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Addition of anti-leukotriene agents to inhaled corticosteroids for adults and adolescents with persistent asthma (Review)

Chauhan BF, Jeyaraman MM, Singh Mann A, Lys J, Abou-Setta AM, Zarychanski R, Ducharme FM

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Addition of anti-leukotriene agents to inhaled corticosteroids for adults and adolescents with persistent asthma (Review)

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TABLE OF CONTENTS

HEADER	1
ABSTRACT	1
PLAIN LANGUAGE SUMMARY	2
SUMMARY OF FINDINGS	4
BACKGROUND	9
OBJECTIVES	9
METHODS	9
RESULTS	11
Figure 1.	12
Figure 2.	16
Figure 3.	19
Figure 4.	20
Figure 5.	21
DISCUSSION	22
AUTHORS' CONCLUSIONS	23
ACKNOWLEDGEMENTS	24
REFERENCES	25
CHARACTERISTICS OF STUDIES	32
DATA AND ANALYSES	110
Analysis 1.1. Comparison 1 Anti-leukotrienes and inhaled corticosteroids versus SAME dose of inhaled corticosteroids, Outcome 1 Patients with ≥ 1 exacerbations requiring oral corticosteroids.	114
Analysis 1.2. Comparison 1 Anti-leukotrienes and inhaled corticosteroids versus SAME dose of inhaled corticosteroids, Outcome 2 Primary outcome: subgroup for funding.	115
Analysis 1.3. Comparison 1 Anti-leukotrienes and inhaled corticosteroids versus SAME dose of inhaled corticosteroids, Outcome 3 Participants with exacerbations requiring hospital admission.	115
Analysis 1.4. Comparison 1 Anti-leukotrienes and inhaled corticosteroids versus SAME dose of inhaled corticosteroids, Outcome 4 Participants with ≥ 1 exacerbations leading to emergency department visit.	116
Analysis 1.5. Comparison 1 Anti-leukotrienes and inhaled corticosteroids versus SAME dose of inhaled corticosteroids, Outcome 5 Change from baseline in morning PEFR (L/min).	116
Analysis 1.6. Comparison 1 Anti-leukotrienes and inhaled corticosteroids versus SAME dose of inhaled corticosteroids, Outcome 6 Change from baseline in evening PEFR (L/min).	116
Analysis 1.7. Comparison 1 Anti-leukotrienes and inhaled corticosteroids versus SAME dose of inhaled corticosteroids, Outcome 7 Change from baseline FEV1 (L).	117
Analysis 1.8. Comparison 1 Anti-leukotrienes and inhaled corticosteroids versus SAME dose of inhaled corticosteroids, Outcome 8 Change from baseline in FEV1 % of predicted.	117
Analysis 1.9. Comparison 1 Anti-leukotrienes and inhaled corticosteroids versus SAME dose of inhaled corticosteroids, Outcome 9 Change from baseline in mean asthma symptom score (daytime).	118
Analysis 1.10. Comparison 1 Anti-leukotrienes and inhaled corticosteroids versus SAME dose of inhaled corticosteroids, Outcome 10 Change from baseline mean daily daytime use of β_2 -agonists (puffs/d).	118
Analysis 1.11. Comparison 1 Anti-leukotrienes and inhaled corticosteroids versus SAME dose of inhaled corticosteroids, Outcome 11 Change in night-time awakenings (episodes/wk).	118
Analysis 1.12. Comparison 1 Anti-leukotrienes and inhaled corticosteroids versus SAME dose of inhaled corticosteroids, Outcome 12 Change from baseline in rescue-free days (%).	119
Analysis 1.13. Comparison 1 Anti-leukotrienes and inhaled corticosteroids versus SAME dose of inhaled corticosteroids, Outcome 13 Change in quality of life.	119
Analysis 1.14. Comparison 1 Anti-leukotrienes and inhaled corticosteroids versus SAME dose of inhaled corticosteroids, Outcome 14 Patients' global evaluation.	119
Analysis 1.15. Comparison 1 Anti-leukotrienes and inhaled corticosteroids versus SAME dose of inhaled corticosteroids, Outcome 15 Physicians' global evaluation.	119
Analysis 1.16. Comparison 1 Anti-leukotrienes and inhaled corticosteroids versus SAME dose of inhaled corticosteroids, Outcome 16 Overall withdrawals.	120
Analysis 1.17. Comparison 1 Anti-leukotrienes and inhaled corticosteroids versus SAME dose of inhaled corticosteroids, Outcome 17 Withdrawals due to adverse effects.	120

Analysis 1.18. Comparison 1 Anti-leukotrienes and inhaled corticosteroids versus SAME dose of inhaled corticosteroids, Outcome 18 Withdrawals due to poor asthma control/exacerbations.	121
Analysis 1.19. Comparison 1 Anti-leukotrienes and inhaled corticosteroids versus SAME dose of inhaled corticosteroids, Outcome 19 Number of participants with serious adverse events.	122
Analysis 1.20. Comparison 1 Anti-leukotrienes and inhaled corticosteroids versus SAME dose of inhaled corticosteroids, Outcome 20 Overall adverse effects.	122
Analysis 1.21. Comparison 1 Anti-leukotrienes and inhaled corticosteroids versus SAME dose of inhaled corticosteroids, Outcome 21 Headache.	122
Analysis 1.22. Comparison 1 Anti-leukotrienes and inhaled corticosteroids versus SAME dose of inhaled corticosteroids, Outcome 22 Upper respiratory tract infections.	123
Analysis 1.23. Comparison 1 Anti-leukotrienes and inhaled corticosteroids versus SAME dose of inhaled corticosteroids, Outcome 23 Rhinitis.	123
Analysis 1.24. Comparison 1 Anti-leukotrienes and inhaled corticosteroids versus SAME dose of inhaled corticosteroids, Outcome 24 Elevated liver enzymes.	124
Analysis 1.25. Comparison 1 Anti-leukotrienes and inhaled corticosteroids versus SAME dose of inhaled corticosteroids, Outcome 25 Nausea.	124
Analysis 1.26. Comparison 1 Anti-leukotrienes and inhaled corticosteroids versus SAME dose of inhaled corticosteroids, Outcome 26 Cough.	125
Analysis 1.27. Comparison 1 Anti-leukotrienes and inhaled corticosteroids versus SAME dose of inhaled corticosteroids, Outcome 27 Abdominal pain.	125
Analysis 1.28. Comparison 1 Anti-leukotrienes and inhaled corticosteroids versus SAME dose of inhaled corticosteroids, Outcome 28 Influenza.	125
Analysis 1.29. Comparison 1 Anti-leukotrienes and inhaled corticosteroids versus SAME dose of inhaled corticosteroids, Outcome 29 Pharyngitis.	125
Analysis 1.30. Comparison 1 Anti-leukotrienes and inhaled corticosteroids versus SAME dose of inhaled corticosteroids, Outcome 30 Bronchitis.	125
Analysis 1.31. Comparison 1 Anti-leukotrienes and inhaled corticosteroids versus SAME dose of inhaled corticosteroids, Outcome 31 Death.	126
Analysis 1.32. Comparison 1 Anti-leukotrienes and inhaled corticosteroids versus SAME dose of inhaled corticosteroids, Outcome 32 Change from baseline eosinophil counts.	126
Analysis 2.1. Comparison 2 Anti-leukotrienes and inhaled corticosteroids versus HIGHER dose of inhaled corticosteroids, Outcome 1 Participants with ≥ 1 exacerbation requiring oral corticosteroids.	130
Analysis 2.2. Comparison 2 Anti-leukotrienes and inhaled corticosteroids versus HIGHER dose of inhaled corticosteroids, Outcome 2 Primary outcome: subgroup for dose of daily ICS.	130
Analysis 2.3. Comparison 2 Anti-leukotrienes and inhaled corticosteroids versus HIGHER dose of inhaled corticosteroids, Outcome 3 Primary outcome: subgroup for funding by pharmaceutical company.	131
Analysis 2.4. Comparison 2 Anti-leukotrienes and inhaled corticosteroids versus HIGHER dose of inhaled corticosteroids, Outcome 4 Participants with ≥ 1 exacerbation requiring hospital admission.	131
Analysis 2.5. Comparison 2 Anti-leukotrienes and inhaled corticosteroids versus HIGHER dose of inhaled corticosteroids, Outcome 5 Change from baseline in morning PEFr (L/min).	132
Analysis 2.6. Comparison 2 Anti-leukotrienes and inhaled corticosteroids versus HIGHER dose of inhaled corticosteroids, Outcome 6 Change from baseline in evening PEFr (L/min).	132
Analysis 2.7. Comparison 2 Anti-leukotrienes and inhaled corticosteroids versus HIGHER dose of inhaled corticosteroids, Outcome 7 Change from baseline in mean diurnal variation in PEFr.	133
Analysis 2.8. Comparison 2 Anti-leukotrienes and inhaled corticosteroids versus HIGHER dose of inhaled corticosteroids, Outcome 8 Change from baseline FEV1 (L).	133
Analysis 2.9. Comparison 2 Anti-leukotrienes and inhaled corticosteroids versus HIGHER dose of inhaled corticosteroids, Outcome 9 Change from baseline mean daily use of β_2 -agonists (puffs/d).	133
Analysis 2.10. Comparison 2 Anti-leukotrienes and inhaled corticosteroids versus HIGHER dose of inhaled corticosteroids, Outcome 10 Change from baseline mean symptom scores.	134
Analysis 2.11. Comparison 2 Anti-leukotrienes and inhaled corticosteroids versus HIGHER dose of inhaled corticosteroids, Outcome 11 Change in nocturnal awakenings per week.	134
Analysis 2.12. Comparison 2 Anti-leukotrienes and inhaled corticosteroids versus HIGHER dose of inhaled corticosteroids, Outcome 12 Change in quality of life.	135
Analysis 2.13. Comparison 2 Anti-leukotrienes and inhaled corticosteroids versus HIGHER dose of inhaled corticosteroids, Outcome 13 Overall withdrawals.	135

Analysis 2.14. Comparison 2 Anti-leukotrienes and inhaled corticosteroids versus HIGHER dose of inhaled corticosteroids, Outcome 14 Withdrawals due to adverse effects.	136
Analysis 2.15. Comparison 2 Anti-leukotrienes and inhaled corticosteroids versus HIGHER dose of inhaled corticosteroids, Outcome 15 Withdrawals due to poor asthma control/exacerbations.	136
Analysis 2.16. Comparison 2 Anti-leukotrienes and inhaled corticosteroids versus HIGHER dose of inhaled corticosteroids, Outcome 16 Participants with serious adverse health events.	137
Analysis 2.17. Comparison 2 Anti-leukotrienes and inhaled corticosteroids versus HIGHER dose of inhaled corticosteroids, Outcome 17 Overall adverse effects.	137
Analysis 2.18. Comparison 2 Anti-leukotrienes and inhaled corticosteroids versus HIGHER dose of inhaled corticosteroids, Outcome 18 Headache.	138
Analysis 2.19. Comparison 2 Anti-leukotrienes and inhaled corticosteroids versus HIGHER dose of inhaled corticosteroids, Outcome 19 Nausea.	138
Analysis 2.20. Comparison 2 Anti-leukotrienes and inhaled corticosteroids versus HIGHER dose of inhaled corticosteroids, Outcome 20 Elevated liver enzymes.	139
Analysis 2.21. Comparison 2 Anti-leukotrienes and inhaled corticosteroids versus HIGHER dose of inhaled corticosteroids, Outcome 21 Oral moniliasis.	139
Analysis 2.22. Comparison 2 Anti-leukotrienes and inhaled corticosteroids versus HIGHER dose of inhaled corticosteroids, Outcome 22 Hoarseness of voice.	140
Analysis 2.23. Comparison 2 Anti-leukotrienes and inhaled corticosteroids versus HIGHER dose of inhaled corticosteroids, Outcome 23 Abdominal pain.	140
Analysis 2.24. Comparison 2 Anti-leukotrienes and inhaled corticosteroids versus HIGHER dose of inhaled corticosteroids, Outcome 24 Death.	140
Analysis 3.1. Comparison 3 Anti-leukotrienes and inhaled corticosteroids versus TAPERING dose of inhaled corticosteroids, Outcome 1 % Change from baseline ICS dose.	144
Analysis 3.2. Comparison 3 Anti-leukotrienes and inhaled corticosteroids versus TAPERING dose of inhaled corticosteroids, Outcome 2 Participants with ≥ 1 exacerbation requiring oral corticosteroids.	144
Analysis 3.3. Comparison 3 Anti-leukotrienes and inhaled corticosteroids versus TAPERING dose of inhaled corticosteroids, Outcome 3 Participants with ≥ 1 exacerbation requiring hospital admission.	145
Analysis 3.4. Comparison 3 Anti-leukotrienes and inhaled corticosteroids versus TAPERING dose of inhaled corticosteroids, Outcome 4 Participants with change from baseline dose of ICS required to maintain control.	145
Analysis 3.5. Comparison 3 Anti-leukotrienes and inhaled corticosteroids versus TAPERING dose of inhaled corticosteroids, Outcome 5 Participants who completely tapered off ICS.	146
Analysis 3.6. Comparison 3 Anti-leukotrienes and inhaled corticosteroids versus TAPERING dose of inhaled corticosteroids, Outcome 6 Participants with $\geq 50\%$ reduction from baseline ICS dose.	146
Analysis 3.7. Comparison 3 Anti-leukotrienes and inhaled corticosteroids versus TAPERING dose of inhaled corticosteroids, Outcome 7 Change from baseline in morning PEFr (L/min).	146
Analysis 3.8. Comparison 3 Anti-leukotrienes and inhaled corticosteroids versus TAPERING dose of inhaled corticosteroids, Outcome 8 Change from baseline in evening PEFr (L/min).	147
Analysis 3.9. Comparison 3 Anti-leukotrienes and inhaled corticosteroids versus TAPERING dose of inhaled corticosteroids, Outcome 9 Change from baseline FEV1 (L).	147
Analysis 3.10. Comparison 3 Anti-leukotrienes and inhaled corticosteroids versus TAPERING dose of inhaled corticosteroids, Outcome 10 Change in PC20.	147
Analysis 3.11. Comparison 3 Anti-leukotrienes and inhaled corticosteroids versus TAPERING dose of inhaled corticosteroids, Outcome 11 Change from baseline in mean daytime asthma symptom score.	147
Analysis 3.12. Comparison 3 Anti-leukotrienes and inhaled corticosteroids versus TAPERING dose of inhaled corticosteroids, Outcome 12 Change from baseline in mean night-time asthma symptom score.	147
Analysis 3.13. Comparison 3 Anti-leukotrienes and inhaled corticosteroids versus TAPERING dose of inhaled corticosteroids, Outcome 13 Change from baseline in mean daily use of β_2 -agonists (puffs/d).	148
Analysis 3.14. Comparison 3 Anti-leukotrienes and inhaled corticosteroids versus TAPERING dose of inhaled corticosteroids, Outcome 14 Overall withdrawals.	148
Analysis 3.15. Comparison 3 Anti-leukotrienes and inhaled corticosteroids versus TAPERING dose of inhaled corticosteroids, Outcome 15 Withdrawals due to adverse effects.	149
Analysis 3.16. Comparison 3 Anti-leukotrienes and inhaled corticosteroids versus TAPERING dose of inhaled corticosteroids, Outcome 16 Withdrawals due to poor asthma control/exacerbations.	149
Analysis 3.17. Comparison 3 Anti-leukotrienes and inhaled corticosteroids versus TAPERING dose of inhaled corticosteroids, Outcome 17 Serious adverse events.	150

Analysis 3.18. Comparison 3 Anti-leukotrienes and inhaled corticosteroids versus TAPERING dose of inhaled corticosteroids, Outcome 18 Overall adverse effects.	150
Analysis 3.19. Comparison 3 Anti-leukotrienes and inhaled corticosteroids versus TAPERING dose of inhaled corticosteroids, Outcome 19 Headache.	151
Analysis 3.20. Comparison 3 Anti-leukotrienes and inhaled corticosteroids versus TAPERING dose of inhaled corticosteroids, Outcome 20 Nausea.	152
Analysis 3.21. Comparison 3 Anti-leukotrienes and inhaled corticosteroids versus TAPERING dose of inhaled corticosteroids, Outcome 21 Elevated liver enzymes.	152
Analysis 3.22. Comparison 3 Anti-leukotrienes and inhaled corticosteroids versus TAPERING dose of inhaled corticosteroids, Outcome 22 Pharyngitis.	153
Analysis 3.23. Comparison 3 Anti-leukotrienes and inhaled corticosteroids versus TAPERING dose of inhaled corticosteroids, Outcome 23 Abdominal pain.	153
Analysis 3.24. Comparison 3 Anti-leukotrienes and inhaled corticosteroids versus TAPERING dose of inhaled corticosteroids, Outcome 24 Vomiting.	153
Analysis 3.25. Comparison 3 Anti-leukotrienes and inhaled corticosteroids versus TAPERING dose of inhaled corticosteroids, Outcome 25 Diarrhoea.	153
Analysis 3.26. Comparison 3 Anti-leukotrienes and inhaled corticosteroids versus TAPERING dose of inhaled corticosteroids, Outcome 26 Death.	154
Analysis 3.27. Comparison 3 Anti-leukotrienes and inhaled corticosteroids versus TAPERING dose of inhaled corticosteroids, Outcome 27 Change from baseline exhaled NO concentration (ppb).	154
Analysis 3.28. Comparison 3 Anti-leukotrienes and inhaled corticosteroids versus TAPERING dose of inhaled corticosteroids, Outcome 28 Change from baseline in sputum eosinophil counts.	154
Analysis 3.29. Comparison 3 Anti-leukotrienes and inhaled corticosteroids versus TAPERING dose of inhaled corticosteroids, Outcome 29 Change from baseline in serum eosinophils at lowest tolerated dose.	155
ADDITIONAL TABLES	156
APPENDICES	160
WHAT'S NEW	162
CONTRIBUTIONS OF AUTHORS	162
DECLARATIONS OF INTEREST	163
SOURCES OF SUPPORT	163
DIFFERENCES BETWEEN PROTOCOL AND REVIEW	163
INDEX TERMS	163

[Intervention Review]

Addition of anti-leukotriene agents to inhaled corticosteroids for adults and adolescents with persistent asthma

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ABSTRACT

Background

Asthma management guidelines recommend low-dose inhaled corticosteroids (ICS) as first-line therapy for adults and adolescents with persistent asthma. The addition of anti-leukotriene agents to ICS offers a therapeutic option in cases of suboptimal control with daily ICS.

Objectives

To assess the efficacy and safety of anti-leukotriene agents added to ICS compared with the same dose, an increased dose or a tapering dose of ICS (in both arms) for adults and adolescents 12 years of age and older with persistent asthma. Also, to determine whether any characteristics of participants or treatments might affect the magnitude of response.

Search methods

We identified relevant studies from the Cochrane Airways Group Specialised Register of Trials, which is derived from systematic searches of bibliographic databases including the Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE, Embase, PsycINFO, the Allied and Complementary Medicine Database (AMED), the Cumulative Index to Nursing and Allied Health Literature (CINAHL) and the trial registries clinicaltrials.gov and ICTRP from inception to August 2016.

Selection criteria

We searched for randomised controlled trials (RCTs) of adults and adolescents 12 years of age and older on a maintenance dose of ICS for whom investigators added anti-leukotrienes to the ICS and compared treatment with the same dose, an increased dose or a tapering dose of ICS for at least four weeks.

Data collection and analysis

We used standard methods expected by Cochrane. The primary outcome was the number of participants with exacerbations requiring oral corticosteroids (except when both groups tapered the dose of ICS, in which case the primary outcome was the % reduction in ICS dose

from baseline with maintained asthma control). Secondary outcomes included markers of exacerbation, lung function, asthma control, quality of life, withdrawals and adverse events.

Main results

We included in the review 37 studies representing 6128 adult and adolescent participants (most with mild to moderate asthma). Investigators in these studies used three leukotriene receptor antagonists (LTRAs): montelukast ($n = 24$), zafirlukast ($n = 11$) and pranlukast ($n = 2$); studies lasted from four weeks to five years.

Anti-leukotrienes and ICS versus same dose of ICS

Of 16 eligible studies, 10 studies, representing 2364 adults and adolescents, contributed data. Anti-leukotriene agents given as adjunct therapy to ICS reduced by half the number of participants with exacerbations requiring oral corticosteroids (risk ratio (RR) 0.50, 95% confidence interval (CI) 0.29 to 0.86; 815 participants; four studies; moderate quality); this is equivalent to a number needed to treat for additional beneficial outcome (NNTB) over six to 16 weeks of 22 (95% CI 16 to 75). Only one trial including 368 participants reported mortality and serious adverse events, but events were too infrequent for researchers to draw a conclusion. Four trials reported all adverse events, and the pooled result suggested little difference between groups (RR 1.06, 95% CI 0.92 to 1.22; 1024 participants; three studies; moderate quality). Investigators noted between-group differences favouring the addition of anti-leukotrienes for morning peak expiratory flow rate (PEFR), forced expiratory volume in one second (FEV_1), asthma symptoms and night-time awakenings, but not for reduction in β_2 -agonist use or evening PEFR.

Anti-leukotrienes and ICS versus higher dose of ICS

Of 15 eligible studies, eight studies, representing 2008 adults and adolescents, contributed data. Results showed no statistically significant difference in the number of participants with exacerbations requiring oral corticosteroids (RR 0.90, 95% CI 0.58 to 1.39; 1779 participants; four studies; moderate quality) nor in all adverse events between groups (RR 0.96, 95% CI 0.89 to 1.03; 1899 participants; six studies; low quality). Three trials reported no deaths among 834 participants. Results showed no statistically significant differences in lung function tests including morning PEFR and FEV_1 nor in asthma control measures including use of rescue β_2 -agonists or asthma symptom scores.

Anti-leukotrienes and ICS versus tapering dose of ICS

Seven studies, representing 1150 adults and adolescents, evaluated the combination of anti-leukotrienes and tapering-dose of ICS compared with tapering-dose of ICS alone and contributed data. Investigators observed no statistically significant difference in % change from baseline ICS dose (mean difference (MD) -3.05, 95% CI -8.13 to 2.03; 930 participants; four studies; moderate quality), number of participants with exacerbations requiring oral corticosteroids (RR 0.46, 95% CI 0.20 to 1.04; 542 participants; five studies; low quality) or all adverse events (RR 0.95, 95% CI 0.83 to 1.08; 1100 participants; six studies; moderate quality). Serious adverse events occurred more frequently among those taking anti-leukotrienes plus tapering ICS than in those taking tapering doses of ICS alone (RR 2.44, 95% CI 1.52 to 3.92; 621 participants; two studies; moderate quality), but deaths were too infrequent for researchers to draw any conclusions about mortality. Data showed no improvement in lung function nor in asthma control measures.

Authors' conclusions

For adolescents and adults with persistent asthma, with suboptimal asthma control with daily use of ICS, the addition of anti-leukotrienes is beneficial for reducing moderate and severe asthma exacerbations and for improving lung function and asthma control compared with the same dose of ICS. We cannot be certain that the addition of anti-leukotrienes is superior, inferior or equivalent to a higher dose of ICS. Scarce available evidence does not support anti-leukotrienes as an ICS sparing agent, and use of LTRAs was not associated with increased risk of withdrawals or adverse effects, with the exception of an increase in serious adverse events when the ICS dose was tapered. Information was insufficient for assessment of mortality.

