
Subtotal ***	**0**		**0**				**Not estimable**
Heterogeneity: Not applicable							
Test for overall effect: Not applicable							
Total ***	**342**		**355**			**100%**	**-0.46[-0.67,-0.25]**
Heterogeneity: Tau²=0.01; Chi²=2.95, df=2(P=0.23); I²=32.2%							
Test for overall effect: Z=4.3(P<0.0001)							
Test for subgroup differences: Not applicable							



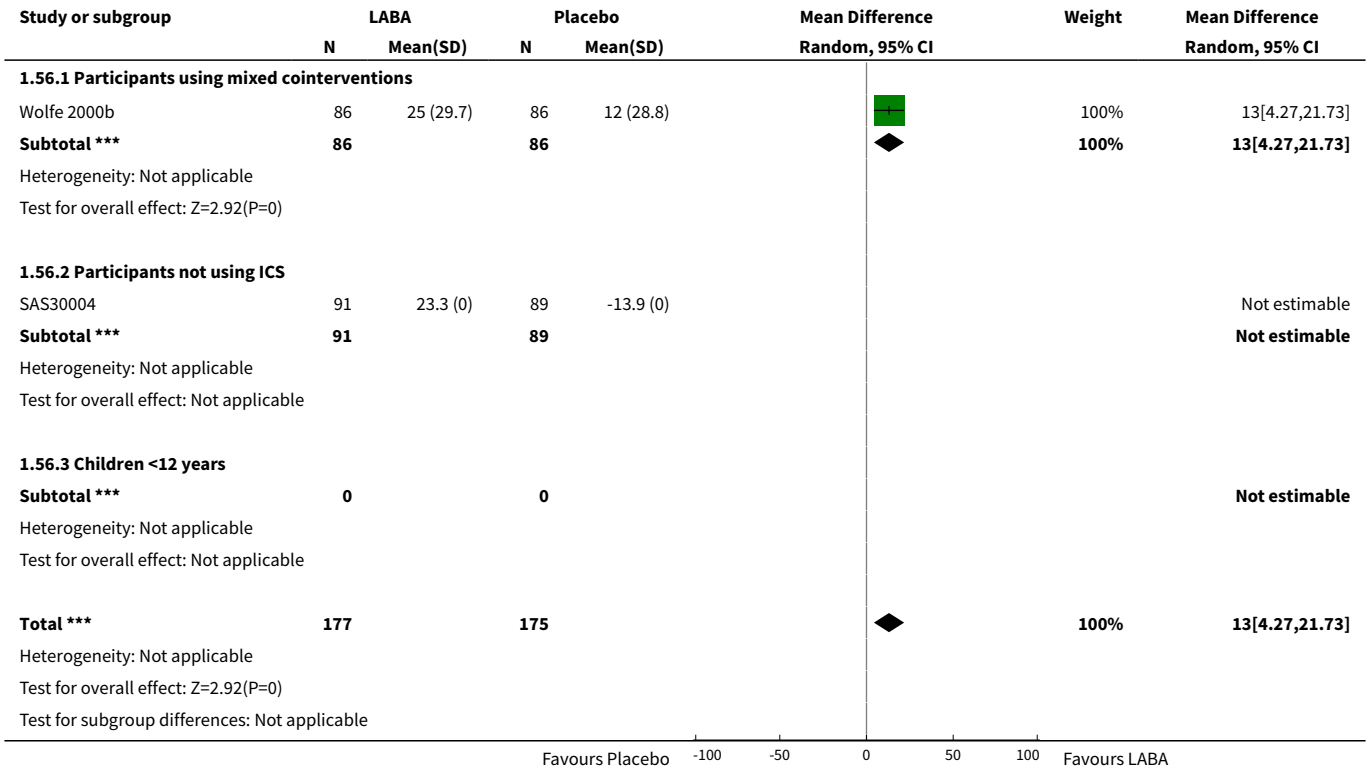
Analysis 1.55. Comparison 1 Studies with parallel group design: efficacy outcomes, Outcome 55 Change in use of rescue bronchodilator/ whole day.

Study or subgroup	LABA N	LABA Mean(SD)	Placebo N	Placebo Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
1.55.1 Participants using mixed cointerventions							
Adinoff 1998	117	-2.3 (0)	121	-1.1 (0)			Not estimable
D'Alonzo 1994	67	-2.7 (3.1)	74	-0.6 (2.8)		6.62%	-2.1[-3.08,-1.12]
Pearlman 1992	67	-2.6 (2.6)	63	-0.9 (2.3)		7.97%	-1.7[-2.54,-0.86]
Wolfe 2000a	80	-1.8 (2.7)	81	-0.7 (1.8)		9.67%	-1.1[-1.81,-0.39]
Wolfe 2000b	86	-1.6 (1.9)	86	-0.7 (1.9)		11.97%	-0.9[-1.45,-0.35]
Subtotal ***	**417**		**425**			**36.23%**	**-1.35[-1.86,-0.83]**
Heterogeneity: Tau²=0.13; Chi²=5.69, df=3(P=0.13); I²=47.31%							
Test for overall effect: Z=5.13(P<0.0001)							
1.55.2 Participants not using ICS							
Kavuru 2000a	77	-0.3 (2.4)	86	1.7 (2.3)		9.45%	-2[-2.72,-1.28]
Pearlman 1999a	21	-1.1 (1.8)	23	-0.2 (1.4)		6.79%	-0.9[-1.86,0.06]
Rosenthal 1999	202	-1.5 (2.1)	206	-0.3 (1.9)		14.85%	-1.18[-1.57,-0.79]
SAS30003	92	-0.8 (2.4)	87	0.2 (1.9)		10.79%	-1[-1.63,-0.37]
SAS30004	91	-0.9 (0)	89	1.6 (0)			Not estimable
Shapiro 2000b	84	0 (2.8)	90	0.9 (2.9)		7.93%	-0.9[-1.75,-0.05]
Subtotal ***	**567**		**581**			**49.81%**	**-1.22[-1.57,-0.86]**
Heterogeneity: Tau²=0.05; Chi²=5.96, df=4(P=0.2); I²=32.89%							
Test for overall effect: Z=6.63(P<0.0001)							
1.55.3 Children <12 years							
Weinstein 1998	102	-0.8 (2)	105	-0.3 (1)		13.96%	-0.5[-0.94,-0.06]

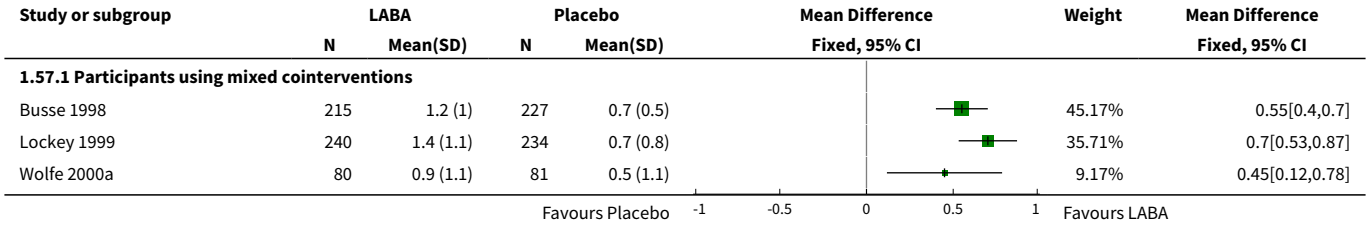


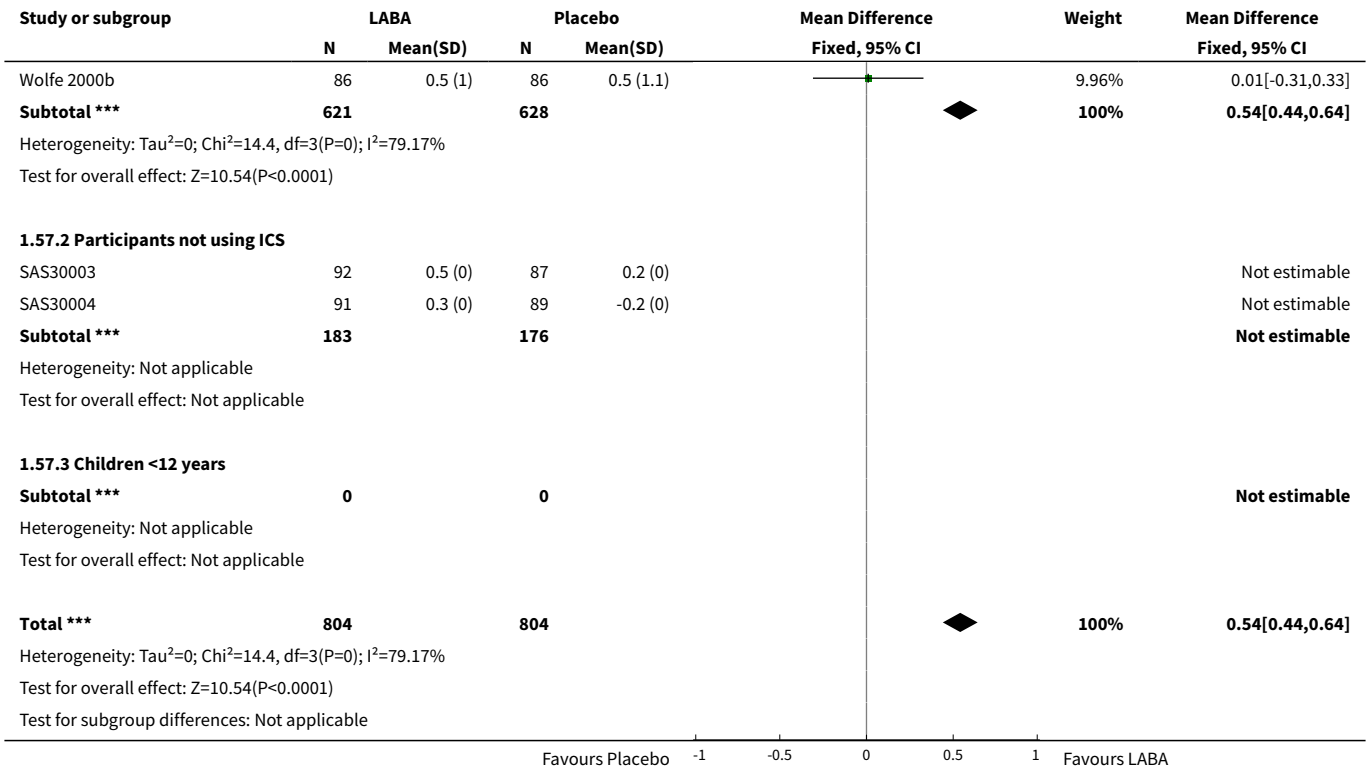


Analysis 1.56. Comparison 1 Studies with parallel group design: efficacy outcomes, Outcome 56 Change in % days without rescue medication.

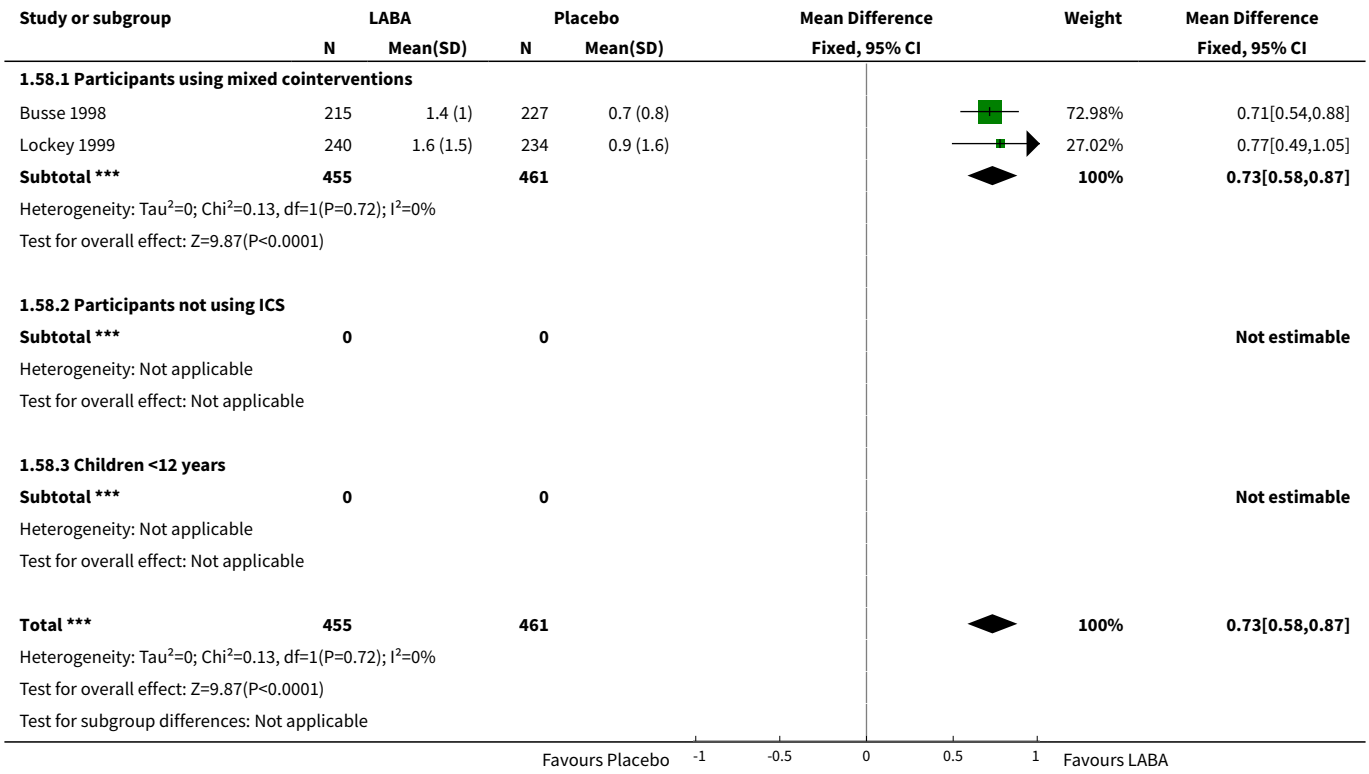


Analysis 1.57. Comparison 1 Studies with parallel group design: efficacy outcomes, Outcome 57 AQOL- Change in Quality of life score: global.



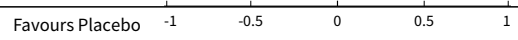


Analysis 1.58. Comparison 1 Studies with parallel group design: efficacy outcomes, Outcome 58 Change in Quality of life score- symptoms.



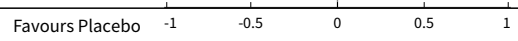
Analysis 1.59. Comparison 1 Studies with parallel group design: efficacy outcomes, Outcome 59 Change in Quality of life score: emotions.

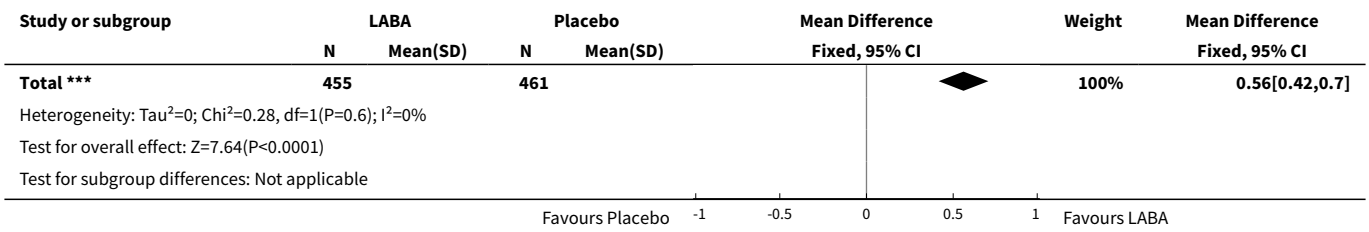
Study or subgroup	LABA N	LABA Mean(SD)	Placebo N	Placebo Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
1.59.1 Participants using mixed cointerventions							
Busse 1998	215	1.2 (1.3)	227	0.7 (0.9)		67.62%	0.57[0.36,0.78]
Lockey 1999	240	1.4 (1.8)	234	0.5 (1.6)		32.38%	0.84[0.53,1.15]
Subtotal ***	**455**		**461**			**100%**	**0.66[0.48,0.83]**
Heterogeneity: Tau^2=0; Chi^2=2.02, df=1(P=0.15); I^2=50.55%							
Test for overall effect: Z=7.4(P<0.0001)							
1.59.2 Participants not using ICS							
Subtotal ***	**0**		**0**				**Not estimable**
Heterogeneity: Not applicable							
Test for overall effect: Not applicable							
1.59.3 Children <12 years							
Subtotal ***	**0**		**0**				**Not estimable**
Heterogeneity: Not applicable							
Test for overall effect: Not applicable							
Total ***	**455**		**461**			**100%**	**0.66[0.48,0.83]**
Heterogeneity: Tau^2=0; Chi^2=2.02, df=1(P=0.15); I^2=50.55%							
Test for overall effect: Z=7.4(P<0.0001)							
Test for subgroup differences: Not applicable							



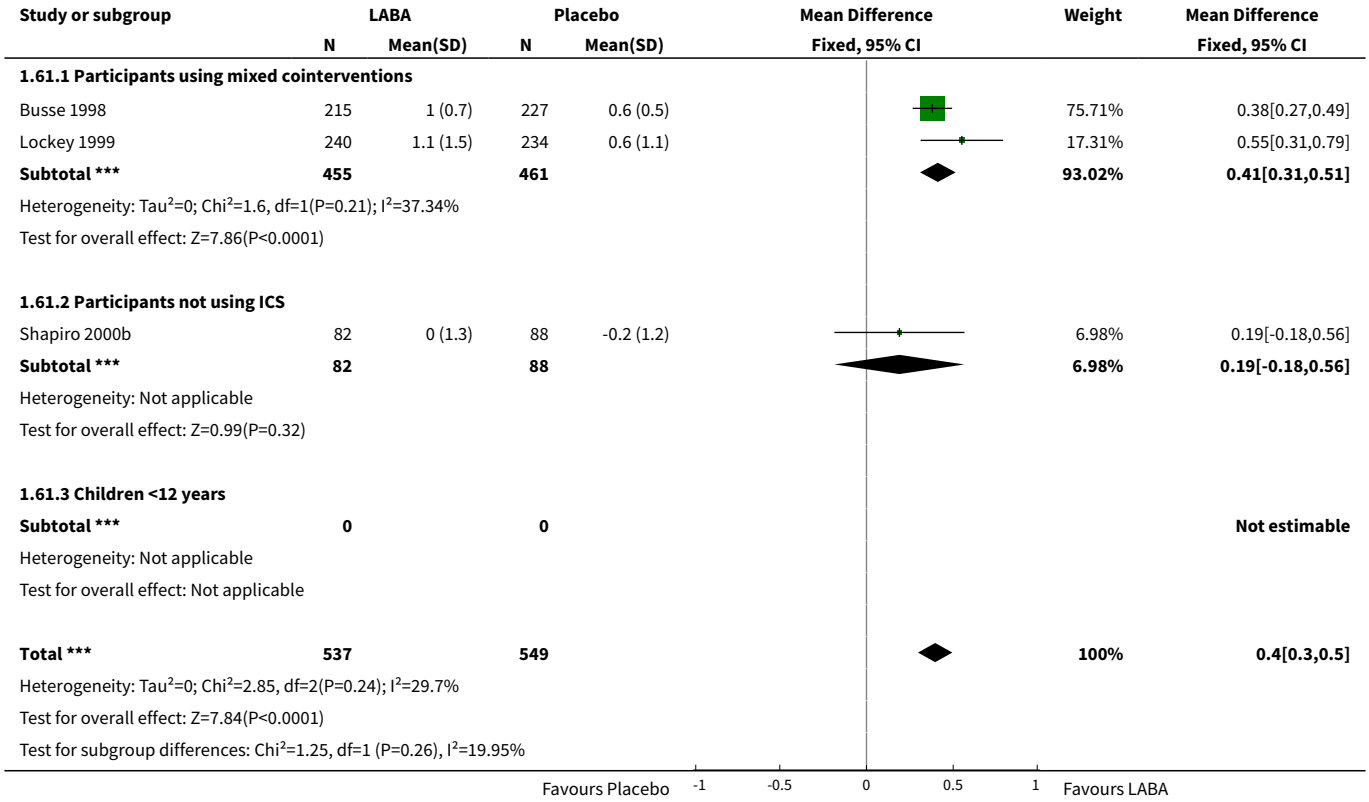
Analysis 1.60. Comparison 1 Studies with parallel group design: efficacy outcomes, Outcome 60 Change in Quality of life score: exposure to environmental stimuli.

Study or subgroup	LABA N	LABA Mean(SD)	Placebo N	Placebo Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
1.60.1 Participants using mixed cointerventions							
Busse 1998	215	1.1 (1)	227	0.6 (0.9)		63.05%	0.53[0.35,0.71]
Lockey 1999	240	1.2 (1.4)	234	0.6 (1.2)		36.95%	0.61[0.37,0.85]
Subtotal ***	**455**		**461**			**100%**	**0.56[0.42,0.7]**
Heterogeneity: Tau^2=0; Chi^2=0.28, df=1(P=0.6); I^2=0%							
Test for overall effect: Z=7.64(P<0.0001)							
1.60.2 Participants not using ICS							
Subtotal ***	**0**		**0**				**Not estimable**
Heterogeneity: Not applicable							
Test for overall effect: Not applicable							
1.60.3 Children <12 years							
Subtotal ***	**0**		**0**				**Not estimable**
Heterogeneity: Not applicable							
Test for overall effect: Not applicable							

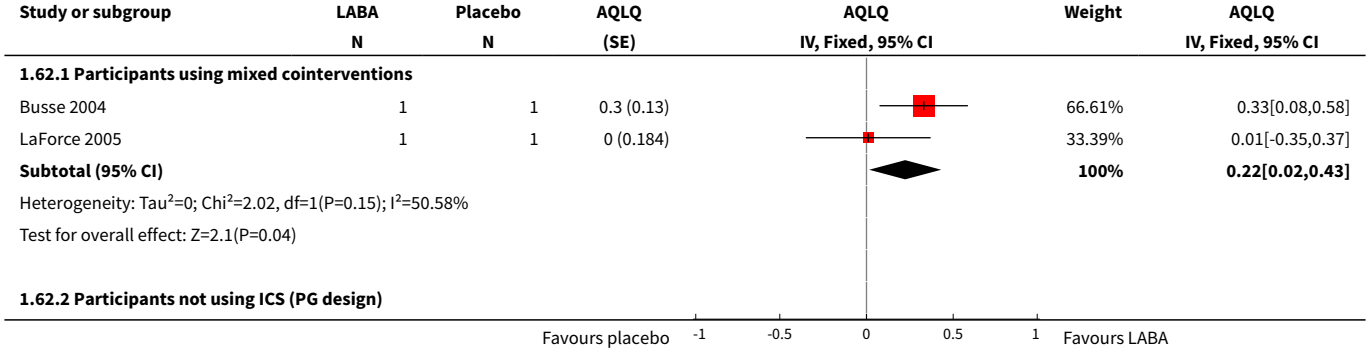


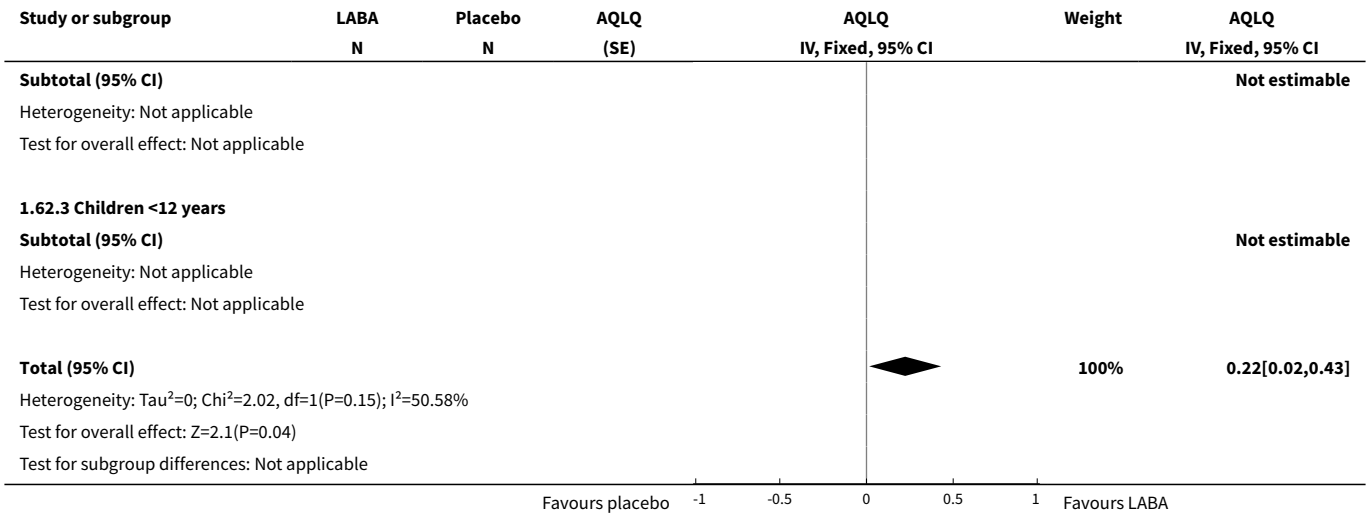


Analysis 1.61. Comparison 1 Studies with parallel group design: efficacy outcomes, Outcome 61 Change in Quality of life score: activity limitations.

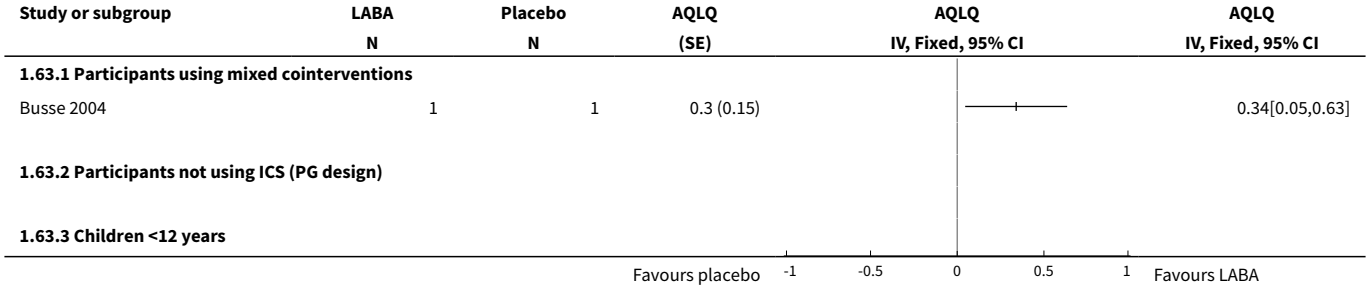


Analysis 1.62. Comparison 1 Studies with parallel group design: efficacy outcomes, Outcome 62 Mini AQLQ (Total).

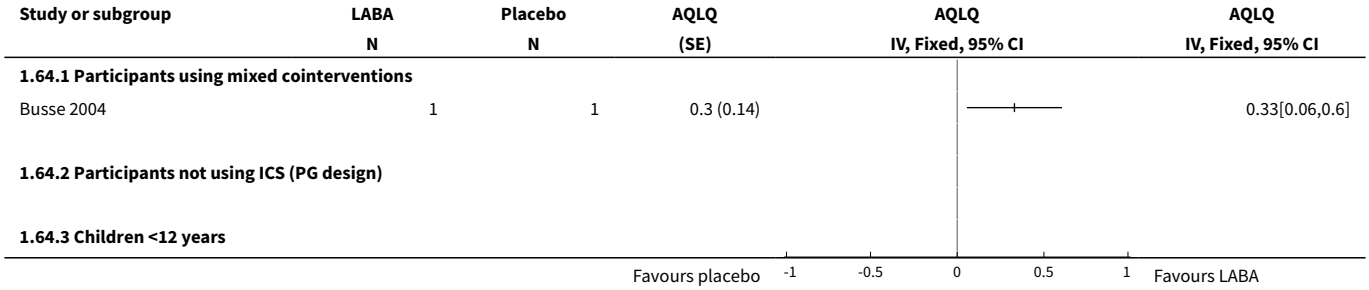




Analysis 1.63. Comparison 1 Studies with parallel group design: efficacy outcomes, Outcome 63 Mini AQLQ (Symptoms).

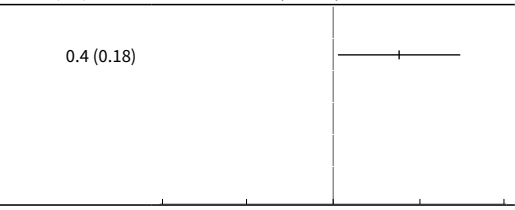


Analysis 1.64. Comparison 1 Studies with parallel group design: efficacy outcomes, Outcome 64 Mini AQLQ (Activity limitation).



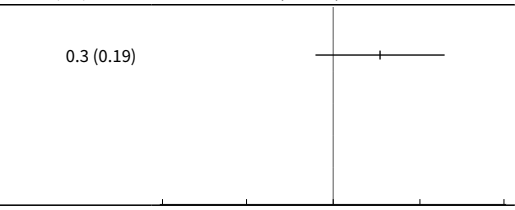
Analysis 1.65. Comparison 1 Studies with parallel group design: efficacy outcomes, Outcome 65 Mini AQLQ (Emotional function).

Study or subgroup	LABA N	Placebo N	AQLQ (SE)	AQLQ IV, Fixed, 95% CI	AQLQ IV, Fixed, 95% CI
1.65.1 Participants using mixed cointerventions					
Busse 2004	1	1	0.4 (0.18)		0.38[0.03,0.73]
1.65.2 Participants not using ICS					
1.65.3 Children <12 years					



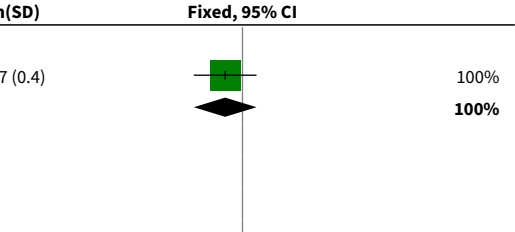
Analysis 1.66. Comparison 1 Studies with parallel group design: efficacy outcomes, Outcome 66 Mini AQLQ (Environmental stimuli).

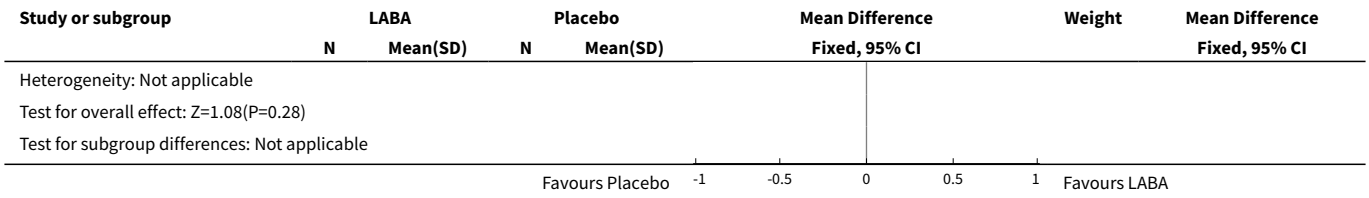
Study or subgroup	LABA N	Placebo N	AQLQ (SE)	AQLQ IV, Fixed, 95% CI	AQLQ IV, Fixed, 95% CI
1.66.1 Participants using mixed cointerventions					
Busse 2004	1	1	0.3 (0.19)		0.27[-0.1,0.64]
1.66.2 Participants not using ICS					
1.66.3 Children <12 years					



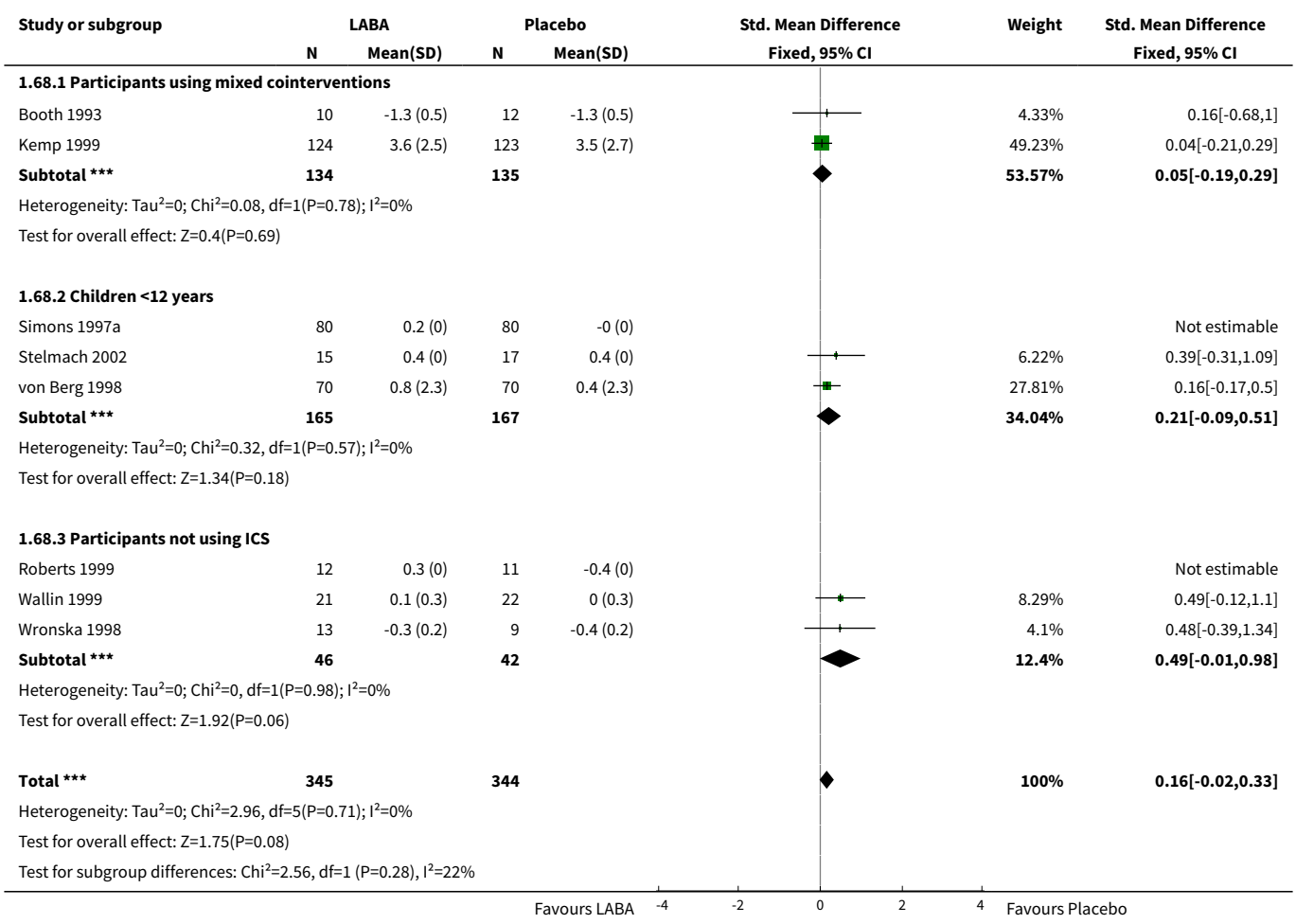
Analysis 1.67. Comparison 1 Studies with parallel group design: efficacy outcomes, Outcome 67 Quality of life score: COMBINED ALL SCALES.

Study or subgroup	LABA N	LABA Mean(SD)	Placebo N	Placebo Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
1.67.1 Participants using mixed cointerventions							
Hyland 1994	41	0.6 (0.4)	38	0.7 (0.4)		100%	-0.1[-0.28,0.08]
Subtotal ***	**41**		**38**			**100%**	**-0.1[-0.28,0.08]**
Heterogeneity: Not applicable							
Test for overall effect: Z=1.08(P=0.28)							
1.67.2 Subjects not using ICS							
Subtotal ***	**0**		**0**				**Not estimable**
Heterogeneity: Not applicable							
Test for overall effect: Not applicable							
1.67.3 Children <12 years							
Mahajan 1998	102	9 (0)	105	1 (0)			Not estimable
Subtotal ***	**102**		**105**				**Not estimable**
Heterogeneity: Not applicable							
Test for overall effect: Not applicable							
Total ***	**143**		**143**			**100%**	**-0.1[-0.28,0.08]**

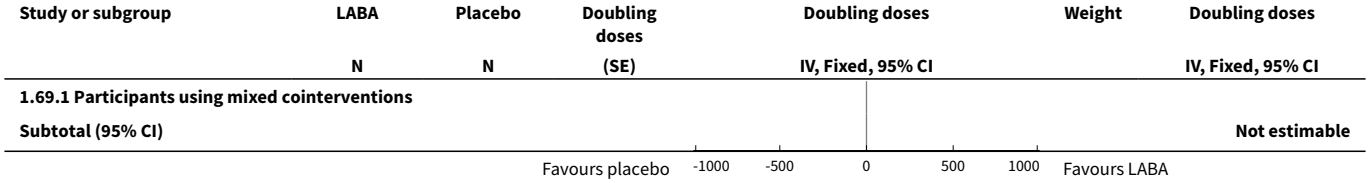




Analysis 1.68. Comparison 1 Studies with parallel group design: efficacy outcomes, Outcome 68 Bronchial hyperreactivity- log PD20/PC20 methacholine or histamine.



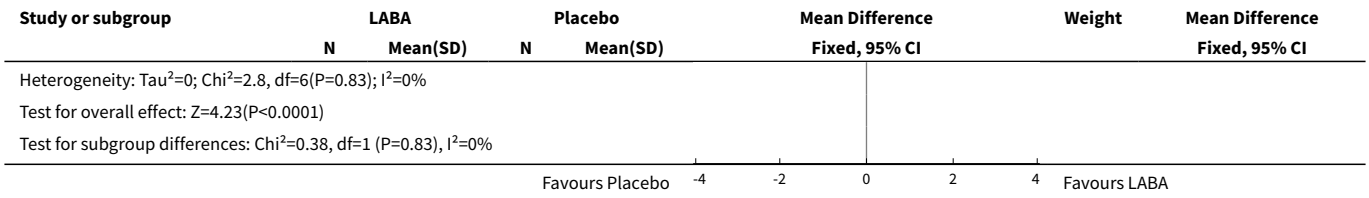
Analysis 1.69. Comparison 1 Studies with parallel group design: efficacy outcomes, Outcome 69 Bronchial hyperreactivity- log PD20/PC20 methacholine or histamine.



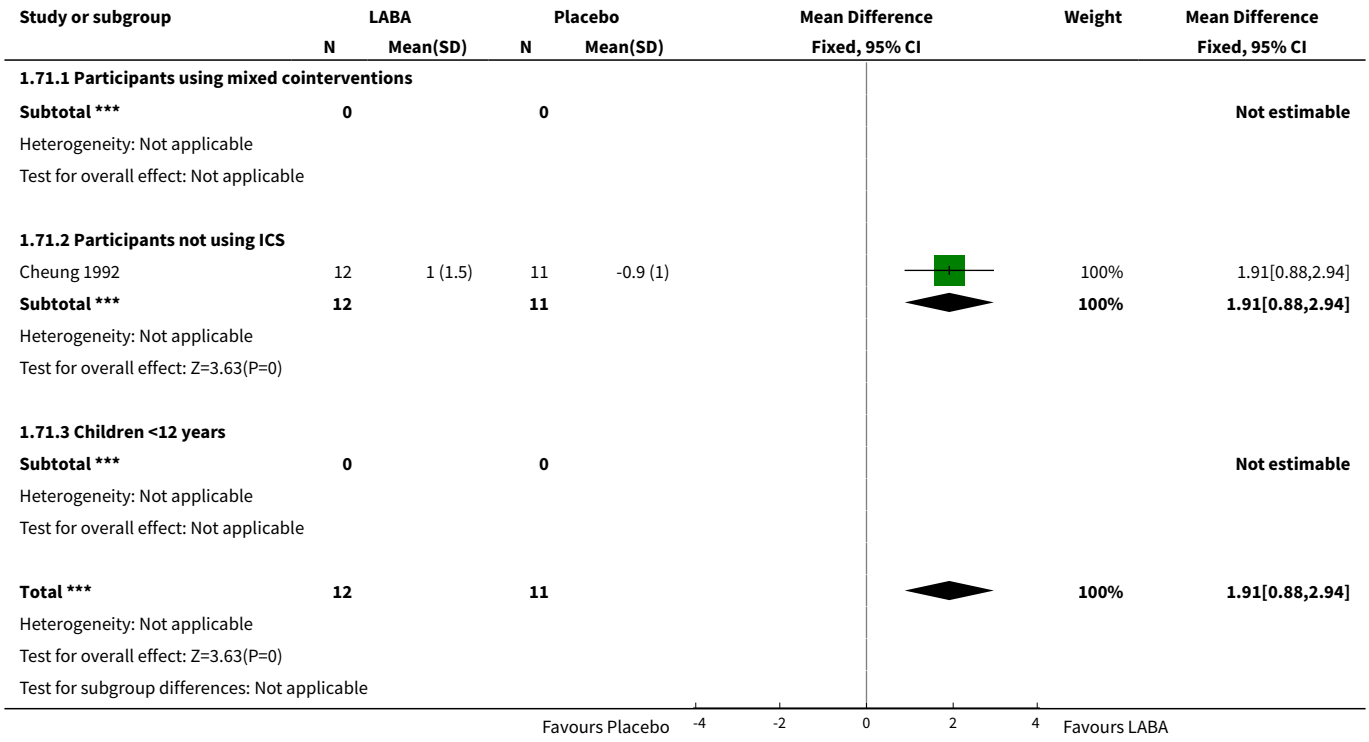
Study or subgroup	LABA N	Placebo N	Doubling doses (SE)	Doubling doses IV, Fixed, 95% CI	Weight	Doubling doses IV, Fixed, 95% CI
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						
1.69.2 Participants not using ICS						
SLMP03	11	13	-0 (0.104)		100%	-0.01[-0.21,0.19]
Subtotal (95% CI)					**100%**	**-0.01[-0.21,0.19]**
Heterogeneity: Not applicable						
Test for overall effect: Z=0.1(P=0.92)						
1.69.3 Children <12 years						
Subtotal (95% CI)						**Not estimable**
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						
Total (95% CI)					**100%**	**-0.01[-0.21,0.19]**
Heterogeneity: Not applicable						
Test for overall effect: Z=0.1(P=0.92)						
Test for subgroup differences: Not applicable						

Analysis 1.70. Comparison 1 Studies with parallel group design: efficacy outcomes, Outcome 70 Change in BHR (end treatment vs. baseline)- doubling doses (DD).

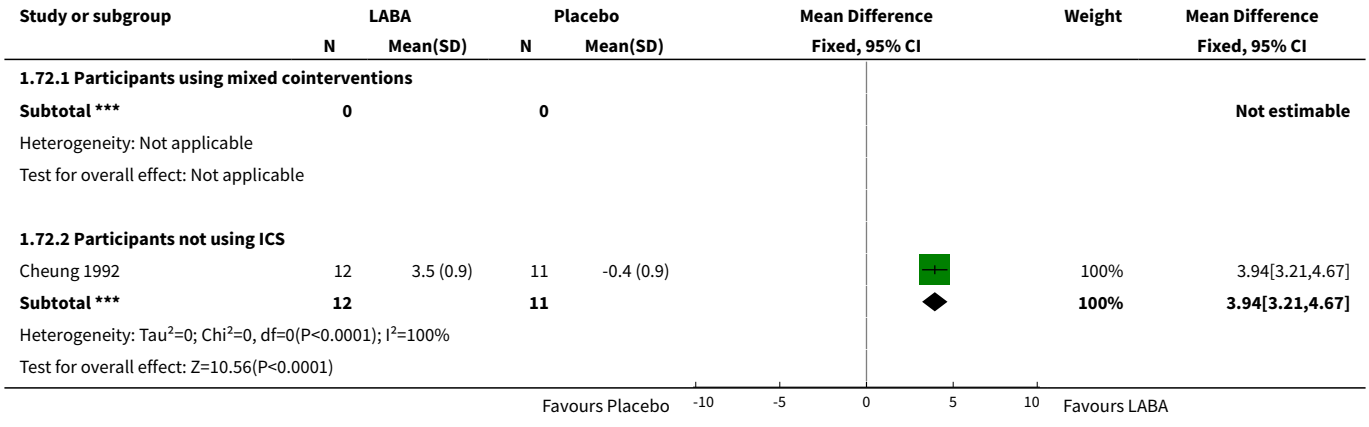
Study or subgroup	LABA N	LABA Mean(SD)	Placebo N	Placebo Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
1.70.1 Participants using mixed cointerventions							
Booth 1993	10	0.6 (1.6)	12	-0.1 (0.7)		6.03%	0.7[-0.35,1.75]
Kemp 1999	132	1.1 (2.4)	123	0.7 (2.2)		20.75%	0.38[-0.19,0.95]
Subtotal ***	**142**		**135**			**26.78%**	**0.45[-0.05,0.95]**
Heterogeneity: Tau^2=0; Chi^2=0.27, df=1(P=0.6); I^2=0%							
Test for overall effect: Z=1.77(P=0.08)							
1.70.2 Children <12 years							
von Berg 1998	20	0.5 (1.3)	22	0.1 (1.4)		9.97%	0.45[-0.37,1.27]
Subtotal ***	**20**		**22**			**9.97%**	**0.45[-0.37,1.27]**
Heterogeneity: Not applicable							
Test for overall effect: Z=1.08(P=0.28)							
1.70.3 Participants not using ICS							
Boulet 1997	7	0 (0.7)	6	-0.1 (1.1)		5.99%	0.16[-0.9,1.22]
Nathan 1999	128	1.3 (2.9)	129	0.2 (3.3)		11.52%	1.05[0.29,1.81]
Prieto 2002	14	-0.2 (1.9)	13	-1 (1.4)		4.26%	0.8[-0.45,2.05]
Rosenthal 1999	202	1 (2)	206	0.5 (2.2)		41.49%	0.55[0.15,0.95]
Subtotal ***	**351**		**354**			**63.26%**	**0.62[0.3,0.95]**
Heterogeneity: Tau^2=0; Chi^2=2.14, df=3(P=0.54); I^2=0%							
Test for overall effect: Z=3.74(P=0)							
Total ***	**513**		**511**			**100%**	**0.56[0.3,0.82]**



Analysis 1.71. Comparison 1 Studies with parallel group design: efficacy outcomes, Outcome 71 Bronchoprotection to methacholine challenge(protection ratio end treatment vs. baseline)- doubling doses (DD).



Analysis 1.72. Comparison 1 Studies with parallel group design: efficacy outcomes, Outcome 72 Bronchoprotection to methacholine challenge (protection ratio first dose treatment vs. baseline)- double dose.



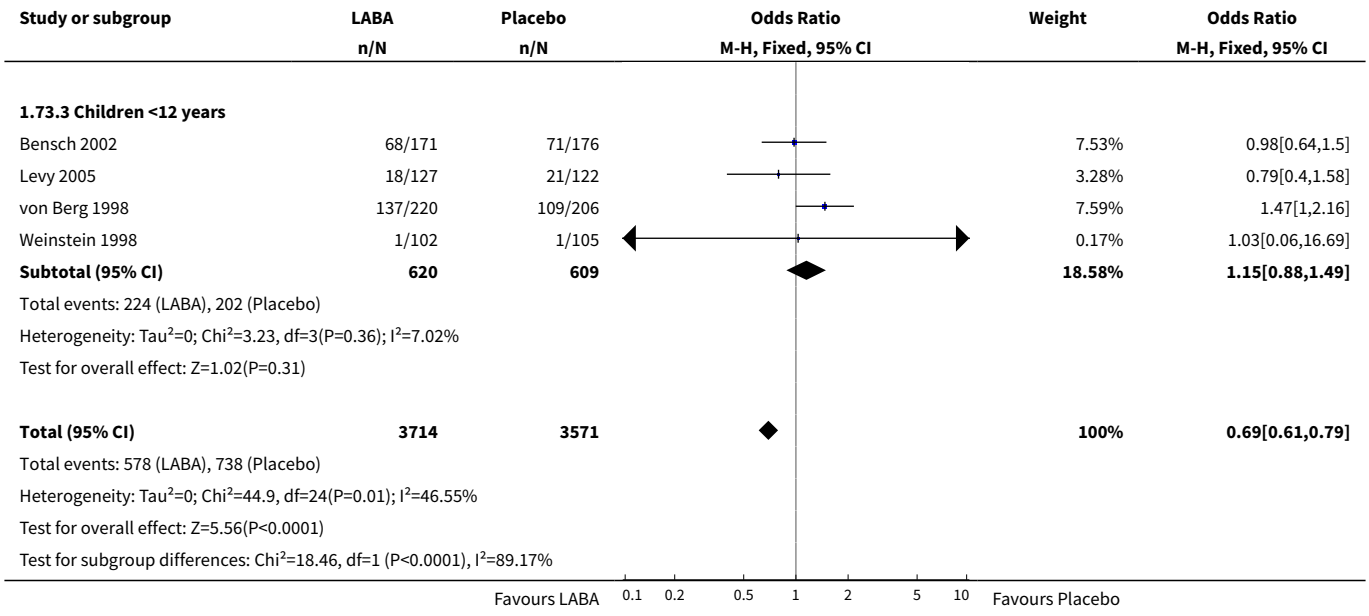
Study or subgroup	LABA N	LABA Mean(SD)	Placebo N	Placebo Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
1.72.3 Children <12 years							
Subtotal ***	**0**		**0**				**Not estimable**
Heterogeneity: Not applicable							
Test for overall effect: Not applicable							
Total ***	**12**		**11**			**100%**	**3.94[3.21,4.67]**
Heterogeneity: Tau²=0; Chi²=0, df=0(P<0.0001); I²=100%							
Test for overall effect: Z=10.56(P<0.0001)							
Test for subgroup differences: Not applicable							

Favours Placebo -10 -5 0 5 10 Favours LABA

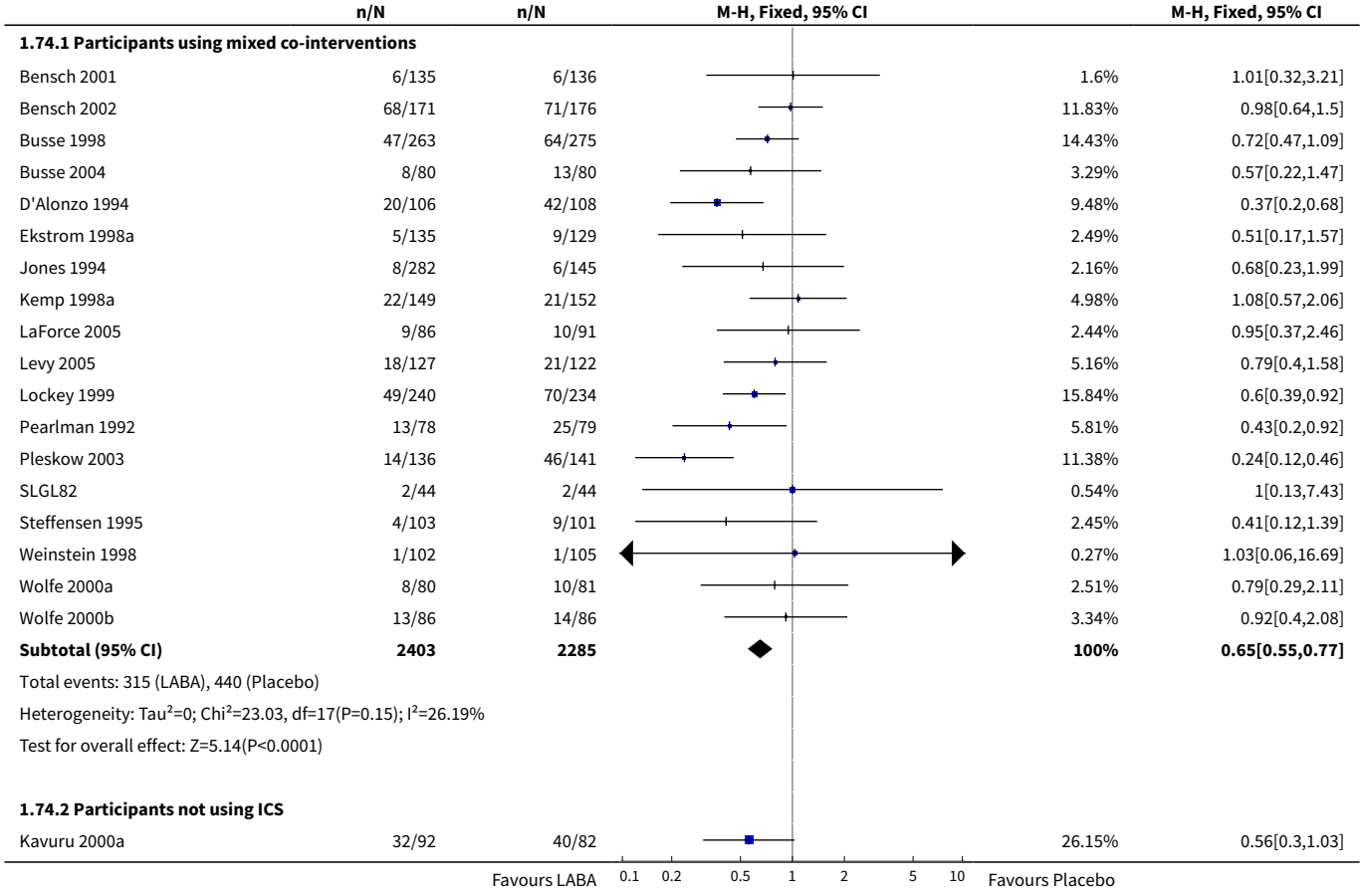
Analysis 1.73. Comparison 1 Studies with parallel group design: efficacy outcomes, Outcome 73 Exacerbations asthma - >1 major.

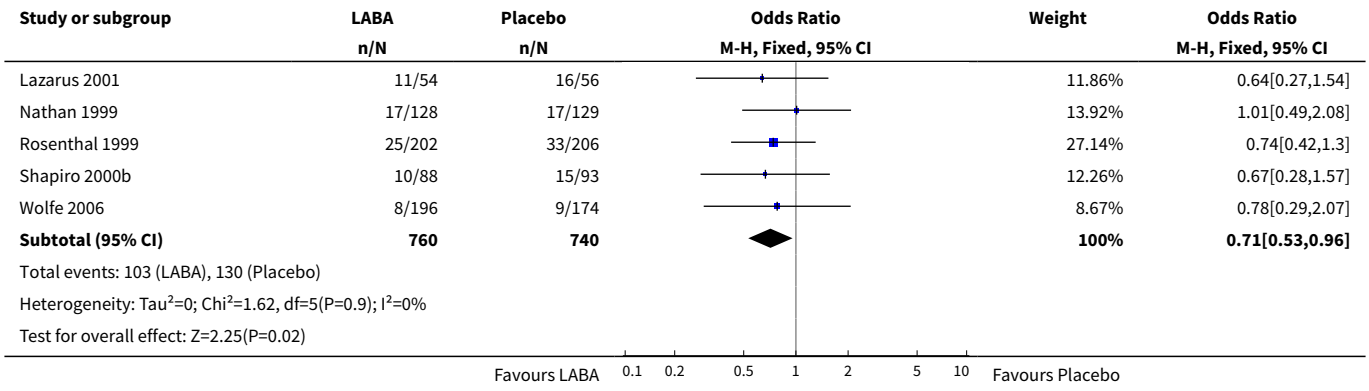
Study or subgroup	LABA n/N	Placebo n/N	Odds Ratio M-H, Fixed, 95% CI	Weight	Odds Ratio M-H, Fixed, 95% CI
1.73.1 Adults- Similar definition of exacerbation					
Bensch 2001	6/135	6/136		1.02%	1.01[0.32,3.21]
D'Alonzo 1994	20/106	42/108		6.03%	0.37[0.2,0.68]
Kavuru 2000a	32/92	40/82		4.93%	0.56[0.3,1.03]
Kemp 1998a	22/149	21/152		3.17%	1.08[0.57,2.06]
Lazarus 2001	11/54	16/56		2.23%	0.64[0.27,1.54]
Lockey 1999	49/240	70/234		10.08%	0.6[0.39,0.92]
Nathan 1999	17/128	17/129		2.62%	1.01[0.49,2.08]
Pearlman 1992	13/78	25/79		3.7%	0.43[0.2,0.92]
Rosenthal 1999	25/202	33/206		5.11%	0.74[0.42,1.3]
Shapiro 2000b	10/88	15/93		2.31%	0.67[0.28,1.57]
Wolfe 2006	31/527	68/514		11.58%	0.41[0.26,0.64]
Subtotal (95% CI)	**1799**	**1789**		**52.78%**	**0.59[0.49,0.71]**
Total events: 236 (LABA), 353 (Placebo)					
Heterogeneity: Tau²=0; Chi²=12.61, df=10(P=0.25); I²=20.67%					
Test for overall effect: Z=5.56(P<0.0001)					
1.73.2 Adults- Definition of exacerbation imprecise					
Busse 1998	47/263	64/275		9.18%	0.72[0.47,1.09]
Busse 2004	8/80	13/80		2.09%	0.57[0.22,1.47]
Ekstrom 1998a	5/135	9/129		1.58%	0.51[0.17,1.57]
Jones 1994	8/282	6/145		1.38%	0.68[0.23,1.99]
LaForce 2005	9/86	10/91		1.55%	0.95[0.37,2.46]
Pleskow 2003	14/136	46/141		7.24%	0.24[0.12,0.46]
SLGL82	2/44	2/44		0.34%	1[0.13,7.43]
Steffensen 1995	4/103	9/101		1.56%	0.41[0.12,1.39]
Wolfe 2000a	8/80	10/81		1.6%	0.79[0.29,2.11]
Wolfe 2000b	13/86	14/86		2.12%	0.92[0.4,2.08]
Subtotal (95% CI)	**1295**	**1173**		**28.64%**	**0.59[0.46,0.76]**
Total events: 118 (LABA), 183 (Placebo)					
Heterogeneity: Tau²=0; Chi²=11.36, df=9(P=0.25); I²=20.8%					
Test for overall effect: Z=4.11(P<0.0001)					

Favours LABA 0.1 0.2 0.5 1 2 5 10 Favours Placebo

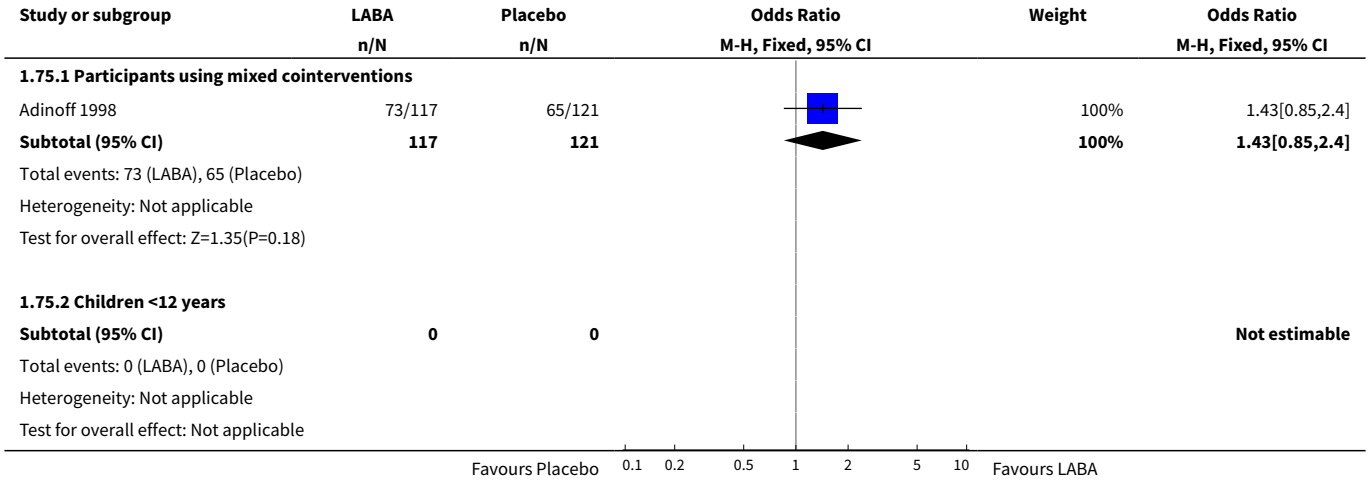


Analysis 1.74. Comparison 1 Studies with parallel group design: efficacy outcomes, Outcome 74 Exacerbations asthma - >1 major(sub-group by use of inhaled corticosteroid).

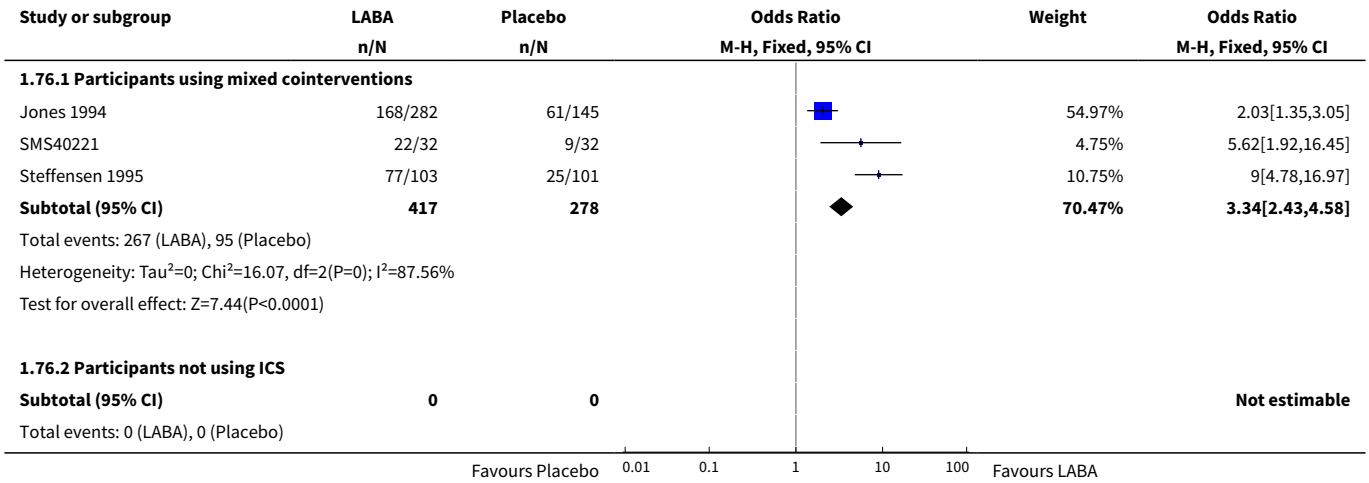


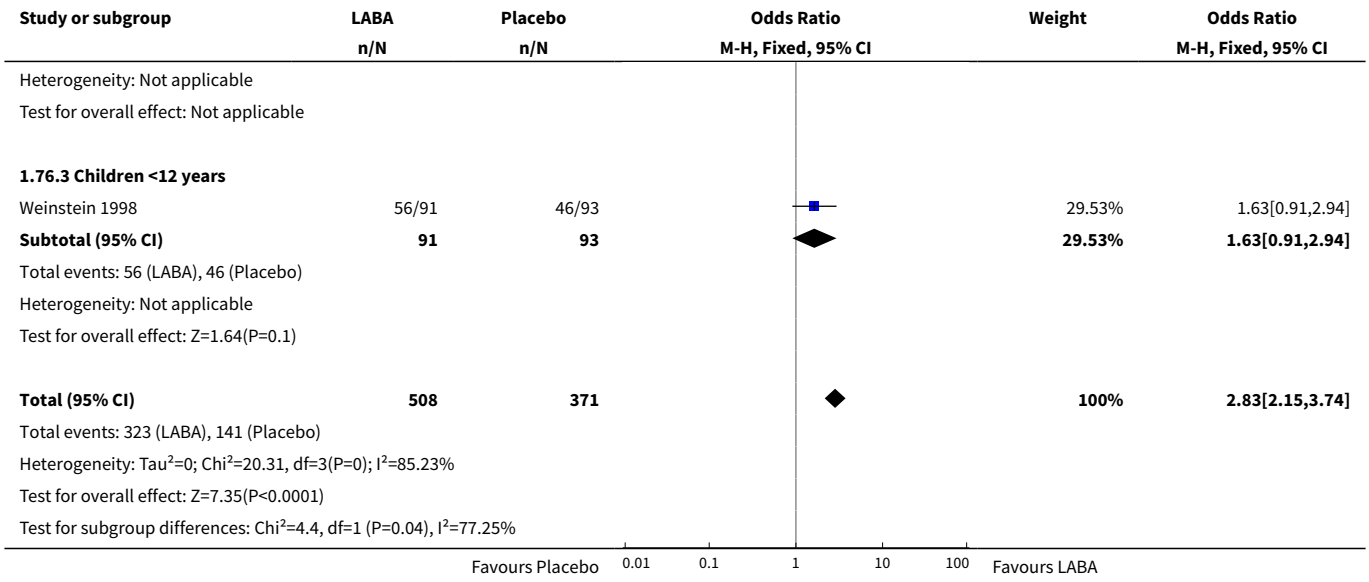


Analysis 1.75. Comparison 1 Studies with parallel group design: efficacy outcomes, Outcome 75 Weaned from at least 1 non steroidal asthma medication.

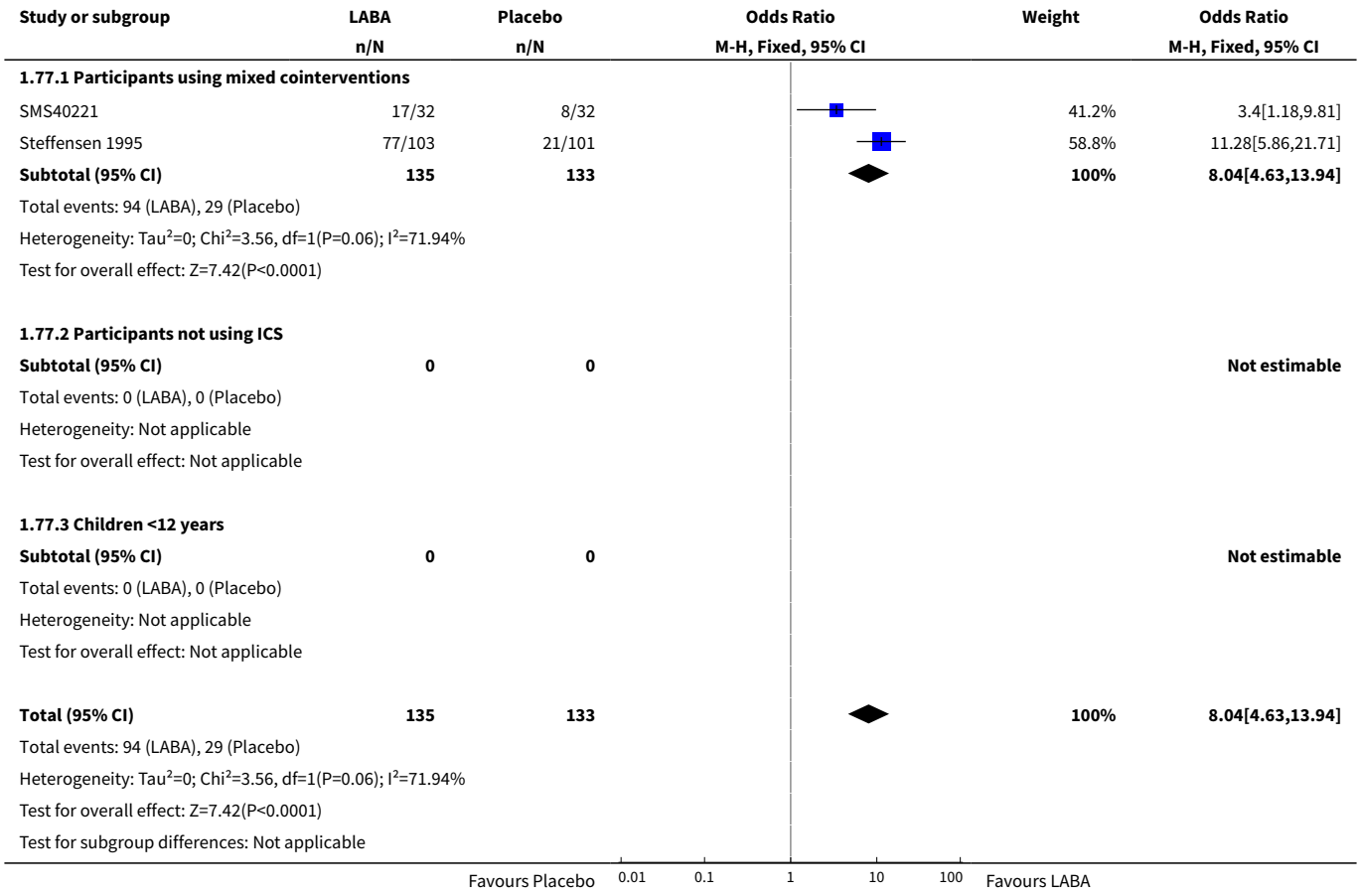


Analysis 1.76. Comparison 1 Studies with parallel group design: efficacy outcomes, Outcome 76 Global assessment of efficacy by patient- very good/good.



