Long-acting beta2-agonists versus anti-leukotrienes as add-on therapy to inhaled corticosteroids for chronic asthma (Review)

Ducharme FM, Lasserson TJ, Cates CJ

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ABSTRACT

Background
Patients who continue to experience asthma symptoms despite taking regular inhaled corticosteroids (ICS) represent a management challenge. Leukotriene receptor antagonists (LTRA) and long-acting β2-agonists (LABA) agents may both be considered as add-on therapy to inhaled corticosteroids (ICS).

Objectives
We compared the efficacy and safety profile of adding either daily LABA or LTRA in asthmatic patients who remained symptomatic on ICS.

Search strategy
The Cochrane Airways Group Specialised Register was searched for randomised controlled trials up to and including March 2006. Reference lists of all included studies and reviews were screened to identify potentially relevant citations. Inquiries regarding other published or unpublished studies supported by the authors of the included studies or pharmaceutical companies who manufacture these agents were made. Conference proceedings of major respiratory meetings were also searched.

Selection criteria
Only randomised controlled trials conducted in adults or children with recurrent asthma where a LABA (for example, salmeterol or formoterol) or LTRA (for example, montelukast, pranlukast, zafirlukast) was added to ICS for a minimum of 28 days were considered for inclusion. Inhaled short-acting β2-agonists and short courses of oral steroids were permitted as rescue medications. Other daily asthma treatments were permitted, providing the dose remained constant during the intervention period. Two reviewers independently reviewed the literature searches.

Data collection and analysis
Data extraction and trial quality assessment were conducted independently by two reviewers. Whenever possible, primary study authors were requested to confirm methodology and data extraction and to provide additional information and clarification when needed. Where necessary, expansion of graphic reproductions and estimation from other data presented in the paper was performed.

Main results
Fifteen randomised controlled trials met the inclusion criteria; eleven trials including 6,030 participants provided data in sufficient detail to permit aggregation. All eleven trials pertained to adults with moderate airway obstruction (% predicted FEV1 66-76%) at baseline. Montelukast (n=9) or Zafirlukast (n=2) was compared to Salmeterol (n=9) or Formoterol (n=2) as add-on therapy to 400-565 mcg of beclomethasone or equivalent. Risk of exacerbations requiring systemic corticosteroids was significantly lower with LABA+ICS when compared to LTRA+ICS (RR= 0.83, 95% Confidence Interval (95%CI): 0.71, 0.97): the number needed to treat with LABA compared to LTRA, to prevent one exacerbation over 48 weeks, was 38 (95% CI: 23 to 247).
The following outcomes also improved significantly with the addition of LABA compared to LTRA to inhaled steroids (Weighted Mean Difference; 95% CI): morning PEF (16 L/min; 13 to 18), evening PEF (12 L/min; 9 to 15), FEV1 (80 mL; 60 to 100), rescue-free days (9%: 5% to 13%), symptom-free days (6%: 2 to 11), rescue β2-agonists (-0.5 puffs/day; -0.2 to -1), quality of life (0.1: 0.05 to 0.2), symptom score (Standard Mean Difference -0.2; -0.1 to -0.3), night awakenings (-0.1/week; -0.06 to -0.2) and patient satisfaction (RR 1.12; 1.07 to 1.16). Risk of withdrawals due to any reason was significantly lower with LABA+ICS compared to LTRA+ICS (Risk Ratio 0.83, 95% CI 0.73 to 0.95). Withdrawals due to adverse events or due to poor asthma control, hospitalisation, osteopenia, serious adverse events, overall adverse events, headache or cardiovascular events were not significantly different between the two study groups.

Authors’ conclusions
In asthmatic adults inadequately controlled on low doses of inhaled steroids, the addition of LABA is superior to LTRA for preventing exacerbations requiring systemic steroids, and for improving lung function, symptoms, and the use of rescue β2-agonists.

PLAIN LANGUAGE SUMMARY
Patients who continue to experience asthma symptoms despite taking regular inhaled corticosteroids represent a management challenge. In these patients it is not clear whether the addition of a long-acting inhaled bronchodilator (formoterol or salmeterol) would provide any additional benefit when compared to adding a oral anti-leukotriene agent (zafirlukast or montelukast). This review of eleven good quality randomised controlled trials has shown that the addition of long-acting bronchodilator provides significantly greater protection against exacerbations, greater improvement in lung function, and modest additional improvement in symptoms, use of rescue medication, quality of life and satisfaction as compared to the use of anti-leukotrienes. Thirty eight patients, experiencing asthma symptoms despite taking regular inhaled corticosteroids (ICS), need to be treated for 48 weeks with additional long-acting bronchodilators rather than with additional anti-leukotriene agents to prevent one exacerbation.

BACKGROUND
Leukotrienes are inflammatory molecules that are one of several substances released by mast cells during the immediate response to inhaled allergen. They are derived from arachidonic acid, the precursor of prostaglandins (Wasserman 1988; Wenzel 1997). There are two families of leukotrienes. Leukotriene B4 acts primarily in conditions in which inflammation is dependent on neutrophils, such as cystic fibrosis, inflammatory bowel disease, and psoriasis. The second group (C4, D4, E4), called cysteinyl-leukotrienes, bind to highly selective receptors to induce eosinophil- and mast cell-induced bronchoconstriction and inflammation associated with asthma (Davis 1997). Drugs that can interfere with the production (leukotriene synthesis inhibitors) and activity (leukotriene receptor antagonists) of leukotrienes have been designed. Leukotriene synthesis inhibitors (e.g. zileuton) inhibit the enzyme 5-lipoxygenase thus blocking the production of many leukotrienes (e.g. B4, C4, D4, and E4) (Georgitis 1999). Leukotriene (cysteinyl) receptor antagonists (e.g. montelukast, zafirlukast, pranlukast) block leukotriene D4 (LTD4) receptors (Georgitis 1999). Both types of leukotriene modifiers are administered orally as tablets. Two Cochrane reviews have concluded that LTRA are mild anti-inflammatory agents when used as monotherapy (Ducharme 2004a) and bring modest benefit as add-on therapy to inhaled steroids (Ducharme 2004).

Long acting β2-agonists (LABA) has similar mode of action to that of short acting β2-agonists. Some LABAs may have a slightly slower onset of action (Lotvall 1996) than short-acting β2-agonist but display prolonged activation of β2-receptors (Johnson 1995) in bronchial smooth muscle resulting in prolonged duration of action for up to 12 hours (Rees 1995). LABA is recommended solely as add-on therapy to inhaled corticosteroids (ICS) in patients with moderate to severe asthma who remain symptomatic despite anti-inflammatory therapy (BTS 2003; GINA 2005; Lemiere 2004).

People with asthma who continue to experience symptoms despite taking regular ICS represent a management challenge. Both leukotriene receptor antagonists (LTRA) and LABA agents may be considered as add-on therapy to ICS. There are several reasons to support the synergistic effect of either combination therapy at the cellular or the pathophysiology level. LABA reduces airway hyper-responsiveness by means of functional antagonism (Lipworth 2002) while corticosteroids increased expression of β2-adrenergic receptors (Baraniuk 1997): a good combination for synergistic effect. LTRA inhibits the production of cysteinyl leukotrienes, important pro-inflammatory mediators in asthma that are unaffected by steroid treatment; they are particularly effective in allergen-, exercise-, and aspirin-induced asthma (Krawiec 2002). Thus both the addition of leukotriene receptor antagonists or long-acting β2-agonist could potentiate the anti-inflammatory effect of inhaled corticosteroids and lead to better asthma control. The current review compares the relative benefits and safety profile of adding either an LTRA or a LABA to patients with asthma who are...
inadequately controlled by ICS, and updates a previous Cochrane review (Ram 2005).

**OBJECTIVES**

To compare the safety and efficacy of adding LABA versus LTRA in asthmatic patients who remain symptomatic in spite of regular treatment with ICS. More specifically, we wish to examine the impact on asthma exacerbations, lung function, symptoms, quality of life, adverse health events, and withdrawals.

**CRITERIA FOR CONSIDERING STUDIES FOR THIS REVIEW**

**Types of studies**

Only randomised controlled trials (RCT) conducted in adults and/or in children in whom a long-acting β2-agonist (LABA) or leukotriene receptor antagonist (LTRA) were added to ICS were considered for inclusion.

**Types of participants**

Children or adults with recurrent or persistent asthma

**Types of intervention**

Interventions included LABA (e.g., salmeterol or formoterol) or LTRA (e.g., montelukast, pranlukast, zafirlukast or zileuton). Participants may or may not have been steroid-naive prior to the onset of the study. During the study, all participants were required to be on a stable dose of ICS throughout the treatment period. The intervention must have been administered for a minimum of 28 days. Inhaled short-acting β2-agonists and short courses of oral steroids were permitted as rescue interventions. Other asthma medications such as xanthines and inhaled anticholinergic were permitted, provided the dose remained constant during the intervention period.

**Types of outcome measures**

*Primary outcome*

Number of patients with asthma exacerbations requiring short courses of systemic corticosteroids.

*Secondary outcomes*

(1) Other measures of severity of exacerbations, such as hospital admissions.

(2) Measures reflecting chronic asthma control such as changes in pulmonary function tests, symptom scores, days and/or nights without symptoms, quality of life, use of rescue fast-acting β2-agonists, and patient satisfaction.

(3) Changes in measures of inflammation such as eosinophilia, serum eosinophil cationic protein and sputum eosinophils were also considered.

(4) Adverse effects including rates of clinical and biochemical adverse effects and withdrawal rates.

**SEARCH METHODS FOR IDENTIFICATION OF STUDIES**

See: methods used in reviews.

Trials were identified using the Cochrane Airways Group Specialised Register of trials (searched up to March 2006), which is derived from systematic searches of bibliographic databases including the Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE, EMBASE and CINAHL, and handsearching of respiratory journals and meeting abstracts. All records in the Specialised Register coded as ‘asthma’ were searched using the following terms:

(((beta* AND agonist*) AND long-acting OR “long acting”) OR ((beta* AND adrenergic*) AND long-acting OR “long acting”) OR (bronchodilat* AND long-acting OR “long acting”) OR (beta2 or formoterol OR eformoterol OR advair OR symbicort))

AND

((steroid* OR glucocorticoid* OR corticosteroid*) AND inhal*)

OR (budesonide OR beclomethasone OR fluticasone OR triamcinolone OR flunisolide))

AND

(leucotrien* OR leukotrien* OR anti-leukotrien* OR anti-leucotrien* OR *lukast)

An additional search of CENTRAL was completed using the above search strategy. Reference lists of all included studies and reviews were reviewed to identify potentially relevant citations. Inquiries regarding other published or unpublished studies supported by the authors of the included studies or pharmaceutical companies who manufacture these agents was made. Abstract books of the ATS and ERS from 1998 until 2005 were also searched.

**METHODS OF THE REVIEW**

**Selection of trials**

From the title, abstract or descriptors, two reviewers independently scanned the literature searches. All studies that were clearly not RCTs or that clearly did not fit the inclusion criteria were excluded. All other citations were reviewed in full text by two reviewers independently, assessing for inclusion based on population, intervention, study design and outcome. Search of bibliographies of articles retrieved in full were conducted to identify any additional studies.

**Assessment of methodological quality**

Studies to be included underwent quality assessment, performed independently by two reviewers, using the Cochrane approach to
assessments of allocation concealment and the scale described by Jadad et al (Jadad 1996).

Trials were scored using the following principles:
- Grade A: Adequate concealment
- Grade B: Uncertain or unclear concealment
- Grade C: Clearly inadequate concealment using non-random procedures (e.g. alternation).

Data extraction
Data for the trials were extracted by two reviewers and entered into the Cochrane Collaboration software program, Review Manager (RevMan), Version 4.2.7. Where necessary, expansions of graphic reproductions and estimations from other data presented in the paper were performed.

Whenever possible, primary study authors were requested to confirm methodology and data extraction as well as to provide additional information and clarification if needed.

Statistical considerations
All included trials were combined using the RevMan 4.2.6. For dichotomous variables, individual and pooled statistics were calculated as relative risk (RR) with 95% confidence intervals (95%CI). For continuous outcomes, individual and pooled statistics were calculated as weighted mean differences (WMD) or standard mean differences (SMD) with 95%CI. Number Needed to Treat (NNT) was calculated using Visual Rx (a web based program available via www.nntonline.net) Cates 2002. Odds ratios were used for NNT as the results are not affected by the programme available via www.nntonline.net) Cates 2002. Odds ratios were used for NNT as the results are not affected by the selection of the reference treatment (LABA or LTRA), and in view of the different duration of the trials the pooled odds ratio was applied to the average exacerbation rate in the longer trials to give an NNT for 48 weeks of treatment.

Heterogeneity of effect sizes between studies being pooled was suggested by an I² value > 25%, a random-effects model was applied to the summary estimates and was reported in the results. Subgroup analyses were planned to explore possible effect modification associated with a priori identified variables and/or to explore the cause of heterogeneity of study results, if any, for the main outcome. Difference in the magnitude of effect attributable to these subgroups was examined with the residual Chi square test from the Odds Ratios (Deeks 2001).

A priori defined subgroups included:
1. Dose and type of long-acting β₂-agonist (salmeterol, formoterol)
2. Dose and type of anti-leukotrienes (montelukast, pranlukast, zafirlukast, zileuton)
3. Dose and type of inhaled glucocorticoids (in beclomethasone-equivalent)
4. Children versus adults
5. Baseline severity of airway obstruction based on the % predicted FEV1 (or PEF) (severe: <60%, moderate: 61% to <80%, mild: ≥80%) GINA 2005
6. Single vs two inhaler devices used to deliver LABA+ICS (added after publication of the protocol).

In the protocol published in April 2001, we had planned to examine the impact of the inhaled glucocorticoids (subgroups 3) and of baseline severity (subgroups 5) as sensitivity analyses but changed it to subgroup analyses because it enhanced the clarity of interpretation. The last subgroup analysis (6), not initially considered in 2001, was added to the list subsequently as recent data indicated that the number of inhaler devices to deliver LABA + ICS might be an important effect modifier (Nelson 2003).

For the main outcome, we planned to perform the following sensitivity analyses to investigate the potential effect of study duration (≤12 weeks, >12 weeks), methodological quality (Jadad’s score <3 vs. ≥4), publication bias, and funding bias (trials funded by producers of LABA, studies funded by producers of LTRA, independently-funded studies) on the study results. Funnel plots were used to test for the presence of publication and other biases for trials contributing data to the main outcomes (Egger 1997). All estimates were reported with their 95% confidence interval.
was moderate, ranging from 66 to 76% predicted FEV₁ doses were reported). The severity of airway obstruction at baseline rofluorocarbon-propelled beclomethasone or equivalent (when 2001; Ringdal 2003; Storms 2004), two unpublished full-text re-
ports (Hultquist 2000; McCarthy 2003) and four abstracts (Green (abs) 2002; Hendeles 2004; Nsouli 2001; Stelmach 2005). The abstracts did not provide data in sufficient detail to contribute to the meta-analyses.

Therefore, the description hereafter pertained to eleven trials which contributed data from 6,030 patients to the meta-analysis. Four of the included trials had more than one published citations for their study, which are listed as secondary citations with the key or primary citation marked with an asterisk (Bjermer 2003 = 3 add-
tional citations; Fish 2001 = 4 additional citations; Grosclaude 2003 = 1 additional citation; McCarthy 2003 = 1 additional ci-
tation; Nelson 2000 = 5 additional citations; Nelson 2001 = 3 additional citations and Ringdal 2003 = 6 additional citations).

Design
The eleven studies were randomised, parallel-group, trials.

Participants
Ten trials focused on adults with mean age ranging from 35 to 44 years, with similar gender representation and mean asthma duration ranging from 10 to 26 years. One study recruited children (Stelmach 2005). Most trials (Bjermer 2003; Ceylan 2004; Grosclaude 2003; Fish 2001; Ilowite 2004; Nelson 2000; Ringdal 2003; Storms 2004) allowed the inclusion of adolescents aged > = 15 years (or > = 12 years for Hultquist 2000 and Nelson 2001) although the number of teenagers randomised, if any, was not re-
ported. All but one trial clearly specified that participants could not be steroid-naïve, the remaining study failed to comment on this issue (Nelson 2001). Subjects were symptomatic at enrolment de-
spite inhaled steroids at the doses of ≤400 to 560 mcg/day of chlo-
rofluorocarbon-propelled beclomethasone or equivalent (when doses were reported). The severity of airway obstruction at baseline was moderate, ranging from 66 to 76% predicted FEV₁ (Bjermer 2003; Ceylan 2004; Ilowite 2004; Hultquist 2000; Ilowite 2004; McCarthy 2003; Nelson 2000; Nelson 2001; Ringdal 2003). Allergic triggers were reported in one study (Bjermer 2003) where 65% of participants were affected. Bjermer 2003; Ceylan 2004 and Grosclaude 2003 reported that 60%; 65% and 51% respec-
tively participants suffered from allergic rhinitis.

Intervention
The intervention period (reported in weeks as “User defined” or-
der) varied between four weeks (Nelson 2001; Storms 2004), eight weeks (Hultquist 2000), 12 weeks (Fish 2001; Grosclaude 2003; McCarthy 2003; Nelson 2000; Ringdal 2003) and 48 weeks of duration (Bjermer 2003; Ilowite 2004). During the intervention period, all participants remained on a stable dose of inhaled glu-
cocorticoids of average 400 to 560 mcg/day of beclometasone or equivalent (Ceylan 2004; Fish 2001; Hultquist 2000; Nelson 2001), including 200-500 mcg/day of fluticasone (Bjermer 2003; Grosclaude 2003; Ilowite 2004; McCarthy 2003; Nelson 2000; Ringdal 2003). One trial (Nelson 2001) failed to report the dose of inhaled glucocorticoids to which either intervention was added.

The LABA used were: salmeterol 50 mcg twice daily (Hultquist 2000; Nelson 2001) and montelukast 10 mg once daily (Bjermer 2003; Ceylan 2004; Fish 2001; Grosclaude 2003; Ilowite 2004; McCarthy 2003; Nelson 2000; Ringdal 2003; Storms 2004).

The LABA used were: salmeterol 50 mcg twice daily in seven trials (Bjermer 2003; Fish 2001; Grosclaude 2003; Ilowite 2004; McCarthy 2003; Nelson 2000; Nelson 2001; Ringdal 2003; Storms 2004) and formoterol 12 mcg twice daily in the remaining two trials (Ceylan 2004; Hultquist 2000). In three trials, the combi-
nation therapy (Seretide®) was administered in a single device (Grosclaude 2003; McCarthy 2003; Nelson 2000; Ringdal 2003) while it was delivered as separate inhaler devices in the remain-
ing trials (Bjermer 2003; Ceylan 2004; Fish 2001; Ilowite 2004; Hultquist 2000; Nelson 2001; Storms 2004).

Outcomes
The primary outcome (the number of participants with exacer-
bations requiring systemic corticosteroids) was documented in six trials (Bjermer 2003; Fish 2001; Ilowite 2004; Nelson 2000; Nel-
sion 2001; Ringdal 2003). Other measures of asthma control (e.g., pulmonary function tests, symptoms, use of rescue β2-agonist, quality of life), withdrawals and adverse effects were reported by several included studies. Standard or modified intention-to-treat analyses data were reported or obtained from all but two trial (Nel-
sion 2001; ).

METHODOLOGICAL QUALITY

The eleven trials contributing data to the meta-analysis had high reported methodological quality with a Jadad score of 5 for eight trials (Bjermer 2003; Fish 2001; Ilowite 2004; McCarthy 2003; Nelson 2000; Nelson 2001; Ringdal 2003; Storms 2004), 4 for Hultquist 2000, and 2 for Ceylan 2004; Grosclaude 2003. Three abstracts contributing no data in sufficient details for the meta-
analyses scored 2 (Green (abs) 2002; Hendeles 2004; Stelmach 2005) one study scored 1 (Nsouli 2001), respectively on the Jadad score. The overall methodological quality of studies contributing data was excellent.

Randomisation: Randomisation was clearly described and appropriate in all trials with the exception of three trials (Ceylan 2004; Grosclaude 2003; Hultquist 2000) contributing data to the review and the four ab-
stracts not contributing data in sufficient details to be meta-anal-
ysed (Green (abs) 2002; Hendeles 2004; Nsouli 2001; Stelmach 2005).

Blinding: Twelve trials reported double-blinding while Ceylan 2004; Grosclaude 2003 and Nsouli 2001 were open-labelled. Nine double-blind trials reported the use of double-dummies to maintain
allocation concealment; while three trial failed to clearly report means of blinding (Green (abs) 2002; Hendele 2004; Stelmach 2005).

The methodology was confirmed by the authors of all trials contributing data with the exception of Ceylan 2004; Grosclaude 2003 and Storms 2004. No confirmation was obtained for four trials reported as abstracts (Green (abs) 2002; Hendele 2004; Nsouli 2001; Stelmach 2005).

Withdrawal rate was described in all but the two studies reported as abstracts (Green (abs) 2002; Nsouli 2001). Although total withdrawals were reported in Ceylan 2004, it was not clear how many participants from each group withdrew. Withdrawal rates varied from 8 to 17% in the LTRA group and 5 to 27% in the LABA group.

RESULTS

Primary outcome
Exacerbations requiring oral corticosteroids [Comparison 01:01]
Six trials with 5,571 patients (Bjermer 2003; Fish 2001; Ilowite 2004; Nelson 2000; Nelson 2001; Ringdal 2003) contributed data towards the primary outcome. The risk of having an exacerbation requiring systemic corticosteroids was 17% lower with the use of LABA+ICS compared to LTRA+ICS (RR 0.83; 95%CI 0.71 to 0.97). The addition of LABA lowered from 11% to 9% the risk of exacerbation, a 2% (95% CI: 0 to 3%) risk difference in the rate of patients with exacerbation requiring systemic steroids over the use of LTRA. The results were homogeneous despite the different LABAs andLTRAs used. We are unable to rule out systematic bias as visual inspection of funnel plot showed asymmetry (Figure 01) and suggests a lack of small studies favouring LTRA. However, the results of the funnel plot failed to confirm systemic bias as the graph line intercept was -1.01 with a 95% CI of -4.23 to 2.10. The fail-safe N (the number of unpublished studies with null results needed to negate the current findings) was nine trials. The number of patients who must be treated with the combination of LABA and ICS instead of LTRA and ICS to prevent one exacerbation over 48 weeks is 38 (95% CI: 23, 247), Figure 02.

Although, there was no heterogeneity between trials, we had planned a priori to perform subgroup analyses on the following variables to explore their possible influence of the magnitude of effect (effect modification). The sub-group comparison between single and combined inhalers was added after publication of the protocol as a result of work published on this topic subsequently (Nelson 2003).

1. Type of LABA: All included studies contributing data towards the meta-analysis used salmeterol as the LABA except one (Hultquist 2000) that used formoterol. This study using formoterol did not contribute any data towards the primary outcome measure, therefore we were unable to observe any possible effect of the type of LABA on asthma exacerbations.

2. Type of LTRA: The type of anti leukotriene used in the included trials did not appear to make a difference on the primary outcome. Indeed the relative risk of exacerbations when LABA+ICS was compared to Montelukast+ICS and Zafirlukast+ICS was 0.83 (95%CI: 0.71 to 0.97) and 0.86 (95%CI 0.29 to 2.52), respectively. There was no statistical difference between the two sub-groups. The P2 values for both the Montelukast subgroup and the overall estimate were low (24.7% and 5.9%, respectively).

3. Dose and type of inhaled glucocorticoids (in beclomethasone-equivalent doses): All six studies included in the primary outcome were reported to have used similar doses of inhaled glucocorticoids ranging from 400 to 565 mcg/day. The same type of ICS was used by four studies (Bjermer 2003; Ilowite 2004; Nelson 2000; Ringdal 2003) each using fluticasone). Fish 2001 used a variety ICS as the authors kept patients on their usual ICS. We were unable to obtain details of the use of ICS in the Nelson 2001 study. Due to the similarity in dose and type of ICS used by majority of the studies a subgroup analyses was not possible based on type and dose of steroid used.

4. Children versus adults: Since the pediatric trial did not contribute any outcome data to this review, the effect of children versus adults could not be examined.

5. Baseline severity of airway obstruction: As the studies pertained to patients with moderate airway obstruction and were relatively homogeneous in the average baseline FEV1 (all within 66% to 76% of predicted), subgroup analyses on baseline severity could not be examined.

6. Single versus two inhaler devices used to deliver LABA+ICS [Comparison 02:01]: Three of the trials included in the review used combination or single inhaler device to deliver LABA+ICS (McCarnthy 2003; Nelson 2000; Ringdal 2003). However, only two of these contributed data towards the primary outcome (Nelson 2000; Ringdal 2003). The remaining four studies (Bjermer 2003; Fish 2001; Ilowite 2004; Nelson 2001) used two separate inhalers. Use of a single inhaler provided greater protective against exacerbations (RR 0.49; 95%CI: 0.29 to 0.82) than use of separate inhalers (RR 0.89; 95%CI: 0.75 to 1.04). The difference in the magnitude of effect, attributable to the number of inhaler devices, was statistically significant (Chi square = 4.40 (1 df), P<0.05, tested on Peto Odds Ratio). It should be noted that these comparisons are indirect, so it is not certain that the differences found are attributable to the number of inhalers used, rather than other patient or study characteristics.

7. Study duration, funding source or methodological quality
The direction and magnitude of effect was not markedly altered by restricting analyses to trials with long intervention periods (Bjermer 2003; Ilowite 2004; both 48 weeks long) (RR 0.88; 95%CI: 0.74 to 1.04), or to those that were funded by producers.
of LTRA (Bjermer 2003; Ilowite 2004: both studies funded by Merck Frosst) (RR 0.88; 95%CI: 0.74 to 1.04). Due to the high reported methodology in all trials contributing data, a sensitivity analysis based on methodological quality was not possible.

**Secondary outcomes**

**Morning PEF (L/min) - change from baseline [Comparison 01:02]**
Ten studies with 5,669 patients reported morning PEF (Bjermer 2003; Ceylan 2004; Fish 2001; Grosclaude 2003; Hultquist 2000; Ilowite 2004; McCarthy 2003; Nelson 2000; Nelson 2001; Ringdal 2003). Salmeterol+ICS showed significantly greater improvement in PEF when compared to Montelukast+ICS (WMD 15.59 L/min; 95%CI: 12.93 to 18.26) and when compared to Zafirlukast+ICS (WMD 13.70 L/min; 95%CI: 6.65 to 20.75). One study reported data on a comparison between formoterol and montelukast (Ceylan 2004). When all studies were combined to provide an overall estimate, LABA+ICS significantly improved morning PEF compared to LTRA+ICS (WMD 15.66 L/min; 95%CI: 13.21 to 18.11).

Findings from a Cochrane review assessing FP versus BDP at half the nominal dose reported a significant difference in favour of FP in the change from baseline in morning PEF (Adams 2005). Although the addition of Grosclaude 2003 did not introduce significant heterogeneity, we nevertheless conducted a sensitivity analysis by removing Grosclaude 2003 from the analysis, which resulted in a mean group difference of 15.79L/min; 95% CI 13.28 to 18.30. The similarity of results with and without Grosclaude 2003 underscores the robustness of the pooled effect estimate for this outcome and confirms that the group difference observed is due to the different of LABA and LTRA and is not affected by the different inhaled steroids used in the two arms of Grosclaude 2003.

**Evening PEF (L/min) - change from baseline [Comparison 01:03]**
Nine studies with 3,958 patients reported evening PEF (Ceylan 2004; Fish 2001; Grosclaude 2003; Hultquist 2000; Ilowite 2004; McCarthy 2003; Nelson 2000; Nelson 2001; Ringdal 2003). LABA+ICS improved evening PEF when compared to Montelukast+ICS (WMD 12.40 L/min; 95%CI: 9.24 to 15.57) and when compared to Zafirlukast+ICS (WMD 9.35 L/min; 95%CI: 2.33 to 16.37). One study reported data on a comparison between formoterol and montelukast (Ceylan 2004). The combined overall estimate significantly favoured LABA+ICS (WMD 12.09 L/min; 95%CI: 9.26 to 14.92).

**FEV1 (L) - change from baseline [Comparison 01:04]**
Seven studies with 4,445 patients reported FEV1 (Bjermer 2003; Hultquist 2000; Ilowite 2004; McCarthy 2003; Nelson 2000; Nelson 2001; Ringdal 2003). LABA+ICS improved FEV1 compared to Montelukast+ICS (WMD 0.08 L; 95%CI: 0.06 to 0.11). No significant difference was seen when LABA+ICS was compared to Zafirlukast+ICS (WMD 0.05 L; 95%CI -0.02 to 0.12). However, there was no significant difference between the two subgroups, and the combined overall estimate for improvement in FEV1 was significantly in favour of LABA+ICS (WMD 0.08 L; 95%CI: 0.06 to 0.10).

**FEV1 (%) change from baseline [Comparison 01:05]**
Ceylan 2004 reported a significant change in favour LTRA (N = 40).

**FEV1 (%) predicted - end of treatment**
Ceylan 2004 reported no significant difference between the two treatments (N = 40).

**FEV1 (%) fall post-exercise - change from baseline**
Ceylan 2004 reported no significant difference between the two treatments (N = 40).

**Rescue free days % [Comparison 01:08]**
Four studies with 2,371 patients reported percentage of days patients were free from using rescue medication (Fish 2001; Nelson 2000; Nelson 2001; Ringdal 2003). LABA+ICS showed increase in percentage of days with no rescue medication use when compared to Montelukast+ICS (WMD 6.83%; 95%CI: 3.70 to 9.97). Only one study comparing LABA+ICS with Zafirlukast+ICS reported days with no rescue medication use (WMD 15.00; 95%CI: 9.43 to 20.57). The combined overall estimate showed significantly greater percentage rescue free days when using LABA+ICS (WMD 8.96%; 95%CI: 4.39 to 13.53. Random effects model), but there was significant heterogeneity in this pooled estimate (I^2 = 61%), with a significant difference between the two subgroups (Chi square =6.26, df=1, P<0.05).