PLAIN LANGUAGE SUMMARY

Is adding an anti-leukotriene to an inhaled corticosteroid better than using an inhaled corticosteroid alone for persistent asthma?

Background: A daily low dose of inhaled corticosteroids (ICS) is the recommended first preventer treatment offered to adults and teenagers with asthma. Patients with inadequate asthma control are often treated by adding an anti-leukotriene (LTRA) or a long-acting β_2 -agonist, or by increasing the dose of ICS.

Review question: Is adding an anti-leukotriene to ICS better than using an ICS alone for adults and adolescents 12 years of age and older with persistent asthma?

Study characteristics: We found 37 studies (representing 6128 adults and adolescents). The people in these trials had mild to moderate asthma. Most (24) studies used the LTRA called montelukast, 11 studies used zafirlukast and only two studies used pranlukast.

We divided all studies into three categories to help us make sense of the evidence.

• *Anti-leukotrienes and ICS versus same dose of ICS*: Ten studies (representing 2364 adults and adolescents) contributed data for analysis. Anti-leukotrienes given with ICS reduced by half the number of patients with exacerbations requiring oral steroids (from 9% to 5% over three months), but we are unsure about effects of this treatment on quality of life or serious side effects. Anti-leukotrienes given with ICS improved lung function and asthma control measures.

• *Anti-leukotrienes and ICS versus higher dose of ICS*: Eight studies (representing 2008 adults and adolescents) contributed data for analysis. Results showed no reduction in the number of patients with exacerbations requiring oral steroids and no difference in quality of life nor in side effects. Data showed no improvement in lung function nor in asthma control measures.

• *Anti-leukotrienes and gradual reduction of ICS dose versus gradual reduction of ICS dose alone*: Seven studies (representing 1150 adults and adolescents) evaluated anti-leukotrienes given with a gradually reduced dose of ICS compared with a gradually reduced dose of ICS without use of anti-leukotriene agents. This approach was not beneficial for % reduction in the amount of ICS over time. More people receiving anti-leukotriene and ICS compared with ICS alone experienced increased serious side effects and showed no improvement in lung function nor in asthma control measures.

Conclusion: For adolescents and adults with asthma not controlled with daily low-dose ICS, adding anti-leukotriene agents to ICS reduced by half the number of patients with asthma exacerbations requiring an oral corticosteroid. Anti-leukotrienes and ICS also improved lung function and asthma control. However, we are not sure whether the combination of anti-leukotrienes and ICS is superior to higher-dose ICS. Limited available evidence does not support use of anti-leukotrienes as a way to decrease ICS dose. In general, addition of anti-leukotrienes to ICS therapy was not associated with increased side effects, if the dose of ICS was maintained.

Quality of the results: Our confidence in the evidence was moderate or low for most outcomes.

SUMMARY OF FINDINGS

Summary of findings for the main comparison. Summary of findings table 1

Anti-leukotrienes and inhaled corticosteroids compared with SAME dose of inhaled corticosteroids for adults and adolescents with persistent asthma

Patient or population: adults and adolescents with persistent asthma

Setting: outpatients

Intervention: anti-leukotrienes and inhaled corticosteroids

Comparison: SAME dose of inhaled corticosteroids

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	Number of participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk: risk with SAME dose of inhaled corticosteroids	Corresponding risk: risk with anti-leukotrienes and inhaled corticosteroids (95% CI)				
Patients with ≥ 1 exacerbations requiring oral corticosteroids Duration of trials: 6 to 16 weeks	92 per 1000	46 per 1000 (27 to 79 per 1000)	RR 0.50 (0.29 to 0.86)	815 (4 RCTs)	⊕⊕⊕⊖ MODERATE ^a	Number needed to treat to prevent 1 participant from needing oral steroids for an exacerbation over 6 to 16 weeks of 22 (95% CI 16 to 78)
Change from baseline in morning PEFR (L/min) Duration of trials: 6 to 16 weeks	21.7 L/min mean change from baseline PEFR due to ICS alone	Mean change from baseline in morning PEFR (L/min) in the intervention group was 8.36 higher (3.64 higher to 13.07 higher)	-	1489 (4 RCTs)	⊕⊕⊕⊕ HIGH	
Change from baseline FEV ₁ (L) Duration of trials: 6 to 16 weeks	0.1 L mean change from baseline FEV ₁ due to ICS alone	Mean change from baseline FEV ₁ (L) in the intervention group was 0.11 higher (0.03 higher to 0.19 higher)	-	760 (3 RCTs)	⊕⊕⊕⊕ HIGH	
Change from baseline in mean asthma symptom score (daytime)	0.19 mean change from baseline asthma score due to ICS alone	SMD -0.15 lower (-0.26 lower to -0.05 lower)	-	1386 (3 RCTs)	⊕⊕⊕⊕ HIGH	

Greater the reduction, better the outcome					
Duration of trials: 6 to 16 weeks					
Overall adverse effects	411 per 1000	436 per 1000	RR 1.06	1024 (3 RCTs)	⊕⊕⊕⊕ MODERATE ^b
Duration of trials: 6 to 16 weeks		(378 to 501 per 1000)	(0.92 to 1.22)		
Death	3 per 1000	1 per 1000	RR 0.35	761 (2 RCTs)	⊕⊕⊕⊕ LOW ^c
Duration of trials: 6 to 16 weeks		(0 to 22 per 1000)	(0.01 to 8.49)		Deaths were too infrequent to allow any conclusions about mortality

***The risk in the intervention group** (and its 95% confidence interval) is based on the average risk in the comparison group and the **relative effect** of the intervention (and its 95% CI)

CI: confidence interval; RR: risk ratio

GRADE Working Group grades of evidence

High quality: We are very confident that the true effect lies close to the estimate of effect

Moderate quality: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of effect but may be substantially different

Low quality: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of effect

Very low quality: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

^aTwo (Riccioni 2001; Riccioni 2002) of four included studies were judged at high risk of bias

^bImprecision (95% CI is compatible with both more and fewer adverse events)

^cOnly one death occurred in total in these trials (downgraded twice for imprecision)

Summary of findings 2. Summary of findings table 2

Anti-leukotrienes and inhaled corticosteroids compared with HIGHER dose of inhaled corticosteroids for adults and adolescents with persistent asthma

Patient or population: adults and adolescents with persistent asthma

Setting: outpatients

Intervention: anti-leukotrienes and inhaled corticosteroids

Comparison: HIGHER dose of inhaled corticosteroids

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	Number of participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk: risk with HIGHER dose	Corresponding risk: risk with anti-leukotrienes and

	of inhaled corticosteroids	inhaled corticosteroids (95% CI)				
Patients with ≥ 1 exacerbation requiring oral corticosteroids Duration of trials: 8 to 13 weeks	51 per 1000	46 per 1000 (30 to 71 per 1000)	RR 0.90 (0.58 to 1.39)	1779 (4 RCTs)	⊕⊕⊕⊖ MODERATE ^a	
Change from baseline in morning PEFR (L/min) Duration of trials: 8 to 13 weeks	24.2 L/min mean change from baseline PEFR due to ICS alone	Mean change from baseline in morning PEFR (L/min) in the intervention group was 10.38 higher (1.32 lower to 22.08 higher)	-	952 (5 RCTs)	⊕⊕⊕⊖ LOW ^{b,c}	Barnes 2007 was judged at high risk of bias
Change from baseline FEV ₁ (L) Duration of trials: 8 to 13 weeks	0.15 L mean change from baseline FEV ₁ due to ICS alone	Mean change from baseline FEV ₁ (L) in the intervention group was 0.06 higher (0.01 lower to 0.13 higher)	-	958 (4 RCTs)	⊕⊕⊕⊖ LOW ^{a,c}	
Change from baseline in mean asthma symptom score Greater the reduction, better the outcome Duration of trials: 12 to 13 weeks	-0.41 mean change from baseline asthma score due to ICS alone	SMD -0.02 lower (-0.13 lower to 0.08 higher)	-	1539 (3 RCTs)	⊕⊕⊕⊖ MODERATE ^a	
Overall adverse effects Duration of trials: 8 to 16 weeks	513 per 1000	493 per 1000 (457 to 528)	RR 0.96 (0.89 to 1.03)	1899 (6 RCTs)	⊕⊕⊕⊖ LOW ^{a,b}	Two (Barnes 2007; Tomary 2001) included studies contributing data were judged to be at high risk of bias
Death Duration of trials: 12 to 13 weeks	0 per 1000	0 per 1000 (0 to 0)	Not estimable	834 (3 RCTs)	⊕⊕⊕⊖ LOW ^d	Deaths were too infrequent to allow any conclusions about mortality

***The risk in the intervention group** (and its 95% confidence interval) is based on the average risk in the comparison group and the **relative effect** of the intervention (and its 95% CI)

CI: confidence interval; RR: risk ratio

GRADE Working Group grades of evidence

High quality: We are very confident that the true effect lies close to the estimate of effect

Moderate quality: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of effect but may be substantially different

Low quality: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of effect

Very low quality: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

^aImprecision (95% CI is compatible with both benefits and harms of treatment or no difference)

^bHigh risk of bias

^cInconsistency due to high heterogeneity

^dNo deaths in any of the studies (downgraded twice for imprecision)

Summary of findings 3. Summary of findings table 3

Anti-leukotrienes and inhaled corticosteroids compared with TAPERING dose of inhaled corticosteroids for adults and adolescents with persistent asthma

Patient or population: adults and adolescents with persistent asthma

Setting: outpatients

Intervention: anti-leukotrienes and inhaled corticosteroids

Comparison: TAPERING dose of inhaled corticosteroids

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	Number of participants (studies)	Quality of the evidence (GRADE)	Comments
	Risk with TAPERING dose of inhaled corticosteroids	Risk with anti-leukotrienes and inhaled corticosteroids (95% CI)				
% change from baseline ICS dose Duration of trials: 12 to 24 weeks More reduction is better	Mean change from baseline ICS dose was -48.4%	Mean % change from baseline ICS dose in the intervention group was 3.05 lower (8.13 lower to 2.03 higher)	-	930 (4 RCTs)	⊕⊕⊕⊙ MODERATE ^a	
Participants with ≥ 1 exacerbation requiring oral corticosteroids Duration of trials: 8 to 24 weeks	66 per 1000	30 per 1000 (13 to 69)	RR 0.46 (0.20 to 1.04)	542 (5 RCTs)	⊕⊕⊙⊙ LOW ^{a,b}	One (Riccioni 2005) included study contributing data was judged at high risk of bias

Change from baseline in morning PEFR (L/min) Duration of trials: 12 to 24 weeks	18.5 L/min mean change from baseline PEFR due to ICS alone	Mean change from baseline in morning PEFR (L/min) in the intervention group was 2.45 lower (10.96 lower to 6.06 higher)	-	218 (2 RCTs)	⊕⊕⊕⊖ MODERATE ^a	
Overall adverse effects Duration of trials: 8 to 24 weeks	672 per 1000	638 per 1000 (558 to 726)	RR 0.95 (0.83 to 1.08)	1100 (6 RCTs)	⊕⊕⊕⊖ MODERATE ^a	
Serious adverse events Duration of trials: 12 to 20 weeks	88 per 1000	215 per 1000 (134 to 346)	RR 2.44 (1.52 to 3.92)	621 (2 RCTs)	⊕⊕⊕⊖ MODERATE ^c	
Death Duration of trials: 8 to 24 weeks	0 per 1000	0 per 1000 (0 to 0)	RR 3.10 (0.13 to 75.10)	1100 (6 RCTs)	⊕⊕⊖⊖ LOW ^d	Very wide imprecision; deaths were too infrequent to allow any conclusions about mortality

***The risk in the intervention group** (and its 95% confidence interval) is based on the average risk in the comparison group and the **relative effect** of the intervention (and its 95% CI)

CI: confidence interval; RR: risk ratio

GRADE Working Group grades of evidence

High quality: We are very confident that the true effect lies close to the estimate of effect

Moderate quality: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of effect but may be substantially different

Low quality: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of effect

Very low quality: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

^aImprecision (95% CI is compatible with both benefits and harms of treatment)

^bHigh risk of bias

^cDowngraded for indirectness (no clear definition of serious adverse events); data obtained from study authors as not reported in the published abstract

^dOnly one death occurred in total in these trials (downgraded twice for imprecision)

BACKGROUND

Description of the condition

Asthma typically is characterised by airway obstruction, cough, shortness of breath, chest tightness and wheezing (Fanta 2009). Asthma affects around 334 million people worldwide, and the estimated number of people living with asthma is projected to rise by up to 100 million persons by the year 2025 (Vos 2012). Approximately 8.1% of Canadians (aged ≥ 12 years) suffer from asthma (Statistics Canada 2014).

Description of the intervention

Anti-leukotrienes are anti-inflammatory drugs that interfere with leukotriene production (5-lipoxygenase inhibitors) or with receptors (leukotriene receptor antagonists) (Calhoun 2001). Anti-leukotriene agents are administered orally in a once- or twice-daily dose and do not seem to cause some of the adverse effects associated with long-term use of inhaled corticosteroids (ICS), such as decreased bone mineral density, skin thinning, bruising, cataracts and growth suppression (Dahl 2006; Jarvis 2000; Pruteanu 2014; Spector 2001).

How the intervention might work

Anti-leukotriene agents act by blocking leukotriene receptors through a mechanism different from that of ICS (Jarvis 2000; Spector 2001). The benefits of ICS therapy clearly outweigh those of alternative monotherapies (e.g. anti-leukotriene agents; Chauhan 2012), and ICS are recommended as first-line daily monotherapy for adults with asthma (National Asthma Campaign 2014; BTS 2014; GINA 2015; Loughheed 2012; NAEPP 2010). Most people can achieve asthma control by taking low doses of ICS and experience minimal adverse effects (Chauhan 2012).

For patients with inadequate asthma control taking low doses of ICS, guidelines recommend the following options as step -3 therapy.

- Adding a long-acting β_2 -agonist (LABA).
- Increasing the dose of ICS to moderate or high.
- Adding anti-leukotriene agents (National Asthma Campaign 2014; BTS 2014; GINA 2015; Loughheed 2012; NAEPP 2010).

Investigators (Chauhan 2015; Ducharme 2010a; Ducharme 2010b) have evaluated the effect of LABA as add-on therapy to ICS for children and adults and have raised concerns about the safety of this treatment for adults (Cates 2009a; Cates 2009b). Two Cochrane reviews concluded that anti-leukotrienes have mild to moderate anti-inflammatory effects when used as monotherapy (Chauhan 2012) or as add-on therapy to ICS for children (Chauhan 2013) and adults (Ducharme 2004).

Why it is important to do this review

In 2004, a Cochrane review containing 27 eligible trials (25 in adults and two in children) evaluated the addition of anti-leukotrienes to ICS for children and adults with asthma (Ducharme 2004). This review showed no additional benefit of adding anti-leukotrienes to existing ICS compared with the same or an increased dose of ICS. Since that time, several published trials have examined the efficacy of anti-leukotrienes as adjunct therapy, and a separate paediatric update was recently published (Chauhan 2013). We

wished to conduct this Cochrane review using recent evidence obtained exclusively from studies of adults and adolescents.

OBJECTIVES

To assess the efficacy and safety of anti-leukotriene agents added to ICS compared with the same dose, an increased dose or a tapering dose of ICS (in both arms) for adults and adolescents 12 years of age and older with persistent asthma. Also, to determine whether any characteristics of participants or treatments might affect the magnitude of response.

METHODS

Criteria for considering studies for this review

Types of studies

We considered for inclusion of randomised controlled trials (RCTs) of parallel-group design including adults and adolescents with asthma that compared anti-leukotrienes added to ICS versus ICS alone.

Types of participants

Adults and adolescents 12 years of age and older with asthma who were taking a stable maintenance dose of ICS.

Types of interventions

Intervention group

Combination of oral anti-leukotrienes (leukotriene synthesis inhibitors or leukotriene receptor antagonists) with fixed or tapering doses of ICS. Investigators must have administered the intervention for a minimum of four weeks.

Control group

ICS alone at the same dose, at a higher dose than that used in the intervention group or at tapering doses (in both intervention and control groups).

In this review, we considered the following three comparisons.

- Anti-leukotrienes and ICS versus an identical dose of ICS.
- Anti-leukotrienes and ICS versus a higher dose of ICS.
- Anti-leukotrienes and tapering doses of ICS versus tapering doses of ICS (tapering protocol).

Types of outcome measures

We considered the following outcomes for the longest period of treatment.

Primary outcomes

- Exacerbations
 - * Number of participants with one or more exacerbations requiring oral corticosteroids (unless both groups were tapering their dose of ICS, in which case, the primary outcome was the % reduction in ICS dose from baseline with maintained asthma control)

Secondary outcomes

- Exacerbations
 - * Hospital admission: number of participants hospitalised as the result of exacerbations
 - * Emergency department visit: number of participants visiting the emergency department owing to exacerbations
- Lung function
 - * Change from baseline in pulmonary function tests (i.e. forced expiratory volume in one second (FEV₁), peak expiratory flow rate (PEFR), provocative concentration of methacholine causing a 20% fall in FEV₁ (PC₂₀))
- Clinical or physiological outcomes reflecting long-term asthma control as change from baseline
 - * Symptoms score
 - * Use of β_2 -agonist
 - * Days (absolute or %) without symptoms
 - * Days (absolute or %) without rescue treatment
 - * Night-time awakenings
- Change in quality of life (as measured by a validated questionnaire)
- Biological markers of inflammation as change from baseline
 - * Eosinophil counts in blood or sputum
 - * Leukotrienes in biological fluids, expired nitric oxide
 - * Eosinophilic cationic protein
- Clinical and biochemical adverse effects as number of participants with the following
 - * Overall adverse effects
 - * Serious adverse health events (including death)
 - * Other adverse effects (elevation of liver enzymes, headache, adrenal suppression)
- Withdrawal rate
 - * Overall withdrawals
 - * Withdrawals due to poor asthma control/exacerbation
 - * Withdrawals due to adverse effects

Search methods for identification of studies

Electronic searches

We identified trials from the Cochrane Airways Group Specialised Register (CAGR) using the search strategy presented in [Appendix 1](#). The CAGR is derived from systematic searches of bibliographic databases including the Cochrane Central Register of Controlled Trials, MEDLINE, Embase, the Cumulative Index to Nursing and Allied Health Literature (CINAHL), the Allied and Complementary Medicine Database (AMED) and PsycINFO, and by handsearching of respiratory journals and meeting abstracts (see [Appendix 2](#) for details).

We also conducted a search of ClinicalTrials.gov (www.ClinicalTrials.gov) and the World Health Organization (WHO) trials portal (www.who.int/ictrp/en/). We searched all databases from their inception to August 2016, and we imposed no restriction on the language of publication.

Searching other resources

We checked the websites of international pharmaceutical companies producing anti-leukotrienes for reports of completed relevant trials.

Data collection and analysis

Two review authors independently collected data and resolved disagreements by reaching consensus or by seeking the input of a third review author. When necessary, we contacted the authors of included studies to provide important data missing from the trial reports.

Selection of studies

Two review authors independently selected articles on the basis of title and abstract screening. We reviewed each citation or abstract and annotated each as included, excluded or unclear. Two review authors retrieved and reviewed the full texts of citations identified as included or unclear (i.e. clearly relevant and potentially relevant trials). We resolved disagreements by reaching consensus or by seeking input from an expert review author.

Data extraction and management

Two review authors independently extracted data and resolved disagreements by reaching consensus or by seeking input from an expert review author.

Assessment of risk of bias in included studies

We assessed the methodological quality of eligible controlled trials by using the Cochrane tool for assessing risk of bias ([Higgins 2011](#)), which is based on seven criteria, namely:

- random sequence generation;
- allocation concealment;
- blinding of participants and personnel;
- blinding of outcome assessment;
- incomplete outcome data;
- selective outcome reporting; and
- other bias.

We graded each potential source of bias as high, low or unclear. Two review authors independently completed the risk of bias assessment and resolved disagreements by reaching consensus or by seeking the input of a third review author.

Measures of treatment effect

We calculated treatment effects for dichotomous variables as risk ratios (RRs) with 95% confidence intervals (CIs). For continuous outcomes, such as lung function tests, we calculated pooled statistics as mean differences (MDs) or standardised mean differences (SMD) with 95% CIs. We summarised differences between group event rates by using rate ratios. We derived the number needed to treat for an additional beneficial outcome (NNTB) over six to 16 weeks from pooled odds ratios using Visual Rx (www.nntonline.net) for the primary outcome. We assumed equivalence if the RR estimate and its 95% CI were between 0.9 and 1.1.

Unit of analysis issues

The unit of analysis was the study participant. We considered articles that reported multiple comparison groups as separate studies.

Dealing with missing data

When possible, we contacted study authors or study sponsors to obtain missing numerical outcome data. We did not use imputation for missing data. We calculated standard deviation if articles reported standard error of the mean or 95% CI. If studies used intention-to-treat analysis, we reported this information in the [Characteristics of included studies](#) tables.

Assessment of heterogeneity

We tested the homogeneity of effect sizes between included and pooled studies by using the DerSimonian and Laird method and reported data as P values or as I^2 measurements. In light of high heterogeneity between included studies, we used a random-effects model to analyse summary estimates for all outcomes.

Assessment of reporting biases

We planned to use funnel plots to examine the possibility of publication bias ([Egger 1997](#)) and to perform sensitivity analysis by excluding trials with poor methods as well as unpublished studies to examine the possibility of bias.

Data synthesis

We planned analysis that would focus on the following three comparisons.

- Anti-leukotrienes + ICS versus an identical dose of ICS.
- Anti-leukotrienes + ICS versus a higher dose of ICS.
- Anti-leukotrienes + tapering doses of ICS versus tapering doses of ICS (tapering protocol).

We presented data based on the type of anti-leukotriene agent used (montelukast, zafirlukast, pranlukast). We performed meta-analysis using RevMan version 5.3 ([RevMan](#)) and created 'Summary of findings' tables using GRADEpro software according to recommendations provided in the *Cochrane Handbook for Systematic Reviews of Interventions* ([Higgins 2011](#)). In the case of a trial with more than one intervention or control group, we considered an additional study to represent two different comparisons, if appropriate. In such cases, we halved the number of participants in the group that served twice as a comparator to avoid over-representation. For dichotomous outcomes, we halved both the numerator and the denominator of the group that served twice as a comparator.

Subgroup analysis and investigation of heterogeneity

We performed subgroup analysis to identify factors influencing the magnitude of response. We based a priori defined subgroups on the following.

- Dose of daily ICS in intervention group (we considered ≤ 250 , 251 to 500 and > 500 μg hydrofluoroalkane beclomethasone dipropionate or equivalent (HFA-BDPeq) as low-, medium- and

high-dose; and HFA-beclomethasone dipropionate-equivalent based on 1 μg of fluticasone = 1 μg of HFA-propelled beclomethasone = 1 μg of ciclesonide = 1 μg of mometasone = 2 μg of budesonide = 2 μg of chlorofluorocarbon (CFC)-propelled beclomethasone = 4 μg of triamcinolone = 4 μg of flunisolide) ([NAEPP 2010](#)).