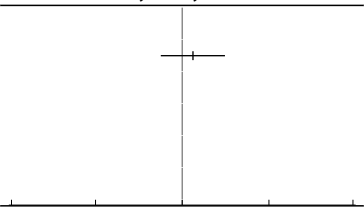


Analysis 1.77. Comparison 1 Studies with parallel group design: efficacy outcomes, Outcome 77 Global assessment of efficacy by investigator- very good/good.



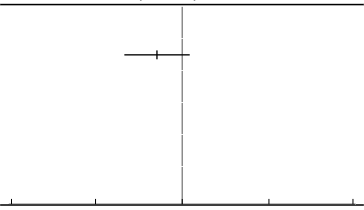
Analysis 1.78. Comparison 1 Studies with parallel group design: efficacy outcomes, Outcome 78 Global assessment of efficacy by patient - improved.

Study or subgroup	LABA n/N	Placebo n/N	Odds Ratio M-H, Fixed, 95% CI	Odds Ratio M-H, Fixed, 95% CI
1.78.1 Participants using mixed cointerventions				
SLGL82	25/43	22/43		1.33[0.57,3.11]
1.78.2 Participants all using ICS				
1.78.3 Children <12 years				



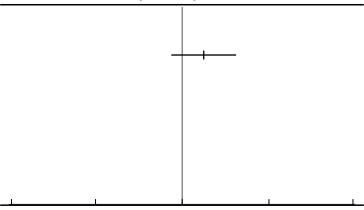
Analysis 1.79. Comparison 1 Studies with parallel group design: efficacy outcomes, Outcome 79 Global assessment of efficacy by patient - not improved.

Study or subgroup	LABA n/N	Placebo n/N	Odds Ratio M-H, Fixed, 95% CI	Odds Ratio M-H, Fixed, 95% CI
1.79.1 Participants using mixed cointerventions				
SLGL82	15/43	22/43		0.51[0.21,1.22]
1.79.2 Participants all using ICS				
1.79.3 Children <12 years				



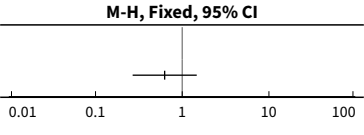
Analysis 1.80. Comparison 1 Studies with parallel group design: efficacy outcomes, Outcome 80 Global assessment of efficacy by investigator - improved.

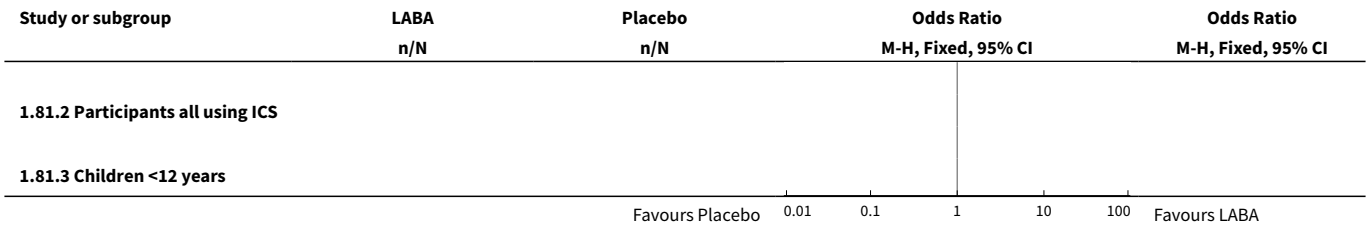
Study or subgroup	LABA n/N	Placebo n/N	Odds Ratio M-H, Fixed, 95% CI	Odds Ratio M-H, Fixed, 95% CI
1.80.1 Participants using mixed cointerventions				
SLGL82	22/43	16/43		1.77[0.75,4.18]
1.80.2 Participants all using ICS				
1.80.3 Children <12 years				



Analysis 1.81. Comparison 1 Studies with parallel group design: efficacy outcomes, Outcome 81 Global assessment of efficacy by investigator - not improved.

Study or subgroup	LABA n/N	Placebo n/N	Odds Ratio M-H, Fixed, 95% CI	Odds Ratio M-H, Fixed, 95% CI
1.81.1 Participants using mixed cointerventions				
SLGL82	19/43	24/43		0.63[0.27,1.47]





Comparison 2. Studies with parallel group design: withdrawal & safety outcomes

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Death (asthma related) subgrouped by ICS at baseline	1	26355	Risk Ratio (M-H, Fixed, 95% CI)	3.86 [1.19, 12.51]
1.1 Participants using ICS at baseline	1	12265	Risk Ratio (M-H, Fixed, 95% CI)	1.34 [0.30, 5.97]
1.2 Participants not using ICS at baseline	1	14090	Risk Ratio (M-H, Fixed, 95% CI)	18.98 [1.10, 326.01]
2 Death (asthma related) subgrouped Caucasians and African Americans	1	23327	Odds Ratio (M-H, Fixed, 95% CI)	6.47 [1.46, 28.68]
2.1 Caucasians	1	18642	Odds Ratio (M-H, Fixed, 95% CI)	6.05 [0.73, 50.30]
2.2 African Americans	1	4685	Odds Ratio (M-H, Fixed, 95% CI)	6.88 [0.85, 55.95]
3 Death (respiratory related)	1	26355	Risk Ratio (M-H, Fixed, 95% CI)	2.18 [1.07, 4.45]
3.1 Participants using ICS at baseline	1	12265	Risk Ratio (M-H, Fixed, 95% CI)	2.00 [0.69, 5.86]
3.2 Participants not using ICS at baseline	1	14090	Risk Ratio (M-H, Fixed, 95% CI)	2.33 [0.90, 6.06]
4 Death (all cause) - SMART non-ICS subgroup	3	14534	Risk Ratio (M-H, Fixed, 95% CI)	1.33 [0.76, 2.35]
4.1 Participants using mixed cointerventions	1	277	Risk Ratio (M-H, Fixed, 95% CI)	3.11 [0.13, 75.68]
4.2 Participants not using ICS	1	14090	Risk Ratio (M-H, Fixed, 95% CI)	1.25 [0.69, 2.25]
4.3 Children <12 years	1	167	Risk Ratio (M-H, Fixed, 95% CI)	3.04 [0.13, 73.47]
5 Death (all cause) - SMART all participants	3	26799	Risk Ratio (M-H, Fixed, 95% CI)	1.37 [0.87, 2.14]
5.1 Participants using mixed cointerventions	2	26632	Risk Ratio (M-H, Fixed, 95% CI)	1.34 [0.85, 2.11]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
5.2 Participants not using ICS	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
5.3 Children <12 years	1	167	Risk Ratio (M-H, Fixed, 95% CI)	3.04 [0.13, 73.47]
6 SMART primary endpoint subgroups (Caucasians and African Americans)	1	23327	Risk Ratio (M-H, Fixed, 95% CI)	1.49 [0.96, 2.31]
6.1 Caucasians	1	18642	Risk Ratio (M-H, Fixed, 95% CI)	1.04 [0.62, 1.75]
6.2 African Americans	1	4685	Risk Ratio (M-H, Fixed, 95% CI)	3.92 [1.47, 10.43]
7 Serious adverse event - life threatening adverse events	1		Peto Odds Ratio (Peto, Fixed, 95% CI)	Totals not selected
7.1 Participants using mixed cointerventions	1		Peto Odds Ratio (Peto, Fixed, 95% CI)	0.0 [0.0, 0.0]
7.2 Participants not using ICS	1		Peto Odds Ratio (Peto, Fixed, 95% CI)	0.0 [0.0, 0.0]
7.3 Children <12 years	0		Peto Odds Ratio (Peto, Fixed, 95% CI)	0.0 [0.0, 0.0]
8 Serious adverse event - asthma related	3	895	Odds Ratio (M-H, Fixed, 95% CI)	7.46 [2.21, 25.16]
8.1 Participants using mixed cointerventions	2	548	Odds Ratio (M-H, Fixed, 95% CI)	4.01 [0.98, 16.36]
8.2 Participants not using ICS	0	0	Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
8.3 Children <12 years	1	347	Odds Ratio (M-H, Fixed, 95% CI)	25.29 [1.48, 432.68]
9 Serious adverse event related to study drug - total	4	973	Odds Ratio (M-H, Fixed, 95% CI)	2.11 [1.03, 4.31]
9.1 Participants using mixed cointerventions	1	161	Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
9.2 Participants not using ICS	0	0	Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
9.3 Children <12 years	3	812	Odds Ratio (M-H, Fixed, 95% CI)	2.11 [1.03, 4.31]
10 Withdrawals (all reasons)	19	30599	Odds Ratio (M-H, Fixed, 95% CI)	0.91 [0.86, 0.96]
10.1 Participants using mixed cointerventions	10	28834	Odds Ratio (M-H, Fixed, 95% CI)	0.91 [0.86, 0.97]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
10.2 Participants not using ICS	4	564	Odds Ratio (M-H, Fixed, 95% CI)	0.53 [0.38, 0.75]
10.3 Children <12 years	4	1061	Odds Ratio (M-H, Fixed, 95% CI)	1.15 [0.81, 1.65]
10.4 Unclear	1	140	Odds Ratio (M-H, Fixed, 95% CI)	1.15 [0.37, 3.61]
11 Withdrawals (adverse events)	21	30943	Odds Ratio (M-H, Fixed, 95% CI)	1.11 [0.93, 1.32]
11.1 Participants using mixed cointerventions	11	29110	Odds Ratio (M-H, Fixed, 95% CI)	1.07 [0.89, 1.29]
11.2 Subjects not using ICS	5	674	Odds Ratio (M-H, Fixed, 95% CI)	2.31 [1.05, 5.07]
11.3 Children <12 years	4	1019	Odds Ratio (M-H, Fixed, 95% CI)	0.92 [0.46, 1.85]
11.4 Unclear	1	140	Odds Ratio (M-H, Fixed, 95% CI)	1.97 [0.17, 22.25]
12 Withdrawals (asthma-related adverse events)	1		Odds Ratio (M-H, Fixed, 95% CI)	Totals not selected
12.1 Participants using mixed cointerventions	0		Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
12.2 Participants not using ICS	1		Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
12.4 Children <12 years	0		Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
13 Withdrawals (abnormal cadiovascular test)	1		Odds Ratio (M-H, Fixed, 95% CI)	Totals not selected
13.1 Participants using mixed cointerventions	0		Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
13.2 Participants not using ICS	0		Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
13.3 Children <12 years	1		Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
14 Withdrawals (lack of efficacy)	14	29466	Odds Ratio (M-H, Fixed, 95% CI)	0.60 [0.53, 0.68]
14.1 Participants using mixed cointerventions	6	27883	Odds Ratio (M-H, Fixed, 95% CI)	0.62 [0.54, 0.71]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
14.2 Participants not using ICS	4	564	Odds Ratio (M-H, Fixed, 95% CI)	0.43 [0.30, 0.62]
14.3 Children <12 years	4	1019	Odds Ratio (M-H, Fixed, 95% CI)	0.70 [0.33, 1.47]
15 Withdrawals (exacerbation of asthma)	7	1658	Odds Ratio (M-H, Fixed, 95% CI)	0.82 [0.46, 1.46]
15.1 Participants using mixed cointerventions	2	548	Odds Ratio (M-H, Fixed, 95% CI)	1.26 [0.51, 3.10]
15.2 Participants not using ICS	0	0	Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
15.3 Children <12 years	4	970	Odds Ratio (M-H, Fixed, 95% CI)	0.56 [0.25, 1.29]
15.4 Unclear	1	140	Odds Ratio (M-H, Fixed, 95% CI)	0.97 [0.13, 7.09]
16 Adverse events - total	19	3696	Odds Ratio (M-H, Fixed, 95% CI)	1.17 [1.02, 1.35]
16.1 Participants using mixed cointerventions	7	1280	Odds Ratio (M-H, Fixed, 95% CI)	1.12 [0.89, 1.41]
16.2 Participants not using ICS	6	1008	Odds Ratio (M-H, Fixed, 95% CI)	1.25 [0.94, 1.66]
16.3 Children <12 years	5	1268	Odds Ratio (M-H, Fixed, 95% CI)	1.22 [0.96, 1.55]
16.4 Unclear	1	140	Odds Ratio (M-H, Fixed, 95% CI)	0.89 [0.42, 1.90]
17 Adverse events - any drug related	7	2130	Odds Ratio (M-H, Fixed, 95% CI)	1.37 [1.01, 1.87]
17.1 Participants using mixed cointerventions	7	2130	Odds Ratio (M-H, Fixed, 95% CI)	1.37 [1.01, 1.87]
17.2 Subjects not using ICS	0	0	Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
17.3 Children <12 years	0	0	Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
18 Adverse events - asthma related	1	1041	Odds Ratio (M-H, Fixed, 95% CI)	0.85 [0.60, 1.19]
18.1 Participants mixed cointerventions	1	1041	Odds Ratio (M-H, Fixed, 95% CI)	0.85 [0.60, 1.19]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
18.2 Participants not using ICS	0	0	Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
18.3 Children <12 years	0	0	Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
19 Adverse events - pharyngitis	7	1419	Odds Ratio (M-H, Fixed, 95% CI)	1.45 [0.94, 2.24]
19.1 Participants using mixed cointerventions	2	437	Odds Ratio (M-H, Fixed, 95% CI)	1.68 [0.79, 3.55]
19.2 Participants not using ICS	0	0	Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
19.3 Children <12 years	4	842	Odds Ratio (M-H, Fixed, 95% CI)	1.31 [0.76, 2.25]
19.4 Unclear	1	140	Odds Ratio (M-H, Fixed, 95% CI)	2.96 [0.12, 73.85]
20 Adverse events - cough	13	2571	Odds Ratio (M-H, Fixed, 95% CI)	1.16 [0.82, 1.65]
20.1 Participants using mixed cointerventions	7	1346	Odds Ratio (M-H, Fixed, 95% CI)	1.09 [0.64, 1.86]
20.2 Participants not using ICS	2	203	Odds Ratio (M-H, Fixed, 95% CI)	3.26 [0.84, 12.63]
20.3 Children <12 years	3	882	Odds Ratio (M-H, Fixed, 95% CI)	1.05 [0.64, 1.71]
20.4 Unclear	1	140	Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
21 Adverse events - nasopharyngitis	1		Odds Ratio (M-H, Fixed, 95% CI)	Totals not selected
21.1 Participants using mixed cointerventions	1		Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
21.2 Participants not using ICS	0		Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
21.3 Children <12 years	0		Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
22 Adverse events - throat irritation	8	1357	Odds Ratio (M-H, Fixed, 95% CI)	1.68 [1.10, 2.56]
22.1 Participants using mixed cointerventions	4	598	Odds Ratio (M-H, Fixed, 95% CI)	2.20 [1.17, 4.13]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
22.2 Subjects not using ICS	3	540	Odds Ratio (M-H, Fixed, 95% CI)	1.26 [0.63, 2.54]
22.3 Children <12 years	1	219	Odds Ratio (M-H, Fixed, 95% CI)	1.49 [0.54, 4.06]
23 Adverse events - upper respiratory tract infection	12	2459	Odds Ratio (M-H, Fixed, 95% CI)	1.08 [0.86, 1.36]
23.1 Participants using mixed cointerventions	6	1077	Odds Ratio (M-H, Fixed, 95% CI)	0.68 [0.46, 1.01]
23.2 Subjects not using ICS	3	540	Odds Ratio (M-H, Fixed, 95% CI)	1.61 [0.99, 2.63]
23.3 Children <12 years	3	842	Odds Ratio (M-H, Fixed, 95% CI)	1.27 [0.89, 1.82]
24 Adverse events - dyspnea	1		Odds Ratio (M-H, Fixed, 95% CI)	Totals not selected
24.1 Participants using mixed cointerventions	1		Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
24.2 Participants not using ICS	0		Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
24.3 Children <12 years	0		Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
25 Adverse events - exacerbation of asthma	5	1110	Odds Ratio (M-H, Fixed, 95% CI)	0.86 [0.54, 1.38]
25.1 Participants using mixed cointerventions	3	680	Odds Ratio (M-H, Fixed, 95% CI)	0.87 [0.45, 1.69]
25.2 Participants not using ICS	1	181	Odds Ratio (M-H, Fixed, 95% CI)	3.21 [0.13, 79.74]
25.3 Children <12 years	1	249	Odds Ratio (M-H, Fixed, 95% CI)	0.79 [0.40, 1.58]
26 Adverse events - otitis media	1		Odds Ratio (M-H, Fixed, 95% CI)	Totals not selected
26.1 Participants using mixed cointerventions	0		Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
26.2 Participants not using ICS	0		Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
26.3 Children <12 years	1		Odds 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
27 Adverse events - sinus headache	1	277	Odds Ratio (M-H, Fixed, 95% CI)	1.04 [0.14, 7.47]
27.1 Participants using mixed cointerventions	1	277	Odds Ratio (M-H, Fixed, 95% CI)	1.04 [0.14, 7.47]
27.2 Participants not using ICS	0	0	Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
27.3 Children <12 years	0	0	Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
28 Adverse events - pyrexia	1		Odds Ratio (M-H, Fixed, 95% CI)	Totals not selected
28.1 Participants using mixed cointerventions	1		Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
28.2 Participants not using ICS	0		Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
28.3 Children <12 years	0		Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
29 Adverse events - chest pain	1		Odds Ratio (M-H, Fixed, 95% CI)	Totals not selected
29.1 Participants using mixed cointerventions	1		Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
29.2 Subjects not using ICS	0		Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
29.3 Children <12 years	0		Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
30 Adverse events - abnormal cardiovascular test	1		Odds Ratio (M-H, Fixed, 95% CI)	Totals not selected
30.1 Participants using mixed cointerventions	0		Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
30.2 Participants not using ICS	0		Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
30.3 Children <12 years	1		Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
31 Adverse events - palpitations	6	1729	Odds Ratio (M-H, Fixed, 95% CI)	1.36 [0.64, 2.89]
31.1 Participants using mixed cointerventions	6	1729	Odds Ratio (M-H, Fixed, 95% CI)	1.36 [0.64, 2.89]

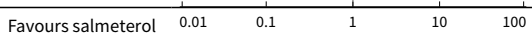
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
31.2 Participants not using ICS	0	0	Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
31.3 Children <12 years	0	0	Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
32 Adverse events - insomnia	2	546	Odds Ratio (M-H, Fixed, 95% CI)	2.06 [0.61, 6.92]
32.1 Participants using mixed cointerventions	2	546	Odds Ratio (M-H, Fixed, 95% CI)	2.06 [0.61, 6.92]
32.2 Participants not using ICS	0	0	Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
32.3 Children <12 years	0	0	Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
33 Adverse events - tremor	8	2257	Odds Ratio (M-H, Fixed, 95% CI)	3.86 [1.91, 7.78]
33.1 Participants using mixed cointerventions	8	2257	Odds Ratio (M-H, Fixed, 95% CI)	3.86 [1.91, 7.78]
33.2 Participants not using ICS	0	0	Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
33.3 Children <12 years	0	0	Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
34 Adverse events - headache	23	5667	Odds Ratio (M-H, Fixed, 95% CI)	1.28 [1.04, 1.57]
34.1 Participants using mixed cointerventions	13	3474	Odds Ratio (M-H, Fixed, 95% CI)	1.06 [0.79, 1.42]
34.2 Participants not using ICS	5	992	Odds Ratio (M-H, Fixed, 95% CI)	1.75 [1.12, 2.72]
34.3 Children <12 years	4	1061	Odds Ratio (M-H, Fixed, 95% CI)	1.39 [0.95, 2.05]
34.4 Unclear	1	140	Odds Ratio (M-H, Fixed, 95% CI)	1.31 [0.28, 6.10]
35 Adverse events - cramps	3	892	Odds Ratio (M-H, Fixed, 95% CI)	1.40 [0.56, 3.51]
35.1 Participants using mixed cointerventions	3	892	Odds Ratio (M-H, Fixed, 95% CI)	1.40 [0.56, 3.51]
35.2 Participants not using ICS	0	0	Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]

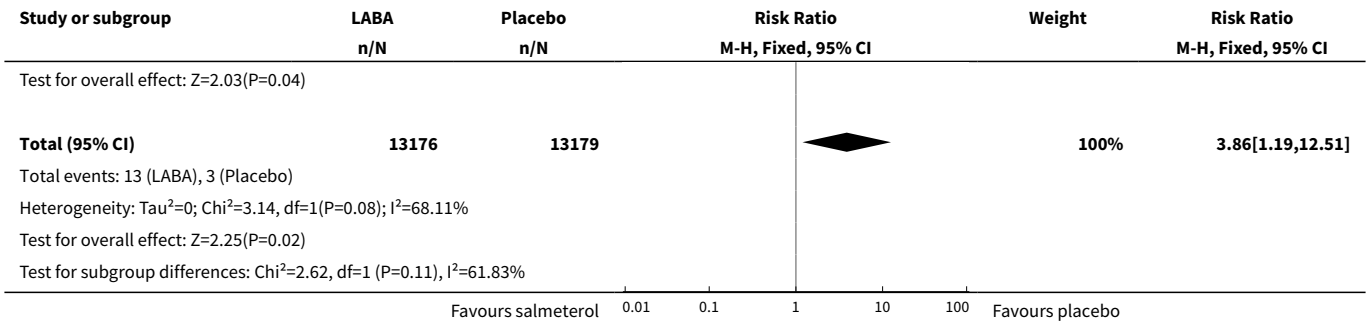
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
35.3 Children <12 years	0	0	Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
36 Adverse events - anxiety	1		Odds Ratio (M-H, Fixed, 95% CI)	Totals not selected
36.1 Participants using mixed cointerventions	1		Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
36.2 Participants not using ICS	0		Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
36.3 Children <12 years	0		Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
37 Adverse events - nervousness	2	546	Odds Ratio (M-H, Fixed, 95% CI)	5.11 [1.72, 15.22]
37.1 Participants using mixed cointerventions	2	546	Odds Ratio (M-H, Fixed, 95% CI)	5.11 [1.72, 15.22]
37.2 Participants not using ICS	0	0	Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
37.3 Children <12 years	0	0	Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
38 Adverse events - nausea	1		Odds Ratio (M-H, Fixed, 95% CI)	Totals not selected
38.1 Participants using mixed cointerventions	1		Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
38.2 Participants not using ICS	0		Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
38.3 Children <12 years	0		Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
39 Adverse events - myalgia/fatigue	2	496	Odds Ratio (M-H, Fixed, 95% CI)	1.72 [0.41, 7.24]
39.1 Participants using mixed cointerventions	1	277	Odds Ratio (M-H, Fixed, 95% CI)	4.24 [0.47, 38.45]
39.2 Participants not using ICS	0	0	Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
39.3 Children <12 years	1	219	Odds Ratio (M-H, Fixed, 95% CI)	0.5 [0.04, 5.60]
40 Adverse events - pain in limb	1		Odds Ratio (M-H, Fixed, 95% CI)	Totals not selected

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
40.1 Participants using mixed cointerventions	0		Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
40.2 Participants not using ICS	0		Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
40.3 Children <12 years	1		Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
41 Adverse events - musculoskeletal pain	2	333	Odds Ratio (M-H, Fixed, 95% CI)	1.13 [0.45, 2.84]
41.1 Participants using mixed cointerventions	2	333	Odds Ratio (M-H, Fixed, 95% CI)	1.13 [0.45, 2.84]
41.2 Participants not using ICS	0	0	Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
41.3 Children <12 years	0	0	Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
42 Serious adverse event - respiratory	2		Odds Ratio (M-H, Fixed, 95% CI)	Totals not selected
42.1 Participants using mixed cointerventions	2		Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
42.2 Pariticipants not using ICS	0		Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
42.3 Children <12 years	0		Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]

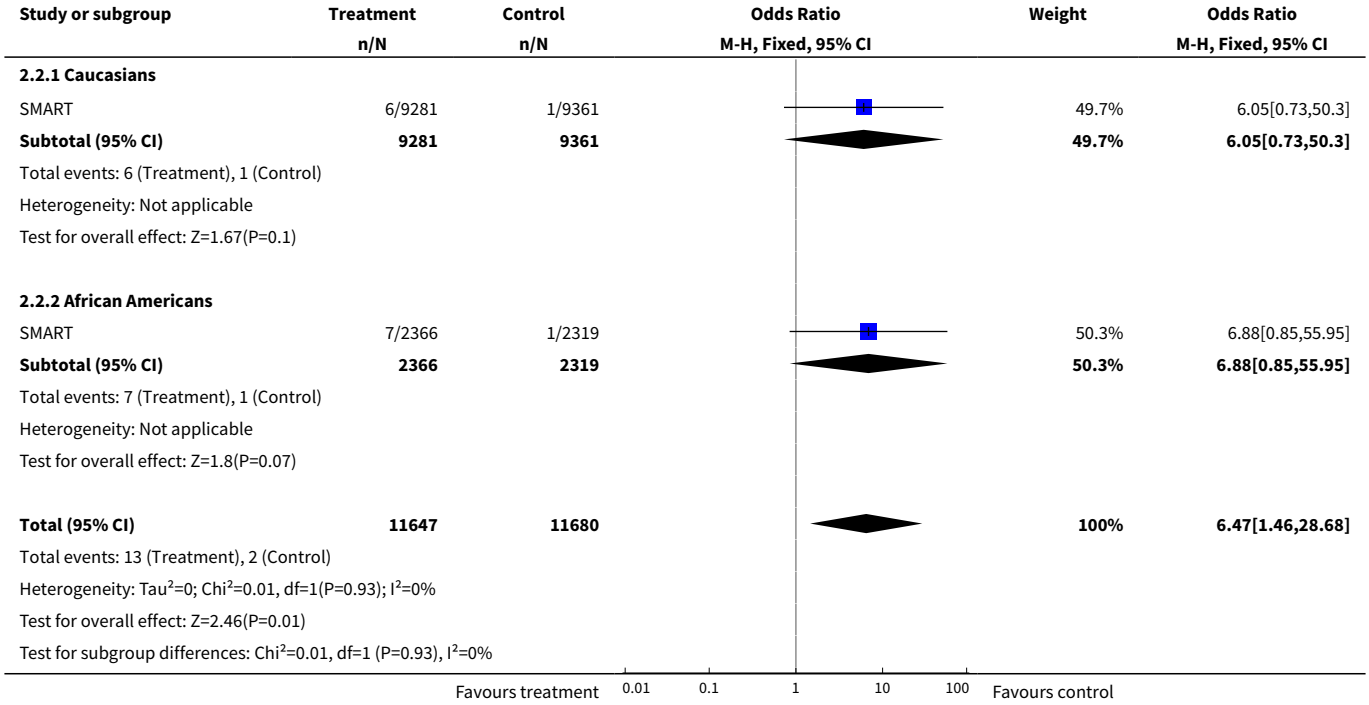
Analysis 2.1. Comparison 2 Studies with parallel group design: withdrawal & safety outcomes, Outcome 1 Death (asthma related) subgrouped by ICS at baseline.

Study or subgroup	LABA n/N	Placebo n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
2.1.1 Participants using ICS at baseline					
SMART	4/6127	3/6138		85.7%	1.34[0.3,5.97]
Subtotal (95% CI)	**6127**	**6138**		**85.7%**	**1.34[0.3,5.97]**
Total events: 4 (LABA), 3 (Placebo)					
Heterogeneity: $Tau^2=0$; $Chi^2=0$, df=0(P<0.0001); $I^2=100\%$					
Test for overall effect: Z=0.38(P=0.7)					
2.1.2 Participants not using ICS at baseline					
SMART	9/7049	0/7041		14.3%	18.98[1.1,326.01]
Subtotal (95% CI)	**7049**	**7041**		**14.3%**	**18.98[1.1,326.01]**
Total events: 9 (LABA), 0 (Placebo)					
Heterogeneity: Not applicable					

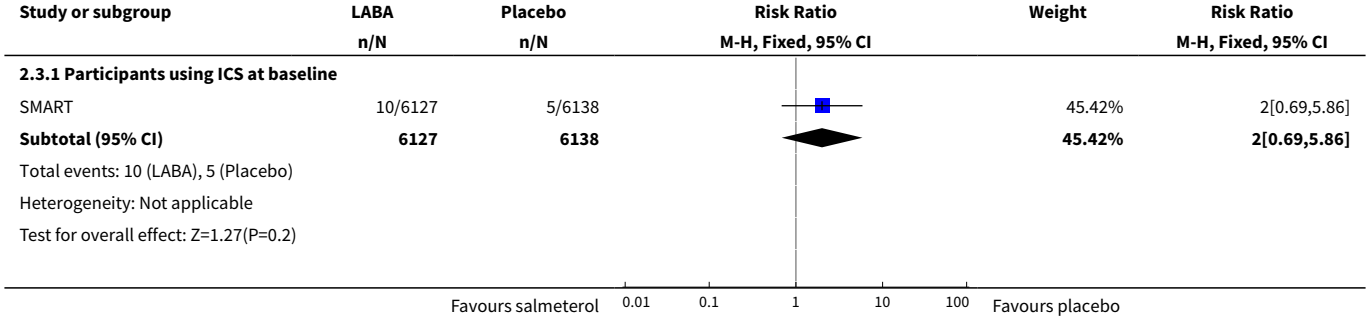


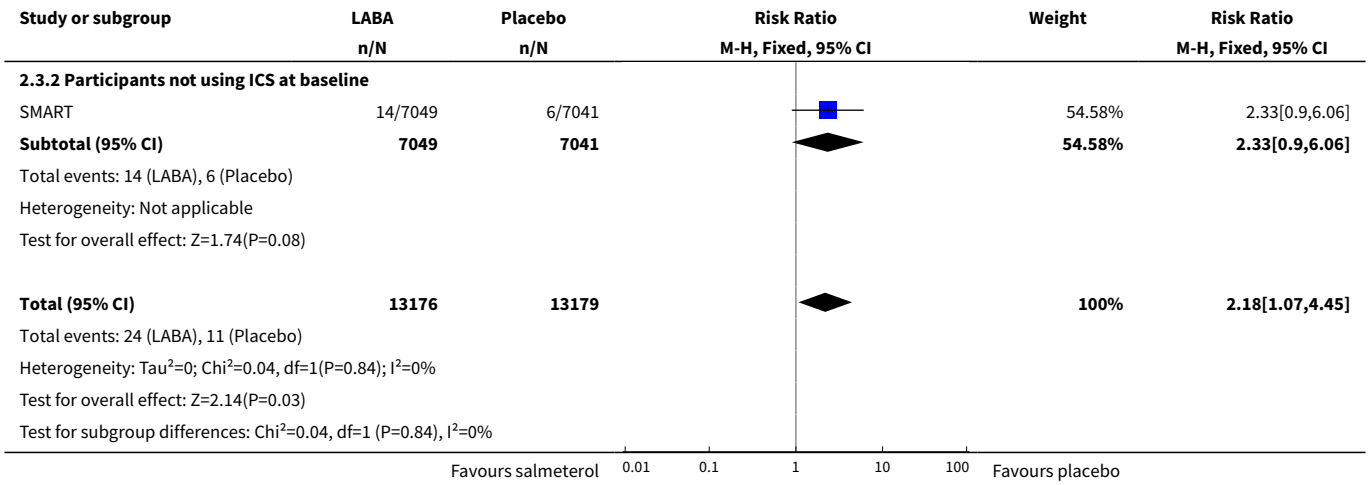


Analysis 2.2. Comparison 2 Studies with parallel group design: withdrawal & safety outcomes, Outcome 2 Death (asthma related) subgrouped Caucasians and African Americans.

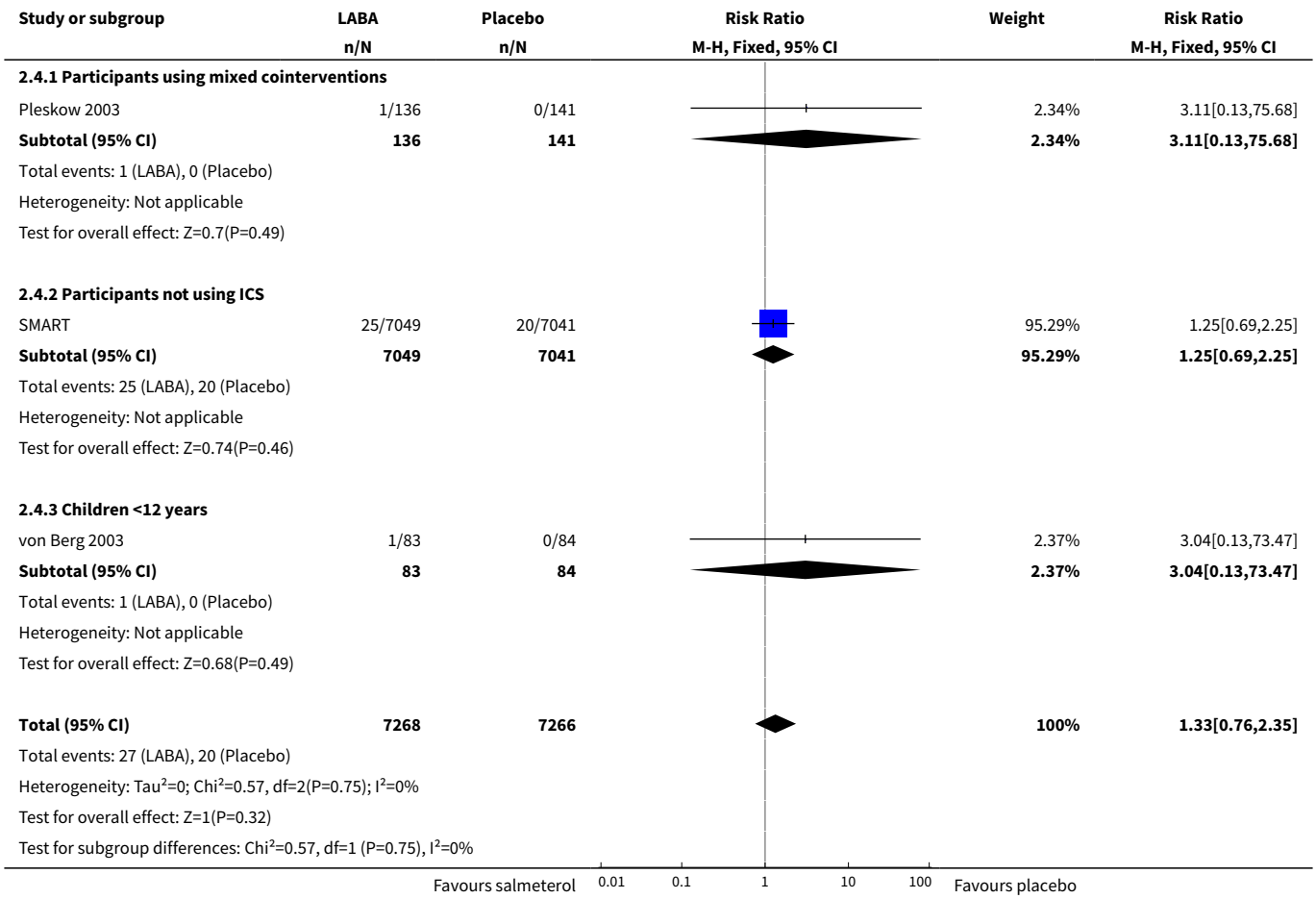


Analysis 2.3. Comparison 2 Studies with parallel group design: withdrawal & safety outcomes, Outcome 3 Death (respiratory related).

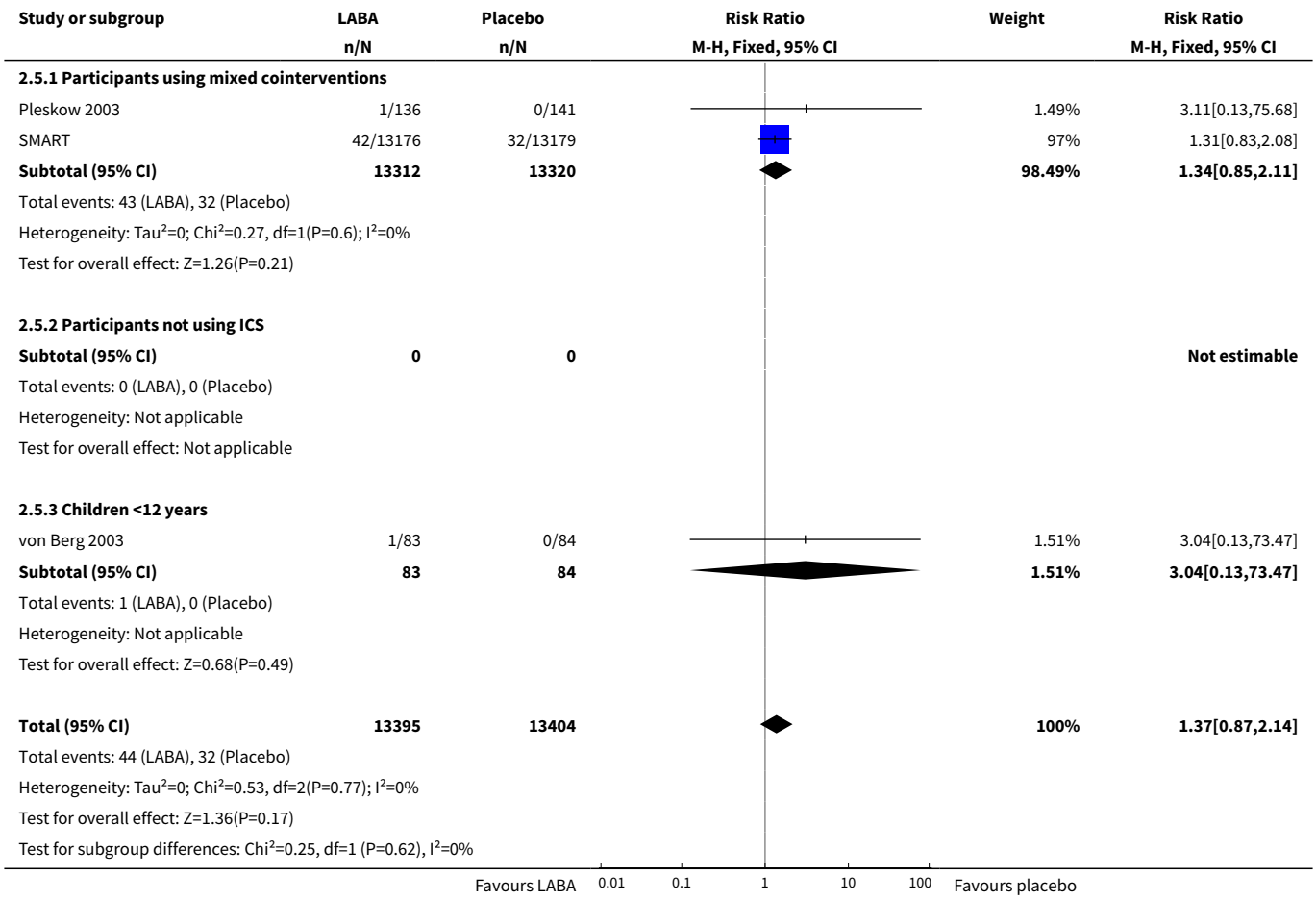




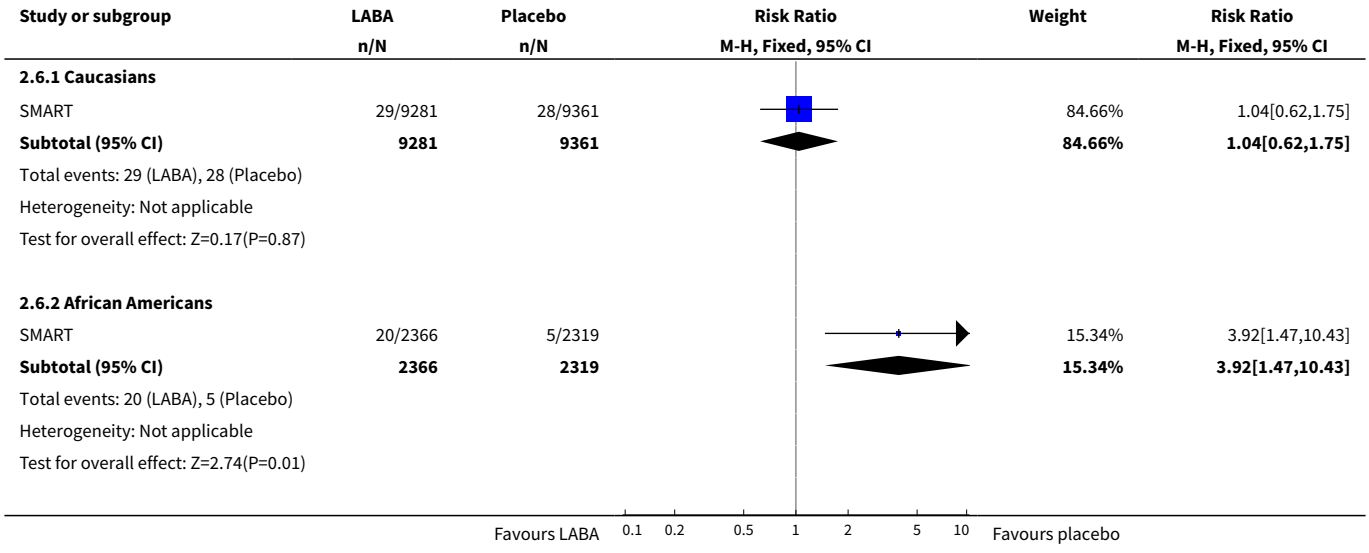
Analysis 2.4. Comparison 2 Studies with parallel group design: withdrawal & safety outcomes, Outcome 4 Death (all cause) - SMART non-ICS subgroup.

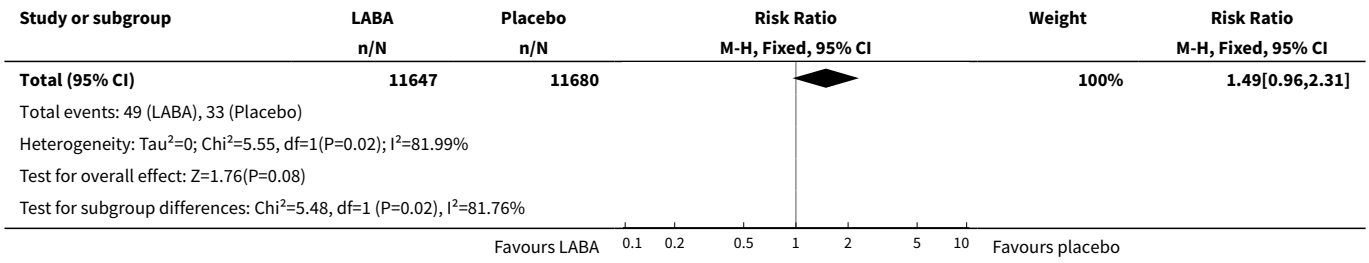


Analysis 2.5. Comparison 2 Studies with parallel group design: withdrawal & safety outcomes, Outcome 5 Death (all cause) - SMART all participants.

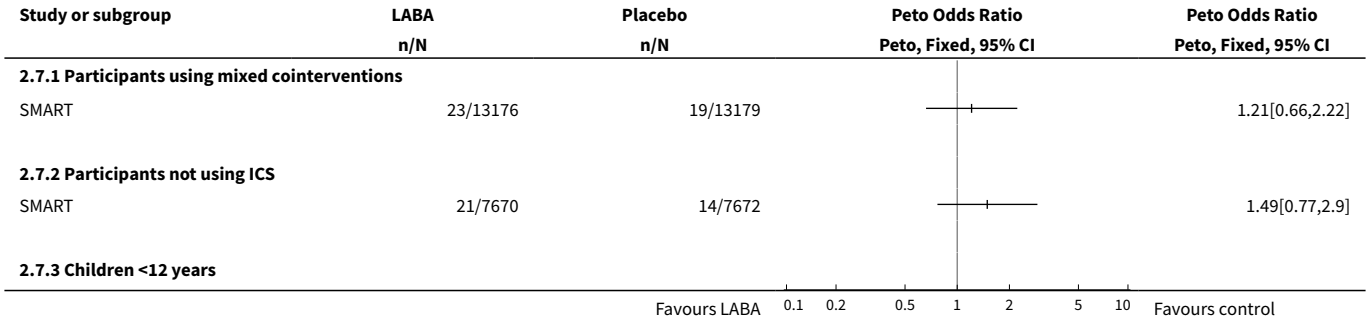


Analysis 2.6. Comparison 2 Studies with parallel group design: withdrawal & safety outcomes, Outcome 6 SMART primary endpoint subgroups (Caucasians and African Americans).

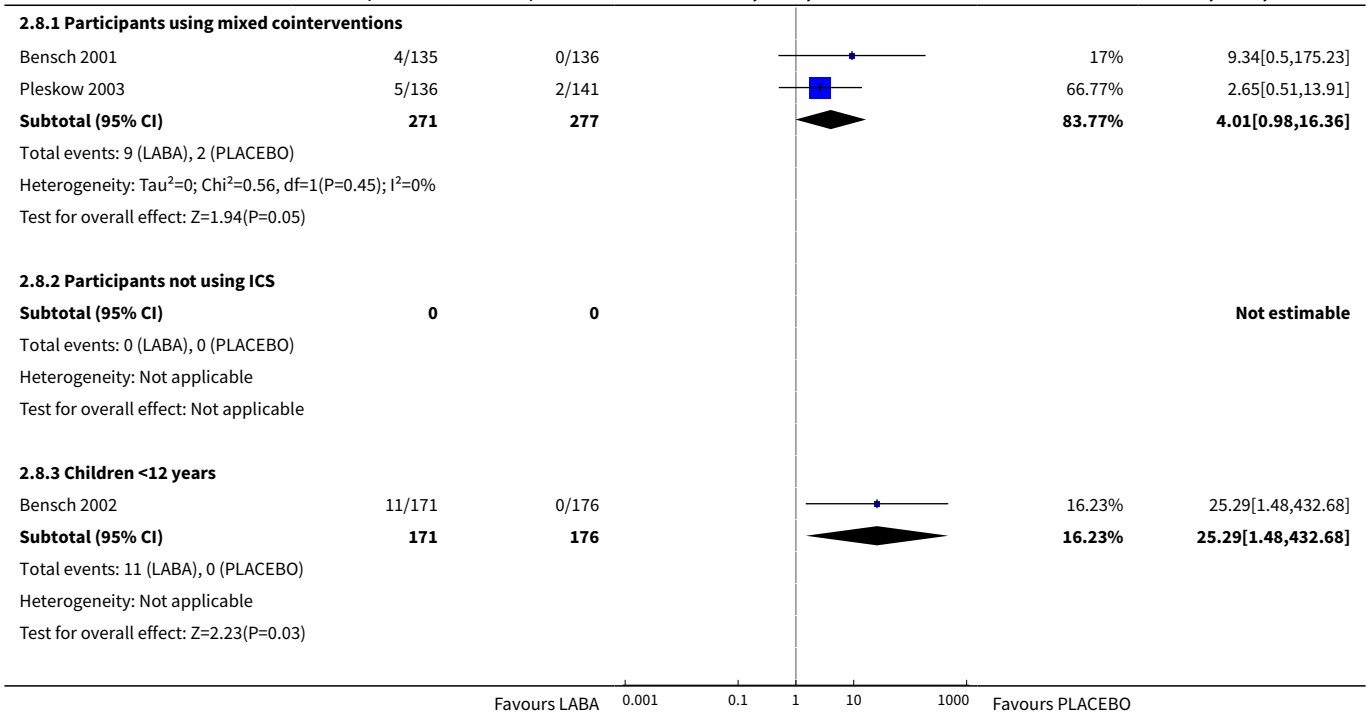


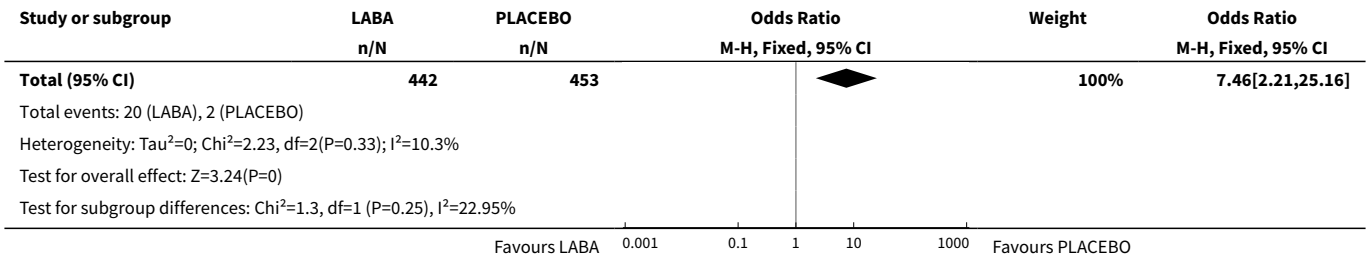


Analysis 2.7. Comparison 2 Studies with parallel group design: withdrawal & safety outcomes, Outcome 7 Serious adverse event - life threatening adverse events.

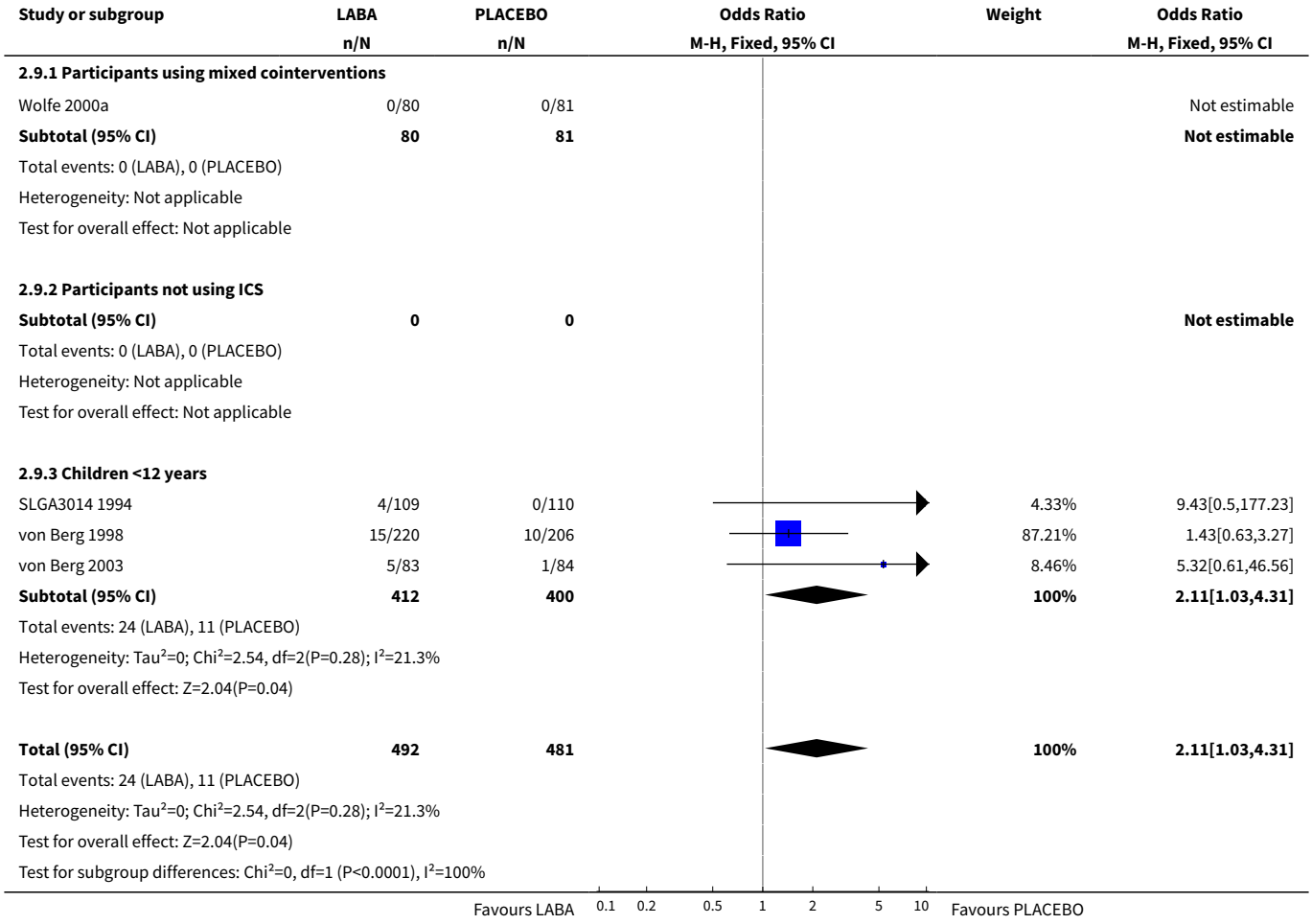


Analysis 2.8. Comparison 2 Studies with parallel group design: withdrawal & safety outcomes, Outcome 8 Serious adverse event - asthma related.

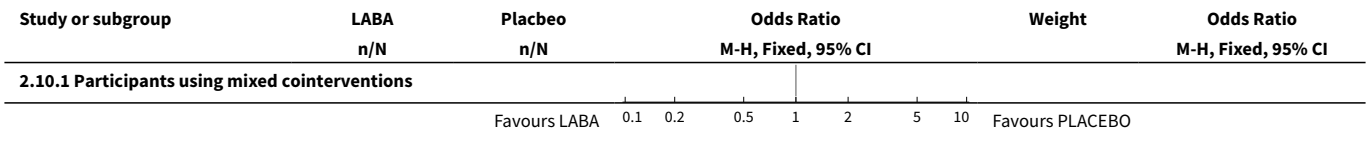


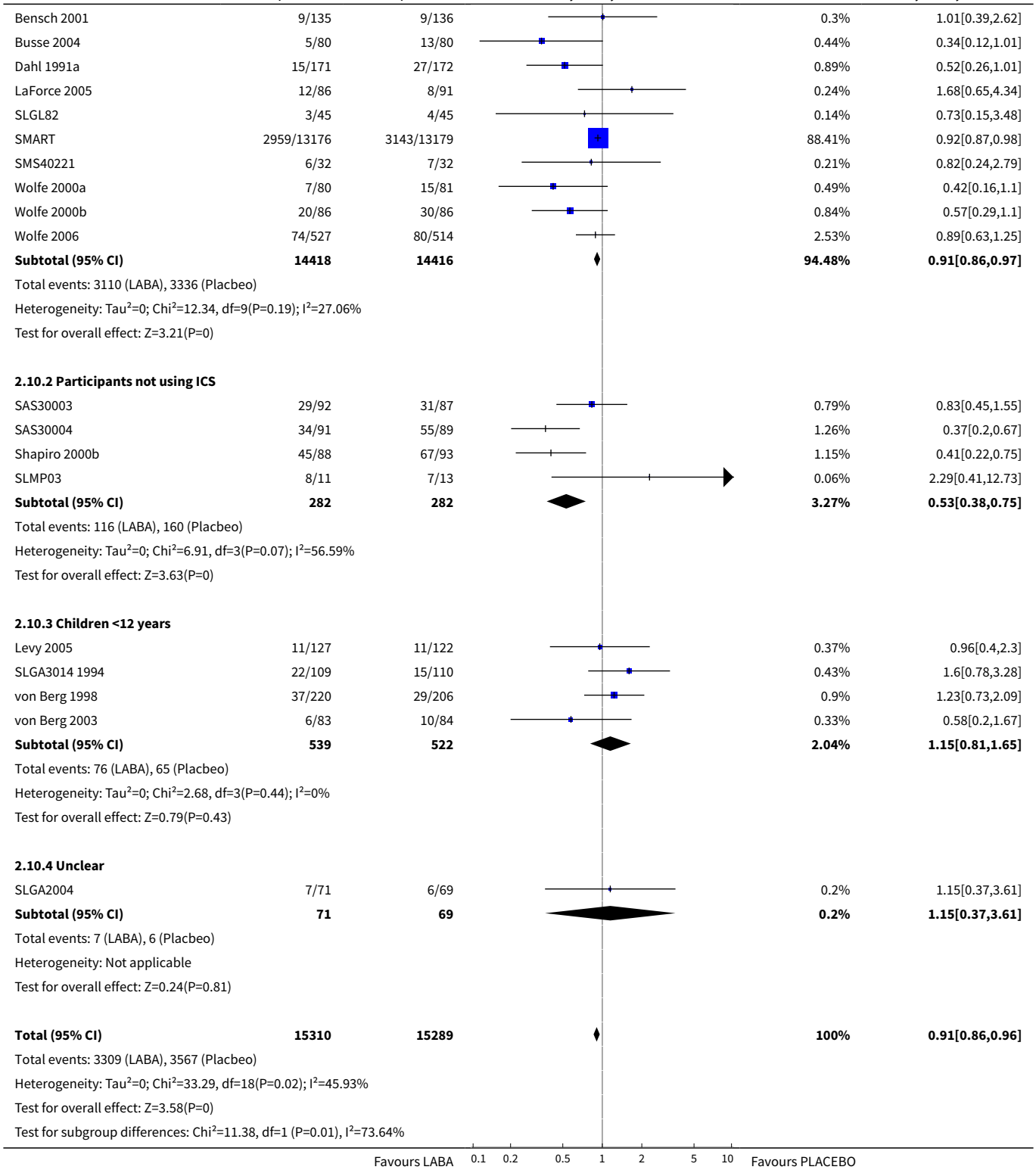


Analysis 2.9. Comparison 2 Studies with parallel group design: withdrawal & safety outcomes, Outcome 9 Serious adverse event related to study drug - total.



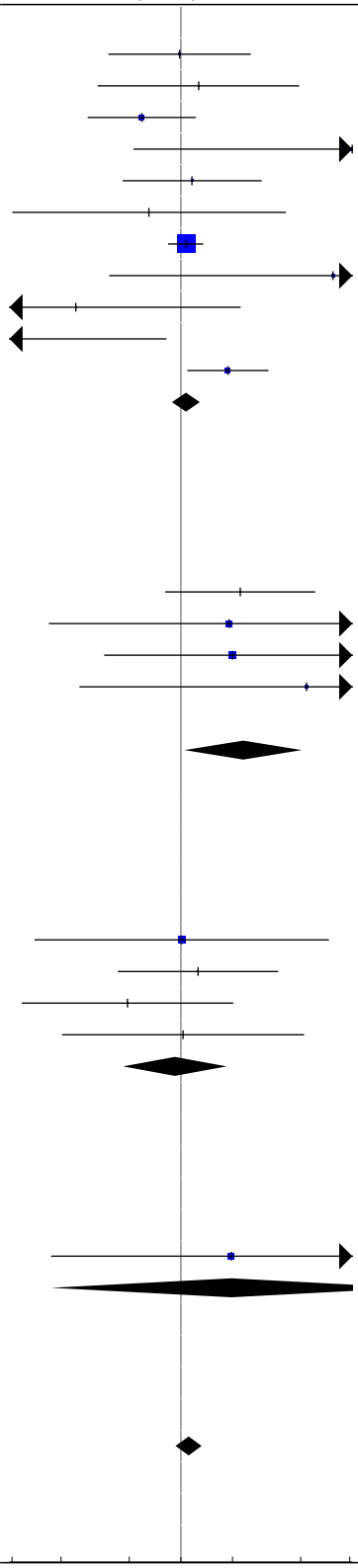
Analysis 2.10. Comparison 2 Studies with parallel group design: withdrawal & safety outcomes, Outcome 10 Withdrawals (all reasons).



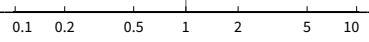


Analysis 2.11. Comparison 2 Studies with parallel group design: withdrawal & safety outcomes, Outcome 11 Withdrawals (adverse events).

Study or subgroup	LABA n/N	Placbeo n/N	Odds Ratio M-H, Fixed, 95% CI	Weight	Odds Ratio M-H, Fixed, 95% CI
2.11.1 Participants using mixed cointerventions					
Bensch 2001	9/136	9/134		3.6%	0.98[0.38,2.56]
Busse 2004	5/80	4/80		1.59%	1.27[0.33,4.9]
Dahl 1991a	13/171	21/172		8.22%	0.59[0.29,1.22]
LaForce 2005	4/86	0/91		0.2%	9.98[0.53,188.22]
Pleskow 2003	10/136	9/141		3.48%	1.16[0.46,2.96]
SLGL82	2/45	3/45		1.22%	0.65[0.1,4.1]
SMART	143/13176	134/13179		56.33%	1.07[0.84,1.35]
SMS40221	3/32	0/32		0.19%	7.71[0.38,155.64]
Wolfe 2000a	1/80	4/81		1.67%	0.24[0.03,2.23]
Wolfe 2000b	0/86	9/86		4.01%	0.05[0,0.82]
Wolfe 2006	39/527	21/514		8.37%	1.88[1.09,3.24]
Subtotal (95% CI)	**14555**	**14555**		**88.88%**	**1.07[0.89,1.29]**
Total events: 229 (LABA), 214 (Placbeo)					
Heterogeneity: Tau^2=0; Chi^2=17.2, df=10(P=0.07); I^2=41.87%					
Test for overall effect: Z=0.71(P=0.48)					
2.11.2 Subjects not using ICS					
Lazarus 2001	13/54	7/56		2.22%	2.22[0.81,6.08]
SAS30003	2/92	1/87		0.43%	1.91[0.17,21.46]
SAS30004	4/91	2/89		0.82%	2[0.36,11.2]
Shapiro 2000b	2/88	0/93		0.2%	5.4[0.26,114.17]
SLMP03	0/11	0/13			Not estimable
Subtotal (95% CI)	**336**	**338**		**3.67%**	**2.31[1.05,5.07]**
Total events: 21 (LABA), 10 (Placbeo)					
Heterogeneity: Tau^2=0; Chi^2=0.35, df=3(P=0.95); I^2=0%					
Test for overall effect: Z=2.09(P=0.04)					
2.11.3 Children <12 years					
SLGA3014 1994	2/109	2/110		0.83%	1.01[0.14,7.3]
von Berg 1998	8/220	6/206		2.54%	1.26[0.43,3.69]
von Berg 2003	3/83	6/84		2.44%	0.49[0.12,2.02]
Weinstein 1998	3/102	3/105		1.22%	1.03[0.2,5.23]
Subtotal (95% CI)	**514**	**505**		**7.03%**	**0.92[0.46,1.85]**
Total events: 16 (LABA), 17 (Placbeo)					
Heterogeneity: Tau^2=0; Chi^2=1.12, df=3(P=0.77); I^2=0%					
Test for overall effect: Z=0.23(P=0.82)					
2.11.4 Unclear					
SLGA2004	2/71	1/69		0.42%	1.97[0.17,22.25]
Subtotal (95% CI)	**71**	**69**		**0.42%**	**1.97[0.17,22.25]**
Total events: 2 (LABA), 1 (Placbeo)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.55(P=0.58)					
Total (95% CI)	**15476**	**15467**		**100%**	**1.11[0.93,1.32]**
Total events: 268 (LABA), 242 (Placbeo)					
Heterogeneity: Tau^2=0; Chi^2=22.27, df=19(P=0.27); I^2=14.7%					
Test for overall effect: Z=1.15(P=0.25)					

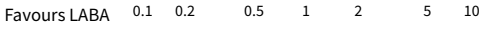


Study or subgroup	LABA n/N	Placbeo n/N	Odds Ratio M-H, Fixed, 95% CI	Weight	Odds Ratio M-H, Fixed, 95% CI
Test for subgroup differences: Chi²=3.97, df=1 (P=0.27), I²=24.37%					



Analysis 2.12. Comparison 2 Studies with parallel group design: withdrawal & safety outcomes, Outcome 12 Withdrawals (asthma-related adverse events).

Study or subgroup	LABA n/N	PLACEBO n/N	Odds Ratio M-H, Fixed, 95% CI	Odds Ratio M-H, Fixed, 95% CI
2.12.1 Participants using mixed cointerventions				
2.12.2 Participants not using ICS				
Wolfe 2006	3/182	4/174		0.71[0.16,3.23]
2.12.4 Children <12 years				

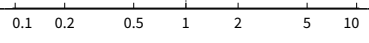


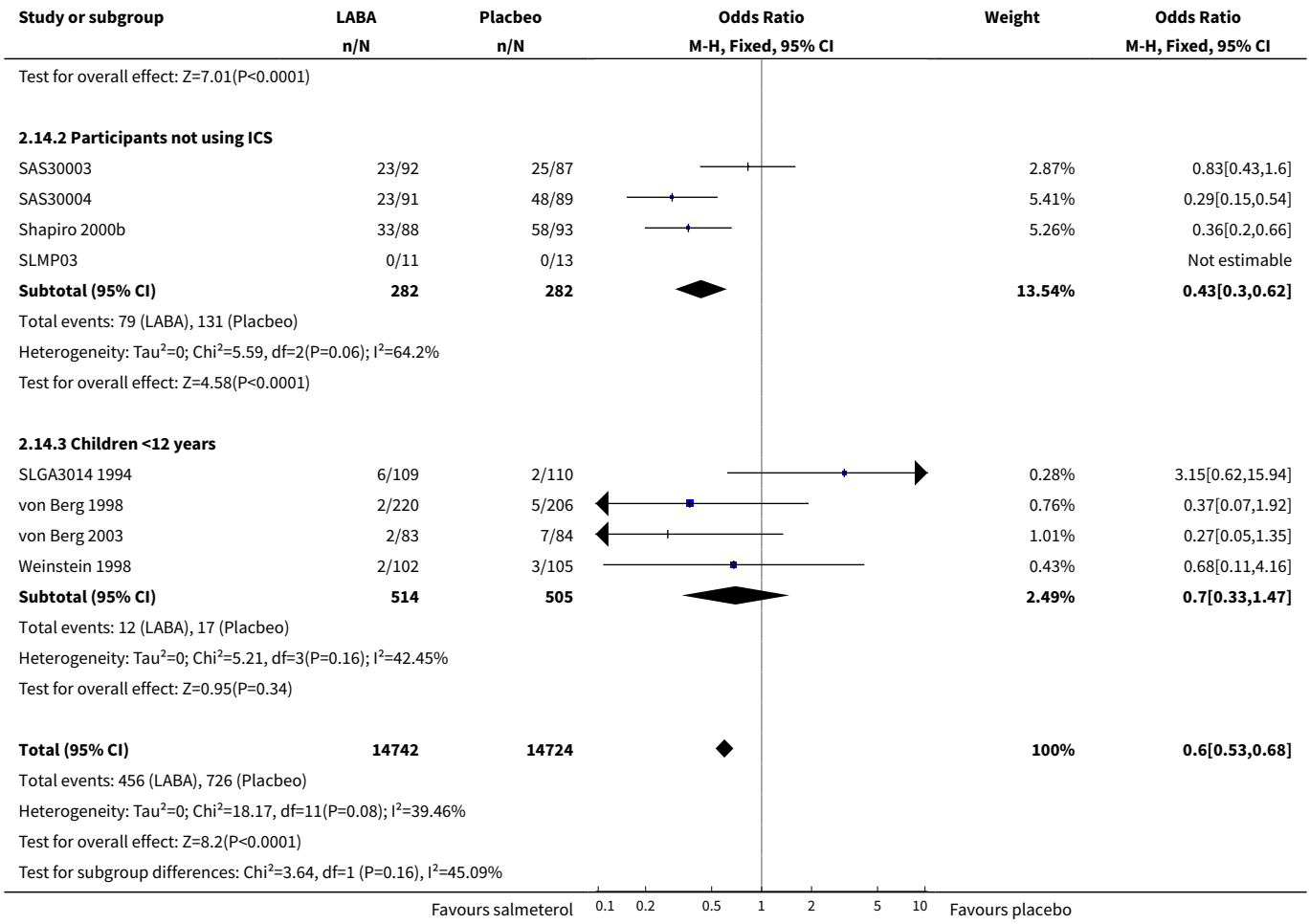
Analysis 2.13. Comparison 2 Studies with parallel group design: withdrawal & safety outcomes, Outcome 13 Withdrawals (abnormal cadiovascular test).