**Rescue medication use (puffs/day) - change from baseline [Comparison 01:09]**
Seven studies with 4,055 patients reported rescue medication usage (Ceylan 2004; Fish 2001; Hultquist 2000; Ilowite 2004; Nelson 2000; Nelson 2001; Ringdal 2003). Four studies (Fish 2001; Ilowite 2004; Nelson 2000; Ringdal 2003) compared LABA+ICS with Montelukast+ICS and showed decreased use of rescue medication with LABA+ICS (WMD -0.37 puffs/day; 95%CI -0.56 to -0.19). Two studies comparing LABA+ICS with Zafirlukast+ICS also showed significant decrease in rescue medication use with LABA+ICS (WMD -0.36 puff/day; 95%CI -0.72 to 0.00). Ceylan 2004 reported a significant difference in favour of formoterol+ICS versus montelukast+ICS. The combined overall estimate showed significant decrease in the use of rescue medication with LABA+ICS (WMD -0.49 puffs/day; 95%CI: -0.75 to -0.24). Random effects modelling was used for this outcome as I^2 was 79.4%.

**Change in Global asthma quality of life score (higher score is better) - change from baseline [Comparison 01:10]**
Three studies with 2,893 patients reported Global asthma quality of life scores (Bjermer 2003 & Ilowite 2004 using Montelukast & Nelson 2001 using Zafirlukast). LABA+ICS was significantly better than both Montelukast+ICS (WMD 0.09; 95%CI 0.03 to 0.16) and Zafirlukast+ICS (WMD 0.19; 95%CI 0.02 to 0.36), however the latter only included one study. The overall estimate
showed improvement in Global asthma quality of life with LABA+ICS, (WMD 0.11; 95%CI: 0.05 to 0.17).

**Symptom free days (%) - change from baseline [Comparison 01:11]**

Five studies with 2,626 patients reported symptom free days (Fish 2001; Grosclaude 2003; Nelson 2000; Nelson 2001; Ringdal 2003). Four studies compared LABA+ICS with Montelukast+ICS which showed increased percentage of days symptom free with LABA+ICS (WMD 4.22%; 95%CI 1.8 to 9.05). One study using Zafirlukast also reported increased percentage of symptom free days with LABA+ICS (Mean Difference 11.00, 95% CI 6.10 to 15.90). The combined overall estimate showed a significant increase in the percentage of symptom free days in favour of LABA+ICS (WMD 6.75%; 95%CI 3.11 to 10.39). Random Effects modelling was used as there was significant heterogeneity in the Montelukast subgroup (I² = 25% and overall (I²=46.1%).

**Night-time symptom score (5 point scale, higher score is worse) - change from baseline [Comparison 01:12]**

One study with 429 patients reported improvement in night-time symptom score with LABA+ICS when compared to LTRA+ICS (Nelson 2001).

**Day-time symptom scores (high score is worse) - change from baseline [Comparison 01:13]**

Five studies with 3,823 patients reported day-time symptom scores (Fish 2001; Ilowite 2004; Nelson 2000; Nelson 2001; Ringdal 2003). Four of the studies comparing LABA+ICS to Montelukast+ICS showed improvement in day-time symptom score with LABA+ICS (SMD -0.17; 95%CI: -0.24 to -0.10). One study reported improvement with LABA+ICS when compared to Zafirlukast+ICS (Nelson 2001). The overall combined symptom score was in favour of LABA+ICS (SMD -0.18; 95%CI: -0.25 to -0.12).

**Change in morning symptom scores [Comparison 01:14]**

Ceylan 2004 reported a significant difference in favour of LABAs (N = 40).

**Change in number of night awakenings per week - change from baseline [Comparison 01:15]**

Four studies with 4,214 patients reported night awakenings (Bjermer 2003; Fish 2001; Ilowite 2004; Nelson 2000). There was significant difference in night awakenings when LABA+ICS was compared to Montelukast+ICS (WMD -0.30; 95%CI: -0.50 to -0.10) and in the one study comparing LABA+ICS to Zafirlukast+ICS. The combined overall estimate was in favour of less awakenings with LABA+ICS (WMD -0.12; 95%CI: -0.19 to 0.06).

**Change in % of nights with no awakenings per week - change from baseline [Comparison 01:16]**

Two studies reported this outcome based on data from 673 participants (Grosclaude 2003; Nelson 2001), showing a greater percentage of awakening-free nights per week with LABA+ICS (WMD 6.89% (95% CI 2.87 to 10.91).

**Change in % rescue free nights [Comparison 01:17]**

Grosclaude 2003 reported no significant difference between treatments (N = 243).

**Withdrawals for any reason [Comparison 01:18]**

Ten studies with 6,225 patients reported withdrawals due to any reason (Bjermer 2003; Fish 2001; Grosclaude 2003; Hultquist 2000; Ilowite 2004; McCarthy 2003; Nelson 2000; Nelson 2001; Ringdal 2003; Storms 2004). Eight studies (Bjermer 2003; Fish 2001; Grosclaude 2003; Ilowite 2004; McCarthy 2003; Nelson 2000; Ringdal 2003; Storms 2004) compared LABA+ICS with Montelukast+ICS which showed decreased risk of patient withdrawal with LABA+ICS (RR 0.86; 95%CI: 0.74 to 0.97). Two studies reporting LABA+ICS versus Zafirlukast+ICS (Hultquist 2000; Nelson 2001) also showed a reduced risk of withdrawal but the difference did not achieve significance. (RR 0.65; 95%CI 0.40 to 1.06). The overall estimate showed significant reduction in risk of withdrawal in patients who used LABA+ICS compared to LTRA+ICS (RR 0.83; 95%CI: 0.73 to 0.95). The risk difference for this outcome is -0.02 (95% CI -0.4 to -0.01).

**Withdrawals due to adverse effects [Comparison 01:19]**

Ten studies with 6,225 patients reported withdrawals due to adverse effects (Bjermer 2003; Fish 2001; Grosclaude 2003; Hultquist 2000; Ilowite 2004; McCarthy 2003; Nelson 2000; Nelson 2001; Ringdal 2003; Storms 2004). The overall estimate comparing LABA+ICS with LTRA+ICS did not show a significant difference between the groups (RR 1.02; 95%CI 0.80 to 1.32). There was also no significant difference in withdrawals due to adverse effects between subgroups when the studies were subgrouped according to type of LTRA.

**Withdrawals due to poor asthma control/exacerbations [Comparison 01:20]**

Seven studies with 5,276 patients reported this outcome measure (Bjermer 2003; Fish 2001; Grosclaude 2003; Hultquist 2000; Ilowite 2004; Nelson 2000; Nelson 2001). There were no significant differences in the overall estimate (RR 0.87; 95%CI 0.49 to 1.56) or between the subgroups. There was heterogeneity present (I² = 46.6%).

**Patients with one or more exacerbations requiring hospital admission [Comparison 01:21]**

Three studies with 3,747 patients reported this outcome (Bjermer 2003; Ilowite 2004; Ringdal 2003) comparing LABA+ICS to Montelukast+ICS. There was no significant difference between the two study groups (RR 1.31; 95%CI: 0.58 to 2.98).

**Severe adverse events [Comparison 01:22 & Comparison 02:02]**

Six studies with 5,592 patients reported this outcome (Bjermer 2003; Fish 2001; Ilowite 2004; Nelson 2000; Nelson 2001; Ringdal 2003). There was no significant difference in the overall result (RR 1.32; 95%CI: 0.98 to 1.79) nor between subgroup comparisons according to the type of LTRA. When the data were stratified according to the number of devices for delivering the combination of LABA+ICS, the risk of serious adverse events was lower if 1
device rather than 2 devices were used (1 device: RR=0.55, 95% CI: 0.19, 1.64 vs 2 devices: RR = 1.43, 95% CI 1.04, 1.97); however, the difference between the two subgroup estimates did not reach statistical significance (P = 0.095). The overall confidence interval of severe adverse events is wide (95% CI 0.98, 1.79) and includes the possibility that LABA + ICS increases risk by more than the prespecified level of 10% (i.e. RR =1.1).

Deaths [Comparison 01:23]
Only one study reported deaths (Bjermer 2003) with no significant difference between the two study groups (only one death occurred).

Headache [Comparison 01:24]
Ten studies with 6,187 patients reported headache as an adverse event (Bjermer 2003; Ceylan 2004; Fish 2001; Grosclaude 2003; Hultquist 2000; Ilowite 2004; McCarthy 2003; Nelson 2000; Nelson 2001; Ringdal 2003). There was no significant difference in the overall result or when the two different types of LTRA were compared to LABA+ICS, (RR 1.07; 95% CI 0.9, 1.26).

Cardiovascular events [Comparison 01:25]
Five studies with 5,163 patients reported cardiovascular events (Bjermer 2003; Fish 2001; Ilowite 2004; Nelson 2000; Ringdal 2003). There was no significant difference when LABA+ICS was compared to Montelukast+ICS (RR 1.09; 95%CI: 0.77 to 1.52).

Oral moniliasis [Comparison 01:26]
Six studies with 5,203 patients reported number of patients with oral moniliasis (Bjermer 2003; Ceylan 2004; Fish 2001; Ilowite 2004; Nelson 2000; Ringdal 2003). The studies compared LABA+ICS to Montelukast+ICS showing an overall significant increase in risk of oral moniliasis with LABA+ICS (RR 1.86; 95%CI 1 to 3.44). The occurrence rates were low and this represents an average risk of oral moniliasis of 1% for LABA and 0.5% for LTRA. The risk difference for this outcome was 0.01 (95% CI 0 to 0.01).

Osteopenia/osteoporosis [Comparison 01:27]
Two studies reported this outcome (Bjermer 2003; Ilowite 2004) with no significant difference between the study groups (RR 0.56; 95%CI: 0.12 to 2.63).

Elevated liver enzymes [Comparison 01:28]
One study reported this outcome (Bjermer 2003) with no difference between the study groups.

Overall adverse events [Comparison 01:29]
Eight studies (Bjermer 2003; Fish 2001; Ilowite 2004; McCarthy 2003; Nelson 2000; Nelson 2001; Ringdal 2003) with 5,911 patients reported adverse events which did not show a significant difference when LABA+ICS was compared to LTRA+ICS. The absence of group difference (RR 1.03; 95%CI 0.99 to 1.07) met our a priori definition of equivalence.

Patient treatment satisfaction [Comparison 01:30]
Three studies with 2,020 patients (Fish 2001; Nelson 2001; Ringdal 2003) reported significantly higher patient satisfaction with LABA+ICS. Two studies comparing LABA+ICS with Montelukast+ICS showed greater patient satisfaction with LABA+ICS (RR 1.09; 95%CI: 1.05 to 1.14). One study comparing LABA+ICS with Zafirlukast+ICS also favoured LABA+ICS. The overall combined estimate favoured LABA+ICS (RR 1.12; 95%CI: 1.04 to 1.20). Satisfaction rates were high in both groups, LABA were 85% satisfied and LTRA were 76% satisfied. Random Effects modelling was used due to the high level of statistical heterogeneity (I² =61.8%). The risk difference for this outcome was 0.09 (95% CI 0.04 to 0.14).

Change from baseline in serum eosinophils ( x 10e9/L) [Comparison 01:31]
Two studies reported this outcome (Bjermer 2003; Ilowite 2004) which showed a statistically significant decrease in serum eosinophils with Montelukast+ICS when compared to LABA+ICS (WMD 0.94; 95%CI: 0.02 to 0.05).

**Discussion**

**Primary outcome**

In adult patients who remain symptomatic on low dose inhaled steroids, the addition of a long-acting β2-agonist reduces the relative risk of exacerbations requiring systemic steroids by 17% as compared to that observed with the addition of a leukotriene receptor antagonist. Compared to an 11% rate of exacerbation in patients treated with a combination of LTRA + ICS, the rate observed with the use of long-acting β2-agonist is 2% lower, at 9%. Thirty eight patients need to be treated with LABA + ICS instead of LTRA + ICS to avoid one patient from experiencing an exacerbation requiring systemic corticosteroids.

The results were homogeneous between trials. The leukotriene receptor antagonist did not affect the magnitude of the benefit related to LABA. There was insufficient variation between trials to examine the potential effect of factors such as severity of baseline airway obstruction, selection of long-acting β2-agonist, baseline dose of inhaled steroids, and methodological trial quality on the magnitude of effect. In absence of pediatric trials contributing data to this outcome, efficacy in children was not assessed. Subgroup comparison showed that the use of a single inhaler was associated with a 50% reduction in the risk of exacerbations requiring systemic steroids compared to 10% reduction with two inhalers. The size of this difference must be interpreted with caution as it is not based on a head-to-head comparison and the baseline risk in the two subgroups is not the same. However the direction of effect is in accord with the findings with head-to-head comparisons of single versus two inhalers (Nelson 2003), where around 8% more patients achieved a 15 L/min increase in morning PEF with combined rather than separate inhalers. Publication status, funding by producers of LABA or LTRA, and treatment duration (<=12 versus 48 weeks), did not notably affect the direction or
events, headache, cardiovascular events, osteopenia/osteoporosis

Secondary outcomes

Significant improvements were seen with LABA + ICS compared to LTRA + ICS for other outcome measures. The following outcome measures were significantly better with LABA + ICS (when compared to LTRA + ICS): morning PEFR, evening PEFR, FEV1, days free of rescue medication use, rescue medication use, asthma quality of life, symptom free days, day time symptom score, number and percent of night awakenings, withdrawals for any reason and patient satisfaction.

Only two trials examined the impact of both strategies on inflammatory markers, namely serum eosinophils. The addition of a LTRA to ICS was associated with a greater (4%) reduction from baseline serum eosinophils when compared to LABA + ICS. In addition, the use of leukotriene receptor antagonist showed lower risks for oral moniliasis, (0.5% in comparison to 1% for LABA).

Outcomes that did not differ between the two intervention groups included: withdrawal due to adverse events, withdrawals due to poor asthma control, hospitalisation, serious adverse events, headache, cardiovascular events, osteopenia/osteoporosis and overall adverse events. Outcomes for which only a single study contributed data (thus unable to be meta-analysed) included night-time symptom scores, protection against exercise challenge, percentage of nights with awakenings per week, death and elevated liver enzymes.

The average difference in the improvement from baseline in FEV1 between LABA and LTRA was 80 mL (95% CI: 60 to 100 mL). The average improvement in FEV1 observed with LABA + ICS was 215 mL, and with LTRA + ICS it was 134 mL. A change of 200 ml or more in FEV1 is considered a clinically important difference, exceeding normal intra-subject variation (ATS 1991). However, one must recognise that in the absence of a placebo group treated with ICS alone in this review, these changes from baseline probably overestimate the true benefit of the addition of each drug to ICS in comparison with the use of ICS alone. Indeed, other Cochrane reviews have quantified the magnitude of improvement in FEV1 attributable to each drug over that of ICS and placebo; the use of LABA + ICS was associated with an additional increase of 210 mL (Ni Chroinin 2004) while an increase of 60 mL was observed for the combination of LTRA and ICS (Ducharme 2004a) over ICS alone. The observed improvement in FEV1 in this review is in keeping with former Cochrane review on LABA (Ni Chroinin 2004), but suggest a greater benefit of LTRA then suggested in the review on LTRA as add-on therapy to ICS alone where the ICS dose was less homogeneous (Ducharme 2004a). Thus, the group difference in improvement of 80 mL in FEV1 observed in this review between LABA and LTRA is smaller than anticipated: both treatment options appear to lead to significant improvements in lung function.

One of the entry criteria common to all trials was the need to demonstrate significant reversibility in FEV1 (e.g., ≥12% improvement post-bronchodilatation). Is it possible that the selection of patients with significant reversibility has favoured the combination of LABA + ICS over LTRA + ICS? This may explain the greater group differences observed with measures of lung function as compared to other outcomes. Although reversibility to bronchodilator is one of the standard diagnostic criteria of asthma (BTS 2003; Boulet 2001; GINA 2005; USA 2002), in fact only a minority of asthmatic patients display significant reversibility at a given point in time. Storms 2003 Perhaps, the reversibility to short-acting β2-agonists selected patients who were more likely to be responders to long-acting β2-agonists.

With regards to safety, the risk of overall adverse effects was similar in both groups, meeting our a priori definition of equivalence. However, the confidence interval for severe adverse events was wide and included the possibility of an increase in the group treated with LABA as compared to LTRA. As indicated in the original version of this review, we performed a post-hoc analysis to investigate the use of one or two devices for LABA + ICS influenced the risk of severe adverse outcomes. Perhaps, this effect is mediated by non-compliance with concurrent inhaled steroids and thus use of LABA as monotherapy, a clear possibility with the use of two devices for LABA + ICS; Perera 2003). Use of leukotriene receptor antagonist was protective for oral moniliasis. There was no group difference in the risk of cardiovascular events, headaches, and osteopenia/osteoporosis. Although significantly less patients allocated to the combination of LABA + ICS withdrew from the study for any reason, there was no group difference in withdrawals due to adverse effects or poor asthma control.

The extensive search strategy resulting in the identification and voluntary disclosure of two high quality unpublished reports help to reduce the risk of publication bias. This is also supported by negative test for funnel plot asymmetry, although one must acknowledge the low sensitivity of this test in presence of few trials. The high methodological quality of all 11 trials contributing data and the confirmation of methodology and extracted data by their authors strengthen the value of this review. The homogeneity of the tested population and interventions, supported by the absence of statistical heterogeneity for most outcomes, attests to the internal validity of the review. However, the generalisability of results is a major issue. Indeed, the relative homogeneity of trials limits the application of results to other age groups (children and patients older than 65 years old), patients with mild or severe airway obstruction, smokers, use of other long-acting β2-agonist than salmeterol, and use of higher (or lower) dose of ICS than 400-560 mcg/day of BDP or equivalent. The only pediatric trial was an unpublished conference abstract which reported insufficient data to contribute to any outcome in the review (Stelmach 2005). The inadequate documentation or reporting also limits generalisation of results to adolescents. An individual data meta-analysis might provide critical information to determine if the presence of allergic
rhinitis modifies the observed superiority of LABA over LTRA as add-on therapy to ICS.

With well documented decreases in adherence with the time (Storms 2003), one wonders how undocumented lack of compliance may have affected the results. Was there poor adherence to twice daily regimen for LABA? With the documented flat dose-response curve to inhaled steroids (Powell 2003) one may even wonder whether the similar improvement observed with LTRA and LABA, is derived from enhanced compliance to inhaled steroids per se as result of study participation rather than the selection of add-on therapies. Is the greater improvement associated with use of a single rather than two devices for delivering LABA and ICS mostly attributable to better lung deposition of, and interaction between, both drugs (Buhl 2003; Rosenhall 2003) or rather to better adherence to inhaled glucocorticoids? In absence of measure of adherence, these questions remain unanswered. Perception of more rapid and greater benefit by the patients leading to enhanced compliance is often portrayed by clinicians selecting LABA over LTRA; n the two trials reporting this outcome, percentage of patient satisfied (RR=1.12) was greater in the group receiving LABA + ICS (85%) than those treated LTRA + ICS (76%) as compared to ICS alone. The absence of cross-over study design where all patients can experience both combination therapy prevent firm conclusion related to the actually their preference of LABA or LTRA as add-on therapy to ICS.

Although derived from over 6000 patients in eleven trials, the results of this meta-analysis could be reversed by 9 additional trials (of similar size to those included) showing no group difference. Direction of results may be seriously influenced by patient selection. It is possible that a differential effect of add-on options may be influenced by age, airway reversibility, smoking status, severity of baseline airway obstruction, type of asthma (eosinophilic vs non-eosinophilic), triggers (e.g., allergic rhinitis), compliance, etc. Future studies should now focus on comparing these add-on strategies in selected groups of patients, so that characteristics of responders to either option may be better delineated. Measures of adherence (before and after randomisation) should also be integrated in future studies.

This review summarises the best evidence available until March 2006. The results apply to adult asthmatic adults who remain symptomatic despite 400-560 mcg/day of beclometasone or equivalent, and who present with a moderate (baseline FEV1 of 65 to 75%) but reversible airway obstruction. The results may not be generalisable to children and adolescents, or patients over 65 years. With most trials comparing salmeterol to montelukast as add-on to fluticasone, there is insufficient data to suggest any differential effect associated with the type of LABA or ICS. Importantly, the use of a single, rather than two, devices to administer the combination of LABA and ICS maximise the effect and the superiority of LABA + ICS over LTRA + ICS.

**AUTHORS’ CONCLUSIONS**

Implications for practice

In asthmatic adults with moderate and reversible airway obstruction despite low doses of inhaled corticosteroids, the addition of LABA to inhaled corticosteroids, in comparison to adding LTRA, reduces the risk of exacerbation over 12 to 48 weeks from 11% to 9%. Both treatment options lead to improvements in asthma control. Compared to leukotriene receptor antagonists, the addition of long-acting β2-agonist to inhaled corticosteroids is associated with significantly improved lung function, symptom-free days, use of rescue β2-agonists, symptoms, symptom-free days, night awakenings, and quality of life, although it could be argued that the magnitude of some of these differences is small. To date, LABA and LTRA have comparable safety profiles. The evidence could be useful to support the use of both options as add-on to inhaled steroids, although improvements were consistently greater with LABA across most outcome measures. The combination of LABA with ICS in a single device appears even more effective and possibly safer than use of two separate devices as compared to LTRA and ICS.

Implications for research

Future trials should focus address the main gaps in knowledge, namely the generalisability of results to:

- Children, adolescents and elderly patients
- Patients with severe (or milder) airway obstruction
- Asthmatic patients with minimal (<12%) airway reversibility to bronchodilators at time of enrollment but with positive provocation challenge
- Patients with co-morbidities, such as allergic rhinitis, aspirin-induced asthma, smokers or environmental exposure to cigarette smoke, etc.
- Add-on therapy to higher dose of inhaled corticosteroids than 400–500 mcg/day of BDP or equivalent
- Monitoring of adherence to both combination therapies
- Use of single inhalers for delivery of LABA + ICS compared to LTRA + ICS
- Comparison of LABA + LTRA vs LABA + ICS (in a single device)
- Careful monitoring and reporting of outcomes that are important to the patient, namely exacerbations requiring systemic steroids or hospital admission, symptoms, symptom-free days, night awakenings, quality of life, and satisfaction and life-threatening asthma as defined by admission to ICU or requiring intubation and/or ventilation.
POTENTIAL CONFLICT OF INTEREST

Francine M. Ducharme has received travel support for meeting attendance, research funds, fees for speaking and/or consulting fees from AstraZeneca (producer of Zafirlukast, formoterol, and budesonide), Merck Frosst Inc (producer of Montelukast), GlaxoSmithKline (producer of fluticasone, beclomethasone, salmeterol), and Novartis (producer of formoterol). No conflict reported by Toby Lasserson or Christopher Cates.

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REFERENCES

References to studies included in this review

Bjermer 2003 (published and unpublished data)


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Long-acting beta-2-agonists versus anti-leukotrienes as add-on therapy to inhaled corticosteroids for chronic asthma (Review)

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**Lemanske 2003**

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**Pavord 2002**

Ongoing study Starting date of trial not provided. Contact author for more information.

**Price 2001**

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**Ruggins 2003**

Ongoing study Starting date of trial not provided. Contact author for more information.

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**Adams 2005**

Long-acting beta-2-agonists versus anti-leukotrienes as add-on therapy to inhaled corticosteroids for chronic asthma (Review)

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Perera 2003

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Reiss 1998

Rosenhall 2003

Shrewsbury 2000

Storms 2003

Thomson 2003

USA 2002

Virchow 2000

Walters 2004

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**Long-acting beta2-agonists versus anti-leukotrienes as add-on therapy to inhaled corticosteroids for chronic asthma (Review)**

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Wasserman 1988

Wenzel 1997

Westbroek 2000

Xun 1999

References to other published versions of this review
Ram 2005

*Indicates the major publication for the study

**TABLES**

**Characteristics of included studies**

<table>
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<tr>
<th>Study</th>
<th>Bjermer 2003</th>
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<td>Methods</td>
<td>DESIGN</td>
</tr>
<tr>
<td></td>
<td>-parallel-group</td>
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<td></td>
<td>-multicentre trial (148 centres in 37 countries)</td>
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<tr>
<td>ALLOCATION</td>
<td>-Random</td>
</tr>
<tr>
<td></td>
<td>-Randomisation by computer generated random numbers</td>
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<tr>
<td></td>
<td>-means of assignment: by number coded MDI/tablets supplied by pharmacy</td>
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<tr>
<td>BLINDING</td>
<td>-triple-blind (patient, assessor &amp; treating physician)</td>
</tr>
<tr>
<td></td>
<td>-double-dummy</td>
</tr>
<tr>
<td></td>
<td>-identical placebo</td>
</tr>
<tr>
<td>WITHDRAWAL/DROPOUT</td>
<td>-described</td>
</tr>
<tr>
<td>JADAD's Quality Score</td>
<td>= 5</td>
</tr>
<tr>
<td>Confirmation of methodology</td>
<td>obtained</td>
</tr>
</tbody>
</table>
Characteristics of included studies (Continued)

Participants INADEQUATELY controlled participants on inhaled glucocorticoids at baseline

BASELINE INHALED STEROID DOSAGE:
LTRA : 638±285 ug of beclomethasone-equivalent/day
LABA : 647±229 ug of beclomethasone-equivalent/day

RANDOMISED =1490
-LTRA= 747
-LABA = 743

WITHDRAWALS:
-LTRA= 125 (17%)
-LABA = 110 (15%)

AGE in years: mean ± SD
-LTRA= 41.2 ± 13.6
-LABA = 41.0± 13.7

GENDER (% male)
-LTRA= 45.4 %
-LABA = 44.8 %

SEVERITY:
MODERATE asthma

BASELINE % PRED FEV1
-LTRA= 71.3 ± 13.2
-LABA = 72.7 ± 13.9

ALLERGIC RHINITIS:
-LTRA= 61.7 %
-LABA = 60.4 %

ALLERGEN TRIGGERS:
not reported

ASTHMA DURATION in years: Mean ± SD
-LTRA= 16.3 ± 13.0
-LABA = 16.2 ± 12.7

ELIGIBILITY CRITERIA
-age: 15-72 years
-clear history of chronic asthma for at least 1 year
-regular use of inhaled corticosteroids over 8 weeks prior to study entry
-FEV1 values between 50% and 90% of predicted
->=12% improvement in FEV1 or PEFR after B-agonists
-minimum pre-determined level of daytime and night-time inhaled short-acting b-agonist use (>= 1 puff/day)
-minimum asthma symptom score (biweekly score of >=56 on a scale of 0 to 336)
-current treatment includes only short-acting beta2-agonists and inhaled corticosteroids (200-1000 ug/day or equivalent)
-women with negative urine pregnancy test at screening
EXCLUSION CRITERIA:
- Emergency treatment for asthma within 1 month of 1st visit
- Hospitalisation for asthma within 3 months
- Unresolved upper respiratory tract infection within 3 weeks
- Active sinus infection
- Received the following asthma medications: oral corticosteroids within 1 month; cromolyn, nedocromil, leukotriene-receptor antagonists, long-acting or oral b-agonists, inhaled anticholinergics within 2 weeks; theophylline, terfenadine, fexofenadine, loratadine, or cetirizine within 1 week.

Interventions

<table>
<thead>
<tr>
<th>Interventions</th>
<th>LTRA + ICS vs LABA + ICS (Stable dose of ICS)</th>
</tr>
</thead>
<tbody>
<tr>
<td>DURATION</td>
<td>Run-in Period: 4 weeks Intervention Period: 48 weeks</td>
</tr>
<tr>
<td>INTERVENTION GROUP 1</td>
<td>LTRA = Montelukast @ 10 mg/day p.o. + ICS = FP 100 ug bid, via discus</td>
</tr>
<tr>
<td>INTERVENTION GROUP 2</td>
<td>LABA = Salmeterol 50 ug bid, via MDI + ICS = FP 100 ug/day, via discus</td>
</tr>
<tr>
<td>2 inhalers used for combination therapy.</td>
<td>-CO-TREATMENT: none</td>
</tr>
</tbody>
</table>

Outcomes

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>INTENTION-TO-TREAT ANALYSES outcomes used at endpoint or 48 weeks</th>
</tr>
</thead>
<tbody>
<tr>
<td>PULMONARY FUNCTION TESTS</td>
<td>Change from baseline FEV1 Change from baseline in AM PEFR</td>
</tr>
<tr>
<td>SYMPTOM SCORES</td>
<td>Change from baseline NIGHT-TIME awakenings</td>
</tr>
<tr>
<td><strong>EXACERBATIONS</strong></td>
<td>Exacerbations requiring systemic steroids Exacerbations requiring hospital admission Exacerbations requiring unscheduled office visit Exacerbations requiring emergency room visit Time to first exacerbation</td>
</tr>
<tr>
<td>Definition: An asthma attack was defined by one or all of the following: hospitalisation; unscheduled office visit; ER visit; CS use (oral, IM, IV or rectal use)</td>
<td></td>
</tr>
<tr>
<td>FUNCTIONAL STATUS</td>
<td>Change in quality of life Change in night-time awakenings</td>
</tr>
<tr>
<td>INFLAMMATORY MARKERS</td>
<td>Change in serum eosinophils</td>
</tr>
<tr>
<td>ADVERSE EFFECTS</td>
<td>Elevated liver enzymes, headache, nausea, death, neutropenia, increased lymphocytes</td>
</tr>
</tbody>
</table>
**Characteristics of included studies (Continued)**

WITHDRAWALS
- due to adverse effects
- due to poor control
- overall reported

(*** denotes primary outcome)

### Notes
- Full-text report
- Received additional unpublished data provided by Peter Polos, June 2003
- Funded by Merck Frost
- Confirmation of methodology and data extraction received (Peter Polos, June 2003)
- User-defined number: 48 weeks

### Allocation concealment
- Adequate

### Study  Ceylan 2004

#### Methods
- **DESIGN**
  - parallel group; single centre study (Turkey)

- **ALLOCATION**
  - Random; method unclear

- **BLINDING**
  - Open label

- **WITHDRAWAL/DROP-OUT**
  - Described

- JADAD’s Quality score: 2

#### Participants
- INADEQUATELY controlled participants on inhaled glucocorticoids and SABA prn

- **BASELINE INHALED STEROID DOSAGE**
  - not reported (400mcg/d BUD given as standard during 4 week run-in period)

- **RANDOMISED**
  - LTRA: 48 - NB Baseline data only reported for those who completed the study: LTRA: 20; LABA: 20.