- Severity of baseline asthma obstruction (mild: mean $\text{FEV}_1 \geq 80\%$ of predicted; moderate: FEV_1 60% to 79% of predicted; and severe: $\text{FEV}_1 < 60\%$ of predicted) or, if FEV_1 is not available, rate of exacerbations requiring systemic corticosteroids in the control group) ([GINA 2015](#)).
- Atopy (atopic vs non-atopic).
- Anti-leukotriene used (montelukast, zafirlukast, pranlukast).
- Duration of intervention (≤ 24 weeks vs > 24 weeks).
- Funding source (funding from pharmaceutical companies vs no funding or funding not reported).

We examined the difference in the magnitude of effect attributable to these subgroups by performing the residual Chi^2 test ([Deeks 2001](#)).

Sensitivity analysis

For the primary outcome, we performed sensitivity analyses to determine effects of publication status and risk of bias. We performed the sensitivity analysis of publication status by removing reports not published as full-text articles, and of methodological quality by removing trials with inadequate information on random sequence generation and blinding procedures and with notable differential loss to follow-up in both groups. We explored potential publication bias by using a funnel plot if we identified more than 10 studies for a specific outcome ([Egger 1997](#)).

RESULTS

Description of studies

Results of the search

A literature search yielded 743 citations. Of these, we found 102 abstracts to be potentially relevant and retrieved the full-text articles. After screening, we included in the review 37 studies involving control and intervention comparisons (see [Characteristics of included studies](#), [Table 1](#), [Table 2](#) and [Table 3](#) for full details). We presented reasons for exclusion in the [Characteristics of excluded studies](#) section. We reported the study selection process using a PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) diagram ([Figure 1](#)). [Farzan 2016](#) published the study as an abstract and did not report much information on type and dose of ICS, nor on outcomes; this prevented its classification and description among included studies. We have provided further details in the [Characteristics of studies awaiting classification](#) section.

Figure 1. Study selection flow diagram.

Included studies

We found a total of 37 eligible studies, representing 6128 adults and adolescents with asthma on a stable maintenance dose of ICS. One study ([Riccioni 2003](#)) compared a combination of anti-leukotrienes and ICS with the same or higher doses of ICS. Two studies reported the use of two different doses of zafirlukast when comparing the combination of anti-leukotrienes with ICS versus ICS alone ([Nayak 1998](#); [Ringdal 1999](#)).

All included studies were RCTs of parallel-group design. Of 37 studies, 26 were available as full-text publications, 10 were published as abstracts and one was provided as a summary report on [clinicaltrials.gov](#). Pharmaceutical companies that were producers of ICS and anti-leukotrienes funded 18 studies ([Barnes](#)

[2007](#); [Bateman 1993](#); [Djukanovic 2010](#); [Kanniess 2002](#); [Laitinen 1993](#); [Laviolette 1999](#); [Lofdahl 1999](#); [Nayak 1998](#); [Price 2003](#); [Ringdal 1999](#); [SD-004-0216](#); [Shingo 2002](#); [Storms 2004](#); [Tohda 2002](#); [Ulrik 2010](#); [Vaquerizo 2003](#); [Virchow 2000](#); [Ye 2015](#)). Merck funded 10 of those 18 studies ([Barnes 2007](#); [Kanniess 2002](#); [Laviolette 1999](#); [Lofdahl 1999](#); [Price 2003](#); [Shingo 2002](#); [Storms 2004](#); [Ulrik 2010](#); [Vaquerizo 2003](#); [Ye 2015](#)), GlaxoSmithKline one ([Djukanovic 2010](#)), AstraZeneca six ([Bateman 1993](#); [Laitinen 1993](#); [Nayak 1998](#); [Ringdal 1999](#); [SD-004-0216](#); [Virchow 2000](#)) and Banyu Pharmaceuticals Ltd one ([Tohda 2002](#)). An educational grant was provided to fund one study ([Kirishi 2013](#)), and the remaining studies did not report the funding source ([Beg 2014](#); [Bilancia 2000](#); [Cakmak 2004](#); [Chlumský 2000](#); [Demuro-Mercon 2001](#); [Huang 2003](#); [Korzh 2004](#); [Nsouli 2000](#); [Riccioni 2001](#); [Riccioni 2002](#); [Riccioni 2003](#); [Riccioni 2005](#); [Sano](#)

2008; Shah 2006; Tognella 2004; Tomari 2001; Xiang 2001; Yildirim 2004). The duration of the intervention among eligible studies ranged between four and 24 weeks, except for one study (Sano 2008), which was a five-year prospective trial. Three studies permitted theophylline as a co-intervention that was maintained at the same dose throughout the study (Sano 2008; Tomari 2001; Xiang 2001). For a complete description of all eligible studies, see the [Characteristics of included studies](#) tables.

Author verification

We made an attempt to contact study authors and/or sponsors of studies for which data on relevant outcomes were missing. We contacted authors of 22 eligible studies (Bilancia 2000; Cakmak 2004; Chlumský 2000; Demuro-Mercon 2001; Djukanovic 2010; Kirishi 2013; Korzh 2004; Laviolette 1999; Nayak 1998; Nsouli 2000; Price 2003; Riccioni 2001; Riccioni 2002; Riccioni 2005; Sano 2008; SD-004-0216; Shingo 2002; Tognella 2004; Tohda 2002; Ulrik 2010; Virchow 2000; Yildirim 2004). One study author provided data (Kirishi 2013), and the three studies failed to reply or replied but did not provide data (Price 2003; Ulrik 2010; Farzan 2016). We obtained data from the previous version of this Cochrane review (Ducharme 2004) for the following articles: Bateman 1993; Kannies 2002; Laitinen 1993; Laviolette 1999; Lofdahl 1999; Nayak 1998; Price 2003; Riccioni 2001; Riccioni 2002; Ringdal 1999; Shingo 2002; Tohda 2002; and Virchow 2000.

On the basis of the research question, we classified all included studies into three comparisons.

- Anti-leukotrienes and ICS versus SAME dose of ICS.
- Anti-leukotrienes and ICS versus HIGHER dose of ICS.
- Anti-leukotrienes and TAPERING dose of ICS versus TAPERING dose of ICS.

Anti-leukotrienes and ICS versus same dose of ICS

Of 37 studies, 16 compared the combination of anti-leukotrienes and ICS with the same dose of ICS alone (Cakmak 2004; Demuro-Mercon 2001; Djukanovic 2010; Huang 2003; Korzh 2004; Laviolette 1999; Riccioni 2001; Riccioni 2002; Riccioni 2003; Sano 2008; SD-004-0216; Storms 2004; Tognella 2004; Ulrik 2010; Vaquerizo 2003; Virchow 2000). Ten of these studies (63%) (Djukanovic 2010; Huang 2003; Laviolette 1999; Riccioni 2001; Riccioni 2002; SD-004-0216; Storms 2004; Ulrik 2010; Vaquerizo 2003; Virchow 2000) contributed data representing 2364 adults and adolescents.

We presented baseline characteristics of 16 included studies as follows (Table 1).

Participants

The age of enrolled participants ranged from 15 to 79 years, and 20% to 62% were male. Four studies (Riccioni 2001; Riccioni 2002; Riccioni 2003; Tognella 2004) described participants as having mild asthma, six studies (Cakmak 2004; Djukanovic 2010; Korzh 2004; Sano 2008; Ulrik 2010; Vaquerizo 2003) as having mild to moderate asthma and two studies (Huang 2003; Storms 2004) as having moderate asthma. Remaining studies did not report the severity of asthma in enrolled participants. Mean baseline FEV₁% predicted was 60% to 70% in five studies (Djukanovic 2010; Huang 2003; Laviolette 1999; SD-004-0216; Virchow 2000), was greater than 80% in three studies (Storms 2004; Ulrik 2010; Vaquerizo 2003) and was not reported in the remaining studies. Two studies (Ulrik

2010; Vaquerizo 2003) reported asthma as well controlled, two studies (SD-004-0216; Storms 2004) as inadequately controlled and three studies (Djukanovic 2010; Laviolette 1999; Virchow 2000) as symptomatic. Remaining studies did not report details on asthma control with baseline doses of ICS.

Interventions

Ten studies (Demuro-Mercon 2001; Djukanovic 2010; Korzh 2004; Laviolette 1999; Riccioni 2002; Riccioni 2003; Storms 2004; Tognella 2004; Ulrik 2010; Vaquerizo 2003) administered montelukast (10 mg once daily), three studies (Huang 2003; Riccioni 2001; SD-004-0216) zafirlukast 20 mg twice daily, one study (Cakmak 2004) zafirlukast 40 mg once daily in one comparison and one study (Virchow 2000) zafirlukast 80 mg twice daily in a single comparison. Sano 2008 administered pranlukast 450 mg once daily in a single comparison. Sano 2008 administered beclomethasone as 800 µg daily and Laviolette 1999 as 400 µg daily; Cakmak 2004, Korzh 2004 and SD-004-0216 administered budesonide as 400 µg daily and Riccioni 2001, Riccioni 2002 and Riccioni 2003 as 800 µg daily; Demuro-Mercon 2001, Djukanovic 2010 and Storms 2004 administered fluticasone as 200 µg daily and Tognella 2004 as 250 µg daily. Study participants received multiple doses of ICS in four studies (Huang 2003; Ulrik 2010; Vaquerizo 2003; Virchow 2000), and in Sano 2008, participants were permitted to use theophylline as co-treatment in a single comparison. In one comparison, Laviolette 1999 allowed participants to take β_2 -agonist and antihistamines as-needed during the study and did not permit use of terfenadine (within two weeks of pre-study visit) nor astemizole (within three months of pre-study visit). Two studies did not report the use of any co-treatment (Ulrik 2010; Virchow 2000).

The duration of the intervention was four weeks in Demuro-Mercon 2001, Huang 2003 and Storms 2004; six weeks in Cakmak 2004, Tognella 2004 and Virchow 2000; eight weeks in Korzh 2004, Riccioni 2001 and SD-004-0216; 12 weeks in Djukanovic 2010, Ulrik 2010 and Riccioni 2003; and 16 weeks in Laviolette 1999, Riccioni 2002 and Vaquerizo 2003. The run-in period ranged from two to eight weeks. Two studies did not report information on the run-in period (SD-004-0216; Tognella 2004).

Outcomes

Four studies contributed data to the primary outcome - the number of participants with one or more exacerbations requiring oral corticosteroids.

Data were available for some secondary outcomes, including participants with one or more exacerbations requiring hospital admission (Laviolette 1999), participants with one or more exacerbations leading to emergency department visit (Huang 2003), morning PEFR (L/min) (Djukanovic 2010; Huang 2003; Laviolette 1999; Vaquerizo 2003; Virchow 2000), evening PEFR (L/min) (Djukanovic 2010; Huang 2003; Laviolette 1999; Virchow 2000), FEV₁ (L) (Djukanovic 2010, Laviolette 1999; Virchow 2000), FEV₁ % of predicted (Djukanovic 2010; Laviolette 1999; Vaquerizo 2003), mean asthma symptom score (Laviolette 1999; Vaquerizo 2003; Virchow 2000), change from baseline in mean daytime use of β_2 -agonists (puffs/d) (Laviolette 1999; Vaquerizo 2003; Virchow 2000), night-time awakenings (episodes/wk) (Laviolette 1999; Virchow 2000), rescue-free days (%) (Djukanovic 2010), quality of life (Vaquerizo 2003), eosinophil counts (Laviolette 1999) and patients' or physicians' global evaluation (Laviolette

1999). Investigators reported overall adverse events (Djukanovic 2010; Huang 2003; Laviolette 1999; Riccioni 2001; Riccioni 2002; SD-004-0216; Storms 2004; Vaquerizo 2003; Virchow 2000), serious adverse events (Virchow 2000) or specific clinical adverse events (Laviolette 1999; Vaquerizo 2003; Virchow 2000). They also reported overall withdrawals (Djukanovic 2010; Huang 2003; Laviolette 1999; Riccioni 2001; Riccioni 2002; SD-004-0216; Storms 2004; Vaquerizo 2003; Virchow 2000), withdrawals due to asthma exacerbation (Djukanovic 2010; Huang 2003; Laviolette 1999; Riccioni 2002; Vaquerizo 2003; Virchow 2000) and withdrawals due to adverse events (Laviolette 1999; Vaquerizo 2003; Virchow 2000).

Anti-leukotrienes and ICS versus higher dose of ICS

Of the 37 studies, 15 evaluated the combination of anti-leukotrienes and ICS versus a higher dose of ICS alone (Barnes 2007; Beg 2014; Bilancia 2000; Chlumský 2000; Kirishi 2013; Nayak 1998; Nsouli 2000; Price 2003; Riccioni 2003; Ringdal 1999; Shah 2006; Tomari 2001; Xiang 2001; Ye 2015; Yildirim 2004). Eight of these studies (Barnes 2007; Kirishi 2013; Nayak 1998; Price 2003; Ringdal 1999; Shah 2006; Tomari 2001; Yildirim 2004) contributed data representing 2008 adolescents and adults. One included comparison arms for both the same dose of ICS and a higher dose of ICS but did not contribute data for either comparison (Riccioni 2003).

Investigators presented baseline characteristics of the 15 included studies in Table 2.

Participants

The calculated mean age of participants was 43 years, and 20% to 87% were male. Researchers described participants as having mild asthma (Riccioni 2003), mild to moderate asthma (Bilancia 2000; Ringdal 1999; Xiang 2001), moderate asthma (Beg 2014; Tomari 2001; Yildirim 2004) and moderate to severe asthma (Chlumský 2000). Remaining studies did not report adequate information on asthma severity. In three studies (Barnes 2007; Bilancia 2000; Price 2003), mean baseline FEV₁% predicted was 60% to 70%, and in three studies (Riccioni 2003; Ringdal 1999; Ye 2015) it was greater than 80%; the remaining studies did not report this information. Four studies (Barnes 2007; Price 2003; Tomari 2001; Yildirim 2004) reported that participants were symptomatic despite the use of daily ICS. The remaining studies did not provide clear information on asthma control.

Interventions

Nine studies (Barnes 2007; Beg 2014; Bilancia 2000; Kirishi 2013; Nsouli 2000; Price 2003; Riccioni 2003; Shah 2006; Yildirim 2004) administered montelukast (10 mg daily), four studies (Chlumský 2000; Nayak 1998; Ringdal 1999; Xiang 2001) zafirlukast (40 mg or 80 mg daily) and one study (Tomari 2001) pranlukast 450 mg once daily in a single comparison. Researchers administered beclomethasone as 336 µg daily ex-valve (Nayak 1998), as 168 to 500 µg daily (Nsouli 2000), as 400 to 500 µg daily (Ringdal 1999) and as 800 µg daily (Tomari 2001); budesonide as 400 µg daily (Shah 2006; Yildirim 2004; Ye 2015) or 800 µg daily (Barnes 2007; Bilancia 2000; Price 2003); and fluticasone as 125 µg daily (Beg 2014). Remaining studies did not report the dose of ICS. Participants in the control group took twice the dose of ICS taken by those in the intervention group. Two studies (Tomari 2001; Xiang 2001) allowed participants to use theophylline, and six studies (Barnes 2007; Kirishi 2013; Price 2003;

Shah 2006; Tomari 2001; Yildirim 2004) permitted β_2 -agonist use as needed.

The duration of the intervention was four weeks in Xiang 2001; six weeks in Chlumský 2000 and Yildirim 2004; eight weeks in Shah 2006; 12 weeks in Barnes 2007, Beg 2014, Bilancia 2000, Kirishi 2013, Nsouli 2000, Price 2003 and Ringdal 1999; and 13 to 16 weeks in Nayak 1998 and Tomari 2001. The run-in period was two to eight weeks.

Outcomes

Four studies (Nayak 1998; Price 2003; Ringdal 1999; Shah 2006) contributed data to the primary outcome - participants with one or more exacerbations requiring oral corticosteroids.

Several studies contributed data to secondary outcomes including participants with one or more exacerbations requiring hospital admission (Nayak 1998; Price 2003; Ringdal 1999), change from baseline in morning PEFR (L/min) (Barnes 2007; Kirishi 2013; Nayak 1998; Ringdal 1999; Shah 2006), evening PEFR (L/min) (Kirishi 2013), mean diurnal variation in PEFR (L/min) (Nayak 1998; Ringdal 1999), FEV₁ (L) (Kirishi 2013; Nayak 1998; Ringdal 1999; Shah 2006), mean daytime use of β_2 -agonists (puffs/d) (Nayak 1998; Price 2003; Ringdal 1999; Shah 2006), mean symptom scores (Nayak 1998; Price 2003; Ringdal 1999) and nocturnal awakenings (Ringdal 1999). Six studies (Barnes 2007; Nayak 1998; Price 2003; Ringdal 1999; Shah 2006; Tomari 2001) reported overall withdrawals. Three studies (Price 2003; Nayak 1998; Ringdal 1999) reported withdrawals due to asthma exacerbation and withdrawals due to adverse events. Six studies (Barnes 2007; Nayak 1998; Price 2003; Ringdal 1999; Shah 2006; Tomari 2001) reported overall adverse events, and a single comparison (Barnes 2007) reported the number of serious adverse events. Five studies (Nayak 1998; Price 2003; Ringdal 1999; Shah 2006; Yildirim 2004) reported specific clinical adverse events.

Anti-leukotrienes and tapering dose of ICS versus tapering dose of ICS

Seven studies, representing 1150 adults and adolescents, assessed the combination of anti-leukotrienes and ICS versus ICS as a means of tapering the dose over time (Bateman 1993; Kannie 2002; Laitinen 1993; Lofdahl 1999; Riccioni 2005; Shingo 2002; Tohda 2002).

Investigators presented baseline characteristics for the seven included studies as follows (Table 3).

Participants

The age of enrolled participants ranged from 15 to 70 years, and 25% to 60% were male. Study authors described participants as having mild asthma (Bateman 1993), mild to moderate asthma (Riccioni 2005), moderate asthma (Kannie 2002) and moderate to severe asthma (Shingo 2002; Tohda 2002). Remaining studies did not report the severity of asthma. Four studies (Kannie 2002; Lofdahl 1999; Riccioni 2005; Tohda 2002) reported mean baseline FEV₁% predicted greater than 80%, and the remaining studies did not report this measure. Four studies (Kannie 2002; Lofdahl 1999; Shingo 2002; Tohda 2002) revealed that participants' condition was well controlled with daily ICS, and the remaining comparison did not report details on asthma control (Riccioni 2005).

Interventions

Five studies ([Kanniess 2002](#); [Lofdahl 1999](#); [Riccioni 2005](#); [Shingo 2002](#); [Tohda 2002](#)) administered montelukast (10 mg daily), and the remaining studies used zafirlukast 20 mg twice daily. None of the studies evaluated pranlukast. Two studies tapered budesonide 800 µg daily by half at four, eight and 12 weeks ([Riccioni 2005](#)) or 800 µg daily to half at six weeks ([Kanniess 2002](#)). One comparison tapered beclomethasone 800 to 1600 µg daily on the basis of symptom score, PEFR and inhaled β_2 -agonist use ([Tohda 2002](#)). One comparison permitted use of various ICS, including fluticasone, beclomethasone, budesonide, flunisolide or triamcinolone at multiple doses, with tapering every two weeks by 25% ([Lofdahl 1999](#)). Another comparison ([Shingo 2002](#)) reported administration of various ICS (beclomethasone, flunisolide or triamcinolone) and multiple doses of ICS with tapering every two weeks.

The duration of the intervention was six weeks in [Kanniess 2002](#); eight weeks in [Shingo 2002](#); 12 weeks in [Lofdahl 1999](#) and [Riccioni 2005](#); and 24 weeks in [Tohda 2002](#). [Kanniess 2002](#), [Lofdahl 1999](#), [Riccioni 2005](#), [Shingo 2002](#) and [Tohda 2002](#) permitted participants to use a β_2 -agonist as needed).

The run-in period was one to four weeks in [Bateman 1993](#), [Kanniess 2002](#), [Riccioni 2005](#), [Shingo 2002](#) and [Tohda 2002](#) and five to seven weeks in the remaining comparison ([Lofdahl 1999](#)).

Outcomes

Four studies contributed data to the primary outcome - % change from baseline ICS dose ([Bateman 1993](#); [Laitinen 1993](#); [Lofdahl](#)

[1999](#); [Tohda 2002](#)). Secondary outcomes included change from baseline ICS dose required to maintain control ([Kanniess 2002](#); [Riccioni 2005](#); [Shingo 2002](#)), one or more exacerbations requiring oral corticosteroids ([Kanniess 2002](#); [Laitinen 1993](#); [Riccioni 2005](#); [Shingo 2002](#); [Tohda 2002](#)), one or more exacerbations leading to hospital admission ([Kanniess 2002](#); [Tohda 2002](#)), 50% or greater reduction from baseline ICS dose ([Lofdahl 1999](#)), complete tapering off of ICS ([Bateman 1993](#); [Lofdahl 1999](#); [Shingo 2002](#)), morning PEFR (L/min) ([Kanniess 2002](#); [Tohda 2002](#)) and other measures of lung function and asthma control ([Kanniess 2002](#)).

[Kanniess 2002](#) reported exhaled nitric oxide concentration (ppb) and sputum eosinophilic counts as geometric means in a single comparison. Six studies ([Bateman 1993](#); [Kanniess 2002](#); [Laitinen 1993](#); [Lofdahl 1999](#); [Shingo 2002](#); [Tohda 2002](#)) reported overall or specific adverse events. Seven studies ([Bateman 1993](#); [Kanniess 2002](#); [Laitinen 1993](#); [Lofdahl 1999](#); [Riccioni 2005](#); [Shingo 2002](#); [Tohda 2002](#)) reported overall withdrawals and withdrawals due to asthma exacerbation or adverse events.

Excluded studies

Of 102 full-text articles assessed for eligibility, 55 studies failed to meet review eligibility criteria. See the [Characteristics of excluded studies](#) table for full details.

Risk of bias in included studies

We provided full details on risk of bias for each included study in the [Characteristics of included studies](#) tables. We provided in [Figure 2](#) a graphical summary of the 'Risk of bias' judgements.

Figure 2. Risk of bias summary: review authors' judgements about each risk of bias item for each included study.