Study or subgroup	LABA n/N	PLACEBO n/N	Odds Ratio M-H, Fixed, 95% CI	Odds Ratio M-H, Fixed, 95% CI
2.13.1 Participants using mixed cointerventions				
2.13.2 Participants not using ICS				
2.13.3 Children <12 years				
Levy 2005	2/127	1/122		1.94[0.17,21.63]

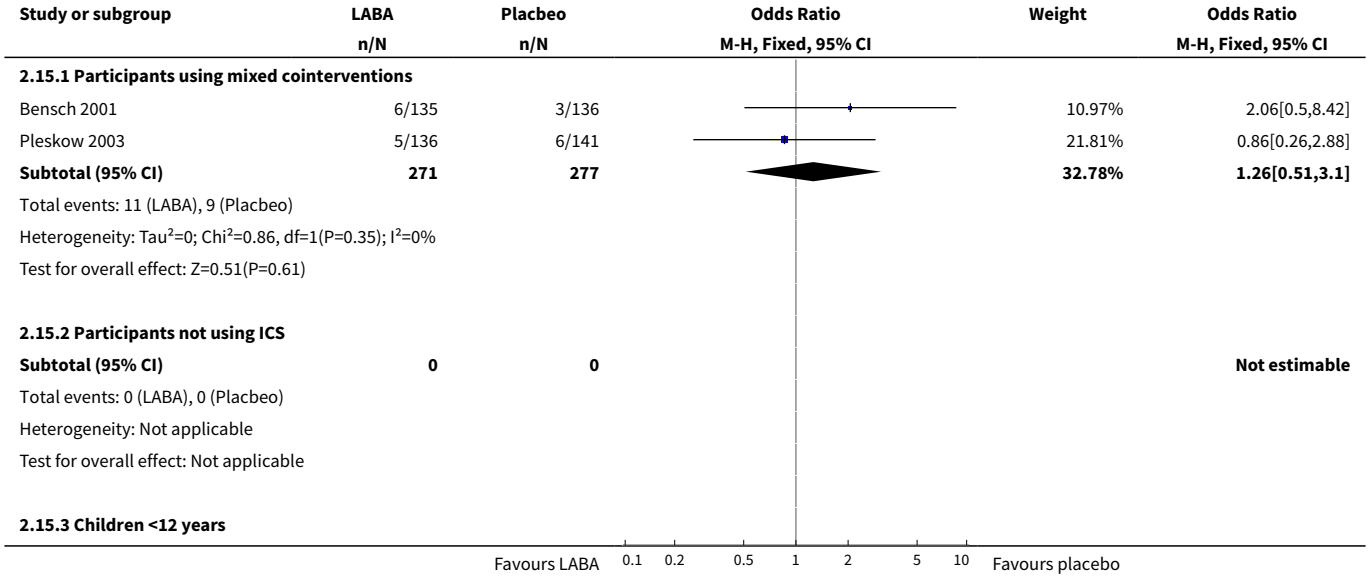
Analysis 2.14. Comparison 2 Studies with parallel group design: withdrawal & safety outcomes, Outcome 14 Withdrawals (lack of efficacy).

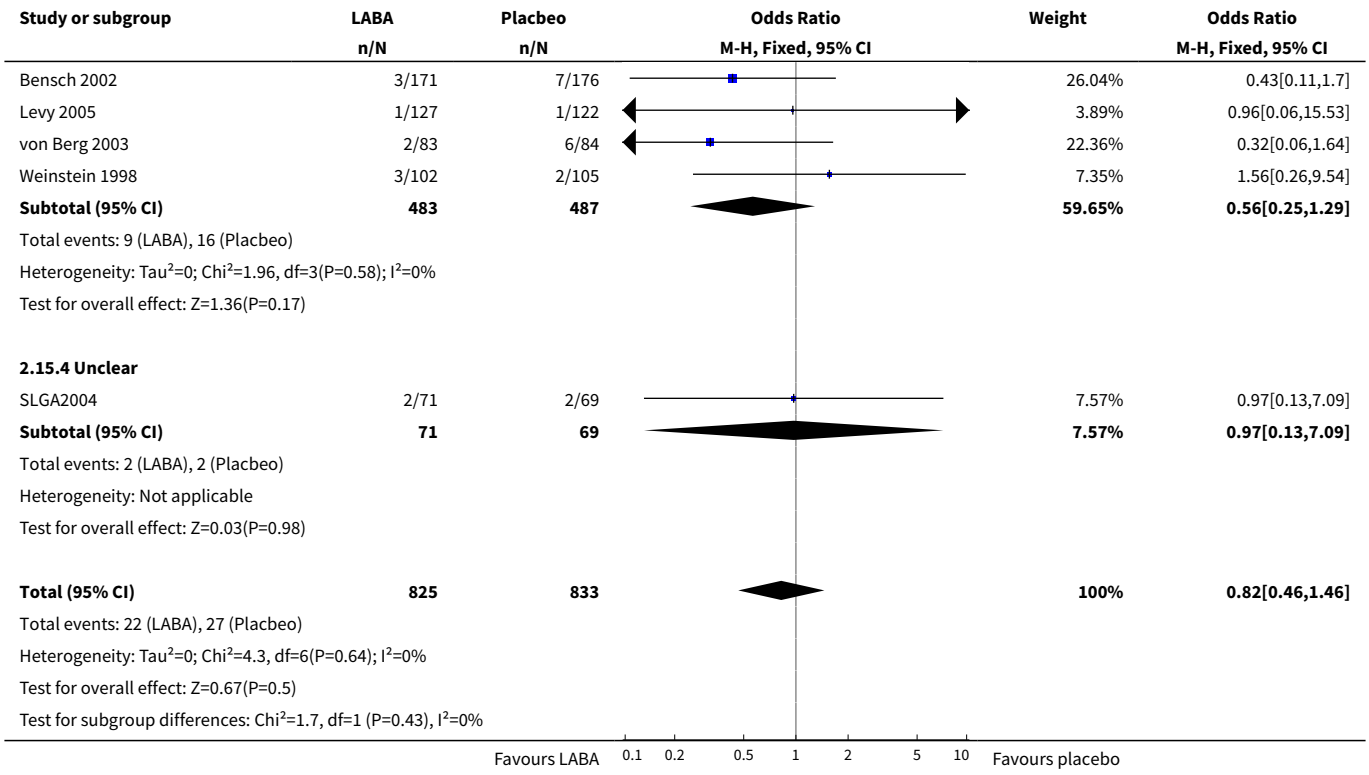
Study or subgroup	LABA n/N	Placbeo n/N	Odds Ratio M-H, Fixed, 95% CI	Weight	Odds Ratio M-H, Fixed, 95% CI
2.14.1 Participants using mixed cointerventions					
SLGL82	0/45	0/45			Not estimable
SMART	343/13176	535/13179		77.69%	0.63[0.55,0.72]
SMS40221	0/32	6/32		0.95%	0.06[0,1.17]
Wolfe 2000a	2/80	6/81		0.87%	0.32[0.06,1.64]
Wolfe 2000b	8/86	9/86		1.22%	0.88[0.32,2.39]
Wolfe 2006	12/527	22/514		3.25%	0.52[0.26,1.06]
Subtotal (95% CI)	**13946**	**13937**		**83.97%**	**0.62[0.54,0.71]**
Total events: 365 (LABA), 578 (Placbeo)					
Heterogeneity: Tau²=0; Chi²=3.74, df=4(P=0.44); I²=0%					



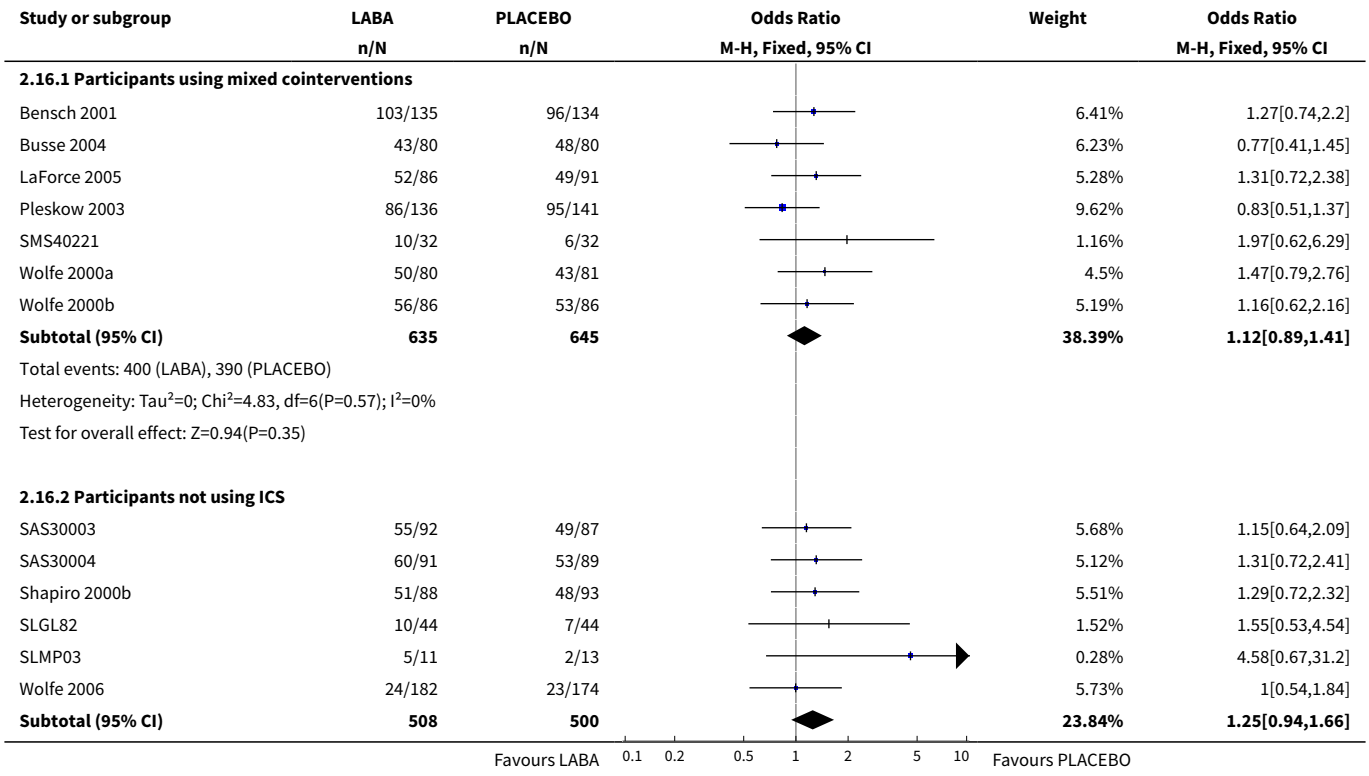


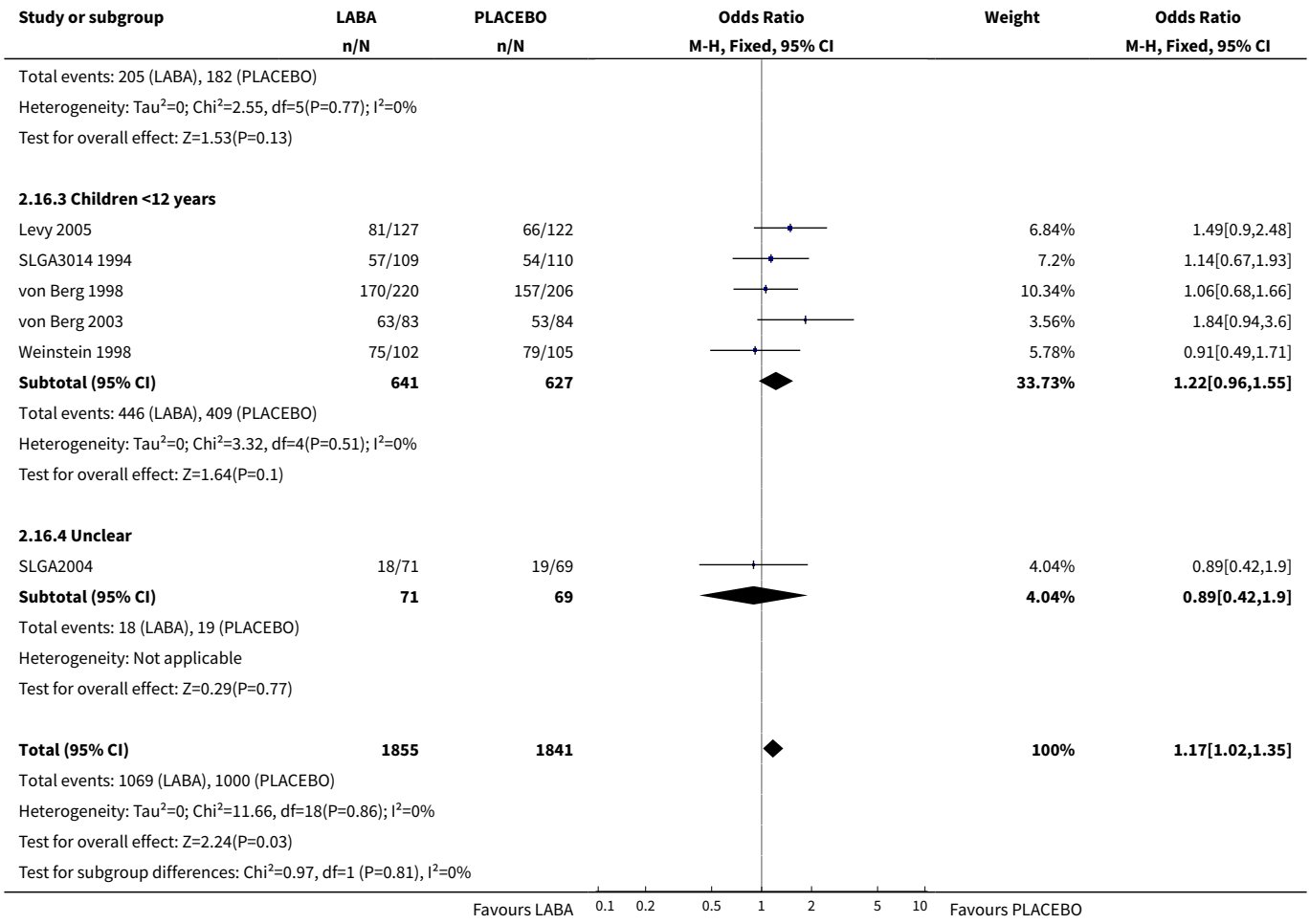
Analysis 2.15. Comparison 2 Studies with parallel group design: withdrawal & safety outcomes, Outcome 15 Withdrawals (exacerbation of asthma).



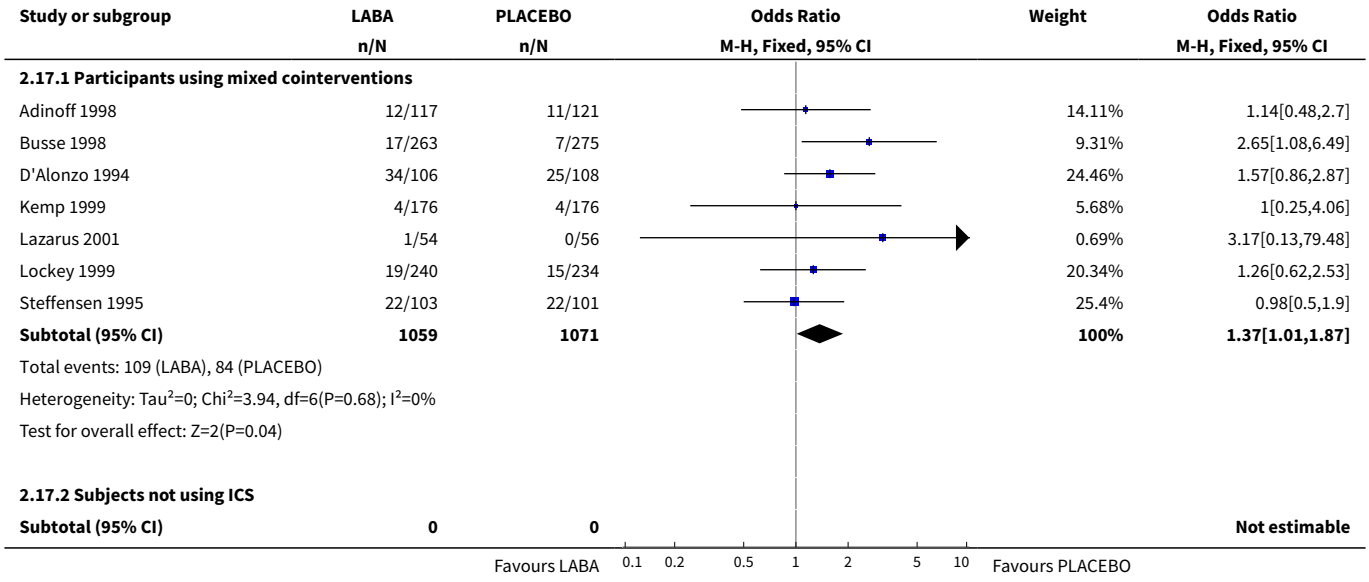


Analysis 2.16. Comparison 2 Studies with parallel group design: withdrawal & safety outcomes, Outcome 16 Adverse events - total.

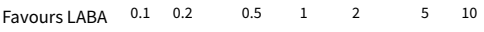




Analysis 2.17. Comparison 2 Studies with parallel group design: withdrawal & safety outcomes, Outcome 17 Adverse events - any drug related.

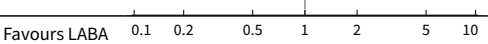


Study or subgroup	LABA n/N	PLACEBO n/N	Odds Ratio M-H, Fixed, 95% CI	Weight	Odds Ratio M-H, Fixed, 95% CI
Total events: 0 (LABA), 0 (PLACEBO)					
Heterogeneity: Not applicable					
Test for overall effect: Not applicable					
2.17.3 Children <12 years					
Subtotal (95% CI)	**0**	**0**			**Not estimable**
Total events: 0 (LABA), 0 (PLACEBO)					
Heterogeneity: Not applicable					
Test for overall effect: Not applicable					
Total (95% CI)	**1059**	**1071**		**100%**	**1.37[1.01,1.87]**
Total events: 109 (LABA), 84 (PLACEBO)					
Heterogeneity: Tau^2=0; Chi^2=3.94, df=6(P=0.68); I^2=0%					
Test for overall effect: Z=2(P=0.04)					
Test for subgroup differences: Not applicable					



Analysis 2.18. Comparison 2 Studies with parallel group design: withdrawal & safety outcomes, Outcome 18 Adverse events - asthma related.

Study or subgroup	LABA n/N	Placebo n/N	Odds Ratio M-H, Fixed, 95% CI	Weight	Odds Ratio M-H, Fixed, 95% CI
2.18.1 Participants mixed cointerventions					
Wolfe 2006	72/527	81/514		100%	0.85[0.6,1.19]
Subtotal (95% CI)	**527**	**514**		**100%**	**0.85[0.6,1.19]**
Total events: 72 (LABA), 81 (Placebo)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.95(P=0.34)					
2.18.2 Participants not using ICS					
Subtotal (95% CI)	**0**	**0**			**Not estimable**
Total events: 0 (LABA), 0 (Placebo)					
Heterogeneity: Not applicable					
Test for overall effect: Not applicable					
2.18.3 Children <12 years					
Subtotal (95% CI)	**0**	**0**			**Not estimable**
Total events: 0 (LABA), 0 (Placebo)					
Heterogeneity: Not applicable					
Test for overall effect: Not applicable					
Total (95% CI)	**527**	**514**		**100%**	**0.85[0.6,1.19]**
Total events: 72 (LABA), 81 (Placebo)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.95(P=0.34)					
Test for subgroup differences: Not applicable					

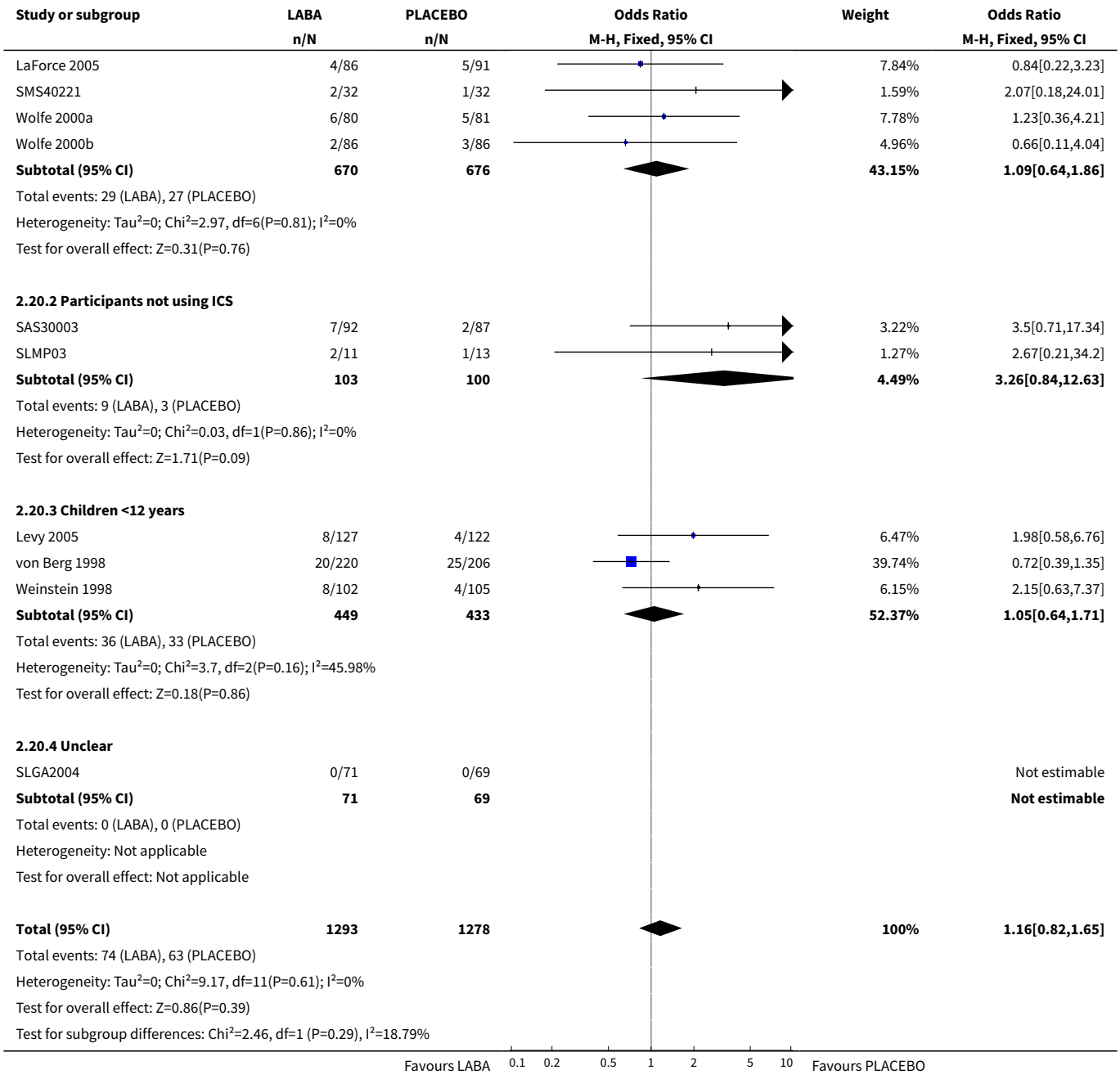


Analysis 2.19. Comparison 2 Studies with parallel group design: withdrawal & safety outcomes, Outcome 19 Adverse events - pharyngitis.

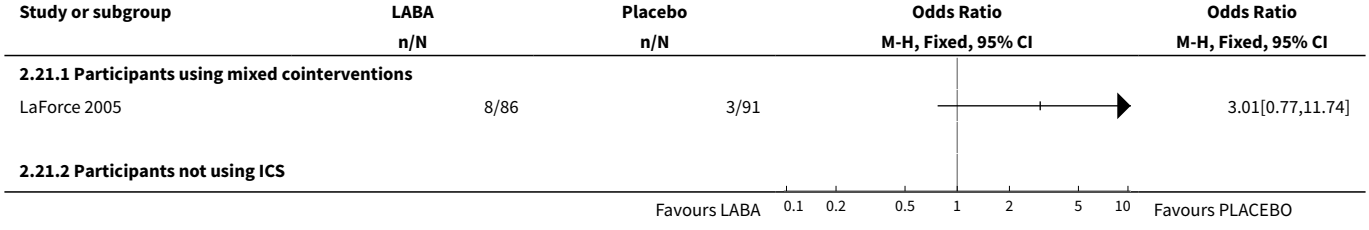
Study or subgroup	LABA n/N	PLACEBO n/N	Odds Ratio M-H, Fixed, 95% CI	Weight	Odds Ratio M-H, Fixed, 95% CI
2.19.1 Participants using mixed cointerventions					
Busse 2004	8/80	5/80		13.07%	1.67[0.52,5.33]
Pleskow 2003	11/136	7/141		18.35%	1.68[0.63,4.48]
Subtotal (95% CI)	**216**	**221**		**31.43%**	**1.68[0.79,3.55]**
Total events: 19 (LABA), 12 (PLACEBO)					
Heterogeneity: Tau^2=0; Chi^2=0, df=1(P=0.99); I^2=0%					
Test for overall effect: Z=1.35(P=0.18)					
2.19.2 Participants not using ICS					
Subtotal (95% CI)	**0**	**0**			**Not estimable**
Total events: 0 (LABA), 0 (PLACEBO)					
Heterogeneity: Not applicable					
Test for overall effect: Not applicable					
2.19.3 Children <12 years					
Levy 2005	9/127	6/122		16.52%	1.47[0.51,4.27]
SLGA3014 1994	4/109	2/110		5.57%	2.06[0.37,11.47]
von Berg 2003	5/83	4/84		10.85%	1.28[0.33,4.95]
Weinstein 1998	15/102	14/105		34.19%	1.12[0.51,2.46]
Subtotal (95% CI)	**421**	**421**		**67.13%**	**1.31[0.76,2.25]**
Total events: 33 (LABA), 26 (PLACEBO)					
Heterogeneity: Tau^2=0; Chi^2=0.47, df=3(P=0.93); I^2=0%					
Test for overall effect: Z=0.98(P=0.33)					
2.19.4 Unclear					
SLGA2004	1/71	0/69		1.44%	2.96[0.12,73.85]
Subtotal (95% CI)	**71**	**69**		**1.44%**	**2.96[0.12,73.85]**
Total events: 1 (LABA), 0 (PLACEBO)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.66(P=0.51)					
Total (95% CI)	**708**	**711**		**100%**	**1.45[0.94,2.24]**
Total events: 53 (LABA), 38 (PLACEBO)					
Heterogeneity: Tau^2=0; Chi^2=0.94, df=6(P=0.99); I^2=0%					
Test for overall effect: Z=1.68(P=0.09)					
Test for subgroup differences: Chi^2=0.47, df=1 (P=0.79), I^2=0%					

Analysis 2.20. Comparison 2 Studies with parallel group design: withdrawal & safety outcomes, Outcome 20 Adverse events - cough.

Study or subgroup	LABA n/N	PLACEBO n/N	Odds Ratio M-H, Fixed, 95% CI	Weight	Odds Ratio M-H, Fixed, 95% CI
2.20.1 Participants using mixed cointerventions					
Bensch 2001	11/135	6/134		9.37%	1.89[0.68,5.27]
Busse 2004	2/80	4/80		6.6%	0.49[0.09,2.74]
Dahl 1991a	2/171	3/172		5.01%	0.67[0.11,4.04]



Analysis 2.21. Comparison 2 Studies with parallel group design: withdrawal & safety outcomes, Outcome 21 Adverse events - nasopharyngitis.



Study or subgroup	LABA n/N	Placebo n/N	Odds Ratio M-H, Fixed, 95% CI	Odds Ratio M-H, Fixed, 95% CI
2.21.3 Children <12 years				

Favours LABA 0.1 0.2 0.5 1 2 5 10 Favours PLACEBO

Analysis 2.22. Comparison 2 Studies with parallel group design: withdrawal & safety outcomes, Outcome 22 Adverse events - throat irritation.

Study or subgroup	LABA n/N	PLACEBO n/N	Odds Ratio M-H, Fixed, 95% CI	Weight	Odds Ratio M-H, Fixed, 95% CI
2.22.1 Participants using mixed cointerventions					
LaForce 2005	5/86	7/91		18.79%	0.74[0.23,2.43]
SLGL82	3/44	0/44		1.35%	7.51[0.38,149.74]
Wolfe 2000a	16/80	4/81		9.33%	4.81[1.53,15.12]
Wolfe 2000b	7/86	4/86		10.78%	1.82[0.51,6.45]
Subtotal (95% CI)	**296**	**302**		**40.25%**	**2.2[1.17,4.13]**
Total events: 31 (LABA), 15 (PLACEBO)					
Heterogeneity: Tau^2=0; Chi^2=5.76, df=3(P=0.12); I^2=47.89%					
Test for overall effect: Z=2.45(P=0.01)					
2.22.2 Subjects not using ICS					
SAS30003	8/92	7/87		19.27%	1.09[0.38,3.14]
SAS30004	6/91	5/89		13.85%	1.19[0.35,4.04]
Shapiro 2000b	5/88	3/93		8.07%	1.81[0.42,7.8]
Subtotal (95% CI)	**271**	**269**		**41.19%**	**1.26[0.63,2.54]**
Total events: 19 (LABA), 15 (PLACEBO)					
Heterogeneity: Tau^2=0; Chi^2=0.32, df=2(P=0.85); I^2=0%					
Test for overall effect: Z=0.65(P=0.51)					
2.22.3 Children <12 years					
SLGA3014 1994	10/109	7/110		18.56%	1.49[0.54,4.06]
Subtotal (95% CI)	**109**	**110**		**18.56%**	**1.49[0.54,4.06]**
Total events: 10 (LABA), 7 (PLACEBO)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.77(P=0.44)					
Total (95% CI)	**676**	**681**		**100%**	**1.68[1.1,2.56]**
Total events: 60 (LABA), 37 (PLACEBO)					
Heterogeneity: Tau^2=0; Chi^2=7.07, df=7(P=0.42); I^2=1.03%					
Test for overall effect: Z=2.41(P=0.02)					
Test for subgroup differences: Chi^2=1.4, df=1 (P=0.5), I^2=0%					

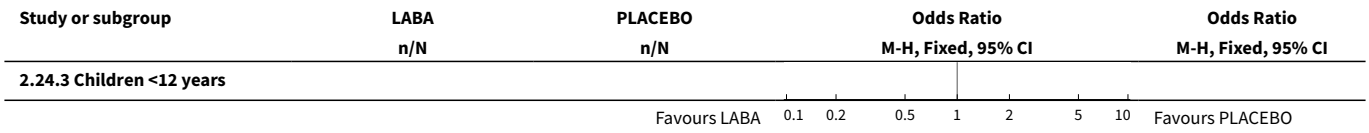
Favours LABA 0.1 0.2 0.5 1 2 5 10 Favours PLACEBO

Analysis 2.23. Comparison 2 Studies with parallel group design: withdrawal & safety outcomes, Outcome 23 Adverse events - upper respiratory tract infection.

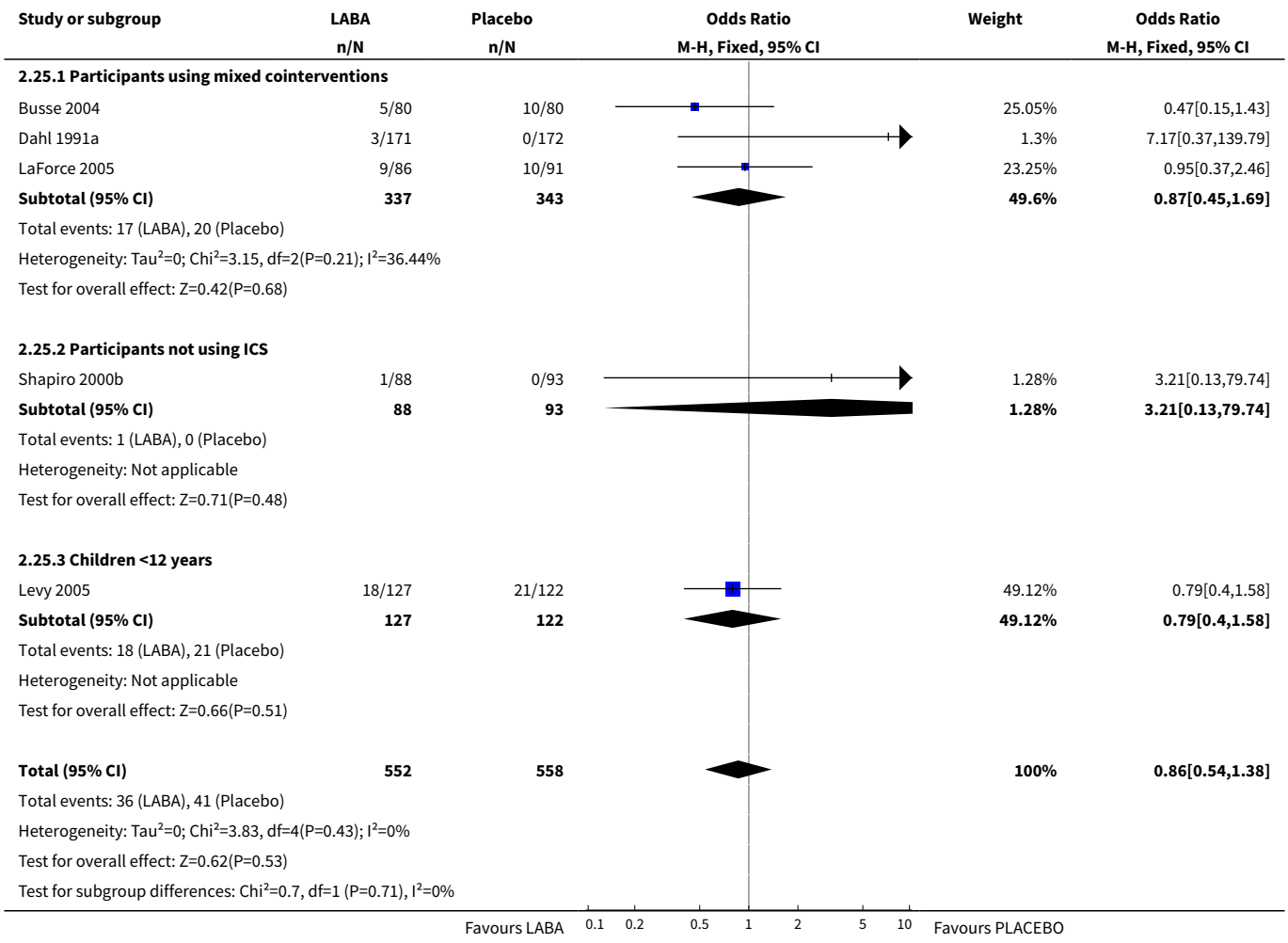
Study or subgroup	LABA n/N	Placebo n/N	Odds Ratio M-H, Fixed, 95% CI	Weight	Odds Ratio M-H, Fixed, 95% CI
2.23.1 Participants using mixed cointerventions					
Busse 2004	6/80	8/80		5.3%	0.73[0.24,2.21]
Dahl 1991a	1/171	4/172		2.84%	0.25[0.03,2.23]
LaForce 2005	6/86	10/91		6.48%	0.61[0.21,1.75]
SMS40221	3/32	3/32		1.95%	1[0.19,5.37]
Wolfe 2000a	12/80	20/81		12.11%	0.54[0.24,1.19]
Wolfe 2000b	27/86	30/86		14.75%	0.85[0.45,1.61]
Subtotal (95% CI)	**535**	**542**		**43.42%**	**0.68[0.46,1.01]**
Total events: 55 (LABA), 75 (Placebo)					
Heterogeneity: Tau^2=0; Chi^2=1.9, df=5(P=0.86); I^2=0%					
Test for overall effect: Z=1.91(P=0.06)					
2.23.2 Subjects not using ICS					
SAS30003	11/92	11/87		7.13%	0.94[0.38,2.29]
SAS30004	17/91	11/89		6.48%	1.63[0.72,3.71]
Shapiro 2000b	19/88	9/93		4.92%	2.57[1.09,6.04]
Subtotal (95% CI)	**271**	**269**		**18.53%**	**1.61[0.99,2.63]**
Total events: 47 (LABA), 31 (Placebo)					
Heterogeneity: Tau^2=0; Chi^2=2.56, df=2(P=0.28); I^2=21.81%					
Test for overall effect: Z=1.92(P=0.05)					
2.23.3 Children <12 years					
Levy 2005	6/127	2/122		1.39%	2.98[0.59,15.04]
von Berg 1998	61/220	47/206		25.14%	1.3[0.84,2.01]
von Berg 2003	22/83	22/84		11.52%	1.02[0.51,2.02]
Subtotal (95% CI)	**430**	**412**		**38.05%**	**1.27[0.89,1.82]**
Total events: 89 (LABA), 71 (Placebo)					
Heterogeneity: Tau^2=0; Chi^2=1.47, df=2(P=0.48); I^2=0%					
Test for overall effect: Z=1.32(P=0.19)					
Total (95% CI)	**1236**	**1223**		**100%**	**1.08[0.86,1.36]**
Total events: 191 (LABA), 177 (Placebo)					
Heterogeneity: Tau^2=0; Chi^2=14.03, df=11(P=0.23); I^2=21.62%					
Test for overall effect: Z=0.65(P=0.52)					
Test for subgroup differences: Chi^2=8.68, df=1 (P=0.01), I^2=76.97%					

Analysis 2.24. Comparison 2 Studies with parallel group design: withdrawal & safety outcomes, Outcome 24 Adverse events - dyspnea.

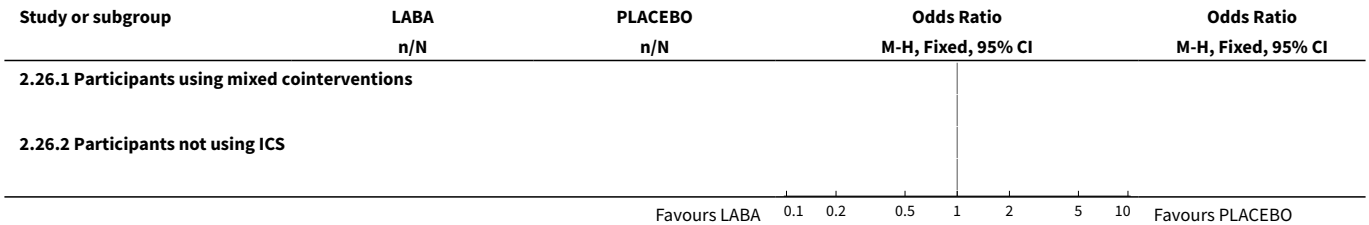
Study or subgroup	LABA n/N	PLACEBO n/N	Odds Ratio M-H, Fixed, 95% CI	Odds Ratio M-H, Fixed, 95% CI
2.24.1 Participants using mixed cointerventions				
Bensch 2001	2/135	1/134		2[0.18,22.32]
2.24.2 Participants not using ICS				



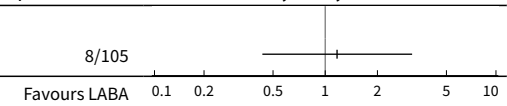
Analysis 2.25. Comparison 2 Studies with parallel group design: withdrawal & safety outcomes, Outcome 25 Adverse events - exacerbation of asthma.



Analysis 2.26. Comparison 2 Studies with parallel group design: withdrawal & safety outcomes, Outcome 26 Adverse events - otitis media.

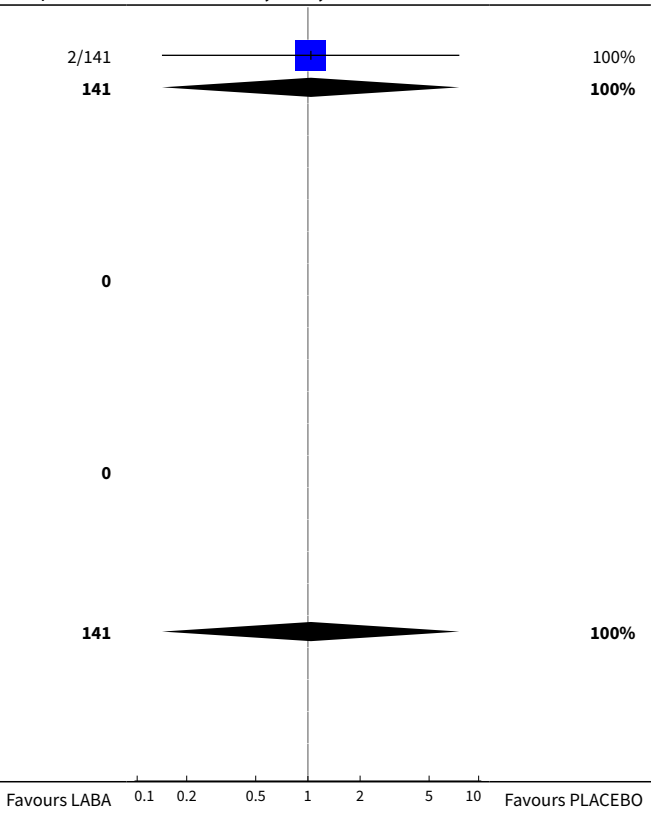


Study or subgroup	LABA n/N	PLACEBO n/N	Odds Ratio M-H, Fixed, 95% CI	Odds Ratio M-H, Fixed, 95% CI
2.26.3 Children <12 years				
Weinstein 1998	9/102	8/105		1.17[0.43,3.17]



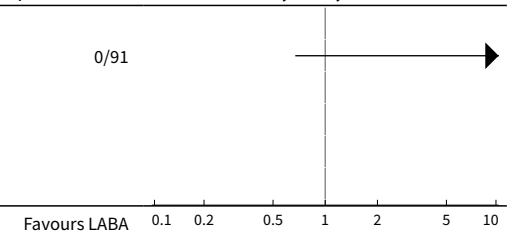
Analysis 2.27. Comparison 2 Studies with parallel group design: withdrawal & safety outcomes, Outcome 27 Adverse events - sinus headache.

Study or subgroup	LABA n/N	Placebo n/N	Odds Ratio M-H, Fixed, 95% CI	Weight	Odds Ratio M-H, Fixed, 95% CI
2.27.1 Participants using mixed cointerventions					
Pleskow 2003	2/136	2/141		100%	1.04[0.14,7.47]
Subtotal (95% CI)	**136**	**141**		**100%**	**1.04[0.14,7.47]**
Total events: 2 (LABA), 2 (Placebo)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.04(P=0.97)					
2.27.2 Participants not using ICS					
Subtotal (95% CI)	**0**	**0**			**Not estimable**
Total events: 0 (LABA), 0 (Placebo)					
Heterogeneity: Not applicable					
Test for overall effect: Not applicable					
2.27.3 Children <12 years					
Subtotal (95% CI)	**0**	**0**			**Not estimable**
Total events: 0 (LABA), 0 (Placebo)					
Heterogeneity: Not applicable					
Test for overall effect: Not applicable					
Total (95% CI)	**136**	**141**		**100%**	**1.04[0.14,7.47]**
Total events: 2 (LABA), 2 (Placebo)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.04(P=0.97)					
Test for subgroup differences: Not applicable					



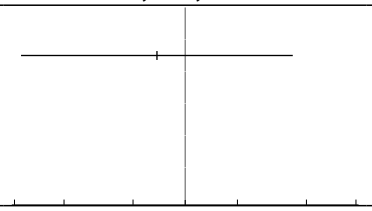
Analysis 2.28. Comparison 2 Studies with parallel group design: withdrawal & safety outcomes, Outcome 28 Adverse events - pyrexia.

Study or subgroup	LABA n/N	Placebo n/N	Odds Ratio M-H, Fixed, 95% CI	Odds Ratio M-H, Fixed, 95% CI
2.28.1 Participants using mixed cointerventions				
LaForce 2005	5/86	0/91		12.35[0.67,226.79]
2.28.2 Participants not using ICS				
2.28.3 Children <12 years				



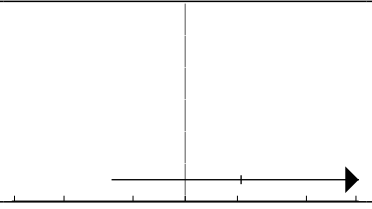
Analysis 2.29. Comparison 2 Studies with parallel group design: withdrawal & safety outcomes, Outcome 29 Adverse events - chest pain.

Study or subgroup	LABA n/N	Placebo n/N	Odds Ratio M-H, Fixed, 95% CI	Odds Ratio M-H, Fixed, 95% CI
2.29.1 Participants using mixed cointerventions				
Pleskow 2003	2/136	3/141		0.69[0.11,4.17]
2.29.2 Subjects not using ICS				
2.29.3 Children <12 years				



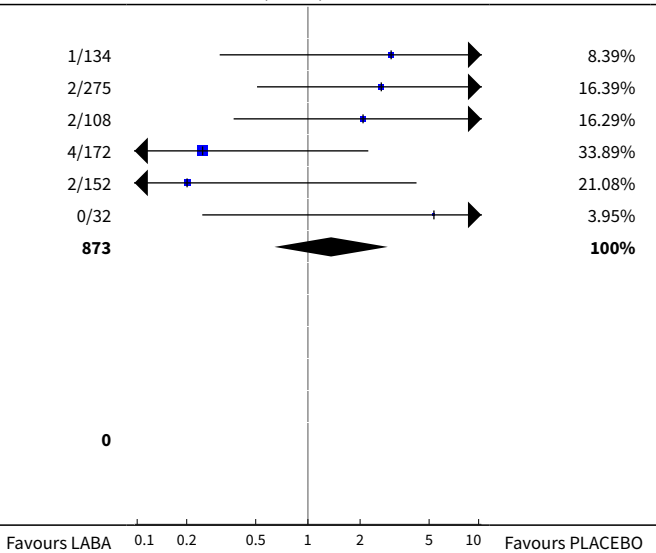
Analysis 2.30. Comparison 2 Studies with parallel group design: withdrawal & safety outcomes, Outcome 30 Adverse events - abnormal cardiovascular test.

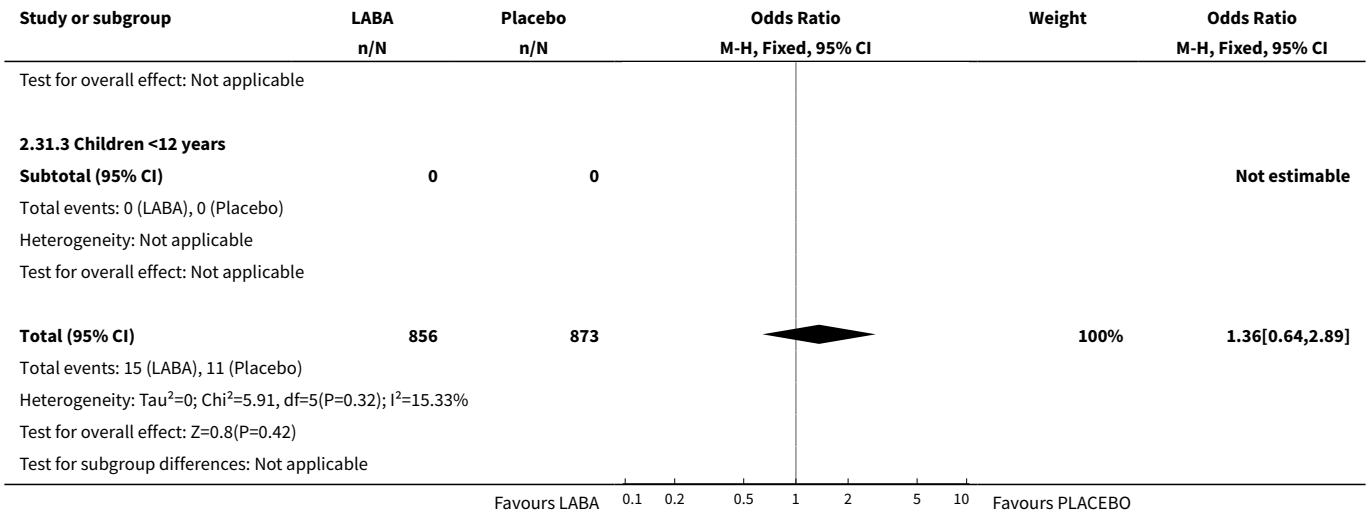
Study or subgroup	LABA n/N	Placebo n/N	Odds Ratio M-H, Fixed, 95% CI	Odds Ratio M-H, Fixed, 95% CI
2.30.1 Participants using mixed cointerventions				
2.30.2 Participants not using ICS				
2.30.3 Children <12 years				
Weinstein 1998	4/102	2/105		2.1[0.38,11.74]



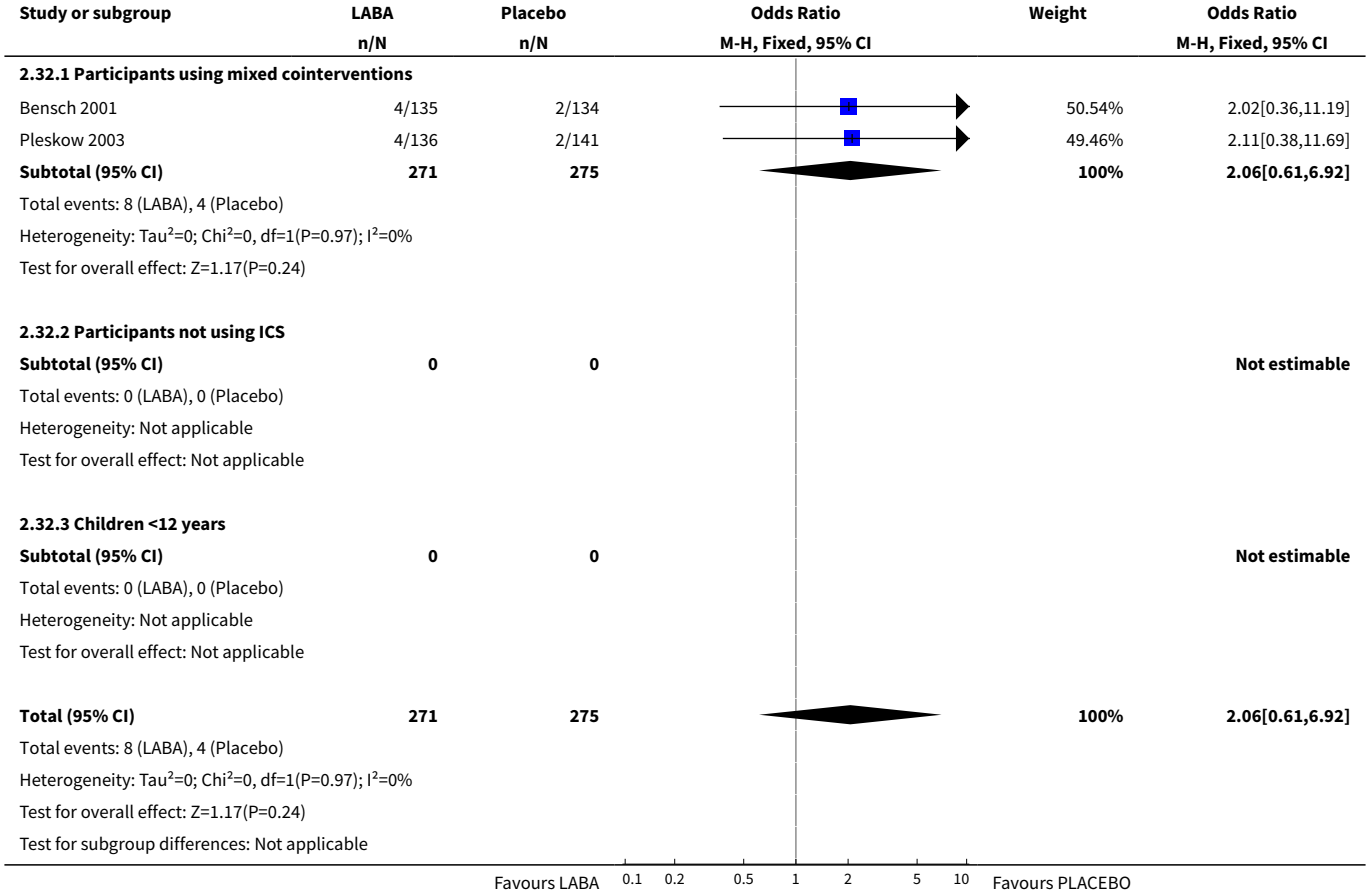
Analysis 2.31. Comparison 2 Studies with parallel group design: withdrawal & safety outcomes, Outcome 31 Adverse events - palpitations.

Study or subgroup	LABA n/N	Placebo n/N	Odds Ratio M-H, Fixed, 95% CI	Weight	Odds Ratio M-H, Fixed, 95% CI
2.31.1 Participants using mixed cointerventions					
Bensch 2001	3/135	1/134		8.39%	3.02[0.31,29.43]
Busse 1998	5/263	2/275		16.39%	2.65[0.51,13.76]
D'Alonzo 1994	4/106	2/108		16.29%	2.08[0.37,11.6]
Dahl 1991a	1/171	4/172		33.89%	0.25[0.03,2.23]
Kemp 1998a	0/149	2/152		21.08%	0.2[0.01,4.23]
SMS40221	2/32	0/32		3.95%	5.33[0.25,115.5]
Subtotal (95% CI)	**856**	**873**		**100%**	**1.36[0.64,2.89]**
Total events: 15 (LABA), 11 (Placebo)					
Heterogeneity: Tau^2=0; Chi^2=5.91, df=5(P=0.32); I^2=15.33%					
Test for overall effect: Z=0.8(P=0.42)					
2.31.2 Participants not using ICS					
Subtotal (95% CI)	**0**	**0**			**Not estimable**
Total events: 0 (LABA), 0 (Placebo)					
Heterogeneity: Not applicable					



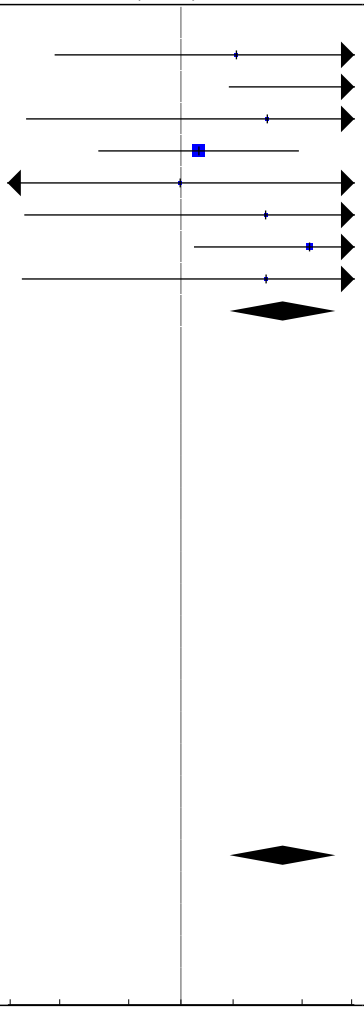


Analysis 2.32. Comparison 2 Studies with parallel group design: withdrawal & safety outcomes, Outcome 32 Adverse events - insomnia.



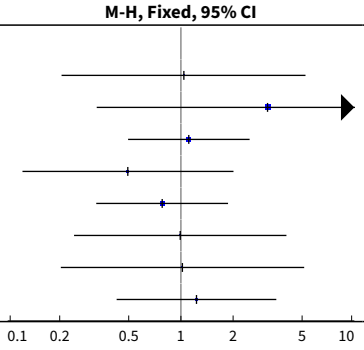
Analysis 2.33. Comparison 2 Studies with parallel group design: withdrawal & safety outcomes, Outcome 33 Adverse events - tremor.

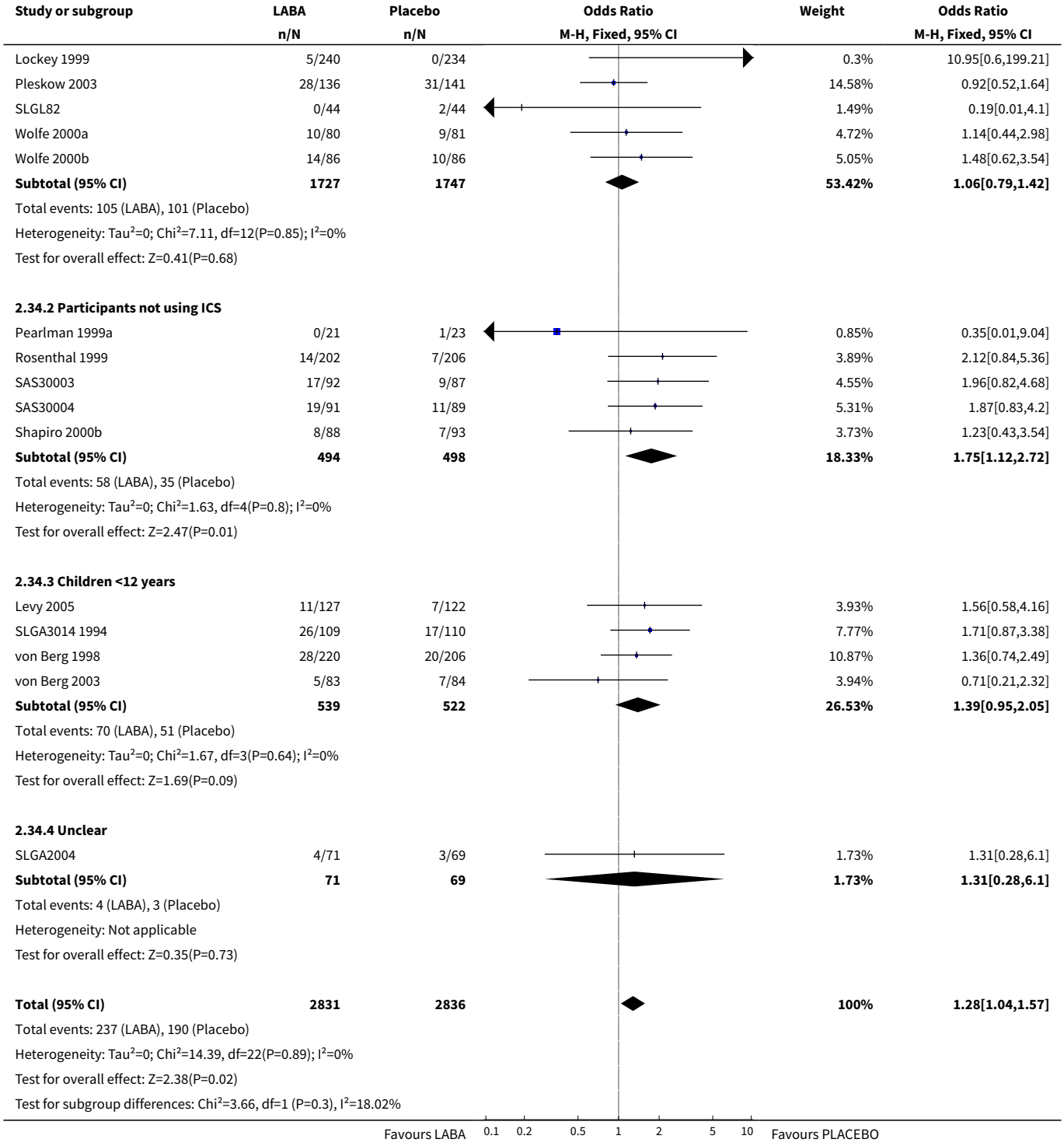
Study or subgroup	LABA n/N	Placebo n/N	Odds Ratio M-H, Fixed, 95% CI	Weight	Odds Ratio M-H, Fixed, 95% CI
2.33.1 Participants using mixed cointerventions					
Adinoff 1998	2/117	1/121		10.11%	2.09[0.19,23.33]
Bensch 2001	14/135	0/134		4.69%	32.1[1.89,543.91]
Busse 1998	1/263	0/275		5.09%	3.15[0.13,77.63]
Dahl 1991a	5/171	4/172		40.52%	1.27[0.33,4.79]
Ekstrom 1998b	1/114	1/113		10.42%	0.99[0.06,16.04]
Kemp 1998a	1/149	0/152		5.13%	3.08[0.12,76.23]
Pleskow 2003	10/136	2/141		19.04%	5.52[1.19,25.66]
SMS40221	1/32	0/32		4.99%	3.1[0.12,78.87]
Subtotal (95% CI)	**1117**	**1140**		**100%**	**3.86[1.91,7.78]**
Total events: 35 (LABA), 8 (Placebo)					
Heterogeneity: Tau^2=0; Chi^2=6.27, df=7(P=0.51); I^2=0%					
Test for overall effect: Z=3.77(P=0)					
2.33.2 Participants not using ICS					
Subtotal (95% CI)	**0**	**0**			**Not estimable**
Total events: 0 (LABA), 0 (Placebo)					
Heterogeneity: Not applicable					
Test for overall effect: Not applicable					
2.33.3 Children <12 years					
Subtotal (95% CI)	**0**	**0**			**Not estimable**
Total events: 0 (LABA), 0 (Placebo)					
Heterogeneity: Not applicable					
Test for overall effect: Not applicable					
Total (95% CI)	**1117**	**1140**		**100%**	**3.86[1.91,7.78]**
Total events: 35 (LABA), 8 (Placebo)					
Heterogeneity: Tau^2=0; Chi^2=6.27, df=7(P=0.51); I^2=0%					
Test for overall effect: Z=3.77(P=0)					
Test for subgroup differences: Not applicable					



Analysis 2.34. Comparison 2 Studies with parallel group design: withdrawal & safety outcomes, Outcome 34 Adverse events - headache.

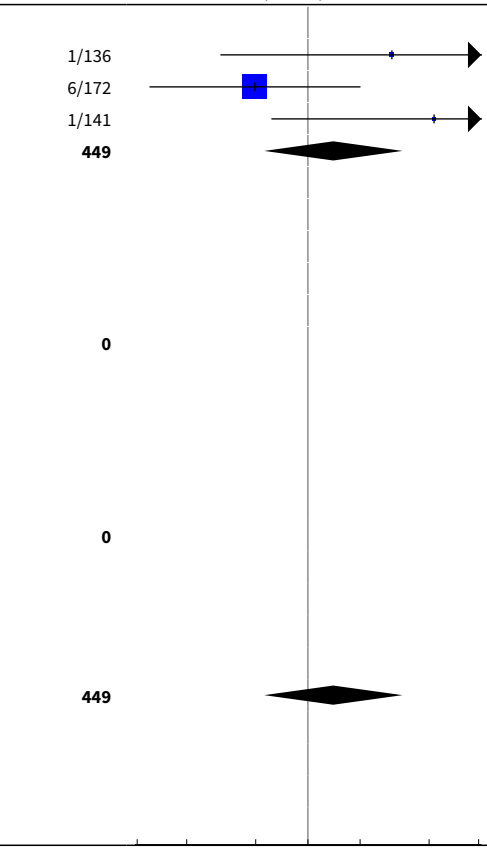
Study or subgroup	LABA n/N	Placebo n/N	Odds Ratio M-H, Fixed, 95% CI	Weight	Odds Ratio M-H, Fixed, 95% CI
2.34.1 Participants using mixed cointerventions					
Adinoff 1998	3/117	3/121		1.73%	1.04[0.2,5.23]
Busse 1998	3/263	1/275		0.58%	3.16[0.33,30.59]
D'Alonzo 1994	14/106	13/108		6.74%	1.11[0.5,2.49]
Dahl 1991a	3/171	6/172		3.55%	0.49[0.12,2.01]
Ekstrom 1998a	10/135	12/129		6.85%	0.78[0.32,1.87]
Ekstrom 1998b	4/114	4/113		2.34%	0.99[0.24,4.06]
Kemp 1998a	3/149	3/152		1.76%	1.02[0.2,5.14]
LaForce 2005	8/86	7/91		3.72%	1.23[0.43,3.55]





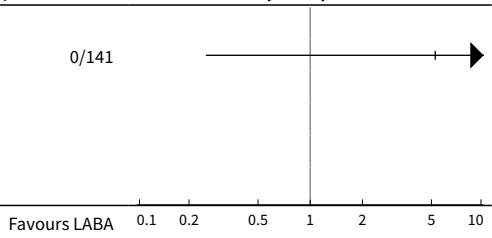
Analysis 2.35. Comparison 2 Studies with parallel group design: withdrawal & safety outcomes, Outcome 35 Adverse events - cramps.

Study or subgroup	LABA n/N	Placebo n/N	Odds Ratio M-H, Fixed, 95% CI	Weight	Odds Ratio M-H, Fixed, 95% CI
2.35.1 Participants using mixed cointerventions					
Bensch 2001	3/136	1/136		12.54%	3.05[0.31,29.65]
Dahl 1991a	3/171	6/172		75.34%	0.49[0.12,2.01]
Pleskow 2003	5/136	1/141		12.12%	5.34[0.62,46.34]
Subtotal (95% CI)	**443**	**449**		**100%**	**1.4[0.56,3.51]**
Total events: 11 (LABA), 8 (Placebo)					
Heterogeneity: Tau^2=0; Chi^2=4.04, df=2(P=0.13); I^2=50.55%					
Test for overall effect: Z=0.72(P=0.47)					
2.35.2 Participants not using ICS					
Subtotal (95% CI)	**0**	**0**			**Not estimable**
Total events: 0 (LABA), 0 (Placebo)					
Heterogeneity: Not applicable					
Test for overall effect: Not applicable					
2.35.3 Children <12 years					
Subtotal (95% CI)	**0**	**0**			**Not estimable**
Total events: 0 (LABA), 0 (Placebo)					
Heterogeneity: Not applicable					
Test for overall effect: Not applicable					
Total (95% CI)	**443**	**449**		**100%**	**1.4[0.56,3.51]**
Total events: 11 (LABA), 8 (Placebo)					
Heterogeneity: Tau^2=0; Chi^2=4.04, df=2(P=0.13); I^2=50.55%					
Test for overall effect: Z=0.72(P=0.47)					
Test for subgroup differences: Not applicable					



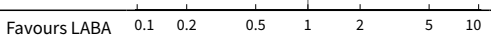
Analysis 2.36. Comparison 2 Studies with parallel group design: withdrawal & safety outcomes, Outcome 36 Adverse events - anxiety.