- **WITHDRAWALS**
  - Not stated

- **AGE in years: mean**
  - LTRA: 33.2
  - LABA: 39.1

- **GENDER (% male)**
  - LTRA: 55
  - LABA: 50

- **SEVERITY**
  - Moderate persistent asthma

- **BASELINE % PRED FEV1L**
  - LTRA: 69.7
  - LABA: 71.2

- **ALLERGIC RHINITIS (%)**
  - LTRA: 60
  - LABA: 70
Characteristics of included studies (Continued)

ALLERGEN TRIGGERS:
- Not reported

ASTHMA DURATION in years: Mean ± SD:
- LTRA: 8.1 ± 4
- LABA: 9 ± 8.8

ELIGIBILITY CRITERIA:
- Age 15-60 years
- Diagnosis of asthma (GINA)
- Persistent asthma symptoms for at least 1 year
- Use of ICS for at least 6 months
- Post-run in period: FEV1 or PEF ≥ 60 and ≤80% predicted
- ≥15% reversibility increase in FEV1
- Mean am PEF value <≤85% max after SABA
- Use of SABA ≥ 2 times per day or am /night symptom score ≥2 on 4 or less days per week

EXCLUSION CRITERIA:
- Smokers
- Pregnant or lactating women
- Life-threatening asthma
- Patients hospitalised due to asthma in last 3 months
- Upper/lower RTI

Interventions

LTRA + ICS vs LABA + ICS (Stable dose of ICS)

DURATION:
- Run-in Period: 4 weeks
- Intervention Period: 8 weeks
- Outcomes at 4, 8, and 12 weeks

INTERVENTION GROUP 1
- LTRA = Montelukast @ 10 mg/day p.o. + BUD 200 mcg BID, unclear inhaler device

INTERVENTION GROUP 2
- LABA = Formoterol 12 ug bid, unclear inhaler device + ICS = BUD 200mcg BID (unclear inhaler)

CO-TREATMENT:
- SABA prn

Outcomes

INTENTION-TO-TREAT ANALYSES
- Not clear. Stated ITT for efficacy and safety, however baseline data are only presented for 40 participants who completed the study

PULMONARY FUNCTION TESTS
- Change in FEV1 % predicted
- Change in FEV1 L
- Change in am PEF*
- Change in pm PEF

SYMPTOM SCORES
- Morning symptom scores
- Night symptom scores

EXACERBATIONS
- Not reported (participants who exacerbated were excluded from the study)

FUNCTIONAL STATUS
- Rescue medication usage (puffs/d)
- % days without rescue medication usage
### Characteristics of included studies (Continued)

**INFLAMMATORY MARKERS**  
- Not reported

**EXACERBATIONS**  
- Need for a drug not included in the protocol

**ADVERSE EFFECTS**  
- Candidiasis  
- Sore throat  
- Voice problems  
- Headache

**WITHDRAWALS**  
- Not clear  

#### Notes
- Full-text report  
- No funding body  
- User-defined number: 8 weeks

<table>
<thead>
<tr>
<th>Allocation concealment</th>
<th>B – Unclear</th>
</tr>
</thead>
</table>

#### Study  
**Fish 2001**

**Methods**  
**DESIGN**  
- Parallel-group study  
- Multicentre trial (71 centres in USA & Puerto Rico)

**ALLOCATION**  
- Random  
- Methods of randomisation: by computer generated random number  
- Means of assignment by number coded inhaler/pills supplied by pharmacy

**BLINDING**  
- Double-blind  
- Double-dummy

**WITHDRAWAL/DROPOUT**  
- Described by treatment groups

**JADAD's Quality Score** = 5

**Confirmation of methodology** : received

**Participants**  
**INADEQUATELY** controlled participants on inhaled glucocorticoids at baseline

**BASELINE INHALED STEROID DOSAGE:**  
84-4000 ug of beclomethasone-equivalent/day

**RANDOMISED** = 948  
- LTRA = 472  
- LABA = 476
Characteristics of included studies (Continued)

WITHDRAWALS:
- LTRA= 70 (15%)
- LABA = 61 (13%)

AGE in years: mean ± SD
- LTRA= 39.5 ± 14.0
- LABA = 39.9 ± 13.5

GENDER (% male)
- LTRA= 38%
- LABA = 39%

SEVERITY:
Not described

BASELINE FEV1 (% pred)
- LTRA= 68.6 (0.4) SE
- LABA = 68.1 (0.4) SE

ALLERGEN TRIGGERS:
Not reported

ASTHMA DURATION in years: %
Less than 10 years
- LTRA= 26%
- LABA = 24%
Over 10 years
- LTRA= 74%
- LABA = 76 %

ELIGIBILITY CRITERIA
FEV1
aged >= 15 years
male or nonpregnant, non lactating female
asthma for >= 6 months
Symptomatic despite ICS for at least 6 weeks prior to screening
50-80% predicted FEV1
>=12% increase in FEV1 post bronchodilator (200 mcg albuterol)

In the 7 to 14 days prior to randomisation one or more of the following:
- an FEV1 of 50 to 80% of predicted
- an average of 4 or more puffs per day albuterol
- a symptom score of 2 or more for 3 or more days
- 3 or more nights when patient woke at night due to asthma symptoms

EXCLUSION CRITERIA:
Not described

SETTING: Outpatients in private and university clinics

Interventions
LTRA + ICS vs LABA + ICS
(Stable dose of ICS)

DURATION:
- Run-in Period: 1-2 weeks
- Intervention Period: 12 weeks

INTERVENTION GROUP 1
- LTRA = Montelukast 10 mg qd
-
Characteristics of included studies (Continued)

ICS = continued current medication (which included fluticasone, triamcinolone, BDP, BUD and Flunisolide)
Mean 565 ug in BDP-equivalent

INTERVENTION GROUP 2
-LABA = Salmeterol 50 ug bid, via Diskus
+ ICS = continued current medication
Mean 546 ug in BDP-equivalent
2 inhalers used for combination therapy
-CO-TREATMENT: None permitted

Outcomes

INTENTION-TO-TREAT ANALYSES
-outcomes used at endpoint

PULMONARY FUNCTION TESTS
-**Change from baseline in AM PEFR
-Change from baseline in PM PEFR

SYMPTOM SCORES
-Change from baseline OVERALL symptom scores
-Change in symptom-free days
- Patient satisfaction

EXACERBATIONS
Definition: Any worsening of asthma symptoms requiring treatment beyond the use of blinded study drug &/or supplemental albuterol. Patients who experienced an asthma exacerbation were withdrawn from the study

FUNCTIONAL STATUS
-Change from baseline in mean OVERALL use of B2-agonists (puffs/DAY)
-Change from baseline in mean DAYTIME use of B2-agonists (puffs/DAY)
-Change from baseline in mean NIGHT-TIME use of B2-agonists (puffs/DAY)
-Change in rescue-free days
-Change in night-time awakenings

INFLAMMATORY MARKERS:
Not reported

ADVERSE EFFECTS
-drug related & non-drug related

WITHDRAWALS
-due to adverse effects reported

(** denotes primary outcome)

Notes
- Full-text report
-Received additional unpublished data provided by Karen Richardson, GSK, UK, August 2003
-Funded by Glaxo Wellcome, studies SMS40003 & SMS40004
-Confirmation of methodology and data extraction received
-User-defined order: 12 weeks

Allocation concealment: A – Adequate

Study Green (abs) 2002
Methods DESIGN
-crossover-group study
Characteristics of included studies (Continued)

**ALLOCATION**
- randomised
- method not stated

**BLINDING**
- double-blind
- Unclear if double-dummy

**WITHDRAWAL/DROP OUT**
- not stated

JADAD’s Quality Score = 2

Confirmation of methodology: not received

<table>
<thead>
<tr>
<th>Participants</th>
<th>INADEQUATELY controlled participants on inhaled glucocorticoids at baseline</th>
</tr>
</thead>
<tbody>
<tr>
<td>BASELINE INHALED STEROID DOSAGE:</td>
<td>- not stated</td>
</tr>
<tr>
<td>RANDOMISED = 98</td>
<td>LTRA= 49</td>
</tr>
<tr>
<td>LABA = 49</td>
<td>WITHDRAWALS:</td>
</tr>
<tr>
<td>AGE in years: mean ± SD</td>
<td>- not reported</td>
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<tr>
<td>GENDER (% male)</td>
<td>- not stated</td>
</tr>
<tr>
<td>SEVERITY:</td>
<td>- not stated</td>
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<tr>
<td>BASELINE FEV1 (L)</td>
<td>- not stated</td>
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<tr>
<td>ALLERGEN TRIGGERS:</td>
<td>- not stated</td>
</tr>
<tr>
<td>ASTHMA DURATION in years: %</td>
<td>- not stated</td>
</tr>
<tr>
<td>ELIGIBILITY CRITERIA</td>
<td>- patients with symptoms consistent with asthma and objective evidence of variable airflow obstruction despite low dose inhaled corticosteroids.</td>
</tr>
<tr>
<td>EXCLUSION CRITERIA:</td>
<td>- not stated</td>
</tr>
<tr>
<td>SETTING:</td>
<td>- not stated</td>
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<table>
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<tr>
<th>Interventions</th>
<th>LTRA + ICS vs LABA + ICS (Stable low dose of ICS)</th>
</tr>
</thead>
<tbody>
<tr>
<td>DURATION:</td>
<td>Intervention Period: 1 month (x 4, as four-way crossover) with 1 month washout.</td>
</tr>
<tr>
<td>INTERVENTION GROUP 1</td>
<td>LTRA = Montelukast 10 mg once daily</td>
</tr>
</tbody>
</table>
Characteristics of included studies (Continued)

ICS = BUD 100ug twice daily

INTERVENTION GROUP 2
-LABA = Formoterol 12 ug bid, via Turbhaler
+ ICS = BUD 100ug bid
2 inhalers to deliver LABA + ICS

INTERVENTION GROUP 3
-BUD 100ug bid, via Turbhaler + BUD 300ug bid

INTERVENTION GROUP 4
-BUD 100 ug bid, via Turbhaler + Placebo

-CO-TREATMENT
-not reported

Outcomes

INTENTION-TO-TREAT ANALYSES
-not stated

PULMONARY FUNCTION TESTS
-FEV1, PEFR but only improvements when groups compared, no individual group results were presented.

SYMPTOM SCORES
-VAS (individual group values not presented, but rather differences between groups)

EXACERBATIONS
-not reported

FUNCTIONAL STATUS
-not stated

INFLAMMATORY MARKERS:
-not stated

ADVERSE EFFECTS
-not stated

WITHDRAWALS
-not reported

Notes

- Conference abstract only
- Funding source not disclosed
- Confirmation of methodology and data extraction not yet received
- User-defined order: 4 weeks

Allocation concealment B – Unclear

Study

Grosclaude 2003

Methods

DESIGN
-parallel group; multicentre study (115 centres in France).

ALLOCATION
-random
-method of randomisation unclear

BLINDING
-open label
Characteristics of included studies (Continued)

WITHDRAWAL/DROP-OUT
-described
JADAD's Quality score
- 2

Participants
INADEQUATELY controlled participants on inhaled glucocorticoids at baseline

BASELINE INHALED STEROID DOSAGE
-not reported (Min: 1000 mcg of CFC-BDP-eq)

RANDOMISED = 253
-LTRA: 130
-LABA: 123

WITHDRAWALS
-LTRA: 16 (12%)  
-LABA: 7 (6%)

AGE in years: mean ± SD
-LTRA: 44.6 (18.2)
-LABA: 43.1 (17.8)

GENDER (% male)
-LTRA: 39; LABA: 39

SEVERITY
-not described

BASELINE % PRED FEV1L
-not reported

BASELINE PEF (L/min):
-LTRA: 327
-LABA: 344

ALLERGIC RHINITIS (%):
-LTRA: 51%
-LABA: 52%

ALLERGEN TRIGGERS:
-not reported

ASThma DURATION in years: Mean ± SD
-reported as % with asthma duration:
<1 year: 6; between 1 and 5 years: 17; Between 5 and 10 years: 15; Between 10 and 15 years: 19; More than 15 years: 43

ELIGIBILITY CRITERIA:
- less than or equal to 15 years of age diagnosed asthma
- treatment for at least four weeks with BDP equivalent of >=1000mcg/d and inhaled SABA prn
- able to use Mini Wright PEF metre
- able to fill in daily record card

Over last seven days of run-in:
-mean am PEF between 60-80% predicted best (as obtained post-BD at visit 2)
- asthma symptoms on at least two days
- used SABA at least four times
Characteristics of included studies (Continued)

EXCLUSION CRITERIA:
- use of systemic CS, anti-leukotriene agent, LABA, lower RTI within previous four weeks
- hospitalisation within previous 4 weeks
- hypersensitivity to one of compound study drugs
- serious uncontrolled concurrent disease
- allergen specific immunotherapy in incremental phase
- smoker or ex-smoker with 10 pack year
- participation in clinical study in previous month.

Interventions
LTRA + ICS vs LABA + ICS (Stable dose of ICS)

DURATION:
- Run-in Period: 1-2 weeks
- Intervention Period: 12 weeks

INTERVENTION GROUP 1
- LTRA = Montelukast @ 10 mg/day p.o. + BDP 250 ug two puffs bid, via diskus MDI

INTERVENTION GROUP 2
- LABA = Salmeterol 50 ug bid, via MDI + ICS = FP 250 mcg one puff bid, via diskus (separate same inhalers)

CO-TREATMENT: SABA prn

Outcomes
INTENTION-TO-TREAT ANALYSES - outcomes used at endpoint or 12 weeks

PULMONARY FUNCTION TESTS
- **change from baseline in AM PEF;
- change from baseline in PM PEFR

SYMPTOM SCORES
- change from baseline % nights with awakenings
- change from baseline in % days with no symptoms
- change from baseline in % nights with no symptoms

EXACERBATIONS
- one or more of:
  - Mild: reduction in AM PEF of >20% of baseline; increased bronchodilator usage; awakenings due to asthma on one or more consecutive nights
  - Moderate: reduction in AM PEF >30% of baseline; change in maintenance therapy or premature termination of trial therapy; oral steroids
  - Severe: Hospitalisation

FUNCTIONAL STATUS
- change from baseline in % nights without rescue medication usage
- change from baseline in % days without rescue medication usage
- % of patients with good asthma control 10 of 12 weeks (as defined by presence of two of: PEF >/=80% predicted; No more than four puffs of BD on no more than 2 days; Symptom free for at least two days; and by presence of all the following criteria on a weekly basis: no nocturnal awakening; no exacerbation; no unscheduled medical contact; no adverse effect of treatment leading to withdrawal)

INFLAMMATORY MARKERS
- not reported

ADVERSE EFFECTS
- Headache; gastroenteritis; upper respiratory inflammation; pharyngitis; viral respiratory infections; malaise and fatigue; allergic rhinitis; diarrhoea; digestive discomfort & pain; ENT symptoms; muscle cramps and spasms; regurgitation & reflux; nasal inflammation; vertigo; nausea & vomiting; cough; lower respiratory infections; dyspeptic symptoms
**Characteristics of included studies (Continued)**

WITHDRAWALS
- due to poor completion of diary cards
- due to adverse effects
- due to poor control
- overall
(all reported)

(** denotes primary outcome)

Notes
- Full-text report & unpublished trial report
- Received additional unpublished data (SFCF4007) from GSK website
- Funded by GSK
- User-defined number: 12 weeks

Allocation concealment

\[ B \] – Unclear

**Study**

**Hendeles 2004**

**Methods**

**DESIGN**
- parallel group; number of sites and countries unclear

**ALLOCATION**
- random
- unclear method

**BLINDING**
- double-blind
- method: unclear

**WITHDRAWAL/DROP-OUT**
- not described.

**JADAD’s Quality score:**
- 2

**Participants**

INADEQUATELY controlled participants on inhaled glucocorticoids and SABA prn with history of EIB at baseline

**BASELINE INHALED STEROID DOSAGE**
- not reported

**RANDOMISED = 91** (unclear allocation between groups)

**WITHDRAWALS**
- not reported

**AGE in years (range)**
- 15-60

**GENDER (% male)**
- not reported

**SEVERITY**
- not described

**BASELINE % PRED FEV1L**
- LTRA: 81.3
- LABA: 78.9
**Characteristics of included studies (Continued)**

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Information</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>ALLERGIC RHINITIS (%)</strong></td>
<td>-not reported</td>
</tr>
<tr>
<td><strong>ALLERGEN TRIGGERS</strong></td>
<td>-not reported</td>
</tr>
<tr>
<td><strong>ASTHMA DURATION in years: Mean ± SD:</strong></td>
<td>-not reported</td>
</tr>
</tbody>
</table>
| **ELIGIBILITY CRITERIA**                     | -participants with asthma who remained symptomatic on ICS  
- age 15-60 years  
- history of EIB                                    |
| **EXCLUSION CRITERIA:**                      | -not reported                                    |

**Interventions**

<table>
<thead>
<tr>
<th>Interventions</th>
<th>LTRA + ICS vs LABA + ICS (Stable dose of ICS)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>DURATION</strong></td>
<td>- Intervention Period: 4 weeks</td>
</tr>
<tr>
<td><strong>INTERVENTION GROUP 1</strong></td>
<td>- LTRA = Montelukast @ 10 mg/day p.o. + FP 125 mcg one puff bid, via inhalation</td>
</tr>
<tr>
<td><strong>INTERVENTION GROUP 2</strong></td>
<td>- LABA = Salmeterol 50 ug bid, via MDI + montelukast placebo + ICS = FP 125 mcg one puff bid, via inhalation (separate inhalers)</td>
</tr>
<tr>
<td><strong>CO-TREATMENT</strong></td>
<td>- not reported</td>
</tr>
</tbody>
</table>

**Outcomes**

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>INTENTION-TO-TREAT ANALYSES - outcomes used at endpoint or 4 weeks</th>
</tr>
</thead>
</table>
| **PULMONARY FUNCTION TESTS**                       | -challenge FEV1 % predicted  
- change in FEV1 % predicted  
- rescue bronchodilation                               |
| **SYMPTOM SCORES**                                 | -not reported                                                 |
| **EXACERBATIONS**                                  | -not reported                                                 |
| **FUNCTIONAL STATUS**                              | -not reported                                                 |
| **INFLAMMATORY MARKERS**                           | -not reported                                                 |
| **ADVERSE EFFECTS**                                | -not reported                                                 |
| **WITHDRAWALS**                                    | -due to adverse events: not reported  
- due to poor control: not reported  
- overall: reported                                  |
| **Primary outcome not identified**                 |                                                               |

**Notes**

- Unpublished: conference abstract
Characteristics of included studies (Continued)

- Funded by Merck
- User-defined number: 4 weeks
- No data could be used for aggregation

Allocation concealment: B – Unclear

<table>
<thead>
<tr>
<th>Study</th>
<th>Hultquist 2000</th>
</tr>
</thead>
<tbody>
<tr>
<td>Methods</td>
<td>DESIGN</td>
</tr>
<tr>
<td></td>
<td>- parallel-group study</td>
</tr>
<tr>
<td></td>
<td>- multicentre trial (49 centres in 6 countries)</td>
</tr>
<tr>
<td>ALLOCATION</td>
<td>Random</td>
</tr>
<tr>
<td></td>
<td>- Methods of randomisation not specified</td>
</tr>
<tr>
<td>BLINDING</td>
<td>- double-blind</td>
</tr>
<tr>
<td></td>
<td>- double-dummy</td>
</tr>
<tr>
<td>WITHDRAWAL/DROPOUT</td>
<td>- described by treatment groups</td>
</tr>
<tr>
<td></td>
<td>JADAD's Quality Score = 4</td>
</tr>
<tr>
<td>Confirmation of methodology: received August 2003</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Participants</th>
<th>INADEQUATELY controlled participants on inhaled glucocorticoids at baseline</th>
</tr>
</thead>
<tbody>
<tr>
<td>BASELINE INHALED STEROID DOSAGE:</td>
<td>400-1000 ug of ICS (not specified)/day</td>
</tr>
<tr>
<td>RANDOMISED</td>
<td>- LTRA= 118</td>
</tr>
<tr>
<td></td>
<td>- LABA = 118</td>
</tr>
<tr>
<td>WITHDRAWALS:</td>
<td>- LTRA= 19/118 (16%)</td>
</tr>
<tr>
<td></td>
<td>- LABA = 12/118 (10%)</td>
</tr>
<tr>
<td>AGE in years: mean ± SD</td>
<td>- LTRA= 38.3 ± NS</td>
</tr>
<tr>
<td></td>
<td>- LABA = 38.1 ± NS</td>
</tr>
<tr>
<td>GENDER (% male)</td>
<td>- LTRA= 47%</td>
</tr>
<tr>
<td></td>
<td>- LABA = 49%</td>
</tr>
<tr>
<td>SEVERITY:</td>
<td>Not described</td>
</tr>
<tr>
<td>BASELINE FEV1 (% pred)</td>
<td>- LTRA= 72.03 ± SD</td>
</tr>
<tr>
<td></td>
<td>- LABA = 69.71 ± SD</td>
</tr>
<tr>
<td>ALLERGEN TRIGGERS:</td>
<td>Not reported</td>
</tr>
<tr>
<td>ALLERGIC RHINITIS:</td>
<td>Not reported</td>
</tr>
</tbody>
</table>
Characteristics of included studies (Continued)

ASTHMA DURATION in years
-LTRA = 10.1 ± SD
-LABA = 12.1 ± SD

ELIGIBILITY CRITERIA
-male or female outpatient
-age 12-70 years
-treated for at least 3 mo with 400-1000 mcg of inhaled glucocorticoids
-asthma diagnosis
-FEV1 50-80% predicted
-=>12 % reversibility in FEV1 and at least 200 mL after inhalation of 1 mg of terbutaline
-smoking history of <=10 pack years

In the 7 days prior to randomisation one or more of the following:
- an symptom score of =>1 on 4 days
-awakening on >= 1 night due to asthma symptoms
-use of B2-agonists =>10 puffs as weekly mean

EXCLUSION CRITERIA:
-Respiratory infection
-clinical obstructive pulmonary disease, or pulmonary dysfunction other than asthma
-pregnant or lactating women
-use of LABA within 1 month prior to visit 1
-previous use ever of a leukotriene antagonist
-known intolerance to study drugs or inhaled lactose

SETTING: not described

Interventions

LTRA + ICS vs LABA + ICS
(Stable dose of ICS)

DURATION:
-Run-in Period: 10-14 days
-Intervention Period: 8 weeks

INTERVENTION GROUP 1
-LTRA = Zafirlukast 20 mg bid
+ Budesonide 200 mcg bid via Turbuhaler

INTERVENTION GROUP 2
-LABA = Formoterol 12 ug bid, via Turbohaler
+ Budesonide 200 mcg bid via Turbuhaler

- 2 inhalers used for combination therapy

-CO-TREATMENT: Not specified

Outcomes

modified INTENTION-TO-TREAT ANALYSES for patients who received at least one dose of medication
-outcomes used at endpoint

PULMONARY FUNCTION TESTS
-**Change from baseline in AM PEFR
-Change from baseline in PM PEFR
-Change from baseline in FEV1
Characteristics of included studies (Continued)

SYMPTOM SCORES
- Change from baseline DAYTIME symptom scores
- Change from baseline NIGHTTIME symptom scores

EXACERBATIONS
- Exacerbations requiring systemic steroids

FUNCTIONAL STATUS
- Change from baseline in mean OVERALL use of B2-agonists (puffs/DAY)
- Change from baseline in mean DAYTIME use of B2-agonists (puffs/DAY)
- Change from baseline in mean NIGHT-TIME use of B2-agonists (puffs/DAY)
- % night-time awakenings

INFLAMMATORY MARKERS:
Not reported

ADVERSE EFFECTS
- drug related & non-drug related

WITHDRAWALS
- due to adverse effects reported

(** denotes primary outcome)

Notes
- Unpublished data
- Received full disclosure of unpublished data provided by Roger Metcalf, AstraZeneca, July 2003
- Funded by Astra Zeneca
  Report #SD-004CR-0216
  Confirmation with supportive documents received for methodology and data extraction
- user-defined number: 12 weeks

Allocation concealment
A – Adequate

Study
Ilowite 2004

Methods
DESIGN
- parallel-group study
- multicentre trial (132 centres in USA for 48 weeks)

ALLOCATION
- random
- randomisation was determined by computer generated allocation schedule (block size 4)

BLINDING
- double-blind
- double-dummy

WITHDRAWAL/DROPOUT
- described by treatment groups
  JADAD's Quality Score = 5
  Confirmation of methodology: received from author March 2004

Participants
INADEQUATELY controlled participants on inhaled glucocorticoids at baseline

BASELINE INHALED STEROID DOSAGE:
220 ug of ICS per day
Characteristics of included studies (Continued)

RANDOMISED = 1473
- LTRA = 743
- LABA = 730

WITHDRAWALS:
- LTRA = 128/743
- LABA = 113/730

AGE in years: mean ± SD
- LTRA = 39.0 (range 14-73)
- LABA = 38.1 (range 15-70)

GENDER (% male)
- LTRA = 41.2%
- LABA = 37.5%

SEVERITY:
moderate-to-severe persistent asthma

BASELINE FEV1 (% pred)
- LTRA = 74.3 ± (SD 11.5)
- LABA = 74.3 ± (SD 11.7)

ALLERGEN TRIGGERS:
Not reported

ALLERGIC RHINITIS:
Not reported

ASTHMA DURATION in years
- LTRA = NS
- LABA = NS

ELIGIBILITY CRITERIA
age 15-65 years
asthma for >=1 year
ICS use daily for at least 8 weeks prior to first visit
Baseline FEV1 of 50 to 90% of predicted
>=12 % change in FEV1 after albuterol

and, in the 14 days prior to randomisation one or more of the following:
- asthma symptom that required the use of B2-agonist medication on average once per day
- minimum biweekly daytime symptom score of 56 for a 14-day period

EXCLUSION CRITERIA:
- Emergency department visit in < 1 month
- Admission for asthma in < 3 months
- Upper respiratory infection in < 3 weeks of 1st visit or during run-in
- pregnant or lactating women
- use of LABA within 1 month prior to visit 1
- use < 1 month of oral, intravenous, intramuscular, or intra-articular corticosteroids
- use < 2 weeks of leukotriene antagonist, cromolyn, or nedocromil,
- use of theophylline in < 1 week
- use in < 2 weeks of oral or inhaled long-acting b2-agonists or inhaled anti-cholinergics

SETTING: not described

<table>
<thead>
<tr>
<th>Interventions</th>
<th>LTRA + ICS vs LABA + ICS</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(Stable dose of ICS)</td>
</tr>
</tbody>
</table>
Characteristics of included studies (Continued)

DURATION:
- Run-in Period: 2 weeks
- Intervention Period: 48 weeks

INTERVENTION GROUP 1
- LTEA = Montelukast 10 mg once daily
  + Fluticasone 125 mcg bid via MDI

INTERVENTION GROUP 2
- LABA = Salmeterol 50 mcg bid, via MDI
  + Fluticasone 125 mcg bid via MDI
- 2 inhalers used for combination therapy
- CO-TREATMENT: Not specified

Outcomes

INTENTION-TO-TREAT ANALYSES for patients who received at least one dose of medication
- outcomes used at endpoint

PULMONARY FUNCTION TESTS
- **Change from baseline in AM PEFR
- Change from baseline in PM PEFR
- Change from baseline in FEV1

SYMPTOM SCORES
- Change from baseline DAYTIME symptom scores
- Change from baseline NIGHTTIME symptom scores

EXACERBATIONS
- Exacerbations requiring systemic steroids

FUNCTIONAL STATUS
- Change from baseline in mean OVERALL use of beta2-agonists (puffs/DAY)
- Change from baseline in mean DAYTIME use of beta2-agonists (puffs/DAY)
- Change from baseline in mean NIGHT-TIME use of B2-agonists (puffs/DAY)
- % night-time awakenings

INFLAMMATORY MARKERS:
- not reported

ADVERSE EFFECTS
- Drug related & non-drug related

WITHDRAWALS
- due to adverse effects reported

(** denotes trials primary outcome)

Notes
- Unpublished data
- Received full disclosure of unpublished data provided by Peter Polos, March 2004
- Funded by Merck & Co
- Confirmation with supportive documents received for methodology and data extraction
- User-defined number: 48 weeks
Characteristics of included studies (Continued)

Allocation concealment A – Adequate

Study McCarthy 2003

Methods
- parallel-group study
- multicentre trial

ALLOCATION
- Random
- Methods of randomisation: computer generated
- Allocation by opaque consecutive envelopes containing assessment
- Means by numbered coded inhalers / pills

BLINDING
- double-blind
- Mode of blinding: both patient and assessor blinded and used identical placebo's

WITHDRAWAL/DROPOUT
- Provided by authors

JADAD's Quality Score = 5

Confirmation of methodology: received.