	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bias)	Blinding of outcome assessment (detection bias)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)	Other bias
Barnes 2007	?	?	+	+	-	+	+
Bateman 1993	+	+	+	+	?	?	?
Beg 2014	?	-	-	-	+	?	?
Bilancia 2000	?	?	?	?	?	?	?
Cakmak 2004	-	?	+	+	?	-	+
Chlumský 2000	?	?	-	-	?	?	?
Demuro-Mercon 2001	?	?	+	+	?	?	?
Djukanovic 2010	?	?	+	+	+	+	+
Huang 2003	?	?	+	+	+	+	+
Kanniess 2002	?	?	+	+	+	+	+
Kirishi 2013	?	?	?	?	?	?	?
Korzh 2004	?	?	?	?	?	?	?
Laitinen 1993	+	+	+	+	?	?	?
Lavolette 1999	+	?	+	+	+	+	+
Lofdahl 1999	+	?	+	+	+	+	+
Nayak 1998	?	?	+	+	?	?	?
Nsouli 2000	?	?	-	-	?	?	?
Price 2003	?	?	+	+	+	+	+
Riccioni 2001	?	?	-	-	?	+	+
Riccioni 2002	?	?	-	-	?	+	+

Figure 2. (Continued)

Riccioni 2002	?	?	-	-	?	+	+
Riccioni 2003	?	?	?	?	?	+	+
Riccioni 2005	?	?	+	-	+	+	+
Ringdal 1999	+	+	+	+	?	?	?
Sano 2008	?	?	+	-	?	?	?
SD-004-0216	?	?	+	+	+	?	+
Shah 2006	+	?	+	+	+	+	+
Shingo 2002	?	?	+	+	+	+	+
Storms 2004	+	?	+	+	+	+	+
Tognella 2004	?	?	?	?	?	+	?
Tohda 2002	?	?	+	+	+	+	+
Tomari 2001	?	?	-	-	+	+	+
Ulrik 2010	?	?	+	+	+	+	+
Vaquerizo 2003	+	?	+	+	+	+	+
Virchow 2000	?	?	+	+	+	+	+
Xiang 2001	?	?	?	?	?	?	?
Ye 2015	+	-	-	-	+	+	?
Yildirim 2004	?	?	-	-	?	+	+

Allocation

Only nine of the 37 included studies (Bateman 1993; Laitinen 1993; Laviolette 1999; Lofdahl 1999; Ringdal 1999; Shah 2006; Storms 2004; Vaquerizo 2003; Ye 2015) provided adequate details on the randomisation technique; we judged these studies as having low risk of bias. We judged one comparison (Cakmak 2004) as having high risk of bias because researchers randomised participants according to their order of presentation at the outpatient clinic. We judged the remaining studies as having unclear risk of bias, as study authors did not provide adequate details on randomisation. Three studies (Bateman 1993; Laitinen 1993; Ringdal 1999) provided adequate information on allocation concealment. Other studies did not provide adequate information on allocation concealment, and we judged these studies as having unclear risk of bias.

Blinding

Blinding of participants and personnel

We judged 23 studies as having low risk of bias because they were double-blinded (Barnes 2007; Bateman 1993; Cakmak 2004; Demuro-Mercon 2001; Djukanovic 2010; Huang 2003; Kanness 2002; Laitinen 1993; Laviolette 1999; Lofdahl 1999; Nayak 1998; Price 2003; Ringdal 1999; Sano 2008; SD-004-0216; Shah 2006; Shingo 2002; Storms 2004; Tognella 2004; Tohda 2002; Ulrik 2010;

Vaquerizo 2003; Virchow 2000). We judged eight studies as having high risk of bias owing to their open-label design (Beg 2014; Chlumský 2000; Nsouli 2000; Riccioni 2001; Riccioni 2002; Tomari 2001; Ye 2015; Yildirim 2004). The remaining studies did not provide enough information on blinding, and we judged them as having unclear risk of bias.

Blinding of outcome assessors

We assumed that 23 studies reported to be employing double-blind study design had blinded outcomes assessors, and we judged these studies as having low risk of bias (Barnes 2007; Bateman 1993; Cakmak 2004; Demuro-Mercon 2001; Djukanovic 2010; Huang 2003; Kanness 2002; Laitinen 1993; Laviolette 1999; Lofdahl 1999; Nayak 1998; Price 2003; Ringdal 1999; Sano 2008; SD-004-0216; Shah 2006; Shingo 2002; Storms 2004; Tognella 2004; Tohda 2002; Ulrik 2010; Vaquerizo 2003; Virchow 2000). We judged eight studies as having high risk of bias owing to their open-label design (Beg 2014; Chlumský 2000; Nsouli 2000; Riccioni 2001; Riccioni 2002; Tomari 2001; Ye 2015; Yildirim 2004). Two studies (Riccioni 2005; Sano 2008) employed single-blind study design, and we judged them as having high risk of bias.

Incomplete outcome data

We judged 18 studies as having low risk of bias (Beg 2014; Djukanovic 2010; Huang 2003; Kanniess 2002; Laviolette 1999; Lofdahl 1999; Price 2003; Riccioni 2005; SD-004-0216; Shah 2006; Shingo 2002; Storms 2004; Tohda 2002; Tomari 2001; Ulrik 2010; Vaquerizo 2003; Virchow 2000; Ye 2015). One study reported unbalanced withdrawals (2.7% vs 13.2%) with no intention-to-treat analysis, and data on the primary outcome were not available for 35% versus 26% (Barnes 2007); we judged this study to be at high risk of bias. We judged the remaining studies as having unclear risk of bias.

Selective reporting

We judged 22 studies as having low risk of bias because outcomes mentioned in the Methods and Results sections matched and we could extract the data (Barnes 2007; Djukanovic 2010; Huang 2003; Kanniess 2002; Laviolette 1999; Lofdahl 1999; Price 2003; Riccioni 2001; Riccioni 2002; Riccioni 2003; Riccioni 2005; Shah 2006; Shingo 2002; Storms 2004; Tognella 2004; Tohda 2002; Tomari 2001; Ulrik 2010; Vaquerizo 2003; Virchow 2000; Ye 2015; Yildirim 2004). We judged a single comparison as having high risk of bias because investigators reported certain outcomes in the Methods section (daytime and night-time symptoms, night-time awakening, use of rescue medications) but did not present data in the Results section (Cakmak 2004). The remaining studies did not include adequate information for assessment of risk of bias for this domain, and we judged these studies as having unclear risk of bias.

Other potential sources of bias

We judged 22 studies as having low risk of bias arising from baseline imbalances (Barnes 2007; Cakmak 2004; Djukanovic 2010;

Huang 2003; Kanniess 2002; Laviolette 1999; Lofdahl 1999; Price 2003; Riccioni 2001; Riccioni 2002; Riccioni 2003; Riccioni 2005; SD-004-0216; Shah 2006; Shingo 2002; Storms 2004; Tohda 2002; Tomari 2001; Ulrik 2010; Vaquerizo 2003; Virchow 2000; Yildirim 2004). It was not possible to assess other sources of bias in the remaining studies because researchers primarily reported these studies as abstracts.

Effects of interventions

See: [Summary of findings for the main comparison](#) Summary of findings table 1; [Summary of findings 2](#) Summary of findings table 2; [Summary of findings 3](#) Summary of findings table 3

Anti-leukotrienes and ICS versus same dose of ICS

See [Summary of findings for the main comparison](#) for details on participant relevant outcomes in this comparison.

Primary outcome

Number of participants with one or more exacerbations requiring oral corticosteroids

The combination of anti-leukotriene agents and ICS was superior to the same dose of ICS (risk ratio (RR) 0.50, 95% confidence interval (CI) 0.29 to 0.86; $I^2 = 0\%$; four trials; 815 participants; moderate quality; [Analysis 1.1](#); [Figure 3](#)), reducing from 9.2% to 4.6% the risk of having an asthma exacerbation requiring rescue oral corticosteroids. This is equivalent to a number needed to treat for an additional beneficial outcome over six to 16 weeks of 22 (95% CI 16 to 75).

Figure 3. Forest plot of comparison: 1 Anti-leukotrienes and inhaled corticosteroids versus SAME dose of inhaled corticosteroids, outcome: 1.1 Patients with ≥ 1 exacerbations requiring oral corticosteroids.

Types of anti-leukotriene agents ($\chi^2 = 0.18$; $df = 1$; $P = 0.67$) and funding ($\chi^2 = 0.58$; $df = 1$; $P = 0.45$) did not influence the magnitude of effect. As the result of lack of heterogeneity between studies or insufficient data reporting, we could not perform subgroup analyses for duration of the intervention, dose of ICS, severity of asthma and atopy. As all trials were published, we did not perform the sensitivity analysis on publication.

Secondary outcomes

Exacerbations

Only one study contributed data on participants with one or more exacerbations leading to hospital admission (Lavolette 1999) or an emergency department visit (Huang 2003) (Analysis 1.3; Analysis 1.4); each showed no statistically significant group difference.

Lung function

Results showed a statistically significant group difference in change from baseline in morning PEF (mean difference (MD) 8.36 L/min, 95% CI 3.64 to 13.07; $I^2 = 26\%$; four studies; 1489 participants; Analysis 1.5) and in change from baseline FEV₁ (MD 0.11 L, 95% CI 0.03 to 0.19; $I^2 = 55\%$; three studies; 760 participants; Analysis 1.7) favouring the combination of anti-leukotrienes and ICS. However, change from baseline in FEV₁% of predicted and evening PEF showed no statistically significant group difference (MD 1.84%, 95% CI -1.08 to 4.77; $I^2 = 69\%$; three studies; 1121 participants; Analysis 1.8; and MD 7.87 L/min, 95% CI -0.54 to 16.29; $I^2 = 43\%$; three studies; 864 participants; Analysis 1.6, respectively).

Asthma control measures

Compared with the same dose of ICS, the combination of anti-leukotrienes and ICS showed statistically significant improvement in daytime asthma symptom score (SMD -0.15, 95% CI -0.26 to -0.05; $I^2 = 0\%$; three studies; 1386 participants; Analysis 1.9) and change in night-time awakenings (MD -0.56 episodes/wk, 95% CI -1.02 to -0.10; $I^2 = 0\%$; two studies; 761 participants; Analysis 1.11).

With only one comparison reporting data, we did not aggregate the following outcomes: change from baseline in puffs/d of β_2 -agonists (Analysis 1.10), rescue-free days (Analysis 1.12), quality of life (Analysis 1.13), patients' global evaluation (Analysis 1.14) and physicians' global evaluation (Analysis 1.15).

Withdrawals

Results showed no statistically significant group differences in overall withdrawals (RR 0.98, 95% CI 0.75 to 1.29; $I^2 = 0\%$; nine studies; 1912 participants; Analysis 1.16), withdrawals due to adverse effects (RR 0.90, 95% CI 0.48 to 1.68; $I^2 = 6\%$; three studies; 1400 participants; Analysis 1.17) or withdrawals due to poor asthma control/exacerbation (RR 0.68, 95% CI 0.34 to 1.37; $I^2 = 0\%$; six studies; 1571 participants; Analysis 1.18).

Safety

A single comparison reported data on serious adverse events, preventing aggregation (Analysis 1.19). Analysis revealed no statistically significant group differences in overall adverse effects (RR 1.06, 95% CI 0.92 to 1.22; $I^2 = 0\%$; three studies; 1024 participants; Analysis 1.20) nor in specific adverse effects including

headache (RR 1.22, 95% CI 0.93 to 1.60; $I^2 = 0\%$; three studies; 1386 participants; [Analysis 1.21](#)), upper respiratory tract infection (RR 0.90, 95% CI 0.71 to 1.14; $I^2 = 0\%$; two studies; 1018 participants; [Analysis 1.22](#)), rhinitis (RR 0.88, 95% CI 0.42 to 1.83; $I^2 = 0\%$; two studies; 993 participants; [Analysis 1.23](#)) and elevated liver enzymes (RR 1.22, 95% CI 0.30 to 5.04; $I^2 = 18\%$; two studies; 754 participants; [Analysis 1.24](#)).

Only one comparison reported nausea ([Analysis 1.25](#)), cough ([Analysis 1.26](#)), abdominal pain ([Analysis 1.27](#)), influenza ([Analysis 1.28](#)), pharyngitis ([Analysis 1.29](#)) and bronchitis ([Analysis 1.30](#)), preventing aggregation. Two trials recorded data on death and reported one death in the ICS group ([Analysis 1.31](#)).

Biological markers of inflammation

Only one comparison contributed data on change from baseline eosinophil counts, significantly favouring combination therapy ([Analysis 1.32](#)).

Anti-leukotrienes and ICS versus higher dose of ICS

See [Summary of findings 2](#) for details on participant relevant outcomes in this comparison.

Primary outcome

Number of participants with one or more exacerbations requiring oral corticosteroids

Results showed no statistically significant group difference in the number of participants with one or more exacerbations requiring oral corticosteroids (RR 0.90, 95% CI 0.58 to 1.39; $I^2 = 0\%$; four studies; 1779 participants; high quality; [Analysis 2.1](#); [Figure 4](#)); owing to the large confidence interval, this study did not meet the criterion of equivalence.

Figure 4. Forest plot of comparison: 2 Anti-leukotrienes and inhaled corticosteroids versus HIGHER dose of inhaled corticosteroids, outcome: 2.1 Participants with ≥ 1 exacerbation requiring oral corticosteroids.

Anti-leukotriene agents did not influence the magnitude of effect ($\chi^2 = 0.86$; $df = 1$; $P = 0.35$). We could not aggregate a daily dose of ICS in the intervention group ([Analysis 2.2](#)) and the funding source ([Analysis 2.3](#)) owing to lack of data. We could not perform other subgroup analyses because of suboptimal reporting by eligible studies or trial heterogeneity regarding the severity of airflow obstruction and atopy. We did not perform a funnel test because the number of eligible studies contributing data was insufficient.

Secondary outcomes

Exacerbations

Results showed no statistically significant group difference in the number of participants with one or more exacerbations requiring hospital admission (RR 1.49, 95% CI 0.06 to 36.47; three studies; 1719 participants; [Analysis 2.4](#)).

Lung function

Data showed no statistically significant group differences in change from baseline on lung function tests including morning PEF (MD

10.38 L/min, 95% CI -1.32 to 22.08; $I^2 = 76\%$; five studies; 952 participants; [Analysis 2.5](#)), diurnal variation in PEFR (MD -1.42 L/min, 95% CI -2.94, 0.10; $I^2 = 0\%$; two studies; 738 participants; [Analysis 2.7](#)) and FEV_1 (MD 0.06 L, 95% CI -0.01 to 0.13; $I^2 = 67\%$; four studies; 958 participants; [Analysis 2.8](#)). Only one comparison reported data on the change from baseline in evening PEFR, preventing aggregation ([Analysis 2.6](#)).

Asthma control measures

Investigators reported no statistically significant group difference in change in daily use of β_2 -agonists (MD -0.01 puffs/d, 95% CI -0.20 to 0.19; $I^2 = 0\%$; four studies; 1398 participants; [Analysis 2.9](#)) nor in change from baseline in asthma symptom scores (MD -0.02, 95% CI -0.13 to 0.08; $I^2 = 0\%$; three studies; 1539 participants; [Analysis 2.10](#)). Only one comparison reported data on change in nocturnal awakening ([Analysis 2.11](#)) and quality of life ([Analysis 2.12](#)), preventing aggregation.

Withdrawals

Investigators reported no statistically significant group difference in overall withdrawals (RR 0.94, 95% CI 0.61 to 1.43; $I^2 = 30\%$; six studies; 1899 participants; [Analysis 2.13](#)), withdrawals due to adverse effects (RR 1.34, 95% CI 0.57 to 3.16; $I^2 = 34\%$; three studies; 1723 participants; [Analysis 2.14](#)) or withdrawals due to poor asthma control/exacerbation (RR 0.59, 95% CI 0.25 to 1.38; $I^2 = 0\%$; three studies; 1723 participants; [Analysis 2.15](#)).

Safety

Only one comparison reported data on serious adverse events ([Analysis 2.16](#)), preventing aggregation. Results showed no statistically significant group difference in risk of overall adverse effects (RR 0.96, 95% CI 0.89 to 1.03; $I^2 = 0\%$; six studies; 1899 participants; [Analysis 2.17](#)) nor specific adverse effects including headache (RR 1.13, 95% CI 0.85 to 1.50; $I^2 = 0$; five studies; 1813 participants; [Analysis 2.18](#)), nausea (RR 1.11, 95% CI 0.55 to 2.24; $I^2 = 0\%$; four studies; 1753 participants; [Analysis 2.19](#)) and elevated liver enzymes (RR 1.61, 95% CI 0.36 to 7.21; $I^2 = 60\%$; three studies; 1687 participants; [Analysis 2.20](#)); however, data showed a statistically significant group difference in oral moniliasis (RR 0.30, 95% CI 0.11 to 0.81; $I^2 = 0\%$; two studies; 834 participants; [Analysis 2.21](#)). Only one comparison reported data on hoarseness of voice ([Analysis 2.22](#)) and abdominal pain ([Analysis 2.23](#)).

Anti-leukotrienes and tapering dose of ICS versus tapering dose of ICS

See [Summary of findings 3](#) for details on all participant relevant outcomes in this comparison.

Primary outcome

Percent change in baseline dose of ICS

Results showed no statistically significant group difference in % change from the baseline ICS dose with maintained asthma control (MD -3.05%, 95% CI -8.13 to 2.03; $I^2 = 15\%$; four comparisons; 930 participants; high quality; [Analysis 3.1](#); [Figure 5](#)).

Figure 5. Forest plot of comparison: 3 Anti-leukotrienes and inhaled corticosteroids versus TAPERING dose of inhaled corticosteroids, outcome: 3.1 % Change from baseline ICS dose.

Types of anti-leukotriene agents did not influence the magnitude of effect ($\chi^2 = 1.88$; $df = 1$; $P = 0.17$). Owing to insufficient reporting or lack of heterogeneity between trials contributing data, we could not perform subgroup analyses for daily dose of ICS in the intervention group, duration of the intervention, severity of asthma, atopy

or funding source. Pharmaceutical companies funded all trials. We could not perform sensitivity analyses because of the similar publication status.

Secondary outcomes

Exacerbations

Results showed no statistically significant group difference between participants with at least one exacerbation requiring oral corticosteroids (RR 0.46, 95% CI 0.20 to 1.04; $I^2 = 0\%$; five studies; 542 participants; [Analysis 3.2](#)). Two studies reported that no participants had asthma exacerbations that required hospital admission ([Analysis 3.3](#)).

Number of participants with reduction in baseline dose of ICS

Results showed no statistically significant group difference in the number of participants with change from baseline ICS dose required to maintain control (RR 0.98, 95% CI 0.85 to 1.13; $I^2 = 0\%$; three studies; 112 participants; [Analysis 3.4](#)) nor in the number who completely tapered off of ICS (RR 1.17, 95% CI 0.95 to 1.46; $I^2 = 0\%$; three studies; 607 participants; [Analysis 3.5](#)). Only one comparison reported participants with 50% or greater reduction from baseline ICS dose ([Analysis 3.6](#)).

Lung function

Analyses revealed no statistically significant group difference in morning PEFR (MD -2.45 L/min, 95% CI -10.96 to 6.06; $I^2 = 0\%$; two studies; 218 participants; [Analysis 3.7](#)). Only one comparison reported data on change from baseline in evening PEFR ([Analysis 3.8](#)), FEV₁ ([Analysis 3.9](#)) and PC₂₀ ([Analysis 3.10](#)).

Asthma control measures

One comparison reported asthma control measures including daytime asthma symptom score ([Analysis 3.11](#)), night-time asthma symptom score ([Analysis 3.12](#)) and daily use of β_2 -agonists ([Analysis 3.13](#)), preventing aggregation.

Withdrawals

Data showed no statistically significant group difference in overall withdrawals (RR 0.80, 95% CI 0.62 to 1.04; $I^2 = 0\%$; seven studies; 1150 participants; [Analysis 3.14](#)) or withdrawals due to adverse effects (RR 0.87, 95% CI 0.42 to 1.81; $I^2 = 38\%$; six studies; 1110 participants; [Analysis 3.15](#)). However, results revealed a statistically significant group difference in withdrawals due to poor asthma control/exacerbation (RR 0.61, 95% CI 0.41 to 0.92; $I^2 = 0\%$; seven studies; 1150 participants; [Analysis 3.16](#)), favouring combination therapy.

Safety

Results showed a statistically significant group difference in serious adverse events favouring use of ICS alone over combination therapy (RR 2.44, 95% CI 1.52 to 3.92; $I^2 = 0\%$; two studies; 621 participants; [Analysis 3.17](#)).

Analysis revealed no statistically significant group difference in overall adverse effects (RR 0.95, 95% CI 0.83 to 1.08; $I^2 = 59\%$; six studies; 1100 participants; [Analysis 3.18](#)) nor in specific adverse events including headache (RR 0.79, 95% CI 0.54 to 1.15; $I^2 = 20\%$; seven studies; 1140 participants; [Analysis 3.19](#)), nausea (RR 1.32, 95% CI 0.59 to 2.97; $I^2 = 0\%$; six studies; 1100 participants; [Analysis 3.20](#)) and elevated liver enzymes (RR 1.58, 95% CI 0.82 to 3.04; $I^2 = 0\%$; six studies; 1099 participants; [Analysis 3.21](#)). Only one study reported specific adverse events like pharyngitis ([Analysis 3.22](#)), abdominal pain ([Analysis 3.23](#)), vomiting ([Analysis 3.24](#))

and diarrhoea ([Analysis 3.25](#)), preventing aggregation. Six studies provided data on death and reported one death in the combination anti-leukotrienes and ICS group ([Analysis 3.26](#)).

Biological markers of inflammation

Only one comparison reported data on exhaled nitric oxide ([Analysis 3.27](#)) and sputum eosinophil counts ([Analysis 3.28](#)) and showed no statistically significant group differences.

DISCUSSION

Summary of main results

For adults who primarily remain symptomatic with daily inhaled corticosteroids (ICS), the addition of anti-leukotriene agents to the same dose of ICS as a step 3 strategy reduced by half the risk of asthma exacerbations requiring rescue oral corticosteroids (from 9% to 5% over three months), with significant improvement in lung function including peak expiratory flow rate (PEFR) and forced expiratory volume in one second (FEV₁) and certain markers of asthma control compared with the same ICS dose. However, when this strategy was compared with a higher dose of ICS (step 3 therapy), the combination of anti-leukotriene agents and ICS did not show statistically significant benefit for risk of moderate asthma exacerbations, lung function and asthma control. Types of anti-leukotriene agents, dose of ICS and funding source did not affect the magnitude of response. Anti-leukotriene agents did not provide a statistically significant ICS sparing effect in the few trials in which they were tested. We could identify no effect modifiers because data were insufficient.

Studies showed a modest improvement in asthma symptom score and night-time awakening when comparing combination therapy versus the same dose of ICS, but not when comparing combination therapy with a higher or tapering dose of ICS. Studies poorly reported other measures including quality of life and patients' or physicians' global evaluation.

Evidence shows no statistically significant group differences in overall withdrawals, withdrawals due to adverse events or overall adverse events among patients receiving combination therapy compared with the same or a higher or tapering dose of ICS, with one exception; the combination of ICS and anti-leukotrienes was associated with significantly fewer participant withdrawals due to poor asthma control in the tapering ICS protocol. The addition of anti-leukotriene agents to ICS was not associated with an increase in serious adverse events compared with the same or a higher dose of ICS; in the tapering ICS protocol, combination therapy was associated with a statistically significantly greater number of serious adverse events when compared with ICS alone. This finding should be interpreted cautiously as both reports contributing data were published as abstracts, and data were obtained directly from study authors with no published confirmation or clear definition of serious adverse events.

Overall completeness and applicability of evidence

Despite an adequate number of trials evaluating the combination of anti-leukotriene agents and ICS, only 25 of 37 trials provided useable data for this review through a full-text publication or a complete report of unpublished data. We excluded cross-over trials to avoid issues associated with study design. Only three studies reported information on inflammatory markers, including exhaled

nitric oxide or eosinophil count in blood or sputum samples. Only one comparison reported patients' or physicians' global evaluation.

We emphasise the need for better reporting of outcomes as a change from baseline, specifically, exacerbations requiring rescue oral corticosteroids, hospital admission and asthma control parameters. If possible, surrogate markers of inflammation of the airways should be evaluated and reported.