Study or subgroup	LABA n/N	Placebo n/N	Odds Ratio M-H, Fixed, 95% CI	Odds Ratio M-H, Fixed, 95% CI
2.36.1 Participants using mixed cointerventions				
Pleskow 2003	2/136	0/141		5.26[0.25,110.58]
2.36.2 Participants not using ICS				
2.36.3 Children <12 years				



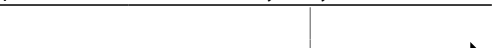
Analysis 2.37. Comparison 2 Studies with parallel group design: withdrawal & safety outcomes, Outcome 37 Adverse events - nervousness.

Study or subgroup	LABA n/N	Placebo n/N	Odds Ratio M-H, Fixed, 95% CI	Weight	Odds Ratio M-H, Fixed, 95% CI
2.37.1 Participants using mixed cointerventions					
Bensch 2001	9/135	2/134		50.73%	4.71[1,22.24]
Pleskow 2003	10/136	2/141		49.27%	5.52[1.19,25.66]
Subtotal (95% CI)	**271**	**275**		**100%**	**5.11[1.72,15.22]**
Total events: 19 (LABA), 4 (Placebo)					
Heterogeneity: Tau^2=0; Chi^2=0.02, df=1(P=0.89); I^2=0%					
Test for overall effect: Z=2.93(P=0)					
2.37.2 Participants not using ICS					
Subtotal (95% CI)	**0**	**0**			**Not estimable**
Total events: 0 (LABA), 0 (Placebo)					
Heterogeneity: Not applicable					
Test for overall effect: Not applicable					
2.37.3 Children <12 years					
Subtotal (95% CI)	**0**	**0**			**Not estimable**
Total events: 0 (LABA), 0 (Placebo)					
Heterogeneity: Not applicable					
Test for overall effect: Not applicable					
Total (95% CI)	**271**	**275**		**100%**	**5.11[1.72,15.22]**
Total events: 19 (LABA), 4 (Placebo)					
Heterogeneity: Tau^2=0; Chi^2=0.02, df=1(P=0.89); I^2=0%					
Test for overall effect: Z=2.93(P=0)					
Test for subgroup differences: Not applicable					



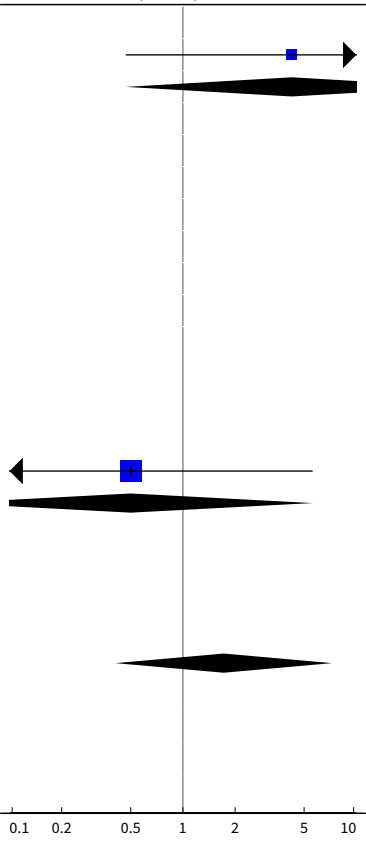
Analysis 2.38. Comparison 2 Studies with parallel group design: withdrawal & safety outcomes, Outcome 38 Adverse events - nausea.

Study or subgroup	LABA n/N	Placebo n/N	Odds Ratio M-H, Fixed, 95% CI	Odds Ratio M-H, Fixed, 95% CI
2.38.1 Participants using mixed cointerventions				
SLGL82	1/44	0/44		3.07[0.12,77.41]
2.38.2 Participants not using ICS				
2.38.3 Children <12 years				



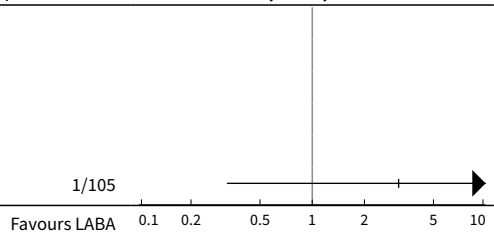
Analysis 2.39. Comparison 2 Studies with parallel group design: withdrawal & safety outcomes, Outcome 39 Adverse events - myalgia/fatigue.

Study or subgroup	LABA n/N	Placebo n/N	Odds Ratio M-H, Fixed, 95% CI	Weight	Odds Ratio M-H, Fixed, 95% CI
2.39.1 Participants using mixed cointerventions					
Pleskow 2003	4/136	1/141		32.58%	4.24[0.47,38.45]
Subtotal (95% CI)	**136**	**141**		**32.58%**	**4.24[0.47,38.45]**
Total events: 4 (LABA), 1 (Placebo)					
Heterogeneity: Not applicable					
Test for overall effect: Z=1.29(P=0.2)					
2.39.2 Participants not using ICS					
Subtotal (95% CI)	**0**	**0**			**Not estimable**
Total events: 0 (LABA), 0 (Placebo)					
Heterogeneity: Not applicable					
Test for overall effect: Not applicable					
2.39.3 Children <12 years					
SLGA3014 1994	1/109	2/110		67.42%	0.5[0.04,5.6]
Subtotal (95% CI)	**109**	**110**		**67.42%**	**0.5[0.04,5.6]**
Total events: 1 (LABA), 2 (Placebo)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.56(P=0.57)					
Total (95% CI)	**245**	**251**		**100%**	**1.72[0.41,7.24]**
Total events: 5 (LABA), 3 (Placebo)					
Heterogeneity: Tau^2=0; Chi^2=1.65, df=1(P=0.2); I^2=39.38%					
Test for overall effect: Z=0.74(P=0.46)					
Test for subgroup differences: Chi^2=1.64, df=1 (P=0.2), I^2=39.13%					



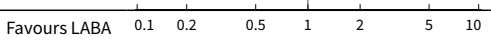
Analysis 2.40. Comparison 2 Studies with parallel group design: withdrawal & safety outcomes, Outcome 40 Adverse events - pain in limb.

Study or subgroup	LABA n/N	Placebo n/N	Odds Ratio M-H, Fixed, 95% CI	Odds Ratio M-H, Fixed, 95% CI
2.40.1 Participants using mixed cointerventions				
2.40.2 Participants not using ICS				
2.40.3 Children <12 years				
Weinstein 1998	3/102	1/105		3.15[0.32,30.81]



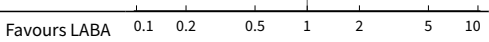
Analysis 2.41. Comparison 2 Studies with parallel group design: withdrawal & safety outcomes, Outcome 41 Adverse events - musculoskeletal pain.

Study or subgroup	LABA n/N	Placebo n/N	Odds Ratio M-H, Fixed, 95% CI	Weight	Odds Ratio M-H, Fixed, 95% CI
2.41.1 Participants using mixed cointerventions					
Wolfe 2000a	4/80	6/81		66.99%	0.66[0.18,2.43]
Wolfe 2000b	6/86	3/86		33.01%	2.08[0.5,8.58]
Subtotal (95% CI)	**166**	**167**		**100%**	**1.13[0.45,2.84]**
Total events: 10 (LABA), 9 (Placebo)					
Heterogeneity: Tau^2=0; Chi^2=1.36, df=1(P=0.24); I^2=26.69%					
Test for overall effect: Z=0.25(P=0.8)					
2.41.2 Participants not using ICS					
Subtotal (95% CI)	**0**	**0**			**Not estimable**
Total events: 0 (LABA), 0 (Placebo)					
Heterogeneity: Not applicable					
Test for overall effect: Not applicable					
2.41.3 Children <12 years					
Subtotal (95% CI)	**0**	**0**			**Not estimable**
Total events: 0 (LABA), 0 (Placebo)					
Heterogeneity: Not applicable					
Test for overall effect: Not applicable					
Total (95% CI)	**166**	**167**		**100%**	**1.13[0.45,2.84]**
Total events: 10 (LABA), 9 (Placebo)					
Heterogeneity: Tau^2=0; Chi^2=1.36, df=1(P=0.24); I^2=26.69%					
Test for overall effect: Z=0.25(P=0.8)					
Test for subgroup differences: Not applicable					



Analysis 2.42. Comparison 2 Studies with parallel group design: withdrawal & safety outcomes, Outcome 42 Serious adverse event - respiratory.

Study or subgroup	LABA n/N	PLACEBO n/N	Odds Ratio M-H, Fixed, 95% CI	Odds Ratio M-H, Fixed, 95% CI
2.42.1 Participants using mixed cointerventions				
Bensch 2001	0/135	0/136		Not estimable
Pleskow 2003	0/136	0/141		Not estimable
2.42.2 Pariticipants not using ICS				
2.42.3 Children <12 years				



Comparison 3. Studies by severity of asthma

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Peak expiratory flow: morning	20	3682	L/min (Fixed, 95% CI)	15.17 [10.99, 19.36]
1.1 Mild asthma	4	140	L/min (Fixed, 95% CI)	20.74 [-5.26, 46.73]
1.2 Mild-moderate asthma	11	2410	L/min (Fixed, 95% CI)	16.12 [11.17, 21.07]
1.3 Persistent/symptomatic	3	809	L/min (Fixed, 95% CI)	15.04 [1.95, 28.13]
1.4 Severe asthma	0	0	L/min (Fixed, 95% CI)	0.0 [0.0, 0.0]
1.5 Unclear	2	323	L/min (Fixed, 95% CI)	9.94 [-0.72, 20.59]
2 Peak expiratory flow: evening	15	2751	L/min (Fixed, 95% CI)	12.29 [7.53, 17.04]
2.1 Mild asthma	3	79	L/min (Fixed, 95% CI)	35.87 [-6.69, 78.43]
2.2 Mild-moderate asthma	8	1685	L/min (Fixed, 95% CI)	13.29 [8.12, 18.46]
2.3 Persistent/symptomatic	2	661	L/min (Fixed, 95% CI)	3.68 [-10.23, 17.58]
2.4 Severe asthma	0	0	L/min (Fixed, 95% CI)	0.0 [0.0, 0.0]
2.5 Unclear	2	326	L/min (Fixed, 95% CI)	7.0 [-22.52, 36.52]
3 Change in PEF morning	25	5512	L/min (Random, 95% CI)	24.84 [20.41, 29.27]
3.1 Mild	1	408	L/min (Random, 95% CI)	20.9 [14.62, 27.18]
3.2 Mild-moderate asthma	9	2164	L/min (Random, 95% CI)	25.31 [16.25, 34.38]
3.3 Persistent/symptomatic	6	1661	L/min (Random, 95% CI)	26.31 [17.56, 35.06]
3.4 Moderate	2	274	L/min (Random, 95% CI)	19.11 [-13.72, 51.93]
3.5 Severe asthma	0	0	L/min (Random, 95% CI)	0.0 [0.0, 0.0]
3.6 Unclear	7	1005	L/min (Random, 95% CI)	24.23 [18.59, 29.88]
4 Change in PEF evening	22	5350	L/min (Random, 95% CI)	16.16 [12.25, 20.07]
4.1 Mild	2	835	L/min (Random, 95% CI)	6.51 [-5.98, 19.00]
4.2 Mild-moderate asthma	5	997	L/min (Random, 95% CI)	17.42 [7.37, 27.47]
4.3 Persistent/symptomatic	6	1802	L/min (Random, 95% CI)	13.54 [10.19, 16.89]
4.4 Moderate	3	748	L/min (Random, 95% CI)	23.11 [2.54, 43.68]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
4.5 Severe asthma	0	0	L/min (Random, 95% CI)	0.0 [0.0, 0.0]
4.6 Unclear	6	968	L/min (Random, 95% CI)	20.07 [14.13, 26.01]
5 Amplitude PEF: diurnal variation (l/min or %)	1	454	Std. Mean Difference (IV, Fixed, 95% CI)	-0.43 [-0.62, -0.25]
5.1 Mild-moderate asthma	1	454	Std. Mean Difference (IV, Fixed, 95% CI)	-0.43 [-0.62, -0.25]
5.2 Mild asthma	0	0	Std. Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
5.3 Severe asthma	0	0	Std. Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
6 Change in Amplitude PEF: diurnal variation (l/min or %)	2	1001	Std. Mean Difference (IV, Fixed, 95% CI)	-0.43 [-0.55, -0.30]
6.1 Mild-moderate asthma	2	1001	Std. Mean Difference (IV, Fixed, 95% CI)	-0.43 [-0.55, -0.30]
6.2 Mild asthma	0	0	Std. Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
6.3 Severe asthma	0	0	Std. Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
7 FEV1	15	4047	Litres (Fixed, 95% CI)	0.24 [0.21, 0.28]
7.1 Mild	3	152	Litres (Fixed, 95% CI)	0.10 [-0.11, 0.30]
7.2 Mild-moderate asthma	7	1932	Litres (Fixed, 95% CI)	0.22 [0.16, 0.29]
7.3 Persistent/symptomatic	1	442	Litres (Fixed, 95% CI)	0.12 [-0.03, 0.27]
7.4 Moderate	0	0	Litres (Fixed, 95% CI)	0.0 [0.0, 0.0]
7.5 Severe asthma	0	0	Litres (Fixed, 95% CI)	0.0 [0.0, 0.0]
7.7 Unclear	4	1521	Litres (Fixed, 95% CI)	0.28 [0.23, 0.33]
8 FEV1 predicted	5	637	% (Fixed, 95% CI)	3.13 [0.57, 5.69]
8.1 Mild	0	0	% (Fixed, 95% CI)	0.0 [0.0, 0.0]
8.2 Mild-moderate asthma	3	408	% (Fixed, 95% CI)	3.16 [-0.04, 6.36]
8.3 Persistent/symptomatic asthma	1	207	% (Fixed, 95% CI)	3.60 [-0.84, 8.04]
8.4 Moderate asthma	0	0	% (Fixed, 95% CI)	0.0 [0.0, 0.0]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
8.5 Severe asthma	0	0	% (Fixed, 95% CI)	0.0 [0.0, 0.0]
8.6 Unclear	1	22	% (Fixed, 95% CI)	-3.6 [-19.50, 12.30]
9 Change in FEV (litres)	15	3295	Mean Difference (IV, Fixed, 95% CI)	0.17 [0.14, 0.20]
9.1 Mild asthma	1	408	Mean Difference (IV, Fixed, 95% CI)	0.18 [0.08, 0.28]
9.2 Mild-moderate asthma	2	505	Mean Difference (IV, Fixed, 95% CI)	0.08 [-0.00, 0.16]
9.3 Persistent/symptomatic	4	1336	Mean Difference (IV, Fixed, 95% CI)	0.20 [0.15, 0.26]
9.4 Moderate asthma	2	274	Mean Difference (IV, Fixed, 95% CI)	0.15 [0.06, 0.24]
9.5 Severe asthma	0	0	Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
9.6 Unclear	6	772	Mean Difference (IV, Fixed, 95% CI)	0.19 [0.12, 0.27]
10 Change in FEV %predicted	3	695	Std. Mean Difference (IV, Fixed, 95% CI)	0.34 [0.13, 0.56]
10.1 Mild-moderate asthma	2	507	Std. Mean Difference (IV, Fixed, 95% CI)	0.34 [0.13, 0.56]
10.2 Persistent/symptomatic asthma	1	188	Std. Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
10.3 Severe asthma	0	0	Std. Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
11 Forced Vital Capacity (litres)	2	302	Mean Difference (IV, Fixed, 95% CI)	0.09 [-0.14, 0.32]
11.1 Mild-moderate asthma	2	302	Mean Difference (IV, Fixed, 95% CI)	0.09 [-0.14, 0.32]
11.2 Mild asthma	0	0	Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
12 Change in Forced Vital Capacity (litres)	5	626	Mean Difference (IV, Fixed, 95% CI)	0.13 [0.03, 0.22]
12.1 Mild-moderate asthma	4	562	Mean Difference (IV, Fixed, 95% CI)	0.09 [-0.01, 0.19]
12.2 Unknown	1	64	Mean Difference (IV, Fixed, 95% CI)	0.63 [0.26, 1.00]
13 FEF25-75 (litres/sec)	3	462	Mean Difference (IV, Fixed, 95% CI)	0.17 [-0.06, 0.40]
13.1 Mild-moderate asthma	3	462	Mean Difference (IV, Fixed, 95% CI)	0.17 [-0.06, 0.40]
13.2 Mild asthma	0	0	Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
14 Symptom score- whole day	4	905	Std. Mean Difference (IV, Random, 95% CI)	-0.41 [-0.64, -0.18]
14.1 Mild asthma	0	0	Std. Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]
14.2 Mild-moderate asthma	3	873	Std. Mean Difference (IV, Random, 95% CI)	-0.36 [-0.58, -0.14]
14.3 Moderate	1	32	Std. Mean Difference (IV, Random, 95% CI)	-0.93 [-1.67, -0.20]
15 Symptom score - day time	11	1995	Std. Mean Difference (IV, Fixed, 95% CI)	-0.33 [-0.41, -0.24]
15.1 Mild asthma	3	79	Std. Mean Difference (IV, Fixed, 95% CI)	-0.39 [-0.84, 0.05]
15.2 Mild-moderate asthma	1	264	Std. Mean Difference (IV, Fixed, 95% CI)	-0.28 [-0.52, -0.04]
15.3 Persistent/symptomatic asthma	1	301	Std. Mean Difference (IV, Fixed, 95% CI)	-0.14 [-0.36, 0.09]
15.4 Moderate asthma	2	681	Std. Mean Difference (IV, Fixed, 95% CI)	-0.44 [-0.60, -0.29]
15.5 Severe asthma	0	0	Std. Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
15.6 Unclear	4	670	Std. Mean Difference (IV, Fixed, 95% CI)	-0.30 [-0.45, -0.15]
16 Symptom score - night time	9	1917	Std. Mean Difference (IV, Random, 95% CI)	-0.48 [-0.62, -0.34]
16.1 Mild asthma	2	66	Std. Mean Difference (IV, Random, 95% CI)	-0.39 [-0.88, 0.10]
16.2 Mild-moderate asthma	3	804	Std. Mean Difference (IV, Random, 95% CI)	-0.48 [-0.70, -0.25]
16.3 Persistent/symptomatic asthma	1	457	Std. Mean Difference (IV, Random, 95% CI)	-0.66 [-0.85, -0.48]
16.4 Moderate asthma	1	227	Std. Mean Difference (IV, Random, 95% CI)	-0.44 [-0.71, -0.18]
16.5 Severe asthma	0	0	Std. Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]
16.6 Unclear	2	363	Std. Mean Difference (IV, Random, 95% CI)	-0.41 [-1.00, 0.18]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
17 Change in symptom score - day time	13	2629	Std. Mean Difference (IV, Random, 95% CI)	-0.48 [-0.60, -0.37]
17.1 Mild asthma	1	408	Std. Mean Difference (IV, Random, 95% CI)	-0.38 [-0.57, -0.18]
17.2 Mild-moderate asthma	2	226	Std. Mean Difference (IV, Random, 95% CI)	-0.65 [-1.21, -0.09]
17.3 Persistent/symptomatic asthma	3	1037	Std. Mean Difference (IV, Random, 95% CI)	-0.65 [-0.80, -0.50]
17.4 Moderate asthma	1	174	Std. Mean Difference (IV, Random, 95% CI)	-0.32 [-0.62, -0.02]
17.5 Severe asthma	0	0	Std. Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]
17.6 Unclear	6	784	Std. Mean Difference (IV, Random, 95% CI)	-0.41 [-0.57, -0.25]
18 Change in symptom score - night time	4	823	Std. Mean Difference (IV, Random, 95% CI)	-0.54 [-0.87, -0.22]
18.1 Mild asthma	0	0	Std. Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]
18.2 Mild-moderate asthma	2	226	Std. Mean Difference (IV, Random, 95% CI)	-0.66 [-1.24, -0.08]
18.3 Moderate asthma	0	0	Std. Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]
18.4 Persistent/symptomatic asthma	1	533	Std. Mean Difference (IV, Random, 95% CI)	-0.70 [-0.88, -0.53]
18.5 Severe asthma	0	0	Std. Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]
18.6 Unclear	1	64	Std. Mean Difference (IV, Random, 95% CI)	-0.01 [-0.50, 0.48]
19 %days without asthma symptoms	7	2254	Mean Difference (IV, Random, 95% CI)	15.77 [9.75, 21.79]
19.1 Mild-moderate asthma	7	2254	Mean Difference (IV, Random, 95% CI)	15.77 [9.75, 21.79]
19.2 Mild asthma	0	0	Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]
19.3 Severe asthma	0	0	Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]
20 % nights without asthma awakenings	12	3687	Mean Difference (IV, Random, 95% CI)	16.51 [11.86, 21.15]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
20.1 Mild asthma	1	427	Mean Difference (IV, Random, 95% CI)	15.00 [8.16, 21.84]
20.2 Mild-moderate asthma	6	1656	Mean Difference (IV, Random, 95% CI)	16.32 [9.50, 23.13]
20.3 Persistent/symptomatic asthma	4	1427	Mean Difference (IV, Random, 95% CI)	17.27 [7.47, 27.07]
20.4 Moderate asthma	0	0	Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]
20.5 Severe asthma	0	0	Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]
20.6 Unclear	1	177	Mean Difference (IV, Random, 95% CI)	16.0 [7.23, 24.77]
21 Change in %days without asthma symptoms	9	2060	Mean Difference (IV, Fixed, 95% CI)	15.55 [12.93, 18.17]
21.1 Mild asthma	1	408	Mean Difference (IV, Fixed, 95% CI)	13.30 [7.75, 18.85]
21.2 Mild-moderate asthma	1	130	Mean Difference (IV, Fixed, 95% CI)	17.0 [6.82, 27.18]
21.3 Persistent/symptomatic asthma	3	947	Mean Difference (IV, Fixed, 95% CI)	15.02 [11.13, 18.91]
21.4 Moderate asthma	1	174	Mean Difference (IV, Fixed, 95% CI)	10.0 [0.29, 19.71]
21.5 Severe asthma	0	0	Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
21.6 Unclear	3	401	Mean Difference (IV, Fixed, 95% CI)	21.31 [15.18, 27.44]
22 Change in % nights without asthma symptoms	9	2093	Mean Difference (IV, Fixed, 95% CI)	11.00 [8.67, 13.33]
22.1 Mild asthma	1	408	Mean Difference (IV, Fixed, 95% CI)	8.1 [3.91, 12.29]
22.2 Mild-moderate asthma	1	130	Mean Difference (IV, Fixed, 95% CI)	8.0 [-2.02, 18.02]
22.3 Persistent/symptomatic asthma	4	1160	Mean Difference (IV, Fixed, 95% CI)	13.72 [10.22, 17.21]
22.4 Moderate asthma	1	174	Mean Difference (IV, Fixed, 95% CI)	4.0 [-5.71, 13.71]
22.5 Severe asthma	0	0	Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
22.6 Unclear	2	221	Mean Difference (IV, Fixed, 95% CI)	12.82 [6.58, 19.07]
23 Rescue bronchodilator use: whole day	8	1885	Mean Difference (IV, Random, 95% CI)	-1.38 [-2.03, -0.72]
23.1 Mild asthma	1	43	Mean Difference (IV, Random, 95% CI)	-0.30 [-0.53, -0.07]
23.2 Mild-moderate asthma	4	1158	Mean Difference (IV, Random, 95% CI)	-1.66 [-2.46, -0.86]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
23.3 Persistent/symptomatic asthma	2	508	Mean Difference (IV, Random, 95% CI)	-1.04 [-2.31, 0.24]
23.4 Moderate asthma	0	0	Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]
23.5 Severe asthma	0	0	Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]
23.6 Unclear	1	176	Mean Difference (IV, Random, 95% CI)	-2.2 [-2.93, -1.47]
24 Rescue bronchodilator use: day time	5	1172	Mean Difference (IV, Random, 95% CI)	-0.95 [-1.65, -0.25]
24.1 Mild asthma	1	23	Mean Difference (IV, Random, 95% CI)	-0.56 [-1.67, 0.55]
24.2 Mild-moderate asthma	2	491	Mean Difference (IV, Random, 95% CI)	-0.38 [-0.80, 0.05]
24.3 Persistent/symptomatic asthma	1	454	Mean Difference (IV, Random, 95% CI)	-1.25 [-1.71, -0.79]
24.4 Moderate asthma	0	0	Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]
24.5 Severe asthma	0	0	Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]
24.6 Unclear	1	204	Mean Difference (IV, Random, 95% CI)	0.00 [-2.53, -1.47]
25 Rescue bronchodilator use: night time	5	1176	Mean Difference (IV, Random, 95% CI)	-0.56 [-0.87, -0.25]
25.1 Mild asthma	1	23	Mean Difference (IV, Random, 95% CI)	0.14 [-1.30, 1.58]
25.2 Mild-moderate asthma	2	491	Mean Difference (IV, Random, 95% CI)	-0.40 [-0.86, 0.05]
25.3 Persistent/symptomatic asthma	1	458	Mean Difference (IV, Random, 95% CI)	-0.64 [-0.84, -0.44]
25.4 Moderate asthma	0	0	Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]
25.5 Severe asthma	0	0	Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]
25.6 Unclear	1	204	Mean Difference (IV, Random, 95% CI)	1.00 [-1.52, -0.48]
26 Change in use of rescue bronchodilator/day	3	691	Mean Difference (IV, Random, 95% CI)	-0.93 [-1.35, -0.52]
26.1 Mild asthma	0	0	Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]
26.2 Mild-moderate asthma	1	100	Mean Difference (IV, Random, 95% CI)	-0.78 [-1.30, -0.26]
26.3 Persistent/symptomatic asthma	1	527	Mean Difference (IV, Random, 95% CI)	-1.31 [-1.70, -0.92]
26.4 Moderate asthma	0	0	Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
26.5 Severe asthma	0	0	Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]
26.6 Unclear	1	64	Mean Difference (IV, Random, 95% CI)	-0.67 [-1.08, -0.26]
27 Change in use of rescue bronchodilator/night	3	697	Mean Difference (IV, Random, 95% CI)	-0.46 [-0.67, -0.25]
27.1 Mild asthma	0	0	Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]
27.2 Mild-moderate asthma	2	633	Mean Difference (IV, Random, 95% CI)	-0.54 [-0.72, -0.37]
27.3 Persistent/symptomatic asthma	0	0	Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]
27.4 Moderate asthma	0	0	Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]
27.5 Severe asthma	0	0	Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]
27.6 Unclear	1	64	Mean Difference (IV, Random, 95% CI)	-0.21 [-0.56, 0.14]
28 Change in use of rescue bronchodilator/ whole day	12	2232	Mean Difference (IV, Random, 95% CI)	-1.28 [-1.60, -0.95]
28.1 Mild asthma	1	408	Mean Difference (IV, Random, 95% CI)	-1.18 [-1.57, -0.79]
28.2 Mild to moderate asthma	3	463	Mean Difference (IV, Random, 95% CI)	-1.15 [-1.58, -0.71]
28.3 Persistent/symptomatic asthma	2	370	Mean Difference (IV, Random, 95% CI)	-1.22 [-2.69, 0.25]
28.4 Moderate asthma	1	174	Mean Difference (IV, Random, 95% CI)	-0.9 [-1.75, -0.05]
28.5 Severe asthma	0	0	Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]
28.6 Unclear	5	817	Mean Difference (IV, Random, 95% CI)	-1.50 [-2.09, -0.90]
29 AQOL- Change in Quality of life score: global	6	1608	Mean Difference (IV, Fixed, 95% CI)	0.51 [0.42, 0.60]
29.1 Mild asthma	0	0	Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
29.2 Mild-moderate asthma	2	333	Mean Difference (IV, Fixed, 95% CI)	0.22 [-0.01, 0.45]
29.3 Persistent/symptomatic asthma	2	916	Mean Difference (IV, Fixed, 95% CI)	0.62 [0.50, 0.73]
29.4 Moderate asthma	0	0	Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
29.5 Severe asthma	0	0	Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
29.6 Unclear	2	359	Mean Difference (IV, Fixed, 95% CI)	0.41 [0.22, 0.59]

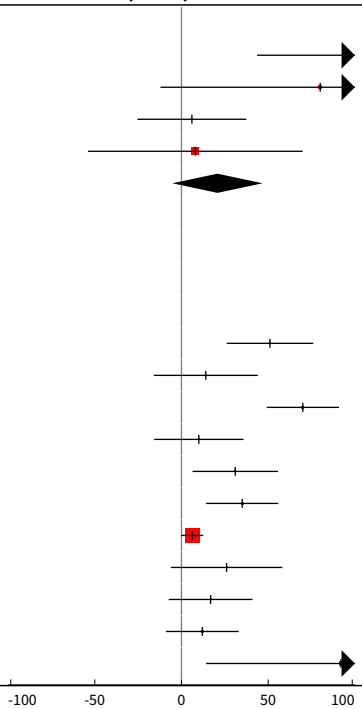
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
30 Change in Quality of life score- symptoms	2	916	Mean Difference (IV, Fixed, 95% CI)	0.73 [0.58, 0.87]
30.1 Mild asthma	0	0	Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
30.2 Mild-moderate asthma	0	0	Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
30.3 Persistent/symptomatic asthma	2	916	Mean Difference (IV, Fixed, 95% CI)	0.73 [0.58, 0.87]
30.4 Moderate asthma	0	0	Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
30.5 Severe asthma	0	0	Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
30.6 Unclear	0	0	Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
31 Change in Quality of life score: emotions	2	916	Mean Difference (IV, Fixed, 95% CI)	0.66 [0.48, 0.83]
31.1 Mild asthma	0	0	Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
31.2 Mild-moderate asthma	0	0	Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
31.3 Persistent/symptomatic asthma	2	916	Mean Difference (IV, Fixed, 95% CI)	0.66 [0.48, 0.83]
31.4 Moderate asthma	0	0	Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
31.5 Severe asthma	0	0	Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
31.6 Unclear	0	0	Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
32 Change in Quality of life score: exposure to environmental stimuli	2	916	Mean Difference (IV, Fixed, 95% CI)	0.56 [0.42, 0.70]
32.1 Mild asthma	0	0	Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
32.2 Mild-moderate asthma	0	0	Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
32.3 Persistent/symptomatic asthma	2	916	Mean Difference (IV, Fixed, 95% CI)	0.56 [0.42, 0.70]
32.4 Moderate asthma	0	0	Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
32.5 Severe asthma	0	0	Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
32.6 Unclear	0	0	Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
33 Change in Quality of life score: activity limitations	2	916	Mean Difference (IV, Fixed, 95% CI)	0.41 [0.31, 0.51]

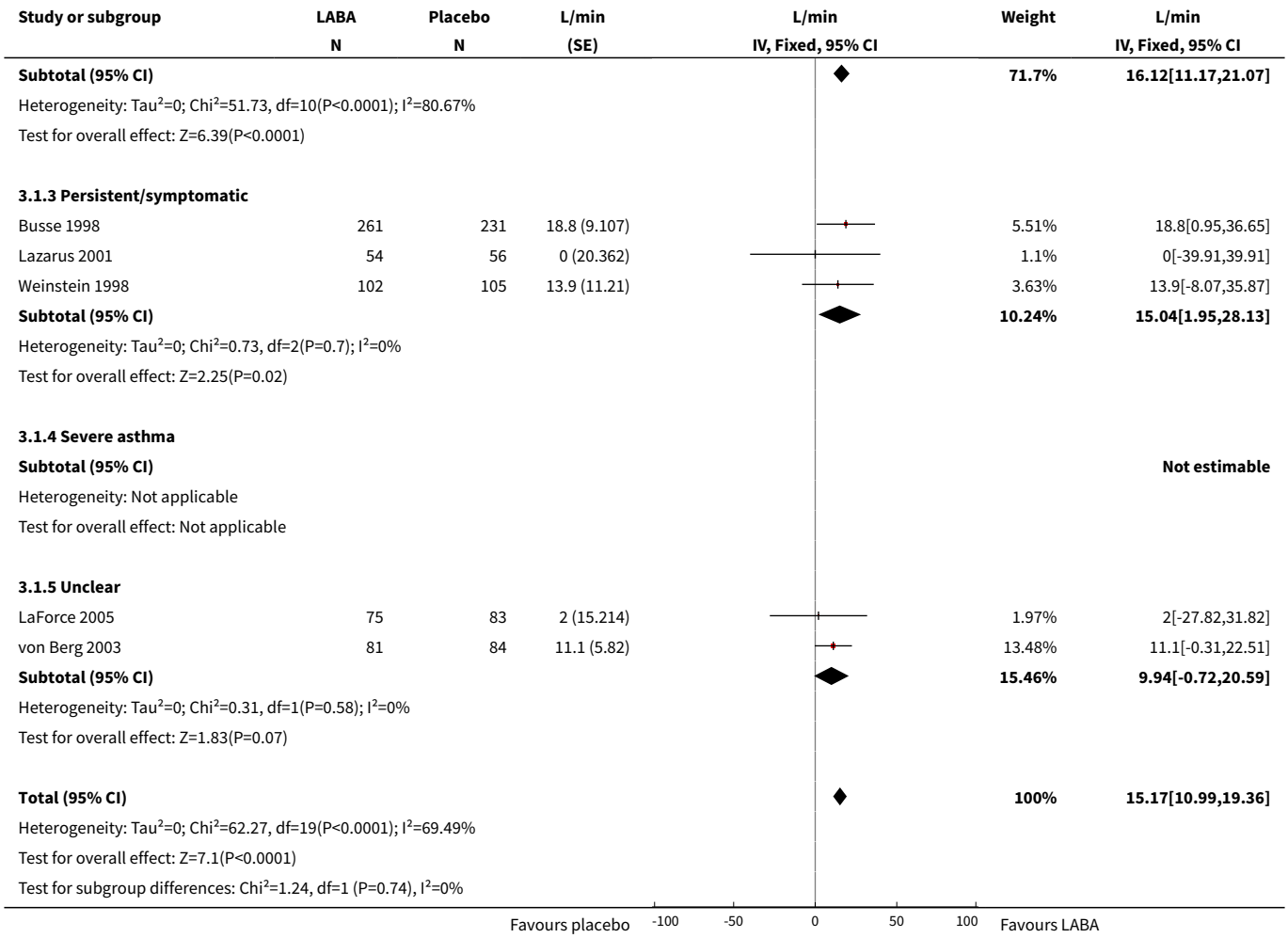
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
33.1 Mild asthma	0	0	Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
33.2 Mild-moderate asthma	0	0	Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
33.3 Persistent/symptomatic asthma	2	916	Mean Difference (IV, Fixed, 95% CI)	0.41 [0.31, 0.51]
33.4 Moderate asthma	0	0	Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
33.5 Severe asthma	0	0	Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
33.6 Unclear	0	0	Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
34 Bronchial hyperreactivity- log PD20/PC20 methacholine or histamine	8	689	Mean Difference (IV, Fixed, 95% CI)	0.01 [-0.00, 0.03]
34.1 Mild asthma	2	66	Mean Difference (IV, Fixed, 95% CI)	0.13 [-0.03, 0.29]
34.2 Mild-moderate asthma	5	601	Mean Difference (IV, Fixed, 95% CI)	0.01 [-0.01, 0.03]
34.3 Persistent/symptomatic asthma	0	0	Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
34.4 Moderate asthma	0	0	Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
34.5 Severe asthma	0	0	Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
34.6 Unclear	1	22	Mean Difference (IV, Fixed, 95% CI)	0.10 [-0.06, 0.26]
35 Bronchodilator response to salbutamol (peak FEV1)	0		Std. Mean Difference (IV, Fixed, 95% CI)	Subtotals only
35.1 Mild-moderate asthma	0	0	Std. Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
35.2 Mild asthma	0	0	Std. Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
35.3 Severe asthma	0	0	Std. Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
36 Exacerbations asthma (all)- >1 major	25	7285	Odds Ratio (M-H, Fixed, 95% CI)	0.69 [0.61, 0.79]
36.1 Mild asthma	2	835	Odds Ratio (M-H, Fixed, 95% CI)	0.73 [0.44, 1.20]
36.2 Mild-moderate asthma	10	3106	Odds Ratio (M-H, Fixed, 95% CI)	0.68 [0.55, 0.83]
36.3 Persistent/symptomatic asthma	8	2408	Odds Ratio (M-H, Fixed, 95% CI)	0.76 [0.63, 0.93]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
36.4 Moderate asthma	1	181	Odds Ratio (M-H, Fixed, 95% CI)	0.67 [0.28, 1.57]
36.5 Severe asthma	0	0	Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
36.6 Unclear	4	755	Odds Ratio (M-H, Fixed, 95% CI)	0.49 [0.32, 0.75]
37 Global assessment of efficacy by patient- very good/good	4		Odds Ratio (M-H, Fixed, 95% CI)	Subtotals only
37.1 Mild asthma	1	427	Odds Ratio (M-H, Fixed, 95% CI)	2.03 [1.35, 3.05]
37.2 Mild-moderate asthma	0	0	Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
37.3 Persistent/symptomatic asthma	1	184	Odds Ratio (M-H, Fixed, 95% CI)	1.63 [0.91, 2.94]
37.4 Moderate asthma	0	0	Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
37.5 Severe asthma	0	0	Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
37.6 Unclear	2	268	Odds Ratio (M-H, Fixed, 95% CI)	7.97 [4.62, 13.74]

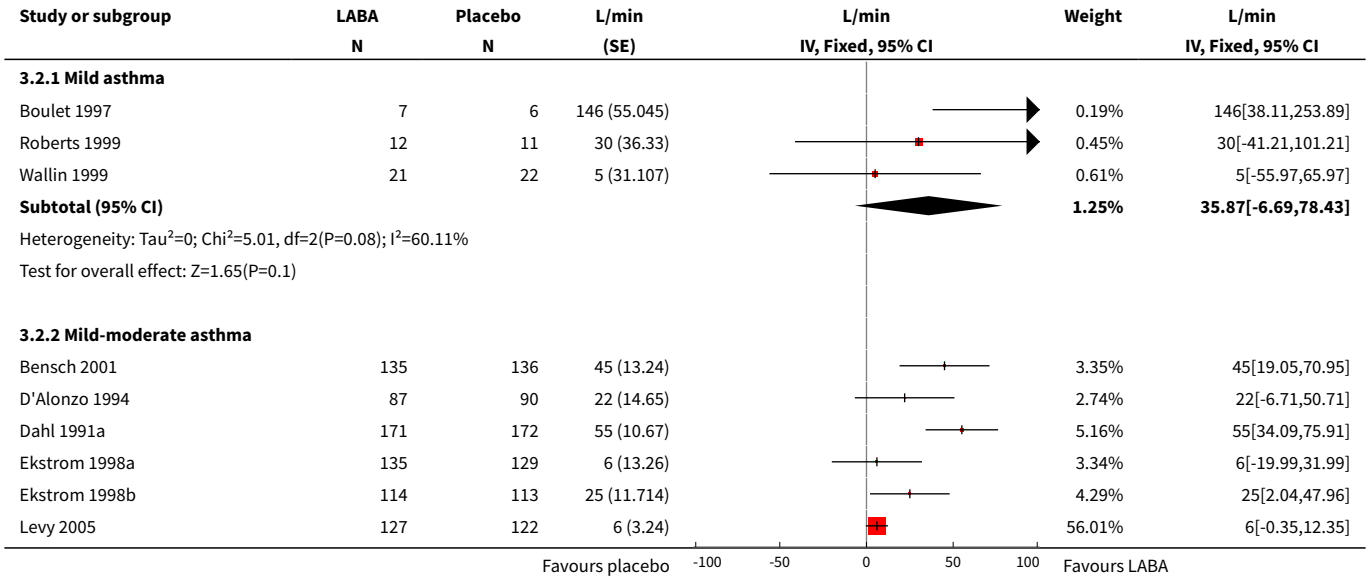
Analysis 3.1. Comparison 3 Studies by severity of asthma, Outcome 1 Peak expiratory flow: morning.

Study or subgroup	LABA N	Placebo N	L/min (SE)	L/min IV, Fixed, 95% CI	Weight	L/min IV, Fixed, 95% CI
3.1.1 Mild asthma						
Boulet 1997	7	6	151 (54.79)		0.15%	151[43.61,258.39]
Roberts 1999	12	11	80 (47.01)		0.21%	80[-12.14,172.14]
SLGL82	41	41	6 (16.02)		1.78%	6[-25.4,37.4]
Wallin 1999	13	9	8 (31.566)		0.46%	8[-53.87,69.87]
Subtotal (95% CI)					**2.6%**	**20.74[-5.26,46.73]**
Heterogeneity: Tau²=0; Chi²=8.25, df=3(P=0.04); I²=63.64%						
Test for overall effect: Z=1.56(P=0.12)						
3.1.2 Mild-moderate asthma						
Bensch 2001	135	136	51 (12.724)		2.82%	51[26.06,75.94]
D'Alonzo 1994	87	90	14 (15.3)		1.95%	14[-15.99,43.99]
Dahl 1991a	171	172	70 (10.627)		4.04%	70[49.17,90.83]
Ekstrom 1998a	135	129	10 (13.153)		2.64%	10[-15.78,35.78]
Ekstrom 1998b	114	113	31 (12.566)		2.89%	31[6.37,55.63]
Kemp 1999	176	176	35 (10.627)		4.04%	35[14.17,55.83]
Levy 2005	127	122	6.2 (3.21)		44.32%	6.2[-0.09,12.49]
Pearlman 1992	66	62	26 (16.393)		1.7%	26[-6.13,58.13]
SLMP03	11	13	16.8 (12.32)		3.01%	16.8[-7.35,40.95]
Wolfe 2000a	165	167	12 (10.699)		3.99%	12[-8.97,32.97]
Wronska 1998	21	22	92 (39.69)		0.29%	92[14.21,169.79]

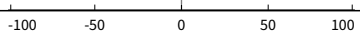




Analysis 3.2. Comparison 3 Studies by severity of asthma, Outcome 2 Peak expiratory flow: evening.

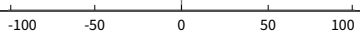


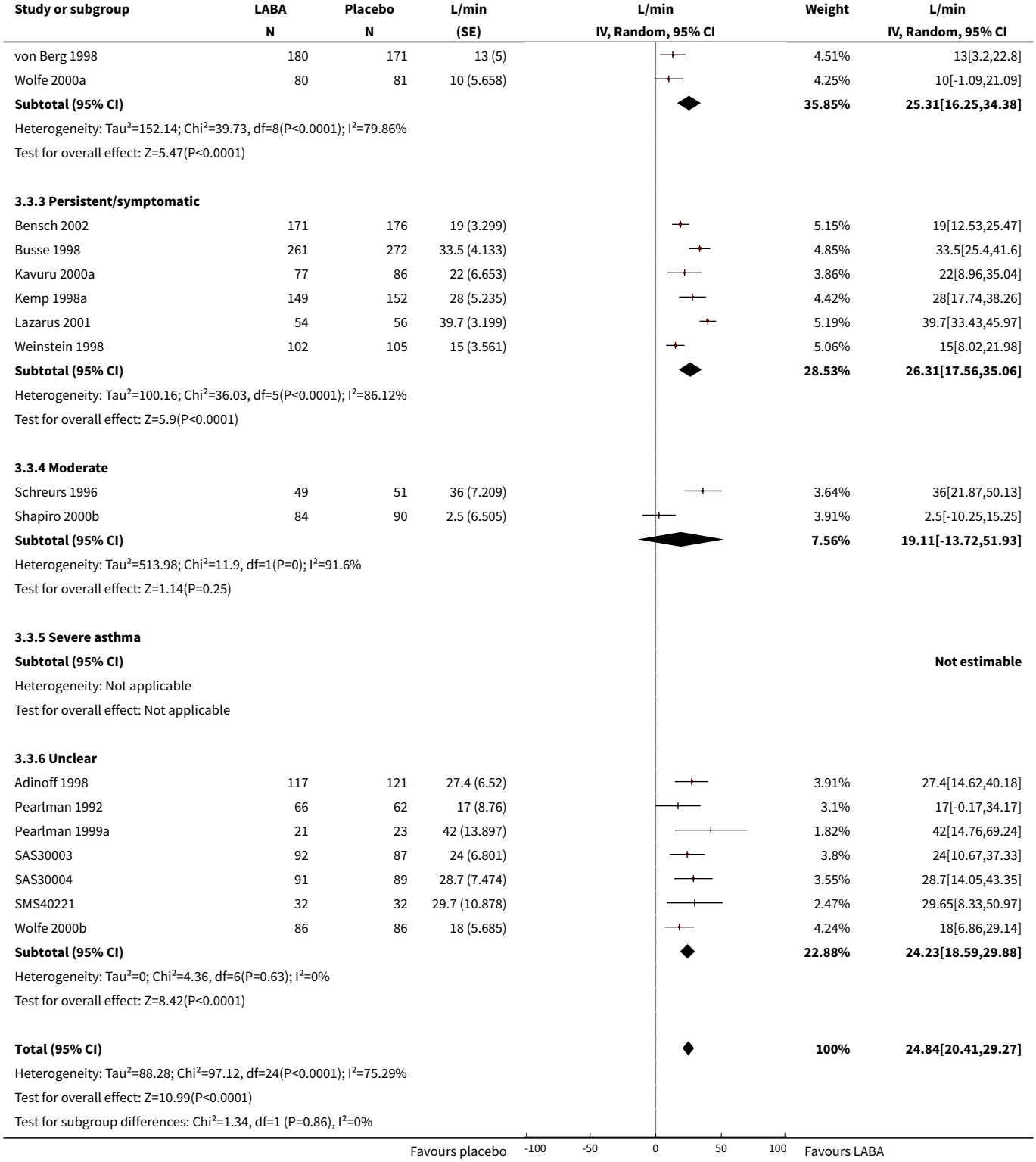
Study or subgroup	LABA N	Placebo N	L/min (SE)	L/min IV, Fixed, 95% CI	Weight	L/min IV, Fixed, 95% CI
Pearlman 1992	67	63	23.5 (16.87)		2.07%	23.48[-9.58,56.54]
SLMP03	11	13	15.4 (8.85)		7.51%	15.4[-1.95,32.75]
Subtotal (95% CI)					**84.48%**	**13.29[8.12,18.46]**
Heterogeneity: Tau²=0; Chi²=28.16, df=7(P=0); I²=75.14%						
Test for overall effect: Z=5.04(P<0.0001)						
3.2.3 Persistent/symptomatic						
Busse 1998	224	230	-1 (9.21)		6.93%	-1[-19.05,17.05]
Weinstein 1998	102	105	10.5 (11.122)		4.75%	10.5[-11.3,32.3]
Subtotal (95% CI)					**11.69%**	**3.68[-10.23,17.58]**
Heterogeneity: Tau²=0; Chi²=0.63, df=1(P=0.43); I²=0%						
Test for overall effect: Z=0.52(P=0.6)						
3.2.4 Severe asthma						
Subtotal (95% CI)						**Not estimable**
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						
3.2.5 Unclear						
LaForce 2005	77	84	7 (15.061)		2.59%	7[-22.52,36.52]
von Berg 2003	81	84	8.4 (0)			Not estimable
Subtotal (95% CI)					**2.59%**	**7[-22.52,36.52]**
Heterogeneity: Not applicable						
Test for overall effect: Z=0.46(P=0.64)						
Total (95% CI)					**100%**	**12.29[7.53,17.04]**
Heterogeneity: Tau²=0; Chi²=36.72, df=13(P=0); I²=64.6%						
Test for overall effect: Z=5.07(P<0.0001)						
Test for subgroup differences: Chi²=2.92, df=1 (P=0.4), I²=0%						



Analysis 3.3. Comparison 3 Studies by severity of asthma, Outcome 3 Change in PEF morning.

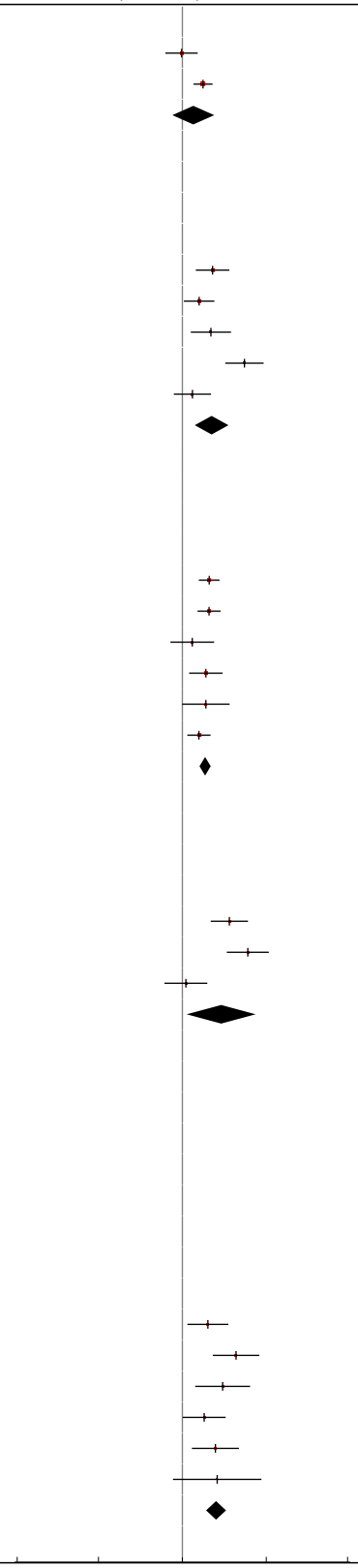
Study or subgroup	LABA N	Placebo N	L/min (SE)	L/min IV, Random, 95% CI	Weight	L/min IV, Random, 95% CI
3.3.1 Mild						
Rosenthal 1999	202	206	20.9 (3.204)		5.19%	20.9[14.62,27.18]
Subtotal (95% CI)					**5.19%**	**20.9[14.62,27.18]**
Heterogeneity: Not applicable						
Test for overall effect: Z=6.52(P<0.0001)						
3.3.2 Mild-moderate asthma						
D'Alonzo 1994	87	90	27 (7.949)		3.37%	27[11.42,42.58]
Dahl 1991a	107	104	45 (6.12)		4.06%	45[33.01,56.99]
Jones 1994	162	85	19 (6.638)		3.86%	19[5.99,32.01]
Lockey 1999	240	234	45 (5.658)		4.25%	45[33.91,56.09]
Nathan 1999	128	129	24 (7.066)		3.7%	24[10.15,37.85]
Simons 1997a	80	80	16 (5.786)		4.2%	16[4.66,27.34]
SLGA2004	63	63	30 (7.209)		3.64%	30[15.87,44.13]





Analysis 3.4. Comparison 3 Studies by severity of asthma, Outcome 4 Change in PEF evening.

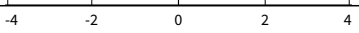
Study or subgroup	LABA N	Placebo N	L/min (SE)	L/min IV, Random, 95% CI	Weight	L/min IV, Random, 95% CI
3.4.1 Mild						
Jones 1994	282	145	-0.5 (4.904)		5.09%	-0.5[-10.11,9.11]
Rosenthal 1999	202	206	12.3 (2.898)		6.37%	12.3[6.62,17.98]
Subtotal (95% CI)					**11.46%**	**6.51[-5.98,19]**
Heterogeneity: Tau^2=65.7; Chi^2=5.05, df=1(P=0.02); I^2=80.2%						
Test for overall effect: Z=1.02(P=0.31)						
3.4.2 Mild-moderate asthma						
Dahl 1991a	101	100	18 (5.1)		4.97%	18[8,28]
Simons 1997a	80	80	10 (4.638)		5.26%	10[0.91,19.09]
SLGA2004	63	63	17 (6.112)		4.35%	17[5.02,28.98]
von Berg 1998	179	170	37 (5.831)		4.52%	37[25.57,48.43]
Wolfe 2000a	80	81	6 (5.652)		4.62%	6[-5.08,17.08]
Subtotal (95% CI)					**23.72%**	**17.42[7.37,27.47]**
Heterogeneity: Tau^2=101.56; Chi^2=17.86, df=4(P=0); I^2=77.6%						
Test for overall effect: Z=3.4(P=0)						
3.4.3 Persistent/symptomatic						
Bensch 2002	171	176	16 (3.148)		6.22%	16[9.83,22.17]
Busse 1998	258	269	15.9 (3.505)		5.99%	15.9[9.03,22.77]
Kavuru 2000a	77	86	5.9 (6.643)		4.05%	5.9[-7.12,18.92]
Kemp 1998a	149	152	14 (5.092)		4.97%	14[4.02,23.98]
Nathan 1999	128	129	14 (7.219)		3.75%	14[-0.15,28.15]
Weinstein 1998	102	105	9.9 (3.536)		5.97%	9.87[2.94,16.8]
Subtotal (95% CI)					**30.95%**	**13.54[10.19,16.89]**
Heterogeneity: Tau^2=0; Chi^2=3.48, df=5(P=0.63); I^2=0%						
Test for overall effect: Z=7.93(P<0.0001)						
3.4.4 Moderate						
Lockey 1999	240	234	28 (5.658)		4.62%	28[16.91,39.09]
Schreurs 1996	49	51	39 (6.383)		4.2%	39[26.49,51.51]
Shapiro 2000b	84	90	2.1 (6.51)		4.12%	2.1[-10.66,14.86]
Subtotal (95% CI)					**12.94%**	**23.11[2.54,43.68]**
Heterogeneity: Tau^2=292.14; Chi^2=17.33, df=2(P=0); I^2=88.46%						
Test for overall effect: Z=2.2(P=0.03)						
3.4.5 Severe asthma						
Subtotal (95% CI)						**Not estimable**
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						
3.4.6 Unclear						
Adinoff 1998	117	121	15.2 (6.214)		4.29%	15.2[3.02,27.38]
D'Alonzo 1994	87	90	32 (7.066)		3.82%	32[18.15,45.85]
Pearlman 1992	67	63	24 (8.337)		3.22%	24[7.66,40.34]
SAS30003	92	87	13 (6.528)		4.11%	13[0.21,25.79]
SAS30004	91	89	19.7 (7.143)		3.78%	19.7[5.7,33.7]
SMS40221	32	32	20.8 (13.444)		1.69%	20.76[-5.59,47.11]
Subtotal (95% CI)					**20.93%**	**20.07[14.13,26.01]**
Heterogeneity: Tau^2=0; Chi^2=4.86, df=5(P=0.43); I^2=0%						



Study or subgroup	LABA N	Placebo N	L/min (SE)	L/min IV, Random, 95% CI	Weight	L/min IV, Random, 95% CI
Test for overall effect: Z=6.62(P<0.0001)						
Total (95% CI)					**100%**	**16.16[12.25,20.07]**
Heterogeneity: Tau²=54.06; Chi²=64.45, df=21(P<0.0001); I²=67.42%						
Test for overall effect: Z=8.1(P<0.0001)						
Test for subgroup differences: Chi²=6.13, df=1 (P=0.19), I²=34.7%						

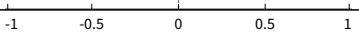
Analysis 3.5. Comparison 3 Studies by severity of asthma, Outcome 5 Amplitude PEF: diurnal variation (l/min or %).

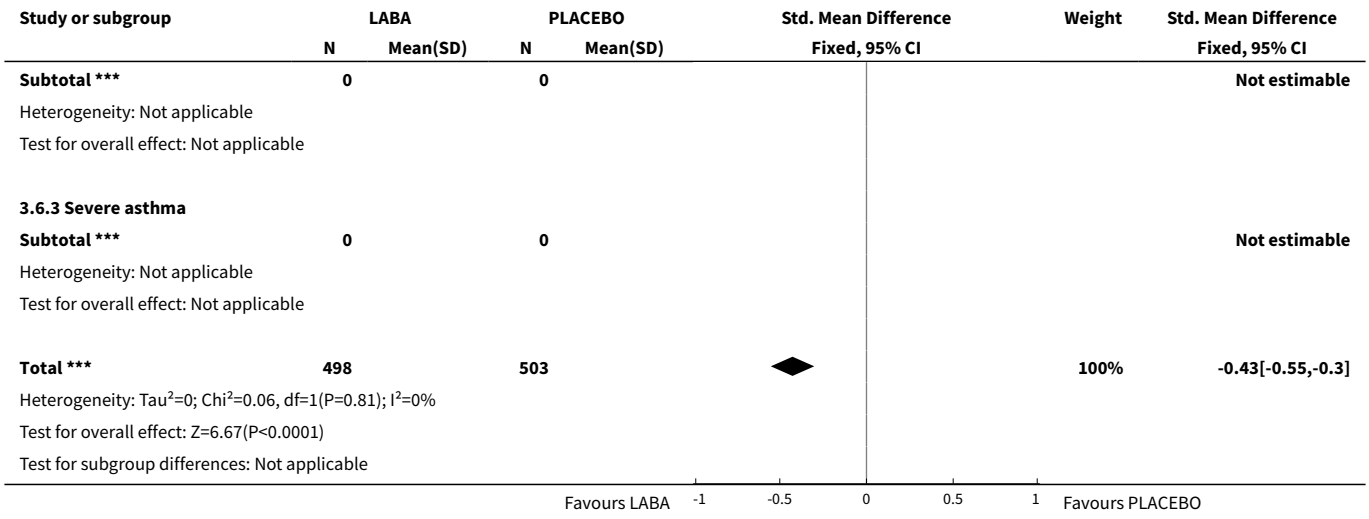
Study or subgroup	LABA N	LABA Mean(SD)	Placebo N	Placebo Mean(SD)	Std. Mean Difference Fixed, 95% CI	Weight	Std. Mean Difference Fixed, 95% CI
3.5.1 Mild-moderate asthma							
Busse 1998	224	25.3 (40.6)	230	44.2 (46)		100%	-0.43[-0.62,-0.25]
Subtotal ***	**224**		**230**			**100%**	**-0.43[-0.62,-0.25]**
Heterogeneity: Not applicable							
Test for overall effect: Z=4.57(P<0.0001)							
3.5.2 Mild asthma							
Subtotal ***	**0**		**0**				**Not estimable**
Heterogeneity: Not applicable							
Test for overall effect: Not applicable							
3.5.3 Severe asthma							
Subtotal ***	**0**		**0**				**Not estimable**
Heterogeneity: Not applicable							
Test for overall effect: Not applicable							
Total ***	**224**		**230**			**100%**	**-0.43[-0.62,-0.25]**
Heterogeneity: Not applicable							
Test for overall effect: Z=4.57(P<0.0001)							
Test for subgroup differences: Not applicable							



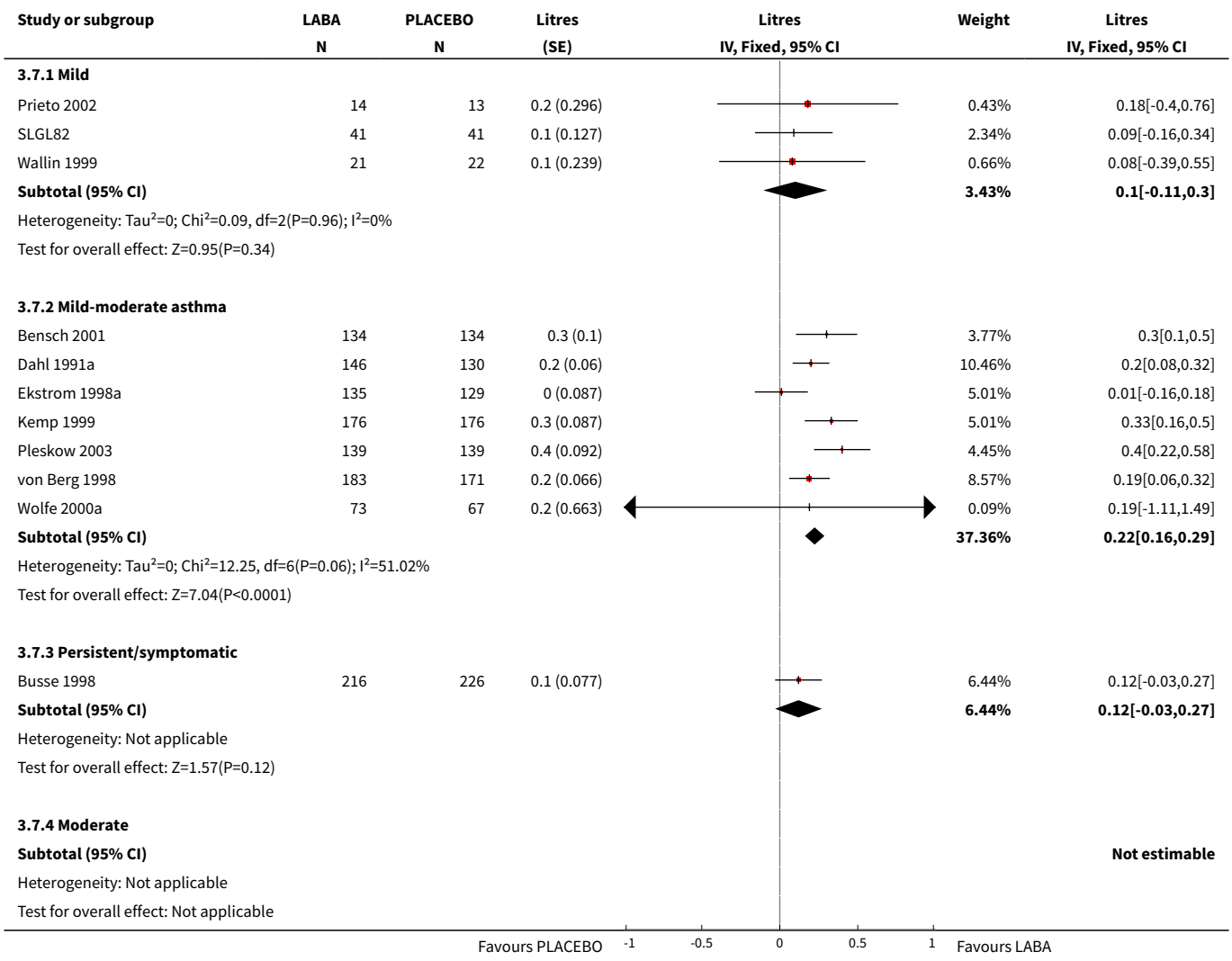
Analysis 3.6. Comparison 3 Studies by severity of asthma, Outcome 6 Change in Amplitude PEF: diurnal variation (l/min or %).

Study or subgroup	LABA N	LABA Mean(SD)	PLACEBO N	PLACEBO Mean(SD)	Std. Mean Difference Fixed, 95% CI	Weight	Std. Mean Difference Fixed, 95% CI
3.6.1 Mild-moderate asthma							
Busse 1998	258	-42.7 (45.3)	269	-23.5 (41.7)		52.56%	-0.44[-0.61,-0.27]
Lockey 1999	240	-18 (46.5)	234	1 (45.9)		47.44%	-0.41[-0.59,-0.23]
Subtotal ***	**498**		**503**			**100%**	**-0.43[-0.55,-0.3]**
Heterogeneity: Tau²=0; Chi²=0.06, df=1(P=0.81); I²=0%							
Test for overall effect: Z=6.67(P<0.0001)							
3.6.2 Mild asthma							

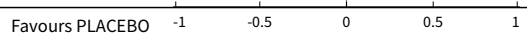




Analysis 3.7. Comparison 3 Studies by severity of asthma, Outcome 7 FEV1.

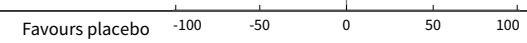


Study or subgroup	LABA N	PLACEBO N	Litres (SE)	Litres IV, Fixed, 95% CI	Weight	Litres IV, Fixed, 95% CI
3.7.5 Severe asthma						
Subtotal (95% CI)						**Not estimable**
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						
3.7.7 Unclear						
D'Alonzo 1994	84	87	0.1 (0.112)		2.99%	0.07[-0.15,0.29]
Pearlman 1992	68	63	0.2 (0.147)		1.74%	0.16[-0.13,0.45]
von Berg 2003	81	84	0.1 (0)			Not estimable
Wolfe 2006	527	527	0.3 (0.028)		48.05%	0.3[0.25,0.35]
Subtotal (95% CI)					**52.78%**	**0.28[0.23,0.33]**
Heterogeneity: Tau^2=0; Chi^2=4.67, df=2(P=0.1); I^2=57.19%						
Test for overall effect: Z=10.57(P<0.0001)						
Total (95% CI)					**100%**	**0.24[0.21,0.28]**
Heterogeneity: Tau^2=0; Chi^2=24.01, df=13(P=0.03); I^2=45.86%						
Test for overall effect: Z=12.55(P<0.0001)						
Test for subgroup differences: Chi^2=7, df=1 (P=0.07), I^2=57.16%						

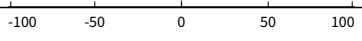


Analysis 3.8. Comparison 3 Studies by severity of asthma, Outcome 8 FEV1 predicted.