Participants

INADEQUATELY controlled participants on inhaled glucocorticoids at baseline

BASELINE INHALED STEROID DOSAGE:
<= 400 ug of BDP/day or equivalent

RANDOMISED = 66
- LTRA = 33
- LABA = 33

WITHDRAWALS:
- LTRA = 4/33 (12.12%)
- LABA = 9/33 (27.27%)

AGE in years: mean ± SD

- 35 years
  - LTRA = 34.36 (SD 7.71)
  - LABA = 36.33 (SD 8.11)

GENDER (% male)
- LTRA = 58%
- LABA = 45%

SEVERITY:
Mild-moderate

BASELINE FEV1 (% pred)
- LTRA = 76.08 (SD 6.64)
- LABA = 75.12 (SD 9.12)

ALLERGEN TRIGGERS:
- Not reported

ALLERGIC RHINITIS:
Characteristics of included studies (Continued)

Not reported

ASTHMA DURATION in years
-not reported

ELIGIBILITY CRITERIA
-age 18-50 years
-confirmed diagnosis of asthma
-have received constant daily dose of up to 400 mcg of inhaled BDP (CFC containing) or equivalent in the last 4 weeks

During run-in period
-FEV1 61-85% of predicted
-\geq 20 \% fall in FEV1 on methacholine challenge
-symptom score of \geq 1 on 4/7 days
-use of rescue Beta2-agonists on \geq 2/7 days
-\geq 10\% period variation in PEFR over the last 7 days of run-in

EXCLUSION CRITERIA:
-Intake of asthma medication other than inhaled steroids or SA beta2-agonists in the past 4 weeks
-oral steroids in the past 3 months
-Respiratory infection within 4 weeks
-hospital admission in past 12 months
-evidence of underlying chronic lung disease
-smoking history of 10 pack-years or more
-pregnant or lactating women
-oother chronic diseases
-use of LABA or LTRAs within 1 month prior to visit 1
-known intolerance to study drugs or inhaled lactose

SETTING: not described

Interventions

LTRA + ICS vs LABA + ICS
(Stable dose of ICS)

DURATION:
-Run-in Period: not reported
-Intervention Period: 12 weeks

INTERVENTION GROUP 1
-LTRA = Montelukast 10 mg die
  + Fluticasone (Flixotide) 100 bid via MDI

INTERVENTION GROUP 2
-LABA = Salmeterol 50 ug bid via MDI
  + Fluticasone 100 mcg bid
  (in single MDI: Seretide 50)

1 inhaler used for combination therapy

-CO-TREATMENT: Not specified

Outcomes

modified INTENTION-TO-TREAT ANALYSES
-outcomes used at 12 weeks or endpoint
Characteristics of included studies (Continued)

PULMONARY FUNCTION TESTS
- Change from baseline in AM PEFR (L/min)
- Change from baseline in PM PEFR (L/min)
- Change from baseline in FEV1 (L)

SYMPTOMS (reported as medians)
- Change in symptom-free days
- Change in symptom-free nights

EXACERBATIONS REQUIRING SYSTEMIC STEROIDS
not reported

FUNCTIONAL STATUS (reported as medians):
- Change from baseline in mean DAYTIME use of B2-agonists
- Change from baseline in mean NIGHT-TIME use of B2-agonists
- Change in rescue-free days
- Change in night-time awakenings

INFLAMMATORY MARKERS (reported as medians):
- sputum **eosinophils, neutrophils, total cell counts, C-LT, histamine, IL-8

ADVERSE EFFECTS
- reported

WITHDRAWALS
- reported

(** denotes primary outcome)

Notes
- Unpublished data
- Received full disclosure of unpublished data provided by Karen Richardson, GSK (July 2003)
- Funded by GSK; study #40030

Confirmation of methodology and data extraction obtained from Karen Richardson, GSK, UK

<table>
<thead>
<tr>
<th>Study</th>
<th>Nelson 2000</th>
</tr>
</thead>
<tbody>
<tr>
<td>Methods</td>
<td>DESIGN</td>
</tr>
<tr>
<td></td>
<td>- parallel-group study</td>
</tr>
<tr>
<td></td>
<td>- multicentre trial (39 centres)</td>
</tr>
<tr>
<td>ALLOCATION</td>
<td>- Random</td>
</tr>
<tr>
<td></td>
<td>- Methods of randomisation: computer generated</td>
</tr>
<tr>
<td></td>
<td>- means of allocation: by numbered coded inhaler/pills supplied by pharmacy</td>
</tr>
<tr>
<td>BLINDING</td>
<td>- double-blind</td>
</tr>
<tr>
<td></td>
<td>- double-dummy</td>
</tr>
<tr>
<td></td>
<td>- identical placebo</td>
</tr>
<tr>
<td>WITHDRAWAL/DROPOUT</td>
<td>- described by treatment groups</td>
</tr>
<tr>
<td></td>
<td>JADAD’s Quality Score = 5</td>
</tr>
<tr>
<td></td>
<td>Confirmation of methodology: received</td>
</tr>
</tbody>
</table>

Allocation concealment A – Adequate
Characteristics of included studies (Continued)

Participants

INADEQUATELY controlled participants on inhaled glucocorticoids at baseline

BASELINE INHALED STEROID DOSAGE:
For the three week run in period 100ug twice daily FP (equivalent to 400 ug daily of beclomethasone)

RANDOMISED = 447
- LTRA= 225
- LABA = 222

WITHDRAWALS:
- LTRA= 30 (13%)
- LABA = 24 (11%)

AGE in years: mean ± SD
- LTRA= 43 ± 13.7
- LABA = 40.2 ± 14.4

GENDER (% male)
- LTRA= 40 %
- LABA = 39 %

SEVERITY:
Not reported

BASELINE FEV1 (% predicted)
- LTRA= 70.8 ± 0.05 (SEM)
- LABA = 70.0 ± 0.05

ALLERGEN TRIGGERS:
Not reported

ASTHMA DURATION in years: %
Under 10 years
- LTRA= 23%
- LABA = 24%
10 years or more
- LTRA= 77 %
- LABA = 76 %

ELIGIBILITY CRITERIA

FEV1
- age >=15 years
- asthma >= 6 months
- low-moderate dose of ICS for >= 1month (BDP: 252-420 mcg/day; BUD 400 mcg/day; FP 176- 220 mcg/day; triamcinolone 600 - 800 mcg/day)
- 50-80% of predicted normal
- >=12 % increase in FEV1 post 200 mcg albuterol
- at randomisation:
  - FEV1 50% to 80% of predicted
  - and 1 additional sign of inadequate asthma control in the preceding 7 days; i.e.,
    - >= 4 puffs/day albuterol
    - symptom score >=2 on a scale of (0-5) for >= 3 days
    - >=3 nights waking for asthma

EXCLUSION CRITERIA:
- Pregnant or lactating female patients
- Life threatening asthma
- Hospitalised for asthma in the last three months

---

44 Long-acting beta2-agonists versus anti-leukotrienes as add-on therapy to inhaled corticosteroids for chronic asthma (Review)
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Characteristics of included studies (Continued)

Significant concurrent diseases
<30 days of screening: use of theophylline, other bronchodilators, other leukotriene modifiers, cromolyn or nedocromil

SETTING: not specified

<table>
<thead>
<tr>
<th>Interventions</th>
<th>LTRA + ICS vs LABA + ICS</th>
</tr>
</thead>
<tbody>
<tr>
<td>(Stable dose of ICS)</td>
<td></td>
</tr>
</tbody>
</table>

DURATION:
- Run-in Period: 3 weeks
- Intervention Period: 12 weeks

INTERVENTION GROUP 1
- LTRA = oral montelukast 10 mg once daily
+ ICS = FP 100 ug twice daily, via diskus

INTERVENTION GROUP 2
- LABA = Salmeterol 50 ug twice daily, via Diskus
+ ICS = FP 100 ug twice daily, via Diskus

1 inhaler used for combination therapy.

CO-TREATMENT: none

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>modified INTENTION-TO-TREAT ANALYSES</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>- outcomes used at endpoint for exacerbations and withdrawals only (not available for continuous values)</td>
</tr>
</tbody>
</table>

PULMONARY FUNCTION TESTS
- Change from baseline FEV1
- Change from baseline in AM PEFR
- Change from baseline in PM PEFR

SYMPTOM SCORES
- Change from baseline OVERALL symptom scores
- Change from baseline in nighttime awakenings
- Change in symptom-free days

EXACERBATIONS
- Exacerbations requiring hospital admission
- Exacerbations requiring systemic steroids (data provided)

FUNCTIONAL STATUS
- Change from baseline in mean OVERALL use of B2-agonists (puffs/DAY)
- Change in rescue-free days

INFLAMMATORY MARKERS:
Not reported

ADVERSE EFFECTS
- Included oral candidiasis, sore throat, hoarseness & headache

WITHDRAWALS
- Due to adverse effects
- Due to poor control
- Overall
- Reported

Long-acting beta2-agonists versus anti-leukotrienes as add-on therapy to inhaled corticosteroids for chronic asthma (Review)
Copyright © 2007 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd
### Characteristics of included studies (Continued)

(** denotes primary outcome)

**Notes**
- Full-text report
- Received additional unpublished data provided by Karen Richardson, GSK (July 2003)
- Funded by Glaxo Wellcome, study SAS40018
- Confirmation of methodology and data extraction received
- User-defined order: 12 weeks

**Allocation concealment**
- Adequate

#### Study Nelson 2001

**Methods**
- **DESIGN**
  - parallel-group
  - multicentre trial (54 centres)

**ALLOCATION**
- Random
  - Methods of randomisation: computer generated
  - Means of allocation: numbered coded inhaler/pills.

**BLINDING**
- double-blind
- double-dummy
- identical placebo

**WITHDRAWAL/DROPOUT**
- described by treatment groups

**JADAD’s Quality Score** = 5

**Confirmation of methodology** received

**Participants**
- INADEQUATELY controlled adolescent & adult participants on inhaled glucocorticoids at baseline

**BASELINE INHALED STEROID DOSAGE:**
- Not described

**RANDOMISED = 429**
- LTRA = 215
- LABA = 214

**WITHDRAWALS:**
- LTRA = 18 (8%)
- LABA = 12 (6%)

**AGE in years: mean ± SD**
- LTRA = 39.3 ± 13.20
- LABA = 40.9 ± 13.17

**GENDER (% male)**
- LTRA = 44%
- LABA = 44%

**SEVERITY:**
- Not described

**BASELINE FEV1 (% predicted)**
- LTRA = 65.86 ± 0.58 (SEM)
- LABA = 66.62 ± 0.58
Characteristics of included studies (Continued)

ALLERGEN TRIGGERS:
Not reported

ASTHMA DURATION in years: %
Under 10 years
-LTRA = 24%
-LABA = 24%
10 years or over
-LTRA = 76%
-LABA = 76%

ELIGIBILITY CRITERIA
age >=12 years
asthma >= 6 months
FEV1 50-80% of predicted normal
>=12 % increase in FEV1 post 200 mcg albuterol
following 7-14 day run-in:
In the six days prior to randomisation one or more of the following:
- an average of 4 or more puffs/day of albuterol
- a symptom score of 2 or more on at least 2 days for any of the asthma symptom categories
- at least one night when the patient woke due to asthma
- two or more days where am PEF variation was 20% or more.
* intake of daily inhaled steroids prior to randomisation is NOT specified as inclusion criteria*
Patients also must have been using an oral or inhaled SABA for 6 weeks

EXCLUSION CRITERIA:
not described

SETTING:
Clinical centres

<table>
<thead>
<tr>
<th>Interventions</th>
<th>AL + ICS vs LABA + ICS</th>
</tr>
</thead>
<tbody>
<tr>
<td>(Stable dose of ICS)</td>
<td></td>
</tr>
</tbody>
</table>

DURATION:
-Run-in Period: 1-2 weeks
-Intervention Period: 4 weeks

INTERVENTION GROUP 1
-AL = Zafirlukast 20 mg twice daily
+ ICS = Constant dose of existing ICS medication

INTERVENTION GROUP 2
-LABA = Salmeterol 42 ug, 2 puffs twice daily via MDI
+ ICS = Constant dose of existing ICS medication

- 2 inhalers used for combination therapy

-CO-TREATMENT:
Theophylline or other medications that could potentially interact with study treatment not allowed
Albuterol inhalers provided for use on an as needed basis but all other bronchodilators not permitted
Antihistamines, nasal decongestants & intranasal medications for rhinitis were permitted

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>INTENTION-TO-TREAT ANALYSES</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>-outcomes used at endpoint</td>
</tr>
</tbody>
</table>
Characteristics of included studies (Continued)

PULMONARY FUNCTION TESTS
- Change from baseline FEV1
- ** Change from baseline in AM PEFR
- Change from baseline in PM PEFR
- Change in PEF variability

SYMPTOM SCORES
- Change from baseline DAYTIME symptom scores
- Change from baseline NIGHT-TIME symptom scores
- Change in symptom-free days
- Patient satisfaction

EXACERBATIONS
- Exacerbations requiring systemic steroids
- Exacerbations defined as any worsening of asthma symptoms requiring a change in the patients asthma therapy other than increased use of supplemental albuterol. Patients who experienced an exacerbation were withdrawn from the study

FUNCTIONAL STATUS
- Change from baseline in mean DAYTIME use of B2-agonists (/DAY)
- Change from baseline in mean NIGHT-TIME use of B2-agonists (/DAY)
- Change in rescue-free days
- Change/absolute in rescue-free nights
- Change in quality of life
- Change in night-time awakenings

INFLAMMATORY MARKERS:
Not reported

ADVERSE EFFECTS
- Upper respiratory tract infection, headache, nausea

WITHDRAWALS
- Due to adverse effects
- Due to poor control
- Overall reported

(** denotes primary outcome)

Notes
- Full-text report
- Received additional unpublished data provided by Karen Richardson, GSK
- Funded by Glaxo Wellcome, protocols SLGA5024 & SLGA5025
- Confirmation of methodology and data extraction received
- User-defined order: 4 weeks

Allocation concealment
A – Adequate

Study | Nsouli 2001
--- | ---
Methods | DESIGN
| unclear if parallel group or cross-sectional study
ALLOCATION | Random
| Methods of randomisation: not specified
Characteristics of included studies (Continued)

BLINDING
no blinding: reported as open-labelled

WITHDRAWAL/DROPOUT
-not described

JADAD's Quality Score = 1

Confirmation of methodology: not received

Participants
INADEQUATELY controlled participants on inhaled glucocorticoids at baseline

BASELINE INHALED STEROID DOSAGE:
FP 100-300 or BDP 200-550 or BUD 200-400 or flunisolide 500-1000 or triamcinolone 400-1000

RANDOMISED =30
-LTRA = unknown
-LABA = unknown

WITHDRAWALS:
Not described

AGE in years: mean ± SD
Not described

GENDER (% male)
Not described

SEVERITY:
Not described

BASELINE FEV1 (L) OR % PRED
Not described

ALLERGEN TRIGGERS:
Not described

ASTHMA DURATION in years: mean ± SD
Not described

ELIGIBILITY CRITERIA
Not described

EXCLUSION CRITERIA:
Not described

SETTING:
Not described

Interventions
AL + ICS vs LABA + ICS
(Stable dose of ICS)

DURATION:
-Run-in Period: not described
-Intervention Period: 8 weeks

INTERVENTION GROUP 1
-AL = Montelukast 10 mg QD pm
+ ICS = low dose ICS

INTERVENTION GROUP 2
-LABA = Salmeterol 50 ug BID
+
<table>
<thead>
<tr>
<th>Characteristics of included studies (Continued)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ICS = low dose ICS</td>
</tr>
<tr>
<td>2 inhalers used for combination therapy</td>
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<tr>
<td>-CO-TREATMENT:</td>
</tr>
<tr>
<td>Not reported</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>ANALYSES: Not Reported</th>
</tr>
</thead>
<tbody>
<tr>
<td>PULMONARY FUNCTION TESTS</td>
<td>FEV1 &amp; FEF25-75</td>
</tr>
<tr>
<td>SYMPTOM SCORES</td>
<td>None described</td>
</tr>
<tr>
<td>EXACERBATIONS</td>
<td>Not described</td>
</tr>
<tr>
<td>FUNCTIONAL STATUS</td>
<td>quality of life</td>
</tr>
<tr>
<td>INFLAMMATORY MARKERS:</td>
<td>Not described</td>
</tr>
<tr>
<td>ADVERSE EFFECTS</td>
<td>Not described</td>
</tr>
<tr>
<td>WITHDRAWALS</td>
<td>Not described</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Notes</th>
<th>-Abstract</th>
</tr>
</thead>
<tbody>
<tr>
<td>-Funding of study unknown</td>
<td></td>
</tr>
<tr>
<td>-Confirmation of methodology and data extraction not obtained.</td>
<td></td>
</tr>
<tr>
<td>-user defined order: 8 weeks</td>
<td></td>
</tr>
</tbody>
</table>

| Allocation concealment   | D – Not used |

<table>
<thead>
<tr>
<th>Study</th>
<th>Ringdal 2003</th>
</tr>
</thead>
<tbody>
<tr>
<td>Methods</td>
<td>DESIGN</td>
</tr>
<tr>
<td>-parallel-group</td>
<td></td>
</tr>
<tr>
<td>-multicentre trial (114 centres in 19 countries)</td>
<td></td>
</tr>
<tr>
<td>ALLOCATION</td>
<td>Random</td>
</tr>
<tr>
<td>-Methods of randomisation: computer generated</td>
<td></td>
</tr>
<tr>
<td>-Means of allocation: numbered coded inhalers/pills supplied by pharmacy</td>
<td></td>
</tr>
<tr>
<td>BLINDING</td>
<td>double-blind</td>
</tr>
<tr>
<td>-double-dummy</td>
<td>identical placebo</td>
</tr>
<tr>
<td>WITHDRAWAL/DROPOUT</td>
<td>described by treatment groups</td>
</tr>
<tr>
<td>JADAD’s Quality Score = 5</td>
<td>Confirmation of methodology: received</td>
</tr>
</tbody>
</table>

| Participants               | INADEQUATELY controlled participants on ‘moderate or high doses’ of inhaled glucocorticoids at baseline |
BASELINE INHALED STEROID DOSAGE:
800 ug or more of beclomethasone-equivalent/day (moderate or high dose)

RANDOMISED =806, 81 excluded due to not meeting eligibility criteria for randomisation
-LTRA= 369
-LABA = 356

WITHDRAWALS:
-LTRA= 37 (10%)
-LABA = 19 (5%)

AGE in years: mean ± SD
-LTRA= 43 (14-79)
-LABA = 43 (15-75)

GENDER (% male)
-LTRA= 45 %
-LABA = 46%

SEVERITY:
MODERATE PERSISTENT asthma

BASELINE FEV1 % PRED
-LTRA= 74.3 ± 16.1
-LABA = 75.8 ± 15.3

ALLERGEN TRIGGERS:
Not described

ASTHMA DURATION in years: mean ± SD
Not described

ELIGIBILITY CRITERIA
-age >=15 years
-moderate persistent asthma as per the ATS and NAEPP Report 2
-using inhaled corticosteroids at moderate or high dose (400-1000 mcg/day of BDP, BUD or flunisolide; or 200-500 mcg/day of FP) for at least 4 weeks
-history of reversible airway obstruction
->= 15% change in FEV1 after 800 mcg of salbutamol
At end of run-in:
- mean PEF of 50% to < 85% of value in clinic after 400 mcg of salbutamol
-cumulative symptom score of >=8 in past 7 days or >=4 of the last 7 days of run-in.

EXCLUSION CRITERIA:
-recent change in asthma medication
-Respiratory tract infection or admission for asthma in < 4 weeks
-intake of oral, depot, or parenteral corticosteroids in < 4 weeks or >=2 occasions in past 12 weeks
-cigarette smoking >=10 pack year
-pregnancy or lactating women or those likely to become pregnant during study
-FEV1 < 50%

Interventions
AL + ICS vs LABA + ICS
(Stable dose of ICS)

DURATION:
-Run-in Period: 4 weeks
-Intervention Period: 12 weeks plus a 2 week follow up

INTERVENTION GROUP 1
-AL = Montelukast 10 mg/day + ICS = FP 100 ug twice daily, via diskus
INTERVENTION GROUP 2
-LABA = Salmeterol 50 ug bid + ICS = FP 100 ug twice daily, via Diskus
-1 inhaler used for combination therapy.
-CO-TREATMENT:
Salbutamol provided for relief of symptoms, no other SABAs permitted
Other oral, parenteral or depot CS not allowed except where documented for treatment of exacerbations
Other existing asthma treatment allowed at constant dose

Outcomes
INTENTION-TO-TREAT ANALYSES, but excluding those who were incorrectly randomised because they failed major inclusion criteria
-outcomes used at endpoint
PULMONARY FUNCTION TESTS
-change from baseline in FEV1
-** Change from baseline in AM PEFR
-Change from baseline in PM PEFR
SYMPTOM SCORES
-change in total symptom score
-% change in symptom-free days & nights
-Patient satisfaction
-Physician assessment of effectiveness
-Compliance with study treatment
EXACERBATIONS
-exacerbations requiring systemic steroids
-exacerbations requiring hospital admission
-exacerbations defined as MILD: deterioration in asthma requiring a clinically relevant increase in salbutamol use defined as more than 3 additional inhalations per 24 hour period with respect to baseline for more than 2 consecutive days. MODERATE: requiring oral CS &/or antibiotics. SEVERE: requiring hospitalisation
FUNCTIONAL STATUS
- % rescue-free days
- % change in use of rescue medication (puffs/day)
- % symptom-free days
INFLAMMATORY MARKERS:
Not reported
ADVERSE EFFECTS
-serious adverse events, headache, oral thrush
WITHDRAWALS
-due to adverse effects
-overall reported
(** denotes primary outcome)

Notes
-Full-text report
-Received additional unpublished data provided by Karen Richardson, GSK.
-Funded by Glaxo SmithKline, study SAS40015
-Confirmation of methodology and data extraction received
-User-defined order: 12 weeks
### Characteristics of included studies (Continued)

Allocation concealment  A – Adequate

<table>
<thead>
<tr>
<th>Study</th>
<th>Stelmach 2005</th>
</tr>
</thead>
<tbody>
<tr>
<td>Methods</td>
<td></td>
</tr>
<tr>
<td>DESIGN</td>
<td></td>
</tr>
<tr>
<td>- parallel group; number of sites and countries unclear</td>
<td></td>
</tr>
<tr>
<td>ALLOCATION</td>
<td></td>
</tr>
<tr>
<td>- random</td>
<td></td>
</tr>
<tr>
<td>- unclear method</td>
<td></td>
</tr>
<tr>
<td>BLINDING</td>
<td></td>
</tr>
<tr>
<td>- double-blind</td>
<td></td>
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<tr>
<td>- method: unclear</td>
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</tr>
<tr>
<td>WITHDRAWAL/DROP-OUT</td>
<td></td>
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<tr>
<td>- not described</td>
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<tr>
<td>JADAD's Quality score</td>
<td>2</td>
</tr>
</tbody>
</table>

**Participants**

UNCLEAR symptomatic status of participants (described only as mild to moderate asthma)

<table>
<thead>
<tr>
<th>BASELINE INHALED STEROID DOSAGE</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>- not reported</td>
<td></td>
</tr>
</tbody>
</table>

| RANDOMISED = 80               |               |
| - LTRA: 20                     |               |
| - LABA: 20                     |               |
| - LTRA + ICS: 20               |               |
| - LABA + ICS: 20               |               |

| WITHDRAWALS                    |               |
| - not reported                 |               |

<table>
<thead>
<tr>
<th>AGE in years (range)</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>6-16</td>
<td></td>
</tr>
</tbody>
</table>

| GENDER (% male)                |               |
| - not reported                 |               |

| SEVERITY                       |               |
| - mild to moderate             |               |

| BASELINE % PRED FEV1L          |               |
| - not reported                 |               |

| ALLERGIC RHINITIS (%)          |               |
| - not reported                 |               |

| ALLERGEN TRIGGERS              |               |
| - dust mite                    |               |

| ASTHMA DURATION in years       |               |
| - not reported                 |               |

| ELIGIBILITY CRITERIA           |               |

Long-acting beta2-agonists versus anti-leukotrienes as add-on therapy to inhaled corticosteroids for chronic asthma (Review)
Characteristics of included studies (Continued)

- 6-16 years
  -mild to moderate asthma
  -atopic asthma (HDM sensitive)

EXCLUSION CRITERIA
-not reported

Interventions
LTRA + ICS vs LABA + ICS (Stable dose of ICS)

DURATION
-intervention period: 4 weeks

INTERVENTION GROUP 1
-LTRA = Montelukast @ 5 or 10 mg/day p.o.(depending on age) + BUD 200mcg/d, via inhalation (unclear inhaler device)

INTERVENTION GROUP 2
-LABA = Formoterol 4.5mcg/d + ICS = BUD 200mcg/d via inhalation (unclear inhaler devices/whether given as combination)

CO-TREATMENT: Not reported.

Outcomes
INTENTION-TO-TREAT ANALYSES
-unclear

PULMONARY FUNCTION TESTS
-absolute FEV1; S Raw;

SYMPTOM SCORES
-reported (unclear metric)

EXACERBATIONS
-not reported

FUNCTIONAL STATUS
-not reported

INFLAMMATORY MARKERS
-not reported

ADVERSE EFFECTS
-not reported

WITHDRAWALS
-not reported

Primary outcome not identified

Notes
- Unpublished: conference abstract
- Unclear funding agency
- User-defined number: 4 weeks

Allocation concealment: B – Unclear

Study
Storms 2004

Methods
DESIGN
-parallel group; multicentre study (sixteen centres in USA)

ALLOCATION
- random; blinded computer-generated randomisation schedule
Characteristics of included studies (Continued)

BLINDING
-open label ICS, double dummy LTRA and LABA

WITHDRAWAL/DROP-OUT
-described

JADAD’s Quality score
- 5

Participants INADEQUATELY controlled participants on inhaled glucocorticoids and SABA prn with history of EIB at baseline

BASELINE INHALED STEROID DOSAGE
-not reported

RANDOMISED = 78
-LTRA: 39
-LABA: 39

WITHDRAWALS
-LTRA: 0 (0%); LABA: 2 (5%)

AGE in years: mean:
-LTRA: 33.3
-LABA: 30

GENDER (% male):
-LTRA: 29.2
-LABA: 41

SEVERITY
-not described

BASELINE % PRED FEV1L
-LTRA: 87.5
-LABA: 88.1

ALLERGIC RHINITIS (%)
-not reported

ALLERGEN TRIGGERS
-not reported

ASTHMA DURATION in years: Mean ± SD:
-LTRA: 17.4 ±11.1
-LABA: 19.7 ±12

ELIGIBILITY CRITERIA:
-age 15-45 years with one year history of asthma
-uncontrolled asthma on ICS for at least 2 months
-treatment at randomisation with only SABA and ICS
-history of EIB (15% drop in FEV1 on ICS, 20% if not on ICS)
-resting FEV1 >=70% predicted
- >=12% increase in baseline FEV1 post-SABA
- requirement for SABA on >=3 days of last week of run-in period
**Characteristics of included studies (Continued)**

EXCLUSION CRITERIA:
- respiratory infection within last 3 weeks and emergency asthma care in previous 3 months
- systemic corticosteroids in previous month
- patients were required to stop an anti-asthma medication with the exception of ICS two weeks before first study visit
- participants requiring oral steroids during the study were withdrawn

<table>
<thead>
<tr>
<th>Interventions</th>
<th>LTRA + ICS vs LABA + ICS (Stable dose of ICS)</th>
</tr>
</thead>
<tbody>
<tr>
<td>DURATION:</td>
<td>Run-in Period: 1-2 weeks; Intervention Period: 4 weeks</td>
</tr>
<tr>
<td>INTERVENTION GROUP 1</td>
<td>LTRA = Montelukast @ 10 mg/day p.o. + placebo salmeterol inhaler + FP 100 mcg one puff bid, via diskus</td>
</tr>
<tr>
<td>INTERVENTION GROUP 2</td>
<td>LABA = Salmeterol 50 ug bid, via MDI + montelukast placebo + ICS = FP 100 mcg one puff bid, via diskus (separate inhalers)</td>
</tr>
<tr>
<td>CO-TREATMENT:</td>
<td>SABA prn</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>INTENTION-TO-TREAT ANALYSES - outcomes used at endpoint or 4 weeks</th>
</tr>
</thead>
<tbody>
<tr>
<td>PULMONARY FUNCTION TESTS</td>
<td>- **challenge FEV1 % predicted</td>
</tr>
<tr>
<td></td>
<td>- absolute FEV1 % predicted</td>
</tr>
<tr>
<td></td>
<td>- fall in FEV1 post-exercise (%)</td>
</tr>
<tr>
<td></td>
<td>- rescue bronchodilation</td>
</tr>
<tr>
<td>SYMPTOM SCORES</td>
<td>- clinic exercise assessment score</td>
</tr>
<tr>
<td>EXACERBATIONS</td>
<td>- none occurred during the study (requirement for OCS)</td>
</tr>
<tr>
<td>FUNCTIONAL STATUS</td>
<td>- not reported</td>
</tr>
<tr>
<td>INFLAMMATORY MARKERS</td>
<td>- not reported</td>
</tr>
<tr>
<td>ADVERSE EFFECTS</td>
<td>- not reported</td>
</tr>
<tr>
<td>WITHDRAWALS</td>
<td>- reported</td>
</tr>
<tr>
<td></td>
<td>- due to adverse events: reported</td>
</tr>
<tr>
<td></td>
<td>- due to poor control: not reported</td>
</tr>
<tr>
<td></td>
<td>- overall: reported</td>
</tr>
<tr>
<td>(** denotes primary outcome)</td>
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</table>

<table>
<thead>
<tr>
<th>Notes</th>
<th>- Full-text report</th>
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<tbody>
<tr>
<td></td>
<td>- Funded by Merck</td>
</tr>
<tr>
<td></td>
<td>- User-defined number: 4 weeks</td>
</tr>
</tbody>
</table>

**Allocation concealment**  A – Adequate

BDP: Beclomethasone; DPI: Dry powder inhaler; FEV1: Forced expiratory volume in one second; FP: Fluticasone; GSK: GlaxoSmithKline; ICS: Inhaled corticosteroids; LABA: Long-acting beta-agonist; LTRA: Leukotriene receptor antagonist; MDI: Metered dose inhaler; PEFR: Peak expiratory flow; challenge FEV1 % predicted: FEV1 measured post-SABA after 6 minutes exercise on a treadmill exacerbating heart rate to 80-90% of individual's predicted maximum
## Characteristics of excluded studies