This evidence will be useful to practicing clinicians who must choose an appropriate step 3 therapy for patients, and to patients who want to make informed choices about their asthma care.

Quality of the evidence

We judged the quality of most of the evidence for the primary outcome comparing the addition of anti-leukotrienes to ICS versus the same ICS dose as moderate or low for the primary outcome of exacerbations and for adverse events, but we are more certain about the impact of treatment on lung function (see [Summary of findings for the main comparison](#)). We determined that the quality of evidence for the primary outcome comparing the addition of anti-leukotrienes to ICS versus a higher dose of ICS is moderate (see [Summary of findings 2](#)). Our confidence in the effect estimates when combination therapy is compared with a tapering ICS dose is moderate or low (see [Summary of findings 3](#)). Eight studies adopted an open-label design, and we downgraded evidence quality for those outcomes when open-label studies contributed data to the meta-analysis.

Potential biases in the review process

We conducted this review by following methods as published in the protocol and standard guidelines of Cochrane. We presented the minor change from the protocol in the [Differences between protocol and review](#) section. We used reported information from included studies as well as data derived from study authors during the previous version of this Cochrane review.

Agreements and disagreements with other studies or reviews

The Cochrane review on addition of anti-leukotriene agents to ICS for chronic asthma in children and adults published in 2004 ([Ducharme 2004](#)) concluded that for patients whose condition was suboptimally controlled on ICS, the addition of licensed doses of anti-leukotrienes to ICS resulted in a non-statistically significant reduction in risk of exacerbations requiring systemic steroids (risk ratio (RR) 0.64, 95% confidence interval (CI) 0.38 to 1.07) with modest improvement in lung function (PEFR mean difference (MD) 7.7 L/min, 95% CI 3.6 to 11.8) and reduced use of rescue short-acting β_2 -agonists (MD 1 puff/wk, 95% CI 0.5 to 2). With only three studies comparing the use of licensed doses of anti-leukotrienes versus an increased dose of ICS, we could draw no firm conclusion about the superiority or equivalence of either treatment option ([Ducharme 2004](#)); now, with 37 included studies, our ability to conclude is enhanced by the addition of this review.

Considering that the prior review was heavily weighted towards adults and did not firmly conclude on the efficacy and safety of the addition of anti-leukotrienes to ICS, we decided to split the review into two: paediatric patients and adolescents ([Chauhan 2013](#)), and adolescents and adults (current review). The current review sheds

light on clear effects and conclusions with data derived from 25 studies of a total of 37 included studies.

In our paediatric review ([Chauhan 2013](#)), we noted the striking paucity of paediatric trials and inadequate evidence to support the use of anti-leukotriene agents as step-3 therapy in children and adolescents with mild to moderate asthma. We found no firm evidence to support the efficacy and safety of anti-leukotrienes as add-on therapy to ICS as a step-3 option in the therapeutic arsenal for children with uncontrolled asthma symptoms taking low-dose ICS.

As another strategy of step-3 therapy (i.e. addition of long-acting β_2 -agonist (LABA) to existing ICS), we reported that add-on LABA is modestly superior to add-on leukotriene receptor antagonist (LTRA) in reducing oral corticosteroid-treated exacerbations among adults with asthma that is inadequately controlled by predominantly low-dose ICS with significant bronchodilator reversibility. Adjunct therapy of LABA was favoured for lung function and, to a lesser extent, rescue medication use, asthma symptoms and quality of life. The lower overall withdrawal rate and the higher proportion of participants satisfied with add-on LABA therapy indirectly favour the combination of LABA + ICS over LTRA + ICS ([Chauhan 2014](#)).

AUTHORS' CONCLUSIONS

Implications for practice

In adolescents and adults with asthma inadequately controlled with daily-dose ICS, available evidence supports the use of anti-leukotriene agents as adjunct therapy to prevent exacerbations by half and improve asthma symptoms compared with the same dose of ICS alone. The combination of anti-leukotriene agents and ICS is not statistically superior or equivalent to doubling the dose of ICS and does not appear to have ICS-sparing effects, although combination therapy appeared to prevent withdrawals due to poor asthma control during ICS tapering. The paucity of trials prevented firm conclusions for the latter two approaches. The use of LTRA was not associated with increased risk of withdrawals or adverse effects, with the exception of an increase in serious adverse events when the ICS dose was tapered. Information was insufficient for assessment of mortality.

Implications for research

We emphasise the need for additional studies comparing anti-leukotriene agents added to ICS versus a tapering dose of ICS or a higher dose of ICS. We also point out the need for complete reporting of efficacy outcomes, especially with regards to people with one or more exacerbations requiring rescue oral corticosteroids, hospital admissions and change from baseline in asthma control indices. We suggest that researchers consider the following issues when designing a trial.

- Enrolling adults and adolescents with mild to moderate asthma incompletely controlled on daily low-dose ICS.
- Using a parallel-group design with a minimum 24-week treatment duration.
- Recording and reporting separately participants with exacerbations requiring oral corticosteroids and hospital admission.

- Analysing and reporting efficacy outcomes (including asthma control) as a change from baseline or as an overall period effect (instead of an end of study value) (Reddel 2009).
- Recording and reporting severe adverse events, including anticipated adverse effects of both treatment strategies such as headache, behavioural changes, etc.
- Reporting overall withdrawals along with reasons.
- Documenting compliance.
- Using anti-leukotriene agents to taper the dose of ICS.
- Clearly reporting the definition of serious adverse events and providing data per group.
- Including cost analysis or cost-effectiveness analysis, if possible.

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CHARACTERISTICS OF STUDIES

Characteristics of included studies [ordered by study ID]

Barnes 2007

Methods	Randomised, double-blind, parallel-group, multi-centre (4 centres in the UK and 2 centres in Canada) controlled clinical study
Participants	<p>SYMPTOMATIC ASTHMA WITH INHALED BUDESONIDE (800 µg/d) DURING LAST 2 WEEKS OF 4-WEEK RUN-IN PERIOD</p> <p>RANDOMISED: 75</p> <ul style="list-style-type: none"> LTRA + ICS: 37 ICS alone: 38 <p>WITHDRAWALS:</p> <ul style="list-style-type: none"> LTRA + ICS: 1 (2.7%) ICS alone: 5 (13.2%) <p>AGE in years: mean ± SD</p> <ul style="list-style-type: none"> LTRA + ICS: 41.5 ± 11.7 ICS alone: 45 ± 14.2 <p>GENDER (% male)</p> <ul style="list-style-type: none"> LTRA + ICS: 38 ICS alone: 53 <p>SEVERITY: not reported</p> <p>ASTHMA DURATION years: longer than 1 year</p> <p>BASELINE FEV₁ (% pred) ± SEM:</p> <ul style="list-style-type: none"> LTRA + ICS: 74.1 ± 13.0 ICS alone: 73.6 ± 14.2 <p>MEAN (±SD) β₂-AGONIST USE (puffs/d): not reported.</p> <p>BASELINE DOSE OF ICS: not reported</p> <p>ATOPY (%): not reported</p> <p>ELIGIBILITY CRITERIA</p> <ul style="list-style-type: none"> Non-smokers aged 15–70 years > 1 year history of asthma symptoms On inhaled steroids (600–1200 mcg/d budesonide or equivalent) and β₂-agonist only Bronchodilator reversibility ≥12% (FEV₁) or ≥15% PEFR > 50% of predicted FEV₁/PEFR

Barnes 2007 (Continued)

- Remained symptomatic during last 2 weeks of 4 week run-in period despite treatment (assessed by a symptom diary and daily β_2 -agonist use (on average at least 1 puff per day))

EXCLUSION CRITERIA

- Any other pulmonary disorder, emergency treatment for asthma within 1 month, hospitalisation within 2 months or respiratory tract infection within 3 weeks

Interventions	<p>PROTOCOL: LTRA + ICS vs HIGHER dose of ICS alone</p> <p>RUN-IN: 4 weeks</p> <p>INTERVENTION PERIOD: 12 weeks</p> <p>TEST GROUP: montelukast 10 mg once daily + budesonide 800 μg/d</p> <p>CONTROL GROUP: budesonide 1600 μg/d + placebo</p> <p>DEVICE: Turbuhaler</p> <p>COMPLIANCE: > 98% for all drugs from the diary card, 77% for montelukast and 84% for placebo from drug accounting</p> <p>CO-TREATMENT: β_2-agonist use permitted</p>
Outcomes	<p>ANALYSIS: NO INTENTION-TO-TREAT ANALYSIS</p> <p>OUTCOMES: reported as change from baseline value</p> <p>PULMONARY FUNCTION TEST:</p> <ul style="list-style-type: none"> %change from baseline in morning PEFR <p>FUNCTIONAL STATUS:</p> <ul style="list-style-type: none"> Quality of life <p>EXACERBATIONS:</p> <ul style="list-style-type: none"> % days with asthma exacerbations <p>INFLAMMATORY MARKERS:</p> <ul style="list-style-type: none"> *Change from baseline sputum eosinophil (%) Sputum inflammatory markers <p>ADVERSE EFFECTS: reported</p> <p>WITHDRAWALS: reported (* denotes primary outcomes)</p>
Notes	<p>Full-text (2007) publication</p> <p>Funding: Merck, Sharp & Dohme Ltd, Hoddlesdon, Hertz, UK</p>

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Study was randomised and provided no further details regarding sequence generation
Allocation concealment (selection bias)	Unclear risk	Allocation concealment was not reported

Barnes 2007 (Continued)

Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blinded study
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Double-blinded study
Incomplete outcome data (attrition bias) All outcomes	High risk	All reported outcomes were presented. Unbalanced withdrawal was observed (2.7% vs 13.2%) and no intention-to-treat analysis was performed; however, reasons for withdrawal were reported. Data on primary outcome were not available (35% vs 26%)
Selective reporting (reporting bias)	Low risk	Study protocol is not available, but published reports include all expected outcomes, including those that were prespecified
Other bias	Low risk	Study appears to be free of other sources of bias

Bateman 1993

Methods	Randomised, double-blind, placebo-controlled, parallel-group, multi-centre clinical study
Participants	<p>WELL-CONTROLLED PARTICIPANTS</p> <p>RANDOMISED: 359</p> <ul style="list-style-type: none"> LTRA + ICS: 242 ICS alone: 117 <p>WITHDRAWALS:</p> <ul style="list-style-type: none"> LTRA + ICS: 20% ICS alone: 22% <p>AGE in years (mean $\pm$ SD):</p> <ul style="list-style-type: none"> LTRA + ICS: 42.2 $\pm$ 14.8 ICS alone: 41.6 $\pm$ 14.2 <p>GENDER (% male):</p> <ul style="list-style-type: none"> LTRA + ICS: 45 ICS alone: 44 <p>SEVERITY: mild asthma</p> <p>Baseline FEV₁ (L):</p> <ul style="list-style-type: none"> LTRA + ICS: 2.64 $\pm$ 0.86 ICS alone: 2.63 $\pm$ 0.85 <p>ALLERGEN TRIGGERS:</p> <ul style="list-style-type: none"> LTRA + ICS: 48% ICS alone: 49% <p>ASTHMA DURATION:</p>

Bateman 1993 (Continued)

- LTRA + ICS: 13.1 ± 12.3 years
- ICS alone: 14.1 ± 13.0 years

ELIGIBILITY CRITERIA:

- AGE: 12 to 70 years
- Reversibility ≥ 15% after inhaled β_2 -agonists
- Well controlled on ICS 400 to 750 mcg daily (beclomethasone or budesonide)

Interventions

PROTOCOL: LTRA + ICS vs same dose of ICS (TAPERING ICS dose)
RUN-IN: 1 week to confirm asthma control

- Dose optimisation period: NONE

INTERVENTION PERIOD: 20 weeks

TEST GROUP:

- ICI 204,219 = zafirlukast 20 mg bid p.o. + ICS 400 to 750 μ g/d
(beclomethasone or budesonide)

CONTROL GROUP:

- Placebo + ICS 400 to 750 μ g/d (beclomethasone or budesonide)

DEVICE: various devices used

CO-TREATMENT: none reported

CRITERIA FOR TAPERING ICS every 2 weeks:

- $FEV_1 \geq 80\%$ of predicted
- β_2 use ≤ 800 μ g/d of salbutamol

MINIMAL DOSE OF ICS ALLOWED: none

Outcomes

PER-PROTOCOL (PP) ANALYSES

- Some intention-to-treat (ITT) analysis
- Outcomes used at 6, 12 and 20 weeks

PULMONARY FUNCTION TESTS (reported as cross-sectional values, not as change from baseline):

- FEV_1 (L) - ITT
- AM PEFR - PP (L/min)

SYMPTOM SCORES (PP):

- Mean daytime symptom scores (range 0 to 3)

FUNCTIONAL STATUS (PP):

- Mean daily use of β_2 -agonists (puffs/d) averaged over a week

ICS DOSE REDUCTION (PP):

- **ICS dose reduction (%)
- % complete ICS withdrawal

INFLAMMATORY MARKERS:

- Not reported

Bateman 1993 (Continued)

ADVERSE EFFECTS:

- Elevated liver enzymes, headache, nausea, death, etc

WITHDRAWALS:

- Reported

(** denotes primary outcomes)

Notes	<p>Abs (1993) and unpublished data graciously provided by Christopher Miller and Susan Shaffer from AstraZeneca, USA (Oct 2000)</p> <p>Funding: Zeneca</p> <p>Confirmation of methods and data extracted graciously received from M. Christopher Miller and Ms. Susan Shaffer, AstraZeneca, Oct 2000</p> <p>User-defined order: 54</p> <p>(mean ICS dose of 540 mcg/d × 0.1)</p> <p>ALLOCATION</p> <ul style="list-style-type: none"> • Random: 2:1 ratio intervention:control - computer-generated <p>Confirmation of methods obtained</p>
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Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated randomisation (2:1 ratio intervention:control)
Allocation concealment (selection bias)	Low risk	Study investigators unaware as to order of treatment group assignment (Cochrane Grade A)
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blinded study, with identical placebo
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Double-blinded study
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Details on drop-outs not reported
Selective reporting (reporting bias)	Unclear risk	Unable to assess owing to lack of details regarding selective reporting of outcomes
Other bias	Unclear risk	Unable to assess bias owing to baseline imbalances

Beg 2014

Methods	Open-label, comparative, randomised study
Participants	<p>50 moderate persistent asthma patients aged between 18 and 60 years, non-smokers</p> <p>RANDOMISED: 50</p> <ul style="list-style-type: none"> • LTRA + ICS: 25 • ICS alone: 25 <p>WITHDRAWAL reported</p> <ul style="list-style-type: none"> • LTRA + ICS: 2 • ICS alone: 2 <p>AGE in years: mean $\pm$ SE</p> <ul style="list-style-type: none"> • LTRA + ICS: 27.0 $\pm$ 3.13 • ICS alone: 35.5 $\pm$ 3.97 <p>GENDER (% male): not reported</p> <ul style="list-style-type: none"> • LTRA + ICS: not reported • ICS alone: reported <p>SEVERITY: moderate persistent</p> <p>ASTHMA DURATION</p> <ul style="list-style-type: none"> • LTRA + ICS (mean $\pm$ SE) 4.5 $\pm$ 1.36 • ICS alone (mean $\pm$ SE) = 7.8 $\pm$ 2.15 <p>BASELINE FEV₁ (% pred) $\pm$ SEM: not reported</p> <ul style="list-style-type: none"> • LTRA + ICS: not reported • ICS alone: not reported <p>MEAN ($\pm$SE) β_2-AGONIST USE (puffs/d): not reported</p> <p>BASELINE DOSE OF ICS: 250 μg twice-daily ATOPY (%): not reported</p> <p>ELIGIBILITY CRITERIA:</p> <ul style="list-style-type: none"> • Patients with moderate persistent asthma aged between 18 and 60 years, non-smokers, who attended the respiratory medicine outpatient department <p>EXCLUSION CRITERIA:</p> <ul style="list-style-type: none"> • Age < 18 years or > 60 years • Patients with respiratory conditions other than asthma • Smokers • Urgent medical care received for asthma • Oral corticosteroid use • Use of additional asthma medication and hospitalisation during run-in period • Pregnancy • Lactation • Any other chronic systemic illness
Interventions	<p>PROTOCOL: LTRA + ICS vs HIGHER dose of ICS alone</p> <p>RUN-IN: 4 weeks</p>

Beg 2014 (Continued)

INTERVENTION PERIOD: 12 weeks

TEST GROUP: montelukast 10 mg daily + fluticasone 125 µg twice daily

CONTROL GROUP: fluticasone 250 µg twice daily

DEVICE: not reported

COMPLIANCE: not reported

CO-TREATMENT: daily theophylline or salbutamol

Outcomes	<p>ANALYSIS: NO INTENTION-TO-TREAT ANALYSIS</p> <p>OUTCOMES: reported as changes from baseline values</p> <p>PULMONARY FUNCTION TEST: PEF_R%, FEV₁%</p> <p>Quality of life: reported</p> <p>EXACERBATIONS: not reported</p> <p>INFLAMMATORY MARKERS:</p> <ul style="list-style-type: none"> *Change from baseline sputum eosinophil (%) not reported Sputum inflammatory markers not reported <p>ADVERSE EFFECTS: reported</p> <p>WITHDRAWALS: reported</p>
Notes	No funding

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	No information on randomisation technique was reported
Allocation concealment (selection bias)	High risk	No allocation concealment owing to open-label study
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open-label study
Blinding of outcome assessment (detection bias) All outcomes	High risk	Open-label study
Incomplete outcome data (attrition bias) All outcomes	Low risk	Well-balanced withdrawals and reasons for withdrawals were reported
Selective reporting (reporting bias)	Unclear risk	Primary and secondary outcomes were not distinguished clearly
Other bias	Unclear risk	Open-label study with inadequate reported information for judgement of other bias

Bilancia 2000

Methods	Randomised clinical study
Participants	<p>RANDOMISED: 42</p> <ul style="list-style-type: none"> LTRA + ICS: 20 ICS alone: 22 <p>WITHDRAWALS: not reported</p> <p>AGE in years: mean $\pm$ SEM: reported as range</p> <p>GENDER (% male):</p> <ul style="list-style-type: none"> LTRA + ICS: 40 ICS alone: 54.5 <p>SEVERITY: mild to moderate asthma</p> <p>ASTHMA DURATION years: not reported</p> <p>BASELINE FEV₁ (% pred) $\pm$ SEM: not reported</p> <ul style="list-style-type: none"> LTRA + ICS: 78.3 ICS alone: 76.1 <p>MEAN ($\pm$SD) β_2-AGONIST USE (puffs/d): not reported</p> <p>BASELINE DOSE OF ICS: not reported</p> <p>ATOPY (%): not reported</p> <p>ELIGIBILITY CRITERIA: not reported</p>
Interventions	<p>PROTOCOL: LTRA + ICS versus HIGHER dose of ICS alone</p> <p>RUN-IN: 1.43 weeks</p> <p>INTERVENTION PERIOD: 12 weeks</p> <p>TEST GROUP: montelukast 10 mg daily + budesonide 800 μg daily</p> <p>CONTROL GROUP: budesonide 1600 μg/d</p> <p>DEVICE: not reported</p> <p>COMPLIANCE: not reported</p> <p>CO-TREATMENT: β_2-agonist as needed</p> <p>CRITERIA FOR WITHDRAWAL FROM STUDY: not reported</p>
Outcomes	<p>INTENTION-TO-TREAT ANALYSIS: not mentioned</p> <p>PULMONARY FUNCTION TEST:</p> <ul style="list-style-type: none"> Morning and evening PEFR <p>FUNCTIONAL STATUS:</p> <ul style="list-style-type: none"> Quality of life Symptom score

Bilancia 2000 (Continued)

- Use of rescue β_2 -agonists (puffs/d)

EXACERBATIONS: not reported

ADVERSE EFFECTS: not reported

WITHDRAWALS: not reported

Notes	Abstract
	Funding: not reported

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Randomisation not reported
Allocation concealment (selection bias)	Unclear risk	Allocation concealment not reported
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Blinding and details of blinding not reported
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Blinding of outcome assessment not reported
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Details on drop-outs not reported
Selective reporting (reporting bias)	Unclear risk	Unable to assess owing to lack of details regarding selective reporting of outcomes
Other bias	Unclear risk	Unable to assess bias owing to baseline imbalances

Cakmak 2004

Methods	Randomised, double-blind, placebo-controlled single-centre clinical study
Participants	<p>PARTICIPANTS WITH WELL-CONTROLLED ASTHMA GIVEN BUDESONIDE (400 μg/d) DURING RUN-IN PERIOD OF 6 WEEKS</p> <p>RANDOMISED: 21</p> <ul style="list-style-type: none"> • LTRA + ICS: 11 • ICS alone: 10 <p>WITHDRAWALS: not reported</p> <p>AGE in years: mean $\pm$ SD</p> <ul style="list-style-type: none"> • LTRA + ICS: 29.72 $\pm$ 10.9 • ICS alone: 28.3 $\pm$ 6.48

Cakmak 2004 (Continued)

GENDER (% male):

- LTRA + ICS: 55
- ICS alone: 20

SEVERITY: mild to moderate persistent asthma (according to International Consensus on Asthma)

ASTHMA DURATION, years: 1-19

- LTRA + ICS: 4.9 ± 3.56
- ICS alone: 5.3 ± 5.5

BASELINE FEV₁ (% pred) $\pm$ SEM:

- LTRA + ICS: 88.3 ± 14.16
- ICS alone: 88.8 ± 14.37

MEAN ($\pm$ SD) β_2 -AGONIST USE (puffs/d): not reported

BASELINE DOSE OF ICS: not reported

ATOPY (%): not reported

ELIGIBILITY CRITERIA:

- Patients given a diagnosis of mild to moderate asthma (with FEV₁ > 70%) according to the report of International Consensus on Asthma (NHLBI)

EXCLUSION CRITERIA:

- Patients with gastroesophageal reflux, nasal symptoms (rhinitis, sinusitis, etc.) and psychological problems were excluded

Interventions

PROTOCOL: LTRA + ICS vs SAME dose of ICS alone

RUN-IN: 6 weeks

INTERVENTION PERIOD: 6 weeks

TEST GROUP: zafirlukast 40 mg daily + budesonide 400 μ g/d

CONTROL GROUP: placebo + budesonide 400 μ g/d

DEVICE: not reported

COMPLIANCE: not reported

CO-TREATMENT: β_2 -agonist as needed

CRITERIA FOR WITHDRAWAL FROM STUDY: not reported

Outcomes

INTENTION-TO-TREAT ANALYSIS: not done

OUTCOMES: reported at 6 weeks as absolute values at baseline and end point

PULMONARY FUNCTION TEST:

- FVC (mL)
- FVC (%)
- FEV₁ (mL)
- FEV₁ (% of predicted)
- FEV₁/FVC
- FEF₂₅₋₇₅ (L/s)

Cakmak 2004 (Continued)

- FEF₂₅₋₇₅ (%)
- PD₂₀ (mg/mL)

FUNCTIONAL STATUS:

- Daytime and night-time symptoms
- Night-time awakening
- Asthma control days
- Rescue medication

EXACERBATIONS: not reported

INFLAMMATORY MARKERS:

- Eosinophilic cationic protein
- Total antioxidant capacity

ADVERSE EFFECTS: not reported

WITHDRAWALS: not reported

Notes Full-text (2004) publication
Funding: not reported

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	Participants were randomised to 2 groups according to their order of presentation at the outpatient clinic
Allocation concealment (selection bias)	Unclear risk	Allocation concealment was not reported
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blinded study
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Double-blinded study
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	No mention of missing data
Selective reporting (reporting bias)	High risk	Certain outcomes were reported in Methods section (daytime and night-time symptoms, night-time awakening, use of rescue medications) but no data were presented
Other bias	Low risk	Study appears to be free of other sources of bias

Chlumský 2000

Methods Randomised, open-label, parallel-group clinical study

Chlumský 2000 (Continued)

Participants	<p>RANDOMISED: 13</p> <ul style="list-style-type: none"> • LTRA + ICS: 7 • ICS alone: 6 <p>WITHDRAWALS: not reported</p> <p>AGE in years: mean $\pm$ SEM: not reported</p> <p>GENDER (% male): not reported</p> <p>SEVERITY: moderate to severe asthma</p> <p>ASTHMA DURATION years: not reported</p> <p>BASELINE FEV₁ (% pred) $\pm$ SEM: not reported</p> <p>MEAN ($\pm$SD) β_2-AGONIST USE (puffs/d): not reported</p> <p>BASELINE DOSE OF ICS: not reported</p> <p>ATOPY (%): not reported</p> <p>ELIGIBILITY CRITERIA: not reported</p>
Interventions	<p>PROTOCOL: LTRA + ICS vs HIGHER dose of ICS alone</p> <p>RUN-IN: 8 weeks</p> <p>INTERVENTION PERIOD: 6 weeks</p> <p>FOLLOW-UP PERIOD: 2 weeks</p> <p>TEST GROUP: Accolate 2 $\times$ 40 mg daily + Inhaled glucocorticoids 400-1000 μg/d</p> <p>CONTROL GROUP: inhaled glucocorticoids 800-2000 μg/d</p> <p>DEVICE: not reported</p> <p>COMPLIANCE: not reported</p> <p>CO-TREATMENT: β_2-agonist</p> <p>CRITERIA FOR WITHDRAWAL FROM STUDY: not reported</p>
Outcomes	<p>INTENTION-TO-TREAT ANALYSIS: not reported</p> <p>PULMONARY FUNCTION TEST:</p> <ul style="list-style-type: none"> • FEV₁ • FEV₁/FVC • FVC <p>FUNCTIONAL STATUS:</p> <ul style="list-style-type: none"> • Use of rescue β_2-agonists (puffs/d) <p>INFLAMMATORY MARKERS:</p> <ul style="list-style-type: none"> • % of sputum eosinophils <p>ADVERSE EFFECTS: not reported</p> <p>WITHDRAWALS: not reported</p>

Chlumský 2000 (Continued)

Notes

Abstract

Funding: not reported

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Study was randomised and provided no further details regarding sequence generation
Allocation concealment (selection bias)	Unclear risk	Allocation concealment was not reported
Blinding of participants and personnel (performance bias) All outcomes	High risk	Reported as an open-label study
Blinding of outcome assessment (detection bias) All outcomes	High risk	Reported as an open-label study
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Details on drop-outs not reported
Selective reporting (reporting bias)	Unclear risk	Unable to assess owing to lack of details regarding selective reporting of outcomes
Other bias	Unclear risk	Unable to assess bias owing to baseline imbalances

Demuro-Mercon 2001

Methods	Randomised, double-blind, double-dummy, placebo-controlled clinical trial
Participants	<p>RANDOMISED: 122</p> <ul style="list-style-type: none"> LTRA + ICS: 39 ICS alone: 44 <p>AGE in years: mean $\pm$ SEM: not reported</p> <p>GENDER (% male): not reported</p> <p>SEVERITY: chronic asthma</p> <p>ASTHMA DURATION years: not reported</p> <p>BASELINE FEV₁ (% pred) $\pm$ SEM: not reported</p> <p>MEAN ($\pm$SD) β_2-AGONIST USE (puffs/d): not reported</p> <p>BASELINE DOSE OF ICS: not reported</p> <p>ATOPY (%): not reported</p> <p>ELIGIBILITY CRITERIA: not reported</p>

Demuro-Mercon 2001 (Continued)

Interventions	<p>PROTOCOL: LTRA + ICS vs same dose of ICS alone</p> <p>RUN-IN: 2 weeks</p> <p>Intervention period: 4 weeks</p> <p>TEST GROUP: montelukast 10 mg QD + fluticasone 200 µg daily</p> <p>CONTROL GROUP: fluticasone 200 µg daily</p> <p>DEVICE: not reported</p> <p>COMPLIANCE: not reported</p> <p>CO-TREATMENT: not reported</p> <p>CRITERIA FOR WITHDRAWAL FROM STUDY: not reported</p>
Outcomes	<p>INTENTION-TO-TREAT: not mentioned</p> <p>PULMONARY FUNCTION TEST:</p> <ul style="list-style-type: none"> • FEV₁ • FEV₁/FVC • FVC <p>FUNCTIONAL STATUS:</p> <ul style="list-style-type: none"> • Asthma Quality of Life Questionnaire <p>INFLAMMATORY MARKERS: not reported</p> <p>ADVERSE EFFECTS: not reported</p> <p>WITHDRAWALS: not reported</p>
Notes	<p>Abstract</p> <p>Funding: not reported</p>

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Randomisation not reported
Allocation concealment (selection bias)	Unclear risk	Allocation concealment not reported
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind study
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Double-blind study
Incomplete outcome data (attrition bias)	Unclear risk	Details on drop-outs not reported

Demuro-Mercon 2001 (Continued)

All outcomes

Selective reporting (reporting bias)	Unclear risk	Unable to assess owing to lack of details regarding selective reporting of outcomes
Other bias	Unclear risk	Unable to assess bias owing to baseline imbalances

Djukanovic 2010

Methods	Randomised, double-blind, parallel-group, multi-centre clinical study
Participants	<p>SYMPTOMATIC ASTHMA INDICATIVE OF NEED OF ICS</p> <p>RANDOMISED: 103</p> <ul style="list-style-type: none"> LTRA + ICS: 50 ICS alone: 53 <p>WITHDRAWALS: reported</p> <ul style="list-style-type: none"> LTRA + ICS: 12% ICS alone: 15.1% <p>AGE in years: mean $\pm$ SD</p> <ul style="list-style-type: none"> LTRA + ICS: 29.4 $\pm$ 8.93 ICS alone: 29.7 $\pm$ 11.56 <p>GENDER (% male):</p> <ul style="list-style-type: none"> LTRA + ICS: 54 ICS alone: 36 <p>SEVERITY: mild to moderate asthma</p> <p>ASTHMA DURATION years: $\geq$ 6 months</p> <p>MEAN ($\pm$SEM) β_2-AGONIST USE (puffs/d):</p> <ul style="list-style-type: none"> LTRA + ICS: 3.17 $\pm$ 0.5 ICS alone: 2.55 $\pm$ 0.31 <p>MEAN ($\pm$SEM) BASELINE FEV₁ (% predicted):</p> <ul style="list-style-type: none"> LTRA + ICS: 77.43 $\pm$ 1.64 ICS alone: 76 $\pm$ 1.64 <p>BASELINE DOSE OF ICS: not reported</p> <p>ATOPY (%): not reported</p> <p>ELIGIBILITY CRITERIA:</p> <ul style="list-style-type: none"> At visit 1A (10 to 14 days before randomisation Visit 2) Composite asthma score on a 0-5 point scale for chest tightness, wheezing and shortness of breath <ul style="list-style-type: none"> Pre-salbutamol forced expiratory volume in 1 second (FEV₁) > 60% of predicted Within 15% of highest pre-salbutamol FEV₁ obtained

Djukanovic 2010 (Continued)

	at screening (visit 1) <ul style="list-style-type: none"> No evidence of respiratory tract infection for ≥ 14 days before randomisation No asthma exacerbation
Interventions	PROTOCOL: LTRA + ICS vs same dose of ICS alone RUN-IN: 3.43 weeks (24 days) Intervention period: 12 weeks TEST GROUP: montelukast 10 mg daily + fluticasone propionate 200 µg daily CONTROL GROUP: fluticasone propionate 200 µg daily DEVICE: Diskus COMPLIANCE: overall compliance 98% CO-TREATMENT: β_2 -agonist as needed CRITERIA FOR WITHDRAWAL FROM STUDY: not reported
Outcomes	INTENTION-TO-TREAT ANALYSIS: not reported PULMONARY FUNCTION TEST: <ul style="list-style-type: none"> Morning and evening PEFr FEV₁ (mL) FEV₁ (% of predicted) FUNCTIONAL STATUS: <ul style="list-style-type: none"> % rescue-free days EXACERBATIONS: not reported INFLAMMATORY MARKERS: <ul style="list-style-type: none"> Submucosal inflammatory cell counts ADVERSE EFFECTS: not reported WITHDRAWALS: reported
Notes	Full-text article Funding: GlaxoSmithKline

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Study was randomised in a 1:1 manner and provided no further details regarding sequence generation
Allocation concealment (selection bias)	Unclear risk	Allocation concealment was not reported
Blinding of participants and personnel (performance bias)	Low risk	Mentioned as a double-blinded study. Participants were assigned a unique treatment number as an identification number for blinded study medication

Djukanovic 2010 (Continued)

All outcomes

Blinding of outcome assessment (detection bias) All outcomes	Low risk	Double-blind study
Incomplete outcome data (attrition bias) All outcomes	Low risk	Withdrawal numbers were similar and reasons were reported
Selective reporting (reporting bias)	Low risk	Study protocol is not available. Outcomes mentioned in the Methods section are reported in the Results section and are extractable
Other bias	Low risk	No imbalance in baseline characteristics

Huang 2003

Methods	Randomised, double-blind controlled trial
Participants	<p>RANDOMISED: 38</p> <ul style="list-style-type: none"> LTRA + ICS: 20 ICS alone: 18 <p>WITHDRAWALS:</p> <ul style="list-style-type: none"> LTRA + ICS: 3 (11.5%) ICS alone: 2 (8.3%) <p>AGE in years: mean $\pm$ SEM:</p> <ul style="list-style-type: none"> LTRA + ICS: 58.6 $\pm$ 3.0 ICS alone: 56.9 $\pm$ 2.8 <p>GENDER (% male):</p> <ul style="list-style-type: none"> LTRA + ICS: 53% ICS alone: 50% <p>SEVERITY: moderate persistent asthma</p> <p>ASTHMA DURATION years: $\geq$ 6 months</p> <p>BASELINE FEV₁ (% pred) $\pm$ SEM</p> <ul style="list-style-type: none"> LTRA + ICS: 67.8 $\pm$ 1.4 ICS alone: 69.1 $\pm$ 1.4 <p>MEAN ($\pm$SD) β_2-AGONIST USE (puffs/d): not reported</p> <p>BASELINE DOSE OF ICS: not reported</p> <p>ATOPY (%): not reported</p> <p>ELIGIBILITY CRITERIA:</p> <ul style="list-style-type: none"> Adults 18 to 75 years of age with diagnosis of moderate persistent asthma for $\geq$ 6 months according to American Thoracic Society criteria Forced expiratory volume in 1 second (FEV₁) within prediction of 60% to 80%

Huang 2003 (Continued)

- Reversibility in measurements of PEFR or $FEV_1 \geq 12\%$ after inhalation of 400 µg albuterol
- Current therapy with ICS (budesonide ≥ 400 µg/d or equivalent)

EXCLUSION CRITERIA:

- History of other significant respiratory diseases or respiratory tract infections preceding entry into the study
- Hospitalised with asthma within 3 months before enrolment in the study
- Smoked during 6 months preceding enrolment
- Received any anti-leukotrienes or cromolyn or nedocromil 3 weeks before entry into the study
- Long-acting antihistamines or aspirin or long-acting β_2 -agonist was used during week before the study

Interventions	<p>PROTOCOL: LTRA + ICS vs same dose of ICS alone</p> <p>RUN-IN: 2 weeks</p> <p>Intervention period: 4 weeks</p> <p>TEST GROUP: zafirlukast 20 mg bid + budesonide ≥ 400 µg/d or equivalent</p> <p>CONTROL GROUP: placebo + budesonide ≥ 400 µg/d or equivalent</p> <p>DEVICE: not reported</p> <p>COMPLIANCE: not reported</p> <p>CO-TREATMENT: β_2-agonist</p> <p>CRITERIA FOR WITHDRAWAL FROM STUDY: not reported</p>
Outcomes	<p>INTENTION-TO-TREAT ANALYSIS: not reported</p> <p>PULMONARY FUNCTION TEST:</p> <ul style="list-style-type: none"> • Change in morning and evening PEFR <p>FUNCTIONAL STATUS:</p> <ul style="list-style-type: none"> • St. George's Respiratory Questionnaire (SGRQ) <p>EXACERBATIONS: reported</p> <p>INFLAMMATORY MARKERS: not reported</p> <p>ADVERSE EFFECTS: not reported</p> <p>WITHDRAWALS: reported</p>
Notes	<p>Full-text article</p> <p>Funding: not reported</p>

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Study was randomised and provided no further details regarding sequence generation
Allocation concealment (selection bias)	Unclear risk	Allocation concealment was not reported

Huang 2003 (Continued)

Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind study
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Double-blind study
Incomplete outcome data (attrition bias) All outcomes	Low risk	Well-balanced withdrawals and reasons for withdrawal were reported
Selective reporting (reporting bias)	Low risk	Study protocol is not available. Outcomes mentioned in the Methods section are reported in the Results section and are extractable
Other bias	Low risk	No imbalance in baseline characteristics

Kanniess 2002

Methods	Randomised, double-blind, placebo-controlled, parallel-group clinical study
Participants	<p>WELL-CONTROLLED PARTICIPANTS</p> <ul style="list-style-type: none"> • RANDOMISED: 50 • LTRA + ICS: 26 • ICS alone: 24 <p>WITHDRAWALS:</p> <ul style="list-style-type: none"> • LTRA + ICS: 3 (11.5%) • ICS alone: 2 (8.3%) <p>AGE in years: mean $\pm$ SEM:</p> <ul style="list-style-type: none"> • LTRA + ICS: 38 $\pm$ 12 • ICS alone: 43 $\pm$ 11 <p>GENDER (% male):</p> <ul style="list-style-type: none"> • LTRA + ICS: 50% • ICS alone: 46% <p>SEVERITY: moderate bronchial asthma</p> <p>ASTHMA DURATION years: not reported</p> <p>BASELINE FEV₁ (% pred) $\pm$ SEM</p> <ul style="list-style-type: none"> • LTRA + ICS: 95.0 $\pm$ 2 • ICS alone: 92.3 $\pm$ 1.8 <p>MEAN ($\pm$SEM) β_2-AGONIST USE (puffs/d): not reported</p> <ul style="list-style-type: none"> • LTRA + ICS: 1.45 $\pm$ 0.3 • ICS alone: 1.63 $\pm$ 0.36 <p>BASELINE DOSE OF ICS: not reported</p>

Kanniess 2002 (Continued)

ATOPY (%): not reported

ELIGIBILITY CRITERIA

- Taking a dose of ICS (beclomethasone or equivalent) 800 µg/d for more than 8 weeks before randomisation
- FEV₁ > 80% of predicted
- No oral corticosteroids within 6 months of entry into the study
- No oral antihistamines within 4 weeks of entry into the study
- Provocative concentration of methacholine causing a 20% fall in FEV₁ (PC₂₀) < 8 mg/mL
- FEV₁ and PC₂₀ reproducible within 15% and 1.5 doubling concentrations, respectively, between visits 1 and 2
- No smokers
- No signs of an acute exacerbation or respiratory tract infection within 4 weeks before screening

EXCLUSION CRITERIA: not reported

Interventions

PROTOCOL: LTRA + ICS vs same dose of ICS alone (TAPERING ICS)

RUN-IN: 1-3 weeks

Intervention period: 6 weeks (× 2 periods)

TEST GROUP: montelukast 10 mg once daily + budesonide 800 µg/d or equivalent

CONTROL GROUP: budesonide 800 µg/d or equivalent

DEVICE: not specified

COMPLIANCE: not reported

CO-TREATMENT: none reported (use of β₂-agonist as needed)

CRITERIA FOR WITHDRAWAL FROM STUDY: not reported

CRITERIA FOR TAPERING

- 1st treatment period ICS reduced to 50% baseline (400 µg/d)
- 2nd treatment period ICS reduced to 50% of 1st treatment (25% of baseline or 200 µg/d)

Outcomes

INTENTION-TO-TREAT ANALYSES: reported

OUTCOMES: at endpoint or 6 weeks

PULMONARY FUNCTION TEST:

- Data are given as changes from baseline to end of study as well as relative to baseline (1st period) and relative to each other (2nd period)
- Change in FEV₁ (L)
- Change in PEFr daytime
- Change in PEFr night-time
- Change in PC₂₀

FUNCTIONAL STATUS:

- Use of rescue β₂-agonists (puffs/d)

SYMPTOM SCORES

- Change in daytime symptoms score (range 0 to 4)
- Change in night-time symptoms score (range 0 to 4)

Kanniess 2002 (Continued)

EXACERBATIONS: reported

INFLAMMATORY MARKERS:

- Data are given as changes relative to baseline (1st period) and relative to each other (2nd period)
- Exhaled NO ppb
- % sputum eosinophils

ADVERSE EFFECTS: not reported

WITHDRAWALS: reported

Notes

Full-text (2002) publication

Funding: educational grant from MSD, Munich, Germany

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Study was randomised and provided no further details regarding sequence generation
Allocation concealment (selection bias)	Unclear risk	Allocation concealment was not reported
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind study, placebo-controlled
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Double-blind study
Incomplete outcome data (attrition bias) All outcomes	Low risk	Missing outcome data < 10%. Reasons for missing data reported
Selective reporting (reporting bias)	Low risk	Study protocol is not available. Outcomes mentioned in the Methods section are reported in the Results section and are extractable
Other bias	Low risk	No imbalance in baseline characteristics

Kirishi 2013

Methods	Randomised, controlled, parallel-group, multi-centre trial
Participants	RANDOMISED: 49 <ul style="list-style-type: none"> • LTRA + ICS: 21 • ICS alone: 19 WITHDRAWALS: not reported <p>AGE in years: mean $\pm$ SEM:</p> <ul style="list-style-type: none"> • LTRA + ICS: 44 $\pm$ 5 • ICS alone: 42 $\pm$ 6

Kirishi 2013 (Continued)

GENDER (% male):

- LTRA + ICS: 47.6%
- ICS alone: 42.1%

SEVERITY: not reported

ASTHMA DURATION: years:

- LTRA + ICS: 17 ± 4.4
- ICS alone: 16.1 ± 5.2

BASELINE FEV₁ (% pred) ± SEM:

- LTRA + ICS: 64.9 ± 6.8
- ICS alone: 67.1 ± 5.9

MEAN (±SD) β₂-AGONIST USE (puffs/d):

- LTRA + ICS: 15.4 ± 5.2
- ICS alone: 17.2 ± 5.7

BASELINE DOSE OF ICS: not reported

ATOPY (%): not reported

ALLERGIC RHINITIS: reported

ELIGIBILITY CRITERIA: not reported

Interventions

PROTOCOL: LTRA + ICS vs HIGHER dose of ICS alone

RUN-IN: 4 weeks

INTERVENTION PERIOD: 12 weeks

TEST GROUP: montelukast 10 mg daily + ICS (dose not reported)

CONTROL GROUP: ICS (dose not reported)

DEVICE: not reported

COMPLIANCE: not reported

CO-TREATMENT: β₂-agonist as needed

CRITERIA FOR WITHDRAWAL FROM STUDY: not reported

Outcomes

INTENTION-TO-TREAT ANALYSES: not reported

OUTCOMES: reported at 12 weeks

PULMONARY FUNCTION TEST:

- Change in FEV₁ (L)
- Change in PEFr daytime
- Change in PEFr night-time

FUNCTIONAL STATUS:

- Use of rescue β₂-agonists (puffs/d)
- Change in mean symptom scores

EXACERBATIONS: not reported

Kirishi 2013 (Continued)

INFLAMMATORY MARKERS: not reported

ADVERSE EFFECTS: not reported

WITHDRAWALS: not reported

Notes	Abstract
	Funding: Ministry of Education, Science and Culture, Japan

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Study was randomised and provided no further details regarding sequence generation
Allocation concealment (selection bias)	Unclear risk	Allocation concealment was not reported
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Details on blinding and methods of blinding were not reported
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Blinding of outcome assessment was not reported
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Number of participants with overall missing data reported (> 10%). Reasons for missing data not mentioned. No mention of intention-to-treat analysis
Selective reporting (reporting bias)	Unclear risk	Unable to assess owing to lack of details regarding selective reporting of outcomes
Other bias	Unclear risk	Unable to assess bias owing to baseline imbalances

Korzh 2004

Methods	Randomised, placebo-controlled clinical study
Participants	<p>RANDOMISED: 27</p> <ul style="list-style-type: none"> LTRA + ICS: 14 ICS alone: 13 <p>WITHDRAWALS: not reported</p> <p>AGE in years: mean $\pm$ SEM: not reported</p> <p>GENDER (% male): 44</p> <p>SEVERITY: mild to moderate asthma</p> <p>ASTHMA DURATION years: not reported</p> <p>BASELINE FEV₁ (% pred) $\pm$ SEM: not reported</p>

Korzh 2004 (Continued)

	<p>MEAN ($\pm$SD) β_2-AGONIST USE (puffs/d): not reported</p> <p>BASELINE DOSE OF ICS: not reported</p> <p>ATOPY (%): not reported</p> <p>ELIGIBILITY CRITERIA: not reported</p>
Interventions	<p>PROTOCOL: LTRA + ICS vs SAME dose of ICS alone</p> <p>RUN-IN: 8 weeks</p> <p>INTERVENTION PERIOD: 8 weeks</p> <p>TEST GROUP: montelukast 10 mg daily + inhaled budesonide 400 μg daily</p> <p>CONTROL GROUP: placebo + budesonide 400 μg daily</p> <p>DEVICE: not reported</p> <p>COMPLIANCE: not reported</p> <p>CO-TREATMENT: not reported</p>
Outcomes	<p>INTENTION-TO-TREAT ANALYSES: not reported</p> <p>OUTCOMES: reported at 8 weeks</p> <p>Exhaled nitric oxide levels</p> <p>EXACERBATIONS: not reported</p> <p>INFLAMMATORY MARKERS: not reported</p> <p>ADVERSE EFFECTS: not reported</p> <p>WITHDRAWALS: not reported</p>
Notes	<p>Abstract</p> <p>Funding: not reported</p>

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Reported as randomised with no details regarding sequence generation
Allocation concealment (selection bias)	Unclear risk	Allocation concealment not reported
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Blinding and methods of blinding not reported
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Blinding of outcome assessment not reported
Incomplete outcome data (attrition bias)	Unclear risk	Details on drop-outs not reported

Korzh 2004 (Continued)

All outcomes

Selective reporting (reporting bias)	Unclear risk	Unable to assess owing to lack of details regarding selective reporting of outcomes
Other bias	Unclear risk	Unable to assess bias owing to baseline imbalances

Laitinen 1993

Methods	Randomised, double-blind, placebo-controlled, parallel-group, multi-centre trial (83 centres)
Participants	<p>WELL-CONTROLLED PARTICIPANTS</p> <p>RANDOMISED: 262</p> <ul style="list-style-type: none"> LTRA + ICS:175 ICS alone:87 <p>WITHDRAWALS:</p> <ul style="list-style-type: none"> Zafirlukast:15% Control:14% <p>AGE in years (mean $\pm$ SD):</p> <ul style="list-style-type: none"> Zafirlukast: 45.5 $\pm$ 13.6 Control: 43.5 $\pm$ 13.4 <p>GENDER (% male):</p> <ul style="list-style-type: none"> LTRA + ICS: 46 ICS alone: 34 <p>SEVERITY: moderate asthma</p> <p>BASELINE FEV₁ (L):</p> <ul style="list-style-type: none"> LTRA + ICS: 2.58 $\pm$ 0.89 (SD) ICS alone: 2.42 $\pm$ 0.78 <p>ALLERGEN TRIGGERS:</p> <ul style="list-style-type: none"> LTRA + ICS: 45% ICS alone:40% <p>ASTHMA DURATION:</p> <ul style="list-style-type: none"> LTRA + ICS: 14.1 $\pm$ 13.1 years ICS alone: 14.3 $\pm$ 12.5 years <p>ELIGIBILITY CRITERIA:</p> <ul style="list-style-type: none"> Taking a dose of ICS (BUD or BDP) between 800 and 2000 μg/d Stable in the preceding month
Interventions	<p>PROTOCOL: LTRA + ICS vs same dose ICS (TAPERING ICS dose)</p> <p>DURATION:</p> <ul style="list-style-type: none"> RUN-IN: 1 week to confirm asthma control

Laitinen 1993 (Continued)

- Dose optimisation period: 2 weeks to 3 months
- LTRA + ICS: 7.7 ± 4.0 weeks
- ICS alone: 7.9 ± 4.0 weeks

INTERVENTION PERIOD: 12 weeks

TEST GROUP:

- ICI 204219 = zafirlukast 20 mg bid p.o. + ICS (BUD or BDP) 800 to 2000 µg/d

CONTROL GROUP:

- Placebo + ICS (BUD or BDP) 800 to 2000 µg/d

DEVICE: various devices used

CO-TREATMENT: none reported

CRITERIA FOR TAPERING every 2 weeks by 200 to 250 mcg/d

- $FEV_1 \geq 80\%$ of predicted
- β_2 -agonist use ≤ 800 µg/d of salbutamol

MINIMAL DOSE OF ICS ALLOWED: 400 mcg/d

CRITERIA TO INCREASE CORTICOSTEROIDS:

- $FEV_1 < 60\%$ of predicted

Outcomes

PER-PROTOCOL (PP) ANALYSES

- Some intention-to-treat (ITT) analysis
- Outcomes used at 6 and 12 weeks

PULMONARY FUNCTION TESTS (reported as cross-sectional values, not as change from baseline):

- FEV_1 (L) - ITT
- Mean AM PEFR (L/min) - PP

SYMPTOM SCORES - PP:

- Mean daytime symptom scores

FUNCTIONAL STATUS - PP:

- Mean daily use of β_2 -agonist (puffs/d) averaged over a week

ICS DOSE REDUCTION:

(PP)

- **ICS dose reduction (% change from baseline)

INFLAMMATORY MARKERS:

- Not reported

ADVERSE EFFECTS:

- Elevated liver enzymes, headache, nausea, death, etc.