Study or subgroup	Treatment N	Control N	% (SE)	% IV, Fixed, 95% CI	Weight	% IV, Fixed, 95% CI
3.8.1 Mild						
Subtotal (95% CI)						**Not estimable**
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						
3.8.2 Mild-moderate asthma						
Booth 1993	10	12	-4.9 (8.607)		2.3%	-4.9[-21.77,11.97]
Stelmach 2002	15	17	7.5 (5.173)		6.38%	7.45[-2.69,17.59]
von Berg 1998	183	171	3 (1.755)		55.44%	3[-0.44,6.44]
Subtotal (95% CI)					**64.12%**	**3.16[-0.04,6.36]**
Heterogeneity: Tau^2=0; Chi^2=1.57, df=2(P=0.46); I^2=0%						
Test for overall effect: Z=1.94(P=0.05)						
3.8.3 Persistent/symptomatic asthma						
Weinstein 1998	102	105	3.6 (2.265)		33.28%	3.6[-0.84,8.04]
Subtotal (95% CI)					**33.28%**	**3.6[-0.84,8.04]**
Heterogeneity: Tau^2=0; Chi^2=0, df=0(P<0.0001); I^2=100%						
Test for overall effect: Z=1.59(P=0.11)						
3.8.4 Moderate asthma						
Subtotal (95% CI)						**Not estimable**
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						

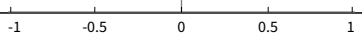


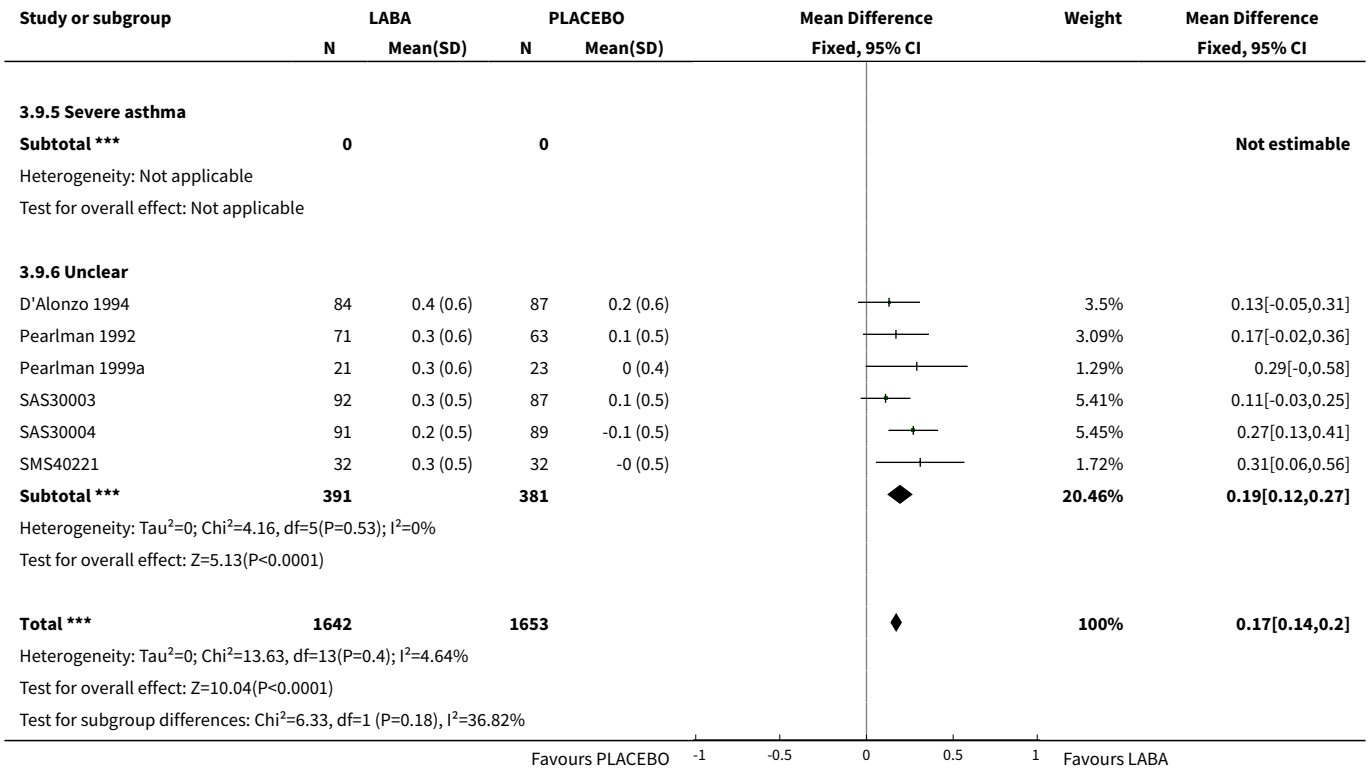
Study or subgroup	Treatment N	Control N	% (SE)	% IV, Fixed, 95% CI	Weight	% IV, Fixed, 95% CI
3.8.5 Severe asthma						
Subtotal (95% CI)						**Not estimable**
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						
3.8.6 Unclear						
Wronska 1998	13	9	-3.6 (8.112)		2.59%	-3.6[-19.5,12.3]
Subtotal (95% CI)					**2.59%**	**-3.6[-19.5,12.3]**
Heterogeneity: Not applicable						
Test for overall effect: Z=0.44(P=0.66)						
Total (95% CI)					**100%**	**3.13[0.57,5.69]**
Heterogeneity: Tau^2=0; Chi^2=2.3, df=4(P=0.68); I^2=0%						
Test for overall effect: Z=2.4(P=0.02)						
Test for subgroup differences: Chi^2=0.73, df=1 (P=0.69), I^2=0%						



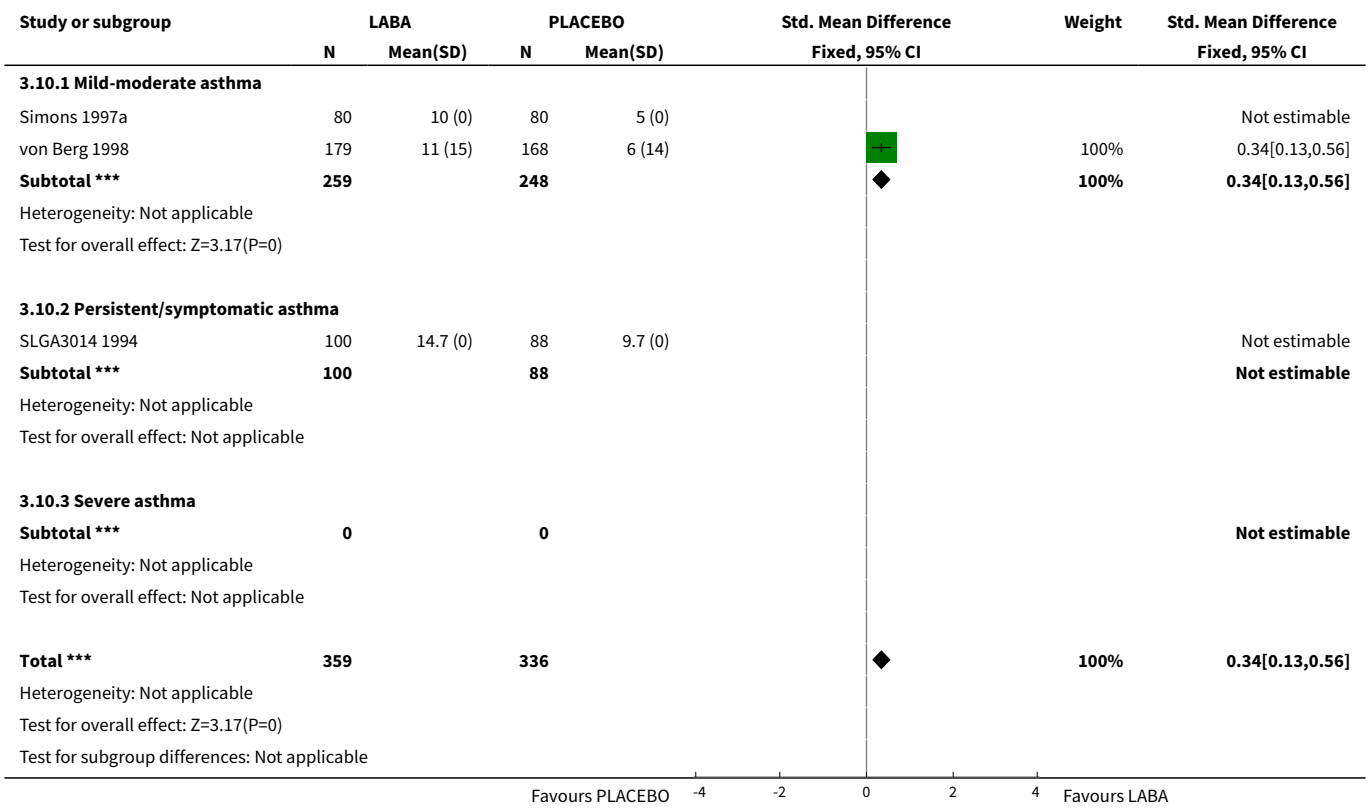
Analysis 3.9. Comparison 3 Studies by severity of asthma, Outcome 9 Change in FEV (litres).

Study or subgroup	LABA N	LABA Mean(SD)	PLACEBO N	PLACEBO Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
3.9.1 Mild asthma							
Rosenthal 1999	202	0.3 (0.5)	206	0.1 (0.5)		12.34%	0.18[0.08,0.28]
Subtotal ***	**202**		**206**			**12.34%**	**0.18[0.08,0.28]**
Heterogeneity: Tau^2=0; Chi^2=0, df=0(P<0.0001); I^2=100%							
Test for overall effect: Z=3.71(P=0)							
3.9.2 Mild-moderate asthma							
Simons 1997a	80	0.2 (0)	80	0.1 (0)			Not estimable
von Berg 1998	176	0.3 (0.4)	169	0.2 (0.4)		16.06%	0.08[-0,0.16]
Subtotal ***	**256**		**249**			**16.06%**	**0.08[-0,0.16]**
Heterogeneity: Not applicable							
Test for overall effect: Z=1.88(P=0.06)							
3.9.3 Persistent/symptomatic							
Busse 1998	215	0.4 (0.5)	227	0.1 (0.5)		12.84%	0.26[0.17,0.35]
Kavuru 2000a	77	0.1 (0.6)	86	0 (0.6)		3.46%	0.1[-0.08,0.28]
Lockey 1999	240	0.4 (0.5)	234	0.2 (0.6)		11.58%	0.17[0.07,0.27]
Nathan 1999	128	0.3 (0.5)	129	0.1 (0.5)		9.22%	0.2[0.09,0.31]
Subtotal ***	**660**		**676**			**37.1%**	**0.2[0.15,0.26]**
Heterogeneity: Tau^2=0; Chi^2=3.13, df=3(P=0.37); I^2=4.29%							
Test for overall effect: Z=7.22(P<0.0001)							
3.9.4 Moderate asthma							
Schreurs 1996	49	0.2 (0.3)	51	0 (0.3)		8.19%	0.15[0.03,0.27]
Shapiro 2000b	84	0.1 (0.5)	90	-0.1 (0.5)		5.84%	0.16[0.02,0.3]
Subtotal ***	**133**		**141**			**14.03%**	**0.15[0.06,0.24]**
Heterogeneity: Tau^2=0; Chi^2=0.01, df=1(P=0.91); I^2=0%							
Test for overall effect: Z=3.39(P=0)							



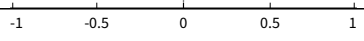


Analysis 3.10. Comparison 3 Studies by severity of asthma, Outcome 10 Change in FEV %predicted.



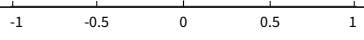
Analysis 3.11. Comparison 3 Studies by severity of asthma, Outcome 11 Forced Vital Capacity (litres).

Study or subgroup	LABA N	LABA Mean(SD)	PLACEBO N	PLACEBO Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
3.11.1 Mild-moderate asthma							
D'Alonzo 1994	84	4 (1.1)	87	3.9 (0.9)		59.1%	0.11[-0.19,0.41]
Pearlman 1992	68	3.8 (1.1)	63	3.7 (1)		40.9%	0.05[-0.31,0.41]
Subtotal ***	**152**		**150**			**100%**	**0.09[-0.14,0.32]**
Heterogeneity: Tau^2=0; Chi^2=0.06, df=1(P=0.8); I^2=0%							
Test for overall effect: Z=0.73(P=0.47)							
3.11.2 Mild asthma							
Subtotal ***	**0**		**0**				**Not estimable**
Heterogeneity: Not applicable							
Test for overall effect: Not applicable							
Total ***	**152**		**150**			**100%**	**0.09[-0.14,0.32]**
Heterogeneity: Tau^2=0; Chi^2=0.06, df=1(P=0.8); I^2=0%							
Test for overall effect: Z=0.73(P=0.47)							
Test for subgroup differences: Not applicable							



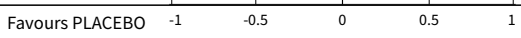
Analysis 3.12. Comparison 3 Studies by severity of asthma, Outcome 12 Change in Forced Vital Capacity (litres).

Study or subgroup	LABA N	LABA Mean(SD)	PLACEBO N	PLACEBO Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
3.12.1 Mild-moderate asthma							
D'Alonzo 1994	84	0.3 (0.6)	87	0.2 (0.6)		29.48%	0.15[-0.03,0.33]
Pearlman 1992	68	0.2 (0.6)	63	0.1 (0.5)		23.65%	0.17[-0.03,0.37]
Schreurs 1996	49	0.1 (0.4)	51	0.1 (0.4)		40.21%	0[-0.15,0.15]
Simons 1997a	80	0.2 (0)	80	0.1 (0)			Not estimable
Subtotal ***	**281**		**281**			**93.35%**	**0.09[-0.01,0.19]**
Heterogeneity: Tau^2=0; Chi^2=2.43, df=2(P=0.3); I^2=17.65%							
Test for overall effect: Z=1.78(P=0.07)							
3.12.2 Unknown							
SMS40221	32	0.4 (0.8)	32	-0.2 (0.8)		6.65%	0.63[0.26,1]
Subtotal ***	**32**		**32**			**6.65%**	**0.63[0.26,1]**
Heterogeneity: Not applicable							
Test for overall effect: Z=3.32(P=0)							
Total ***	**313**		**313**			**100%**	**0.13[0.03,0.22]**
Heterogeneity: Tau^2=0; Chi^2=9.96, df=3(P=0.02); I^2=69.86%							
Test for overall effect: Z=2.58(P=0.01)							
Test for subgroup differences: Chi^2=7.53, df=1 (P=0.01), I^2=86.71%							



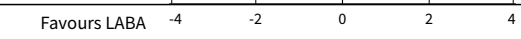
Analysis 3.13. Comparison 3 Studies by severity of asthma, Outcome 13 FEF25-75 (litres/sec).

Study or subgroup	LABA N	LABA Mean(SD)	PLACEBO N	PLACEBO Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
3.13.1 Mild-moderate asthma							
D'Alonzo 1994	84	2.3 (1)	87	2.2 (0.9)		64.29%	0.07[-0.22,0.36]
Pearlman 1992	68	2.7 (1.2)	63	2.3 (1)		35.71%	0.36[-0.03,0.75]
Simons 1997a	80	0.4 (0)	80	0.2 (0)			Not estimable
Subtotal ***	**232**		**230**			**100%**	**0.17[-0.06,0.4]**
Heterogeneity: Tau^2=0; Chi^2=1.39, df=1(P=0.24); I^2=28.31%							
Test for overall effect: Z=1.48(P=0.14)							
3.13.2 Mild asthma							
Subtotal ***	**0**		**0**				**Not estimable**
Heterogeneity: Not applicable							
Test for overall effect: Not applicable							
Total ***	**232**		**230**			**100%**	**0.17[-0.06,0.4]**
Heterogeneity: Tau^2=0; Chi^2=1.39, df=1(P=0.24); I^2=28.31%							
Test for overall effect: Z=1.48(P=0.14)							
Test for subgroup differences: Not applicable							



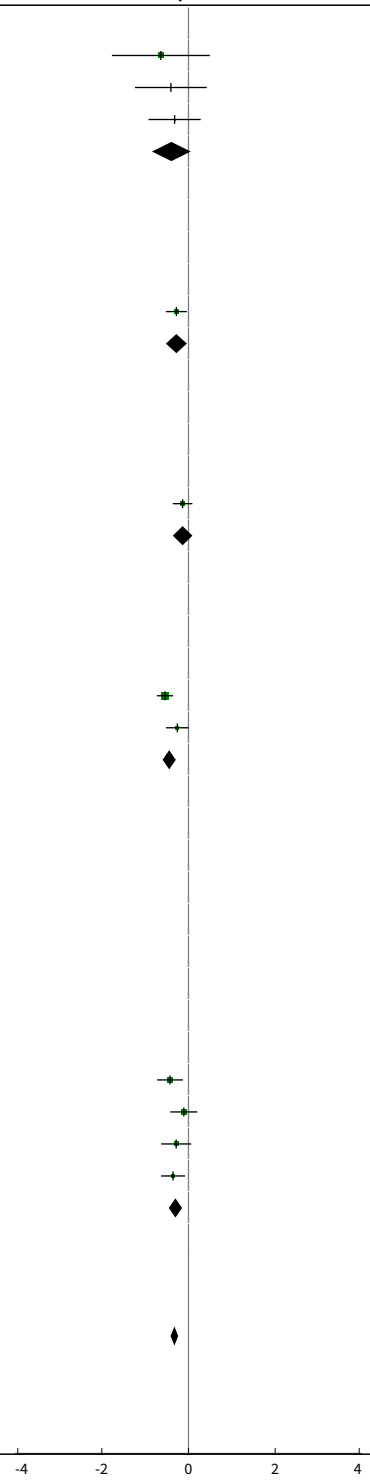
Analysis 3.14. Comparison 3 Studies by severity of asthma, Outcome 14 Symptom score- whole day.

Study or subgroup	LABA N	LABA Mean(SD)	PLACEBO N	PLACEBO Mean(SD)	Std. Mean Difference Random, 95% CI	Weight	Std. Mean Difference Random, 95% CI
3.14.1 Mild asthma							
Subtotal ***	**0**		**0**				**Not estimable**
Heterogeneity: Not applicable							
Test for overall effect: Not applicable							
3.14.2 Mild-moderate asthma							
Bensch 2001	134	0.7 (0.6)	132	1 (0.6)		29.74%	-0.5[-0.74,-0.25]
Pleskow 2003	135	0.7 (0.6)	139	1 (0.7)		30.07%	-0.46[-0.7,-0.22]
Wolfe 2000a	166	1.8 (1.3)	167	2 (1.3)		32.12%	-0.15[-0.37,0.06]
Subtotal ***	**435**		**438**			**91.93%**	**-0.36[-0.58,-0.14]**
Heterogeneity: Tau^2=0.02; Chi^2=5.41, df=2(P=0.07); I^2=63.04%							
Test for overall effect: Z=3.23(P=0)							
3.14.3 Moderate							
Stelmach 2002	15	5.9 (1.2)	17	6.9 (0.9)		8.07%	-0.93[-1.67,-0.2]
Subtotal ***	**15**		**17**			**8.07%**	**-0.93[-1.67,-0.2]**
Heterogeneity: Not applicable							
Test for overall effect: Z=2.48(P=0.01)							
Total ***	**450**		**455**			**100%**	**-0.41[-0.64,-0.18]**
Heterogeneity: Tau^2=0.03; Chi^2=7.72, df=3(P=0.05); I^2=61.14%							
Test for overall effect: Z=3.48(P=0)							
Test for subgroup differences: Chi^2=2.1, df=1 (P=0.15), I^2=52.43%							



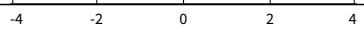
Analysis 3.15. Comparison 3 Studies by severity of asthma, Outcome 15 Symptom score - day time.

Study or subgroup	LABA N	LABA Mean(SD)	PLACEBO N	PLACEBO Mean(SD)	Std. Mean Difference Fixed, 95% CI	Weight	Std. Mean Difference Fixed, 95% CI
3.15.1 Mild asthma							
Boulet 1997	7	0.3 (0.2)	6	0.4 (0.1)		0.61%	-0.64[-1.77,0.49]
Roberts 1999	12	0.5 (0.7)	11	0.8 (0.8)		1.14%	-0.41[-1.23,0.42]
Wallin 1999	21	0.2 (0.3)	22	0.3 (0.3)		2.16%	-0.32[-0.92,0.28]
Subtotal ***	**40**		**39**			**3.92%**	**-0.39[-0.84,0.05]**
Heterogeneity: Tau^2=0; Chi^2=0.24, df=2(P=0.89); I^2=0%							
Test for overall effect: Z=1.73(P=0.08)							
3.15.2 Mild-moderate asthma							
Ekstrom 1998a	135	0.5 (0.5)	129	0.6 (0.5)		13.32%	-0.28[-0.52,-0.04]
Subtotal ***	**135**		**129**			**13.32%**	**-0.28[-0.52,-0.04]**
Heterogeneity: Not applicable							
Test for overall effect: Z=2.26(P=0.02)							
3.15.3 Persistent/symptomatic asthma							
Kemp 1998a	149	0.8 (0.7)	152	0.9 (0.7)		15.31%	-0.14[-0.36,0.09]
Subtotal ***	**149**		**152**			**15.31%**	**-0.14[-0.36,0.09]**
Heterogeneity: Not applicable							
Test for overall effect: Z=1.18(P=0.24)							
3.15.4 Moderate asthma							
Busse 1998	224	0.8 (0.7)	230	1.1 (0.6)		22.31%	-0.54[-0.73,-0.35]
Ekstrom 1998b	114	0.6 (0.6)	113	0.8 (0.7)		11.48%	-0.26[-0.52,0]
Subtotal ***	**338**		**343**			**33.79%**	**-0.44[-0.6,-0.29]**
Heterogeneity: Tau^2=0; Chi^2=3.02, df=1(P=0.08); I^2=66.88%							
Test for overall effect: Z=5.73(P<0.0001)							
3.15.5 Severe asthma							
Subtotal ***	**0**		**0**				**Not estimable**
Heterogeneity: Not applicable							
Test for overall effect: Not applicable							
3.15.6 Unclear							
D'Alonzo 1994	87	0.7 (0.7)	90	1 (0.7)		8.82%	-0.43[-0.72,-0.13]
LaForce 2005	75	0.4 (0.5)	84	0.4 (0.6)		8.07%	-0.11[-0.42,0.2]
Pearlman 1992	67	0.7 (0.7)	63	0.9 (0.7)		6.55%	-0.28[-0.63,0.06]
Steffensen 1995	103	0.4 (0.7)	101	0.7 (0.7)		10.23%	-0.36[-0.63,-0.08]
Subtotal ***	**332**		**338**			**33.67%**	**-0.3[-0.45,-0.15]**
Heterogeneity: Tau^2=0; Chi^2=2.32, df=3(P=0.51); I^2=0%							
Test for overall effect: Z=3.87(P=0)							
Total ***	**994**		**1001**			**100%**	**-0.33[-0.41,-0.24]**
Heterogeneity: Tau^2=0; Chi^2=10.97, df=10(P=0.36); I^2=8.86%							
Test for overall effect: Z=7.2(P<0.0001)							
Test for subgroup differences: Chi^2=5.4, df=1 (P=0.25), I^2=25.91%							



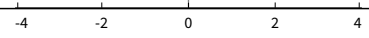
Analysis 3.16. Comparison 3 Studies by severity of asthma, Outcome 16 Symptom score - night time.

Study or subgroup	LABA N	LABA Mean(SD)	PLACEBO N	PLACEBO Mean(SD)	Std. Mean Difference Random, 95% CI	Weight	Std. Mean Difference Random, 95% CI
3.16.1 Mild asthma							
Roberts 1999	12	0.3 (0.5)	11	0.5 (0.8)		2.56%	-0.35[-1.18,0.47]
Wallin 1999	21	0.1 (0.3)	22	0.2 (0.2)		4.37%	-0.41[-1.01,0.2]
Subtotal ***	**33**		**33**			**6.93%**	**-0.39[-0.88,0.1]**
Heterogeneity: Tau^2=0; Chi^2=0.01, df=1(P=0.91); I^2=0%							
Test for overall effect: Z=1.56(P=0.12)							
3.16.2 Mild-moderate asthma							
Bensch 2001	134	0.4 (0.6)	132	0.8 (0.7)		13.57%	-0.61[-0.86,-0.37]
Ekstrom 1998a	135	0.4 (0.5)	129	0.5 (0.5)		13.74%	-0.25[-0.49,-0.01]
Pleskow 2003	135	0.4 (0.6)	139	0.8 (0.8)		13.78%	-0.56[-0.8,-0.32]
Subtotal ***	**404**		**400**			**41.09%**	**-0.48[-0.7,-0.25]**
Heterogeneity: Tau^2=0.02; Chi^2=4.96, df=2(P=0.08); I^2=59.7%							
Test for overall effect: Z=4.21(P<0.0001)							
3.16.3 Persistent/symptomatic asthma							
Busse 1998	226	0.7 (0.7)	231	1.1 (0.7)		16.41%	-0.66[-0.85,-0.48]
Subtotal ***	**226**		**231**			**16.41%**	**-0.66[-0.85,-0.48]**
Heterogeneity: Not applicable							
Test for overall effect: Z=6.92(P<0.0001)							
3.16.4 Moderate asthma							
Ekstrom 1998b	114	0.5 (0.5)	113	0.8 (0.6)		12.79%	-0.44[-0.71,-0.18]
Subtotal ***	**114**		**113**			**12.79%**	**-0.44[-0.71,-0.18]**
Heterogeneity: Not applicable							
Test for overall effect: Z=3.29(P=0)							
3.16.5 Severe asthma							
Subtotal ***	**0**		**0**				**Not estimable**
Heterogeneity: Not applicable							
Test for overall effect: Not applicable							
3.16.6 Unclear							
LaForce 2005	75	0.4 (0.5)	84	0.4 (0.6)		10.83%	-0.11[-0.42,0.2]
Steffensen 1995	103	0.4 (0.7)	101	0.9 (0.7)		11.95%	-0.71[-0.99,-0.43]
Subtotal ***	**178**		**185**			**22.78%**	**-0.41[-1,0.18]**
Heterogeneity: Tau^2=0.16; Chi^2=7.89, df=1(P=0); I^2=87.33%							
Test for overall effect: Z=1.37(P=0.17)							
Total ***	**955**		**962**			**100%**	**-0.48[-0.62,-0.34]**
Heterogeneity: Tau^2=0.02; Chi^2=16.64, df=8(P=0.03); I^2=51.92%							
Test for overall effect: Z=6.77(P<0.0001)							
Test for subgroup differences: Chi^2=3.09, df=1 (P=0.54), I^2=0%							



Analysis 3.17. Comparison 3 Studies by severity of asthma, Outcome 17 Change in symptom score - day time.

Study or subgroup	LABA N	LABA Mean(SD)	PLACEBO N	PLACEBO Mean(SD)	Std. Mean Difference Random, 95% CI	Weight	Std. Mean Difference Random, 95% CI
3.17.1 Mild asthma							
Rosenthal 1999	202	-0.3 (0.6)	206	-0.1 (0.4)		15.6%	-0.38[-0.57,-0.18]
Subtotal ***	**202**		**206**			**15.6%**	**-0.38[-0.57,-0.18]**
Heterogeneity: Not applicable							
Test for overall effect: Z=3.77(P=0)							
3.17.2 Mild-moderate asthma							
Schreurs 1996	49	-0.3 (0.5)	51	0.2 (0.5)		5.94%	-0.94[-1.36,-0.53]
SLGA2004	63	-0.5 (0.8)	63	-0.2 (0.8)		7.61%	-0.38[-0.73,-0.03]
Subtotal ***	**112**		**114**			**13.55%**	**-0.65[-1.21,-0.09]**
Heterogeneity: Tau^2=0.12; Chi^2=4.17, df=1(P=0.04); I^2=76.04%							
Test for overall effect: Z=2.3(P=0.02)							
3.17.3 Persistent/symptomatic asthma							
Bensch 2002	171	-0.3 (0)	176	-0.2 (0)			Not estimable
Busse 1998	258	-0.8 (0.6)	269	-0.4 (0.5)		17.18%	-0.68[-0.85,-0.5]
Kavuru 2000a	77	-0.1 (0.9)	86	0.4 (0.8)		8.99%	-0.57[-0.88,-0.26]
Subtotal ***	**506**		**531**			**26.17%**	**-0.65[-0.8,-0.5]**
Heterogeneity: Tau^2=0; Chi^2=0.34, df=1(P=0.56); I^2=0%							
Test for overall effect: Z=8.32(P<0.0001)							
3.17.4 Moderate asthma							
Shapiro 2000b	84	0.1 (0.9)	90	0.4 (1)		9.6%	-0.32[-0.62,-0.02]
Subtotal ***	**84**		**90**			**9.6%**	**-0.32[-0.62,-0.02]**
Heterogeneity: Not applicable							
Test for overall effect: Z=2.09(P=0.04)							
3.17.5 Severe asthma							
Subtotal ***	**0**		**0**				**Not estimable**
Heterogeneity: Not applicable							
Test for overall effect: Not applicable							
3.17.6 Unclear							
D'Alonzo 1994	93	-0.4 (0.6)	94	-0.1 (0.6)		9.95%	-0.5[-0.79,-0.21]
Pearlman 1992	67	-0.3 (0.8)	63	-0.1 (0.7)		7.84%	-0.26[-0.61,0.08]
Pearlman 1999a	21	-0.5 (0.5)	23	-0.2 (0.5)		3.1%	-0.63[-1.23,-0.02]
SAS30003	92	-0.4 (1)	87	0 (1)		9.72%	-0.41[-0.71,-0.12]
SAS30004	91	-0.3 (0)	89	0.5 (0)			Not estimable
SMS40221	32	-0.7 (1)	32	-0.4 (0.9)		4.46%	-0.27[-0.77,0.22]
Subtotal ***	**396**		**388**			**35.08%**	**-0.41[-0.57,-0.25]**
Heterogeneity: Tau^2=0; Chi^2=1.81, df=4(P=0.77); I^2=0%							
Test for overall effect: Z=4.95(P<0.0001)							
Total ***	**1300**		**1329**			**100%**	**-0.48[-0.6,-0.37]**
Heterogeneity: Tau^2=0.01; Chi^2=14.95, df=10(P=0.13); I^2=33.1%							
Test for overall effect: Z=8.39(P<0.0001)							
Test for subgroup differences: Chi^2=8.09, df=1 (P=0.09), I^2=50.58%							

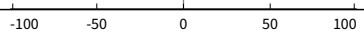


Analysis 3.18. Comparison 3 Studies by severity of asthma, Outcome 18 Change in symptom score - night time.

Study or subgroup	LABA N	LABA Mean(SD)	PLACEBO N	PLACEBO Mean(SD)	Std. Mean Difference Random, 95% CI	Weight	Std. Mean Difference Random, 95% CI
3.18.1 Mild asthma							
Subtotal * **	**0**		**0**				**Not estimable**
Heterogeneity: Not applicable							
Test for overall effect: Not applicable							
3.18.2 Mild-moderate asthma							
Schreurs 1996	49	-0.3 (0.5)	51	0.1 (0.5)		22.66%	-0.97[-1.39,-0.55]
SLGA2004	63	-0.5 (0.8)	63	-0.2 (0.8)		25.22%	-0.38[-0.73,-0.03]
Subtotal * **	**112**		**114**			**47.88%**	**-0.66[-1.24,-0.08]**
Heterogeneity: Tau^2=0.14; Chi^2=4.55, df=1(P=0.03); I^2=78.01%							
Test for overall effect: Z=2.24(P=0.03)							
3.18.3 Moderate asthma							
Subtotal * **	**0**		**0**				**Not estimable**
Heterogeneity: Not applicable							
Test for overall effect: Not applicable							
3.18.4 Persistent/symptomatic asthma							
Busse 1998	261	-0.8 (0.7)	272	-0.3 (0.6)		32.26%	-0.7[-0.88,-0.53]
Subtotal * **	**261**		**272**			**32.26%**	**-0.7[-0.88,-0.53]**
Heterogeneity: Not applicable							
Test for overall effect: Z=7.88(P<0.0001)							
3.18.5 Severe asthma							
Subtotal * **	**0**		**0**				**Not estimable**
Heterogeneity: Not applicable							
Test for overall effect: Not applicable							
3.18.6 Unclear							
SMS40221	32	-0.3 (0.6)	32	-0.3 (1)		19.85%	-0.01[-0.5,0.48]
Subtotal * **	**32**		**32**			**19.85%**	**-0.01[-0.5,0.48]**
Heterogeneity: Not applicable							
Test for overall effect: Z=0.05(P=0.96)							
Total * **	**405**		**418**			**100%**	**-0.54[-0.87,-0.22]**
Heterogeneity: Tau^2=0.08; Chi^2=11.32, df=3(P=0.01); I^2=73.5%							
Test for overall effect: Z=3.25(P=0)							
Test for subgroup differences: Chi^2=6.79, df=1 (P=0.03), I^2=70.54%							

Analysis 3.19. Comparison 3 Studies by severity of asthma, Outcome 19 %days without asthma symptoms.

Study or subgroup	LABA N	LABA Mean(SD)	PLACEBO N	PLACEBO Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
3.19.1 Mild-moderate asthma							
Bensch 2001	135	53 (0)	136	33 (0)			Not estimable
Busse 1998	215	30.8 (40.7)	227	12.1 (25.1)		18.67%	18.7[12.35,25.05]
D'Alonzo 1994	87	35 (40)	90	18 (33)		13.37%	17[6.18,27.82]



Study or subgroup	LABA N	LABA Mean(SD)	PLACEBO N	PLACEBO Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
Jones 1994	282	55 (37)	145	51 (37)		17.36%	4[-3.41,11.41]
Lockey 1999	240	48 (15.5)	234	26 (15.3)		22.44%	22[19.23,24.77]
Pearlman 1992	67	35 (40)	63	16 (31)		11.91%	19[6.74,31.26]
Wolfe 2000a	166	50 (38.6)	167	37 (38.8)		16.25%	13[4.69,21.31]
Subtotal * **	**1192**		**1062**			**100%**	**15.77[9.75,21.79]**
Heterogeneity: Tau²=40.02; Chi²=22.38, df=5(P=0); I²=77.65%							
Test for overall effect: Z=5.14(P<0.0001)							
3.19.2 Mild asthma							
Subtotal * **	**0**		**0**				**Not estimable**
Heterogeneity: Not applicable							
Test for overall effect: Not applicable							
3.19.3 Severe asthma							
Subtotal * **	**0**		**0**				**Not estimable**
Heterogeneity: Not applicable							
Test for overall effect: Not applicable							
Total * **	**1192**		**1062**			**100%**	**15.77[9.75,21.79]**
Heterogeneity: Tau²=40.02; Chi²=22.38, df=5(P=0); I²=77.65%							
Test for overall effect: Z=5.14(P<0.0001)							
Test for subgroup differences: Not applicable							

Analysis 3.20. Comparison 3 Studies by severity of asthma, Outcome 20 % nights without asthma awakenings.

Study or subgroup	LABA N	LABA Mean(SD)	PLACEBO N	PLACEBO Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
3.20.1 Mild asthma							
Jones 1994	282	36 (38)	145	21 (32)		8.12%	15[8.16,21.84]
Subtotal * **	**282**		**145**			**8.12%**	**15[8.16,21.84]**
Heterogeneity: Tau²=0; Chi²=0, df=0(P<0.0001); I²=100%							
Test for overall effect: Z=4.3(P<0.0001)							
3.20.2 Mild-moderate asthma							
Bensch 2001	135	73 (25.9)	136	53 (29.5)		8.21%	20[13.39,26.61]
Dahl 1991a	171	100 (25.9)	172	70 (29.5)		8.51%	30[24.13,35.87]
Ekstrom 1998b	114	60 (25.9)	113	45 (29.5)		7.96%	15[7.78,22.22]
Kemp 1999	176	92.5 (22.2)	176	84 (22.2)		8.97%	8.5[3.87,13.13]
Pearlman 1992	67	89 (21)	63	78 (32)		7.03%	11[1.63,20.37]
Wolfe 2000a	166	84 (25.8)	167	71 (25.8)		8.64%	13[7.46,18.54]
Subtotal * **	**829**		**827**			**49.33%**	**16.32[9.5,23.13]**
Heterogeneity: Tau²=61.19; Chi²=35.58, df=5(P<0.0001); I²=85.95%							
Test for overall effect: Z=4.69(P<0.0001)							
3.20.3 Persistent/symptomatic asthma							
Busse 1998	215	70 (16.1)	227	49 (25.6)		9.19%	21[17.03,24.97]
Kemp 1998a	149	85 (23.2)	152	73 (28.4)		8.52%	12[6.15,17.85]
Lockey 1999	240	72 (27.1)	234	42 (38.2)		8.47%	30[24.02,35.98]

Study or subgroup	LABA N	LABA Mean(SD)	PLACEBO N	PLACEBO Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
Weinstein 1998	105	94.8 (11.1)	105	88.4 (19.5)		9.09%	6.4[2.11,10.69]
Subtotal ***	**709**		**718**			**35.27%**	**17.27[7.47,27.07]**
Heterogeneity: Tau²=93.3; Chi²=48.09, df=3(P<0.0001); I²=93.76%							
Test for overall effect: Z=3.45(P=0)							
3.20.4 Moderate asthma							
Subtotal ***	**0**		**0**				**Not estimable**
Heterogeneity: Not applicable							
Test for overall effect: Not applicable							
3.20.5 Severe asthma							
Subtotal ***	**0**		**0**				**Not estimable**
Heterogeneity: Not applicable							
Test for overall effect: Not applicable							
3.20.6 Unclear							
D'Alonzo 1994	87	86 (25)	90	70 (34)		7.29%	16[7.23,24.77]
Subtotal ***	**87**		**90**			**7.29%**	**16[7.23,24.77]**
Heterogeneity: Not applicable							
Test for overall effect: Z=3.58(P=0)							
Total ***	**1907**		**1780**			**100%**	**16.51[11.86,21.15]**
Heterogeneity: Tau²=57.08; Chi²=83.87, df=11(P<0.0001); I²=86.88%							
Test for overall effect: Z=6.96(P<0.0001)							
Test for subgroup differences: Chi²=0.15, df=1 (P=0.98), I²=0%							

Favours PLACEBO -100 -50 0 50 100 Favours LABA

Analysis 3.21. Comparison 3 Studies by severity of asthma, Outcome 21 Change in %days without asthma symptoms.

Study or subgroup	LABA N	LABA Mean(SD)	PLACEBO N	PLACEBO Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
3.21.1 Mild asthma							
Rosenthal 1999	202	20.9 (29.9)	206	7.6 (27.3)		22.31%	13.3[7.75,18.85]
Subtotal ***	**202**		**206**			**22.31%**	**13.3[7.75,18.85]**
Heterogeneity: Not applicable							
Test for overall effect: Z=4.7(P<0.0001)							
3.21.2 Mild-moderate asthma							
Pearlman 1992	67	21 (33)	63	4 (26)		6.63%	17[6.82,27.18]
Subtotal ***	**67**		**63**			**6.63%**	**17[6.82,27.18]**
Heterogeneity: Not applicable							
Test for overall effect: Z=3.27(P=0)							
3.21.3 Persistent/symptomatic asthma							
Busse 1998	258	24.3 (30.7)	269	8.5 (18.2)		36.63%	15.8[11.47,20.13]
Kavuru 2000a	77	8 (30.5)	86	-3.8 (26.4)		8.86%	11.8[2.99,20.61]
Nathan 1999	128	36 (0)	129	16 (0)			Not estimable
Subtotal ***	**463**		**484**			**45.49%**	**15.02[11.13,18.91]**

Favours PLACEBO -100 -50 0 50 100 Favours LABA

Study or subgroup	LABA N	LABA Mean(SD)	PLACEBO N	PLACEBO Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
Heterogeneity: Tau²=0; Chi²=0.64, df=1(P=0.42); I²=0%							
Test for overall effect: Z=7.57(P<0.0001)							
3.21.4 Moderate asthma							
Shapiro 2000b	84	2.1 (33)	90	-7.9 (32.3)		7.29%	10[0.29,19.71]
Subtotal ***	**84**		**90**			**7.29%**	**10[0.29,19.71]**
Heterogeneity: Not applicable							
Test for overall effect: Z=2.02(P=0.04)							
3.21.5 Severe asthma							
Subtotal ***	**0**		**0**				**Not estimable**
Heterogeneity: Not applicable							
Test for overall effect: Not applicable							
3.21.6 Unclear							
D'Alonzo 1994	87	26 (41)	90	7 (28)		6.38%	19[8.62,29.38]
Pearlman 1999a	21	22 (32.1)	23	2 (28.8)		2.1%	20[1.92,38.08]
SAS30004	91	14 (32.1)	89	-9.1 (24.9)		9.8%	23.1[14.72,31.48]
Subtotal ***	**199**		**202**			**18.28%**	**21.31[15.18,27.44]**
Heterogeneity: Tau²=0; Chi²=0.39, df=2(P=0.82); I²=0%							
Test for overall effect: Z=6.81(P<0.0001)							
Total ***	**1015**		**1045**			**100%**	**15.55[12.93,18.17]**
Heterogeneity: Tau²=0; Chi²=6.45, df=7(P=0.49); I²=0%							
Test for overall effect: Z=11.63(P<0.0001)							
Test for subgroup differences: Chi²=5.43, df=1 (P=0.25), I²=26.29%							

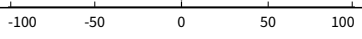
Favours PLACEBO -100 -50 0 50 100 Favours LABA

Analysis 3.22. Comparison 3 Studies by severity of asthma, Outcome 22 Change in % nights without asthma symptoms.

Study or subgroup	LABA N	LABA Mean(SD)	PLACEBO N	PLACEBO Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
3.22.1 Mild asthma							
Rosenthal 1999	202	11.2 (24.2)	206	3.1 (18.7)		30.76%	8.1[3.91,12.29]
Subtotal ***	**202**		**206**			**30.76%**	**8.1[3.91,12.29]**
Heterogeneity: Not applicable							
Test for overall effect: Z=3.78(P=0)							
3.22.2 Mild-moderate asthma							
Pearlman 1992	67	14 (27)	63	6 (31)		5.39%	8[-2.02,18.02]
Subtotal ***	**67**		**63**			**5.39%**	**8[-2.02,18.02]**
Heterogeneity: Not applicable							
Test for overall effect: Z=1.56(P=0.12)							
3.22.3 Persistent/symptomatic asthma							
Busse 1998	261	28.1 (33.5)	272	6.6 (26.7)		20.4%	21.5[16.35,26.65]
Kavuru 2000a	77	-5.3 (23.8)	86	-16.5 (30)		7.9%	11.2[2.92,19.48]
Nathan 1999	128	15 (0)	129	4 (0)			Not estimable

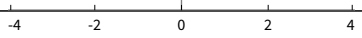
Favours PLACEBO -100 -50 0 50 100 Favours LABA

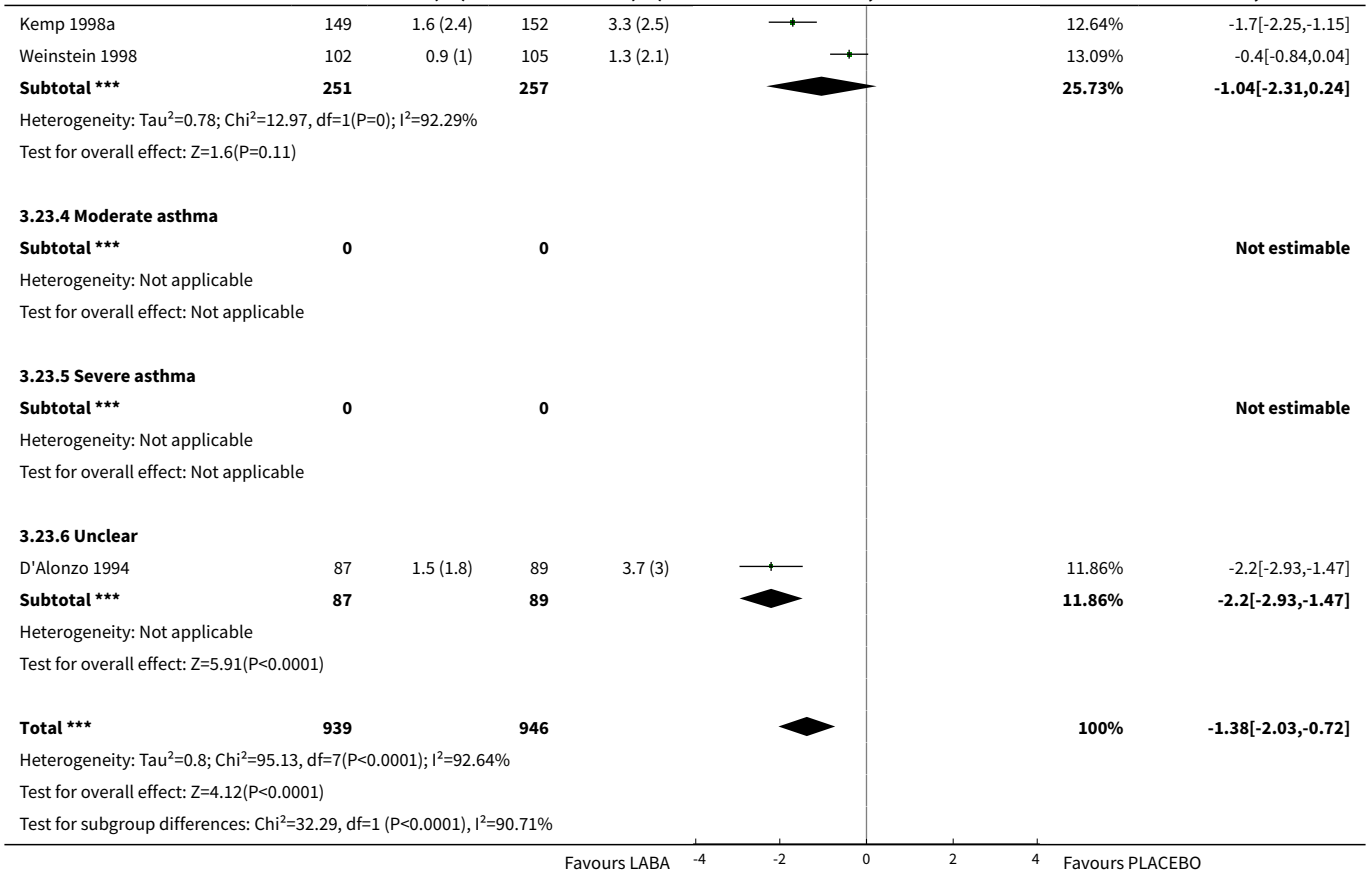
Study or subgroup	LABA N	LABA Mean(SD)	PLACEBO N	PLACEBO Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
Weinstein 1998	102	9.1 (22.2)	105	4.1 (20.5)		15.94%	5[-0.83,10.83]
Subtotal ***	**568**		**592**			**44.24%**	**13.72[10.22,17.21]**
Heterogeneity: Tau²=0; Chi²=17.73, df=2(P=0); I²=88.72%							
Test for overall effect: Z=7.69(P<0.0001)							
3.22.4 Moderate asthma							
Shapiro 2000b	84	-8 (33)	90	-12 (32.3)		5.74%	4[-5.71,13.71]
Subtotal ***	**84**		**90**			**5.74%**	**4[-5.71,13.71]**
Heterogeneity: Not applicable							
Test for overall effect: Z=0.81(P=0.42)							
3.22.5 Severe asthma							
Subtotal ***	**0**		**0**				**Not estimable**
Heterogeneity: Not applicable							
Test for overall effect: Not applicable							
3.22.6 Unclear							
D'Alonzo 1994	87	24 (32)	90	5 (32)		6.09%	19[9.57,28.43]
Pearlman 1999a	21	10 (13.8)	23	2 (14.4)		7.79%	8[-0.33,16.33]
Subtotal ***	**108**		**113**			**13.88%**	**12.82[6.58,19.07]**
Heterogeneity: Tau²=0; Chi²=2.93, df=1(P=0.09); I²=65.92%							
Test for overall effect: Z=4.02(P<0.0001)							
Total ***	**1029**		**1064**			**100%**	**11[8.67,13.33]**
Heterogeneity: Tau²=0; Chi²=27.48, df=7(P=0); I²=74.53%							
Test for overall effect: Z=9.27(P<0.0001)							
Test for subgroup differences: Chi²=6.82, df=1 (P=0.15), I²=41.36%							



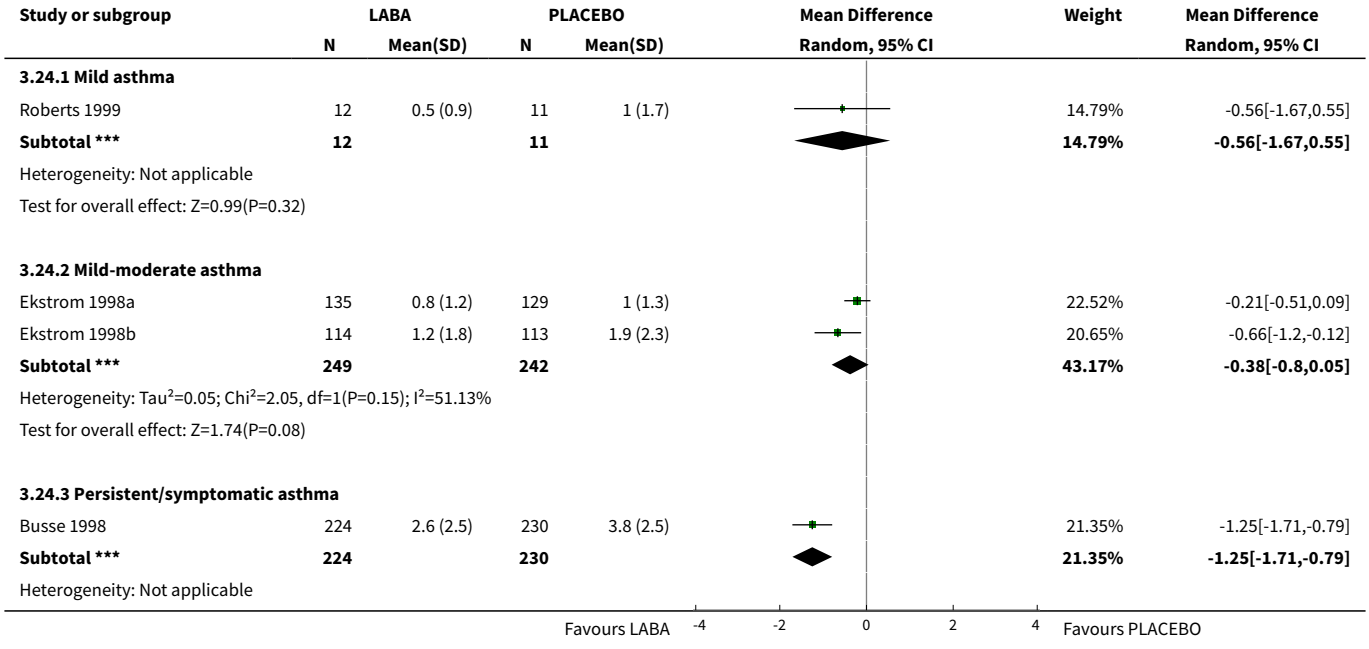
Analysis 3.23. Comparison 3 Studies by severity of asthma, Outcome 23 Rescue bronchodilator use: whole day.

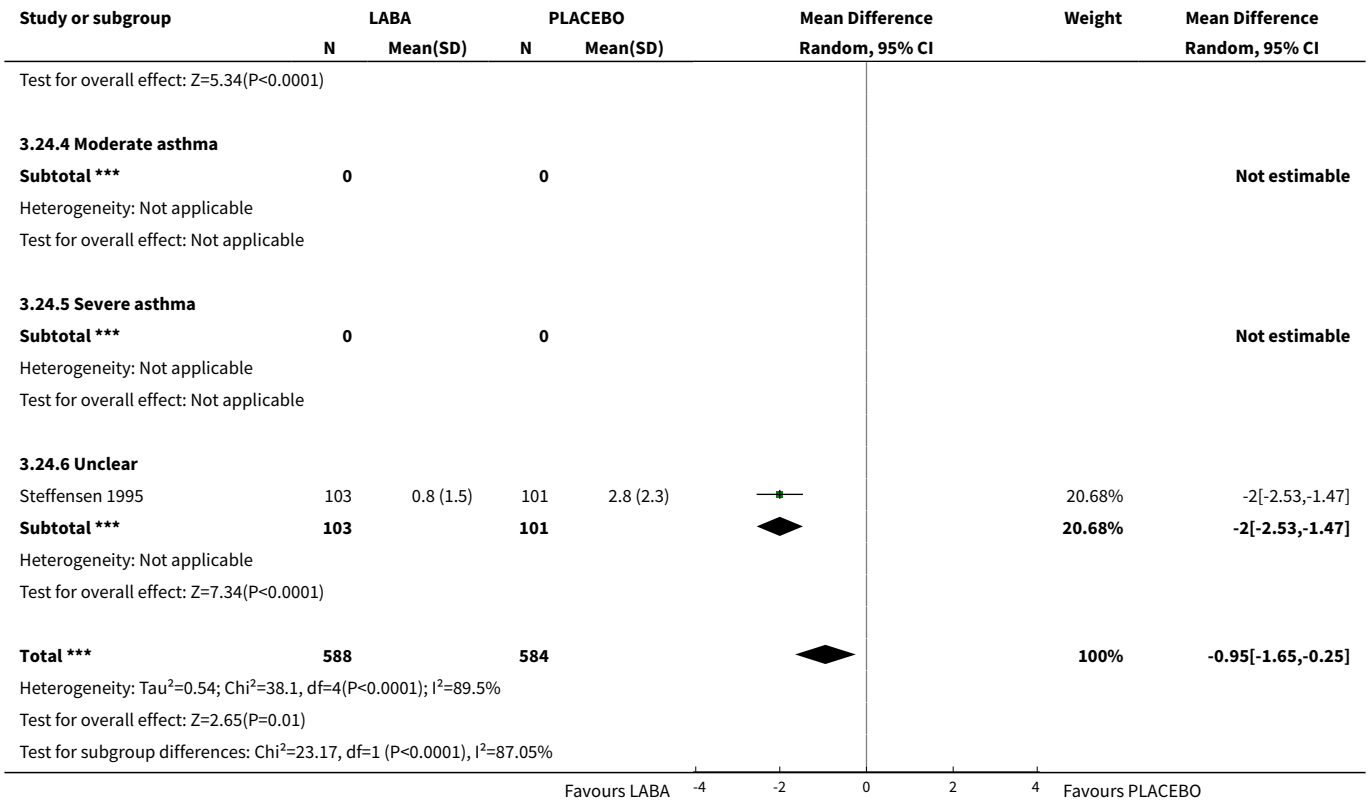
Study or subgroup	LABA N	LABA Mean(SD)	PLACEBO N	PLACEBO Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
3.23.1 Mild asthma							
Wallin 1999	21	0.1 (0.2)	22	0.4 (0.5)		13.68%	-0.3[-0.53,-0.07]
Subtotal ***	**21**		**22**			**13.68%**	**-0.3[-0.53,-0.07]**
Heterogeneity: Not applicable							
Test for overall effect: Z=2.6(P=0.01)							
3.23.2 Mild-moderate asthma							
Dahl 1991a	171	0.3 (2.5)	172	3 (2.8)		12.6%	-2.7[-3.27,-2.13]
Kemp 1999	176	1.5 (3.3)	176	2.7 (3.3)		12.03%	-1.2[-1.89,-0.51]
Pearlman 1992	67	1.2 (1.9)	63	2.8 (2.7)		11.48%	-1.6[-2.41,-0.79]
Wolfe 2000a	166	1.8 (2.6)	167	2.9 (2.6)		12.63%	-1.1[-1.66,-0.54]
Subtotal ***	**580**		**578**			**48.73%**	**-1.66[-2.46,-0.86]**
Heterogeneity: Tau²=0.56; Chi²=18.49, df=3(P=0); I²=83.78%							
Test for overall effect: Z=4.06(P<0.0001)							
3.23.3 Persistent/symptomatic asthma							



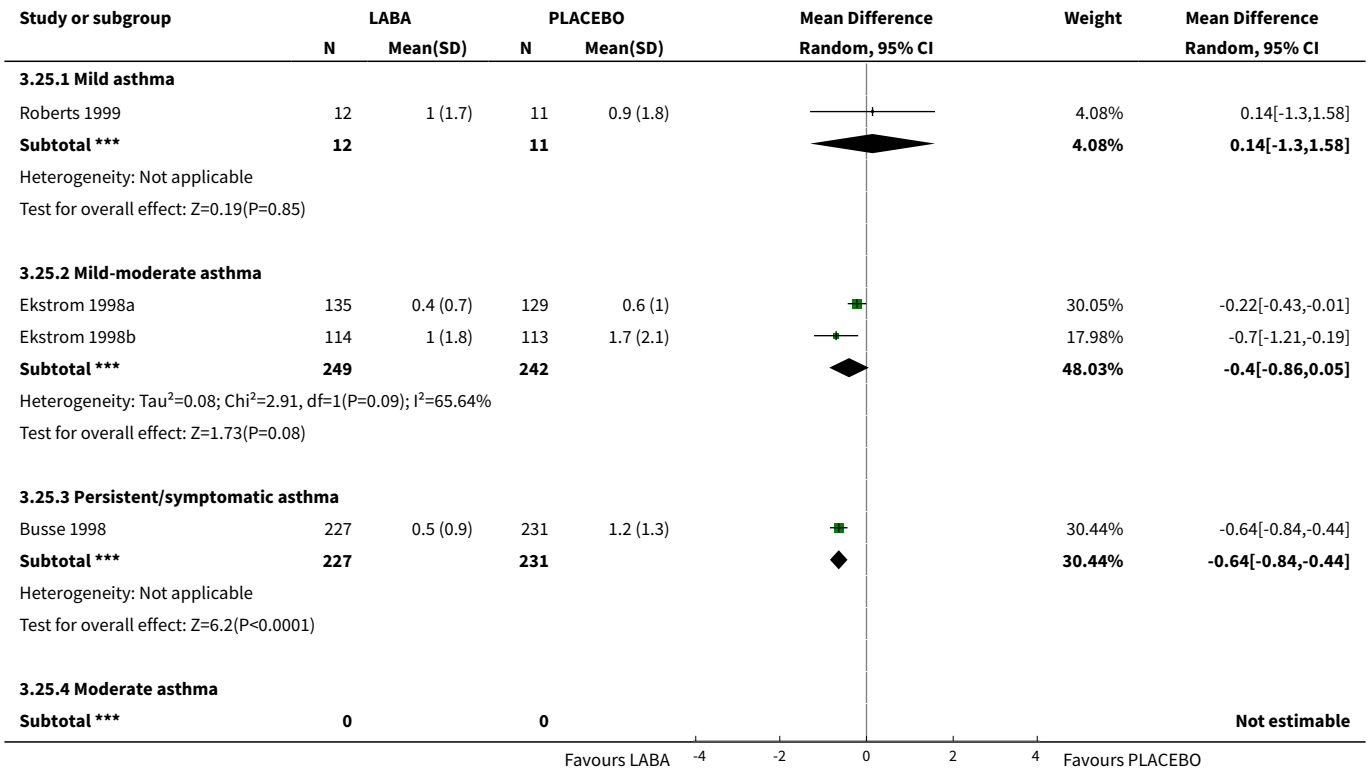


Analysis 3.24. Comparison 3 Studies by severity of asthma, Outcome 24 Rescue bronchodilator use: day time.





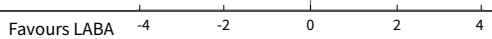
Analysis 3.25. Comparison 3 Studies by severity of asthma, Outcome 25 Rescue bronchodilator use: night time.



Study or subgroup	LABA N	LABA Mean(SD)	PLACEBO N	PLACEBO Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
Heterogeneity: Not applicable							
Test for overall effect: Not applicable							
3.25.5 Severe asthma							
Subtotal ***	**0**		**0**				**Not estimable**
Heterogeneity: Not applicable							
Test for overall effect: Not applicable							
3.25.6 Unclear							
Steffensen 1995	103	0.4 (1)	101	1.4 (2.5)		17.46%	-1[-1.52,-0.48]
Subtotal ***	**103**		**101**			**17.46%**	**-1[-1.52,-0.48]**
Heterogeneity: Not applicable							
Test for overall effect: Z=3.74(P=0)							
Total ***	**591**		**585**			**100%**	**-0.56[-0.87,-0.25]**
Heterogeneity: Tau²=0.07; Chi²=13.36, df=4(P=0.01); I²=70.06%							
Test for overall effect: Z=3.52(P=0)							
Test for subgroup differences: Chi²=3.98, df=1 (P=0.26), I²=24.54%							

Analysis 3.26. Comparison 3 Studies by severity of asthma, Outcome 26 Change in use of rescue bronchodilator/day.

Study or subgroup	LABA N	LABA Mean(SD)	PLACEBO N	PLACEBO Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
3.26.1 Mild asthma							
Subtotal ***	**0**		**0**				**Not estimable**
Heterogeneity: Not applicable							
Test for overall effect: Not applicable							
3.26.2 Mild-moderate asthma							
Schreurs 1996	49	-1.4 (1.5)	51	-0.6 (1.1)		29.06%	-0.78[-1.3,-0.26]
Subtotal ***	**49**		**51**			**29.06%**	**-0.78[-1.3,-0.26]**
Heterogeneity: Not applicable							
Test for overall effect: Z=2.95(P=0)							
3.26.3 Persistent/symptomatic asthma							
Busse 1998	258	-2.7 (2.5)	269	-1.4 (2)		36%	-1.31[-1.7,-0.92]
Subtotal ***	**258**		**269**			**36%**	**-1.31[-1.7,-0.92]**
Heterogeneity: Not applicable							
Test for overall effect: Z=6.54(P<0.0001)							
3.26.4 Moderate asthma							
Subtotal ***	**0**		**0**				**Not estimable**
Heterogeneity: Not applicable							
Test for overall effect: Not applicable							
3.26.5 Severe asthma							
Subtotal ***	**0**		**0**				**Not estimable**



Study or subgroup	LABA N	LABA Mean(SD)	PLACEBO N	PLACEBO Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
Heterogeneity: Not applicable							
Test for overall effect: Not applicable							
3.26.6 Unclear							
SMS40221	32	-0.9 (1.1)	32	-0.2 (0.5)		34.94%	-0.67[-1.08,-0.26]
Subtotal ***	**32**		**32**			**34.94%**	**-0.67[-1.08,-0.26]**
Heterogeneity: Not applicable							
Test for overall effect: Z=3.2(P=0)							
Total ***	**339**		**352**			**100%**	**-0.93[-1.35,-0.52]**
Heterogeneity: Tau^2=0.09; Chi^2=5.43, df=2(P=0.07); I^2=63.15%							
Test for overall effect: Z=4.39(P<0.0001)							
Test for subgroup differences: Chi^2=5.43, df=1 (P=0.07), I^2=63.15%							

Analysis 3.27. Comparison 3 Studies by severity of asthma, Outcome 27 Change in use of rescue bronchodilator/night.

Study or subgroup	LABA N	LABA Mean(SD)	PLACEBO N	PLACEBO Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
3.27.1 Mild asthma							
Subtotal ***	**0**		**0**				**Not estimable**
Heterogeneity: Not applicable							
Test for overall effect: Not applicable							
3.27.2 Mild-moderate asthma							
Busse 1998	261	-0.8 (1.2)	272	-0.3 (1.1)		51.78%	-0.52[-0.72,-0.32]
Schreurs 1996	49	-0.9 (1.1)	51	-0.3 (0.8)		22.26%	-0.62[-1.01,-0.23]
Subtotal ***	**310**		**323**			**74.03%**	**-0.54[-0.72,-0.37]**
Heterogeneity: Tau^2=0; Chi^2=0.2, df=1(P=0.65); I^2=0%							
Test for overall effect: Z=6.06(P<0.0001)							
3.27.3 Persistent/symptomatic asthma							
Subtotal ***	**0**		**0**				**Not estimable**
Heterogeneity: Not applicable							
Test for overall effect: Not applicable							
3.27.4 Moderate asthma							
Subtotal ***	**0**		**0**				**Not estimable**
Heterogeneity: Not applicable							
Test for overall effect: Not applicable							
3.27.5 Severe asthma							
Subtotal ***	**0**		**0**				**Not estimable**
Heterogeneity: Not applicable							
Test for overall effect: Not applicable							
3.27.6 Unclear							
SMS40221	32	-0.5 (0.7)	32	-0.3 (0.7)		25.97%	-0.21[-0.56,0.14]

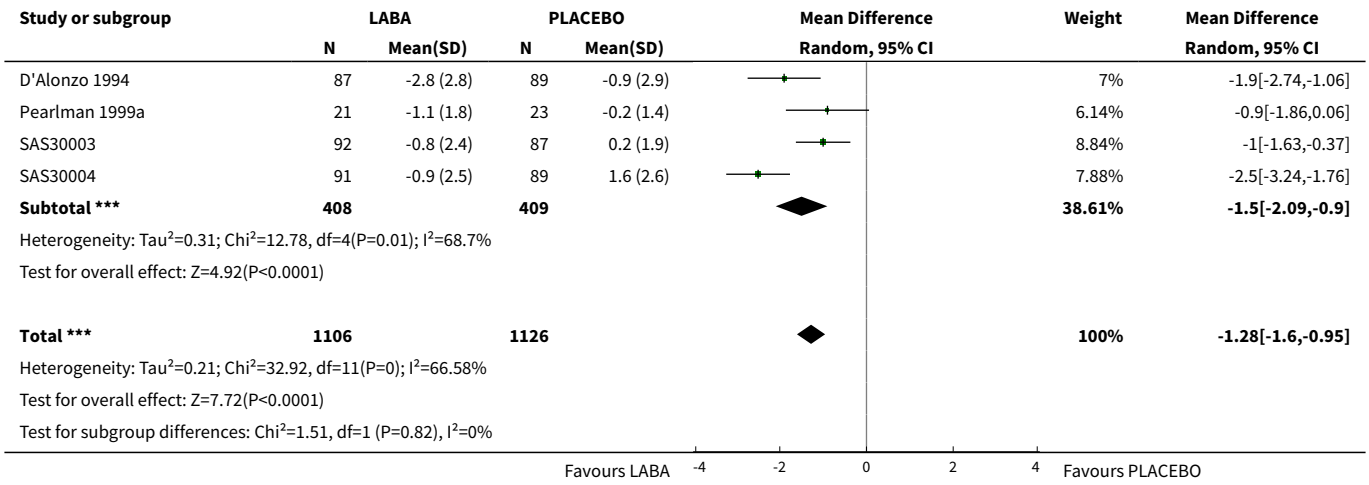
Study or subgroup	LABA N	LABA Mean(SD)	PLACEBO N	PLACEBO Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
Subtotal ***	**32**		**32**			**25.97%**	**-0.21[-0.56,0.14]**
Heterogeneity: Not applicable							
Test for overall effect: Z=1.18(P=0.24)							
Total ***	**342**		**355**			**100%**	**-0.46[-0.67,-0.25]**
Heterogeneity: Tau^2=0.01; Chi^2=2.97, df=2(P=0.23); I^2=32.64%							
Test for overall effect: Z=4.36(P<0.0001)							
Test for subgroup differences: Chi^2=2.76, df=1 (P=0.1), I^2=63.82%							

Favours LABA -4 -2 0 2 4 Favours PLACEBO

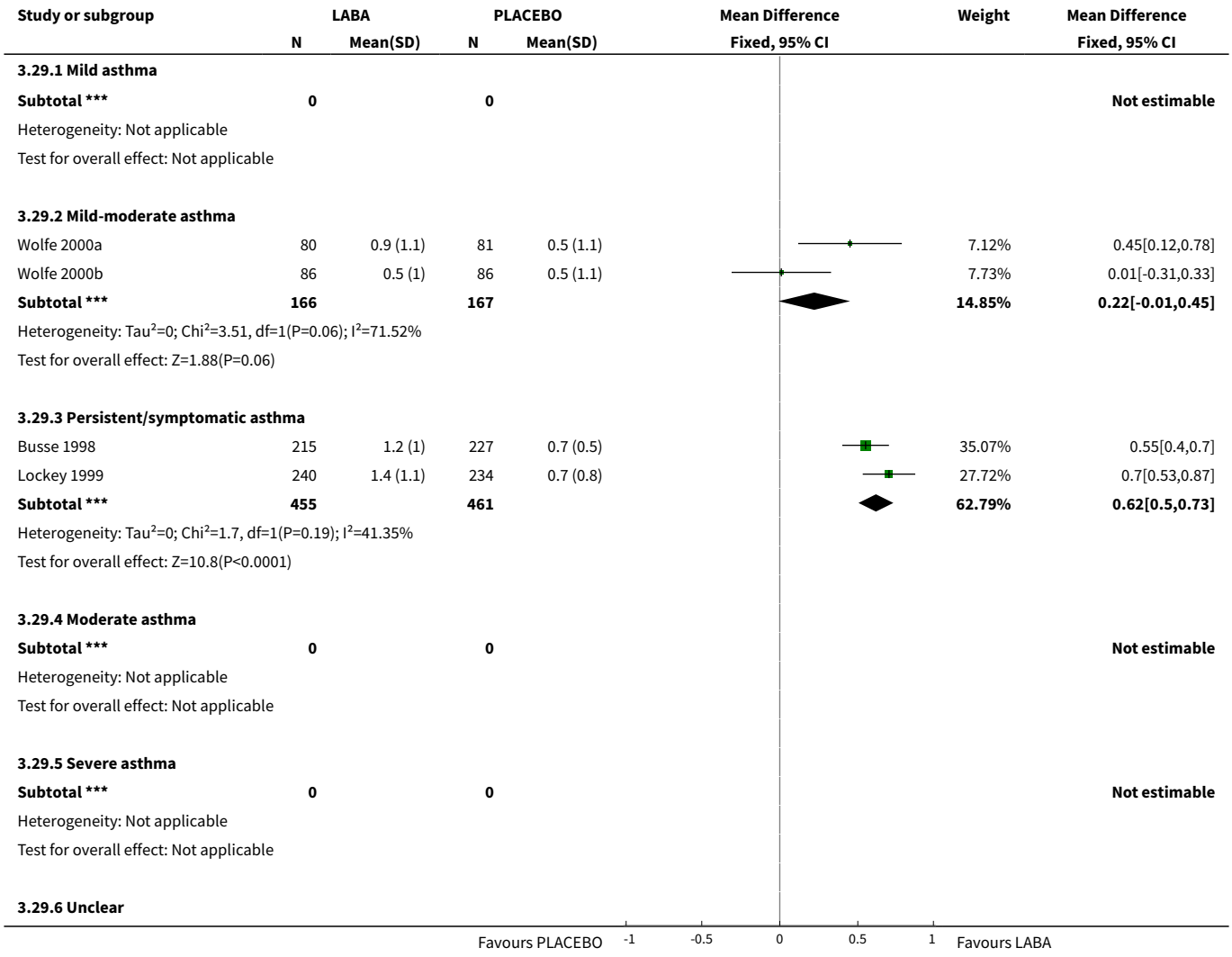
Analysis 3.28. Comparison 3 Studies by severity of asthma, Outcome 28 Change in use of rescue bronchodilator/ whole day.