<table>
<thead>
<tr>
<th>Study</th>
<th>Reason for exclusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adinoff 1998</td>
<td>One of the interventions was not LTRA + ICS</td>
</tr>
<tr>
<td>Anon 1999</td>
<td>Not an RCT - Montelukast vs. zafirlukast review</td>
</tr>
<tr>
<td>Anon 2000</td>
<td>Not an RCT (review)</td>
</tr>
<tr>
<td>Anon 2001</td>
<td>Not an RCT (review)</td>
</tr>
<tr>
<td>Barnes 1997</td>
<td>Not an RCT (review)</td>
</tr>
<tr>
<td>Becker 2000</td>
<td>Not an RCT (Review of montelukast)</td>
</tr>
<tr>
<td>Bergmann 2004</td>
<td>One of the tested interventions was not daily LTRA as add-on to inhaled glucocorticoid</td>
</tr>
<tr>
<td>Borker 2005</td>
<td>No ICS co-treatment in both groups</td>
</tr>
<tr>
<td>Brabson 2002</td>
<td>No co-intervention with ICS</td>
</tr>
<tr>
<td>Buchvald 2003</td>
<td>Study duration was less than 28 days.</td>
</tr>
<tr>
<td>Caffey 2005</td>
<td>No ICS co-treatment in both groups</td>
</tr>
<tr>
<td>Calhoun 2001</td>
<td>Non permitted drugs: study compared montelukast vs. placebo with both group receiving ICS and LABA</td>
</tr>
<tr>
<td>Cash 2001</td>
<td>Not an RCT - Commentary on a previously published trial.</td>
</tr>
<tr>
<td>Chopra 2005</td>
<td>Comparison between two different LABA + ICS combinations</td>
</tr>
<tr>
<td>Chuchalin 2002</td>
<td>One of the interventions was not LTRA + ICS</td>
</tr>
<tr>
<td>Currie 2002</td>
<td>No systematic co-treatment with ICS</td>
</tr>
<tr>
<td>Currie 2003a</td>
<td>Non permitted drug : salmeterol in both groups</td>
</tr>
<tr>
<td>Currie 2003b</td>
<td>LTRA in both groups</td>
</tr>
<tr>
<td>Currie 2003c</td>
<td>Duration of intervention &lt;30 days</td>
</tr>
<tr>
<td>Davis 2001</td>
<td>No co-treatment with ICS and LTRA</td>
</tr>
<tr>
<td>Dekhuijzen 2002</td>
<td>Not an RCT but a review article</td>
</tr>
<tr>
<td>Delaronde 2005</td>
<td>Intervention is educational (not drug)</td>
</tr>
<tr>
<td>Dempsey 2000</td>
<td>Single dose intervention (not &gt; 28 days)</td>
</tr>
<tr>
<td>Dicpinigaitis 2002</td>
<td>No systematic co-treatment with ICS</td>
</tr>
<tr>
<td>Donohue 2001</td>
<td>Review of combination therapies</td>
</tr>
<tr>
<td>Dorinsky 2001</td>
<td>No ICS used</td>
</tr>
<tr>
<td>Dorinsky 2002</td>
<td>One of the interventions was not LTRA + ICS</td>
</tr>
<tr>
<td>Dorinsky 2002a</td>
<td>One of the tested interventions was not daily LTRA as add-on to inhaled glucocorticoid (no ICS in LTRA group)</td>
</tr>
<tr>
<td>Dorinsky 2004</td>
<td>One of the tested interventions was not daily LTRA as add-on to inhaled glucocorticoid (no ICS in LTRA group)</td>
</tr>
<tr>
<td>Dunn 2001</td>
<td>Review of zafirlukast</td>
</tr>
<tr>
<td>Edelman 2000</td>
<td>No co-intervention with ICS</td>
</tr>
<tr>
<td>Edin 2002</td>
<td>One of the interventions was not LTRA + ICS</td>
</tr>
<tr>
<td>Eliraz 2001</td>
<td>No co-treatment with LTRA - Compares two dry powder inhalers</td>
</tr>
<tr>
<td>Eliraz 2002</td>
<td>One of the interventions was not LTRA + ICS</td>
</tr>
<tr>
<td>Everden 2002</td>
<td>One of the interventions was not LTRA + ICS</td>
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<tr>
<td>Gabrijevic 2004</td>
<td>One of the tested interventions was not daily LTRA as add-on to inhaled glucocorticoid</td>
</tr>
<tr>
<td>Giannini 2002</td>
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<tr>
<td>Grelewiska 2003</td>
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</tr>
<tr>
<td>Study</td>
<td>Description</td>
</tr>
<tr>
<td>---------------</td>
<td>-----------------------------------------------------------------------------</td>
</tr>
<tr>
<td>Havlucu 2005</td>
<td>Not an RCT</td>
</tr>
<tr>
<td>Horwitz 1998</td>
<td>Not an RCT (Review)</td>
</tr>
<tr>
<td>Houghton 2004</td>
<td>Comparison of propellants in formoterol - no ICS in both groups</td>
</tr>
<tr>
<td>Jarvis 1998</td>
<td>Not an RCT (Review of zafirlukast)</td>
</tr>
<tr>
<td>Jarvis 1999</td>
<td>Not an RCT but a review article on Zafirlukast.</td>
</tr>
<tr>
<td>Jenkins 2005</td>
<td>LTRA and LABA not compared as add on to ICS</td>
</tr>
<tr>
<td>Jonsson 2004</td>
<td>One of the tested interventions was not daily LTRA as add-on to inhaled glucocorticoid</td>
</tr>
<tr>
<td>Kalberg 1999</td>
<td>Retrospective data analysis, not an RCT</td>
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<tr>
<td>Kanniess 2002</td>
<td>No systematic co-treatment with ICS</td>
</tr>
<tr>
<td>Kanniess 2002b</td>
<td>One of the interventions was not LABA + ICS</td>
</tr>
<tr>
<td>Kardos 2001</td>
<td>One of the interventions was not LABA + ICS</td>
</tr>
<tr>
<td>Kemp 1998</td>
<td>Not an RCT (Review)</td>
</tr>
<tr>
<td>Knorr 2001</td>
<td>No consistent co-tx with ICS in all patients (Montelukast vs placebo)</td>
</tr>
<tr>
<td>Kohrogi 1999</td>
<td>Not an RCT (before and after study)</td>
</tr>
<tr>
<td>Laviolette 1999</td>
<td>One of interventions is not LABA + ICS</td>
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<tr>
<td>Lazarus 2001</td>
<td>One of interventions is not LTRA + ICS</td>
</tr>
<tr>
<td>Lee 2004</td>
<td>No LTRA and No LABA</td>
</tr>
<tr>
<td>Lee 2005</td>
<td>RCT testing two types of ICS</td>
</tr>
<tr>
<td>Leflein 2002</td>
<td>No systematic co-treatment with ICS</td>
</tr>
<tr>
<td>Lipworth 2000</td>
<td>Intervention &lt; 28 days (1 week only)</td>
</tr>
<tr>
<td>Liu 1996</td>
<td>No consistent co-treatment with ICS (Zileuton vs. placebo as add-on therapy to ICS)</td>
</tr>
<tr>
<td>McCarthy 2002</td>
<td>One of the interventions was not LTRA + ICS</td>
</tr>
<tr>
<td>Meltzer 2002</td>
<td>No co-treatment with inhaled corticosteroids</td>
</tr>
<tr>
<td>Mitchell 2005</td>
<td>Intervention is educational (not drug)</td>
</tr>
<tr>
<td>Molitor 2005</td>
<td>One of the interventions not LTRA</td>
</tr>
<tr>
<td>Naedele-Risha 2001</td>
<td>Not a RCT, review of LABA+ICS therapy</td>
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<tr>
<td>Nathan 2000</td>
<td>Good review of add-on therapy to ICS. Not an RCT.</td>
</tr>
<tr>
<td>Nathan 2001b</td>
<td>Not a RCT, review of antileukotrien agents</td>
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<tr>
<td>Nathan 2005</td>
<td>No direct comparison between LABA and LTRA</td>
</tr>
<tr>
<td>Nelson 2004</td>
<td>Both treatment groups received FP and Salmeterol (LTRA tested as add-on to LABA)</td>
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<td>O'Sullivan 2003</td>
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<td>Ollendorf 2000</td>
<td>Not an RCT, but an economic evaluation</td>
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<tr>
<td>Ortega-Cisneros 1998</td>
<td>No leukotriene antagonists used in intervention</td>
</tr>
<tr>
<td>Paterson 1999</td>
<td>No systematic co-treatment with ICS</td>
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<tr>
<td>Pearlman 2002</td>
<td>No consistent co-tx with ICS (FP + S vs Montelukast alone)</td>
</tr>
<tr>
<td>Perez 2000</td>
<td>Not RCT - no control group, all patients treated with montelukast</td>
</tr>
<tr>
<td>Peroni 2002</td>
<td>Short duration &lt; 28 days</td>
</tr>
<tr>
<td>Peroni 2005</td>
<td></td>
</tr>
<tr>
<td>Petermann 2004</td>
<td>Review article</td>
</tr>
<tr>
<td>Plaza 2005</td>
<td>Intervention is educational (not drug)</td>
</tr>
<tr>
<td>Price 2003</td>
<td>One of the interventions was not LABA + ICS</td>
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<tr>
<td>Riccioni 2002</td>
<td>No systematic co-treatment with ICS</td>
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### Characteristics of excluded studies (Continued)

- **Rickard 1998**  
  No systematic co-treatment with ICS
- **Rosenhall 2003**  
  One of the interventions is not LTRA + ICS
- **Serrier 2003**  
  One of the interventions is not LTRA + ICS
- **Sheth 2002**  
  Second report - cost effectiveness analyses
- **Sims 2003**  
  Intervention < 28 days
- **Smith 1998**  
  Not an RCT (Review)
- **Stanford 2003**
- **Stelmach 2001**  
  No consistent co-intervention with ICS (RCT of ICS vs. LABA vs. LTRA)
- **Stelmach 2002**  
  No consistent co-intervention with ICS (RCT of ICS vs. LABA vs. LTRA vs. nedocromil)
- **Stelmach 2002a**  
  No co-intervention with ICS
- **Stempel 1998**  
  Not an RCT (Review)
- **Stempel 2002**  
  Not an RCT (Review)
- **Stevenson 2005**
- **Terzano 2001**  
  One of the interventions is not LTRA + ICS
- **Thien 2000**  
  Not an RCT (Review)
- **Tolley 2002**  
  One of the interventions was not LTRA + ICS
- **Vaquerizo 2003**  
  One of the interventions was not LABA + ICS
- **Volovitz 1999**  
  No consistent co-intervention with ICS in all patients (Montelukast vs. beclomethasone)
- **Warner 2001**  
  Not an RCT (Review)
- **Wilson 1999**  
  Only 14 days intervention (not >=28 days)
- **Wilson 2001**  
  Only 14 days intervention (not >= 28 days)
- **Wytrychowski 2001**  
  Not an RCT - controlled study
- **Yurdakul 2002**  
  Not truly randomised as eligible patients were allocated to each treatment group according to their application month to hospital (consecutive allocation not random).
- **Zarkovic 1998**  
  One of the interventions was not LTRA + ICS
- **Zimmerman 2002**  
  One of the interventions was not LTRA + ICS

### Characteristics of ongoing studies

<table>
<thead>
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<td>LTRAs against alternative treatments at steps 2 and 3 of the BTS guidelines</td>
</tr>
<tr>
<td><strong>Interventions</strong></td>
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</tr>
<tr>
<td><strong>Outcomes</strong></td>
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<td><strong>Starting date</strong></td>
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<tr>
<td><strong>Contact information</strong></td>
<td>Dr Trewinard Barry (The White House Surgery, Weston Lane, Southampton, S019 9HJ, England)</td>
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<td><strong>Notes</strong></td>
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**Study**  
Fardon 2002

### Long-acting beta2-agonists versus anti-leukotrienes as add-on therapy to inhaled corticosteroids for chronic asthma (Review)

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### Characteristics of ongoing studies

(Continued)

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<td>Outcomes</td>
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<td>Interventions</td>
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<td>Outcomes</td>
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<td>Starting date</td>
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<td>Participants</td>
<td></td>
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<tr>
<td>Interventions</td>
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<tr>
<td>Outcomes</td>
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<td>Starting date</td>
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<td>Contact information</td>
<td>Professor D Price (University of East Anglia, Norwich, NR4 7TJ).</td>
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<tr>
<td>Notes</td>
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<tr>
<td>Interventions</td>
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<tr>
<td>Outcomes</td>
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Characteristics of ongoing studies (Continued)

Starting date

Contact information

Notes

ADDITIONAL TABLES

Table 01. ICS at BDP equivalent dose (mcg/day)

<table>
<thead>
<tr>
<th>Study Ref</th>
<th>Actual dose of ICS</th>
<th>BDP equivalent / day</th>
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</thead>
<tbody>
<tr>
<td>Bjerner 2003</td>
<td>200ug FP</td>
<td>400ug</td>
</tr>
<tr>
<td>Fish 2001</td>
<td>560ug (range 175-1700)</td>
<td>560ug</td>
</tr>
<tr>
<td>McCarthy 2003</td>
<td>200ug FP</td>
<td>400ug</td>
</tr>
<tr>
<td>Hultquist 2000</td>
<td></td>
<td>400ug</td>
</tr>
<tr>
<td>Nelson 2000</td>
<td>200ug FP</td>
<td>400ug</td>
</tr>
<tr>
<td>Nelson 2001</td>
<td>not specified</td>
<td>requested from author 08/03</td>
</tr>
<tr>
<td>Nsouli 2001</td>
<td></td>
<td>500ug</td>
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<tr>
<td>Ringdal 2003</td>
<td>200ug FP</td>
<td>400ug</td>
</tr>
<tr>
<td>Gold 2001</td>
<td>100ug FP</td>
<td>200ug</td>
</tr>
<tr>
<td>Green 2002</td>
<td>200ug BUD</td>
<td>200ug</td>
</tr>
<tr>
<td>Ilowite 2004</td>
<td>250ug FP</td>
<td>500ug</td>
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Table 02. Search history

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<thead>
<tr>
<th>Years</th>
<th>Detail</th>
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<tbody>
<tr>
<td>All years to January 2004</td>
<td>Citations: 184 (181 from the literature search and three unpublished trials provided by pharmaceutical companies for a total of 184 citations)</td>
</tr>
<tr>
<td></td>
<td>Citations excluded: 172: (1) duplicate citations (N=29), (2) abstracts of considered full-text publications or secondary analyses of the same study (N = 18), (3) not a randomised controlled trial (N = 72), (4) protocol of ongoing trial (N=1), (5) no consistent co-treatment with inhaled glucocorticoids (N = 21), (6) one of the tested interventions was not daily LTRA (N = 18), (7) one of the tested interventions was not daily LABA (N= 5), (8) interventions were administered for less than 4 weeks (N = 6), and (9) use of prohibited co-interventions such as LABA in both groups (N=2). Studies meeting the entry criteria of the review: 12 (six full-text publications (Bjermer 2003; Fish 2001; Ilowite 2004; Nelson 2000; Nelson 2001; Ringdal 2003), two unpublished full-text reports (Hultquist 2000; McCarthy 2003) and four abstracts (Gold (abs) 2001; Green (abs) 2002; Leibman (abs) 2002; Nsouli 2001). The abstracts did not provide data in sufficient detail to contribute to the meta-analyses.</td>
</tr>
</tbody>
</table>
### Comparison 01. Leukotriene receptor antagonists + ICS versus Long-acting β2-agonists + ICS

<table>
<thead>
<tr>
<th>Outcome title</th>
<th>No. of studies</th>
<th>No. of participants</th>
<th>Statistical method</th>
<th>Effect size</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>01 PRIMARY OUTCOME:</strong> Patients with one or more exacerbations requiring systemic corticosteroids</td>
<td>6</td>
<td>5571</td>
<td>Relative Risk (Fixed) 95% CI</td>
<td>0.83 [0.71, 0.97]</td>
</tr>
<tr>
<td>02 Morning PEF (L/min) - change from baseline</td>
<td>10</td>
<td>5669</td>
<td>Weighted Mean Difference (Fixed) 95% CI</td>
<td>15.66 [13.21, 18.11]</td>
</tr>
<tr>
<td>03 Evening PEF (L/min) - change from baseline</td>
<td>9</td>
<td>3958</td>
<td>Weighted Mean Difference (Fixed) 95% CI</td>
<td>12.09 [9.26, 14.92]</td>
</tr>
<tr>
<td>04 FEV1 (L) - change from baseline</td>
<td>8</td>
<td>4485</td>
<td>Weighted Mean Difference (Fixed) 95% CI</td>
<td>0.08 [0.06, 0.10]</td>
</tr>
<tr>
<td>05 FEV1 (L) - % change from baseline</td>
<td></td>
<td></td>
<td>Weighted Mean Difference (Fixed) 95% CI</td>
<td>Totals not selected</td>
</tr>
<tr>
<td>06 FEV1 (% predicted) @ 4 wks</td>
<td></td>
<td></td>
<td>Weighted Mean Difference (Fixed) 95% CI</td>
<td>Totals not selected</td>
</tr>
<tr>
<td>07 % fall in FEV1 POST-EXERCISE</td>
<td></td>
<td></td>
<td>Weighted Mean Difference (Fixed) 95% CI</td>
<td>Totals not selected</td>
</tr>
<tr>
<td>08 Rescue-free days (%) - change from baseline</td>
<td>5</td>
<td>2612</td>
<td>Weighted Mean Difference (Random) 95% CI</td>
<td>9.18 [5.39, 12.98]</td>
</tr>
<tr>
<td>09 Rescue medication use (puffs/day) - change from baseline</td>
<td>7</td>
<td>4055</td>
<td>Weighted Mean Difference (Random) 95% CI</td>
<td>-0.49 [-0.75, -0.24]</td>
</tr>
<tr>
<td>10 Change in Global asthma QoL AQLQ Score (higher is better) - change from baseline</td>
<td>3</td>
<td>2893</td>
<td>Weighted Mean Difference (Fixed) 95% CI</td>
<td>0.11 [0.05, 0.17]</td>
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<tr>
<td>11 Symptom free days (%) - change from baseline</td>
<td>5</td>
<td>2626</td>
<td>Weighted Mean Difference (Random) 95% CI</td>
<td>6.75 [3.11, 10.39]</td>
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<tr>
<td>12 Night-time symptom score (5pt scale, higher score is worse) - change from baseline</td>
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<td></td>
<td>Weighted Mean Difference (Fixed) 95% CI</td>
<td>Totals not selected</td>
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<tr>
<td>13 Day-time symptom scores (high is worse) - change from baseline</td>
<td>5</td>
<td>3823</td>
<td>Standardised Mean Difference (Fixed) 95% CI</td>
<td>-0.18 [-0.25, -0.12]</td>
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<tr>
<td>14 Morning symptoms - change from baseline</td>
<td></td>
<td></td>
<td>Weighted Mean Difference (Fixed) 95% CI</td>
<td>Totals not selected</td>
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<tr>
<td>15 Change in number of night awakenings per week - change from baseline</td>
<td>4</td>
<td>4214</td>
<td>Weighted Mean Difference (Fixed) 95% CI</td>
<td>-0.12 [-0.19, -0.06]</td>
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<td>16 Change in % of nights with no awakenings per week - change from baseline</td>
<td>2</td>
<td>673</td>
<td>Weighted Mean Difference (Fixed) 95% CI</td>
<td>6.89 [2.87, 10.91]</td>
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<tr>
<td>17 Rescue-free nights (%) - change from baseline</td>
<td></td>
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<td>Weighted Mean Difference (Fixed) 95% CI</td>
<td>Totals not selected</td>
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<tr>
<td>18 Withdrawals for any reason</td>
<td>10</td>
<td>6225</td>
<td>Relative Risk (Fixed) 95% CI</td>
<td>0.83 [0.73, 0.95]</td>
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<tr>
<td>19 Withdrawals due to adverse events</td>
<td>10</td>
<td>6225</td>
<td>Relative Risk (Fixed) 95% CI</td>
<td>1.02 [0.80, 1.32]</td>
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</table>
20 Withdrawals due to poor asthma control/asthma exacerbation

<table>
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<th>No. of participants</th>
<th>Statistical method</th>
<th>Effect size</th>
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<tbody>
<tr>
<td>8</td>
<td>5354</td>
<td>Relative Risk (Random) 95% CI</td>
<td>0.87 [0.49, 1.56]</td>
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21 Patients with one or more exacerbations requiring hospital admission

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<th>No. of participants</th>
<th>Statistical method</th>
<th>Effect size</th>
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<tr>
<td>4</td>
<td>3993</td>
<td>Relative Risk (Fixed) 95% CI</td>
<td>1.31 [0.58, 2.98]</td>
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22 Serious Adverse events

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<th>No. of participants</th>
<th>Statistical method</th>
<th>Effect size</th>
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<tbody>
<tr>
<td>6</td>
<td>5592</td>
<td>Relative Risk (Fixed) 95% CI</td>
<td>1.32 [0.98, 1.79]</td>
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23 Death

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<th>No. of participants</th>
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<th>Effect size</th>
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24 Headache

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<th>No. of participants</th>
<th>Statistical method</th>
<th>Effect size</th>
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<tr>
<td>10</td>
<td>6187</td>
<td>Relative Risk (Fixed) 95% CI</td>
<td>1.07 [0.90, 1.26]</td>
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25 Cardiovascular events

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<th>No. of participants</th>
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<th>Effect size</th>
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<tr>
<td>5</td>
<td>5163</td>
<td>Relative Risk (Fixed) 95% CI</td>
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26 Oral moniliasis

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<th>No. of participants</th>
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<th>Effect size</th>
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</thead>
<tbody>
<tr>
<td>6</td>
<td>5203</td>
<td>Relative Risk (Fixed) 95% CI</td>
<td>1.86 [1.00, 3.44]</td>
</tr>
</tbody>
</table>

27 Osteopenia/osteoporosis

<table>
<thead>
<tr>
<th>No. of studies</th>
<th>No. of participants</th>
<th>Statistical method</th>
<th>Effect size</th>
</tr>
</thead>
<tbody>
<tr>
<td>2</td>
<td>2963</td>
<td>Relative Risk (Fixed) 95% CI</td>
<td>0.56 [0.12, 2.63]</td>
</tr>
</tbody>
</table>

28 Elevated liver enzymes

<table>
<thead>
<tr>
<th>No. of studies</th>
<th>No. of participants</th>
<th>Statistical method</th>
<th>Effect size</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Total not selected</td>
<td></td>
</tr>
</tbody>
</table>

29 Overall adverse events

<table>
<thead>
<tr>
<th>No. of studies</th>
<th>No. of participants</th>
<th>Statistical method</th>
<th>Effect size</th>
</tr>
</thead>
<tbody>
<tr>
<td>8</td>
<td>5911</td>
<td>Relative Risk (Fixed) 95% CI</td>
<td>1.03 [0.99, 1.07]</td>
</tr>
</tbody>
</table>

30 Patient treatment satisfaction

<table>
<thead>
<tr>
<th>No. of studies</th>
<th>No. of participants</th>
<th>Statistical method</th>
<th>Effect size</th>
</tr>
</thead>
<tbody>
<tr>
<td>3</td>
<td>2020</td>
<td>Relative Risk (Random) 95% CI</td>
<td>1.12 [1.04,1.20]</td>
</tr>
</tbody>
</table>

31 Change from baseline in serum eosinophils (x 10e9/L)

<table>
<thead>
<tr>
<th>No. of studies</th>
<th>No. of participants</th>
<th>Statistical method</th>
<th>Effect size</th>
</tr>
</thead>
<tbody>
<tr>
<td>2</td>
<td>2787</td>
<td>Weighted Mean Difference (Fixed) 95% CI</td>
<td>0.04 [0.02, 0.05]</td>
</tr>
</tbody>
</table>

### Comparison 02. LABA + ICS vs LITRA + ICS (subgroup analyses)

<table>
<thead>
<tr>
<th>Outcome title</th>
<th>No. of studies</th>
<th>No. of participants</th>
<th>Statistical method</th>
<th>Effect size</th>
</tr>
</thead>
<tbody>
<tr>
<td>01 PRIMARY OUTCOME: Subgroup analysis (Separate inhalers vs. Single inhaler use for delivery of LABA+ICS)</td>
<td>6</td>
<td>5571</td>
<td>Relative Risk (Fixed) 95% CI</td>
<td>0.83 [0.71, 0.97]</td>
</tr>
<tr>
<td>02 Serious adverse effects stratified by # devices used for LABA + ICS</td>
<td>6</td>
<td>5592</td>
<td>Relative Risk (Fixed) 95% CI</td>
<td>1.32 [0.98, 1.79]</td>
</tr>
</tbody>
</table>

### INDEX TERMS

Medical Subject Headings (MeSH)
Adrenal Cortex Hormones [*therapeutic use*]; Adrenergic beta-Agonists [*therapeutic use*]; Asthma [*drug therapy*]; Chronic Disease; Drug Therapy, Combination; Leukotriene Antagonists [*therapeutic use*]; Randomized Controlled Trials

MeSH check words
Adult; Child; Humans

### COVER SHEET

**Title**
Long-acting beta2-agonists versus anti-leukotrienes as add-on therapy to inhaled corticosteroids for chronic asthma

**Authors**
Ducharme FM, Lasserson TJ, Cates CJ

**Contribution of author(s)**
Francine M. Ducharme overviewed the protocol design, supervised the literature search, reviewed all citations, participated in the selection of trials, methodology assessment, and data extraction, corresponded with authors and/or the pharmaceutical companies to identify other relevant trials, verify methodology and data extraction and request additional information, analysed and interpreted results of the meta-analysis, and took part in writing up the final review.
Toby Lasserson (Update 2006): Assessed studies for inclusion/exclusion, extracted & entered data, revised Results section of the review.
Christopher Cates edited the review, checked the methodology, and contributed to writing up the final review.

Felix Ram participated in the initial version of the review (2005), protocol design, identified and reviewed the full-text publication of all citations of potential or potentially eligible RCTs, extracted the methodology and data, analysed and interpreted results of the meta-analysis, and wrote the first draft of the review.

**Issue protocol first published**
2003/3

**Review first published**
2005/1

**Date of most recent amendment**
22 August 2006

**Date of most recent SUBSTANTIVE amendment**
20 June 2006

**What's New**
Five new studies met the entry criteria of the review (Ceylan 2004; Grosclaude 2003; Hendeles 2004; Stelmach 2005; Storms 2004). Of these, two studies contributed data to this updated review. The additional data did not alter the conclusions of the review.

**Date new studies sought but none found**
03 February 2004

**Date new studies found but not yet included/excluded**
Information not supplied by author

**Date new studies found and included/excluded**
01 March 2006

**Date authors’ conclusions section amended**
Information not supplied by author

**Contact address**
Prof Francine Ducharme
The Montreal Children’s Hospital
Rm C-538E
2300 Tupper Street
Montreal
Quebec
H3H 1P3
CANADA
E-mail: francine.ducharme@muhc.mcgill.ca
Tel: +1 514 412 4400
Fax: +1 514 412 4393

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**Cochrane Library number**
CD003137

**Editorial group**
Cochrane Airways Group

**Editorial group code**
HM-AIRWAYS
Figure 01. Primary outcome funnel plot

Review: Anti-leukotrienes versus long-acting beta2-agonists as add-on therapy to inhaled corticosteroids in chronic asthma
Comparison: Leukotriene receptor antagonists + ICS versus Long-acting beta2-agonists + ICS
Outcome: PRIMARY OUTCOME: PATIENTS WITH ONE OR MORE EXACERBATIONS REQUIRING SYSTEMIC CORTICOSTEROIDS
Figure 02. Number needed to treat with LABA rather than LRTA in addition to ICS to prevent one patient having one or more exacerbations over 48 weeks.
**Analysis 01.01.** Comparison 01 Leukotriene receptor antagonists + ICS versus Long-acting β2-agonists + ICS,
Outcome 01 PRIMARY OUTCOME: PATIENTS WITH ONE OR MORE EXACERBATIONS REQUIRING SYSTEMIC CORTICOSTEROIDS

Review: Long-acting beta2-agonists versus anti-leukotrienes as add-on therapy to inhaled corticosteroids for chronic asthma
Comparison: 01 Leukotriene receptor antagonists + ICS versus Long-acting β2-agonists + ICS
Outcome: 01 PRIMARY OUTCOME: PATIENTS WITH ONE OR MORE EXACERBATIONS REQUIRING SYSTEMIC CORTICOSTEROIDS

<table>
<thead>
<tr>
<th>Study</th>
<th>LABA + ICS n/N</th>
<th>LTRA + ICS n/N</th>
<th>Relative Risk (Fixed)</th>
<th>Weight (%)</th>
<th>Relative Risk (Fixed) 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>01 Montelukast 10 mg once daily vs. Salmeterol 50 mcg twice daily</td>
<td>107/743</td>
<td>118/747</td>
<td>38.8</td>
<td>0.91 [ 0.72, 1.16 ]</td>
<td></td>
</tr>
<tr>
<td>Bjermer 2003</td>
<td>16/476</td>
<td>16/472</td>
<td>5.3</td>
<td>0.99 [ 0.50, 1.96 ]</td>
<td></td>
</tr>
<tr>
<td>Ilowite 2004</td>
<td>102/734</td>
<td>123/734</td>
<td>40.1</td>
<td>0.85 [ 0.67, 1.08 ]</td>
<td></td>
</tr>
<tr>
<td>Nelson 2000</td>
<td>3/222</td>
<td>10/225</td>
<td>3.3</td>
<td>0.30 [ 0.08, 1.09 ]</td>
<td></td>
</tr>
<tr>
<td>Ringdal 2003</td>
<td>17/404</td>
<td>31/401</td>
<td>10.3</td>
<td>0.54 [ 0.31, 0.97 ]</td>
<td></td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td>2563</td>
<td>2579</td>
<td>97.7</td>
<td>0.83 [ 0.71, 0.97 ]</td>
<td></td>
</tr>
<tr>
<td>Total events: 245 (LABA + ICS), 298 (LTRA + ICS)</td>
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<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Test for heterogeneity chi-square=5.31 df=4 p=0.26 I² =24.7%</td>
<td></td>
<td></td>
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<tr>
<td>Test for overall effect z=2.31 p=0.02</td>
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</table>

<table>
<thead>
<tr>
<th>Study</th>
<th>LABA + ICS n/N</th>
<th>LTRA + ICS n/N</th>
<th>Relative Risk (Fixed)</th>
<th>Weight (%)</th>
<th>Relative Risk (Fixed) 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>02 Zafirlukast 20 mg twice daily vs. Salmeterol 50 mcg twice daily</td>
<td>6/214</td>
<td>7/215</td>
<td>2.3</td>
<td>0.86 [ 0.29, 2.52 ]</td>
<td></td>
</tr>
<tr>
<td>Nelson 2001</td>
<td>214</td>
<td>215</td>
<td>2.3</td>
<td>0.86 [ 0.29, 2.52 ]</td>
<td></td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td>2777</td>
<td>2794</td>
<td>100.0</td>
<td>0.83 [ 0.71, 0.97 ]</td>
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</tr>
<tr>
<td>Total events: 6 (LABA + ICS), 7 (LTRA + ICS)</td>
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<td></td>
<td></td>
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<tr>
<td>Test for heterogeneity: not applicable</td>
<td></td>
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<tr>
<td>Test for overall effect z=0.27 p=0.8</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Total (95% CI) 2777 2794 100.0 0.83 [ 0.71, 0.97 ]

Test for heterogeneity chi-square=5.31 df=5 p=0.38 I² =5.9%
Test for overall effect z=2.32 p=0.02
**Analysis 01.02. Comparison 01 Leukotriene receptor antagonists + ICS versus Long-acting β2-agonists + ICS, Outcome 02 Morning PEF (L/min) - change from baseline**