WITHDRAWALS:

Laitinen 1993 (Continued)

- Reported

(** denotes primary outcomes)

Notes

Abs (1993) and unpublished data graciously provided by Christopher Miller and Susan Shaffer from AstraZeneca, USA (Oct 2000)

Funding: Zeneca

Confirmation of methods and data extraction received from M. Christopher Miller and Ms. Susan Shaffer, AstraZeneca, Oct 2000

User-defined order: 114

(mean intervention ICS dose of 1137 mcg/ day $\times$ 0.1)

ALLOCATION

- Random: 2:1 ratio intervention:control
- Computer-generated

BLINDING

- Double-blind
- Placebo-controlled
- Identical placebo

WITHDRAWAL/DROPOUT

- Described

Confirmation of methods obtained

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated randomisation: 2:1 ratio intervention:control
Allocation concealment (selection bias)	Low risk	Study investigators unaware as to order of treatment group assignment (Cochrane Grade A)
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blinded study. Matching placebo used
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Double-blind study
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Details on drop-outs not reported
Selective reporting (reporting bias)	Unclear risk	Unable to assess owing to lack of details regarding selective reporting of outcomes
Other bias	Unclear risk	Unable to assess bias owing to baseline imbalances

Laviolette 1999

Methods	Randomised, parallel-group, double-blind, double-dummy, 4-arm, multi-centre clinical study
Participants	<p>SYMPTOMATIC PARTICIPANTS</p> <p>RANDOMISED: 642</p> <ul style="list-style-type: none"> LTRA + ICS: 193 ICS alone: 200 <p>WITHDRAWALS:</p> <ul style="list-style-type: none"> LTRA + ICS: 8.3% ICS alone: 11% <p>AGE in years: mean: 15 to 78 years: reported as median and range</p> <p>GENDER (% male):</p> <ul style="list-style-type: none"> LTRA + ICS: 56 ICS alone: 52% <p>SEVERITY: not reported</p> <p>ASTHMA DURATION mean years (range): ≥ 1 year</p> <ul style="list-style-type: none"> LTRA + ICS: 19 (0.5 to 62) ICS alone: 18 (0.5 to 59) <p>BASELINE FEV₁ (% pred) $\pm$ SD:</p> <ul style="list-style-type: none"> LTRA + ICS: 72 $\pm$ 12 ICS alone: 71 $\pm$ 12 <p>MEAN ($\pm$SD) β_2-AGONIST USE (puffs/d):</p> <ul style="list-style-type: none"> LTRA + ICS: 3.4 $\pm$ 2.2 ICS alone: 3.5 $\pm$ 2.5 <p>BASELINE DOSE OF ICS: not reported</p> <p>ATOPY (%): ALLERGIC RHINITIS</p> <ul style="list-style-type: none"> LTRA + ICS: 76% ICS alone: 74% <p>ELIGIBILITY CRITERIA</p> <ul style="list-style-type: none"> > 15 years old Healthy, non-smoking History of ≥ 1 year of intermittent or persistent asthma symptoms ICS treatment ≥ 6 weeks before pre-study visit (ICS dose comparable with beclomethasone 400 to 500 μg) 50% to 85% FEV₁ predicted Improvement > 15% FEV₁ after β_2-agonist ≥ 1 puff/d of β_2-agonist <p>EXCLUSION CRITERIA:</p> <ul style="list-style-type: none"> Upper respiratory tract infection < 3 weeks Positive pregnancy test
Interventions	PROTOCOL: LTRA + ICS vs SAME dose of ICS alone

Laviolette 1999 (Continued)

RUN-IN: 4 weeks

INTERVENTION PERIOD: 16 weeks

TEST GROUP: montelukast 10 mg daily + inhaled beclomethasone 200 µg twice daily

CONTROL GROUP: placebo + inhaled beclomethasone 200 µg twice daily

DEVICE: Aerochamber spacer device

COMPLIANCE:

- LTRA + ICS: inhaled medication 92.6 ± 16.3 , montelukast 98.6 ± 1.7
- ICS alone: inhaled medication 92.4 ± 18.7 , placebo 98.7 ± 0.7

CO-TREATMENT: none permitted (other than β_2 -agonist and antihistamines, except terfenadine (within 2 weeks) and astemizole (within 3 months))

Outcomes	INTENTION-TO-TREAT ANALYSIS: reported	
	OUTCOMES: reported at 16 weeks	
	PULMONARY FUNCTION TEST:	
	<ul style="list-style-type: none">• Change from baseline FEV₁• Change from baseline FEV₁ % of predicted• Change from baseline morning and evening PEFR	
	SYMPTOM SCORES	
	<ul style="list-style-type: none">• Change from baseline daytime symptom scores• Change from baseline nocturnal awakenings (nights/wk)	
	FUNCTIONAL STATUS:	
	<ul style="list-style-type: none">• Change from baseline mean daily β₂-agonist use (puffs/d)	
	EXACERBATIONS: reported	
	INFLAMMATORY MARKERS:	
	<ul style="list-style-type: none">• Change from baseline in blood serum eosinophils	
	ADVERSE EFFECTS:	
	<ul style="list-style-type: none">• Elevated liver enzymes, headache, nausea, death, etc.	
	WITHDRAWALS: reported	
Notes	Full-text article (1999) Funding: Merck Research Laboratories	
<i>Risk of bias</i>		
Bias	Authors' judgement	Support for judgement
Random sequence genera- tion (selection bias)	Low risk	Study was randomised with computerised sequence generation
Allocation concealment (selection bias)	Unclear risk	Allocation concealment was not reported

Laviolette 1999 (Continued)

Blinding of participants and personnel (performance bias) All outcomes	Low risk	Mentioned as a double-blinded study. Matching placebo used
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Double-blind study
Incomplete outcome data (attrition bias) All outcomes	Low risk	Missing outcome data < 10%. Reasons for missing data reported
Selective reporting (reporting bias)	Low risk	Study protocol not available. Outcomes mentioned in the Methods section reported in the Results section and extractable
Other bias	Low risk	No imbalance in baseline characteristics

Lofdahl 1999

Methods	Randomised, double blind, placebo-controlled, parallel-group clinical study
Participants	<p>WELL-CONTROLLED PARTICIPANTS</p> <p>RANDOMISED: 226</p> <ul style="list-style-type: none"> LTRA + ICS: 113 ICS alone: 113 <p>WITHDRAWALS:</p> <ul style="list-style-type: none"> LTRA + ICS: 16% ICS alone: 27% <p>AGE in years: mean (16 to 70 years):</p> <ul style="list-style-type: none"> LTRA + ICS: 40 years (17 to 70 years) ICS alone: 41 years (16 to 68 years) <p>GENDER (% male):</p> <ul style="list-style-type: none"> LTRA + ICS: 42 ICS alone: 54 <p>SEVERITY: not reported</p> <p>ASTHMA DURATION mean years $\pm$ SD: more than 1 year</p> <ul style="list-style-type: none"> LTRA + ICS: 18 $\pm$ 13.3 ICS alone: 19 $\pm$ 14 <p>BASELINE FEV₁ (% pred) $\pm$ SD</p> <ul style="list-style-type: none"> LTRA + ICS: 84.8 $\pm$ 11.1 ICS alone: 82.3 $\pm$ 12.9 <p>MEAN ($\pm$SD) β_2-AGONIST USE (puffs/d):</p> <ul style="list-style-type: none"> LTRA + ICS: 2.4 $\pm$ 2.2%

Lofdahl 1999 (Continued)

- ICS alone: $2.8 \pm 2.6\%$

BASELINE DOSE OF ICS: not reported

ATOPY (%): not reported

ELIGIBILITY CRITERIA:

- Non-smoking adults
- Clinical history of asthma for ≥ 1 year
- Treatment with stable ICS bid for ≥ 3 weeks before pre-study visit
- $\geq 70\%$ FEV₁ % pred
- $\geq 15\%$ reversibility after inhaled β_2 -agonist

After 2 ICS dose reductions:

- FEV₁ in 1 second $\geq 90\%$ of baseline value
- Levels < baseline level in asthma symptoms and β_2 -agonist use
- $\geq 65\%$ of maximum peak flow
- Required prespecified minimum ICS dose met

EXCLUSION CRITERIA:

- Emergency treatment in past 1 month
- Hospitalised in past 3 months
- Upper respiratory tract infection within 3 weeks

Interventions	<p>PROTOCOL: LTRA + ICS vs SAME dose of ICS alone (TAPERING ICS dose) - TAPERING, MAINTAINED OR INCREASED DOSE OF ICS</p> <p>RUN-IN: 5 to 7 weeks</p> <p>INTERVENTION PERIOD: 12 weeks</p> <p>TEST GROUP: montelukast 10 mg OD at bedtime + ICS 300 to 2400 µg/d (various ICS including fluticasone 7%, beclomethasone 16%, budesonide 22%, flunisolide 15%, triamcinolone 40%)</p> <p>CONTROL GROUP: placebo + ICS 300 to 2400 µg/d (various ICS including fluticasone 7%, beclomethasone 16%, budesonide 22%, flunisolide 15%, triamcinolone 40%)</p> <p>DEVICE: not reported</p> <p>COMPLIANCE: not reported</p> <p>CO-TREATMENT: β_2-agonist</p> <p>CRITERIA FOR TAPERING every 2 weeks by 25% of ICS dose</p> <ul style="list-style-type: none"> • FEV₁ $\geq 90\%$ of value at randomisation • β_2-agonist use $\leq 135\%$ of pre-allocation • Daytime symptoms score $\beta_2 \leq 120\%$ of pre-allocation baseline
Outcomes	<p>INTENTION-TO-TREAT ANALYSIS: reported</p> <p>OUTCOMES: reported at last tolerated dose or 12 weeks</p> <p>PULMONARY FUNCTION TEST:</p> <ul style="list-style-type: none"> • Change from baseline FEV₁ at visit of lowest tolerated ICS dose <p>SYMPTOM SCORES</p>

Lofdahl 1999 (Continued)

- Change from baseline daily symptom scores at visit of lowest tolerated ICS dose

FUNCTIONAL STATUS:

- Change from baseline mean daily use of β_2 -agonists at visit of lowest tolerated ICS dose

ICS DOSE REDUCTION:

- Mean % change from baseline ICS dose reduction
- **Change from baseline ICS dose (μg)

EXACERBATIONS: not reported

INFLAMMATORY MARKERS: not reported

ADVERSE EFFECTS:

- Elevated liver enzymes, headache, nausea, death.

Notes Full-text 1999
Funding: Merck Research Laboratories

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Study randomised with computerised sequence generation
Allocation concealment (selection bias)	Unclear risk	Allocation concealment not reported
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Mentioned as a double-blinded study
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Mentioned as double-blinded. Outcome assessments done by endpoint committee blinded to participant allocation
Incomplete outcome data (attrition bias) All outcomes	Low risk	Missing outcome data < 10%. Reasons for missing data reported
Selective reporting (reporting bias)	Low risk	Study protocol is not available. Outcomes mentioned in the Methods section are reported in the Results section and are extractable
Other bias	Low risk	No imbalance in baseline characteristics

Nayak 1998

Methods Randomised, parallel-group, double-blind, double-dummy, 3-arm, multi-centre, placebo controlled clinical study

Participants SYMPTOMATIC PARTICIPANTS
RANDOMISED: 394

Nayak 1998 (Continued)

- LTRA + ICS: 130 lower dose and 134 higher dose zafirlukast
- ICS alone: 130

AGE in years: ≥ 12 years

GENDER: (% male): not reported

SEVERITY: not reported

ASTHMA DURATION mean years: not reported

BASELINE FEV₁ (% pred): not reported

MEAN ($\pm$ SD) β_2 -AGONIST USE (puffs/d): not reported

BASELINE DOSE OF ICS: not reported

ATOPY (%): not reported

ELIGIBILITY CRITERIA:

- Age: ≥ 12 years
- Symptomatic on low-dose ICS

Interventions

PROTOCOL: LTRA + ICS vs HIGHER dose of ICS alone

RUN-IN: not reported

INTERVENTION PERIOD: 13 weeks

TEST GROUP 1: zafirlukast 40 mg twice daily + beclomethasone 336 μ g/d

TEST GROUP 2: zafirlukast 80 mg twice daily + beclomethasone 336 μ g/d

CONTROL GROUP: beclomethasone 672 μ g/d

DEVICE: not reported

COMPLIANCE: not reported

CO-TREATMENT: β_2 -agonists as needed

Outcomes

INTENTION-TO-TREAT ANALYSIS: not reported

PULMONARY FUNCTION TEST:

- FEV₁
- Morning PEFr

SYMPTOM SCORES:

- Daytime symptom scores (scale 0 to 3)
- Nocturnal awakenings
- Mornings with asthma

FUNCTIONAL STATUS:

- Mean daily use of β_2 -agonists

INFLAMMATORY MARKERS: not reported

ADVERSE EFFECTS: reported

Notes

Abstract (1998)

Nayak 1998 (Continued)

Funding: AstraZeneca

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Reported as randomised and provided no further details regarding sequence generation
Allocation concealment (selection bias)	Unclear risk	Allocation concealment not reported
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Reported as double-blind, double-dummy but provided no further details
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Double-blind study
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Details on drop-outs not reported
Selective reporting (reporting bias)	Unclear risk	Unable to assess owing to lack of details regarding selective reporting of outcomes
Other bias	Unclear risk	Unable to assess bias owing to baseline imbalances

Nsouli 2000

Methods	Randomised, parallel-group, open-label clinical study
Participants	<p>SYMPTOMATIC PARTICIPANTS</p> <p>RANDOMISED: 30</p> <p>WITHDRAWALS: not reported</p> <p>AGE in years: mean (range): not reported</p> <p>GENDER (% male): not reported</p> <p>SEVERITY: not reported</p> <p>ASTHMA DURATION mean years: not reported</p> <p>BASELINE FEV₁ (% pred): not reported</p> <p>MEAN (±SD) β_2-AGONIST USE (puffs/d): not reported</p> <p>BASELINE DOSE OF ICS: not reported</p> <p>ATOPY (%): not reported</p> <p>ELIGIBILITY CRITERIA:</p>

Nsouli 2000 (Continued)

- Symptomatic on low dose of ICS (fluticasone propionate 88 to 264 µg, Beclomethasone dipropionate 168 to 500 µg, Budesonide turbuhaler 200 to 400 µg, Flunisolide 500 to 1000 µg, TAA 400 to 1000 µg)

EXCLUSION CRITERIA:

- Not reported

Interventions	<p>PROTOCOL: LTRA + ICS vs HIGHER dose of ICS alone</p> <p>Run-in period: not described</p> <p>INTERVENTION PERIOD: 12 weeks</p> <p>TEST GROUP: montelukast 10 mg OD + beclomethasone 168 to 500 µg/d or equivalent</p> <p>CONTROL GROUP: beclomethasone 336 to 1000 µg/d or equivalent</p> <p>DEVICE: not reported</p> <p>COMPLIANCE: not reported</p> <p>CO-TREATMENT: none reported</p>
Outcomes	<p>ANALYSIS: not described</p> <p>OUTCOMES: reported at 12 weeks</p> <p>PULMONARY FUNCTION TESTS:</p> <ul style="list-style-type: none"> • Change in AM PEFR • Change in FEV₁ <p>FUNCTIONAL STATUS:</p> <ul style="list-style-type: none"> • Change from baseline mean daily β_2-agonist use • Nocturnal awakenings <p>INFLAMMATORY MARKERS: not reported</p> <p>ADVERSE EFFECTS: not reported</p> <p>WITHDRAWALS: not reported</p>
Notes	<p>Abstract 2000</p> <p>Funding: not reported</p>

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Reported as randomised and provided no further details regarding sequence generation
Allocation concealment (selection bias)	Unclear risk	Allocation concealment not reported
Blinding of participants and personnel (performance bias) All outcomes	High risk	Reported as open-label clinical trial
Blinding of outcome assessment (detection bias) All outcomes	High risk	No blinding

Nsouli 2000 (Continued)

Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Details on drop-outs not reported
Selective reporting (reporting bias)	Unclear risk	Unable to assess owing to lack of details regarding selective reporting of outcomes
Other bias	Unclear risk	Unable to assess bias owing to baseline imbalances

Price 2003

Methods	Randomised, double-blind, parallel-group, non-inferiority, multi-centre clinical study
Participants	<p>SYMPTOMATIC PARTICIPANTS</p> <p>RANDOMISED: 889</p> <ul style="list-style-type: none"> LTRA + ICS: 448 ICS alone: 441 <p>WITHDRAWALS, number (%):</p> <ul style="list-style-type: none"> LTRA + ICS: 20 (4.5) ICS alone: 26 (6) <p>AGE in years: mean years $\pm$ SD</p> <ul style="list-style-type: none"> LTRA + ICS: 43 ± 14 ICS alone: 43 ± 14 <p>GENDER (% male):</p> <ul style="list-style-type: none"> LTRA + ICS: 41 ICS alone: 39 <p>SEVERITY: not reported</p> <p>ASTHMA DURATION mean years $\pm$ SD or longer than 1 year</p> <ul style="list-style-type: none"> LTRA + ICS: 18 ± 14 ICS alone: 17 ± 15 <p>BASELINE FEV₁ (% pred) $\pm$ SD</p> <ul style="list-style-type: none"> LTRA + ICS: 69.0 ± 13.3 ICS alone: 68.3 ± 13.4 <p>MEAN ($\pm$SD) β_2-AGONIST USE (puffs/d): not reported</p> <ul style="list-style-type: none"> LTRA + ICS: 2.7 ± 2.4 ICS alone: 2.7 ± 2.2 <p>BASELINE DOSE OF ICS: not reported</p> <p>ATOPY (%): not reported</p> <p>ELIGIBILITY CRITERIA:</p> <ul style="list-style-type: none"> Non-smokers or ex-smokers Diagnosis of asthma > 1 year

Price 2003 (Continued)

- Age 15 to 75
- Not optimally controlled on ICS 600 to 1200 µg/d of budesonide, beclomethasone, triamcinolone, flunisolide, or 300 to 800 µg fluticasone
- FEV₁ ≥ 50% of predicted
- ≥ 12% improvement in FEV₁ after β₂-agonist use
- Symptoms requiring at least 1 puff/d of β₂-agonist during last 2 weeks of the run-in

EXCLUSION CRITERIA:

- Other active pulmonary disorders
- Respiratory infection within 3 weeks of visit 1 or during the run-in period
- ER visit for asthma within 2 months of visit 1
- Systemic corticosteroid treatment within 1 month
- Cromones or leukotriene receptor antagonists within 2 weeks
- Long-acting antihistamine within 1 week (astemizole 3 months)
- Long-acting β₂-agonist or anticholinergic agents within 24 hours

Interventions	<p>PROTOCOL: LTRA + ICS vs HIGHER dose of ICS alone</p> <p>RUN-IN: 4 weeks</p> <p>INTERVENTION PERIOD: 12 weeks</p> <p>TEST GROUP: montelukast 10 mg once daily + Inhaled budesonide 800 µg/d</p> <p>CONTROL GROUP: placebo + Inhaled budesonide 1600 µg/d</p> <p>DEVICE: Turbohaler</p> <p>COMPLIANCE: not reported</p> <p>CO-TREATMENT: β₂-agonist as needed</p> <p>CRITERIA FOR WITHDRAWAL FROM STUDY: reported</p>
Outcomes	<p>INTENTION-TO-TREAT ANALYSES: reported</p> <p>OUTCOMES: reported at 12 weeks</p> <p>PULMONARY FUNCTION TESTS:</p> <ul style="list-style-type: none"> • Change in FEV₁ (L) • Change in morning PEFR (L/min) <p>SYMPTOM SCORES:</p> <ul style="list-style-type: none"> • Change in symptom score (scale 0 to 6) <p>FUNCTIONAL STATUS:</p> <ul style="list-style-type: none"> • Change in mean daily use of β₂-agonist (puffs/d) • Change in quality of life score (range 1 to 7) • Change in nocturnal awakenings <p>INFLAMMATORY MARKERS:</p> <ul style="list-style-type: none"> • Change in peripheral blood eosinophil count <p>ADVERSE EFFECTS: reported</p> <p>WITHDRAWALS: reported</p>