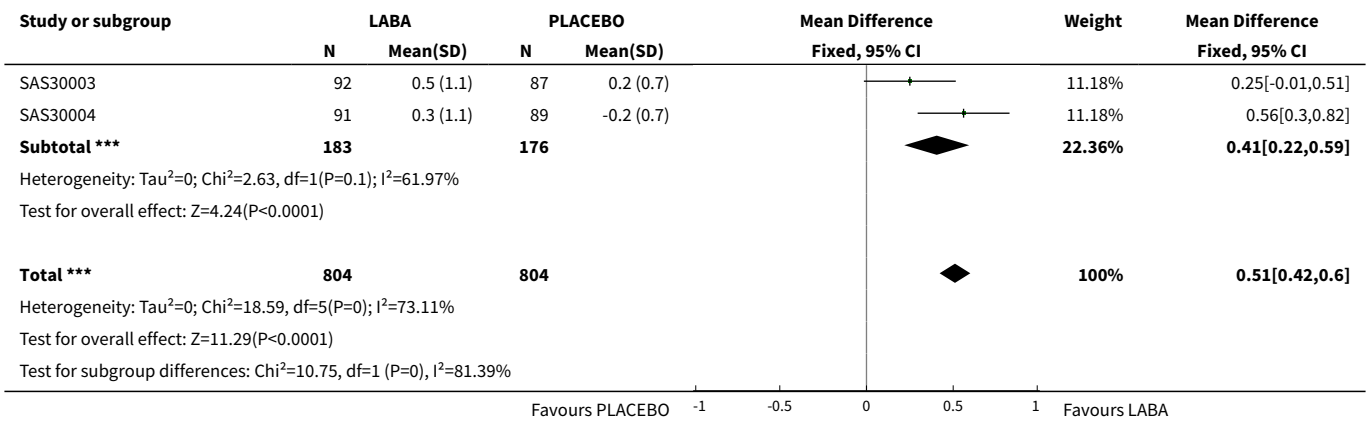
Study or subgroup	LABA N	LABA Mean(SD)	PLACEBO N	PLACEBO Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
3.28.1 Mild asthma							
Rosenthal 1999	202	-1.5 (2.1)	206	-0.3 (1.9)		11.11%	-1.18[-1.57,-0.79]
Subtotal ***	**202**		**206**			**11.11%**	**-1.18[-1.57,-0.79]**
Heterogeneity: Not applicable							
Test for overall effect: Z=5.94(P<0.0001)							
3.28.2 Mild to moderate asthma							
Pearlman 1992	67	-2.6 (2.6)	63	-0.9 (2.3)		6.99%	-1.7[-2.54,-0.86]
Wolfe 2000a	80	-1.8 (2.7)	81	-0.7 (1.8)		8.14%	-1.1[-1.81,-0.39]
Wolfe 2000b	86	-1.6 (1.9)	86	-0.7 (1.9)		9.54%	-0.9[-1.45,-0.35]
Subtotal ***	**233**		**230**			**24.67%**	**-1.15[-1.58,-0.71]**
Heterogeneity: Tau^2=0.03; Chi^2=2.43, df=2(P=0.3); I^2=17.54%							
Test for overall effect: Z=5.19(P<0.0001)							
3.28.3 Persistent/symptomatic asthma							
Kavuru 2000a	77	-0.3 (2.4)	86	1.7 (2.3)		7.99%	-2[-2.72,-1.28]
Weinstein 1998	102	-0.8 (2)	105	-0.3 (1)		10.65%	-0.5[-0.94,-0.06]
Subtotal ***	**179**		**191**			**18.65%**	**-1.22[-2.69,0.25]**
Heterogeneity: Tau^2=1.03; Chi^2=12.1, df=1(P=0); I^2=91.73%							
Test for overall effect: Z=1.63(P=0.1)							
3.28.4 Moderate asthma							
Shapiro 2000b	84	0 (2.8)	90	0.9 (2.9)		6.96%	-0.9[-1.75,-0.05]
Subtotal ***	**84**		**90**			**6.96%**	**-0.9[-1.75,-0.05]**
Heterogeneity: Not applicable							
Test for overall effect: Z=2.08(P=0.04)							
3.28.5 Severe asthma							
Subtotal ***	**0**		**0**				**Not estimable**
Heterogeneity: Not applicable							
Test for overall effect: Not applicable							
3.28.6 Unclear							
Adinoff 1998	117	-2.3 (2.5)	121	-1.1 (2.6)		8.74%	-1.19[-1.83,-0.55]

Favours LABA -4 -2 0 2 4 Favours PLACEBO

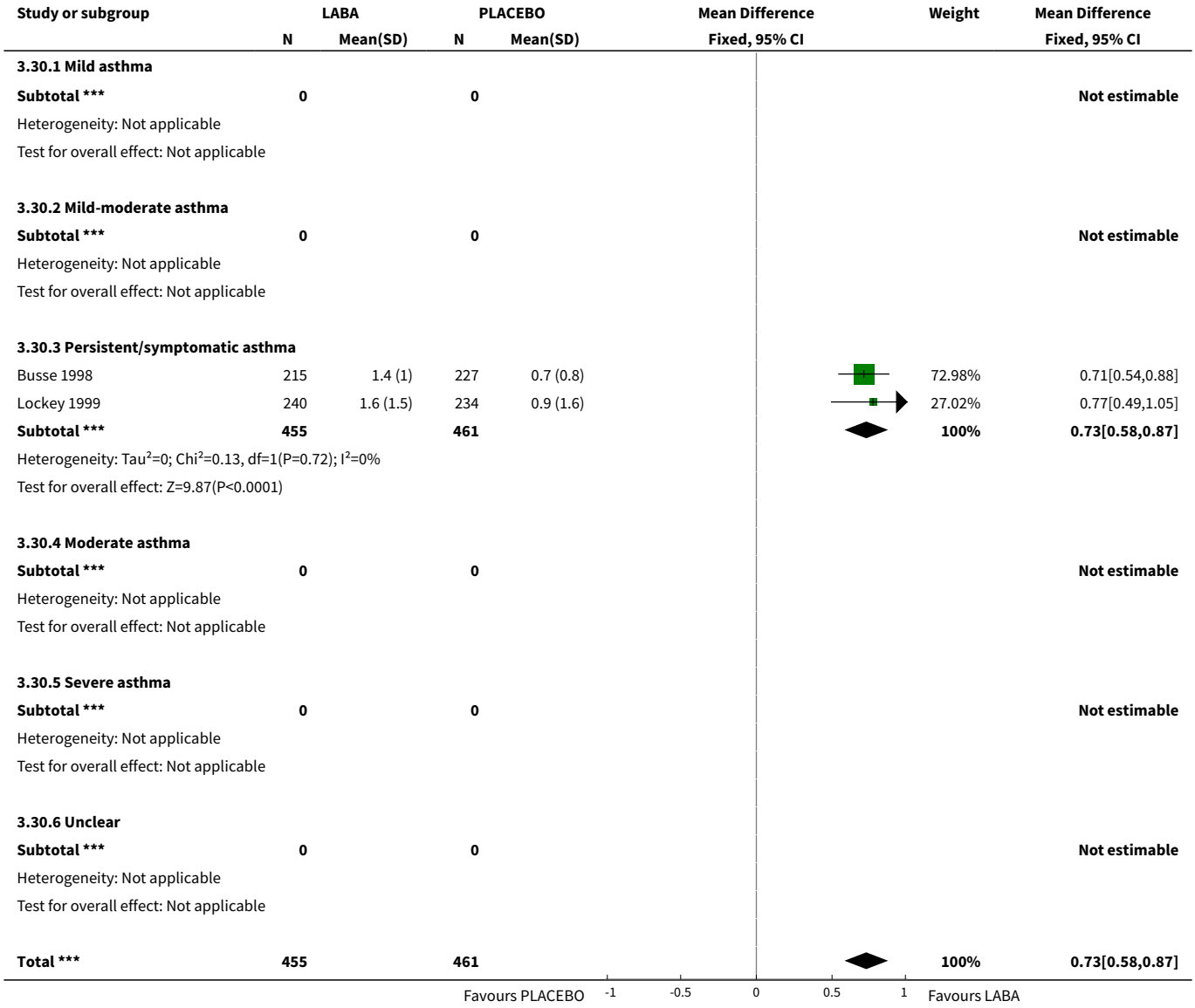


Analysis 3.29. Comparison 3 Studies by severity of asthma, Outcome 29 AQOL- Change in Quality of life score: global.





Analysis 3.30. Comparison 3 Studies by severity of asthma, Outcome 30 Change in Quality of life score- symptoms.



Study or subgroup	LABA N	LABA Mean(SD)	PLACEBO N	PLACEBO Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
Heterogeneity: Tau²=0; Chi²=0.13, df=1(P=0.72); I²=0%							
Test for overall effect: Z=9.87(P<0.0001)							
Test for subgroup differences: Not applicable							

Favours PLACEBO -1 -0.5 0 0.5 1 Favours LABA

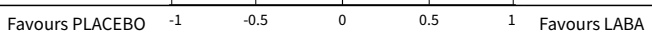
Analysis 3.31. Comparison 3 Studies by severity of asthma, Outcome 31 Change in Quality of life score: emotions.

Study or subgroup	LABA N	LABA Mean(SD)	PLACEBO N	PLACEBO Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
3.31.1 Mild asthma							
Subtotal ***	**0**		**0**				**Not estimable**
Heterogeneity: Not applicable							
Test for overall effect: Not applicable							
3.31.2 Mild-moderate asthma							
Subtotal ***	**0**		**0**				**Not estimable**
Heterogeneity: Not applicable							
Test for overall effect: Not applicable							
3.31.3 Persistent/symptomatic asthma							
Busse 1998	215	1.2 (1.3)	227	0.7 (0.9)		67.62%	0.57[0.36,0.78]
Lockey 1999	240	1.4 (1.8)	234	0.5 (1.6)		32.38%	0.84[0.53,1.15]
Subtotal ***	**455**		**461**			**100%**	**0.66[0.48,0.83]**
Heterogeneity: Tau²=0; Chi²=2.02, df=1(P=0.15); I²=50.55%							
Test for overall effect: Z=7.4(P<0.0001)							
3.31.4 Moderate asthma							
Subtotal ***	**0**		**0**				**Not estimable**
Heterogeneity: Not applicable							
Test for overall effect: Not applicable							
3.31.5 Severe asthma							
Subtotal ***	**0**		**0**				**Not estimable**
Heterogeneity: Not applicable							
Test for overall effect: Not applicable							
3.31.6 Unclear							
Subtotal ***	**0**		**0**				**Not estimable**
Heterogeneity: Not applicable							
Test for overall effect: Not applicable							
Total ***	**455**		**461**			**100%**	**0.66[0.48,0.83]**
Heterogeneity: Tau²=0; Chi²=2.02, df=1(P=0.15); I²=50.55%							
Test for overall effect: Z=7.4(P<0.0001)							
Test for subgroup differences: Not applicable							

Favours PLACEBO -1 -0.5 0 0.5 1 Favours LABA

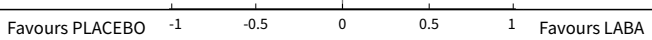
Analysis 3.32. Comparison 3 Studies by severity of asthma, Outcome 32 Change in Quality of life score: exposure to environmental stimuli.

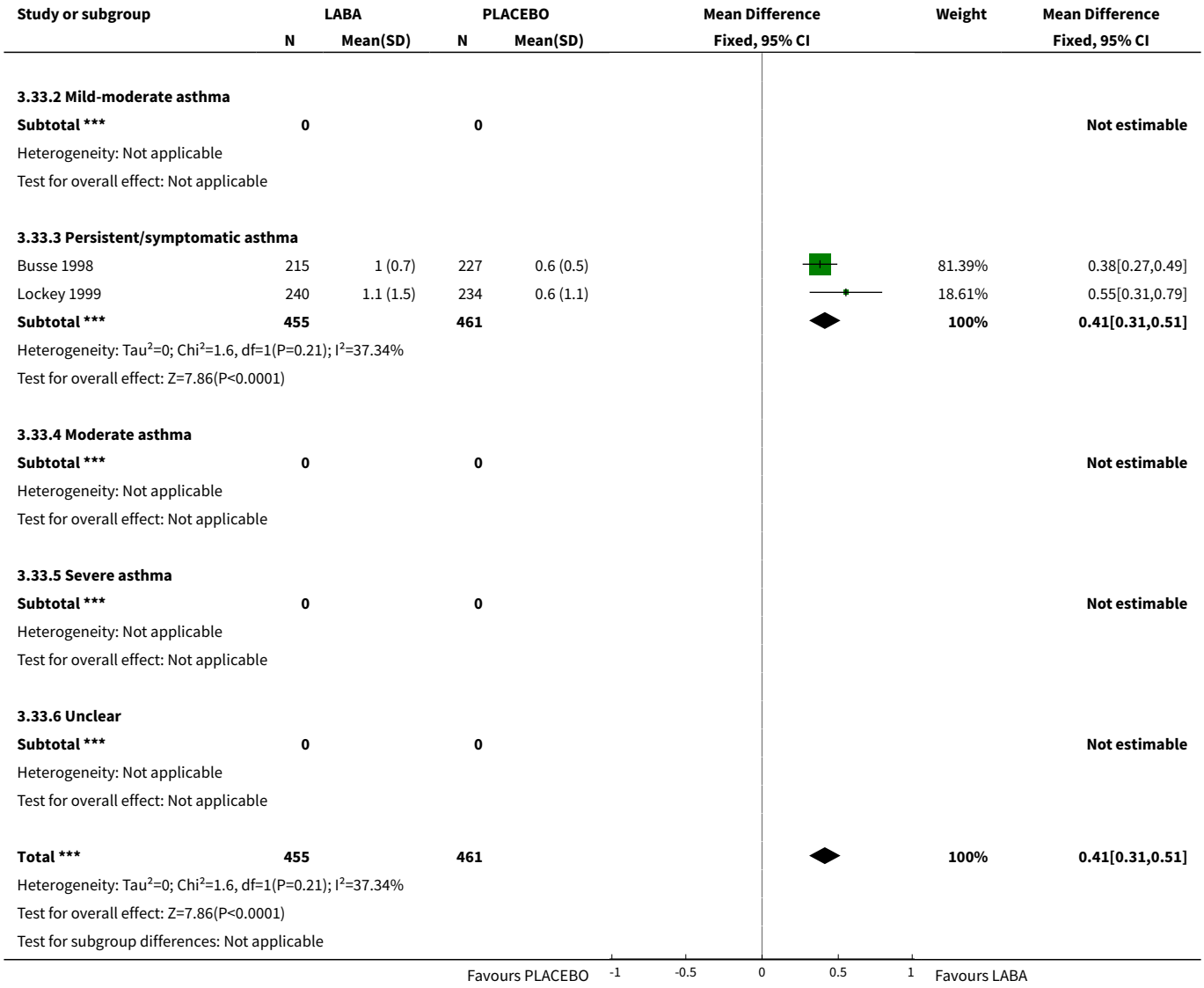
Study or subgroup	LABA N	LABA Mean(SD)	PLACEBO N	PLACEBO Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
3.32.1 Mild asthma							
Subtotal ***	**0**		**0**				**Not estimable**
Heterogeneity: Not applicable							
Test for overall effect: Not applicable							
3.32.2 Mild-moderate asthma							
Subtotal ***	**0**		**0**				**Not estimable**
Heterogeneity: Not applicable							
Test for overall effect: Not applicable							
3.32.3 Persistent/symptomatic asthma							
Busse 1998	215	1.1 (1)	227	0.6 (0.9)		63.05%	0.53[0.35,0.71]
Lockey 1999	240	1.2 (1.4)	234	0.6 (1.2)		36.95%	0.61[0.37,0.85]
Subtotal ***	**455**		**461**			**100%**	**0.56[0.42,0.7]**
Heterogeneity: $Tau^2=0$; $Chi^2=0.28$, df=1(P=0.6); $I^2=0\%$							
Test for overall effect: Z=7.64(P<0.0001)							
3.32.4 Moderate asthma							
Subtotal ***	**0**		**0**				**Not estimable**
Heterogeneity: Not applicable							
Test for overall effect: Not applicable							
3.32.5 Severe asthma							
Subtotal ***	**0**		**0**				**Not estimable**
Heterogeneity: Not applicable							
Test for overall effect: Not applicable							
3.32.6 Unclear							
Subtotal ***	**0**		**0**				**Not estimable**
Heterogeneity: Not applicable							
Test for overall effect: Not applicable							
Total ***	**455**		**461**			**100%**	**0.56[0.42,0.7]**
Heterogeneity: $Tau^2=0$; $Chi^2=0.28$, df=1(P=0.6); $I^2=0\%$							
Test for overall effect: Z=7.64(P<0.0001)							
Test for subgroup differences: Not applicable							



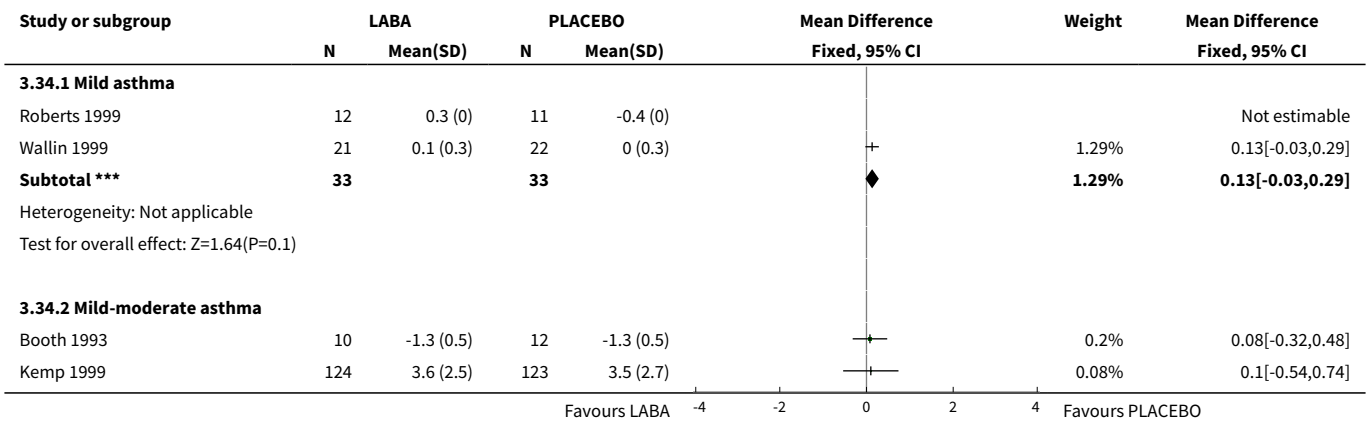
Analysis 3.33. Comparison 3 Studies by severity of asthma, Outcome 33 Change in Quality of life score: activity limitations.

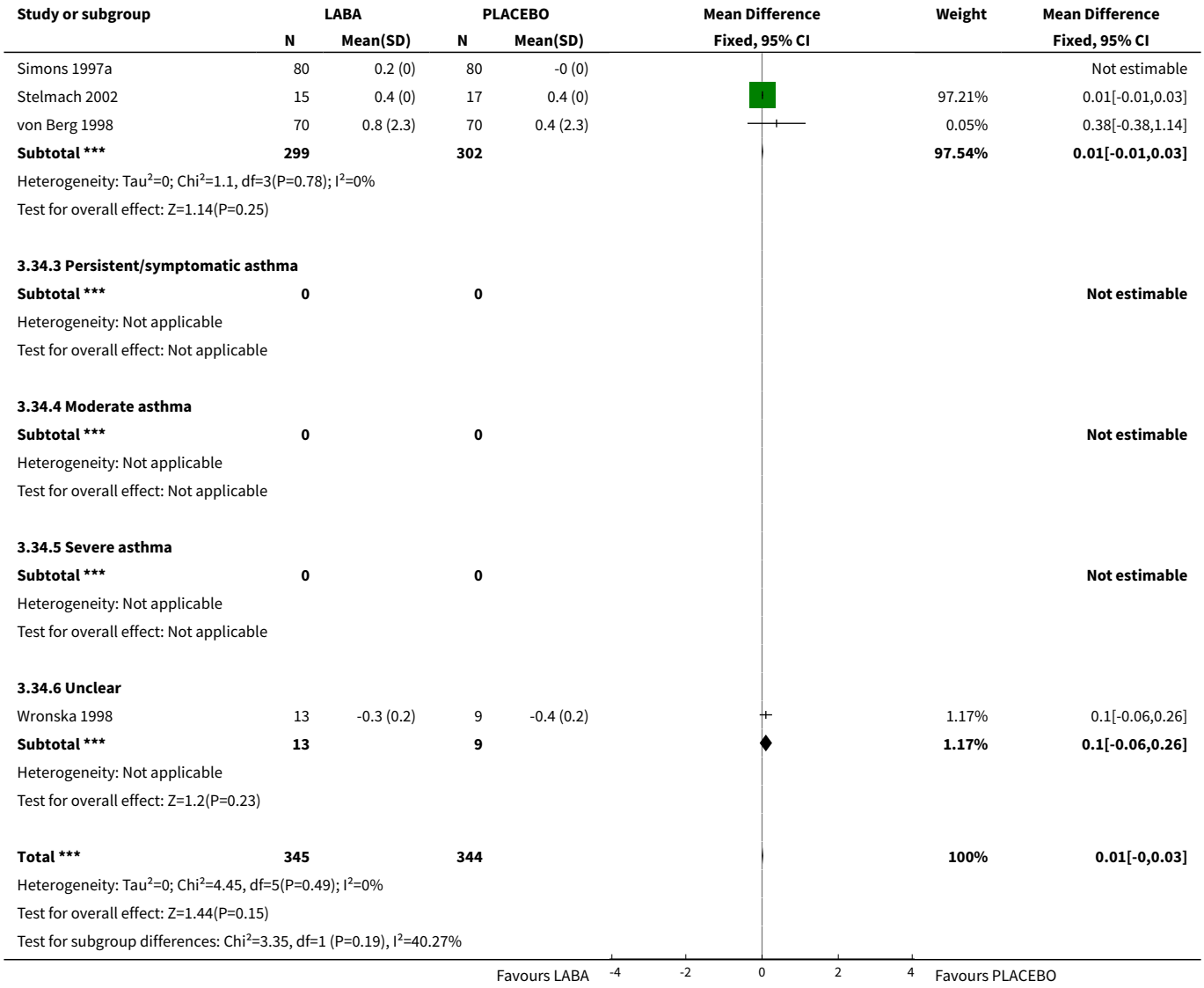
Study or subgroup	LABA N	LABA Mean(SD)	PLACEBO N	PLACEBO Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
3.33.1 Mild asthma							
Subtotal ***	**0**		**0**				**Not estimable**
Heterogeneity: Not applicable							
Test for overall effect: Not applicable							



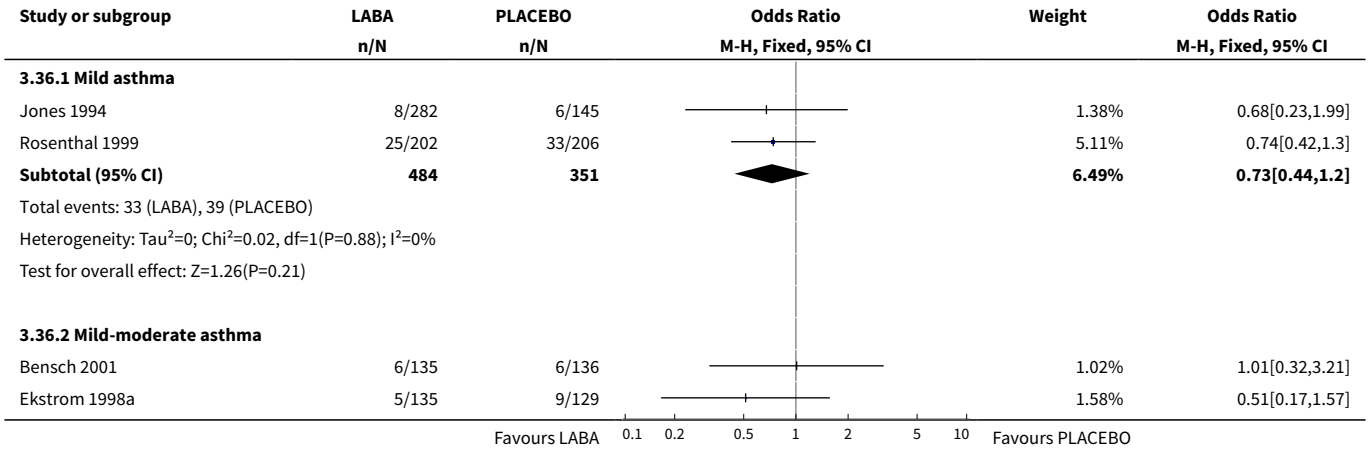


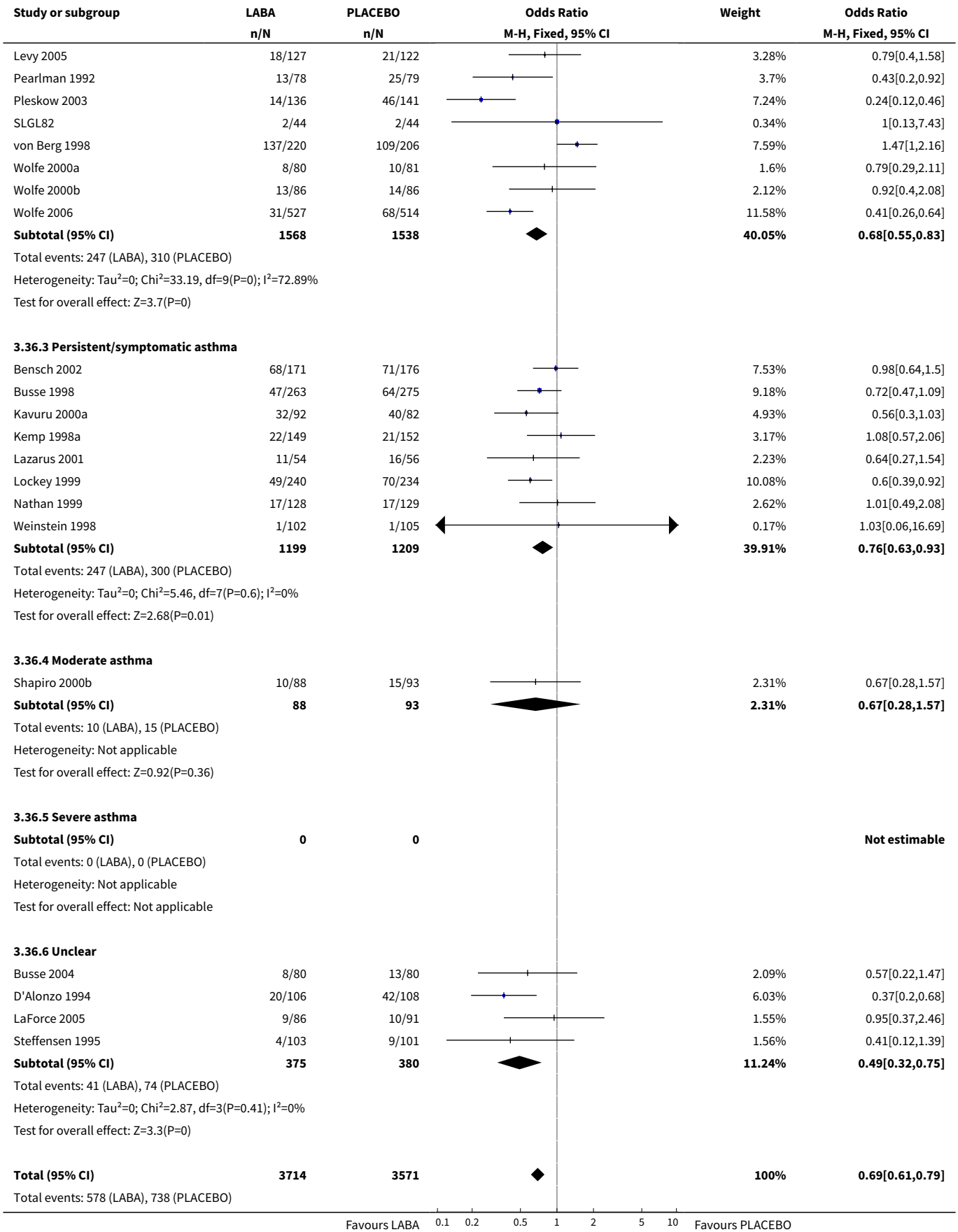
Analysis 3.34. Comparison 3 Studies by severity of asthma, Outcome 34 Bronchial hyperreactivity- log PD20/PC20 methacholine or histamine.



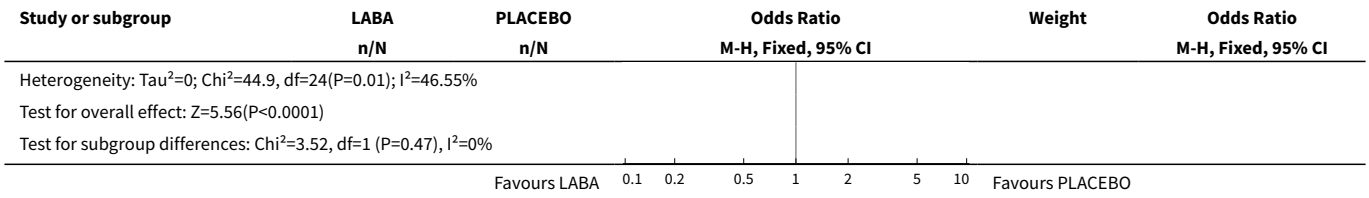


Analysis 3.36. Comparison 3 Studies by severity of asthma, Outcome 36 Exacerbations asthma (all)- >1 major.

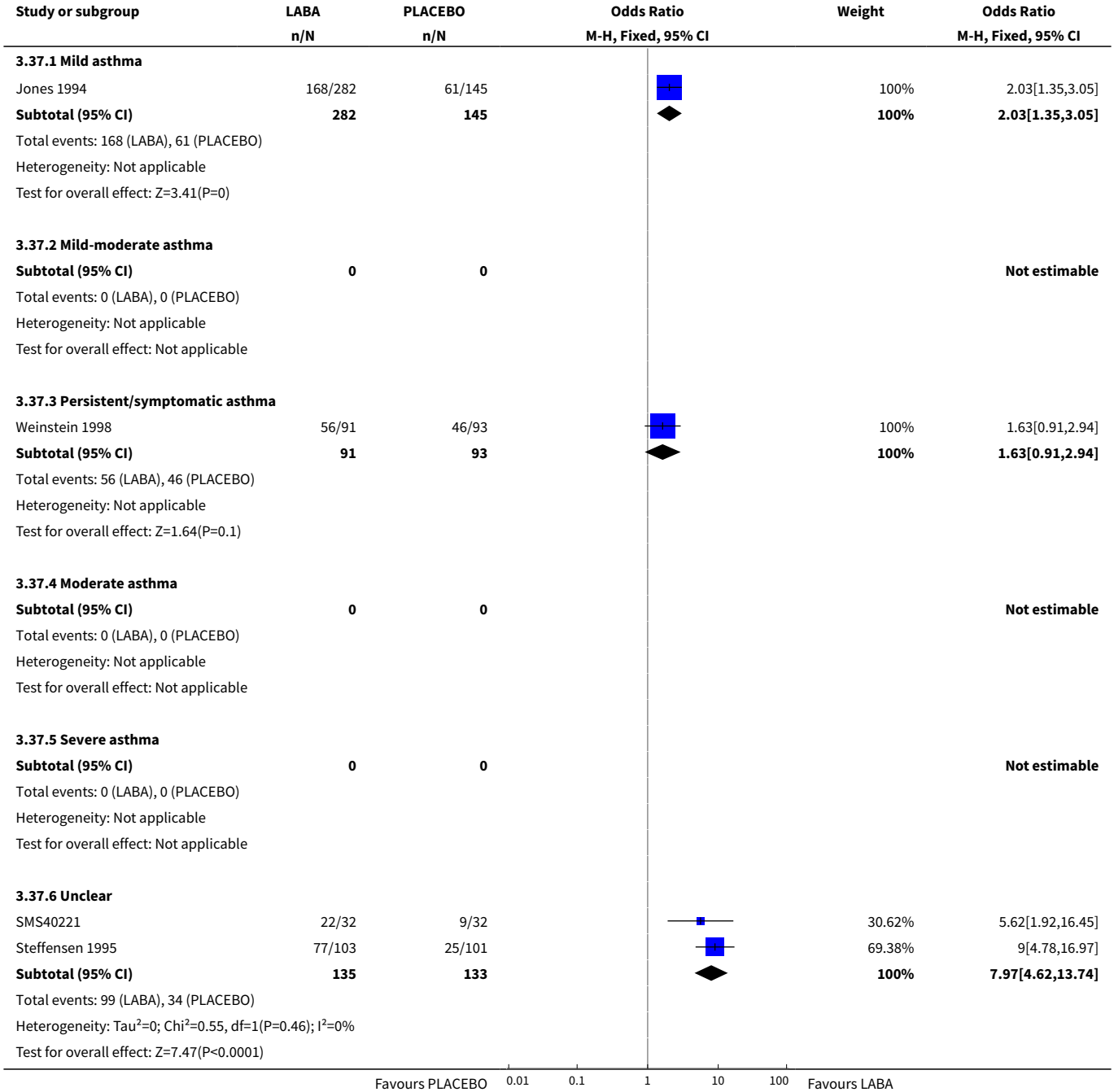




Study or subgroup	LABA n/N	PLACEBO n/N	Odds Ratio M-H, Fixed, 95% CI	Weight	Odds Ratio M-H, Fixed, 95% CI
Levy 2005	18/127	21/122		3.28%	0.79[0.4,1.58]
Pearlman 1992	13/78	25/79		3.7%	0.43[0.2,0.92]
Pleskow 2003	14/136	46/141		7.24%	0.24[0.12,0.46]
SLGL82	2/44	2/44		0.34%	1[0.13,7.43]
von Berg 1998	137/220	109/206		7.59%	1.47[1,2.16]
Wolfe 2000a	8/80	10/81		1.6%	0.79[0.29,2.11]
Wolfe 2000b	13/86	14/86		2.12%	0.92[0.4,2.08]
Wolfe 2006	31/527	68/514		11.58%	0.41[0.26,0.64]
Subtotal (95% CI)	**1568**	**1538**		**40.05%**	**0.68[0.55,0.83]**
Total events: 247 (LABA), 310 (PLACEBO)					
Heterogeneity: Tau^2=0; Chi^2=33.19, df=9(P=0); I^2=72.89%					
Test for overall effect: Z=3.7(P=0)					
3.36.3 Persistent/symptomatic asthma					
Bensch 2002	68/171	71/176		7.53%	0.98[0.64,1.5]
Busse 1998	47/263	64/275		9.18%	0.72[0.47,1.09]
Kavuru 2000a	32/92	40/82		4.93%	0.56[0.3,1.03]
Kemp 1998a	22/149	21/152		3.17%	1.08[0.57,2.06]
Lazarus 2001	11/54	16/56		2.23%	0.64[0.27,1.54]
Lockey 1999	49/240	70/234		10.08%	0.6[0.39,0.92]
Nathan 1999	17/128	17/129		2.62%	1.01[0.49,2.08]
Weinstein 1998	1/102	1/105		0.17%	1.03[0.06,16.69]
Subtotal (95% CI)	**1199**	**1209**		**39.91%**	**0.76[0.63,0.93]**
Total events: 247 (LABA), 300 (PLACEBO)					
Heterogeneity: Tau^2=0; Chi^2=5.46, df=7(P=0.6); I^2=0%					
Test for overall effect: Z=2.68(P=0.01)					
3.36.4 Moderate asthma					
Shapiro 2000b	10/88	15/93		2.31%	0.67[0.28,1.57]
Subtotal (95% CI)	**88**	**93**		**2.31%**	**0.67[0.28,1.57]**
Total events: 10 (LABA), 15 (PLACEBO)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.92(P=0.36)					
3.36.5 Severe asthma					
Subtotal (95% CI)	**0**	**0**			**Not estimable**
Total events: 0 (LABA), 0 (PLACEBO)					
Heterogeneity: Not applicable					
Test for overall effect: Not applicable					
3.36.6 Unclear					
Busse 2004	8/80	13/80		2.09%	0.57[0.22,1.47]
D'Alonzo 1994	20/106	42/108		6.03%	0.37[0.2,0.68]
LaForce 2005	9/86	10/91		1.55%	0.95[0.37,2.46]
Steffensen 1995	4/103	9/101		1.56%	0.41[0.12,1.39]
Subtotal (95% CI)	**375**	**380**		**11.24%**	**0.49[0.32,0.75]**
Total events: 41 (LABA), 74 (PLACEBO)					
Heterogeneity: Tau^2=0; Chi^2=2.87, df=3(P=0.41); I^2=0%					
Test for overall effect: Z=3.3(P=0)					
Total (95% CI)	**3714**	**3571**		**100%**	**0.69[0.61,0.79]**
Total events: 578 (LABA), 738 (PLACEBO)					



Analysis 3.37. Comparison 3 Studies by severity of asthma, Outcome 37 Global assessment of efficacy by patient- very good/good.



Comparison 4. Studies with crossover design

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Peak expiratory flow: morning	5		L/min (Fixed, 95% CI)	38.20 [3.10, 73.29]
2 Peak expiratory flow: evening	5		L/min (Fixed, 95% CI)	35.01 [-0.78, 70.80]
3 Change in PEF morning predicted	1		% (Fixed, 95% CI)	2.0 [-1.92, 5.92]
4 Change in PEF evening predicted	1		% (Fixed, 95% CI)	Totals not selected
5 Change in PEF morning	2		L/min (Fixed, 95% CI)	12.07 [1.75, 22.38]
6 Change in PEF evening	2		L/min (Fixed, 95% CI)	5.61 [-4.97, 16.19]
7 Amplitude PEF: diurnal variation (l/min or %)	1		Std. Mean Difference (IV, Fixed, 95% CI)	Subtotals only
7.2 CROSS OVER STUDIES	1	56	Std. Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
8 Change in Amplitude PEF: diurnal variation (l/min or %)	0	0	Std. Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
8.2 CROSS OVER STUDIES	0	0	Std. Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
9 FEV1	7		Litres (Fixed, 95% CI)	0.13 [0.01, 0.25]
10 Predicted FEV1	3		% (Fixed, 95% CI)	1.82 [-2.86, 6.51]
11 PD20 treatment ratio	1		Doubling doses (Fixed, 95% CI)	1.01 [0.36, 1.66]
12 Forced Vital Capacity (litres)	2		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
12.1 CROSS OVER STUDIES	2	790	Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
13 Change in symptom score- day time	1		Std. Mean Difference (IV, Fixed, 95% CI)	Totals not selected
13.1 CROSS OVER STUDIES	1		Std. Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
14 Change in symptom score- night time	1		Std. Mean Difference (IV, Fixed, 95% CI)	Totals not selected
14.2 CROSS OVER STUDIES	1		Std. Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
15 Days without asthma symptoms	3		% (Fixed, 95% CI)	5.25 [1.30, 9.20]

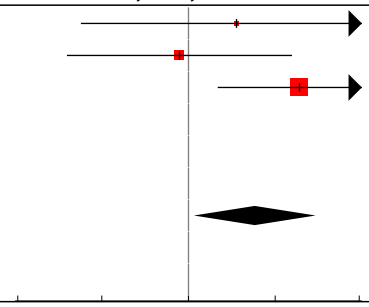
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
16 Nights without asthma awakenings	2		% (Fixed, 95% CI)	33.68 [8.96, 58.39]
17 Rescue bronchodilator use: whole day	1		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
17.1 CROSS OVER STUDIES	1	734	Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
18 Change in use of rescue bronchodilator/day	1		puffs (Fixed, 95% CI)	Totals not selected
19 Change in use of rescue bronchodilator/night	1		puffs (Fixed, 95% CI)	Totals not selected
20 Bronchial hyperreactivity- log PD20/PC20 methacholine or histamine	1	20	Std. Mean Difference (IV, Random, 95% CI)	-0.06 [-0.94, 0.81]
20.2 CROSS OVER STUDIES	1	20	Std. Mean Difference (IV, Random, 95% CI)	-0.06 [-0.94, 0.81]
21 Change in BHR (end treatment vs. baseline)- doubling doses (DD)	1	30	Mean Difference (IV, Fixed, 95% CI)	0.77 [-0.05, 1.59]
21.1 Crossover studies	1	30	Mean Difference (IV, Fixed, 95% CI)	0.77 [-0.05, 1.59]
22 Bronchoprotection to methacholine challenge(protection ratio end treatment vs. baseline)- doubling doses (DD)	1	30	Mean Difference (IV, Fixed, 95% CI)	1.76 [0.81, 2.71]
22.1 CROSS OVER STUDIES	1	30	Mean Difference (IV, Fixed, 95% CI)	1.76 [0.81, 2.71]
23 Bronchoprotection to methacholine challenge(protection ratio first dose treatment vs. baseline)- DD	1	30	Mean Difference (IV, Fixed, 95% CI)	2.95 [2.15, 3.75]
23.1 CROSS OVER STUDIES	1	30	Mean Difference (IV, Fixed, 95% CI)	2.95 [2.15, 3.75]
24 Bronchodilator response to eformoterol (delta peak FEV1)	2		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
24.1 CROSS OVER STUDIES	2	46	Mean Difference (IV, Fixed, 95% CI)	-0.26 [-0.43, -0.09]
25 Adverse events- total adverse events	2	739	Odds Ratio (M-H, Fixed, 95% CI)	1.03 [0.77, 1.38]
26 Days with no rescue medication usage	1		% (Fixed, 95% CI)	Totals not selected

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
27 Adverse events- headache	3	921	Odds Ratio (M-H, Fixed, 95% CI)	0.86 [0.56, 1.33]
27.2 CROSS OVER STUDIES	3	921	Odds Ratio (M-H, Fixed, 95% CI)	0.86 [0.56, 1.33]
28 Adverse events- tremor	1		Odds Ratio (M-H, Fixed, 95% CI)	Totals not selected
28.1 CROSS OVER STUDIES	1		Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
29 Adverse events- cough	1		Odds Ratio (M-H, Fixed, 95% CI)	Totals not selected
30 Exacerbations asthma- >1 major(sub-group by use of inhaled corticosteroid)	3	550	Odds Ratio (M-H, Fixed, 95% CI)	1.08 [0.70, 1.67]
30.4 Cross over studies	3	550	Odds Ratio (M-H, Fixed, 95% CI)	1.08 [0.70, 1.67]
31 Rate of exacerbations asthma (number/patient/year)	1		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
31.1 Major exacerbations	1	314	Mean Difference (IV, Fixed, 95% CI)	-0.18 [-0.38, 0.02]
31.2 Minor exacerbations	1	314	Mean Difference (IV, Fixed, 95% CI)	-0.68 [-0.95, -0.41]
32 Adverse events - upper respiratory tract infection	1		Odds Ratio (M-H, Fixed, 95% CI)	Totals not selected
33 Adverse events - musculoskeletal pain	1		Odds Ratio (M-H, Fixed, 95% CI)	Totals not selected
34 Global assessment of efficacy by patient- very good/good	1		Odds Ratio (M-H, Fixed, 95% CI)	Subtotals only
34.2 CROSS OVER STUDIES	1	56	Odds Ratio (M-H, Fixed, 95% CI)	4.5 [1.23, 16.45]
35 Global assessment of efficacy by investigator- very good/good	1		Odds Ratio (M-H, Fixed, 95% CI)	Subtotals only
35.2 CROSS OVER STUDIES	1	56	Odds Ratio (M-H, Fixed, 95% CI)	3.33 [0.78, 14.23]
36 Adverse events - throat irritation	1		Odds Ratio (M-H, Fixed, 95% CI)	Totals not selected
37 Rescue medication usage (blisters)	1		blisters/d (Fixed, 95% CI)	Totals not selected

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
38 Fall in FEV1post exercise(6-9 hrs post study drug) % or % predicted	1	24	Std. Mean Difference (IV, Fixed, 95% CI)	-0.51 [-1.32, 0.31]
38.2 CROSS OVER STUDIES	1	24	Std. Mean Difference (IV, Fixed, 95% CI)	-0.51 [-1.32, 0.31]
39 Nights without symptoms	1		% (Fixed, 95% CI)	4.0 [1.00, 7.00]
40 Change from baseline PD15	1		Doubling doses (Fixed, 95% CI)	2.67 [2.22, 3.12]

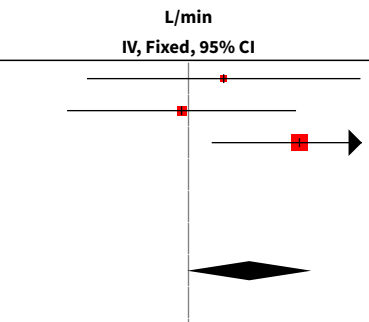
Analysis 4.1. Comparison 4 Studies with crossover design, Outcome 1 Peak expiratory flow: morning.

Study or subgroup	LABA N	Placebo N	L/min (SE)	L/min IV, Fixed, 95% CI	Weight	L/min IV, Fixed, 95% CI
Leblanc 1996	1	1	27.7 (45.79)		15.29%	27.7[-62.05,117.45]
Nelson 1999b	1	1	-5.2 (33.102)		29.27%	-5.2[-70.08,59.68]
Newnham 1994	1	1	64 (24.05)		55.44%	64[16.86,111.14]
Newnham 1995	1	1	0 (0)			Not estimable
Starke 1996	1	1	0 (0)			Not estimable
Total (95% CI)					**100%**	**38.2[3.1,73.29]**
Heterogeneity: Tau²=0; Chi²=2.92, df=2(P=0.23); I²=31.56%						
Test for overall effect: Z=2.13(P=0.03)						



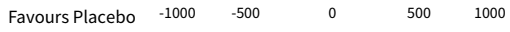
Analysis 4.2. Comparison 4 Studies with crossover design, Outcome 2 Peak expiratory flow: evening.

Study or subgroup	LABA N	Placebo N	L/min (SE)	L/min IV, Fixed, 95% CI	Weight	L/min IV, Fixed, 95% CI
Leblanc 1996	1	1	20.3 (40.23)		20.6%	20.3[-58.55,99.15]
Nelson 1999b	1	1	-4 (33.684)		29.39%	-4[-70.02,62.02]
Newnham 1994	1	1	64 (25.821)		50.01%	64[13.39,114.61]
Newnham 1995	1	1	0 (0)			Not estimable
Starke 1996	1	1	0 (0)			Not estimable
Total (95% CI)					**100%**	**35.01[-0.78,70.8]**
Heterogeneity: Tau²=0; Chi²=2.74, df=2(P=0.25); I²=26.89%						
Test for overall effect: Z=1.92(P=0.06)						



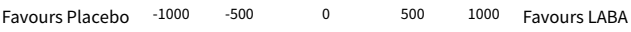
Analysis 4.3. Comparison 4 Studies with crossover design, Outcome 3 Change in PEF morning predicted.

Study or subgroup	LABA N	Placebo N	% (SE)	% IV, Fixed, 95% CI	Weight	% IV, Fixed, 95% CI
Zarkovic 1998	1	1	2 (2)		100%	2[-1.92,5.92]
Total (95% CI)					**100%**	**2[-1.92,5.92]**
Heterogeneity: Not applicable						
Test for overall effect: Z=1(P=0.32)						



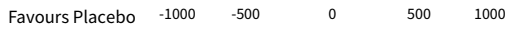
Analysis 4.4. Comparison 4 Studies with crossover design, Outcome 4 Change in PEF evening predicted.

Study or subgroup	LABA N	Placebo N	% (SE)	% IV, Fixed, 95% CI	% IV, Fixed, 95% CI
Zarkovic 1998	1	1	0 (2)		0[-3.92,3.92]



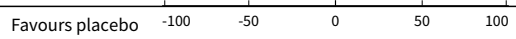
Analysis 4.5. Comparison 4 Studies with crossover design, Outcome 5 Change in PEF morning.

Study or subgroup	LABA N	Placebo N	L/min (SE)	L/min IV, Fixed, 95% CI	Weight	L/min IV, Fixed, 95% CI
Nelson 1999b	1	1	22.3 (10.964)		23.05%	22.3[0.81,43.79]
Zarkovic 1998	1	1	9 (6)		76.95%	9[-2.76,20.76]
Total (95% CI)					**100%**	**12.07[1.75,22.38]**
Heterogeneity: Tau²=0; Chi²=1.13, df=1(P=0.29); I²=11.69%						
Test for overall effect: Z=2.29(P=0.02)						



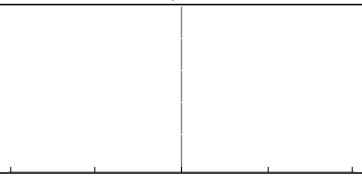
Analysis 4.6. Comparison 4 Studies with crossover design, Outcome 6 Change in PEF evening.

Study or subgroup	LABA N	Placebo N	L/min (SE)	L/min IV, Fixed, 95% CI	Weight	L/min IV, Fixed, 95% CI
Nelson 1999b	1	1	20.9 (12.347)		19.1%	20.9[-3.3,45.1]
Zarkovic 1998	1	1	2 (6)		80.9%	2[-9.76,13.76]
Total (95% CI)					**100%**	**5.61[-4.97,16.19]**
Heterogeneity: Tau²=0; Chi²=1.9, df=1(P=0.17); I²=47.25%						
Test for overall effect: Z=1.04(P=0.3)						



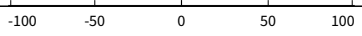
Analysis 4.7. Comparison 4 Studies with crossover design, Outcome 7 Amplitude PEF: diurnal variation (l/min or %).

Study or subgroup	LABA N	LABA Mean(SD)	Placebo N	Placebo Mean(SD)	Std. Mean Difference Fixed, 95% CI	Weight	Std. Mean Difference Fixed, 95% CI
4.7.2 CROSS OVER STUDIES							
Starke 1996	28	-7.3 (0)	28	-17.5 (0)			Not estimable
Subtotal ***	**28**		**28**				**Not estimable**
Heterogeneity: Not applicable							
Test for overall effect: Not applicable							



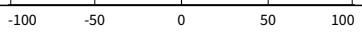
Analysis 4.9. Comparison 4 Studies with crossover design, Outcome 9 FEV1.

Study or subgroup	LABA N	Placebo N	Litres (SE)	Litres IV, Fixed, 95% CI	Weight	Litres IV, Fixed, 95% CI
Leblanc 1996	1	1	0.2 (0.58)		1.13%	0.15[-0.99,1.29]
Nelson 1999b	1	1	0.3 (0.214)		8.27%	0.28[-0.14,0.7]
Newnham 1994	1	1	0.2 (0.097)		40.45%	0.16[-0.03,0.35]
Newnham 1995	1	1	0 (0)			Not estimable
Ramage 1994	1	1	0.3 (0.342)		3.25%	0.3[-0.37,0.97]
Starke 1996	1	1	0 (0)			Not estimable
Zarkovic 1998	1	1	0.1 (0.09)		46.89%	0.06[-0.12,0.24]
Total (95% CI)					**100%**	**0.13[0.01,0.25]**
Heterogeneity: $Tau^2=0$; $Chi^2=1.44$, df=4(P=0.84); $I^2=0\%$						
Test for overall effect: Z=2.07(P=0.04)						



Analysis 4.10. Comparison 4 Studies with crossover design, Outcome 10 Predicted FEV1.

Study or subgroup	LABA N	Placebo N	% (SE)	% IV, Fixed, 95% CI	Weight	% IV, Fixed, 95% CI
Boulet 1998b	1	1	-1.7 (5.091)		22.03%	-1.7[-11.68,8.28]
Kraft 1997	1	1	6.4 (6.265)		14.54%	6.4[-5.88,18.68]
Zarkovic 1998	1	1	2 (3)		63.43%	2[-3.88,7.88]
Total (95% CI)					**100%**	**1.82[-2.86,6.51]**
Heterogeneity: $Tau^2=0$; $Chi^2=1.02$, df=2(P=0.6); $I^2=0\%$						
Test for overall effect: Z=0.76(P=0.44)						



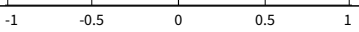
Analysis 4.11. Comparison 4 Studies with crossover design, Outcome 11 PD20 treatment ratio.

Study or subgroup	LABA N	Placebo N	Doubling doses (SE)	Doubling doses IV, Fixed, 95% CI	Weight	Doubling doses IV, Fixed, 95% CI
Zarkovic 1998	1	1	1 (0.33)		100%	1.01[0.36,1.66]

Study or subgroup	LABA N	Placebo N	Doubling doses (SE)	Doubling doses IV, Fixed, 95% CI	Weight	Doubling doses IV, Fixed, 95% CI
Total (95% CI)					**100%**	**1.01[0.36,1.66]**
Heterogeneity: Not applicable						
Test for overall effect: Z=3.06(P=0)						

Analysis 4.12. Comparison 4 Studies with crossover design, Outcome 12 Forced Vital Capacity (litres).

Study or subgroup	LABA N	LABA Mean(SD)	Placebo N	Placebo Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
4.12.1 CROSS OVER STUDIES							
Leblanc 1996	367	3.8 (0)	367	3.7 (0)			Not estimable
Starke 1996	28	2.3 (0)	28	2.3 (0)			Not estimable
Subtotal * **	**395**		**395**				**Not estimable**
Heterogeneity: Not applicable							
Test for overall effect: Not applicable							

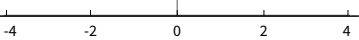


Analysis 4.13. Comparison 4 Studies with crossover design, Outcome 13 Change in symptom score- day time.

Study or subgroup	LABA N	LABA Mean(SD)	PLACEBO N	PLACEBO Mean(SD)	Std. Mean Difference Fixed, 95% CI	Std. Mean Difference Fixed, 95% CI
4.13.1 CROSS OVER STUDIES						
Nelson 1999b	24	-0.4 (0.6)	25	-0.1 (0.6)		-0.5[-1.06,0.07]

Analysis 4.14. Comparison 4 Studies with crossover design, Outcome 14 Change in symptom score- night time.

Study or subgroup	LABA N	LABA Mean(SD)	PLACEBO N	PLACEBO Mean(SD)	Std. Mean Difference Fixed, 95% CI	Std. Mean Difference Fixed, 95% CI
4.14.2 CROSS OVER STUDIES						
Nelson 1999b	24	-0.2 (0.4)	25	0 (0.6)		-0.37[-0.94,0.19]



Analysis 4.15. Comparison 4 Studies with crossover design, Outcome 15 Days without asthma symptoms.

Study or subgroup	LABA N	Placebo N	% (SE)	% IV, Fixed, 95% CI	Weight	% IV, Fixed, 95% CI
Kraft 1997	1	1	15.5 (13.796)		2.13%	15.5[-11.54,42.54]
Leblanc 1996	1	1	11.4 (33.23)		0.37%	11.4[-53.73,76.53]
Zarkovic 1998	1	1	5 (2.04)		97.5%	5[1,9]

Study or subgroup	LABA N	Placebo N	% (SE)	% IV, Fixed, 95% CI	Weight	% IV, Fixed, 95% CI
Total (95% CI)					**100%**	**5.25[1.3,9.2]**
Heterogeneity: Tau²=0; Chi²=0.6, df=2(P=0.74); I²=0%						
Test for overall effect: Z=2.6(P=0.01)						

Favours treatment -1000 -500 0 500 1000 Favours control

Analysis 4.16. Comparison 4 Studies with crossover design, Outcome 16 Nights without asthma awakenings.

Study or subgroup	LABA N	Placebo N	% (SE)	% IV, Fixed, 95% CI	Weight	% IV, Fixed, 95% CI
Kraft 1997	1	1	39.2 (13.867)		82.68%	39.2[12.02,66.38]
Leblanc 1996	1	1	7.3 (30.3)		17.32%	7.3[-52.09,66.69]
Total (95% CI)					**100%**	**33.68[8.96,58.39]**
Heterogeneity: Tau²=0; Chi²=0.92, df=1(P=0.34); I²=0%						
Test for overall effect: Z=2.67(P=0.01)						

Favours LABA -1000 -500 0 500 1000 Favours Placebo

Analysis 4.17. Comparison 4 Studies with crossover design, Outcome 17 Rescue bronchodilator use: whole day.

Study or subgroup	LABA N	LABA Mean(SD)	Placebo N	Placebo Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
4.17.1 CROSS OVER STUDIES							
Leblanc 1996	367	1.2 (0)	367	2.6 (0)			Not estimable
Subtotal ***	**367**		**367**				**Not estimable**
Heterogeneity: Not applicable							
Test for overall effect: Not applicable							

Favours LABA -4 -2 0 2 4 Favours Placebo

Analysis 4.18. Comparison 4 Studies with crossover design, Outcome 18 Change in use of rescue bronchodilator/day.

Study or subgroup	LABA N	Placebo N	puffs (SE)	puffs IV, Fixed, 95% CI	puffs IV, Fixed, 95% CI
Nelson 1999b	1	1	-1.2 (0.612)		-1.25[-2.45,-0.05]

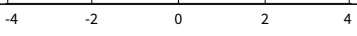
Favours LABA -1000 -500 0 500 1000 Favours placebo

Analysis 4.19. Comparison 4 Studies with crossover design, Outcome 19 Change in use of rescue bronchodilator/night.

Study or subgroup	LABA N	Placebo N	puffs (SE)	puffs IV, Fixed, 95% CI	puffs IV, Fixed, 95% CI
Nelson 1999b	1	1	-0.5 (0.27)		-0.49[-1.02,0.04]

Analysis 4.20. Comparison 4 Studies with crossover design, Outcome 20 Bronchial hyperreactivity- log PD20/PC20 methacholine or histamine.

Study or subgroup	LABA N	LABA Mean(SD)	Placebo N	Placebo Mean(SD)	Std. Mean Difference Random, 95% CI	Weight	Std. Mean Difference Random, 95% CI
4.20.2 CROSS OVER STUDIES							
Kraft 1997	10	-0.9 (0.7)	10	-0.8 (0.5)		100%	-0.06[-0.94,0.81]
Subtotal ***	**10**		**10**			**100%**	**-0.06[-0.94,0.81]**
Heterogeneity: Not applicable							
Test for overall effect: Z=0.14(P=0.89)							
Total ***	**10**		**10**			**100%**	**-0.06[-0.94,0.81]**
Heterogeneity: Not applicable							
Test for overall effect: Z=0.14(P=0.89)							

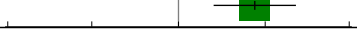


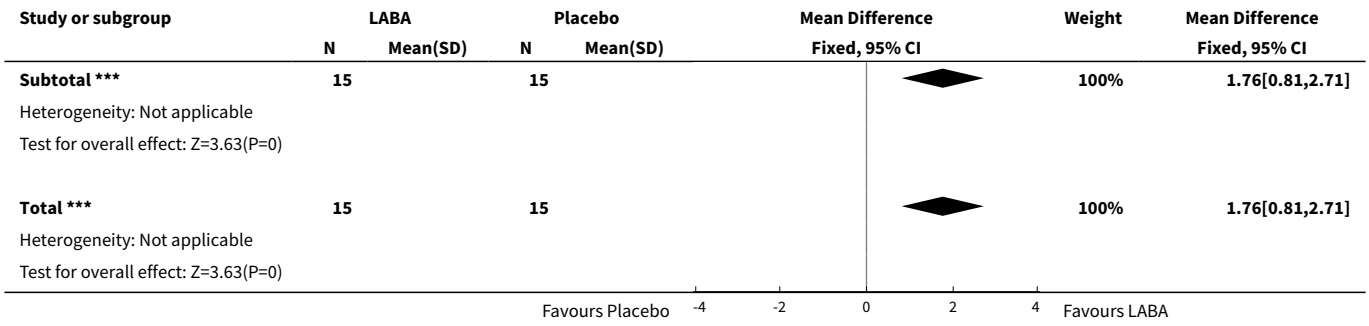
Analysis 4.21. Comparison 4 Studies with crossover design, Outcome 21 Change in BHR (end treatment vs. baseline)- doubling doses (DD).

Study or subgroup	LABA N	LABA Mean(SD)	Placebo N	Placebo Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
4.21.1 Crossover studies							
Boulet 1998b	15	1.1 (1.4)	15	0.4 (0.8)		100%	0.77[-0.05,1.59]
Subtotal ***	**15**		**15**			**100%**	**0.77[-0.05,1.59]**
Heterogeneity: Not applicable							
Test for overall effect: Z=1.84(P=0.07)							
Total ***	**15**		**15**			**100%**	**0.77[-0.05,1.59]**
Heterogeneity: Not applicable							
Test for overall effect: Z=1.84(P=0.07)							

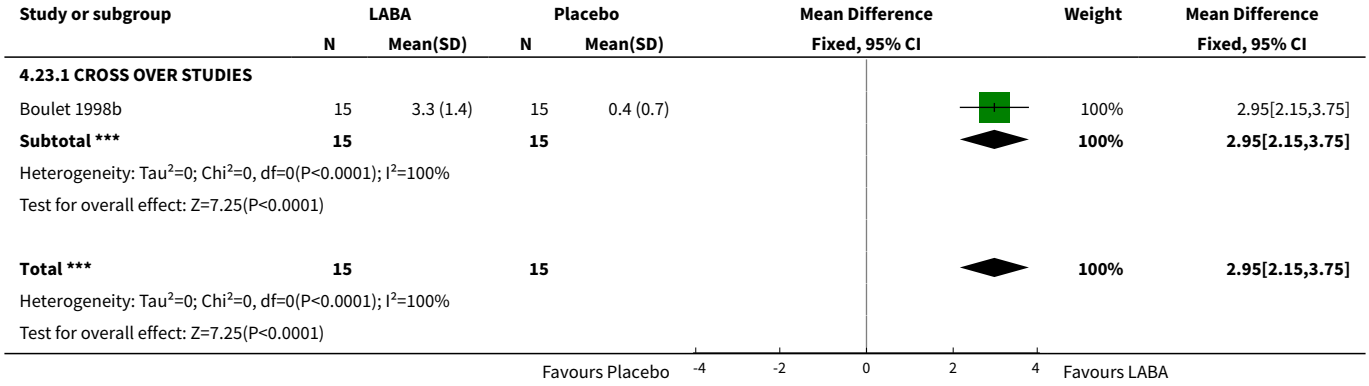
Analysis 4.22. Comparison 4 Studies with crossover design, Outcome 22 Bronchoprotection to methacholine challenge(protection ratio end treatment vs. baseline)- doubling doses (DD).

Study or subgroup	LABA N	LABA Mean(SD)	Placebo N	Placebo Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
4.22.1 CROSS OVER STUDIES							
Boulet 1998b	15	1.7 (1.7)	15	-0 (0.7)		100%	1.76[0.81,2.71]

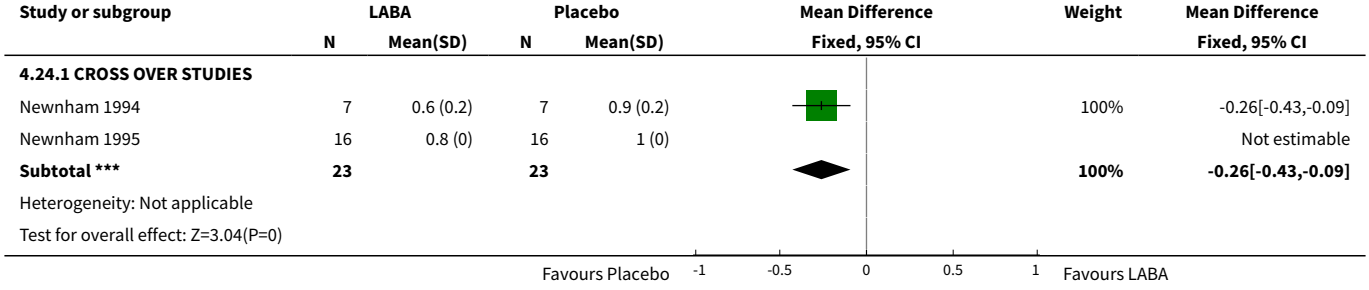




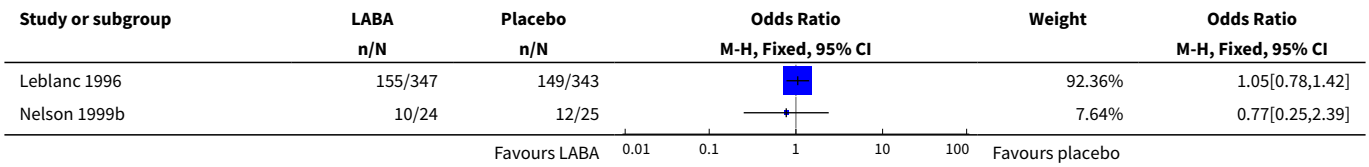
Analysis 4.23. Comparison 4 Studies with crossover design, Outcome 23 Bronchoprotection to methacholine challenge(protection ratio first dose treatment vs. baseline)- DD.

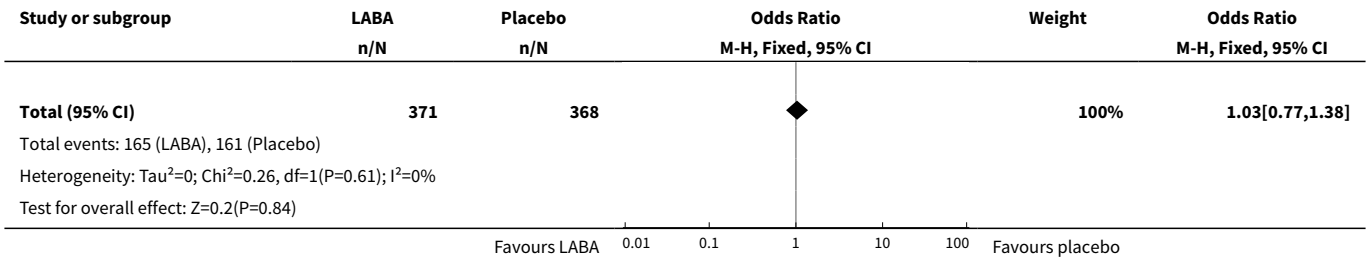


Analysis 4.24. Comparison 4 Studies with crossover design, Outcome 24 Bronchodilator response to eformoterol (delta peak FEV1).

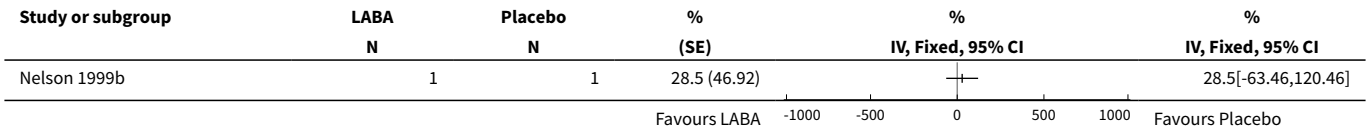


Analysis 4.25. Comparison 4 Studies with crossover design, Outcome 25 Adverse events- total adverse events.