**Review:** Long-acting β2-agonists versus anti-leukotrienes as add-on therapy to inhaled corticosteroids for chronic asthma

**Comparison:** 01 Leukotriene receptor antagonists + ICS versus Long-acting β2-agonists + ICS

**Outcome:** 02 Morning PEF (L/min) - change from baseline

<table>
<thead>
<tr>
<th>Study</th>
<th>LABA +ICS</th>
<th>LTRA +ICS</th>
<th>Weighted Mean Difference (Fixed)</th>
<th>Weight (%)</th>
<th>Weighted Mean Difference (Fixed)</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>N Mean(SD)</td>
<td>N Mean(SD)</td>
<td>95% CI (%)</td>
<td></td>
<td>95% CI</td>
</tr>
<tr>
<td>01 Montelukast 10 mg once daily vs. Salmeterol 50 mcg twice daily</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bjørner 2003</td>
<td>725 34.59 (45.77)</td>
<td>732 17.73 (45.72)</td>
<td>27.1</td>
<td>16.86 [12.16, 21.56]</td>
<td></td>
</tr>
<tr>
<td>Fish 2001</td>
<td>476 35.00 (44.60)</td>
<td>472 21.70 (44.20)</td>
<td>18.7</td>
<td>13.30 [7.65, 18.95]</td>
<td></td>
</tr>
<tr>
<td>Grosclaude 2003</td>
<td>119 44.20 (43.63)</td>
<td>127 31.00 (42.82)</td>
<td>5.1</td>
<td>13.20 [2.39, 24.01]</td>
<td></td>
</tr>
<tr>
<td>Ilowite 2004</td>
<td>646 55.00 (71.17)</td>
<td>651 40.80 (71.44)</td>
<td>9.9</td>
<td>14.20 [6.44, 21.96]</td>
<td></td>
</tr>
<tr>
<td>McCarthy 2003</td>
<td>33 61.50 (37.30)</td>
<td>33 29.60 (50.20)</td>
<td>1.3</td>
<td>31.90 [10.56, 53.24]</td>
<td></td>
</tr>
<tr>
<td>Nelson 2000</td>
<td>197 29.60 (37.89)</td>
<td>190 13.20 (37.22)</td>
<td>10.7</td>
<td>16.40 [8.92, 23.88]</td>
<td></td>
</tr>
<tr>
<td>Ringdal 2003</td>
<td>288 42.00 (42.43)</td>
<td>279 26.00 (45.10)</td>
<td>11.5</td>
<td>16.00 [8.79, 23.21]</td>
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</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td>2484</td>
<td>2484</td>
<td></td>
<td></td>
<td>84.4 [12.93, 18.26]</td>
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<tr>
<td><strong>Test for heterogeneity chi-square</strong>=3.52 df=6 (p=0.74) (I^2=0.0%)</td>
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<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Test for overall effect</strong> (z=11.48) (p&lt;0.00001)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

| 02 Zafirlukast 20 mg twice daily vs. Salmeterol 50 mcg or Formoterol 9 mg twice daily | | | | | |
| Hultquist 2000 | 117 33.86 (63.71) | 116 29.39 (63.87) | 2.2 | 4.47 \[-11.91, 20.85\] |
| Nelson 2001 | 214 28.80 (45.40) | 214 13.00 (36.60) | 9.8 | 15.80 \[7.99, 23.61\] |
| Subtotal (95% CI) | 331 | 330 | | | 12.0 \[6.65, 20.75\] |
| **Test for heterogeneity chi-square**=1.50 df=1 \(p=0.22\) \(I^2=33.2\%\) | | | | | |
| **Test for overall effect** \(z=3.81\) \(p=0.0001\) | | | | | |

| 03 Montelukast 10 mg once daily versus formoterol 18mg twice daily | | | | | |
| Ceylan 2004 | 20 54.30 (15.10) | 20 30.50 (25.30) | 3.6 | 23.80 \[10.89, 36.71\] |
| Subtotal (95% CI) | 20 | 20 | | | 3.6 \[10.89, 36.71\] |
| **Test for heterogeneity: not applicable** | | | | | |
| **Test for overall effect** \(z=3.61\) \(p=0.0003\) | | | | | |
| Total (95% CI) | 2835 | 2834 | | | 100.0 \[13.21, 18.11\] |
| **Test for heterogeneity chi-square**=6.85 df=9 \(p=0.65\) \(I^2=0.0\%\) | | | | | |
| **Test for overall effect** \(z=12.55\) \(p<0.00001\) | | | | | |
**Analysis 01.03. Comparison 01 Leukotriene receptor antagonists + ICS versus Long-acting ß2-agonists + ICS, Outcome 03 Evening PEF (L/min) - change from baseline**

Review: Long-acting beta2-agonists versus anti-leukotrienes as add-on therapy to inhaled corticosteroids for chronic asthma

Comparison: 01 Leukotriene receptor antagonists + ICS versus Long-acting ß2-agonists + ICS

Outcome: 03 Evening PEF (L/min) - change from baseline

<table>
<thead>
<tr>
<th>Study</th>
<th>LABA + ICS</th>
<th>LTR + ICS</th>
<th>Weighted Mean Difference (Fixed)</th>
<th>Weight (%)</th>
<th>Weighted Mean Difference (Fixed)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N Mean(SD)</td>
<td>N Mean(SD)</td>
<td>95% CI (%)</td>
<td></td>
<td>95% CI</td>
</tr>
<tr>
<td>01 Montelukast 10 mg once daily vs. Salmeterol 50 mcg twice daily</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fish 2001</td>
<td>451</td>
<td>27.80 (42.50)</td>
<td>444</td>
<td>19.00 (42.10)</td>
<td>26.1</td>
</tr>
<tr>
<td>Grosclaude 2003</td>
<td>119</td>
<td>37.40 (40.36)</td>
<td>127</td>
<td>25.20 (41.70)</td>
<td>7.6</td>
</tr>
<tr>
<td>Ilowite 2004</td>
<td>564</td>
<td>47.40 (71.25)</td>
<td>579</td>
<td>33.40 (72.19)</td>
<td>11.6</td>
</tr>
<tr>
<td>McCarthy 2003</td>
<td>33</td>
<td>40.00 (44.80)</td>
<td>33</td>
<td>21.10 (37.00)</td>
<td>2.0</td>
</tr>
<tr>
<td>Nelson 2000</td>
<td>197</td>
<td>21.80 (35.09)</td>
<td>191</td>
<td>10.00 (34.55)</td>
<td>16.7</td>
</tr>
<tr>
<td>Ringdal 2003</td>
<td>271</td>
<td>37.00 (41.16)</td>
<td>250</td>
<td>20.00 (41.11)</td>
<td>16.0</td>
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<tr>
<td>Subtotal (95% CI)</td>
<td>1635</td>
<td>1624</td>
<td>80.0</td>
<td>12.40 [ 9.24, 15.57 ]</td>
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<tr>
<td>Test for heterogeneity chi-square=3.83 df=5 p=0.57 I² =0.0%</td>
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<tr>
<td>Test for overall effect z=7.68 p&lt;0.00001</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>02 Zafirlukast 20 mg twice daily vs. Salmeterol 50 mcg or Formoterol 9 mg twice daily</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hultquist 2000</td>
<td>117</td>
<td>24.02 (63.60)</td>
<td>116</td>
<td>20.10 (62.68)</td>
<td>3.0</td>
</tr>
<tr>
<td>Nelson 2001</td>
<td>213</td>
<td>21.80 (43.80)</td>
<td>213</td>
<td>11.20 (38.00)</td>
<td>13.2</td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td>330</td>
<td>329</td>
<td>16.3</td>
<td>9.35 [ 2.33, 16.37 ]</td>
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</tr>
<tr>
<td>Test for heterogeneity chi-square=0.53 df=1 p=0.47 I² =0.0%</td>
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<tr>
<td>Test for overall effect z=2.61 p=0.009</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>03 Montelukast 10 mg once daily versus formoterol 18mg twice daily</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ceylan 2004</td>
<td>20</td>
<td>44.50 (23.30)</td>
<td>20</td>
<td>27.00 (24.10)</td>
<td>3.7</td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td>20</td>
<td>20</td>
<td>3.7</td>
<td>17.50 [ 2.81, 32.19 ]</td>
<td></td>
</tr>
<tr>
<td>Test for heterogeneity: not applicable</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test for overall effect z=2.33 p=0.02</td>
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<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>1985</td>
<td>1973</td>
<td>100.0</td>
<td>12.09 [ 9.26, 14.92 ]</td>
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</tr>
<tr>
<td>Test for heterogeneity chi-square=5.51 df=8 p=0.70 I² =0.0%</td>
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<td></td>
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<td></td>
</tr>
<tr>
<td>Test for overall effect z=8.37 p&lt;0.00001</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

-100.0  -50.0  0   50.0  100.0
Favours LTRA + ICS  Favours LABA + ICS

Long-acting beta2-agonists versus anti-leukotrienes as add-on therapy to inhaled corticosteroids for chronic asthma (Review) 69
Copyright © 2007 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd
### Analysis 01.04. Comparison 01 Leukotriene receptor antagonists + ICS versus Long-acting β2-agonists + ICS, Outcome 04 FEV1 (L) - change from baseline

**Review:** Long-acting β2-agonists versus anti-leukotrienes as add-on therapy to inhaled corticosteroids for chronic asthma

**Comparison:** 01 Leukotriene receptor antagonists + ICS versus Long-acting β2-agonists + ICS

**Outcome:** 04 FEV1 (L) - change from baseline

<table>
<thead>
<tr>
<th>Study</th>
<th>LABA + ICS</th>
<th>LTRA + ICS</th>
<th>Weighted Mean Difference (Fixed)</th>
<th>Weight (%)</th>
<th>Weighted Mean Difference (Fixed)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N</td>
<td>Mean(SD)</td>
<td>N</td>
<td>Mean(SD)</td>
<td>95% CI (%)</td>
</tr>
<tr>
<td>01 Montelukast 10 mg once daily vs. Salmeterol 50 mcg twice daily</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bjermer 2003</td>
<td>695</td>
<td>0.19 (0.53)</td>
<td>688</td>
<td>0.11 (0.52)</td>
<td>14.2</td>
</tr>
<tr>
<td>Ilowite 2004</td>
<td>602</td>
<td>0.18 (0.25)</td>
<td>621</td>
<td>0.11 (0.25)</td>
<td>55.6</td>
</tr>
<tr>
<td>McCarthy 2003</td>
<td>33</td>
<td>0.39 (0.36)</td>
<td>33</td>
<td>0.31 (0.43)</td>
<td>1.2</td>
</tr>
<tr>
<td>Nelson 2000</td>
<td>197</td>
<td>0.35 (0.42)</td>
<td>195</td>
<td>0.20 (0.42)</td>
<td>6.3</td>
</tr>
<tr>
<td>Ringdal 2003</td>
<td>364</td>
<td>0.28 (0.38)</td>
<td>355</td>
<td>0.17 (0.38)</td>
<td>14.1</td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td>1891</td>
<td></td>
<td>1892</td>
<td></td>
<td>91.4</td>
</tr>
<tr>
<td>Test for heterogeneity chi-square=4.24 df=4 p=0.37 I² =5.6%</td>
<td>Test for overall effect z=7.48 p&lt;0.00001</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

| 02 Zafirlukast 20mg twice daily vs. Salmeterol 50 mcg or Formoterol 9mcg twice daily | | | | | | | | | | | | | |
| Hultquist 2000 | 117 | 0.22 (0.54) | 116 | 0.11 (0.54) | 2.3 | 0.11 [-0.03, 0.25 ] | | | | | |
| Nelson 2001 | 214 | 0.26 (0.44) | 215 | 0.23 (0.44) | 6.3 | 0.03 [-0.05, 0.11 ] | | | | | |
| Subtotal (95% CI) | 331 | | 331 | | 8.6 | 0.05 [-0.02, 0.12 ] | | | | | |
| Test for heterogeneity chi-square=0.94 df=1 p=0.33 I² =0.0% | Test for overall effect z=1.41 p=0.2 |

| 03 Montelukast 10 mg once daily versus formoterol 18mg twice daily | | | | | | | | | | | | | |
| x Ceylan 2004 | 20 | 0.36 (0.00) | 20 | 0.19 (0.00) | 0.0 | Not estimable | | | | | |
| Subtotal (95% CI) | 20 | | 20 | | 0.0 | Not estimable | | | | | |
| Test for heterogeneity: not applicable | Test for overall effect: not applicable |

| Total (95% CI) | 2242 | 2243 | 100.0 | 0.08 [ 0.06, 0.10 ] | | Test for overall effect z=7.57 p<0.00001 |

-0.5 -0.25 0 0.25 0.5

Favours LTRA + ICS Favours LABA + ICS
Analysis 01.05. Comparison 01 Leukotriene receptor antagonists + ICS versus Long-acting β2-agonists + ICS,
Outcome 05 FEV1 (L) - % change from baseline

Review: Long-acting beta2-agonists versus anti-leukotrienes as add-on therapy to inhaled corticosteroids for chronic asthma
Comparison: 01 Leukotriene receptor antagonists + ICS versus Long-acting β2-agonists + ICS
Outcome: 05 FEV1 (L) - % change from baseline

<table>
<thead>
<tr>
<th>Study</th>
<th>LABA + ICS</th>
<th>LTRA + ICS</th>
<th>Weighted Mean Difference (Fixed)</th>
<th>Weighted Mean Difference (Fixed)</th>
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<tbody>
<tr>
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<td>N Mean(SD)</td>
<td>N Mean(SD)</td>
<td>95% CI</td>
<td>95% CI</td>
</tr>
<tr>
<td>01 Montelukast 10 mg once daily vs. Salmeterol 50 mcg twice daily</td>
<td>34 1.70 (9.50)</td>
<td>36 10.90 (8.50)</td>
<td>-9.20 [-13.43, -4.97]</td>
<td></td>
</tr>
<tr>
<td>02 Zafirlukast 20mg twice daily vs. Salmeterol 50 mcg or Formoterol 9mcg twice daily</td>
<td>-</td>
<td>-</td>
<td>-</td>
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</table>

Favours LTRA + ICS  Favours LABA + ICS

Analysis 01.06. Comparison 01 Leukotriene receptor antagonists + ICS versus Long-acting β2-agonists + ICS,
Outcome 06 FEV1 (% predicted) @ 4 wks

Review: Long-acting beta2-agonists versus anti-leukotrienes as add-on therapy to inhaled corticosteroids for chronic asthma
Comparison: 01 Leukotriene receptor antagonists + ICS versus Long-acting β2-agonists + ICS
Outcome: 06 FEV1 (% predicted) @ 4 wks

<table>
<thead>
<tr>
<th>Study</th>
<th>LABA + ICS</th>
<th>LTRA + ICS</th>
<th>Weighted Mean Difference (Fixed)</th>
<th>Weighted Mean Difference (Fixed)</th>
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<tbody>
<tr>
<td></td>
<td>N Mean(SD)</td>
<td>N Mean(SD)</td>
<td>95% CI</td>
<td>95% CI</td>
</tr>
<tr>
<td>01 Montelukast 10 mg once daily vs. Salmeterol 50 mcg twice daily</td>
<td>34 91.20 (10.10)</td>
<td>36 86.60 (11.00)</td>
<td>4.60 [-.34, 9.54]</td>
<td></td>
</tr>
<tr>
<td>02 Zafirlukast 20mg twice daily vs. Salmeterol 50 mcg or Formoterol 9mcg twice daily</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td></td>
</tr>
</tbody>
</table>

Favours LTRA + ICS  Favours LABA + ICS
Analysis 01.07.  Comparison 01 Leukotriene receptor antagonists + ICS versus Long-acting ß2-agonists + ICS,
Outcome 07 % fall in FEV1 POST-EXERCISE

Review:  Long-acting beta2-agonists versus anti-leukotrienes as add-on therapy to inhaled corticosteroids for chronic asthma
Comparison:  01 Leukotriene receptor antagonists + ICS versus Long-acting ß2-agonists + ICS
Outcome:  07 % fall in FEV1 POST-EXERCISE

<table>
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<tr>
<th>Study</th>
<th>LABA + ICS</th>
<th>LTRA + ICS</th>
<th>Weighted Mean Difference (Fixed)</th>
<th>Weighted Mean Difference (Fixed)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N</td>
<td>Mean(SD)</td>
<td>N</td>
<td>Mean(SD)</td>
</tr>
<tr>
<td>01 Montelukast 10 mg once daily vs. Salmeterol 50 mcg twice daily</td>
<td>Storms 2004</td>
<td>34</td>
<td>10.50 (10.00)</td>
<td>36</td>
</tr>
<tr>
<td>02 Zafirlukast 20mg twice daily vs. Salmeterol 50 mcg or Formoterol 9mcg twice daily</td>
<td></td>
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</tbody>
</table>

Analysis 01.08.  Comparison 01 Leukotriene receptor antagonists + ICS versus Long-acting ß2-agonists + ICS,
Outcome 08 Rescue-free days (%) - change from baseline

Review:  Long-acting beta2-agonists versus anti-leukotrienes as add-on therapy to inhaled corticosteroids for chronic asthma
Comparison:  01 Leukotriene receptor antagonists + ICS versus Long-acting ß2-agonists + ICS
Outcome:  08 Rescue-free days (%) - change from baseline

<table>
<thead>
<tr>
<th>Study</th>
<th>LABA + ICS</th>
<th>LTRA + ICS</th>
<th>Weighted Mean Difference (Random)</th>
<th>Weighted Mean Difference (Random)</th>
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</thead>
<tbody>
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<td>N</td>
<td>Mean(SD)</td>
<td>N</td>
<td>Mean(SD)</td>
</tr>
<tr>
<td>01 Montelukast 10 mg once daily vs. Salmeterol 50 mcg twice daily</td>
<td>Fish 2001</td>
<td>45</td>
<td>27.40 (34.00)</td>
<td>443</td>
</tr>
<tr>
<td></td>
<td>Grosclaude 2003</td>
<td>117</td>
<td>40.40 (30.90)</td>
<td>124</td>
</tr>
<tr>
<td></td>
<td>Nelson 2000</td>
<td>196</td>
<td>32.70 (39.20)</td>
<td>189</td>
</tr>
<tr>
<td></td>
<td>Ringdal 2003</td>
<td>337</td>
<td>32.00 (38.55)</td>
<td>326</td>
</tr>
<tr>
<td></td>
<td>Subtotal (95% CI)</td>
<td>1101</td>
<td>1082</td>
<td>78.0</td>
</tr>
<tr>
<td></td>
<td>Test for heterogeneity chi-square =2.15 df=3 p=0.54 I² =0.0%</td>
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</tr>
<tr>
<td></td>
<td>Test for overall effect z=4.92 p&lt;0.00001</td>
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</tr>
<tr>
<td>02 Zafirlukast 20 mg twice daily vs. Salmeterol 50 mcg twice daily</td>
<td>Nelson 2001</td>
<td>214</td>
<td>27.00 (32.20)</td>
<td>215</td>
</tr>
<tr>
<td></td>
<td>Subtotal (95% CI)</td>
<td>214</td>
<td>215</td>
<td>22.0</td>
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<tr>
<td></td>
<td>Test for heterogeneity: not applicable</td>
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</tr>
<tr>
<td></td>
<td>Test for overall effect z=5.27 p&lt;0.00001</td>
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<td></td>
</tr>
<tr>
<td></td>
<td>Total (95% CI)</td>
<td>1315</td>
<td>1297</td>
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<tr>
<td></td>
<td>Test for heterogeneity chi-square =7.85 df=4 p=0.10 I² =49.1%</td>
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<tr>
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<td>Test for overall effect z=4.74 p&lt;0.00001</td>
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</table>
Analysis 01.09. Comparison 01 Leukotriene receptor antagonists + ICS versus Long-acting \( \beta_2 \)-agonists + ICS, Outcome 09 Rescue medication use (puffs/day) - change from baseline

Review: Long-acting beta\( \beta_2 \)-agonists versus anti-leukotrienes as add-on therapy to inhaled corticosteroids for chronic asthma

Comparison: 01 Leukotriene receptor antagonists + ICS versus Long-acting \( \beta_2 \)-agonists + ICS

Outcome: 09 Rescue medication use (puffs/day) - change from baseline

<table>
<thead>
<tr>
<th>Study</th>
<th>LABA + ICS</th>
<th>LTRA + ICS</th>
<th>Weighted Mean Difference (Random)</th>
<th>Weight (%)</th>
<th>Weighted Mean Difference (Random)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N</td>
<td>Mean(SD)</td>
<td>N</td>
<td>Mean(SD)</td>
<td>95% CI</td>
</tr>
<tr>
<td>01 Montelukast 10 mg once daily vs. Salmeterol 50 mcg twice daily</td>
<td>451</td>
<td>-1.90 (2.12)</td>
<td>443</td>
<td>-1.66 (2.32)</td>
<td>15.2 -0.24 [-0.53, 0.05]</td>
</tr>
<tr>
<td>Fish 2001</td>
<td>702</td>
<td>-1.66 (1.59)</td>
<td>709</td>
<td>-1.15 (1.60)</td>
<td>17.6 -0.51 [-0.68, -0.34]</td>
</tr>
<tr>
<td>Ilowite 2004</td>
<td>196</td>
<td>-1.86 (2.24)</td>
<td>189</td>
<td>-1.30 (2.06)</td>
<td>12.3 -0.56 [-0.99, -0.13]</td>
</tr>
<tr>
<td>Nelson 2000</td>
<td>337</td>
<td>-0.98 (1.84)</td>
<td>326</td>
<td>-0.78 (1.26)</td>
<td>16.3 -0.20 [-0.44, 0.04]</td>
</tr>
<tr>
<td>Ringdal 2003</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>61.4 -0.37 [-0.56, -0.19]</td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td>1686</td>
<td></td>
<td>1667</td>
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</tr>
<tr>
<td>Test for heterogeneity chi-square=6.03 df=3 p=0.11 I(^2) =50.3%</td>
<td></td>
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<tr>
<td>Test for overall effect z=3.93 p=0.00009</td>
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<td></td>
</tr>
<tr>
<td>02 Zafirlukast 20 mg twice daily vs. Salmeterol 50 mcg or Formoterol 9 mg twice daily</td>
<td>117</td>
<td>-1.86 (1.84)</td>
<td>116</td>
<td>-1.73 (1.83)</td>
<td>11.4 -0.13 [-0.60, 0.34]</td>
</tr>
<tr>
<td>Hultquist 2000</td>
<td>214</td>
<td>-1.46 (1.90)</td>
<td>215</td>
<td>-0.95 (1.47)</td>
<td>14.6 -0.51 [-0.83, -0.19]</td>
</tr>
<tr>
<td>Nelson 2001</td>
<td>331</td>
<td>-0.98 (1.84)</td>
<td>331</td>
<td>-0.78 (1.26)</td>
<td>26.0 -0.36 [-0.72, 0.00]</td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
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<td></td>
<td></td>
<td></td>
<td>26.0 -0.36 [-0.72, 0.00]</td>
</tr>
<tr>
<td>Test for heterogeneity chi-square=1.70 df=1 p=0.19 I(^2) =41.3%</td>
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<tr>
<td>Test for overall effect z=1.94 p=0.05</td>
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</tr>
<tr>
<td>03 Montelukast 10 mg once daily versus formoterol 18mg twice daily</td>
<td>20</td>
<td>-1.90 (0.50)</td>
<td>20</td>
<td>-0.50 (0.80)</td>
<td>12.6 -1.40 [-1.81, -0.99]</td>
</tr>
<tr>
<td>Ceylan 2004</td>
<td>20</td>
<td>-1.90 (0.50)</td>
<td>20</td>
<td>-0.50 (0.80)</td>
<td>12.6 -1.40 [-1.81, -0.99]</td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td>20</td>
<td></td>
<td>20</td>
<td></td>
<td>12.6 -1.40 [-1.81, -0.99]</td>
</tr>
<tr>
<td>Test for heterogeneity: not applicable</td>
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</tr>
<tr>
<td>Test for overall effect z=6.64 p&lt;0.00001</td>
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<tr>
<td>Total (95% CI)</td>
<td>2037</td>
<td></td>
<td>2018</td>
<td></td>
<td>100.0 -0.49 [-0.75, -0.24]</td>
</tr>
<tr>
<td>Test for heterogeneity chi-square=29.10 df=6 p&lt;0.00001 I(^2) =79.4%</td>
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<tr>
<td>Test for overall effect z=3.84 p&lt;0.00001</td>
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</tbody>
</table>

Favours LABA + ICS  Favours LTRA + ICS
### Analysis 01.10. Comparison 01 Leukotriene receptor antagonists + ICS versus Long-acting ß2-agonists + ICS, Outcome 10 Change in Global asthma QoL AQLQ Score (higher is better) - change from baseline

Review: Long-acting beta2-agonists versus anti-leukotrienes as add-on therapy to inhaled corticosteroids for chronic asthma

Comparison: 01 Leukotriene receptor antagonists + ICS versus Long-acting ß2-agonists + ICS

Outcome: 10 Change in Global asthma QoL AQLQ Score (higher is better) - change from baseline

<table>
<thead>
<tr>
<th>Study</th>
<th>LABA + ICS</th>
<th>LTRA + ICS</th>
<th>Weighted Mean Difference (Fixed)</th>
<th>Weight (%)</th>
<th>Weighted Mean Difference (Fixed)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N Mean(SD)</td>
<td>N Mean(SD)</td>
<td>95% CI</td>
<td></td>
<td>95% CI</td>
</tr>
<tr>
<td>01 Montelukast 10 mg once daily vs. Salmeterol 50 mcg twice daily</td>
<td></td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Björner 2003</td>
<td>581 0.76 (0.96)</td>
<td>581 0.71 (0.96)</td>
<td>-</td>
<td>31.2</td>
<td>0.05 [-0.06, 0.16]</td>
</tr>
<tr>
<td>Ilowite 2004</td>
<td>647 0.90 (0.76)</td>
<td>655 0.78 (0.77)</td>
<td>-</td>
<td>55.1</td>
<td>0.12 [0.04, 0.20]</td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td>1228</td>
<td>1236</td>
<td>-</td>
<td>86.3</td>
<td>0.09 [0.03, 0.16]</td>
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<tr>
<td>Test for heterogeneity chi-square=0.99 df=1 p=0.32 I² =0.0%</td>
<td></td>
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<tr>
<td>Test for overall effect z=2.79 p=0.005</td>
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</tr>
<tr>
<td>02 Zafirlukast 20 mg twice daily vs. Salmeterol 50 mcg twice daily</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nelson 2001</td>
<td>214 0.76 (0.88)</td>
<td>215 0.57 (0.88)</td>
<td>-</td>
<td>13.7</td>
<td>0.19 [0.02, 0.36]</td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
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<td>215</td>
<td>-</td>
<td>13.7</td>
<td>0.19 [0.02, 0.36]</td>
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<td>Test for heterogeneity: not applicable</td>
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<tr>
<td>Test for overall effect z=2.24 p=0.03</td>
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<tr>
<td>Total (95% CI)</td>
<td>1442</td>
<td>1451</td>
<td>-</td>
<td>100.0</td>
<td>0.11 [0.05, 0.17]</td>
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<tr>
<td>Test for heterogeneity chi-square=2.07 df=2 p=0.35 I² =3.5%</td>
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<tr>
<td>Test for overall effect z=3.42 p=0.0006</td>
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</tbody>
</table>

Favours LTRA + ICS  | Favours LABA + ICS

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Long-acting beta2-agonists versus anti-leukotrienes as add-on therapy to inhaled corticosteroids for chronic asthma (Review)  
Copyright © 2007 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd
### Analysis 01.11. Comparison 01 Leukotriene receptor antagonists + ICS versus Long-acting ß2-agonists + ICS,
**Outcome 11 Symptom free days (%) - change from baseline**

Review: Long-acting ß2-agonists versus anti-leukotrienes as add-on therapy to inhaled corticosteroids for chronic asthma

Comparison: 01 Leukotriene receptor antagonists + ICS versus Long-acting ß2-agonists + ICS

Outcome: 11 Symptom free days (%) - change from baseline

<table>
<thead>
<tr>
<th>Study</th>
<th>LABA + ICS</th>
<th>LTRA + ICS</th>
<th>Weighted Mean Difference (Random)</th>
<th>Weight</th>
<th>Weighted Mean Difference (Random)</th>
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<td>N</td>
<td>Mean(SD)</td>
<td>N</td>
<td>Mean(SD)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>01 Montelukast 10 mg once daily vs. Salmeterol 50 mcg twice daily</td>
<td>451</td>
<td>24.10 (31.90)</td>
<td>445</td>
<td>16.12 (40.80)</td>
<td>25.0</td>
</tr>
<tr>
<td>Fish 2001</td>
<td>117</td>
<td>42.70 (31.30)</td>
<td>125</td>
<td>33.40 (34.20)</td>
<td>8.90</td>
</tr>
<tr>
<td>Grosclaude 2003</td>
<td>197</td>
<td>25.10 (36.49)</td>
<td>191</td>
<td>24.00 (34.55)</td>
<td>1.10</td>
</tr>
<tr>
<td>Nelson 2000</td>
<td>341</td>
<td>38.00 (38.78)</td>
<td>330</td>
<td>35.00 (39.96)</td>
<td>3.00</td>
</tr>
<tr>
<td>Ringdal 2003</td>
<td>341</td>
<td>38.00 (38.78)</td>
<td>330</td>
<td>35.00 (39.96)</td>
<td>20.3</td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td>1106</td>
<td>25.0</td>
<td>7.98 [3.18, 12.78]</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Test for heterogeneity: \( \chi^2 = 4.00 \) df = 3 \( p = 0.26 \) \( I^2 = 25.1\% \)

Test for overall effect: \( z = 2.93 \) \( p = 0.003 \)

**Total (95% CI) 1106 75.4 [3.18, 12.78]**

### Analysis 01.12. Comparison 01 Leukotriene receptor antagonists + ICS versus Long-acting ß2-agonists + ICS,
**Outcome 12 Night-time symptom score (5pt scale, higher score is worse) - change from baseline**

Review: Long-acting ß2-agonists versus anti-leukotrienes as add-on therapy to inhaled corticosteroids for chronic asthma

Comparison: 01 Leukotriene receptor antagonists + ICS versus Long-acting ß2-agonists + ICS

Outcome: 12 Night-time symptom score (5pt scale, higher score is worse) - change from baseline

<table>
<thead>
<tr>
<th>Study</th>
<th>LABA + ICS</th>
<th>LTRA + ICS</th>
<th>Weighted Mean Difference (Fixed)</th>
<th>Weight</th>
<th>Weighted Mean Difference (Fixed)</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>Mean(SD)</td>
<td>N</td>
<td>Mean(SD)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>02 Zafirlukast 20 mg twice daily vs. Salmeterol 50 mcg twice daily</td>
<td>214</td>
<td>20.00 (29.30)</td>
<td>215</td>
<td>9.00 (22.00)</td>
<td>24.6</td>
</tr>
<tr>
<td>Nelson 2001</td>
<td>214</td>
<td>20.00 (29.30)</td>
<td>215</td>
<td>9.00 (22.00)</td>
<td>24.6</td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td>428</td>
<td>24.6</td>
<td>11.00 [6.10, 15.90]</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Test for heterogeneity: not applicable

Test for overall effect: \( z = 4.00 \) \( p = 0.00001 \)

**Total (95% CI) 428 6.75 [3.11, 10.39]**

Test for overall effect: \( z = 3.63 \) \( p = 0.0003 \)

### Analysis 01.12. Comparison 01 Leukotriene receptor antagonists + ICS versus Long-acting ß2-agonists + ICS,
**Outcome 12 Night-time symptom score (5pt scale, higher score is worse) - change from baseline**

Review: Long-acting ß2-agonists versus anti-leukotrienes as add-on therapy to inhaled corticosteroids for chronic asthma

Comparison: 01 Leukotriene receptor antagonists + ICS versus Long-acting ß2-agonists + ICS

Outcome: 12 Night-time symptom score (5pt scale, higher score is worse) - change from baseline

<table>
<thead>
<tr>
<th>Study</th>
<th>LABA + ICS</th>
<th>LTRA + ICS</th>
<th>Weighted Mean Difference (Fixed)</th>
<th>Weight</th>
<th>Weighted Mean Difference (Fixed)</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>Mean(SD)</td>
<td>N</td>
<td>Mean(SD)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>01 Zafirlukast 20 mg twice daily vs. Salmeterol 50 mcg twice daily</td>
<td>214</td>
<td>-0.43 (0.59)</td>
<td>215</td>
<td>-0.25 (0.59)</td>
<td>-0.18 [-0.29, -0.07]</td>
</tr>
</tbody>
</table>

-1.00 -0.50 0 0.50 1.00

Favours LTRA + ICS Favours LABA + ICS

Test for heterogeneity: not applicable

Test for overall effect: not applicable

**Total (95% CI) 428 6.75 [3.11, 10.39]**

Test for overall effect: not applicable

**Total (95% CI) 428 6.75 [3.11, 10.39]**
### Analysis 01.13. Comparison 01 Leukotriene receptor antagonists + ICS versus Long-acting ß2-agonists + ICS, Outcome 13 Day-time symptom scores (high is worse) - change from baseline

**Review:** Long-acting ß2-agonists versus anti-leukotrienes as add-on therapy to inhaled corticosteroids for chronic asthma

**Comparison:** 01 Leukotriene receptor antagonists + ICS versus Long-acting ß2-agonists + ICS

**Outcome:** 13 Day-time symptom scores (high is worse) - change from baseline

<table>
<thead>
<tr>
<th>Study</th>
<th>LABA + ICS</th>
<th>LTRA + ICS</th>
<th>Standardised Mean Difference (Fixed)</th>
<th>Weight (%)</th>
<th>Standardised Mean Difference (Fixed)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Montelukast 10 mg once daily versus Salmeterol 50 mcg twice daily</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fish 2001</td>
<td>451</td>
<td>-0.52 (0.64)</td>
<td>445  -0.42 (0.63)</td>
<td>23.5</td>
<td>-0.16 [-0.29, -0.03]</td>
</tr>
<tr>
<td>Ilowite 2004</td>
<td>711</td>
<td>-0.66 (0.80)</td>
<td>728  -0.48 (0.81)</td>
<td>37.6</td>
<td>-0.22 [-0.33, -0.12]</td>
</tr>
<tr>
<td>Nelson 2000</td>
<td>197</td>
<td>-0.59 (0.70)</td>
<td>191  -0.47 (0.69)</td>
<td>10.2</td>
<td>-0.17 [-0.37, 0.03]</td>
</tr>
<tr>
<td>Ringdal 2003</td>
<td>341</td>
<td>-0.97 (1.11)</td>
<td>330  -0.88 (1.27)</td>
<td>17.6</td>
<td>-0.08 [-0.23, 0.08]</td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td>1700</td>
<td></td>
<td></td>
<td>88.8</td>
<td>-0.17 [-0.24, -0.10]</td>
</tr>
</tbody>
</table>

Test for heterogeneity chi-square=2.56 df=3 p=0.47 I² =0.0%
Test for overall effect z=4.96 p=0.00001

<table>
<thead>
<tr>
<th>Study</th>
<th>LABA + ICS</th>
<th>LTRA + ICS</th>
<th>Standardised Mean Difference (Fixed)</th>
<th>Weight (%)</th>
<th>Standardised Mean Difference (Fixed)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Zafirlukast 20 mg twice daily versus Salmeterol 50 mcg twice daily</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nelson 2001</td>
<td>214</td>
<td>-0.39 (0.58)</td>
<td>215  -0.24 (0.44)</td>
<td>11.2</td>
<td>-0.29 [-0.48, -0.10]</td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td>214</td>
<td></td>
<td></td>
<td>11.2</td>
<td>-0.29 [-0.48, -0.10]</td>
</tr>
</tbody>
</table>

Test for heterogeneity: not applicable
Test for overall effect z=3.00 p=0.003

<table>
<thead>
<tr>
<th>Study</th>
<th>LABA + ICS</th>
<th>LTRA + ICS</th>
<th>Weighted Mean Difference (Fixed)</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Montelukast 10 mg once daily versus formoterol 18mg twice daily</td>
<td></td>
<td></td>
<td>-1.80 [-2.20, -1.40]</td>
<td></td>
</tr>
</tbody>
</table>

Analysis 01.14. Comparison 01 Leukotriene receptor antagonists + ICS versus Long-acting ß2-agonists + ICS, Outcome 14 Morning symptoms - change from baseline

**Review:** Long-acting ß2-agonists versus anti-leukotrienes as add-on therapy to inhaled corticosteroids for chronic asthma

**Comparison:** 01 Leukotriene receptor antagonists + ICS versus Long-acting ß2-agonists + ICS

**Outcome:** 14 Morning symptoms - change from baseline

<table>
<thead>
<tr>
<th>Study</th>
<th>LABA + ICS</th>
<th>LTRA + ICS</th>
<th>Weighted Mean Difference (Fixed)</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Montelukast 10 mg once daily versus formoterol 18mg twice daily</td>
<td></td>
<td></td>
<td>-1.80 [-2.20, -1.40]</td>
<td></td>
</tr>
</tbody>
</table>
### Analysis 01.15.  Comparison 01 Leukotriene receptor antagonists + ICS versus Long-acting β2-agonists + ICS, Outcome 15 Change in number of night awakenings per week - change from baseline

Review: Long-acting beta2-agonists versus anti-leukotrienes as add-on therapy to inhaled corticosteroids for chronic asthma

Comparison: Leukotriene receptor antagonists + ICS versus Long-acting β2-agonists + ICS

Outcome: Change in number of night awakenings per week - change from baseline

<table>
<thead>
<tr>
<th>Study</th>
<th>LABA + ICS</th>
<th>LTRA + ICS</th>
<th>Weighted Mean Difference (Fixed)</th>
<th>Weight (%)</th>
<th>Weighted Mean Difference (Fixed)</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>Mean(SD)</td>
<td>N</td>
<td>Mean(SD)</td>
<td></td>
<td>95% CI</td>
</tr>
<tr>
<td>01 Montelukast 10 mg once daily vs. Salmeterol 50 mcg twice daily</td>
<td>724</td>
<td>-1.74 (1.61)</td>
<td>731</td>
<td>-1.68 (1.62)</td>
<td>15.2</td>
</tr>
<tr>
<td>Bjermer 2003</td>
<td>451</td>
<td>-1.42 (2.76)</td>
<td>443</td>
<td>-1.32 (3.16)</td>
<td>2.8</td>
</tr>
<tr>
<td>Fish 2001</td>
<td>709</td>
<td>-1.02 (1.33)</td>
<td>727</td>
<td>-0.79 (1.35)</td>
<td>21.8</td>
</tr>
<tr>
<td>Ilowite 2004</td>
<td>1884</td>
<td>-0.74 (1.33)</td>
<td>1901</td>
<td>-0.79 (1.35)</td>
<td>39.7</td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td>1884</td>
<td>-0.74 (1.33)</td>
<td>1901</td>
<td>-0.79 (1.35)</td>
<td>39.7</td>
</tr>
<tr>
<td>Test for heterogeneity chi-square=2.46 df=2 p=0.29 I² =18.7%</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test for overall effect z=2.98 p=0.003</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>02 Zafirlukast 20 mg twice daily vs. Salmeterol 50 mcg twice daily</td>
<td>214</td>
<td>-0.19 (0.44)</td>
<td>215</td>
<td>-0.09 (0.44)</td>
<td>60.3</td>
</tr>
<tr>
<td>Nelson 2000</td>
<td>214</td>
<td>-0.19 (0.44)</td>
<td>215</td>
<td>-0.09 (0.44)</td>
<td>60.3</td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td>2098</td>
<td>2116</td>
<td>100.0</td>
<td>-0.12 [-0.19, -0.06]</td>
<td></td>
</tr>
<tr>
<td>Test for heterogeneity chi-square=3.15 df=3 p=0.37 I² =4.7%</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test for overall effect z=3.70 p=0.0002</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

-0.5 -0.25 0 0.25 0.5

Favours LABA + ICS  Favours LTRA + ICS
### Analysis 01.16. Comparison 01 Leukotriene receptor antagonists + ICS versus Long-acting β2-agonists + ICS, Outcome 16 Change in % of nights with no awakenings per week - change from baseline

**Review:** Long-acting beta2-agonists versus anti-leukotrienes as add-on therapy to inhaled corticosteroids for chronic asthma  
**Comparison:** Leukotriene receptor antagonists + ICS versus Long-acting β2-agonists + ICS  
**Outcome:** 16 Change in % of nights with no awakenings per week - change from baseline

<table>
<thead>
<tr>
<th>Study</th>
<th>LABA + ICS</th>
<th>LTRA + ICS</th>
<th>Weighted Mean Difference (Fixed)</th>
<th>Weight (%)</th>
<th>Weighted Mean Difference (Fixed)</th>
</tr>
</thead>
<tbody>
<tr>
<td>01 Montelukast 10 mg once daily vs. Salmeterol 50 mcg twice daily</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Grosclaude 2003</td>
<td>118</td>
<td>26.40 (31.00)</td>
<td>126</td>
<td>19.80 (30.00)</td>
<td>27.5</td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td>118</td>
<td>26.40 (31.00)</td>
<td>126</td>
<td>19.80 (30.00)</td>
<td>27.5</td>
</tr>
</tbody>
</table>
| Test for heterogeneity: not applicable  
Test for overall effect \( z = 1.69 \) \( p = 0.09 \) |
| 02 Zafirlukast 20 mg twice daily vs. Salmeterol 50 mcg twice daily | | | | | |
| Nelson 2001 | 214 | 15.00 (26.30) | 215 | 8.00 (23.50) | 72.5 | 7.00 [ 2.28, 11.72 ] |
| Subtotal (95% CI) | 214 | 15.00 (26.30) | 215 | 8.00 (23.50) | 72.5 | 7.00 [ 2.28, 11.72 ] |
| Test for heterogeneity: not applicable  
Test for overall effect \( z = 2.91 \) \( p = 0.004 \) |
| Total (95% CI) | 332 | 21.40 (41.10) | 341 | 9.80 (31.30) | 100.0 | 6.89 [ 2.87, 10.91 ] |
| Test for heterogeneity \( \chi^2 = 0.01 \) \( df = 1 \) \( p = 0.93 \) \( I^2 = 0.0\%
| Test for overall effect \( z = 3.36 \) \( p = 0.0008 \) |

### Analysis 01.17. Comparison 01 Leukotriene receptor antagonists + ICS versus Long-acting β2-agonists + ICS, Outcome 17 Rescue-free nights (%) - change from baseline

**Review:** Long-acting beta2-agonists versus anti-leukotrienes as add-on therapy to inhaled corticosteroids for chronic asthma  
**Comparison:** Leukotriene receptor antagonists + ICS versus Long-acting β2-agonists + ICS  
**Outcome:** 17 Rescue-free nights (%) - change from baseline

<table>
<thead>
<tr>
<th>Study</th>
<th>LABA + ICS</th>
<th>LTRA + ICS</th>
<th>Weighted Mean Difference (Fixed)</th>
<th>Weighted Mean Difference (Fixed)</th>
</tr>
</thead>
<tbody>
<tr>
<td>01 Montelukast 10 mg once daily vs. Salmeterol 50 mcg twice daily</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Grosclaude 2003</td>
<td>119</td>
<td>26.60 (35.10)</td>
<td>124</td>
<td>24.50 (34.80)</td>
</tr>
<tr>
<td>02 Zafirlukast 20 mg twice daily vs. Salmeterol 50 mcg twice daily</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Long-acting beta2-agonists versus anti-leukotrienes as add-on therapy to inhaled corticosteroids for chronic asthma (Review)  
Copyright © 2007 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd
## Analysis 01.18. Comparison 01 Leukotriene receptor antagonists + ICS versus Long-acting β2-agonists + ICS, Outcome 18 Withdrawals for any reason

**Review:** Long-acting beta2-agonists versus anti-leukotrienes as add-on therapy to inhaled corticosteroids for chronic asthma  
**Comparison:** 01 Leukotriene receptor antagonists + ICS versus Long-acting β2-agonists + ICS  
**Outcome:** 18 Withdrawals for any reason

<table>
<thead>
<tr>
<th>Study</th>
<th>LABA + ICS n/N</th>
<th>LTRA + ICS n/N</th>
<th>Relative Risk (Fixed) 95% CI</th>
<th>Weight (%)</th>
<th>Relative Risk (Fixed) 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>01 Montelukast 10mg/day vs Salmeterol 50ug twice daily</td>
<td>110/743 125/747</td>
<td>28.0 0.88 [0.70, 1.12]</td>
<td>28.0 0.88 [0.70, 1.12]</td>
<td>110/743 125/747</td>
<td>28.0 0.88 [0.70, 1.12]</td>
</tr>
<tr>
<td>Bjermer 2003</td>
<td>61476 70472</td>
<td>15.8 0.86 [0.63, 1.19]</td>
<td>61476 70472</td>
<td>15.8 0.86 [0.63, 1.19]</td>
<td></td>
</tr>
<tr>
<td>Fish 2001</td>
<td>7/123 16/130</td>
<td>3.5 0.46 [0.20, 1.09]</td>
<td>7/123 16/130</td>
<td>3.5 0.46 [0.20, 1.09]</td>
<td></td>
</tr>
<tr>
<td>Grosclaude 2003</td>
<td>113730 128743</td>
<td>28.5 0.90 [0.71, 1.13]</td>
<td>113730 128743</td>
<td>28.5 0.90 [0.71, 1.13]</td>
<td></td>
</tr>
<tr>
<td>Ilowite 2004</td>
<td>9/33 4/33</td>
<td>0.9 2.25 [0.77, 6.59]</td>
<td>9/33 4/33</td>
<td>0.9 2.25 [0.77, 6.59]</td>
<td></td>
</tr>
<tr>
<td>McCarthy 2003</td>
<td>24222 30225</td>
<td>6.7 0.81 [0.49, 1.34]</td>
<td>24222 30225</td>
<td>6.7 0.81 [0.49, 1.34]</td>
<td></td>
</tr>
<tr>
<td>Nelson 2000</td>
<td>19404 37401</td>
<td>8.3 0.51 [0.30, 0.87]</td>
<td>19404 37401</td>
<td>8.3 0.51 [0.30, 0.87]</td>
<td></td>
</tr>
<tr>
<td>Ringdal 2003</td>
<td>2/39 0/39</td>
<td>0.1 5.00 [0.25, 100.89]</td>
<td>2/39 0/39</td>
<td>0.1 5.00 [0.25, 100.89]</td>
<td></td>
</tr>
<tr>
<td>Storms 2004</td>
<td>2770 2790</td>
<td>91.7 0.85 [0.74, 0.97]</td>
<td>2770 2790</td>
<td>91.7 0.85 [0.74, 0.97]</td>
<td></td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td>2770 2790</td>
<td>91.7 0.85 [0.74, 0.97]</td>
<td>2770 2790</td>
<td>91.7 0.85 [0.74, 0.97]</td>
<td></td>
</tr>
<tr>
<td><strong>Total events:</strong></td>
<td>345 (LABA + ICS), 410 (LTRA + ICS)</td>
<td>8.3 0.65 [0.40, 1.06]</td>
<td>345 (LABA + ICS), 410 (LTRA + ICS)</td>
<td>8.3 0.65 [0.40, 1.06]</td>
<td></td>
</tr>
<tr>
<td>Test for heterogeneity</td>
<td>chi-square=10.33 df=7 p=0.17 I² =32.2%</td>
<td>4.3 0.63 [0.32, 1.24]</td>
<td>4.3 0.63 [0.32, 1.24]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test for overall effect</td>
<td>z=2.43 p=0.01</td>
<td>4.0 0.67 [0.33, 1.36]</td>
<td>4.0 0.67 [0.33, 1.36]</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

| 02 Zafirlukast 20 mg twice daily vs Salmeterol 50 mcg twice daily | 12/118 19/118 | 4.3 0.63 [0.32, 1.24] | 12/118 19/118 | 4.3 0.63 [0.32, 1.24] |
| Hultquist 2000        | 12/214 18/215 | 4.0 0.67 [0.33, 1.36] | 12/214 18/215 | 4.0 0.67 [0.33, 1.36] |
| Nelson 2001           | 332 333       | 8.3 0.65 [0.40, 1.06] | 332 333 | 8.3 0.65 [0.40, 1.06] |
| Subtotal (95% CI)      | 3102 3123     | 100.0 0.83 [0.73, 0.95] | 3102 3123 | 100.0 0.83 [0.73, 0.95] |
| **Total events:**      | 24 (LABA + ICS), 37 (LTRA + ICS) | 8.3 0.65 [0.40, 1.06] | 24 (LABA + ICS), 37 (LTRA + ICS) | 8.3 0.65 [0.40, 1.06] |
| Test for heterogeneity | chi-square=0.01 df=1 p=0.91 I² =0.0% | 4.3 0.63 [0.32, 1.24] | 4.3 0.63 [0.32, 1.24] |
| Test for overall effect| z=1.73 p=0.08 | 4.0 0.67 [0.33, 1.36] | 4.0 0.67 [0.33, 1.36] |
| **Total (95% CI)**     | 3102 3123     | 100.0 0.83 [0.73, 0.95] | 3102 3123 | 100.0 0.83 [0.73, 0.95] |
| Test for overall effect| z=2.82 p=0.005 | 8.3 0.65 [0.40, 1.06] | 8.3 0.65 [0.40, 1.06] |

0.1 0.2 0.5 1 2 5 10  
Favours LABA + ICS Favours LTRA + ICS
Analysis 01.19. Comparison 01 Leukotriene receptor antagonists + ICS versus Long-acting ß2-agonists + ICS,
Outcome 19 Withdrawals due to adverse events

Review: Long-acting beta2-agonists versus anti-leukotrienes as add-on therapy to inhaled corticosteroids for chronic asthma
Comparison: 01 Leukotriene receptor antagonists + ICS versus Long-acting ß2-agonists + ICS
Outcome: 19 Withdrawals due to adverse events

<table>
<thead>
<tr>
<th>Study</th>
<th>LABA + ICS</th>
<th>LTRA + ICS</th>
<th>Relative Risk (Fixed)</th>
<th>Weight (%)</th>
<th>Relative Risk (Fixed)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Montelukast 10 mg once daily vs. Salmeterol 50 mcg twice daily</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bjermer 2003</td>
<td>36/743</td>
<td>38/747</td>
<td>32.9</td>
<td>0.95</td>
<td>0.95 [ 0.61, 1.49 ]</td>
</tr>
<tr>
<td>Fish 2001</td>
<td>13/476</td>
<td>13/472</td>
<td>11.1</td>
<td>0.99</td>
<td>0.99 [ 0.46, 2.12 ]</td>
</tr>
<tr>
<td>Grosclaude 2003</td>
<td>3/123</td>
<td>5/130</td>
<td>4.2</td>
<td>0.63</td>
<td>0.63 [ 0.15, 2.60 ]</td>
</tr>
<tr>
<td>Ilowite 2004</td>
<td>32/730</td>
<td>20/743</td>
<td>17.2</td>
<td>1.63</td>
<td>1.63 [ 0.94, 2.82 ]</td>
</tr>
<tr>
<td>McCarthy 2003</td>
<td>2/33</td>
<td>4/33</td>
<td>3.5</td>
<td>0.50</td>
<td>0.50 [ 0.10, 2.55 ]</td>
</tr>
<tr>
<td>Nelson 2000</td>
<td>6/222</td>
<td>4/225</td>
<td>3.4</td>
<td>1.52</td>
<td>1.52 [ 0.43, 5.31 ]</td>
</tr>
<tr>
<td>Ringdal 2003</td>
<td>13/404</td>
<td>19/401</td>
<td>16.6</td>
<td>0.68</td>
<td>0.68 [ 0.34, 1.36 ]</td>
</tr>
<tr>
<td>Storms 2004</td>
<td>1/39</td>
<td>0/39</td>
<td>0.4</td>
<td>3.00</td>
<td>3.00 [ 0.13, 71.46 ]</td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td>2770</td>
<td>2790</td>
<td>89.6</td>
<td>1.04</td>
<td>1.04 [ 0.79, 1.35 ]</td>
</tr>
</tbody>
</table>

Total events: 106 (LABA + ICS), 103 (LTRA + ICS)
Test for heterogeneity chi-square=6.21 df=7 p=0.51 I² =0.0%
Test for overall effect z=0.26 p=0.8

<table>
<thead>
<tr>
<th>Study</th>
<th>LABA + ICS</th>
<th>LTRA + ICS</th>
<th>Relative Risk (Fixed)</th>
<th>Weight (%)</th>
<th>Relative Risk (Fixed)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Zafirlukast 20 mg twice daily vs. Salmeterol 50 mcg twice daily</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hultquist 2000</td>
<td>4/118</td>
<td>5/118</td>
<td>4.3</td>
<td>0.80</td>
<td>0.80 [ 0.22, 2.91 ]</td>
</tr>
<tr>
<td>Nelson 2001</td>
<td>7/214</td>
<td>7/215</td>
<td>6.1</td>
<td>1.00</td>
<td>1.00 [ 0.36, 2.82 ]</td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td>332</td>
<td>333</td>
<td>10.4</td>
<td>0.92</td>
<td>0.92 [ 0.41, 2.05 ]</td>
</tr>
</tbody>
</table>

Total events: 11 (LABA + ICS), 12 (LTRA + ICS)
Test for heterogeneity chi-square=0.07 df=1 p=0.79 I² =0.0%
Test for overall effect z=0.21 p=0.8

<table>
<thead>
<tr>
<th>Study</th>
<th>LABA + ICS</th>
<th>LTRA + ICS</th>
<th>Relative Risk (Fixed)</th>
<th>Weight (%)</th>
<th>Relative Risk (Fixed)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total (95% CI)</td>
<td>3102</td>
<td>3123</td>
<td>100.0</td>
<td>1.02</td>
<td>1.02 [ 0.80, 1.32 ]</td>
</tr>
</tbody>
</table>

Total events: 117 (LABA + ICS), 115 (LTRA + ICS)
Test for heterogeneity chi-square=6.36 df=9 p=0.70 I² =0.0%
Test for overall effect z=0.18 p=0.9

---

Long-acting beta2-agonists versus anti-leukotrienes as add-on therapy to inhaled corticosteroids for chronic asthma (Review)
Copyright © 2007 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd
Analysis 01.20. Comparison 01 Leukotriene receptor antagonists + ICS versus Long-acting β2-agonists + ICS, Outcome 20 Withdrawals due to poor asthma control/asthma exacerbation

Review: Long-acting beta2-agonists versus anti-leukotrienes as add-on therapy to inhaled corticosteroids for chronic asthma
Comparison: 01 Leukotriene receptor antagonists + ICS versus Long-acting β2-agonists + ICS
Outcome: 20 Withdrawals due to poor asthma control/asthma exacerbation

<table>
<thead>
<tr>
<th>Study</th>
<th>LABA + ICS</th>
<th>LTRA + ICS</th>
<th>Relative Risk (Random)</th>
<th>Weight (%)</th>
<th>Relative Risk (Random)</th>
</tr>
</thead>
<tbody>
<tr>
<td>n/N</td>
<td>n/N</td>
<td>95% CI</td>
<td>95% CI</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Montelukast 10 mg once daily vs. Salmeterol 50 mcg twice daily</td>
<td>19/743</td>
<td>11/747</td>
<td>21.9</td>
<td>1.74</td>
<td>[0.83, 3.62]</td>
</tr>
<tr>
<td>Bjermer 2003</td>
<td>19/476</td>
<td>11/472</td>
<td>24.1</td>
<td>1.05</td>
<td>[0.56, 1.97]</td>
</tr>
<tr>
<td>Fish 2001</td>
<td>1/123</td>
<td>3/130</td>
<td>5.6</td>
<td>0.35</td>
<td>[0.04, 3.34]</td>
</tr>
<tr>
<td>Grosclaude 2003</td>
<td>9/730</td>
<td>4/743</td>
<td>14.3</td>
<td>2.29</td>
<td>[0.71, 7.40]</td>
</tr>
<tr>
<td>Ilowite 2004</td>
<td>2/222</td>
<td>10/225</td>
<td>10.4</td>
<td>0.20</td>
<td>[0.04, 0.91]</td>
</tr>
<tr>
<td>Nelson 2000</td>
<td>0/39</td>
<td>0/39</td>
<td>0.0</td>
<td>Not estimable</td>
<td></td>
</tr>
<tr>
<td>Storms 2004</td>
<td>0/39</td>
<td>0/39</td>
<td>0.0</td>
<td>Not estimable</td>
<td></td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td>2333</td>
<td>2356</td>
<td>76.3</td>
<td>1.02</td>
<td>[0.50, 2.07]</td>
</tr>
<tr>
<td>Total events: 50 (LABA + ICS), 46 (LTRA + ICS)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test for heterogeneity chi-square=8.84 df=4 p=0.07 I² =54.8%</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test for overall effect z=0.05 p=1</td>
<td></td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Zafirlukast 20 mg twice daily vs. Salmeterol 50 mcg twice daily</td>
<td>3/118</td>
<td>6/118</td>
<td>11.9</td>
<td>0.50</td>
<td>[0.13, 1.95]</td>
</tr>
<tr>
<td>Hultquist 2000</td>
<td>3/214</td>
<td>6/215</td>
<td>11.8</td>
<td>0.50</td>
<td>[0.13, 1.98]</td>
</tr>
<tr>
<td>Nelson 2001</td>
<td>332</td>
<td>333</td>
<td>23.7</td>
<td>0.50</td>
<td>[0.19, 1.32]</td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td>2665</td>
<td>2689</td>
<td>100.0</td>
<td>0.87</td>
<td>[0.49, 1.56]</td>
</tr>
<tr>
<td>Total events: 6 (LABA + ICS), 12 (LTRA + ICS)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test for heterogeneity chi-square=0.00 df=1 p=1.00 I² =0.0%</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Test for overall effect z=1.40 p=0.2</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>2665</td>
<td>2689</td>
<td>100.0</td>
<td>0.87</td>
<td>[0.49, 1.56]</td>
</tr>
<tr>
<td>Total events: 56 (LABA + ICS), 58 (LTRA + ICS)</td>
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</tr>
<tr>
<td>Test for heterogeneity chi-square=11.24 df=6 p=0.08 I² =46.6%</td>
<td></td>
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</tr>
<tr>
<td>Test for overall effect z=0.46 p=0.6</td>
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</tbody>
</table>

Long-acting beta2-agonists versus anti-leukotrienes as add-on therapy to inhaled corticosteroids for chronic asthma (Review)
Analysis 01.21. Comparison 01 Leukotriene receptor antagonists + ICS versus Long-acting β2-agonists + ICS, Outcome 21 Patients with one or more exacerbations requiring hospital admission

Review: Long-acting beta2-agonists versus anti-leukotrienes as add-on therapy to inhaled corticosteroids for chronic asthma

Comparison: 01 Leukotriene receptor antagonists + ICS versus Long-acting β2-agonists + ICS

Outcome: 21 Patients with one or more exacerbations requiring hospital admission

<table>
<thead>
<tr>
<th>Study</th>
<th>LABA + ICS</th>
<th>LTRA + ICS</th>
<th>Relative Risk (Fixed) 95% CI (%)</th>
<th>Weight (%)</th>
<th>Relative Risk (Fixed) 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Montelukast 10 mg once daily vs. Salmeterol 50 mcg twice daily</td>
<td>7/743</td>
<td>5/747</td>
<td>50.1</td>
<td>1.41 [0.45, 4.41]</td>
<td></td>
</tr>
<tr>
<td>Bjermer 2003</td>
<td></td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Grosclaude 2003</td>
<td>0/119</td>
<td>0/127</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ilowite 2004</td>
<td>5/718</td>
<td>3/734</td>
<td>29.8</td>
<td>1.70 [0.41, 7.10]</td>
<td></td>
</tr>
<tr>
<td>Ringdal 2003</td>
<td>1/404</td>
<td>2/401</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>1984</td>
<td>2009</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total events: 13 (LABA + ICS), 10 (LTRA + ICS)</td>
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<td></td>
<td></td>
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</tr>
<tr>
<td>Test for heterogeneity chi-square=0.78 df=2 p=0.68 I² =0.0%</td>
<td></td>
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<tr>
<td>Test for overall effect z=0.65 p=0.5</td>
<td></td>
<td></td>
<td></td>
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</tr>
</tbody>
</table>

Favours LABA + ICS Favours LTRA + ICS

Analysis 01.22. Comparison 01 Leukotriene receptor antagonists + ICS versus Long-acting β2-agonists + ICS, Outcome 22 Serious Adverse events

Review: Long-acting beta2-agonists versus anti-leukotrienes as add-on therapy to inhaled corticosteroids for chronic asthma