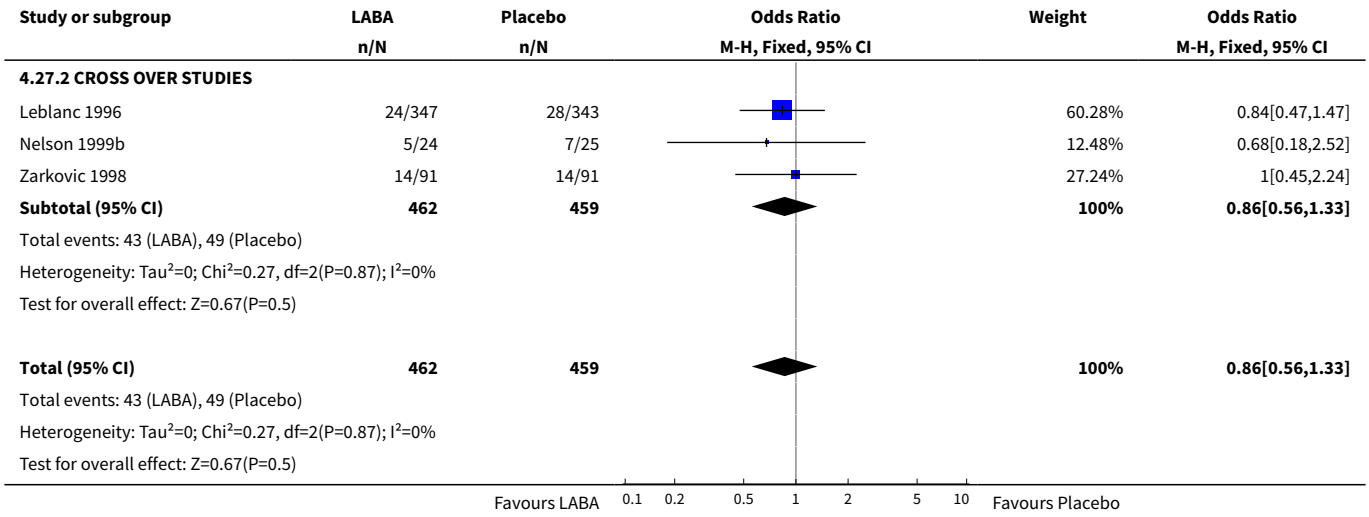




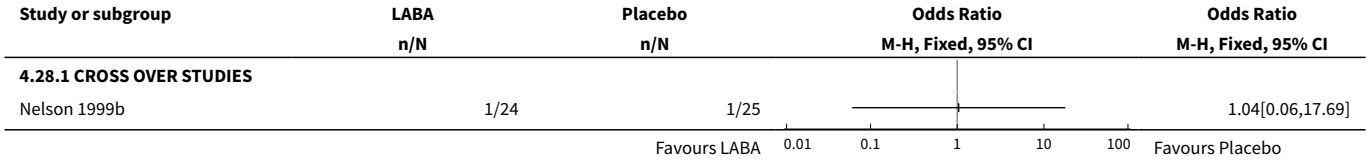
Analysis 4.26. Comparison 4 Studies with crossover design, Outcome 26 Days with no rescue medication usage.



Analysis 4.27. Comparison 4 Studies with crossover design, Outcome 27 Adverse events- headache.

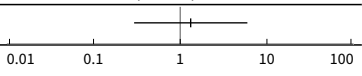


Analysis 4.28. Comparison 4 Studies with crossover design, Outcome 28 Adverse events- tremor.



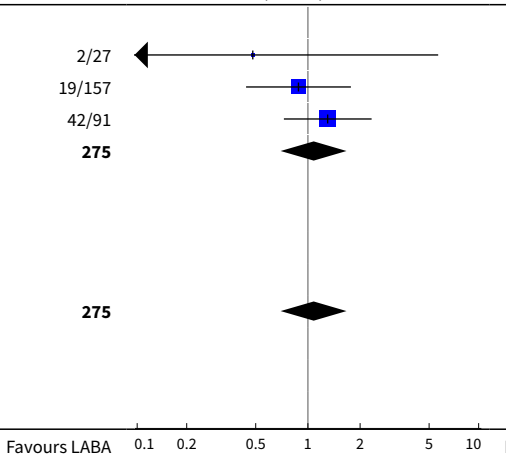
Analysis 4.29. Comparison 4 Studies with crossover design, Outcome 29 Adverse events- cough.

Study or subgroup	LABA n/N	Placebo n/N	Odds Ratio M-H, Fixed, 95% CI	Odds Ratio M-H, Fixed, 95% CI
Leblanc 1996	4/347	3/343		1.32[0.29,5.95]



Analysis 4.30. Comparison 4 Studies with crossover design, Outcome 30 Exacerbations asthma- >1 major(sub-group by use of inhaled corticosteroid).

Study or subgroup	LABA n/N	Placebo n/N	Odds Ratio M-H, Fixed, 95% CI	Weight	Odds Ratio M-H, Fixed, 95% CI
4.30.4 Cross over studies					
Nelson 1999b	1/27	2/27		4.97%	0.48[0.04,5.64]
Taylor 1998	17/157	19/157		43.76%	0.88[0.44,1.77]
Zarkovic 1998	48/91	42/91		51.26%	1.3[0.73,2.33]
Subtotal (95% CI)	**275**	**275**		**100%**	**1.08[0.7,1.67]**
Total events: 66 (LABA), 63 (Placebo)					
Heterogeneity: Tau^2=0; Chi^2=1.14, df=2(P=0.57); I^2=0%					
Test for overall effect: Z=0.33(P=0.74)					
Total (95% CI)	**275**	**275**		**100%**	**1.08[0.7,1.67]**
Total events: 66 (LABA), 63 (Placebo)					
Heterogeneity: Tau^2=0; Chi^2=1.14, df=2(P=0.57); I^2=0%					
Test for overall effect: Z=0.33(P=0.74)					

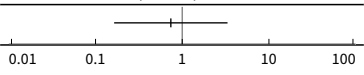


Analysis 4.31. Comparison 4 Studies with crossover design, Outcome 31 Rate of exacerbations asthma (number/patient/year).

Study or subgroup	LABA N	LABA Mean(SD)	Placebo N	Placebo Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
4.31.1 Major exacerbations							
Taylor 1998	157	0.2 (0.8)	157	0.4 (1)		100%	-0.18[-0.38,0.02]
Subtotal ***	**157**		**157**			**100%**	**-0.18[-0.38,0.02]**
Heterogeneity: Not applicable							
Test for overall effect: Z=1.8(P=0.07)							
4.31.2 Minor exacerbations							
Taylor 1998	157	0.3 (0.9)	157	1 (1.5)		100%	-0.68[-0.95,-0.41]
Subtotal ***	**157**		**157**			**100%**	**-0.68[-0.95,-0.41]**
Heterogeneity: Not applicable							
Test for overall effect: Z=4.9(P<0.0001)							
Test for subgroup differences: Chi^2=8.56, df=1 (P=0), I^2=88.31%							

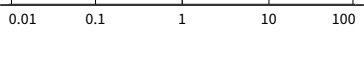
Analysis 4.32. Comparison 4 Studies with crossover design, Outcome 32 Adverse events - upper respiratory tract infection.

Study or subgroup	LABA n/N	Placebo n/N	Odds Ratio M-H, Fixed, 95% CI	Odds Ratio M-H, Fixed, 95% CI
Leblanc 1996	3/347	4/343		0.74[0.16,3.33]



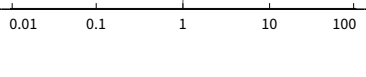
Analysis 4.33. Comparison 4 Studies with crossover design, Outcome 33 Adverse events - musculoskeletal pain.

Study or subgroup	LABA n/N	Placebo n/N	Odds Ratio M-H, Fixed, 95% CI	Odds Ratio M-H, Fixed, 95% CI
Leblanc 1996	7/347	4/343		1.74[0.51,6.02]



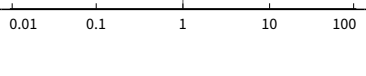
Analysis 4.34. Comparison 4 Studies with crossover design, Outcome 34 Global assessment of efficacy by patient- very good/good.

Study or subgroup	LABA n/N	Placebo n/N	Odds Ratio M-H, Fixed, 95% CI	Weight	Odds Ratio M-H, Fixed, 95% CI
4.34.2 CROSS OVER STUDIES					
Starke 1996	12/28	4/28		100%	4.5[1.23,16.45]
Subtotal (95% CI)	**28**	**28**		**100%**	**4.5[1.23,16.45]**
Total events: 12 (LABA), 4 (Placebo)					
Heterogeneity: Not applicable					
Test for overall effect: Z=2.27(P=0.02)					



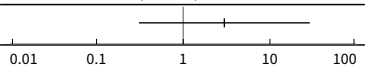
Analysis 4.35. Comparison 4 Studies with crossover design, Outcome 35 Global assessment of efficacy by investigator- very good/good.

Study or subgroup	LABA n/N	Placebo n/N	Odds Ratio M-H, Fixed, 95% CI	Weight	Odds Ratio M-H, Fixed, 95% CI
4.35.2 CROSS OVER STUDIES					
Starke 1996	8/28	3/28		100%	3.33[0.78,14.23]
Subtotal (95% CI)	**28**	**28**		**100%**	**3.33[0.78,14.23]**
Total events: 8 (LABA), 3 (Placebo)					
Heterogeneity: Not applicable					
Test for overall effect: Z=1.63(P=0.1)					



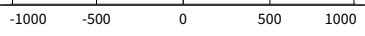
Analysis 4.36. Comparison 4 Studies with crossover design, Outcome 36 Adverse events - throat irritation.

Study or subgroup	LABA n/N	Placebo n/N	Odds Ratio M-H, Fixed, 95% CI	Odds Ratio M-H, Fixed, 95% CI
Leblanc 1996	3/347	1/343		2.98[0.31,28.82]



Analysis 4.37. Comparison 4 Studies with crossover design, Outcome 37 Rescue medication usage (blisters).

Study or subgroup	LABA N	Placebo N	blisters/d (SE)	blisters/d IV, Fixed, 95% CI	blisters/d IV, Fixed, 95% CI
Zarkovic 1998	1	1	0 (0.26)		0[-0.51,0.51]



Analysis 4.38. Comparison 4 Studies with crossover design, Outcome 38 Fall in FEV1post exercise(6-9 hrs post study drug) % or % predicted.

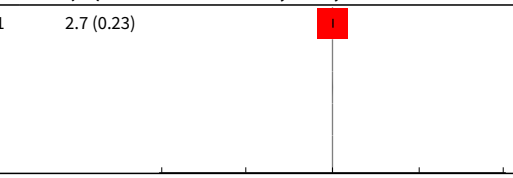
Study or subgroup	LABA N	LABA Mean(SD)	Placebo N	Placebo Mean(SD)	Std. Mean Difference Fixed, 95% CI	Weight	Std. Mean Difference Fixed, 95% CI
4.38.2 CROSS OVER STUDIES							
Ramage 1994	12	24 (15.2)	12	32.9 (18.4)		100%	-0.51[-1.32,0.31]
Subtotal ***	**12**		**12**			**100%**	**-0.51[-1.32,0.31]**
Heterogeneity: Not applicable							
Test for overall effect: Z=1.22(P=0.22)							
Total ***	**12**		**12**			**100%**	**-0.51[-1.32,0.31]**
Heterogeneity: Not applicable							
Test for overall effect: Z=1.22(P=0.22)							

Analysis 4.39. Comparison 4 Studies with crossover design, Outcome 39 Nights without symptoms.

Study or subgroup	LABA N	Placebo N	% (SE)	% IV, Fixed, 95% CI	Weight	% IV, Fixed, 95% CI
Zarkovic 1998	1	1	4 (1.53)		100%	4[1,7]
Total (95% CI)					**100%**	**4[1,7]**
Heterogeneity: Not applicable						
Test for overall effect: Z=2.61(P=0.01)						

Analysis 4.40. Comparison 4 Studies with crossover design, Outcome 40 Change from baseline PD15.

Study or subgroup	LABA N	Placebo N	Doubling doses (SE)	Doubling doses IV, Fixed, 95% CI	Weight	Doubling doses IV, Fixed, 95% CI
Lindqvist 2003	1	1	2.7 (0.23)		100%	2.67[2.22,3.12]
Total (95% CI)					**100%**	**2.67[2.22,3.12]**
Heterogeneity: Not applicable						
Test for overall effect: Z=11.61(P<0.0001)						



Comparison 5. Imputed standard deviations

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Change in PEF morning	25	5512	L/min (Random, 95% CI)	24.84 [20.41, 29.27]
1.1 Participants using mixed cointerventions	12	2739	L/min (Random, 95% CI)	28.99 [22.63, 35.35]
1.2 Participants not using ICS	8	1582	L/min (Random, 95% CI)	23.57 [14.60, 32.55]
1.3 Children <12 years	4	1065	L/min (Random, 95% CI)	16.32 [12.32, 20.31]
1.4 Unclear	1	126	L/min (Random, 95% CI)	30.00 [15.87, 44.13]
2 Peak expiratory flow: morning	20	3682	L/min (Fixed, 95% CI)	15.17 [10.99, 19.36]
2.1 Participants using mixed cointerventions	11	2826	L/min (Fixed, 95% CI)	27.66 [20.40, 34.91]
2.3 Participants not using ICS	6	235	L/min (Fixed, 95% CI)	23.08 [4.74, 41.41]
2.4 Children <12 years	3	621	L/min (Fixed, 95% CI)	7.73 [2.39, 13.07]
3 FEV1	15	4047	Litres (Fixed, 95% CI)	0.24 [0.21, 0.28]
3.1 Participants using mixed cointerventions	11	3458	Litres (Fixed, 95% CI)	0.25 [0.21, 0.29]
3.2 Participants not using ICS	2	70	Litres (Fixed, 95% CI)	0.12 [-0.24, 0.48]
3.3 Children <12 years	2	519	Litres (Fixed, 95% CI)	0.19 [0.06, 0.32]
4 Change in PEF evening	22	5350	L/min (Random, 95% CI)	16.16 [12.25, 20.07]
4.1 Participants using mixed cointerventions	12	2980	L/min (Random, 95% CI)	18.67 [12.41, 24.93]
4.2 Participants not using ICS (PG design)	5	1181	L/min (Random, 95% CI)	10.68 [6.38, 14.98]
4.3 Children <12 years	4	1063	L/min (Random, 95% CI)	17.46 [7.69, 27.22]

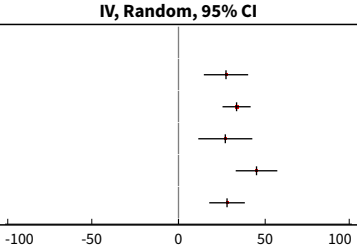
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
4.4 Unclear	1	126	L/min (Random, 95% CI)	17.0 [5.02, 28.98]
5 Change in FEV (litres)	15	3295	Mean Difference (IV, Fixed, 95% CI)	0.17 [0.14, 0.20]
5.1 Participants using mixed cointerventions	7	1565	Mean Difference (IV, Fixed, 95% CI)	0.21 [0.16, 0.25]
5.2 Participants not using ICS	6	1225	Mean Difference (IV, Fixed, 95% CI)	0.17 [0.11, 0.22]
5.3 Children <12 years	2	505	Mean Difference (IV, Fixed, 95% CI)	0.08 [-0.00, 0.16]
6 Change in FEV %predicted	3	693	Mean Difference (IV, Fixed, 95% CI)	4.10 [2.22, 5.97]
6.1 Participants using mixed cointerventions	0	0	Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
6.2 Participants not using ICS	0	0	Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
6.3 Children <12 years	3	693	Mean Difference (IV, Fixed, 95% CI)	4.10 [2.22, 5.97]
7 Change in % days without asthma symptoms	9	2060	Mean Difference (IV, Random, 95% CI)	16.10 [13.64, 18.55]
7.1 Participants using mixed cointerventions	3	834	Mean Difference (IV, Random, 95% CI)	16.37 [12.65, 20.09]
7.2 Participants not using ICS	6	1226	Mean Difference (IV, Random, 95% CI)	16.02 [11.83, 20.22]
7.3 Children <12 years	0	0	Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]
8 Change in % nights without asthma symptoms	9	2093	Mean Difference (IV, Random, 95% CI)	10.79 [6.48, 15.10]
8.1 Participants using mixed cointerventions	3	840	Mean Difference (IV, Random, 95% CI)	17.00 [9.27, 24.73]
8.2 Children <12 years	1	207	Mean Difference (IV, Random, 95% CI)	5.00 [-0.83, 10.83]
8.4 Participants not using ICS	5	1046	Mean Difference (IV, Random, 95% CI)	8.64 [5.73, 11.55]
9 Change in use of rescue bronchodilator/day	3	691	Mean Difference (IV, Random, 95% CI)	-1.03 [-1.65, -0.41]
9.1 Participants using mixed cointerventions	3	691	Mean Difference (IV, Random, 95% CI)	-1.03 [-1.65, -0.41]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
9.2 Participants not using ICS	0	0	Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]
9.3 Children <12 years	0	0	Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]
10 Peak expiratory flow: evening l/min	11	2152	Mean Difference (IV, Fixed, 95% CI)	22.09 [13.92, 30.26]
10.1 Participants using mixed cointerventions	7	1866	Mean Difference (IV, Fixed, 95% CI)	23.46 [14.45, 32.46]
10.2 Participants not using ICS	3	79	Mean Difference (IV, Fixed, 95% CI)	35.80 [-6.78, 78.37]
10.3 Children <12 years	1	207	Mean Difference (IV, Fixed, 95% CI)	10.5 [-11.30, 32.30]
11 Rescue bronchodilator use: whole day	8	1885	Mean Difference (IV, Random, 95% CI)	-1.38 [-2.03, -0.72]
11.1 Participants using mixed cointerventions	6	1635	Mean Difference (IV, Random, 95% CI)	-1.75 [-2.28, -1.23]
11.2 Participants not using ICS	1	43	Mean Difference (IV, Random, 95% CI)	-0.30 [-0.53, -0.07]
11.3 Children <12 years	1	207	Mean Difference (IV, Random, 95% CI)	-0.4 [-0.84, 0.04]
12 Change in use of rescue bronchodilator/night	2	633	Mean Difference (IV, Random, 95% CI)	-0.54 [-0.72, -0.36]
12.1 Participants using mixed cointerventions	2	633	Mean Difference (IV, Random, 95% CI)	-0.54 [-0.72, -0.36]
12.2 Participants not using ICS	0	0	Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]
12.3 Children <12 years	0	0	Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]
13 Change in use of rescue bronchodilator/ whole day	12	2197	Mean Difference (IV, Random, 95% CI)	-1.29 [-1.62, -0.96]
13.1 Participants using mixed cointerventions	5	842	Mean Difference (IV, Random, 95% CI)	-1.29 [-1.67, -0.90]
13.2 Participants not using ICS	6	1148	Mean Difference (IV, Random, 95% CI)	-1.42 [-1.92, -0.92]
13.3 Children <12 years	1	207	Mean Difference (IV, Random, 95% CI)	-0.5 [-0.94, -0.06]
14 FEV1 predicted	4	615	% (Fixed, 95% CI)	3.32 [0.73, 5.91]

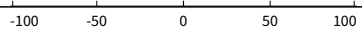
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
14.1 Participants using mixed cointerventions	0	0	% (Fixed, 95% CI)	0.0 [0.0, 0.0]
14.2 Participants not using ICS	1	22	% (Fixed, 95% CI)	-3.6 [-19.50, 12.30]
14.3 Children <12 years	3	593	% (Fixed, 95% CI)	3.51 [0.88, 6.13]
15 Peak expiratory flow: evening	15	2751	L/min (Fixed, 95% CI)	12.29 [7.53, 17.04]
15.1 Participants using mixed cointerventions	8	2027	L/min (Fixed, 95% CI)	22.38 [13.77, 30.99]
15.2 Participants not using ICS	4	103	L/min (Fixed, 95% CI)	18.32 [2.25, 34.38]
15.3 Children <12 years	3	621	L/min (Fixed, 95% CI)	6.35 [0.26, 12.45]
16 AQOL- Change in Quality of life score: global	6	1608	Mean Difference (IV, Fixed, 95% CI)	0.51 [0.42, 0.60]
16.1 Participants using mixed cointerventions	4	1249	Mean Difference (IV, Fixed, 95% CI)	0.54 [0.44, 0.64]
16.2 Participants not using ICS	2	359	Mean Difference (IV, Fixed, 95% CI)	0.41 [0.22, 0.59]
16.3 Children <12 years	0	0	Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
17 % nights without asthma awakenings	13	3925	Mean Difference (IV, Random, 95% CI)	16.11 [11.74, 20.49]
17.1 Participants using mixed cointerventions	12	3715	Mean Difference (IV, Random, 95% CI)	17.02 [12.76, 21.29]
17.2 Participants not using ICS	0	0	Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]
17.3 Children <12 years	1	210	Mean Difference (IV, Random, 95% CI)	6.40 [2.11, 10.69]

Analysis 5.1. Comparison 5 Imputed standard deviations, Outcome 1 Change in PEF morning.

Study or subgroup	LABA N	Placebo N	L/min (SE)	L/min IV, Random, 95% CI	Weight	L/min IV, Random, 95% CI
5.1.1 Participants using mixed cointerventions						
Adinoff 1998	117	121	27.4 (6.52)		3.91%	27.4[14.62,40.18]
Busse 1998	261	272	33.5 (4.133)		4.85%	33.5[25.4,41.6]
D'Alonzo 1994	87	90	27 (7.949)		3.37%	27[11.42,42.58]
Dahl 1991a	107	104	45 (6.12)		4.06%	45[33.01,56.99]
Kemp 1998a	149	152	28 (5.235)		4.42%	28[17.74,38.26]

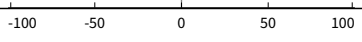


Study or subgroup	LABA N	Placebo N	L/min (SE)	L/min IV, Random, 95% CI	Weight	L/min IV, Random, 95% CI
Lockey 1999	240	234	45 (5.658)		4.25%	45[33.91,56.09]
Pearlman 1992	66	62	17 (8.76)		3.1%	17[-0.17,34.17]
SAS30004	91	89	28.7 (7.474)		3.55%	28.7[14.05,43.35]
Schreurs 1996	49	51	36 (7.209)		3.64%	36[21.87,50.13]
SMS40221	32	32	29.7 (10.878)		2.47%	29.65[8.33,50.97]
Wolfe 2000a	80	81	10 (5.658)		4.25%	10[-1.09,21.09]
Wolfe 2000b	86	86	18 (5.685)		4.24%	18[6.86,29.14]
Subtotal (95% CI)					**46.11%**	**28.99[22.63,35.35]**
Heterogeneity: Tau^2=81.79; Chi^2=33.97, df=11(P=0); I^2=67.62%						
Test for overall effect: Z=8.93(P<0.0001)						
5.1.2 Participants not using ICS						
Jones 1994	162	85	19 (6.638)		3.86%	19[5.99,32.01]
Kavuru 2000a	77	86	22 (6.653)		3.86%	22[8.96,35.04]
Lazarus 2001	54	56	39.7 (3.199)		5.19%	39.7[33.43,45.97]
Nathan 1999	128	129	24 (7.066)		3.7%	24[10.15,37.85]
Pearlman 1999a	21	23	42 (13.897)		1.82%	42[14.76,69.24]
Rosenthal 1999	202	206	20.9 (3.204)		5.19%	20.9[14.62,27.18]
SAS30003	92	87	24 (6.801)		3.8%	24[10.67,37.33]
Shapiro 2000b	84	90	2.5 (6.505)		3.91%	2.5[-10.25,15.25]
Subtotal (95% CI)					**31.32%**	**23.57[14.6,32.55]**
Heterogeneity: Tau^2=123.67; Chi^2=36.89, df=7(P<0.0001); I^2=81.02%						
Test for overall effect: Z=5.15(P<0.0001)						
5.1.3 Children <12 years						
Bensch 2002	171	176	19 (3.299)		5.15%	19[12.53,25.47]
Simons 1997a	80	80	16 (5.786)		4.2%	16[4.66,27.34]
von Berg 1998	180	171	13 (5)		4.51%	13[3.2,22.8]
Weinstein 1998	102	105	15 (3.561)		5.06%	15[8.02,21.98]
Subtotal (95% CI)					**18.93%**	**16.32[12.32,20.31]**
Heterogeneity: Tau^2=0; Chi^2=1.24, df=3(P=0.74); I^2=0%						
Test for overall effect: Z=8.01(P<0.0001)						
5.1.4 Unclear						
SLGA2004	63	63	30 (7.209)		3.64%	30[15.87,44.13]
Subtotal (95% CI)					**3.64%**	**30[15.87,44.13]**
Heterogeneity: Tau^2=0; Chi^2=0, df=0(P<0.0001); I^2=100%						
Test for overall effect: Z=4.16(P<0.0001)						
Total (95% CI)					**100%**	**24.84[20.41,29.27]**
Heterogeneity: Tau^2=88.28; Chi^2=97.12, df=24(P<0.0001); I^2=75.29%						
Test for overall effect: Z=10.99(P<0.0001)						
Test for subgroup differences: Chi^2=13.19, df=1 (P=0), I^2=77.26%						



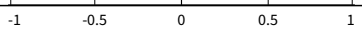
Analysis 5.2. Comparison 5 Imputed standard deviations, Outcome 2 Peak expiratory flow: morning.

Study or subgroup	LABA N	Placebo N	L/min (SE)	L/min IV, Fixed, 95% CI	Weight	L/min IV, Fixed, 95% CI
5.2.1 Participants using mixed cointerventions						
Bensch 2001	135	136	51 (12.724)		2.82%	51[26.06,75.94]
Busse 1998	261	231	18.8 (9.107)		5.51%	18.8[0.95,36.65]
D'Alonzo 1994	87	90	14 (15.3)		1.95%	14[-15.99,43.99]
Dahl 1991a	171	172	70 (10.627)		4.04%	70[49.17,90.83]
Ekstrom 1998a	135	129	10 (13.153)		2.64%	10[-15.78,35.78]
Ekstrom 1998b	114	113	31 (12.566)		2.89%	31[6.37,55.63]
Kemp 1999	176	176	35 (10.627)		4.04%	35[14.17,55.83]
LaForce 2005	75	83	2 (15.214)		1.97%	2[-27.82,31.82]
Pearlman 1992	66	62	26 (16.393)		1.7%	26[-6.13,58.13]
SLGL82	41	41	6 (16.02)		1.78%	6[-25.4,37.4]
Wolfe 2000a	165	167	12 (10.699)		3.99%	12[-8.97,32.97]
Subtotal (95% CI)					**33.34%**	**27.66[20.4,34.91]**
Heterogeneity: Tau²=0; Chi²=30.16, df=10(P=0); I²=66.84%						
Test for overall effect: Z=7.47(P<0.0001)						
5.2.3 Participants not using ICS						
Boulet 1997	7	6	151 (54.79)		0.15%	151[43.61,258.39]
Lazarus 2001	54	56	0 (20.362)		1.1%	0[-39.91,39.91]
Roberts 1999	12	11	80 (47.01)		0.21%	80[-12.14,172.14]
SLMP03	11	13	16.8 (12.32)		3.01%	16.8[-7.35,40.95]
Wallin 1999	13	9	8 (31.566)		0.46%	8[-53.87,69.87]
Wronska 1998	21	22	92 (39.69)		0.29%	92[14.21,169.79]
Subtotal (95% CI)					**5.22%**	**23.08[4.74,41.41]**
Heterogeneity: Tau²=0; Chi²=11.71, df=5(P=0.04); I²=57.28%						
Test for overall effect: Z=2.47(P=0.01)						
5.2.4 Children <12 years						
Levy 2005	127	122	6.2 (3.21)		44.32%	6.2[-0.09,12.49]
von Berg 2003	81	84	11.1 (5.82)		13.48%	11.1[-0.31,22.51]
Weinstein 1998	102	105	13.9 (11.21)		3.63%	13.9[-8.07,35.87]
Subtotal (95% CI)					**61.44%**	**7.73[2.39,13.07]**
Heterogeneity: Tau²=0; Chi²=0.87, df=2(P=0.65); I²=0%						
Test for overall effect: Z=2.84(P=0)						
Total (95% CI)					**100%**	**15.17[10.99,19.36]**
Heterogeneity: Tau²=0; Chi²=62.27, df=19(P<0.0001); I²=69.49%						
Test for overall effect: Z=7.1(P<0.0001)						
Test for subgroup differences: Chi²=19.54, df=1 (P<0.0001), I²=89.76%						



Analysis 5.3. Comparison 5 Imputed standard deviations, Outcome 3 FEV1.

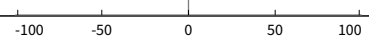
Study or subgroup	LABA N	Placebo N	Litres (SE)	Litres IV, Fixed, 95% CI	Weight	Litres IV, Fixed, 95% CI
5.3.1 Participants using mixed cointerventions						
Bensch 2001	134	134	0.3 (0.1)		3.77%	0.3[0.1,0.5]
Busse 1998	216	226	0.1 (0.077)		6.44%	0.12[-0.03,0.27]

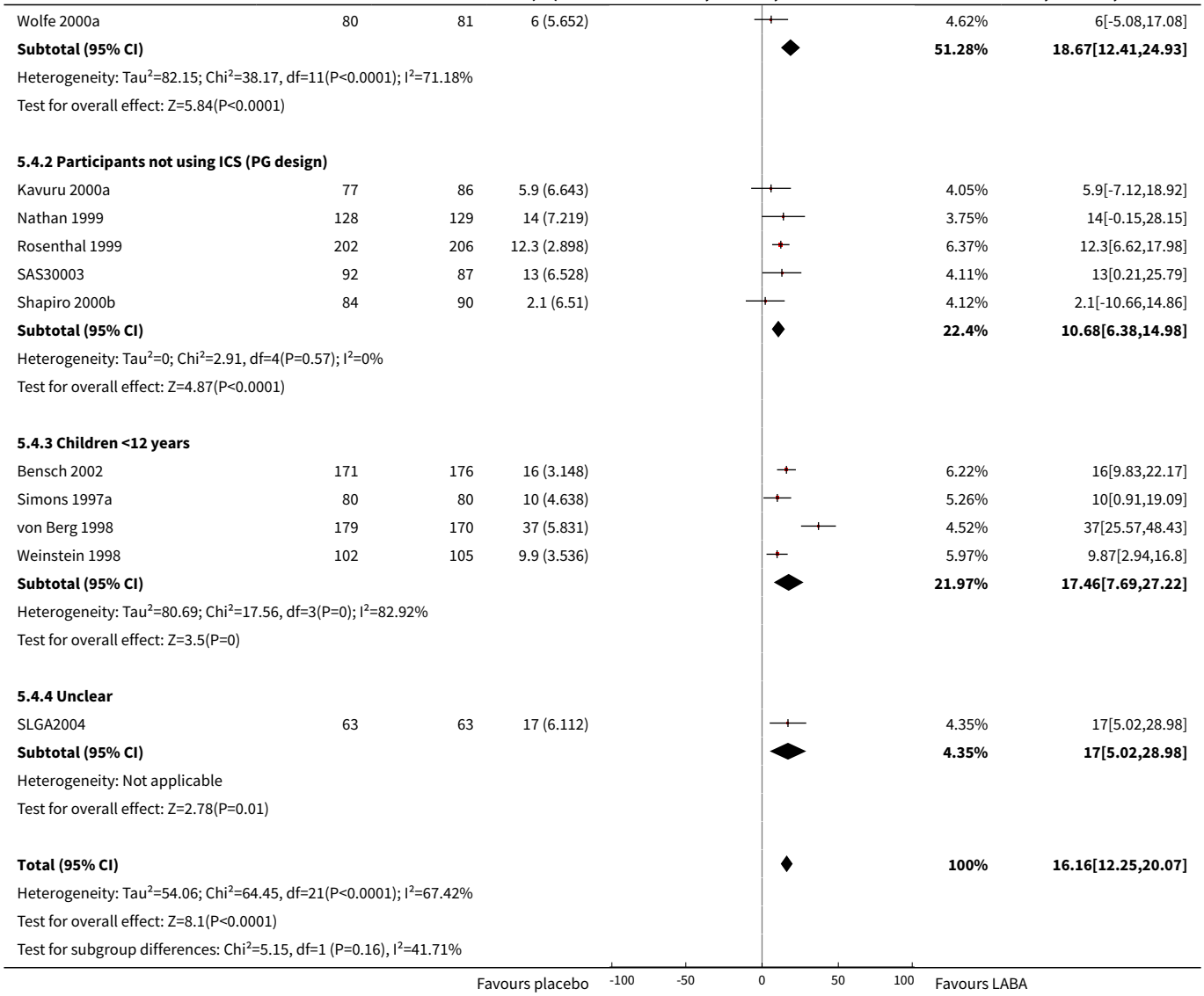


Study or subgroup	LABA N	Placebo N	Litres (SE)	Litres IV, Fixed, 95% CI	Weight	Litres IV, Fixed, 95% CI
D'Alonzo 1994	84	87	0.1 (0.112)		2.99%	0.07[-0.15,0.29]
Dahl 1991a	146	130	0.2 (0.06)		10.46%	0.2[0.08,0.32]
Ekstrom 1998a	135	129	0 (0.087)		5.01%	0.01[-0.16,0.18]
Kemp 1999	176	176	0.3 (0.087)		5.01%	0.33[0.16,0.5]
Pearlman 1992	68	63	0.2 (0.147)		1.74%	0.16[-0.13,0.45]
Pleskow 2003	139	139	0.4 (0.092)		4.45%	0.4[0.22,0.58]
SLGL82	41	41	0.1 (0.127)		2.34%	0.09[-0.16,0.34]
Wolfe 2000a	73	67	0.2 (0.663)		0.09%	0.19[-1.11,1.49]
Wolfe 2006	527	527	0.3 (0.028)		48.05%	0.3[0.25,0.35]
Subtotal (95% CI)					**90.34%**	**0.25[0.21,0.29]**
Heterogeneity: Tau²=0; Chi²=22.74, df=10(P=0.01); I²=56.02%						
Test for overall effect: Z=12.26(P<0.0001)						
5.3.2 Participants not using ICS						
Prieto 2002	14	13	0.2 (0.296)		0.43%	0.18[-0.4,0.76]
Wallin 1999	21	22	0.1 (0.239)		0.66%	0.08[-0.39,0.55]
Subtotal (95% CI)					**1.09%**	**0.12[-0.24,0.48]**
Heterogeneity: Tau²=0; Chi²=0.07, df=1(P=0.79); I²=0%						
Test for overall effect: Z=0.64(P=0.52)						
5.3.3 Children <12 years						
von Berg 1998	183	171	0.2 (0.066)		8.57%	0.19[0.06,0.32]
von Berg 2003	81	84	0.1 (0)			Not estimable
Subtotal (95% CI)					**8.57%**	**0.19[0.06,0.32]**
Heterogeneity: Not applicable						
Test for overall effect: Z=2.87(P=0)						
Total (95% CI)					**100%**	**0.24[0.21,0.28]**
Heterogeneity: Tau²=0; Chi²=24.01, df=13(P=0.03); I²=45.86%						
Test for overall effect: Z=12.55(P<0.0001)						
Test for subgroup differences: Chi²=1.21, df=1 (P=0.55), I²=0%						

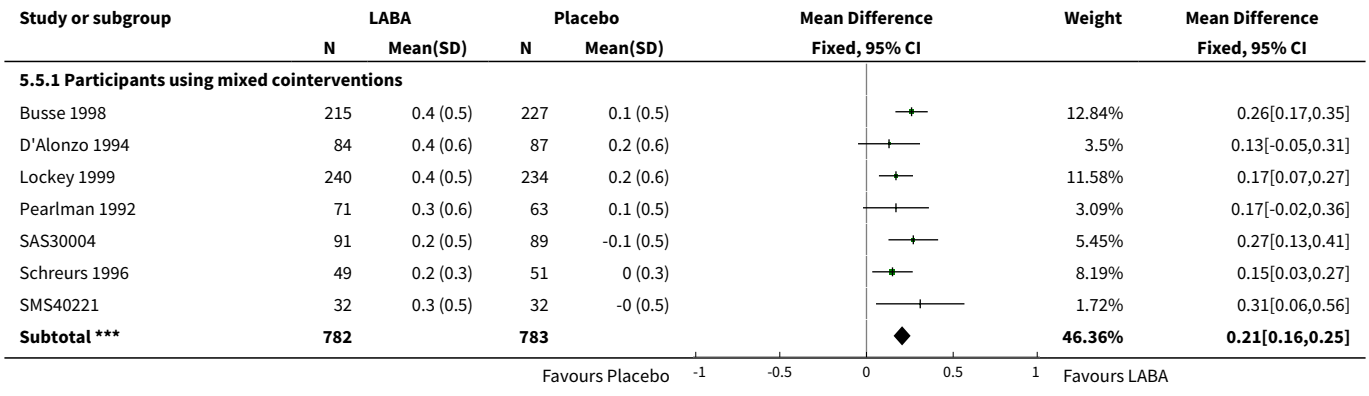
Analysis 5.4. Comparison 5 Imputed standard deviations, Outcome 4 Change in PEF evening.

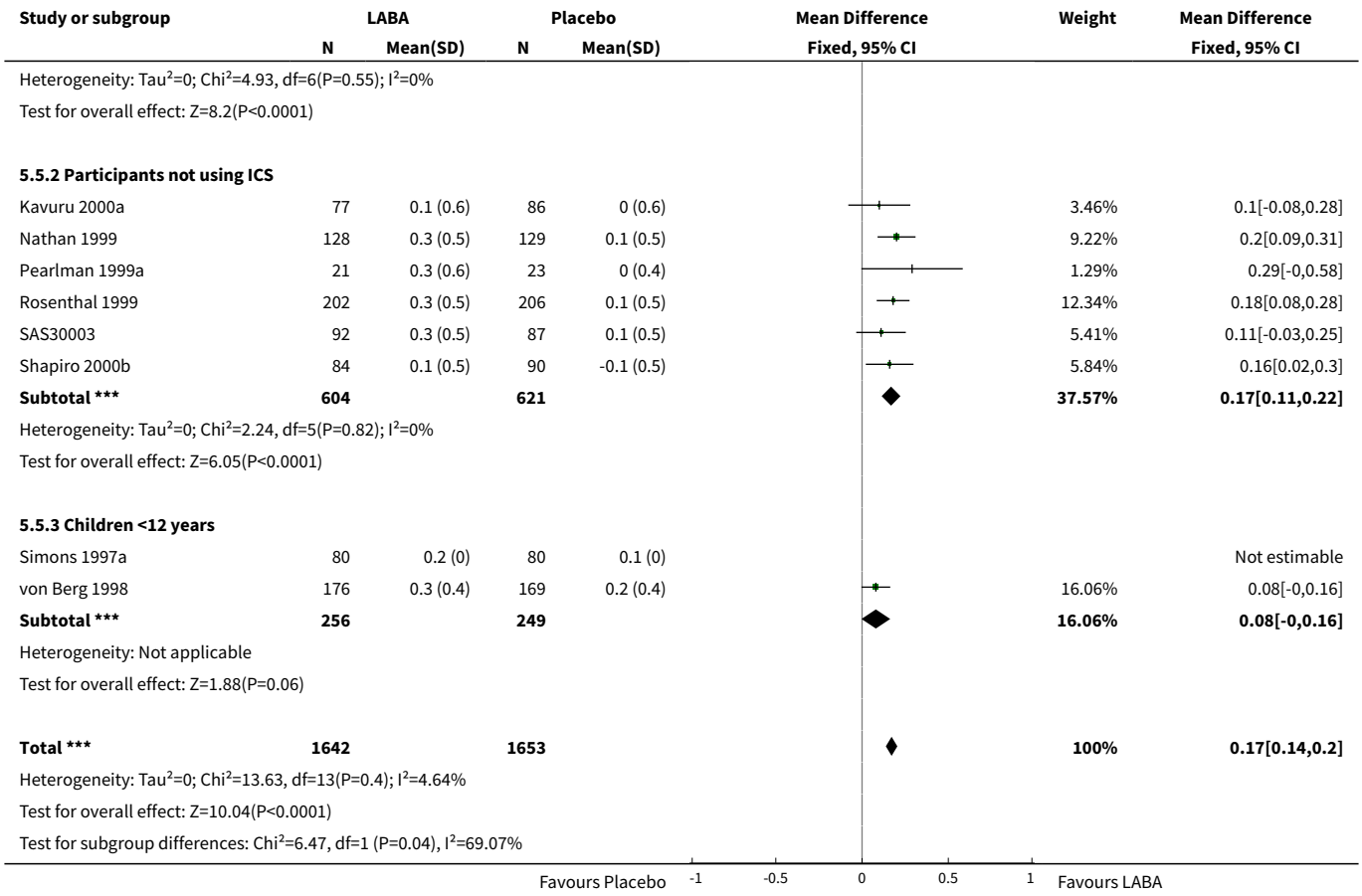
Study or subgroup	LABA N	Placebo N	L/min (SE)	L/min IV, Random, 95% CI	Weight	L/min IV, Random, 95% CI
5.4.1 Participants using mixed cointerventions						
Adinoff 1998	117	121	15.2 (6.214)		4.29%	15.2[3.02,27.38]
Busse 1998	258	269	15.9 (3.505)		5.99%	15.9[9.03,22.77]
D'Alonzo 1994	87	90	32 (7.066)		3.82%	32[18.15,45.85]
Dahl 1991a	101	100	18 (5.1)		4.97%	18[8,28]
Jones 1994	282	145	-0.5 (4.904)		5.09%	-0.5[-10.11,9.11]
Kemp 1998a	149	152	14 (5.092)		4.97%	14[4.02,23.98]
Lockey 1999	240	234	28 (5.658)		4.62%	28[16.91,39.09]
Pearlman 1992	67	63	24 (8.337)		3.22%	24[7.66,40.34]
SAS30004	91	89	19.7 (7.143)		3.78%	19.7[5.7,33.7]
Schreurs 1996	49	51	39 (6.383)		4.2%	39[26.49,51.51]
SMS40221	32	32	20.8 (13.444)		1.69%	20.76[-5.59,47.11]



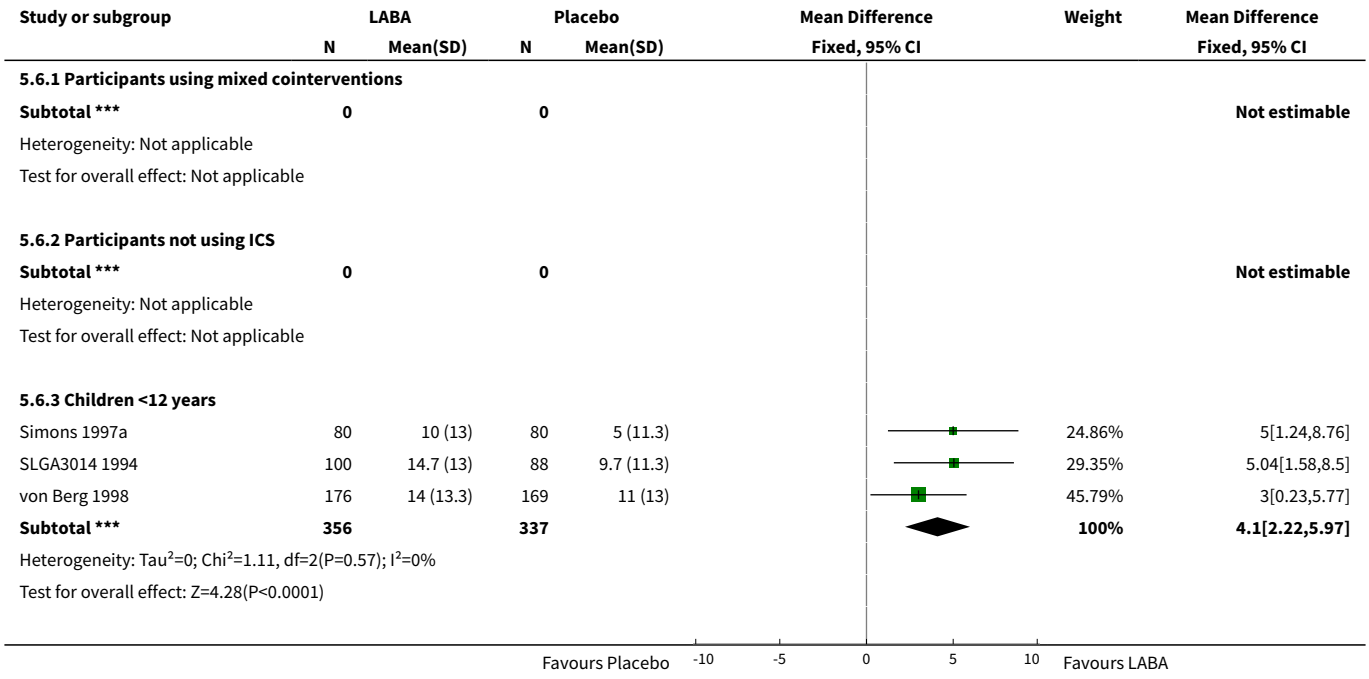


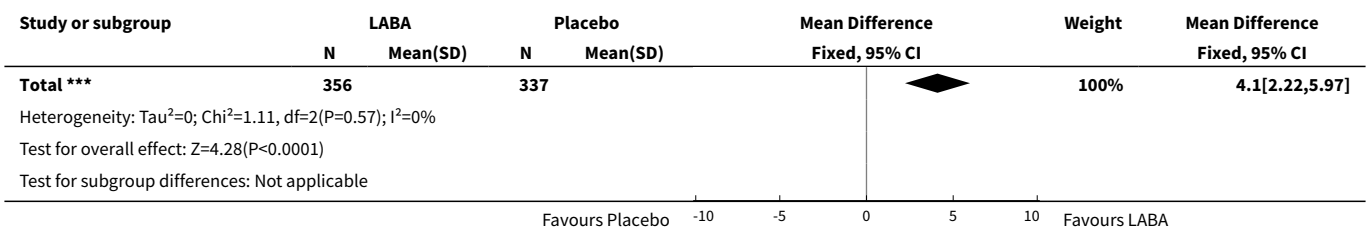
Analysis 5.5. Comparison 5 Imputed standard deviations, Outcome 5 Change in FEV (litres).



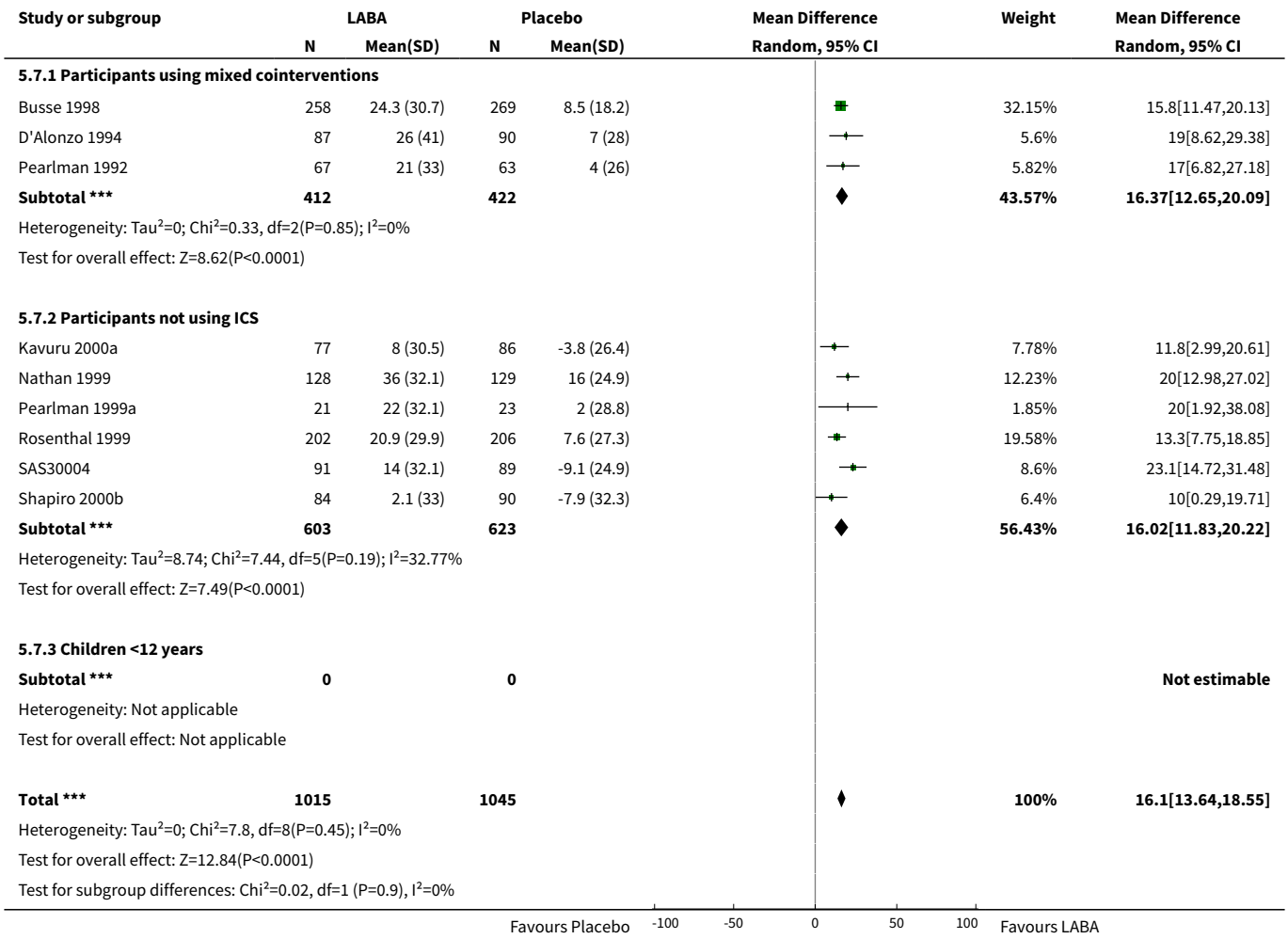


Analysis 5.6. Comparison 5 Imputed standard deviations, Outcome 6 Change in FEV %predicted.

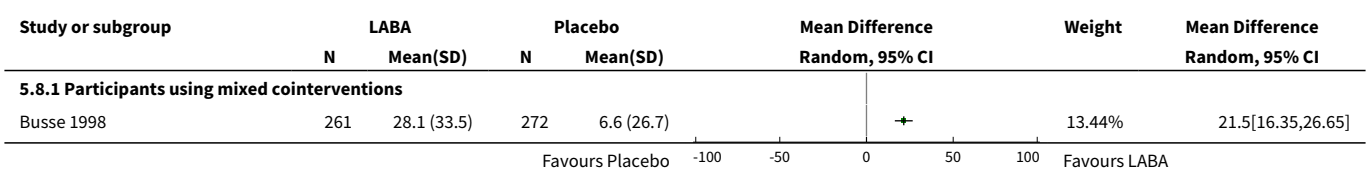


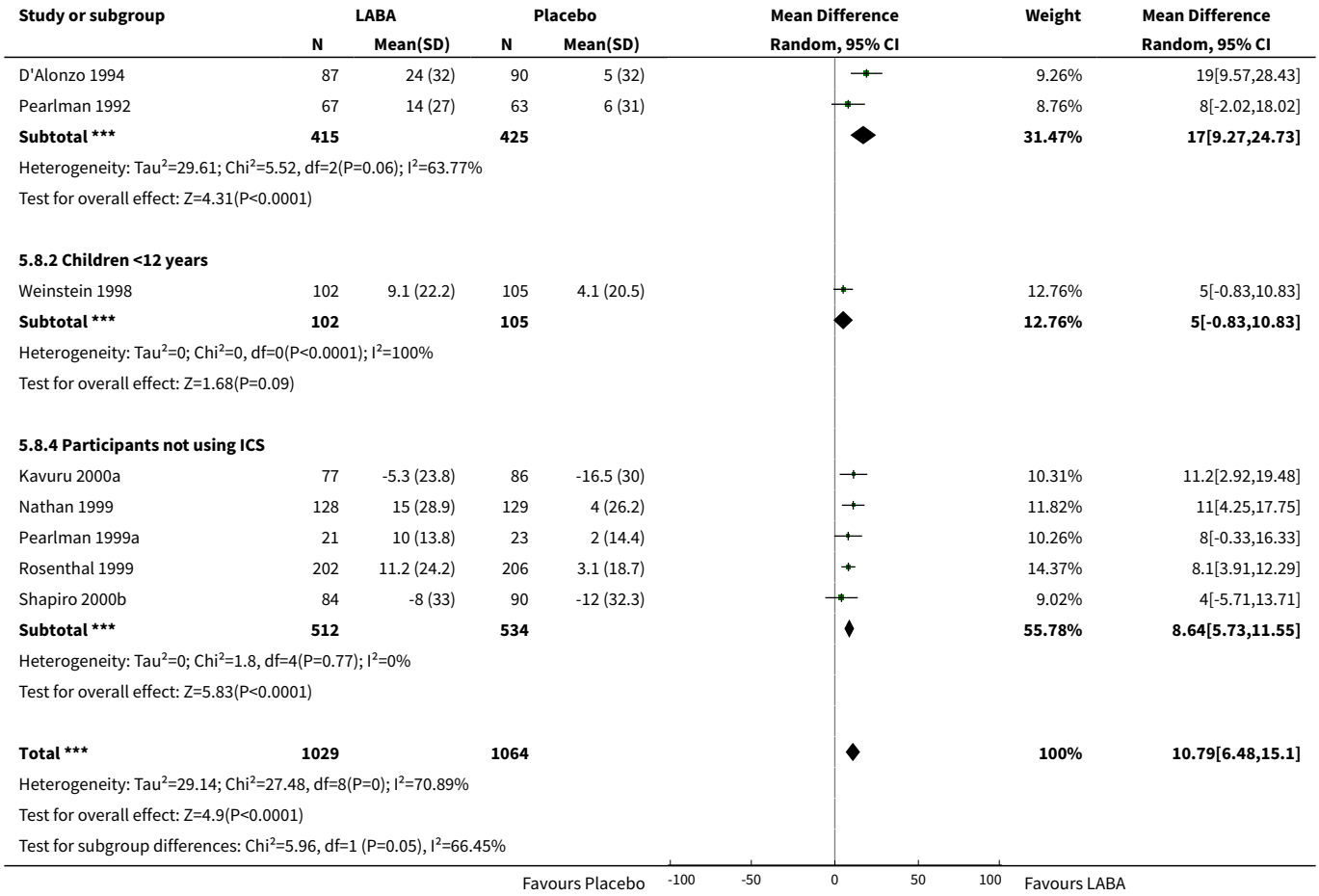


Analysis 5.7. Comparison 5 Imputed standard deviations, Outcome 7 Change in % days without asthma symptoms.

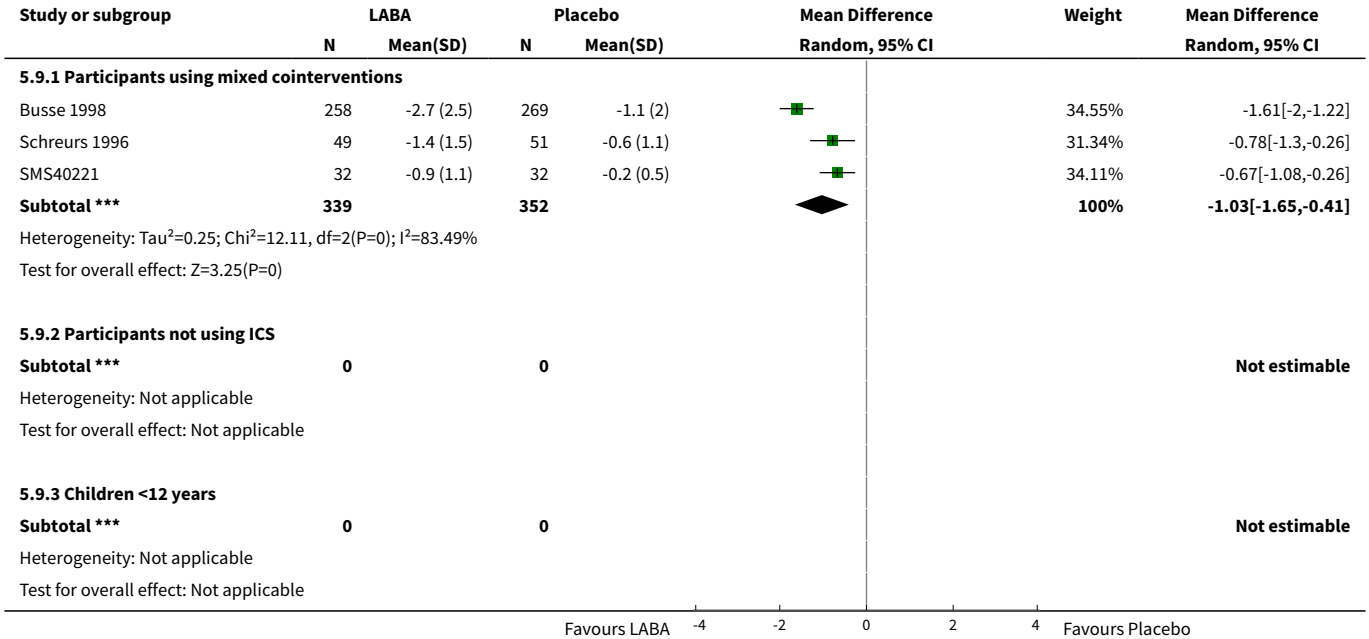


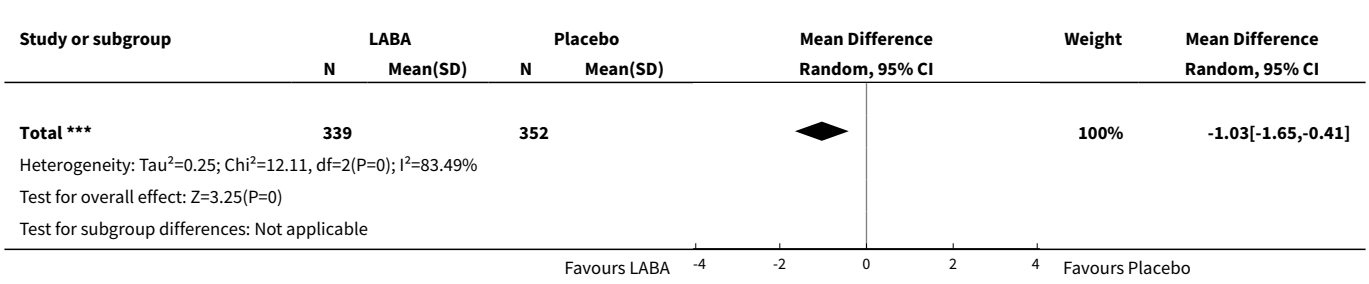
Analysis 5.8. Comparison 5 Imputed standard deviations, Outcome 8 Change in % nights without asthma symptoms.



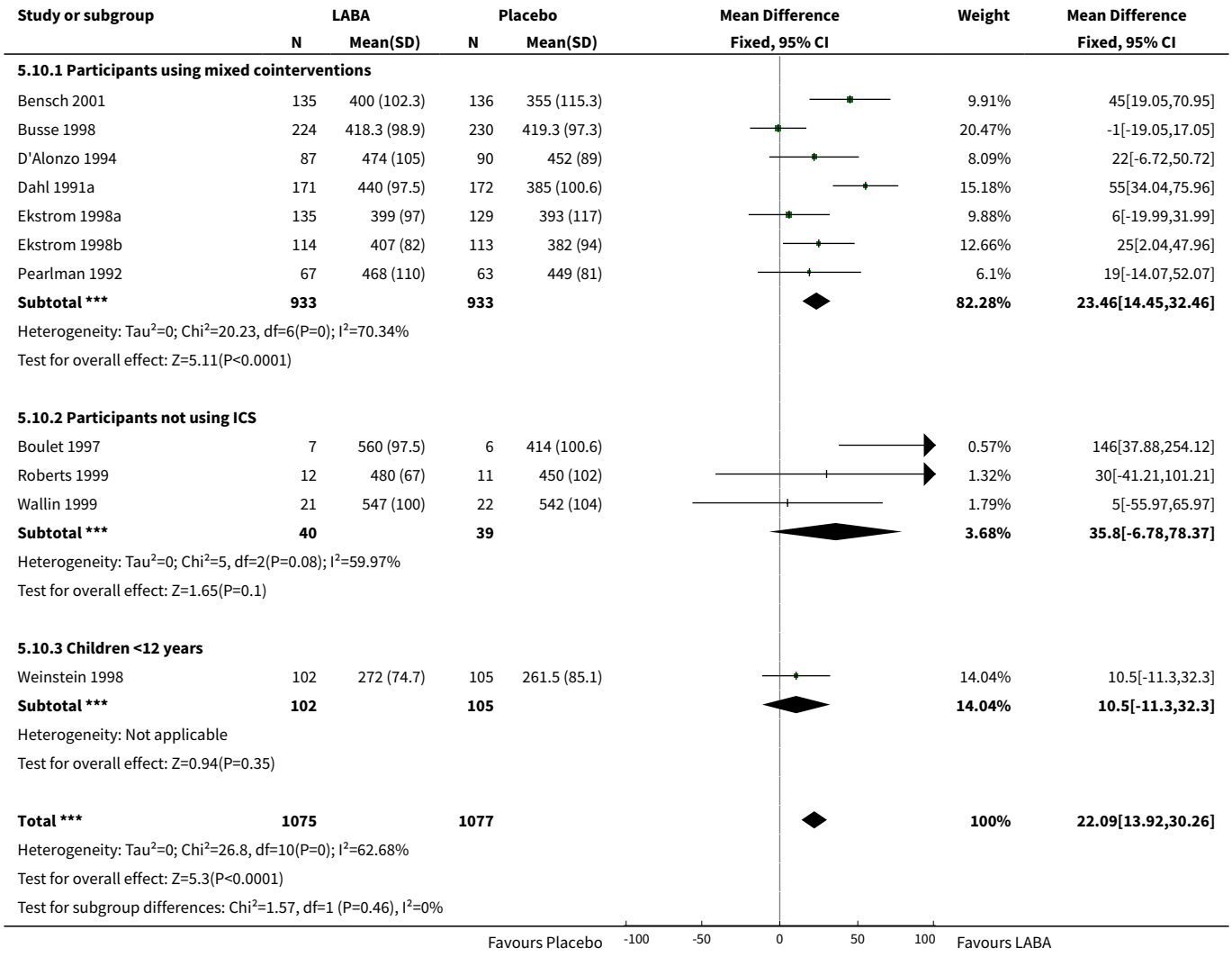


Analysis 5.9. Comparison 5 Imputed standard deviations, Outcome 9 Change in use of rescue bronchodilator/day.



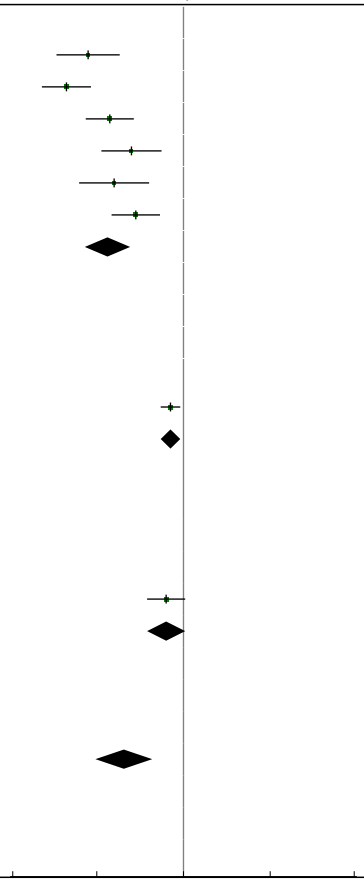


Analysis 5.10. Comparison 5 Imputed standard deviations, Outcome 10 Peak expiratory flow: evening l/min.



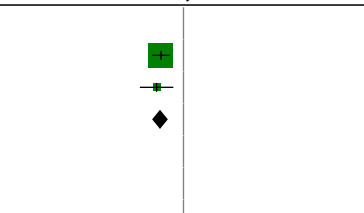
Analysis 5.11. Comparison 5 Imputed standard deviations, Outcome 11 Rescue bronchodilator use: whole day.

Study or subgroup	LABA N	LABA Mean(SD)	Placebo N	Placebo Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
5.11.1 Participants using mixed cointerventions							
D'Alonzo 1994	87	1.5 (1.8)	89	3.7 (3)		11.86%	-2.2[-2.93,-1.47]
Dahl 1991a	171	0.3 (2.5)	172	3 (2.8)		12.6%	-2.7[-3.27,-2.13]
Kemp 1998a	149	1.6 (2.4)	152	3.3 (2.5)		12.64%	-1.7[-2.25,-1.15]
Kemp 1999	176	1.5 (3.3)	176	2.7 (3.3)		12.03%	-1.2[-1.89,-0.51]
Pearlman 1992	67	1.2 (1.9)	63	2.8 (2.7)		11.48%	-1.6[-2.41,-0.79]
Wolfe 2000a	166	1.8 (2.6)	167	2.9 (2.6)		12.63%	-1.1[-1.66,-0.54]
Subtotal ***	**816**		**819**			**73.24%**	**-1.75[-2.28,-1.23]**
Heterogeneity: Tau^2=0.32; Chi^2=20.07, df=5(P=0); I^2=75.09%							
Test for overall effect: Z=6.57(P<0.0001)							
5.11.2 Participants not using ICS							
Wallin 1999	21	0.1 (0.2)	22	0.4 (0.5)		13.68%	-0.3[-0.53,-0.07]
Subtotal ***	**21**		**22**			**13.68%**	**-0.3[-0.53,-0.07]**
Heterogeneity: Not applicable							
Test for overall effect: Z=2.6(P=0.01)							
5.11.3 Children <12 years							
Weinstein 1998	102	0.9 (1)	105	1.3 (2.1)		13.09%	-0.4[-0.84,0.04]
Subtotal ***	**102**		**105**			**13.09%**	**-0.4[-0.84,0.04]**
Heterogeneity: Not applicable							
Test for overall effect: Z=1.78(P=0.07)							
Total ***	**939**		**946**			**100%**	**-1.38[-2.03,-0.72]**
Heterogeneity: Tau^2=0.8; Chi^2=95.13, df=7(P<0.0001); I^2=92.64%							
Test for overall effect: Z=4.12(P<0.0001)							
Test for subgroup differences: Chi^2=25.27, df=1 (P<0.0001), I^2=92.08%							



Analysis 5.12. Comparison 5 Imputed standard deviations, Outcome 12 Change in use of rescue bronchodilator/night.

Study or subgroup	LABA N	LABA Mean(SD)	Placebo N	Placebo Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
5.12.1 Participants using mixed cointerventions							
Busse 1998	261	-0.8 (1.3)	272	-0.3 (1.1)		77.94%	-0.52[-0.73,-0.31]
Schreurs 1996	49	-0.9 (1.1)	51	-0.3 (0.8)		22.06%	-0.62[-1.01,-0.23]
Subtotal ***	**310**		**323**			**100%**	**-0.54[-0.72,-0.36]**
Heterogeneity: Tau^2=0; Chi^2=0.2, df=1(P=0.65); I^2=0%							
Test for overall effect: Z=5.86(P<0.0001)							
5.12.2 Participants not using ICS							
Subtotal ***	**0**		**0**				**Not estimable**
Heterogeneity: Not applicable							
Test for overall effect: Not applicable							
5.12.3 Children <12 years							
Subtotal ***	**0**		**0**				**Not estimable**



Study or subgroup	LABA N	LABA Mean(SD)	Placebo N	Placebo Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
Heterogeneity: Not applicable							
Test for overall effect: Not applicable							
Total ***	**310**		**323**			**100%**	**-0.54[-0.72,-0.36]**
Heterogeneity: Tau²=0; Chi²=0.2, df=1(P=0.65); I²=0%							
Test for overall effect: Z=5.86(P<0.0001)							
Test for subgroup differences: Not applicable							

Favours LABA -4 -2 0 2 4 Favours Placebo

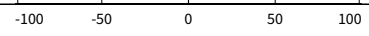
Analysis 5.13. Comparison 5 Imputed standard deviations, Outcome 13 Change in use of rescue bronchodilator/ whole day.

Study or subgroup	LABA N	LABA Mean(SD)	Placebo N	Placebo Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
5.13.1 Participants using mixed cointerventions							
Adinoff 1998	117	-2.3 (2.5)	121	-1.1 (2.6)		8.83%	-1.19[-1.83,-0.55]
D'Alonzo 1994	67	-2.7 (3.1)	74	-0.6 (2.8)		6.11%	-2.1[-3.08,-1.12]
Pearlman 1992	67	-2.6 (2.6)	63	-0.9 (2.3)		7.1%	-1.7[-2.54,-0.86]
Wolfe 2000a	80	-1.8 (2.7)	81	-0.7 (1.8)		8.23%	-1.1[-1.81,-0.39]
Wolfe 2000b	86	-1.6 (1.9)	86	-0.7 (1.9)		9.61%	-0.9[-1.45,-0.35]
Subtotal ***	**417**		**425**			**39.88%**	**-1.29[-1.67,-0.9]**
Heterogeneity: Tau²=0.06; Chi²=5.73, df=4(P=0.22); I²=30.18%							
Test for overall effect: Z=6.57(P<0.0001)							
5.13.2 Participants not using ICS							
Kavuru 2000a	77	-0.3 (2.4)	86	1.7 (2.3)		8.09%	-2[-2.72,-1.28]
Pearlman 1999a	21	-1.1 (1.8)	23	-0.2 (1.4)		6.25%	-0.9[-1.86,0.06]
Rosenthal 1999	202	-1.5 (2.1)	206	-0.3 (1.9)		11.14%	-1.18[-1.57,-0.79]
SAS30003	92	-0.8 (2.4)	87	0.2 (1.9)		8.92%	-1[-1.63,-0.37]
SAS30004	91	-0.9 (2.5)	89	1.6 (2.6)		7.97%	-2.5[-3.24,-1.76]
Shapiro 2000b	84	0 (2.8)	90	0.9 (2.9)		7.06%	-0.9[-1.75,-0.05]
Subtotal ***	**567**		**581**			**49.43%**	**-1.42[-1.92,-0.92]**
Heterogeneity: Tau²=0.26; Chi²=16.34, df=5(P=0.01); I²=69.41%							
Test for overall effect: Z=5.58(P<0.0001)							
5.13.3 Children <12 years							
Weinstein 1998	102	-0.8 (2)	105	-0.3 (1)		10.69%	-0.5[-0.94,-0.06]
Subtotal ***	**102**		**105**			**10.69%**	**-0.5[-0.94,-0.06]**
Heterogeneity: Not applicable							
Test for overall effect: Z=2.23(P=0.03)							
Total ***	**1086**		**1111**			**100%**	**-1.29[-1.62,-0.96]**
Heterogeneity: Tau²=0.22; Chi²=33.5, df=11(P=0); I²=67.17%							
Test for overall effect: Z=7.63(P<0.0001)							
Test for subgroup differences: Chi²=9.58, df=1 (P=0.01), I²=79.12%							

Favours LABA -4 -2 0 2 4 Favours Placebo

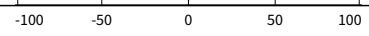
Analysis 5.14. Comparison 5 Imputed standard deviations, Outcome 14 FEV1 predicted.

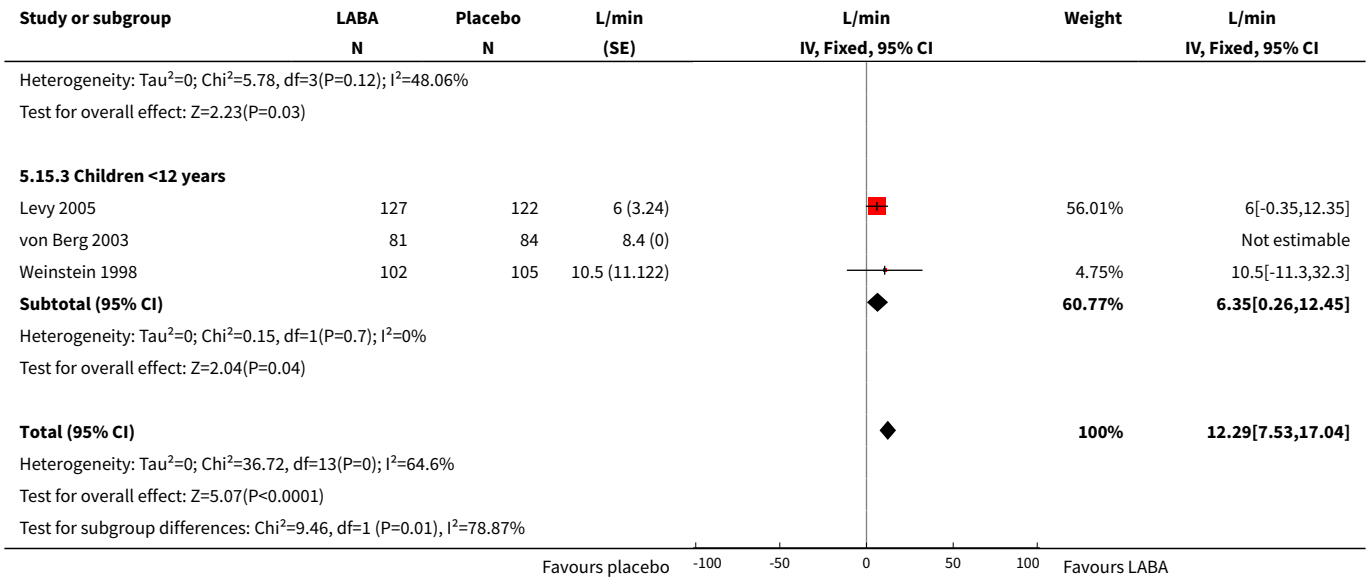
Study or subgroup	LABA N	Placebo N	% (SE)	% IV, Fixed, 95% CI	Weight	% IV, Fixed, 95% CI
5.14.1 Participants using mixed cointerventions						
Subtotal (95% CI)						**Not estimable**
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						
5.14.2 Participants not using ICS						
Wronska 1998	13	9	-3.6 (8.112)		2.66%	-3.6[-19.5,12.3]
Subtotal (95% CI)					**2.66%**	**-3.6[-19.5,12.3]**
Heterogeneity: Not applicable						
Test for overall effect: Z=0.44(P=0.66)						
5.14.3 Children <12 years						
Stelmach 2002	15	17	7.5 (5.173)		6.53%	7.45[-2.69,17.59]
von Berg 1998	183	171	3 (1.755)		56.74%	3[-0.44,6.44]
Weinstein 1998	102	105	3.6 (2.265)		34.07%	3.6[-0.84,8.04]
Subtotal (95% CI)					**97.34%**	**3.51[0.88,6.13]**
Heterogeneity: Tau^2=0; Chi^2=0.67, df=2(P=0.72); I^2=0%						
Test for overall effect: Z=2.62(P=0.01)						
Total (95% CI)					**100%**	**3.32[0.73,5.91]**
Heterogeneity: Tau^2=0; Chi^2=1.41, df=3(P=0.7); I^2=0%						
Test for overall effect: Z=2.51(P=0.01)						
Test for subgroup differences: Chi^2=0.75, df=1 (P=0.39), I^2=0%						



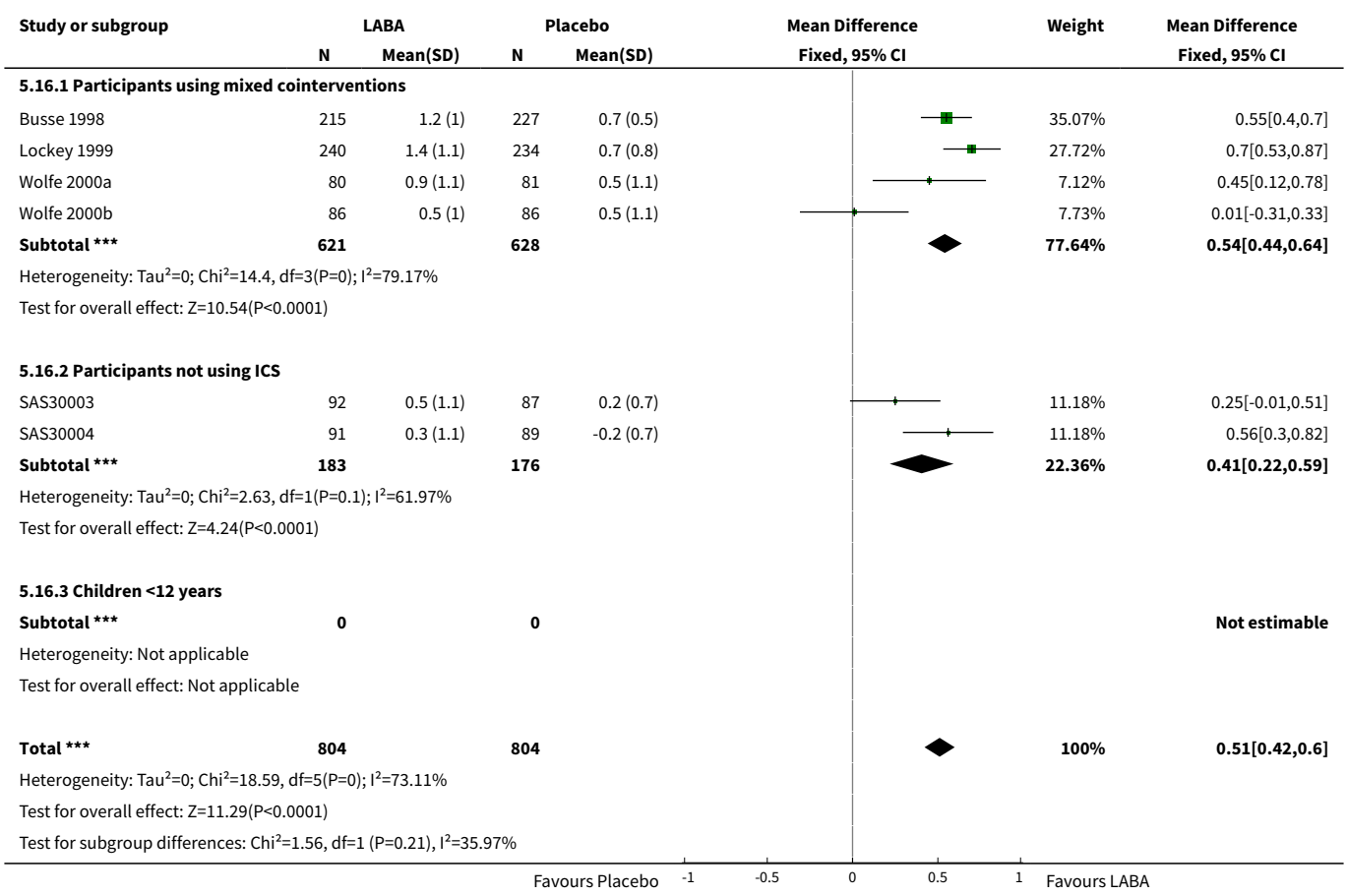
Analysis 5.15. Comparison 5 Imputed standard deviations, Outcome 15 Peak expiratory flow: evening.

Study or subgroup	LABA N	Placebo N	L/min (SE)	L/min IV, Fixed, 95% CI	Weight	L/min IV, Fixed, 95% CI
5.15.1 Participants using mixed cointerventions						
Bensch 2001	135	136	45 (13.24)		3.35%	45[19.05,70.95]
Busse 1998	224	230	-1 (9.21)		6.93%	-1[-19.05,17.05]
D'Alonzo 1994	87	90	22 (14.65)		2.74%	22[-6.71,50.71]
Dahl 1991a	171	172	55 (10.67)		5.16%	55[34.09,75.91]
Ekstrom 1998a	135	129	6 (13.26)		3.34%	6[-19.99,31.99]
Ekstrom 1998b	114	113	25 (11.714)		4.29%	25[2.04,47.96]
LaForce 2005	77	84	7 (15.061)		2.59%	7[-22.52,36.52]
Pearlman 1992	67	63	23.5 (16.87)		2.07%	23.48[-9.58,56.54]
Subtotal (95% CI)					**30.48%**	**22.38[13.77,30.99]**
Heterogeneity: Tau^2=0; Chi^2=21.33, df=7(P=0); I^2=67.19%						
Test for overall effect: Z=5.1(P<0.0001)						
5.15.2 Participants not using ICS						
Boulet 1997	7	6	146 (55.045)		0.19%	146[38.11,253.89]
Roberts 1999	12	11	30 (36.33)		0.45%	30[-41.21,101.21]
SLMP03	11	13	15.4 (8.85)		7.51%	15.4[-1.95,32.75]
Wallin 1999	21	22	5 (31.107)		0.61%	5[-55.97,65.97]
Subtotal (95% CI)					**8.75%**	**18.32[2.25,34.38]**



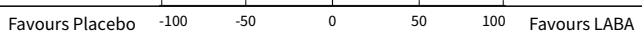


Analysis 5.16. Comparison 5 Imputed standard deviations, Outcome 16 AQOL- Change in Quality of life score: global.



Analysis 5.17. Comparison 5 Imputed standard deviations, Outcome 17 % nights without asthma awakenings.

Study or subgroup	LABA N	LABA Mean(SD)	Placebo N	Placebo Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
5.17.1 Participants using mixed cointerventions							
Adinoff 1998	117	91.7 (25.9)	121	80.5 (29.5)		7.42%	11.2[4.15,18.25]
Bensch 2001	135	73 (25.9)	136	53 (29.5)		7.6%	20[13.39,26.61]
Busse 1998	215	70 (16.1)	227	49 (25.6)		8.54%	21[17.03,24.97]
D'Alonzo 1994	87	86 (25)	90	70 (34)		6.71%	16[7.23,24.77]
Dahl 1991a	171	100 (25.9)	172	70 (29.5)		7.88%	30[24.13,35.87]
Ekstrom 1998b	114	60 (25.9)	113	45 (29.5)		7.35%	15[7.78,22.22]
Jones 1994	282	36 (38)	145	21 (32)		7.5%	15[8.16,21.84]
Kemp 1998a	149	85 (23.2)	152	73 (28.4)		7.89%	12[6.15,17.85]
Kemp 1999	176	92.5 (22.2)	176	84 (22.2)		8.33%	8.5[3.87,13.13]
Lockey 1999	240	72 (27.1)	234	42 (38.2)		7.84%	30[24.02,35.98]
Pearlman 1992	67	89 (21)	63	78 (32)		6.47%	11[1.63,20.37]
Wolfe 2000a	166	84 (25.8)	167	71 (25.8)		8.01%	13[7.46,18.54]
Subtotal * **	**1919**		**1796**			**91.56%**	**17.02[12.76,21.29]**
Heterogeneity: Tau^2=45.83; Chi^2=64.15, df=11(P<0.0001); I^2=82.85%							
Test for overall effect: Z=7.82(P<0.0001)							
5.17.2 Participants not using ICS							
Subtotal * **	**0**		**0**				**Not estimable**
Heterogeneity: Not applicable							
Test for overall effect: Not applicable							
5.17.3 Children <12 years							
Weinstein 1998	105	94.8 (11.1)	105	88.4 (19.5)		8.44%	6.4[2.11,10.69]
Subtotal * **	**105**		**105**			**8.44%**	**6.4[2.11,10.69]**
Heterogeneity: Not applicable							
Test for overall effect: Z=2.92(P=0)							
Total * **	**2024**		**1901**			**100%**	**16.11[11.74,20.49]**
Heterogeneity: Tau^2=54.21; Chi^2=85.61, df=12(P<0.0001); I^2=85.98%							
Test for overall effect: Z=7.22(P<0.0001)							
Test for subgroup differences: Chi^2=11.84, df=1 (P=0), I^2=91.55%							



Comparison 6. WMD archive

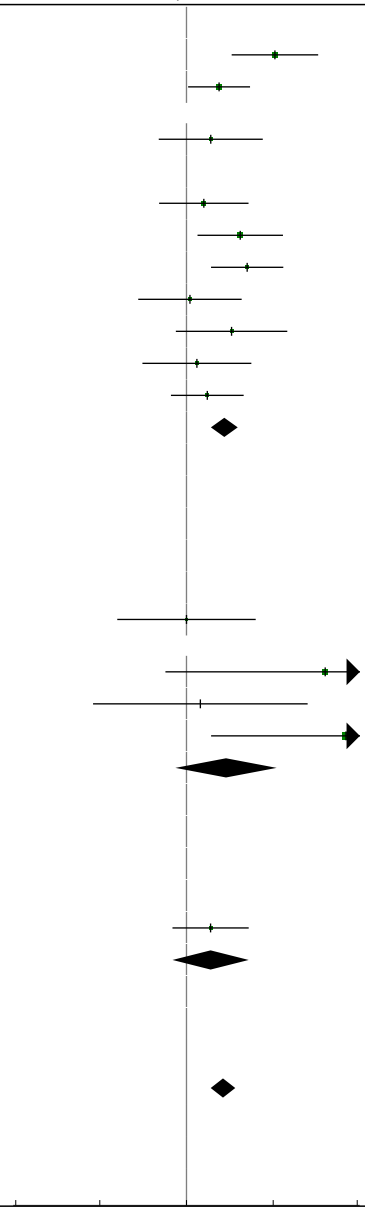
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Peak expiratory flow: morning l/min	17	3244	Mean Difference (IV, Fixed, 95% CI)	21.04 [13.96, 28.13]
1.1 Participants using mixed cointerventions	11	2826	Mean Difference (IV, Fixed, 95% CI)	21.81 [14.07, 29.55]
1.2 Participants not using ICS	5	211	Mean Difference (IV, Fixed, 95% CI)	22.79 [-6.42, 52.00]
1.3 Children <12 years	1	207	Mean Difference (IV, Fixed, 95% CI)	13.90 [-8.08, 35.88]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
2 FEV1 (litres)	11	2655	Mean Difference (IV, Fixed, 95% CI)	0.15 [0.09, 0.21]
2.1 Participants using mixed cointerventions	9	2136	Mean Difference (IV, Fixed, 95% CI)	0.14 [0.08, 0.21]
2.2 Participants not using ICS	0	0	Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
2.5 Children <12 years	2	519	Mean Difference (IV, Fixed, 95% CI)	0.19 [0.06, 0.32]
3 Peak expiratory flow: evening l/min	13	2395	Mean Difference (IV, Fixed, 95% CI)	19.76 [12.15, 27.37]
3.1 Participants using mixed cointerventions	9	2109	Mean Difference (IV, Fixed, 95% CI)	20.49 [12.21, 28.76]
3.2 Participants not using ICS	3	79	Mean Difference (IV, Fixed, 95% CI)	35.87 [-6.69, 78.43]
3.3 Children <12 years	1	207	Mean Difference (IV, Fixed, 95% CI)	10.5 [-11.30, 32.30]
4 Bronchial hyperreactivity-log PD20/PC20 methacholine or histamine	7	549	Std. Mean Difference (IV, Fixed, 95% CI)	0.15 [-0.05, 0.36]
4.1 Participants using mixed cointerventions	2	269	Std. Mean Difference (IV, Fixed, 95% CI)	0.05 [-0.19, 0.29]
4.2 Participants not using ICS	3	88	Std. Mean Difference (IV, Fixed, 95% CI)	0.49 [-0.01, 0.98]
4.3 Children <12 years	2	192	Std. Mean Difference (IV, Fixed, 95% CI)	0.39 [-0.31, 1.09]
5 % Predicted FEV1	4	615	Mean Difference (IV, Fixed, 95% CI)	3.32 [0.73, 5.91]
5.1 Participants using mixed cointerventions	0	0	Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
5.2 Participants not using ICS	1	22	Mean Difference (IV, Fixed, 95% CI)	-3.60 [-19.50, 12.30]
5.3 Children <12 years	3	593	Mean Difference (IV, Fixed, 95% CI)	3.51 [0.88, 6.14]
6 Change in PEF morning (l/min)	25	5561	Mean Difference (IV, Random, 95% CI)	24.64 [19.29, 29.99]
6.1 Participants using mixed cointerventions	12	2788	Mean Difference (IV, Random, 95% CI)	27.30 [19.72, 34.87]
6.2 Participants not using ICS	8	1582	Mean Difference (IV, Random, 95% CI)	24.24 [14.23, 34.24]
6.3 Children <12 years	4	1065	Mean Difference (IV, Random, 95% CI)	14.33 [8.64, 20.01]
6.4 Unclear	1	126	Mean Difference (IV, Random, 95% CI)	30.00 [15.87, 44.13]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
7 Change in PEF evening (l/min)	21	5149	Mean Difference (IV, Random, 95% CI)	17.67 [12.62, 22.72]
7.1 Participants using mixed cointerventions	11	2779	Mean Difference (IV, Random, 95% CI)	21.92 [14.25, 29.59]
7.2 Participants not using ICS	5	1181	Mean Difference (IV, Random, 95% CI)	10.68 [6.37, 14.98]
7.3 Children <12 years	4	1063	Mean Difference (IV, Random, 95% CI)	23.04 [-3.54, 49.61]
7.4 Unclear	1	126	Mean Difference (IV, Random, 95% CI)	17.0 [5.02, 28.98]
8 Peak expiratory flow: morning l/min (crossover studies)	5	878	Mean Difference (IV, Fixed, 95% CI)	43.68 [5.54, 81.82]
8.1 CROSS OVER STUDIES	5	878	Mean Difference (IV, Fixed, 95% CI)	43.68 [5.54, 81.82]
9 Peak expiratory flow: evening l/min (crossover studies)	5	878	Mean Difference (IV, Fixed, 95% CI)	39.46 [-0.70, 79.63]
9.1 CROSS OVER STUDIES	5	878	Mean Difference (IV, Fixed, 95% CI)	39.46 [-0.70, 79.63]
10 FEV1 (litres; crossover studies)	6	902	Mean Difference (IV, Fixed, 95% CI)	0.19 [0.02, 0.35]
10.4 CROSS OVER STUDIES	6	902	Mean Difference (IV, Fixed, 95% CI)	0.19 [0.02, 0.35]
11 AUC- mean area under 12 hr serial FEV1 curve (L-h)	6	1063	Mean Difference (IV, Fixed, 95% CI)	3.49 [2.75, 4.23]
11.1 Participants using mixed cointerventions	4	726	Mean Difference (IV, Fixed, 95% CI)	3.79 [2.98, 4.60]
11.2 Participants not on ICS	2	337	Mean Difference (IV, Fixed, 95% CI)	2.01 [0.21, 3.81]
11.3 Children <12 years	0	0	Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
12 Mini-AQLQ (total score)	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
12.1 Participants using mixed cointerventions	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
12.2 Participants not using ICS	0		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
12.3 Children <12 years	0		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]

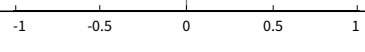
Analysis 6.1. Comparison 6 WMD archive, Outcome 1 Peak expiratory flow: morning l/min.

Study or subgroup	LABA N	LABA Mean(SD)	PLACEBO N	PLACEBO Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
6.1.1 Participants using mixed cointerventions							
Bensch 2001	135	384 (101)	136	333 (108.4)		8.06%	51[26.06,75.94]
Busse 1998	261	392.5 (102.2)	231	373.7 (99.6)		15.74%	18.8[0.95,36.65]
D'Alonzo 1994	87	435 (112)	90	421 (90)		5.58%	14[-15.99,43.99]
Dahl 1991a	171	420 (0)	172	350 (0)			Not estimable
Ekstrom 1998a	135	380 (95)	129	370 (117)		7.55%	10[-15.78,35.78]
Ekstrom 1998b	114	385 (89)	113	354 (100)		8.26%	31[6.37,55.63]
Kemp 1999	176	470 (106.1)	176	435 (92.9)		11.55%	35[14.17,55.83]
LaForce 2005	75	366 (101)	83	364 (89)		5.64%	2[-27.82,31.82]
Pearlman 1992	66	444 (102)	62	418 (83)		4.86%	26[-6.13,58.13]
SLGL82	41	345 (75)	41	339 (70)		5.09%	6[-25.4,37.4]
Wolfe 2000a	165	420 (87)	167	408 (107)		11.41%	12[-8.97,32.97]
Subtotal * **	**1426**		**1400**			**83.74%**	**21.81[14.07,29.55]**
Heterogeneity: Tau^2=0; Chi^2=12.09, df=9(P=0.21); I^2=25.54%							
Test for overall effect: Z=5.52(P<0.0001)							
6.1.2 Participants not using ICS							
Boulet 1997	7	558 (0)	6	407 (0)			Not estimable
Lazarus 2001	54	430.8 (106.6)	56	430.8 (107)		3.15%	0[-39.91,39.91]
Roberts 1999	12	460 (93)	11	380 (128)		0.59%	80[-12.14,172.14]
Wallin 1999	21	544 (101)	22	536 (106)		1.31%	8[-53.87,69.87]
Wronska 1998	13	450 (114)	9	358 (72)		0.83%	92[14.2,169.8]
Subtotal * **	**107**		**104**			**5.88%**	**22.79[-6.42,52]**
Heterogeneity: Tau^2=0; Chi^2=5.99, df=3(P=0.11); I^2=49.94%							
Test for overall effect: Z=1.53(P=0.13)							
6.1.3 Children <12 years							
Weinstein 1998	102	262.2 (72.7)	105	248.3 (88.1)		10.38%	13.9[-8.08,35.88]
Subtotal * **	**102**		**105**			**10.38%**	**13.9[-8.08,35.88]**
Heterogeneity: Not applicable							
Test for overall effect: Z=1.24(P=0.22)							
Total * **	**1635**		**1609**			**100%**	**21.04[13.96,28.13]**
Heterogeneity: Tau^2=0; Chi^2=18.54, df=14(P=0.18); I^2=24.47%							
Test for overall effect: Z=5.82(P<0.0001)							
Test for subgroup differences: Chi^2=0.46, df=1 (P=0.8), I^2=0%							

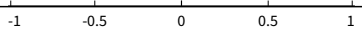


Analysis 6.2. Comparison 6 WMD archive, Outcome 2 FEV1 (litres).

Study or subgroup	LABA N	LABA Mean(SD)	PLACEBO N	PLACEBO Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
6.2.1 Participants using mixed cointerventions							
Bensch 2001	134	2.6 (0.9)	134	2.3 (0.8)		8.46%	0.3[0.1,0.5]
Busse 1998	216	2.6 (0.7)	226	2.5 (0.8)		16.61%	0.12[-0.03,0.27]
D'Alonzo 1994	84	2.9 (0.8)	87	2.8 (0.7)		7.52%	0.07[-0.15,0.29]

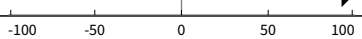


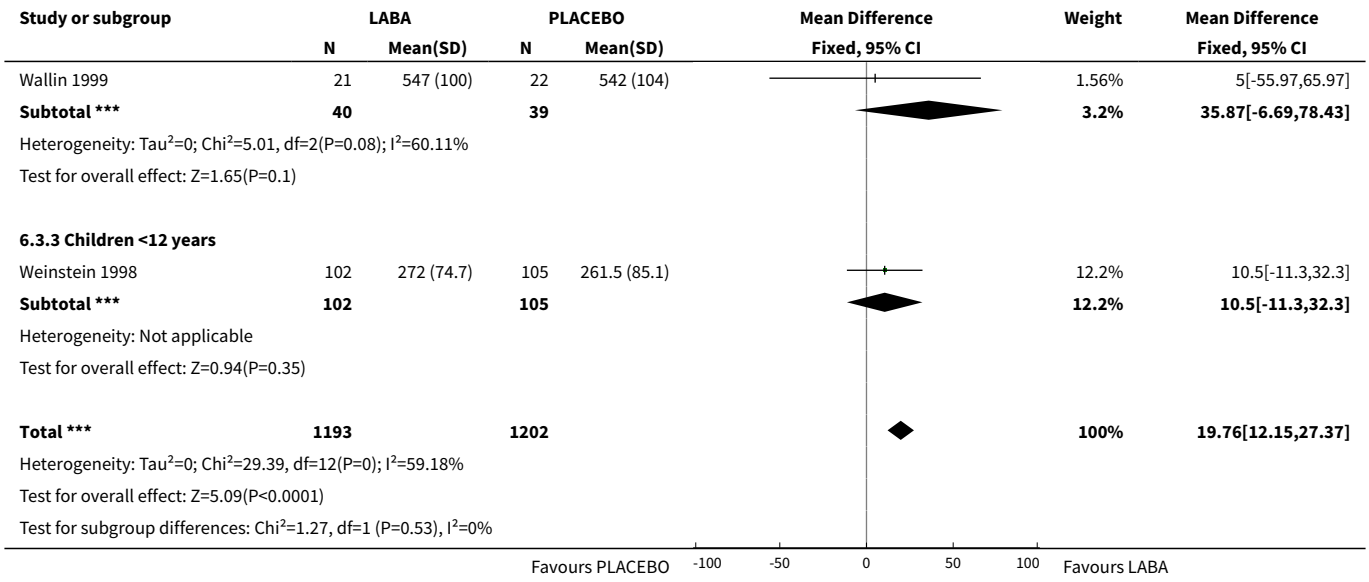
Study or subgroup	LABA N	LABA Mean(SD)	PLACEBO N	PLACEBO Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
Ekstrom 1998a	135	2.2 (0.7)	129	2.1 (0.7)		12.31%	0.01[-0.16,0.18]
Kemp 1999	176	3.2 (0.9)	176	2.8 (0.7)		12.39%	0.33[0.16,0.5]
Pearlman 1992	68	2.9 (0.9)	63	2.8 (0.8)		4.25%	0.16[-0.13,0.45]
Pleskow 2003	139	2.8 (0)	139	2.4 (0)			Not estimable
SLGL82	45	1.9 (0.6)	45	1.8 (0.6)		5.62%	0.09[-0.16,0.34]
Wolfe 2000a	73	2.5 (0.6)	67	2.4 (0.5)		10.75%	0.06[-0.12,0.24]
Subtotal * **	**1070**		**1066**			**77.91%**	**0.14[0.08,0.21]**
Heterogeneity: Tau²=0; Chi²=10.92, df=7(P=0.14); I²=35.89%							
Test for overall effect: Z=4.16(P<0.0001)							
6.2.2 Participants not using ICS							
Subtotal * **	**0**		**0**				**Not estimable**
Heterogeneity: Not applicable							
Test for overall effect: Not applicable							
6.2.5 Children <12 years							
von Berg 1998	183	2 (0.7)	171	1.8 (0.6)		22.09%	0.19[0.06,0.32]
von Berg 2003	81	2.2 (0)	84	2 (0)			Not estimable
Subtotal * **	**264**		**255**			**22.09%**	**0.19[0.06,0.32]**
Heterogeneity: Not applicable							
Test for overall effect: Z=2.95(P=0)							
Total * **	**1334**		**1321**			**100%**	**0.15[0.09,0.21]**
Heterogeneity: Tau²=0; Chi²=11.34, df=8(P=0.18); I²=29.47%							
Test for overall effect: Z=5.06(P<0.0001)							
Test for subgroup differences: Chi²=0.43, df=1 (P=0.51), I²=0%							



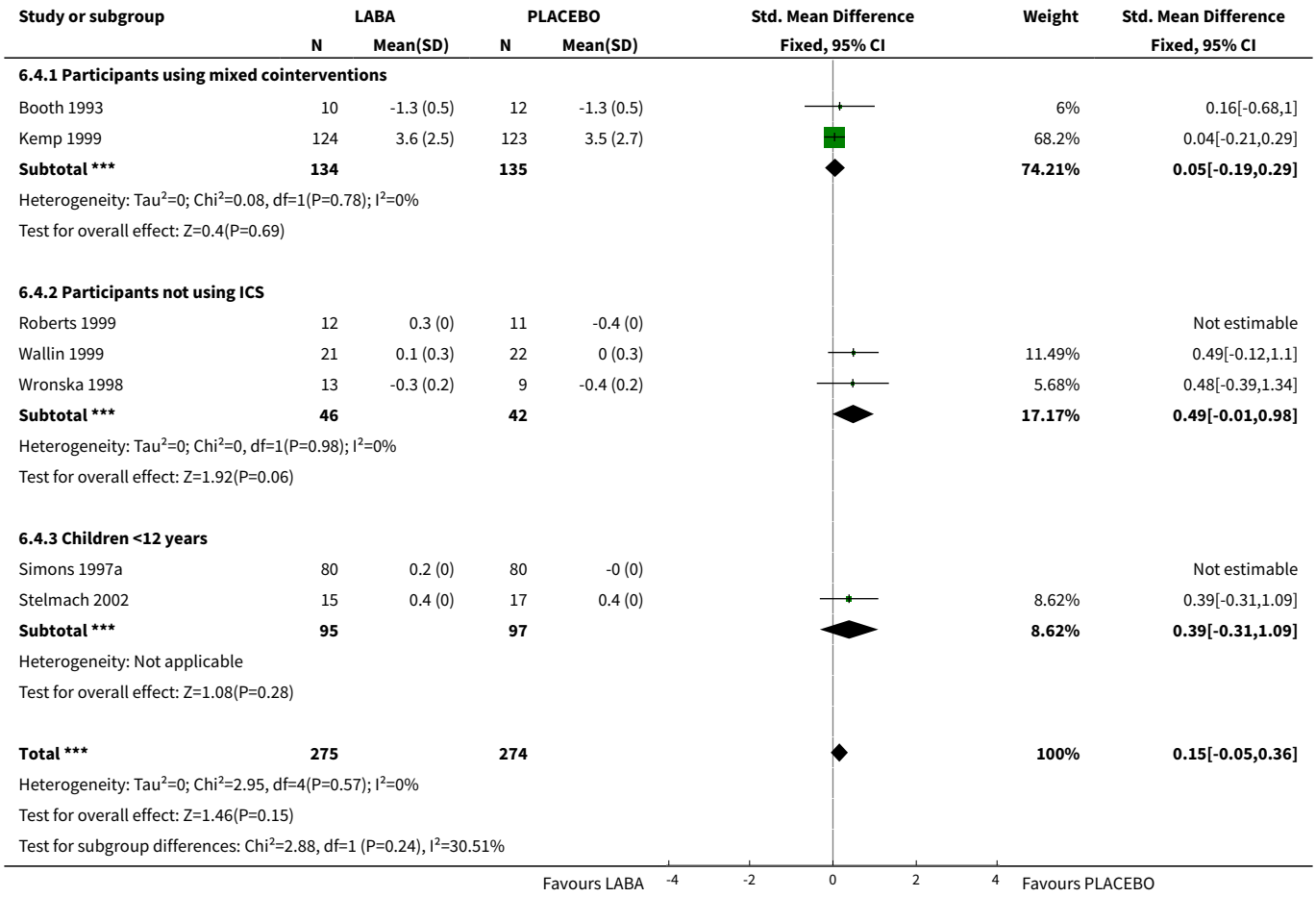
Analysis 6.3. Comparison 6 WMD archive, Outcome 3 Peak expiratory flow: evening l/min.

Study or subgroup	LABA N	LABA Mean(SD)	PLACEBO N	PLACEBO Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
6.3.1 Participants using mixed cointerventions							
Bensch 2001	135	400 (102.3)	136	355 (115.3)		8.61%	45[19.05,70.95]
Busse 1998	224	418.3 (98.9)	230	419.3 (97.3)		17.78%	-1[-19.05,17.05]
D'Alonzo 1994	87	474 (105)	90	452 (89)		7.03%	22[-6.72,50.72]
Dahl 1991a	171	440 (97)	172	385 (100.6)		13.25%	55[34.09,75.91]
Ekstrom 1998a	135	399 (97)	129	393 (117)		8.58%	6[-19.99,31.99]
Ekstrom 1998b	114	407 (82)	113	382 (94)		11%	25[2.04,47.96]
LaForce 2005	77	377 (101)	84	370 (89)		6.65%	7[-22.52,36.52]
Pearlman 1992	67	468 (110)	63	449 (81)		5.3%	19[-14.07,52.07]
SLGL82	41	345 (70)	41	344 (69)		6.4%	1[-29.09,31.09]
Subtotal * **	**1051**		**1058**			**84.6%**	**20.49[12.21,28.76]**
Heterogeneity: Tau²=0; Chi²=23.11, df=8(P=0); I²=65.38%							
Test for overall effect: Z=4.85(P<0.0001)							
6.3.2 Participants not using ICS							
Boulet 1997	7	560 (97)	6	414 (100.6)		0.5%	146[38.11,253.89]
Roberts 1999	12	480 (67)	11	450 (102)		1.14%	30[-41.21,101.21]



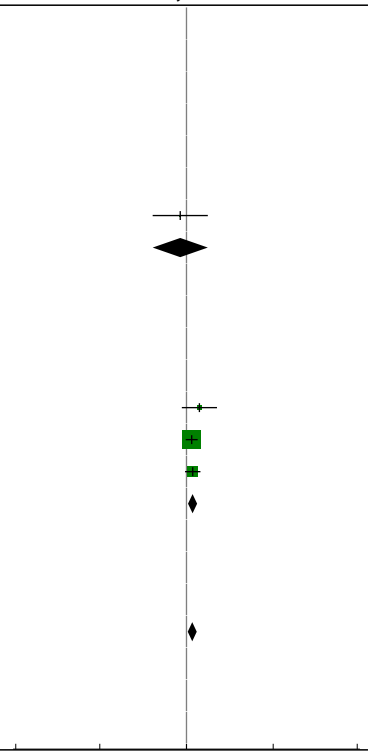


Analysis 6.4. Comparison 6 WMD archive, Outcome 4 Bronchial hyperreactivity- log PD20/PC20 methacholine or histamine.



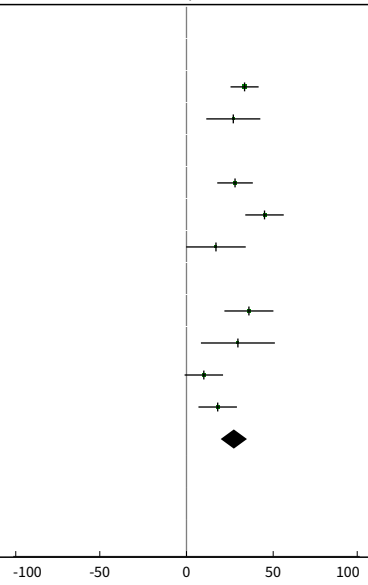
Analysis 6.5. Comparison 6 WMD archive, Outcome 5 % Predicted FEV1.

Study or subgroup	LABA N	LABA Mean(SD)	PLACEBO N	PLACEBO Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
6.5.1 Participants using mixed cointerventions							
Subtotal * **	**0**		**0**				**Not estimable**
Heterogeneity: Not applicable							
Test for overall effect: Not applicable							
6.5.2 Participants not using ICS							
Wronska 1998	13	72.6 (13)	9	76.2 (21.8)		2.66%	-3.6[-19.5,12.3]
Subtotal * **	**13**		**9**			**2.66%**	**-3.6[-19.5,12.3]**
Heterogeneity: Not applicable							
Test for overall effect: Z=0.44(P=0.66)							
6.5.3 Children <12 years							
Stelmach 2002	15	79.8 (16.4)	17	72.4 (12.3)		6.55%	7.45[-2.69,17.59]
von Berg 1998	183	88 (16)	171	85 (17)		56.7%	3[-0.44,6.44]
Weinstein 1998	102	78.9 (16)	105	75.3 (16.6)		34.09%	3.6[-0.84,8.04]
Subtotal * **	**300**		**293**			**97.34%**	**3.51[0.88,6.14]**
Heterogeneity: Tau^2=0; Chi^2=0.67, df=2(P=0.72); I^2=0%							
Test for overall effect: Z=2.62(P=0.01)							
Total * **	**313**		**302**			**100%**	**3.32[0.73,5.91]**
Heterogeneity: Tau^2=0; Chi^2=1.41, df=3(P=0.7); I^2=0%							
Test for overall effect: Z=2.51(P=0.01)							
Test for subgroup differences: Chi^2=0.75, df=1 (P=0.39), I^2=0%							

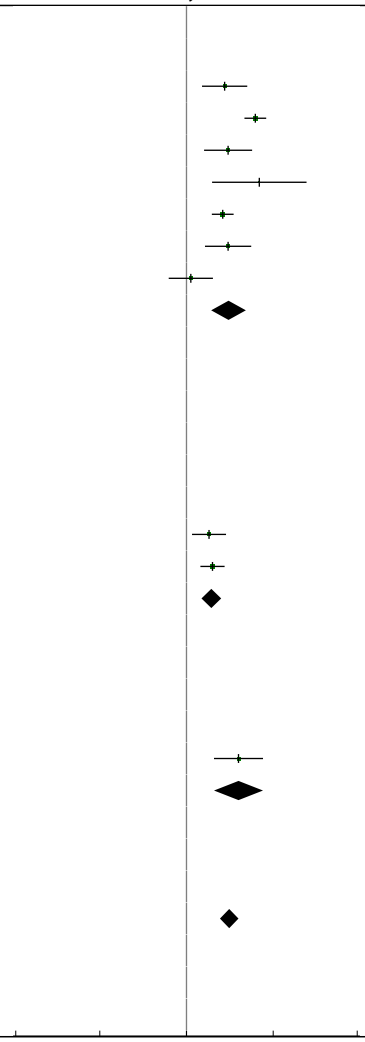


Analysis 6.6. Comparison 6 WMD archive, Outcome 6 Change in PEF morning (l/min).

Study or subgroup	LABA N	LABA Mean(SD)	PLACEBO N	PLACEBO Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
6.6.1 Participants using mixed cointerventions							
Adinoff 1998	117	32.3 (0)	121	4.9 (0)			Not estimable
Busse 1998	261	53.7 (50.9)	272	20.2 (44)		6.35%	33.5[25.4,41.6]
D'Alonzo 1994	87	25 (58)	90	-2 (47)		4.55%	27[11.42,42.58]
Dahl 1991a	131	40 (0)	129	-4 (0)			Not estimable
Kemp 1998a	149	33 (45.2)	152	5 (45.6)		5.83%	28[17.74,38.26]
Lockey 1999	240	47 (62)	234	2 (61.2)		5.63%	45[33.91,56.09]
Pearlman 1992	66	26 (49)	62	9 (50)		4.21%	17[-0.17,34.17]
SAS30004	91	13.2 (0)	89	-15.5 (0)			Not estimable
Schreurs 1996	49	33 (41)	51	-3 (30)		4.89%	36[21.87,50.13]
SMS40221	32	42.6 (50.5)	32	13 (35.1)		3.41%	29.65[8.33,50.97]
Wolfe 2000a	80	22 (35.8)	81	12 (36)		5.63%	10[-1.09,21.09]
Wolfe 2000b	86	23 (37.1)	86	5 (37.1)		5.63%	18[6.91,29.09]
Subtotal * **	**1389**		**1399**			**46.13%**	**27.3[19.72,34.87]**
Heterogeneity: Tau^2=89.77; Chi^2=26.9, df=8(P=0); I^2=70.26%							
Test for overall effect: Z=7.06(P<0.0001)							

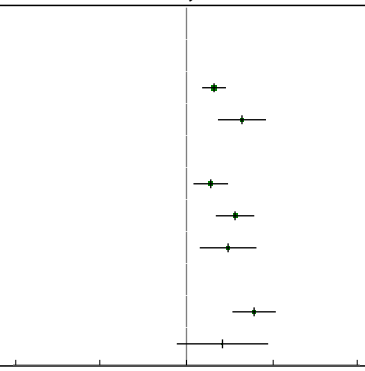


Study or subgroup	LABA N	LABA Mean(SD)	PLACEBO N	PLACEBO Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
6.6.2 Participants not using ICS							
Jones 1994	162	22 (0)	85	3 (0)			Not estimable
Kavuru 2000a	77	-1.7 (42.7)	86	-23.7 (42.1)		5.15%	22[8.96,35.04]
Lazarus 2001	54	21.3 (16.9)	56	-18.4 (16.6)		6.74%	39.7[33.43,45.97]
Nathan 1999	128	36 (56.5)	129	12 (56.8)		4.96%	24[10.15,37.85]
Pearlman 1999a	21	41 (55)	23	-1 (33.6)		2.54%	42[14.76,69.24]
Rosenthal 1999	202	26.2 (35.5)	206	5.3 (28.7)		6.74%	20.9[14.62,27.18]
SAS30003	92	25 (47)	87	1 (44)		5.08%	24[10.67,37.33]
Shapiro 2000b	84	-11.6 (47.7)	90	-14.1 (37)		5.22%	2.5[-10.25,15.25]
Subtotal ***	**820**		**762**			**36.43%**	**24.24[14.23,34.24]**
Heterogeneity: Tau^2=137.67; Chi^2=35.65, df=6(P<0.0001); I^2=83.17%							
Test for overall effect: Z=4.75(P<0.0001)							
6.6.3 Children <12 years							
Bensch 2002	171	40 (0)	176	21 (0)			Not estimable
Simons 1997a	80	41 (0)	80	25 (0)			Not estimable
von Berg 1998	180	56 (40.3)	171	43 (52.3)		5.95%	13[3.2,22.8]
Weinstein 1998	102	25.1 (25.6)	105	10.1 (25.6)		6.6%	15[8.02,21.98]
Subtotal ***	**533**		**532**			**12.54%**	**14.33[8.64,20.01]**
Heterogeneity: Tau^2=0; Chi^2=0.11, df=1(P=0.74); I^2=0%							
Test for overall effect: Z=4.94(P<0.0001)							
6.6.4 Unclear							
SLGA2004	63	42 (47.6)	63	12 (31.8)		4.89%	30[15.87,44.13]
Subtotal ***	**63**		**63**			**4.89%**	**30[15.87,44.13]**
Heterogeneity: Tau^2=0; Chi^2=0, df=0(P<0.0001); I^2=100%							
Test for overall effect: Z=4.16(P<0.0001)							
Total ***	**2805**		**2756**			**100%**	**24.64[19.29,29.99]**
Heterogeneity: Tau^2=100.09; Chi^2=79.62, df=18(P<0.0001); I^2=77.39%							
Test for overall effect: Z=9.03(P<0.0001)							
Test for subgroup differences: Chi^2=9.89, df=1 (P=0.02), I^2=69.65%							



Analysis 6.7. Comparison 6 WMD archive, Outcome 7 Change in PEF evening (l/min).

Study or subgroup	LABA N	LABA Mean(SD)	PLACEBO N	PLACEBO Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
6.7.1 Participants using mixed cointerventions							
Adinoff 1998	117	16.1 (0)	121	0.9 (0)			Not estimable
Busse 1998	258	14 (44.3)	269	-1.9 (35.5)		8.16%	15.9[9.03,22.77]
D'Alonzo 1994	87	29 (47)	90	-3 (47)		5.58%	32[18.15,45.85]
Jones 1994	282	9.9 (0)	145	9.4 (0)			Not estimable
Kemp 1998a	149	15 (42.7)	152	1 (45.6)		6.99%	14[4.02,23.98]
Lockey 1999	240	30 (62)	234	2 (61.2)		6.57%	28[16.91,39.09]
Pearlman 1992	67	26 (47)	63	2 (48)		4.79%	24[7.66,40.34]
SAS30004	91	5.4 (0)	89	-14.3 (0)			Not estimable
Schreurs 1996	49	32 (36)	51	-7 (27)		6.05%	39[26.49,51.51]
SMS40221	32	28.2 (63.2)	32	7.5 (42.3)		2.66%	20.76[-5.59,47.11]



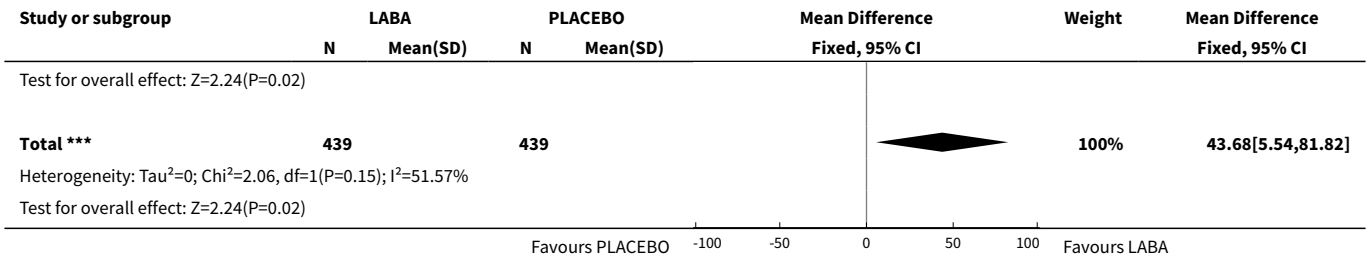
Study or subgroup	LABA N	LABA Mean(SD)	PLACEBO N	PLACEBO Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
Wolfe 2000a	80	14 (35.8)	81	8 (36)		6.57%	6[-5.09,17.09]
Subtotal ***	**1452**		**1327**			**47.38%**	**21.92[14.25,29.59]**
Heterogeneity: Tau²=78.82; Chi²=22.86, df=7(P=0); I²=69.38%							
Test for overall effect: Z=5.6(P<0.0001)							
6.7.2 Participants not using ICS							
Kavuru 2000a	77	-7.4 (45.4)	86	-13.3 (38.6)		5.87%	5.9[-7.12,18.92]
Nathan 1999	128	30 (45.3)	129	16 (68.2)		5.48%	14[-0.15,28.15]
Rosenthal 1999	202	18.7 (29.9)	206	6.4 (28.7)		8.57%	12.3[6.62,17.98]
SAS30003	92	16 (46)	87	3 (42)		5.91%	13[0.1,25.9]
Shapiro 2000b	84	-13.7 (44)	90	-15.8 (41.7)		5.96%	2.1[-10.66,14.86]
Subtotal ***	**583**		**598**			**31.79%**	**10.68[6.37,14.98]**
Heterogeneity: Tau²=0; Chi²=2.9, df=4(P=0.57); I²=0%							
Test for overall effect: Z=4.86(P<0.0001)							
6.7.3 Children <12 years							
Bensch 2002	171	35 (0)	176	19 (0)			Not estimable
Simons 1997a	80	35 (80)	80	25 (0)			Not estimable
von Berg 1998	179	47 (40.1)	170	10 (65.2)		6.44%	37[25.57,48.43]
Weinstein 1998	102	20 (25.2)	105	10.1 (25.6)		8.14%	9.87[2.94,16.8]
Subtotal ***	**532**		**531**			**14.58%**	**23.04[-3.54,49.61]**
Heterogeneity: Tau²=344.77; Chi²=15.83, df=1(P<0.0001); I²=93.68%							
Test for overall effect: Z=1.7(P=0.09)							
6.7.4 Unclear							
SLGA2004	63	29 (36.7)	63	12 (31.8)		6.24%	17[5.02,28.98]
Subtotal ***	**63**		**63**			**6.24%**	**17[5.02,28.98]**
Heterogeneity: Not applicable							
Test for overall effect: Z=2.78(P=0.01)							
Total ***	**2630**		**2519**			**100%**	**17.67[12.62,22.72]**
Heterogeneity: Tau²=69.19; Chi²=51.72, df=15(P<0.0001); I²=71%							
Test for overall effect: Z=6.85(P<0.0001)							
Test for subgroup differences: Chi²=7.07, df=1 (P=0.07), I²=57.57%							

Favours PLACEBO -100 -50 0 50 100 Favours LABA

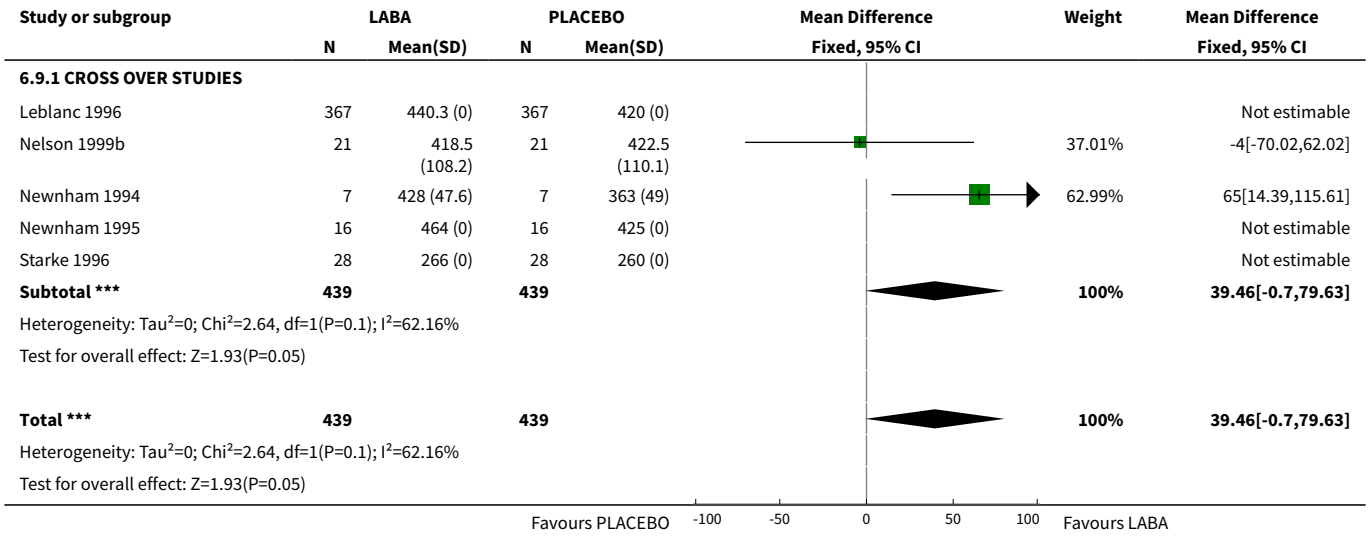
Analysis 6.8. Comparison 6 WMD archive, Outcome 8 Peak expiratory flow: morning l/min (crossover studies).

Study or subgroup	LABA N	LABA Mean(SD)	PLACEBO N	PLACEBO Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
6.8.1 CROSS OVER STUDIES							
Leblanc 1996	367	433.2 (0)	367	405.2 (0)			Not estimable
Nelson 1999b	21	417.2 (105.4)	21	412 (109.1)		34.55%	5.2[-59.68,70.08]
Newnham 1994	7	410 (45)	7	346 (45)		65.45%	64[16.86,111.14]
Newnham 1995	16	451 (0)	16	399 (0)			Not estimable
Starke 1996	28	259 (0)	28	242 (0)			Not estimable
Subtotal ***	**439**		**439**			**100%**	**43.68[5.54,81.82]**
Heterogeneity: Tau²=0; Chi²=2.06, df=1(P=0.15); I²=51.57%							

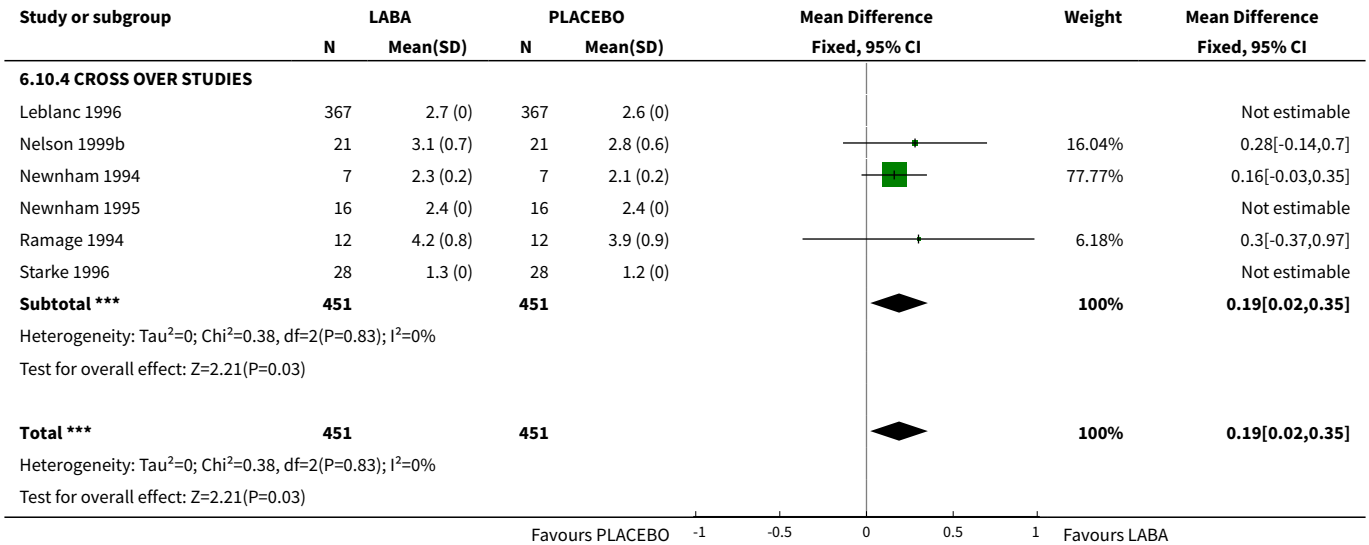
Favours PLACEBO -100 -50 0 50 100 Favours LABA



Analysis 6.9. Comparison 6 WMD archive, Outcome 9 Peak expiratory flow: evening l/min (crossover studies).

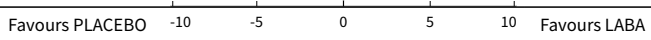


Analysis 6.10. Comparison 6 WMD archive, Outcome 10 FEV1 (litres; crossover studies).



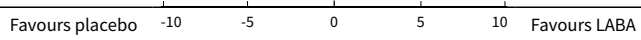
Analysis 6.11. Comparison 6 WMD archive, Outcome 11 AUC- mean area under 12 hr serial FEV1 curve (L-h).

Study or subgroup	LABA N	LABA Mean(SD)	PLACEBO N	PLACEBO Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
6.11.1 Participants using mixed cointerventions							
LaForce 2005	86	5.2 (4.5)	91	1.5 (4.6)		30.26%	3.74[2.4,5.08]
Pleskow 2003	121	6 (6.2)	116	1.7 (6.3)		21.57%	4.3[2.71,5.89]
Wolfe 2000a	73	5.6 (5.1)	67	3 (5.7)		16.73%	2.6[0.79,4.41]
Wolfe 2000b	86	5.8 (6.5)	86	1.3 (6.5)		14.53%	4.5[2.56,6.44]
Subtotal ***	**366**		**360**			**83.09%**	**3.79[2.98,4.6]**
Heterogeneity: Tau²=0; Chi²=2.58, df=3(P=0.46); I²=0%							
Test for overall effect: Z=9.15(P<0.0001)							
6.11.2 Participants not on ICS							
Kavuru 2000a	86	6.4 (6.3)	77	3 (11.2)		6.77%	3.42[0.58,6.26]
Shapiro 2000b	84	4.4 (5)	90	3.3 (10)		10.14%	1.07[-1.25,3.39]
Subtotal ***	**170**		**167**			**16.91%**	**2.01[0.21,3.81]**
Heterogeneity: Tau²=0; Chi²=1.58, df=1(P=0.21); I²=36.55%							
Test for overall effect: Z=2.19(P=0.03)							
6.11.3 Children <12 years							
Subtotal ***	**0**		**0**				**Not estimable**
Heterogeneity: Not applicable							
Test for overall effect: Not applicable							
Total ***	**536**		**527**			**100%**	**3.49[2.75,4.23]**
Heterogeneity: Tau²=0; Chi²=7.28, df=5(P=0.2); I²=31.27%							
Test for overall effect: Z=9.25(P<0.0001)							
Test for subgroup differences: Chi²=3.12, df=1 (P=0.08), I²=67.95%							



Analysis 6.12. Comparison 6 WMD archive, Outcome 12 Mini-AQLQ (total score).

Study or subgroup	LABA N	LABA Mean(SD)	Placebo N	Placebo Mean(SD)	Mean Difference Fixed, 95% CI	Mean Difference Fixed, 95% CI
6.12.1 Participants using mixed cointerventions						
LaForce 2005	71	5.5 (1.1)	67	5.1 (1)		0.37[0.01,0.73]
6.12.2 Participants not using ICS						
6.12.3 Children <12 years						



ADDITIONAL TABLES

Table 1. Studies by description of asthma severity and use of inhaled corticosteroids

Mild	% ICS Mild	Mild to moderate	%ICS M-mod	Moderate to severe	% ICS Mod-sev	Persis-tent/sympto-matic	%ICS Per-sistent	Not reported	NR % ICS
Boulet 1997	0	Bensch 2001	51	Kraft 1997	0	Bensch 2002	70	Adinoff 1998	64
Cheung 1992	0	Booth 1993	73	Shapiro 2000b	0	Busse 1998	65	Busse 2004	64
Clooster-man 2001	0	Boulet 1998	0			Kavuru 2000 a	0	D'Alonzo 1994	22
Jones 1994	42	Creticos 1999	0			Kemp 1998 a	60	Garcia 2001	32
Nelson 1999	0	Dahl 1991 a, b	0			Lazarus 2001	0	Hyland 1994	NK
Prieto 2002	0	Ekstrom 1998 a	80			Lindquist 2003	0	LaForce 2005	60
Rosenthal 1999	0	Ekstrom 1998 b	89			Lockey 1999	62	Nelson 1998	30
Wallin 1999	0	Juniper 1995	77			Nathan 1999	0	Pearlman 1999	0
		Kemp 1999	46			Roberts 1999	0	Ramage 1994	91
		Leblanc 1996	80			SLGA3014	50	SAS3003	0
		Levy 2005	74			Weinstein 1998	57	SAS3004	0
		Majahan 1998	58					SMART	47
		Newnham 1994	70					SMS40221	NK
		Newnham 1995	81					Steffensen 1995	84

Table 1. Studies by description of asthma severity and use of inhaled corticosteroids *(Continued)*

Pearlman 1992	40	Sussman 1995	NK
Pleskow 2003	44	von Berg 2002	82
Schreurs 1996	90	Wronska 1998	0
Simons 1997	0		
SLGA2004	NK		
SLGL82	NK		
SLMP03	0		
Stelmach 2002	0		
Taylor 1998	92		
Von Berg 1998	50		
Wolfe 2000 a,b	30		
Wolfe 2006	58		
Zarkovic 1998	80		

Table 2. Search history

Years	Detail
All years - October 2002	References retrieved: 1362 Unique studies identified and assessed: 196 N failing to meet entry criteria: 111 N included: 85 (94 experimental groups) Total N: 94
October 2002 - October 2005	References retrieved: 1645 Unique studies identified and assessed: 27 N failing to meet entry criteria: N included: Total N:

Table 3. Studies previously included (2003)

Study ID	Reason for exclusion
Akinparli 1999	100% on ICS at baseline
Booth 1996	100% on ICS at baseline
Boulet 1998a	100% on ICS at baseline
Boyd 1995	100% on ICS at baseline
Chuchalin 2002	100% on ICS at baseline
Faurschou 1994	Treatment period < 4 weeks
Fitzgerald 1999	100% on ICS at baseline
Fitzpatrick 1990	Treatment period < 4 weeks
Fuglsang 1998	Treatment period < 4 weeks
Gardiner 1994	100% on ICS at baseline
Grove 1995	100% on ICS at baseline
Jartti 1998	100% on ICS at baseline
Kavuru 2000b	100% on ICS at baseline
Langley 1998	100% on ICS at baseline
Langton Hewer 1995	100% on ICS at baseline
Li 1999	100% on ICS at baseline
Lipworth 1998	100% on ICS at baseline
Lipworth 2000	100% on ICS at baseline

Table 3. Studies previously included (2003) *(Continued)*

McIvor 1998	100% on ICS at baseline
Meijer 1995	100% on ICS at baseline
Nelson 1999a	100% on ICS at baseline
Nielsen 1999	100% on ICS at baseline
Nightingale 2002	100% on ICS at baseline
Norhaya 1999	100% on ICS at baseline
O'Byrne 2001	100% on ICS at baseline
Pauwels 1997	100% on ICS at baseline
Pearlman 1999	Combination therapy versus ICS
Price 2002	100% on ICS at baseline
Russell 1995	100% on ICS at baseline
Self 1998	100% on ICS at baseline
Shapiro 2000a	100% on ICS at baseline
Simons 1997b	100% on ICS at baseline
Tan 1997	100% on ICS at baseline
van der Molen 1996	100% on ICS at baseline
Verberne 1998	100% on ICS at baseline
Wilding 1997	100% on ICS at baseline
Yates 1995	Treatment period < 4 weeks
Yates 1997	Treatment period < 4 weeks

WHAT'S NEW

Date	Event	Description
1 July 2014	Amended	Statement added to abstract and plain language summary to state that the review is no longer to be updated and why. Old material, which has been superseded, has been removed from the review.
1 July 2014	Review declared as stable	LABA is no longer recommended except in addition to ICS. The editorial board of the Cochrane Airways Group in conjunction with the authors of the review have decided not to update the review any more.

Date	Event	Description
		Readers should consult the overviews which summarise the results of Cochrane reviews on the safety of LABAs in adults and children (Cates 2012; Cates 2014).

HISTORY

Protocol first published: Issue 2, 1999
Review first published: Issue 4, 2003

Date	Event	Description
1 August 2008	Amended	Converted to new review format.
10 November 2006	New citation required and conclusions have changed	Substantive amendment

CONTRIBUTIONS OF AUTHORS

Julia Walters carried out initial selection and retrieval of studies, grading, data extraction, correspondence with authors, analyses and writing the first draft of the review.
Haydn Walters assisted with study selection, grading, analyses and writing first and subsequent drafts.
Peter Gibson assisted with protocol development and editorial revision of drafts of the review.
Toby Lasserson assisted with the 2006 update of the review, by extracting, entering and analysing data, converting estimates from WMD to GIV outcomes where appropriate, imputing standard deviations and writing up the results.

DECLARATIONS OF INTEREST

E H Walters has taken part in collaborative clinical pharmacology studies with a number of pharmaceutical companies including GSK, Astra Zeneca, Pfizer, Boehringer, Schering Plough, SKB, and Novartis. He has, in the past, held consultancies with GSK, Pfizer and Zeneca. He has had sponsorship to meetings from a number of the companies listed over the past 15 years. PG Gibson has taken part in collaborative clinical studies with a number of pharmaceutical companies including GSK, AstraZeneca, Boerhinger Ingelheim, and Aventis. He has attended meetings sponsored by a number of companies.

SOURCES OF SUPPORT

Internal sources

- No sources of support supplied

External sources

- Commonwealth Department of Health and Aging, Australia.

NOTES

The US Food and Drug Agency (FDA) has added a warning that LABA should not be used to treat asthma without concurrent ICS. Therefore we have decided not to carry out any further updates to this review.

INDEX TERMS

Medical Subject Headings (MeSH)

Adrenergic beta-Agonists [adverse effects] [*therapeutic use]; Albuterol [analogs & derivatives] [*therapeutic use]; Asthma [*drug therapy]; Bronchodilator Agents [*therapeutic use]; Chronic Disease; Ethanolamines [*therapeutic use]; Quality of Life; Randomized Controlled Trials as Topic

MeSH check words

Adult; Child; Humans