Comparison: 01 Leukotriene receptor antagonists + ICS versus Long-acting β2-agonists + ICS

Outcome: 22 Serious Adverse events

<table>
<thead>
<tr>
<th>Study</th>
<th>LABA + ICS</th>
<th>LTRA + ICS</th>
<th>Relative Risk (Fixed) 95% CI (%)</th>
<th>Weight (%)</th>
<th>Relative Risk (Fixed) 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Montelukast 10 mg once daily vs. Salmeterol 50 mcg twice daily</td>
<td>55/743</td>
<td>34/747</td>
<td>47.9</td>
<td>1.63 [1.07, 2.46]</td>
<td></td>
</tr>
<tr>
<td>Bjermer 2003</td>
<td>54/476</td>
<td>54/472</td>
<td></td>
<td>7.1</td>
<td>0.99 [0.29, 3.40]</td>
</tr>
<tr>
<td>Fish 2001</td>
<td>27/730</td>
<td>22/743</td>
<td></td>
<td>30.8</td>
<td>1.25 [0.72, 2.17]</td>
</tr>
<tr>
<td>Ilowite 2004</td>
<td>1/222</td>
<td>2/225</td>
<td></td>
<td>2.8</td>
<td>0.51 [0.05, 5.55]</td>
</tr>
<tr>
<td>Nelson 2000</td>
<td>4/404</td>
<td>7/401</td>
<td></td>
<td>9.9</td>
<td>0.57 [0.17, 1.92]</td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>2575</td>
<td>2588</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total events: 92 (LABA + ICS), 70 (LTRA + ICS)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test for heterogeneity chi-square=3.67 df=4 p=0.45 I² =0.0%</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test for overall effect z=1.81 p=0.07</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Favours LABA + ICS Favours LTRA + ICS

(Continued . . .)
### Study LABA + ICS LTRA + ICS Relative Risk (Fixed) Weight Relative Risk (Fixed)

<table>
<thead>
<tr>
<th>Study</th>
<th>LABA + ICS</th>
<th>LTRA + ICS</th>
<th>Relative Risk (Fixed)</th>
<th>Weight (%)</th>
<th>Relative Risk (Fixed)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nelson 2001</td>
<td>1/214</td>
<td>1/215</td>
<td>1.4</td>
<td>1.00</td>
<td>[0.06, 15.96]</td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td>214</td>
<td>215</td>
<td>1.4</td>
<td>1.00</td>
<td>[0.06, 15.96]</td>
</tr>
</tbody>
</table>

Total events: 1 (LABA + ICS), 1 (LTRA + ICS)
Test for heterogeneity: not applicable
Test for overall effect z=0.00 p=1

Total (95% CI) 2789 2803
Total events: 93 (LABA + ICS), 71 (LTRA + ICS)
Test for heterogeneity chi-square=3.71 df=5 p=0.59 I² =0.0%
Test for overall effect z=1.80 p=0.07

### Analysis 01.23. Comparison 01 Leukotriene receptor antagonists + ICS versus Long-acting β2-agonists + ICS, Outcome 23 Death

Review: Long-acting β2-agonists versus anti-leukotrienes as add-on therapy to inhaled corticosteroids for chronic asthma
Comparison: 01 Leukotriene receptor antagonists + ICS versus Long-acting β2-agonists + ICS
Outcome: 23 Death

<table>
<thead>
<tr>
<th>Study</th>
<th>LABA + ICS</th>
<th>LTRA + ICS</th>
<th>Relative Risk (Fixed)</th>
<th>Relative Risk (Fixed)</th>
</tr>
</thead>
</table>
| 01 Montelukast 10 mg once daily vs. Salmeterol 50 mcg twice daily
Bjermer 2003    | 1/743      | 0/747      | 3.02                  | 3.02 [0.12, 73.92]    |
|               |            |            | 0.001                 | 0.1                   |

×
Grosclaude 2003 | 0/123      | 0/130      | Not estimable         |                       |
### Analysis 01.24. Comparison 01 Leukotriene receptor antagonists + ICS versus Long-acting ß2-agonists + ICS, Outcome 24 Headache

Review: Long-acting beta2-agonists versus anti-leukotrienes as add-on therapy to inhaled corticosteroids for chronic asthma

Comparison: 01 Leukotriene receptor antagonists + ICS versus Long-acting ß2-agonists + ICS

Outcome: 24 Headache

<table>
<thead>
<tr>
<th>Study</th>
<th>LABA + ICS n/N</th>
<th>LTRA + ICS n/N</th>
<th>Relative Risk (Fixed) 95% CI (%)</th>
<th>Weight (%)</th>
<th>Relative Risk (Fixed) 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>01</td>
<td>Montelukast 10 mg once daily vs. Salmeterol 50 mcg twice daily</td>
<td>93/743 90/747</td>
<td>36.9 1.04 [0.79, 1.36]</td>
<td>1.04 [0.79, 1.36]</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Bjermer 2003 48/476 44/472</td>
<td>18.2 1.08 [0.73, 1.60]</td>
<td>1.08 [0.73, 1.60]</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Grossclaude 2003 1/123 4/130</td>
<td>1.6 0.26 [0.03, 2.33]</td>
<td>0.26 [0.03, 2.33]</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Ilowite 2004 71/730 60/743</td>
<td>24.4 1.20 [0.87, 1.67]</td>
<td>1.20 [0.87, 1.67]</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>McCarty 2003 1/33 1/33</td>
<td>0.4 1.00 [0.07, 15.33]</td>
<td>0.07 [0.07, 15.33]</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Nelson 2000 20/222 10/225</td>
<td>4.1 2.03 [0.97, 4.23]</td>
<td>0.97 [0.97, 4.23]</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Ringdal 2003 12/404 18/401</td>
<td>7.4 0.66 [0.32, 1.36]</td>
<td>0.32 [0.32, 1.36]</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Subtotal (95% CI) 2731 2751</td>
<td>93.0 1.09 [0.92, 1.29]</td>
<td>0.92 [0.92, 1.29]</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Total events: 246 (LABA + ICS), 227 (LTRA + ICS)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Test for heterogeneity chi-square=6.70 df=6 p=0.35 I² =10.4%</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Test for overall effect z=0.99 p=0.3</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>02</td>
<td>Zafirlukast 20 mg twice daily vs. Salmeterol 50 mcg twice daily</td>
<td>6/118 5/118</td>
<td>2.1 1.20 [0.38, 3.82]</td>
<td>0.38 [0.38, 3.82]</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Hultquist 2000 6/118 5/118</td>
<td>2.1 1.20 [0.38, 3.82]</td>
<td>0.38 [0.38, 3.82]</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Nelson 2001 6/214 11/215</td>
<td>4.5 0.55 [0.21, 1.46]</td>
<td>0.21 [0.21, 1.46]</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Subtotal (95% CI) 332 333</td>
<td>6.6 0.75 [0.36, 1.57]</td>
<td>0.36 [0.36, 1.57]</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Total events: 12 (LABA + ICS), 16 (LTRA + ICS)</td>
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</tr>
<tr>
<td></td>
<td>Test for heterogeneity chi-square=1.03 df=1 p=0.31 I² =2.7%</td>
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<tr>
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<td>Test for overall effect z=0.76 p=0.4</td>
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</tr>
<tr>
<td>03</td>
<td>Montelukast 10 mg once daily versus formoterol 18mg twice daily</td>
<td>1/20 1/20</td>
<td>0.4 1.00 [0.07, 14.90]</td>
<td>0.07 [0.07, 14.90]</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Ceylan 2004 1/20 1/20</td>
<td>0.4 1.00 [0.07, 14.90]</td>
<td>0.07 [0.07, 14.90]</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Subtotal (95% CI) 20 20</td>
<td>0.4 1.00 [0.07, 14.90]</td>
<td>0.07 [0.07, 14.90]</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Total events: 1 (LABA + ICS), 1 (LTRA + ICS)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Test for heterogeneity: not applicable</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Test for overall effect z=0.00 p=1</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Total (95% CI) 3083 3104</td>
<td>100.0 1.07 [0.90, 1.26]</td>
<td>0.90 [0.90, 1.26]</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Total events: 259 (LABA + ICS), 244 (LTRA + ICS)</td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td></td>
<td>Test for heterogeneity chi-square=8.60 df=9 p=0.48 I² =0.0%</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Test for overall effect z=0.77 p=0.4</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

---

0.1 0.2 0.5 1 2 5 10
Favours LABA + ICS  Favours LTRA + ICS

---

Long-acting beta2-agonists versus anti-leukotrienes as add-on therapy to inhaled corticosteroids for chronic asthma (Review)

Copyright © 2007 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd
### Analysis 01.25. Comparison 01 Leukotriene receptor antagonists + ICS versus Long-acting ß2-agonists + ICS, Outcome 25 Cardiovascular events

**Review:** Long-acting beta2-agonists versus anti-leukotrienes as add-on therapy to inhaled corticosteroids for chronic asthma  
**Comparison:** 01 Leukotriene receptor antagonists + ICS versus Long-acting ß2-agonists + ICS  
**Outcome:** 25 Cardiovascular events

<table>
<thead>
<tr>
<th>Study</th>
<th>LABA + ICS n/N</th>
<th>LTRA + ICS n/N</th>
<th>Relative Risk (Fixed)</th>
<th>Weight (%)</th>
<th>Relative Risk (Fixed)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Montelukast 10 mg once daily vs. Salmeterol 50 mcg twice daily</td>
<td>31/743 vs. 25/747</td>
<td>41.0</td>
<td>1.25 [0.74, 2.09]</td>
<td>41.0</td>
<td>1.25 [0.74, 2.09]</td>
</tr>
<tr>
<td>Bjermer 2003</td>
<td>4/476 vs. 8/472</td>
<td>13.2</td>
<td>0.50 [0.15, 1.64]</td>
<td>13.2</td>
<td>0.50 [0.15, 1.64]</td>
</tr>
<tr>
<td>Ilowite 2004</td>
<td>22/730 vs. 18/743</td>
<td>29.3</td>
<td>1.24 [0.67, 2.30]</td>
<td>29.3</td>
<td>1.24 [0.67, 2.30]</td>
</tr>
<tr>
<td>Nelson 2000</td>
<td>3/222 vs. 1/225</td>
<td>1.6</td>
<td>3.04 [0.32, 29.01]</td>
<td>1.6</td>
<td>3.04 [0.32, 29.01]</td>
</tr>
<tr>
<td>Ringdal 2003</td>
<td>6/404 vs. 9/401</td>
<td>14.8</td>
<td>0.66 [0.24, 1.84]</td>
<td>14.8</td>
<td>0.66 [0.24, 1.84]</td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>2575/2588</td>
<td>100.0</td>
<td>1.09 [0.77, 1.53]</td>
<td>100.0</td>
<td>1.09 [0.77, 1.53]</td>
</tr>
</tbody>
</table>

Total events: 66 (LABA + ICS), 61 (LTRA + ICS)  
Test for heterogeneity chi-square=3.82 df=4 p=0.43 I² =0.0%  
Test for overall effect z=0.49 p=0.6

### Analysis 01.26. Comparison 01 Leukotriene receptor antagonists + ICS versus Long-acting ß2-agonists + ICS, Outcome 26 Oral moniliasis

**Review:** Long-acting beta2-agonists versus anti-leukotrienes as add-on therapy to inhaled corticosteroids for chronic asthma  
**Comparison:** 01 Leukotriene receptor antagonists + ICS versus Long-acting ß2-agonists + ICS  
**Outcome:** 26 Oral moniliasis

<table>
<thead>
<tr>
<th>Study</th>
<th>LABA + ICS n/N</th>
<th>LTRA + ICS n/N</th>
<th>Relative Risk (Fixed)</th>
<th>Weight (%)</th>
<th>Relative Risk (Fixed)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Montelukast 10 mg once daily vs. Salmeterol 50 mcg twice daily</td>
<td>7/743 vs. 3/747</td>
<td>19.4</td>
<td>2.35 [0.61, 9.04]</td>
<td>19.4</td>
<td>2.35 [0.61, 9.04]</td>
</tr>
<tr>
<td>Bjermer 2003</td>
<td>1/476 vs. 0/472</td>
<td>3.3</td>
<td>2.97 [0.12, 72.84]</td>
<td>3.3</td>
<td>2.97 [0.12, 72.84]</td>
</tr>
<tr>
<td>Ilowite 2004</td>
<td>13/730 vs. 6/743</td>
<td>38.6</td>
<td>2.21 [0.84, 5.77]</td>
<td>38.6</td>
<td>2.21 [0.84, 5.77]</td>
</tr>
<tr>
<td>Nelson 2000</td>
<td>3/222 vs. 4/225</td>
<td>25.8</td>
<td>0.76 [0.17, 3.36]</td>
<td>25.8</td>
<td>0.76 [0.17, 3.36]</td>
</tr>
<tr>
<td>Ringdal 2003</td>
<td>3/404 vs. 1/401</td>
<td>6.5</td>
<td>2.98 [0.31, 28.51]</td>
<td>6.5</td>
<td>2.98 [0.31, 28.51]</td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td>2575/2588</td>
<td>93.5</td>
<td>1.92 [1.02, 3.61]</td>
<td>93.5</td>
<td>1.92 [1.02, 3.61]</td>
</tr>
</tbody>
</table>

Total events: 27 (LABA + ICS), 14 (LTRA + ICS)  
Test for heterogeneity chi-square=1.88 df=4 p=0.76 I² =0.0%  
Test for overall effect z=2.01 p=0.04
Analysis 01.27. Comparison 01 Leukotriene receptor antagonists + ICS versus Long-acting β2-agonists + ICS, Outcome 27 Osteopenia/osteoporosis

Review: Long-acting beta2-agonists versus anti-leukotrienes as add-on therapy to inhaled corticosteroids for chronic asthma
Comparison: 01 Leukotriene receptor antagonists + ICS versus Long-acting β2-agonists + ICS
Outcome: 27 Osteopenia/osteoporosis

<table>
<thead>
<tr>
<th>Study</th>
<th>LABA + ICS</th>
<th>LTRA + ICS</th>
<th>Relative Risk (Fixed)</th>
<th>Weight (%)</th>
<th>Relative Risk (Fixed)</th>
</tr>
</thead>
<tbody>
<tr>
<td>01 Montelukast 10 mg once daily vs. Salmeterol 50 mcg twice daily</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Björner 2003</td>
<td>2/743</td>
<td>3/747</td>
<td>66.8</td>
<td>0.67 [ 0.11, 4.00 ]</td>
<td></td>
</tr>
<tr>
<td>Iłowite 2004</td>
<td>0/730</td>
<td>1/743</td>
<td>33.2</td>
<td>0.34 [ 0.01, 8.31 ]</td>
<td></td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>1473</td>
<td>1490</td>
<td>100.0</td>
<td>0.56 [ 0.12, 2.63 ]</td>
<td></td>
</tr>
<tr>
<td>Test for heterogeneity chi-square=0.13 df=1 p=0.72 I² =0.0%</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test for overall effect z=0.73 p=0.5</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Favours LABA + ICS Favours LTRA + ICS
### Analysis 01.28. Comparison 01 Leukotriene receptor antagonists + ICS versus Long-acting β2-agonists + ICS, Outcome 28 Elevated liver enzymes

Review: Long-acting beta2-agonists versus anti-leukotrienes as add-on therapy to inhaled corticosteroids for chronic asthma  
Comparison: 01 Leukotriene receptor antagonists + ICS versus Long-acting β2-agonists + ICS  
Outcome: 28 Elevated liver enzymes

<table>
<thead>
<tr>
<th>Study</th>
<th>LABA + ICS n/N</th>
<th>LTRA + ICS n/N</th>
<th>Relative Risk (Fixed) 95% CI</th>
<th>Relative Risk (Fixed) 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>01 Montelukast 10 mg once daily vs. Salmeterol 50 mcg twice daily Bjermer 2003</td>
<td>27/727</td>
<td>24/729</td>
<td>1.13 [0.66, 1.94]</td>
<td></td>
</tr>
</tbody>
</table>

### Analysis 01.29. Comparison 01 Leukotriene receptor antagonists + ICS versus Long-acting β2-agonists + ICS, Outcome 29 Overall adverse events

Review: Long-acting beta2-agonists versus anti-leukotrienes as add-on therapy to inhaled corticosteroids for chronic asthma  
Comparison: 01 Leukotriene receptor antagonists + ICS versus Long-acting β2-agonists + ICS  
Outcome: 29 Overall adverse events

<table>
<thead>
<tr>
<th>Study</th>
<th>LABA + ICS n/N</th>
<th>LTRA + ICS n/N</th>
<th>Relative Risk (Fixed) 95% CI</th>
<th>Weight (%)</th>
<th>Relative Risk (Fixed) 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>01 Montelukast 10 mg once daily vs. Salmeterol 50 mcg twice daily Bjermer 2003</td>
<td>538/743</td>
<td>530/747</td>
<td>29.1</td>
<td>1.02 [0.96, 1.09]</td>
<td></td>
</tr>
<tr>
<td>Fish 2001</td>
<td>297/476</td>
<td>279/472</td>
<td>15.4</td>
<td>1.06 [0.95, 1.17]</td>
<td></td>
</tr>
<tr>
<td>Grosclaude 2003</td>
<td>43/123</td>
<td>45/130</td>
<td>2.4</td>
<td>1.01 [0.72, 1.42]</td>
<td></td>
</tr>
<tr>
<td>Ilowite 2004</td>
<td>588/730</td>
<td>576/743</td>
<td>31.5</td>
<td>1.04 [0.99, 1.10]</td>
<td></td>
</tr>
<tr>
<td>McCarthy 2003</td>
<td>19/33</td>
<td>21/33</td>
<td>1.2</td>
<td>0.90 [0.61, 1.34]</td>
<td></td>
</tr>
<tr>
<td>Nelson 2000</td>
<td>117/222</td>
<td>119/225</td>
<td>6.5</td>
<td>1.00 [0.84, 1.19]</td>
<td></td>
</tr>
<tr>
<td>Ringdal 2003</td>
<td>176/404</td>
<td>170/401</td>
<td>9.4</td>
<td>1.03 [0.88, 1.20]</td>
<td></td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td>2731</td>
<td>2751</td>
<td>95.5</td>
<td>1.03 [0.99, 1.07]</td>
<td></td>
</tr>
</tbody>
</table>

Total events: 1778 (LABA + ICS), 1740 (LTRA + ICS)  
Test for heterogeneity: chi-square=0.98 df=6 p=0.99 I² =0.0%  
Test for overall effect z=1.51 p=0.1

<table>
<thead>
<tr>
<th>Study</th>
<th>LABA + ICS n/N</th>
<th>LTRA + ICS n/N</th>
<th>Relative Risk (Fixed) 95% CI</th>
<th>Weight (%)</th>
<th>Relative Risk (Fixed) 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>02 Zafirlukast 20 mg twice daily vs. Salmeterol 50 mcg twice daily Nelson 2001</td>
<td>84/214</td>
<td>82/215</td>
<td>4.5</td>
<td>1.03 [0.81, 1.31]</td>
<td></td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td>214</td>
<td>215</td>
<td>4.5</td>
<td>1.03 [0.81, 1.31]</td>
<td></td>
</tr>
</tbody>
</table>

Total events: 84 (LABA + ICS), 82 (LTRA + ICS)  
Test for heterogeneity: not applicable  
Test for overall effect z=0.24 p=0.8

(Continued ...
### Analysis 01.30. Comparison 01 Leukotriene receptor antagonists + ICS versus Long-acting β2-agonists + ICS, Outcome 30 Patient treatment satisfaction

Review: Long-acting beta2-agonists versus anti-leukotrienes as add-on therapy to inhaled corticosteroids for chronic asthma

Comparison: 01 Leukotriene receptor antagonists + ICS versus Long-acting β2-agonists + ICS

<table>
<thead>
<tr>
<th>Study</th>
<th>LABA +ICS</th>
<th>LTRA +ICS</th>
<th>Relative Risk (Random)</th>
<th>Weight</th>
<th>Relative Risk (Random)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Montelukast 10 mg once daily vs. Salmeterol 50 mcg twice daily</td>
<td>337/400</td>
<td>306/386</td>
<td>38.6</td>
<td>1.06</td>
<td>[0.99, 1.14]</td>
</tr>
<tr>
<td>Fish 2001</td>
<td>375/404</td>
<td>335/401</td>
<td>44.3</td>
<td>1.11</td>
<td>[1.06, 1.17]</td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td>804</td>
<td>787</td>
<td></td>
<td>1.09</td>
<td>[1.05, 1.14]</td>
</tr>
<tr>
<td>Total events: 712 (LABA +ICS), 641 (LTRA + ICS)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test for heterogeneity chi-square=1.13 df=1 p=0.29 I²=17.3%</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test for overall effect z=3.98 p=0.00007</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Zafirlukast 20 mg twice daily vs. Salmeterol 50 mcg twice daily</td>
<td>152/214</td>
<td>120/215</td>
<td>17.1</td>
<td>1.27</td>
<td>[1.10, 1.47]</td>
</tr>
<tr>
<td>Nelson 2001</td>
<td>214</td>
<td>215</td>
<td></td>
<td>1.27</td>
<td>[1.10, 1.47]</td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td>1018</td>
<td>1002</td>
<td></td>
<td>1.12</td>
<td>[1.04, 1.20]</td>
</tr>
<tr>
<td>Total events: 864 (LABA +ICS), 761 (LTRA + ICS)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test for heterogeneity not applicable</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test for overall effect z=3.01 p=0.003</td>
<td></td>
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<td></td>
<td></td>
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</tr>
</tbody>
</table>
Analysis 01.31. Comparison 01 Leukotriene receptor antagonists + ICS versus Long-acting β2-agonists + ICS, Outcome 31 Change from baseline in serum eosinophils (x 10^9/L)

Review: Long-acting β2-agonists versus anti-leukotrienes as add-on therapy to inhaled corticosteroids for chronic asthma
Comparison: 01 Leukotriene receptor antagonists + ICS versus Long-acting β2-agonists + ICS
Outcome: 31 Change from baseline in serum eosinophils (x 10^9/L)

<table>
<thead>
<tr>
<th>Study</th>
<th>LABA + ICS</th>
<th>LTRA + ICS</th>
<th>Weighted Mean Difference (Fixed)</th>
<th>Weight (%)</th>
<th>Weighted Mean Difference (Fixed)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N Mean(SD)</td>
<td>N Mean(SD)</td>
<td>95% CI (%)</td>
<td>95% CI</td>
<td></td>
</tr>
<tr>
<td>01 Montelukast 10 mg once daily vs. Salmeterol 50 mcg twice daily</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bjermer 2003</td>
<td>693 -0.01 (0.27)</td>
<td>699 -0.04 (0.27)</td>
<td>49.0</td>
<td>0.03 [ 0.00, 0.06 ]</td>
<td></td>
</tr>
<tr>
<td>Ilowite 2004</td>
<td>690 0.01 (0.26)</td>
<td>705 -0.03 (0.27)</td>
<td>51.0</td>
<td>0.04 [ 0.01, 0.07 ]</td>
<td></td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>1383</td>
<td>1404</td>
<td>100.0</td>
<td>0.04 [ 0.02, 0.05 ]</td>
<td></td>
</tr>
</tbody>
</table>

Test for heterogeneity chi-square=0.24 df=1 p=0.62 I² =0.0%
Test for overall effect z=3.46 p=0.0005

Analysis 02.01. Comparison 02 LABA + ICS vs LTRA + ICS (subgroup analyses), Outcome 01 PRIMARY OUTCOME: Subgroup analysis (Separate inhalers vs. Single inhaler use for delivery of LABA+ICS)

Review: Long-acting β2-agonists versus anti-leukotrienes as add-on therapy to inhaled corticosteroids for chronic asthma
Comparison: 02 LABA + ICS vs LTRA + ICS (subgroup analyses)
Outcome: 01 PRIMARY OUTCOME: Subgroup analysis (Separate inhalers vs. Single inhaler use for delivery of LABA+ICS)

<table>
<thead>
<tr>
<th>Study</th>
<th>LABA + ICS</th>
<th>LTRA + ICS</th>
<th>Relative Risk (Fixed)</th>
<th>Weight (%)</th>
<th>Relative Risk (Fixed)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n/N</td>
<td>n/N</td>
<td>95% CI (%)</td>
<td>95% CI</td>
<td></td>
</tr>
<tr>
<td>01 Montelukast 10mg od or Zafirlukast 20mg bd vs. Salmeterol 50mcg bd - SEPARATE INHALERS USED</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bjermer 2003</td>
<td>107/743 118/747</td>
<td></td>
<td>38.8</td>
<td>0.91 [ 0.72, 1.16 ]</td>
<td></td>
</tr>
<tr>
<td>Fish 2001</td>
<td>16/476 16/472</td>
<td></td>
<td>5.3</td>
<td>0.99 [ 0.50, 1.96 ]</td>
<td></td>
</tr>
<tr>
<td>Ilowite 2004</td>
<td>102/718 123/734</td>
<td></td>
<td>40.1</td>
<td>0.85 [ 0.67, 1.08 ]</td>
<td></td>
</tr>
<tr>
<td>Nelson 2001</td>
<td>6/214 7/215</td>
<td></td>
<td>2.3</td>
<td>0.86 [ 0.29, 2.52 ]</td>
<td></td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td>2151 2168</td>
<td></td>
<td>86.5</td>
<td>0.89 [ 0.75, 1.04 ]</td>
<td></td>
</tr>
</tbody>
</table>

Total events: 231 (LABA + ICS), 264 (LTRA + ICS)
Test for heterogeneity chi-square=0.29 df=3 p=0.96 I² =0.0%
Test for overall effect z=1.46 p=0.1

02 Montelukast 10mg od vs. Salmeterol 50mcg bd - SINGLE INHALER USED

<table>
<thead>
<tr>
<th>Study</th>
<th>LABA + ICS</th>
<th>LTRA + ICS</th>
<th>Relative Risk (Fixed)</th>
<th>Weight (%)</th>
<th>Relative Risk (Fixed)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n/N</td>
<td>n/N</td>
<td>95% CI (%)</td>
<td>95% CI</td>
<td></td>
</tr>
<tr>
<td>Nelson 2000</td>
<td>3/222 10/225</td>
<td></td>
<td>3.3</td>
<td>0.30 [ 0.08, 1.09 ]</td>
<td></td>
</tr>
<tr>
<td>Ringdal 2003</td>
<td>17/404 31/401</td>
<td></td>
<td>10.3</td>
<td>0.54 [ 0.31, 0.97 ]</td>
<td></td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td>626 626</td>
<td></td>
<td>13.5</td>
<td>0.49 [ 0.29, 0.82 ]</td>
<td></td>
</tr>
</tbody>
</table>

Total events: 20 (LABA + ICS), 41 (LTRA + ICS)
Test for heterogeneity chi-square=0.67 df=1 p=0.41 I² =0.0%

(Continued . . .)
### Analysis 02.02.  Comparison 02 LABA + ICS vs LTRA + ICS (subgroup analyses), Outcome 02 Serious adverse effects stratified by # devices used for LABA + ICS

Review:  Long-acting beta2-agonists versus anti-leukotrienes as add-on therapy to inhaled corticosteroids for chronic asthma
Comparison:  02 LABA + ICS vs LTRA + ICS (subgroup analyses)
Outcome:  02 Serious adverse effects stratified by # devices used for LABA + ICS

<table>
<thead>
<tr>
<th>Study</th>
<th>LABA + ICS</th>
<th>LTRA + ICS</th>
<th>Relative Risk (Fixed)</th>
<th>Weight (%)</th>
<th>Relative Risk (Fixed)</th>
</tr>
</thead>
<tbody>
<tr>
<td>n/N</td>
<td>n/N</td>
<td></td>
<td>95% CI</td>
<td></td>
<td>95% CI</td>
</tr>
<tr>
<td>01 1 device for LABA + ICS</td>
<td></td>
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</tr>
<tr>
<td>Nelson 2000</td>
<td>1/222</td>
<td>2/225</td>
<td>2.8</td>
<td>0.51 [0.05, 5.55]</td>
<td></td>
</tr>
<tr>
<td>Ringdal 2003</td>
<td>4/404</td>
<td>7/401</td>
<td>9.9</td>
<td>0.57 [0.17, 1.92]</td>
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</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td>626</td>
<td>626</td>
<td>12.7</td>
<td>0.55 [0.19, 1.64]</td>
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</tr>
<tr>
<td>Total events: 5 (LABA + ICS), 9 (LTRA + ICS)</td>
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</tr>
<tr>
<td>Test for heterogeneity chi-square=0.01 df=1 p=0.93 I² =0.0%</td>
<td></td>
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<tr>
<td>Test for overall effect z=1.07 p=0.3</td>
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<tr>
<td>02 2 devices for LABA + ICS</td>
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<tr>
<td>Bjærmer 2003</td>
<td>55/743</td>
<td>34/747</td>
<td>47.9</td>
<td>1.63 [1.07, 2.46]</td>
<td></td>
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<tr>
<td>Fish 2001</td>
<td>5/476</td>
<td>5/472</td>
<td>7.1</td>
<td>0.99 [0.29, 3.40]</td>
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<tr>
<td>Ilowite 2004</td>
<td>27/730</td>
<td>22/743</td>
<td>30.8</td>
<td>1.25 [0.72, 2.17]</td>
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<tr>
<td>Nelson 2001</td>
<td>1/214</td>
<td>1/215</td>
<td>1.4</td>
<td>1.00 [0.06, 15.96]</td>
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<tr>
<td>Subtotal (95% CI)</td>
<td>2163</td>
<td>2177</td>
<td>87.3</td>
<td>1.43 [1.04, 1.97]</td>
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<tr>
<td>Total events: 88 (LABA + ICS), 62 (LTRA + ICS)</td>
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<tr>
<td>Test for heterogeneity chi-square=1.00 df=3 p=0.80 I² =0.0%</td>
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<td>Test for overall effect z=2.21 p=0.03</td>
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<tr>
<td>Total (95% CI)</td>
<td>2789</td>
<td>2803</td>
<td>100.0</td>
<td>1.32 [0.98, 1.79]</td>
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<tr>
<td>Total events: 93 (LABA + ICS), 71 (LTRA + ICS)</td>
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<tr>
<td>Test for heterogeneity chi-square=3.71 df=5 p=0.59 I² =0.0%</td>
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<tr>
<td>Test for overall effect z=1.80 p=0.07</td>
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