Price 2003 (Continued)

Notes

Full text 2003

Funding: Merck and Co Inc

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Study was randomised and provided no further details regarding sequence generation
Allocation concealment (selection bias)	Unclear risk	Allocation concealment not reported
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Mentioned as a double-blinded study but provided no further details on blinding
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Double-blinded study
Incomplete outcome data (attrition bias) All outcomes	Low risk	Missing outcome data < 10%. Reasons for missing data reported
Selective reporting (reporting bias)	Low risk	Study protocol is not available. Outcomes mentioned in the Methods section are reported in the Results section and are extractable
Other bias	Low risk	No imbalance in baseline characteristics

Riccioni 2001

Methods	Randomised, parallel-group clinical study
Participants	<p>SYMPTOMATIC PARTICIPANTS</p> <p>RANDOMISED: 24</p> <ul style="list-style-type: none"> LTRA + ICS: 12 ICS alone: 12 <p>AGE in years: mean years $\pm$ SD</p> <ul style="list-style-type: none"> LTRA + ICS: 33.44 $\pm$ 11.12 ICS alone: 32.15 $\pm$ 10.27 <p>GENDER (% male):</p> <ul style="list-style-type: none"> LTRA + ICS: 50 ICS alone: 50 <p>SEVERITY: mild persistent</p> <p>ASTHMA DURATION mean years: $\geq$ 1 year</p> <p>BASELINE FEV₁ (% pred) $\pm$ SD</p>

Riccioni 2001 (Continued)

- LTRA + ICS: 92.16 ± 5.06
- ICS alone: 92.75 ± 9.87

MEAN ($\pm$ SD) β_2 -AGONIST USE (puffs/d): not reported

ATOPY (%): not reported

ELIGIBILITY CRITERIA:

- 1 year of mild persistent bronchial asthma
- PEFR > 80% pred and PEFR daily variability in 20% to 30% range
- Positive salbutamol reversibility test

EXCLUSION CRITERIA:

- URTI in last 3 weeks
- Hospitalisation for asthma in the 3 months before enrolment
- Treatment with antihistamines, anticholinergics, theophylline drugs
- Presence of autoimmune, hepatic or renal disorders
- Malabsorption, drug or alcohol addiction
- Pregnancy or lactation

Interventions	<p>PROTOCOL: LTRA + ICS vs SAME dose of ICS alone</p> <p>RUN-IN: 2 weeks</p> <p>INTERVENTION PERIOD: 8 weeks</p> <p>TEST GROUP: zafirlukast 20 mg twice daily + inhaled budesonide 800 μg/d</p> <p>CONTROL GROUP: inhaled budesonide 800 μg/d</p> <p>DEVICE: not reported</p> <p>COMPLIANCE: not reported</p> <p>CO-TREATMENT: not reported</p>
Outcomes	<p>ANALYSES: NOT BY INTENTION-TO-TREAT</p> <p>OUTCOMES: reported at 8 weeks</p> <p>PULMONARY FUNCTION TEST</p> <ul style="list-style-type: none"> • Pre and post PEFR • Pre and post FVC values • Pre and post FEV₁ • Pre and post PD₂₀ <p>SYMPTOM SCORES: not reported</p> <p>FUNCTIONAL STATUS: not reported</p> <p>INFLAMMATORY MEDIATORS: not reported</p> <p>ADVERSE EFFECTS: reported</p> <p>WITHDRAWALS: not reported</p>
Notes	<p>Full-text publication (2001)</p> <p>Funding: not reported</p>

Risk of bias

Riccioni 2001 (Continued)

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Reported as randomised and provided no further details regarding sequence generation
Allocation concealment (selection bias)	Unclear risk	Allocation concealment not reported
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open-label study design
Blinding of outcome assessment (detection bias) All outcomes	High risk	Open-label study design
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Details on drop-outs not reported
Selective reporting (reporting bias)	Low risk	Study protocol is not available. Outcomes mentioned in the Methods section are reported in the Results section and are extractable
Other bias	Low risk	No imbalance in baseline characteristics

Riccioni 2002

Methods	Randomised, parallel-group clinical study
Participants	<p>RANDOMISED: 45</p> <ul style="list-style-type: none"> LTRA + ICS: 15 ICS alone: 15 <p>AGE in years: mean years $\pm$ SD</p> <ul style="list-style-type: none"> LTRA + ICS: 28.2 $\pm$ 10.1 ICS alone: 26.9 $\pm$ 12.3 <p>GENDER (% male):</p> <ul style="list-style-type: none"> LTRA + ICS: 33.7 ICS alone: 53.3 <p>SEVERITY: mild persistent asthma</p> <p>ASTHMA DURATION mean years: 1 year or longer</p> <p>BASELINE FEV₁ (% pred) (range)</p> <ul style="list-style-type: none"> LTRA + ICS: 99 (84 to 131) ICS alone: 97 (76 to 123) <p>MEAN ($\pm$SD) β_2-AGONIST USE (puffs/d): not reported</p> <p>BASELINE DOSE OF ICS: not reported</p>

Riccioni 2002 (Continued)

ATOPY (%): 100% (definition not mentioned)

ELIGIBILITY CRITERIA:

- Asthma as per ATS criteria
- Confirmation of the presence of BHR by methacholine on initial visit
- Regular attendance at outpatient clinic for over 4 months from initial visit
- PEFR $\geq$ 80% of predicted
- PEFR variability $\leq$ 20% as per NIH criteria

EXCLUSION CRITERIA:

- ER visit for asthma exacerbation within 1 month
- URTI in past 4 weeks
- Hospitalisation for asthma in past 6 months before enrolment
- Treatment with antihistamines, anticholinergics, theophylline and cromones, LABA, inhaled and oral corticosteroids
- Bronchiectasis
- Gastroesophageal reflux
- Poor knowledge of the Italian language

Interventions

PROTOCOL: LTRA + ICS vs SAME dose of ICS alone

RUN-IN: 4 weeks

INTERVENTION PERIOD: 16 weeks

TEST GROUP: montelukast 10 mg once daily + inhaled budesonide 800 μ g/d

CONTROL GROUP: inhaled budesonide 800 μ g/d

DEVICE: Turbuhaler

COMPLIANCE: not reported

CO-TREATMENT: none permitted

CRITERIA FOR WITHDRAWAL FROM STUDY: not reported

Outcomes

ANALYSES: NOT BY INTENTION-TO-TREAT

OUTCOMES: reported at 16 weeks

PULMONARY FUNCTION TEST:

- Change from baseline in FVC
- Change from baseline in FEV₁
- Change from baseline in PC₂₀

SYMPTOM SCORES: not reported

FUNCTIONAL STATUS:

- Change in AQOL (Asthma Quality of Life Questionnaire - Juniper) in each of 4 domains
- Asthma exacerbations (defined as requiring systemic steroids or hospital admission or ED treatment for worsening asthma or decrease in morning PEFR > 25%)

INFLAMMATORY MEDIATORS: not reported

ADVERSE EFFECTS: not reported

WITHDRAWALS: not reported

Riccioni 2002 (Continued)

Notes Full-text publication (2002)

Funding: not reported

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Study was randomised and provided no further details regarding sequence generation
Allocation concealment (selection bias)	Unclear risk	Allocation concealment not reported
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open-label study design
Blinding of outcome assessment (detection bias) All outcomes	High risk	Open-label study design
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	No report of missing outcome data
Selective reporting (reporting bias)	Low risk	Study protocol is not available. Outcomes mentioned in the Methods section are reported in the Results section and are extractable
Other bias	Low risk	No imbalance in baseline characteristics

Riccioni 2003

Methods	Randomised, double-blind, parallel-group clinical trial
Participants	<p>RANDOMISED: 51</p> <ul style="list-style-type: none"> LTRA + ICS: 12 ICS alone (800 mcg): 14 ICS alone (1600 mcg): 13 <p>AGE in years: mean years $\pm$ SD:</p> <ul style="list-style-type: none"> LTRA + ICS: 26.41 $\pm$ 8.12 years ICS alone (800): 25.85 $\pm$ 10.46 years ICS alone (1600): 26.92 $\pm$ 10.52 years <p>GENDER (% male):</p> <ul style="list-style-type: none"> LTRA + ICS: 50% ICS alone (800): 57% ICS alone (1600): 62% <p>SEVERITY: mild persistent asthma</p> <p>ASTHMA DURATION mean years: 1 year</p>

Riccioni 2003 (Continued)

BASELINE FEV₁ (% pred) ±SD:

- LTRA + ICS: 97.58 ± 7.71
- ICS alone (800): 99.85 ± 12.92
- ICS alone (1600): 99.15 ± 11.57

MEAN (±SD) β₂-AGONIST USE (puffs/d): not reported

ATOPY (%): not reported

ELIGIBILITY CRITERIA:

- Non-smoking
- At least 1 year of mild-persistent asthma

EXCLUSION CRITERIA:

- Emergency treatment within 1 month for an asthma exacerbation
- Upper airway infection in past 3 weeks
- Hospitalisation for asthma in the 3 months before enrolment
- Treatment with antihistamines, anticholinergics, theophylline and chromones, β₂-long-acting, inhaled and oral corticosteroids
- Autoimmune, hepatic or renal disorders
- Malabsorption, drug or alcohol addiction
- Pregnancy or lactation

Interventions

PROTOCOL: LTRA + ICS vs same dose of ICS alone

RUN-IN: 2 weeks

INTERVENTION PERIOD: 12 weeks

TEST GROUP: montelukast 10 mg daily + budesonide 800 mcg daily

CONTROL GROUP 1: budesonide 800 mcg daily

CONTROL GROUP 2: budesonide 1600 mcg daily

DEVICE: not reported

COMPLIANCE: not reported

CO-TREATMENT: β₂-agonists as needed

WITHDRAWALS: not reported

Outcomes

INTENTION-TO-TREAT ANALYSIS: not reported

OUTCOMES:

PULMONARY FUNCTION TEST:

- Change in PEFr (% predicted)
- Change from baseline in FEV₁
- Change from baseline in PC₂₀

SYMPTOM SCORES: not reported

FUNCTIONAL STATUS: not reported

INFLAMMATORY MEDIATORS: not reported

ADVERSE EFFECTS: not reported

Riccioni 2003 (Continued)

WITHDRAWALS: not reported

Notes

Published full-text article

Funding: not reported

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Study was randomised and provided no further details regarding sequence generation
Allocation concealment (selection bias)	Unclear risk	Allocation concealment not reported
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	No mention of blinding and no statement that this was a double-blinded study. No further details on blinding
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No mention of blinding and no statement that this was a double-blinded study. No further details on blinding of outcome assessors
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	No report of missing outcome data
Selective reporting (reporting bias)	Low risk	Study protocol is not available. Outcomes mentioned in the Methods section are reported in the Results section and are extractable
Other bias	Low risk	No imbalance in baseline characteristics

Riccioni 2005

Methods	Randomised, single-blind, parallel-group clinical trial
Participants	<p>RANDOMISED: 40</p> <ul style="list-style-type: none"> LTRA + ICS: 20 ICS alone: 20 <p>AGE in years: mean years $\pm$ SD:</p> <ul style="list-style-type: none"> LTRA + ICS: 39.1 $\pm$ 14.5 ICS alone: 37.8 $\pm$ 13.2 <p>GENDER (% male):</p> <ul style="list-style-type: none"> LTRA + ICS: 45 ICS alone: 50 <p>SEVERITY: mild to moderate asthma</p> <p>ASTHMA DURATION mean years: not reported</p> <p>BASELINE FEV₁ (% pred) $\pm$SD:</p>

Riccioni 2005 (Continued)

- LTRA + ICS: 91.0 ± 14.1
- ICS alone: 90.7 ± 10.4

MEAN ($\pm$ SD) β_2 -AGONIST USE (puffs/d): not reported

ATOPY (%): not reported

ELIGIBILITY CRITERIA:

- Non-smoking individuals > 15 years of age
- Mild to moderate persistent bronchial asthma according to GINA guidelines
- FEV₁ between 60% and 85% of predicted value (according to NIH criteria)
- Clinical history of dyspnoea, wheezing, chest tightness or cough $\geq$ 4 months
- Reversible airway obstruction at the time of enrolment visit or during the 4 preceding months (increase in FEV₁ or PEFr > 12% after salbutamol administration)
- Stable therapy with inhaled BUD (400 μ g twice a day) and short-acting 2-agonist (SABA) as needed

EXCLUSION CRITERIA:

- Acute or chronic pulmonary disease documented in the medical history
- Hospitalised for asthma within 4 months before enrolment
- History of serious diseases such as cardiac arrhythmias, unstable diabetes, neoplasms, psychiatric illnesses
- Hepatic insufficiency, renal or gastrointestinal disease
- Upper respiratory infection in the past 3 weeks
- Received oral, IV or IM corticosteroids within 4 months before enrolment
- Received LABA, alone or in combination with corticosteroids

Interventions	<p>PROTOCOL: LTRA + ICS vs tapering dose of ICS alone</p> <p>RUN-IN: 4 weeks</p> <p>INTERVENTION PERIOD: 12 weeks</p> <p>TEST GROUP: montelukast 10 mg daily + budesonide 800 mcg daily (tapered to half at 4, 8 and 12 weeks)</p> <p>CONTROL GROUP: budesonide 800 mcg daily (tapered to half at 4, 8 and 12 weeks)</p> <p>DEVICE: not reported</p> <p>COMPLIANCE: not reported</p> <p>CO-TREATMENT: β_2-agonist as needed</p>
Outcomes	<p>INTENTION-TO-TREAT ANALYSIS: not reported</p> <p>OUTCOMES:</p> <p>PULMONARY FUNCTION TEST:</p> <ul style="list-style-type: none"> • Change in PEFr (% predicted) • Change from baseline in FEV₁ (% predicted) <p>SYMPTOM SCORES: not reported</p> <p>FUNCTIONAL STATUS:</p> <ul style="list-style-type: none"> • SABA use (%) • Asthma exacerbations <p>INFLAMMATORY MEDIATORS: not reported</p>

Riccioni 2005 (Continued)

ADVERSE EFFECTS: not reported
WITHDRAWALS: not reported

Notes

Full-text article (2005)

Funding: not reported

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Study was randomised and provided no further details regarding sequence generation
Allocation concealment (selection bias)	Unclear risk	Allocation concealment not reported
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Mentioned as a single-blinded study
Blinding of outcome assessment (detection bias) All outcomes	High risk	Mentioned as single-blinded study. No further details on blinding of outcome assessors
Incomplete outcome data (attrition bias) All outcomes	Low risk	All participants were included in the analysis. No reported missing data
Selective reporting (reporting bias)	Low risk	Study protocol is not available. Outcomes mentioned in the Methods section are reported in the Results section and are extractable
Other bias	Low risk	No imbalance in baseline characteristics

Ringdal 1999

Methods	Randomised, double-blind, double-dummy, parallel-group, multi-centre 3-arm study
Participants	<p>SYMPTOMATIC PARTICIPANTS</p> <p>RANDOMISED: 440</p> <ul style="list-style-type: none"> LTRA (lower dose) + ICS: 148 LTRA (higher dose) + ICS: 146 ICS alone: 146 <p>WITHDRAWALS:</p> <ul style="list-style-type: none"> LTRA + ICS: 10% (lower) and 12% (higher) ICS alone: 6% <p>AGE in years (mean $\pm$ SD): 12 to 70 years old</p> <ul style="list-style-type: none"> LTRA + ICS: 41.3 $\pm$ 14.36 years (lower) and 40.1 $\pm$ 13.46 years (higher) ICS alone: 42.2 $\pm$ 14.54 years <p>GENDER (% male): not reported</p>

Ringdal 1999 (Continued)

- LTRA + ICS: 49 (lower) and 48 (higher)
- ICS alone: 50

SEVERITY: mild to moderate asthma

BASELINE FEV₁ (% pred):

- LTRA + ICS: 84.1 ± 12.53 % (lower) and 85.0 ± 14.25 (higher)
- ICS alone: 85.1 ± 15.02

ALLERGEN TRIGGERS: not described

ASTHMA DURATION: not described

MEAN ICS DOSE AT ENTRY (mcg/d):

- LTRA + ICS: 432 ± 63 (lower) and 424 ± 63 (higher)
- ICS alone: 426 ± 54

ELIGIBILITY CRITERIA:

- Treated with BDP, BUD or FP and β₂-agonist prn
- FEV₁ ≥ 60 at screening
- ≥ 15% improvement in clinic FEV₁ or PEFR in response to dose ≤ 400 µg albuterol at screening
- Total asthma symptom score ≥ 10 (0 to 3 scale recorded daily) in last 7 days of screening period

Interventions	<p>PROTOCOL: LTRA + ICS vs HIGHER dose of ICS alone</p> <p>RUN-IN PERIOD: 2 week (fixed)</p> <ul style="list-style-type: none"> • Dose optimisation period: none <p>INTERVENTION PERIOD: 12 weeks</p> <p>TEST GROUP (lower dose): zafirlukast 20 mg bid + BDP 400 to 500 µg/d</p> <p>TEST GROUP (higher dose): zafirlukast 80 mg bid + BDP 400 to 500 µg/d</p> <p>CONTROL GROUP: BDP 800 to 1000 µg/d</p> <p>DEVICE: metered-dose aerosol inhaler</p> <p>CO-TREATMENT: none reported</p>
Outcomes	<p>PER PROTOCOL</p> <p>(PP) ANALYSES - some Intention-to-treat (ITT) analyses available</p> <ul style="list-style-type: none"> • Outcomes used at 6 and 12 weeks <p>PULMONARY FUNCTION TESTS:</p> <ul style="list-style-type: none"> • **Change in morning PEFR (L/min) • Change in evening PEFR <p>SYMPTOM SCORES:</p> <ul style="list-style-type: none"> • Change in mean symptom scores • Change in night-time awakenings per week <p>FUNCTIONAL STATUS:</p> <ul style="list-style-type: none"> • Change in mean daily use of β₂-agonists • St Georges' QOL questionnaire (ITT) <p>INFLAMMATORY MARKERS:</p> <ul style="list-style-type: none"> • Not reported

Ringdal 1999 (Continued)

ADVERSE EFFECTS:

- Elevated liver enzymes, headache, nausea, death

WITHDRAWALS:

- Reported

(** denotes primary outcomes)

Notes	<p>Abs (1999) and poster and unpublished report provided by AstraZeneca (Oct 2000) Funding: Astra Zeneca</p> <p>Confirmation of methods and data extraction graciously received from M. Christopher Miller and Ms. Susan Shaffer, AstraZeneca, Oct 2000</p> <p>User-defined order: 45 (mean intervention ICS dose of 450 mcg/d × 0.1)</p> <p>ALLOCATION</p> <ul style="list-style-type: none"> • Random • Computer-generated random numbers • Sealed envelopes containing allocation <p>BLINDING</p> <ul style="list-style-type: none"> • Double-blind • Double-dummy • Identical placebo <p>WITHDRAWAL/DROPOUT</p> <ul style="list-style-type: none"> • Described
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Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated randomisation
Allocation concealment (selection bias)	Low risk	Sealed envelopes containing allocation details were used
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Mentioned as double-blind, double-dummy study. Matching placebo used
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Double-blind study
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Details on drop-outs not reported
Selective reporting (reporting bias)	Unclear risk	Unable to assess owing to lack of details regarding selective reporting of outcomes

Ringdal 1999 (Continued)

Other bias	Unclear risk	Unable to assess bias owing to baseline imbalance
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Sano 2008

Methods	Randomised, single-blind, parallel-group clinical study
Participants	<p>RANDOMISED: 52</p> <ul style="list-style-type: none"> LTRA + ICS: 27 ICS alone: 25 <p>AGE in years: mean years $\pm$ SD: not reported</p> <p>GENDER (% male): not reported</p> <p>SEVERITY: mild to moderate asthma</p> <p>ASTHMA DURATION mean years: not reported</p> <p>BASELINE FEV₁ (% pred) $\pm$SD: not reported</p> <p>MEAN ($\pm$SD) β_2-AGONIST USE (puffs/d):</p> <p>ATOPY (%): not reported</p> <p>ELIGIBILITY CRITERIA: not reported</p>
Interventions	<p>PROTOCOL: LTRA + ICS vs same dose of ICS alone</p> <p>RUN-IN: 8 weeks</p> <p>Intervention period: 5-year trial</p> <p>TEST GROUP: pranlukast 450 mg daily + beclomethasone 800 mcg daily and low-dose theophylline</p> <p>CONTROL GROUP: beclomethasone 800 mcg daily and low-dose theophylline</p> <p>DEVICE: not reported</p> <p>COMPLIANCE: not reported</p> <p>CO-TREATMENT: not reported</p>
Outcomes	<p>INTENTION-TO-TREAT ANALYSIS: reported</p> <p>PULMONARY FUNCTION TEST:</p> <ul style="list-style-type: none"> Change in PEFR (% predicted) Change from baseline in FEV₁ (% predicted) <p>SYMPTOM SCORES: not reported</p> <p>FUNCTIONAL STATUS:</p> <ul style="list-style-type: none"> SABA use (%) Asthma exacerbations <p>INFLAMMATORY MEDIATORS: not reported</p> <p>ADVERSE EFFECTS: not reported</p> <p>WITHDRAWALS: not reported</p>

Sano 2008 (Continued)

Notes Conference Abstract for poster presentation

Funding: not reported

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Reported as randomised and provided no further details regarding sequence generation
Allocation concealment (selection bias)	Unclear risk	Allocation concealment not reported
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Reported as single-blind but provided no further details of blinding
Blinding of outcome assessment (detection bias) All outcomes	High risk	Blinding of outcome assessment not reported
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Details on drop-outs not reported
Selective reporting (reporting bias)	Unclear risk	Unable to assess owing to lack of details regarding selective reporting of outcomes
Other bias	Unclear risk	Unable to assess bias owing to baseline imbalances

SD-004-0216

Methods	Randomised, double-blind, placebo-controlled, parallel-group, multi-centre (49 centres in 6 countries) clinical study
Participants	<p>INADEQUATELY controlled participants taking ICS at baseline</p> <p>BASELINE INHALED STEROID DOSAGE: 400-1000 µg of ICS (not specified)/d</p> <p>RANDOMISED: 352</p> <ul style="list-style-type: none"> LTRA + ICS: 118 ICS alone: 116 <p>WITHDRAWALS: reported as number of participants who completed the study</p> <ul style="list-style-type: none"> LTRA + ICS: 19 (16.1%) ICS alone: 9 (7.8%) <p>AGE in years: mean</p> <ul style="list-style-type: none"> LTRA + ICS: 38.3 ICS alone: 38.1 <p>GENDER (% male):</p>

SD-004-0216 (Continued)

- LTRA + ICS: 46.6%
- ICS alone: 53.4%

SEVERITY: not reported

ASTHMA DURATION:

- LTRA + ICS: 10.1 years
- ICS alone: 10.6 years

BASELINE FEV₁ (% pred)

- LTRA + ICS: 72.03
- ICS alone: 72.12

MEAN ($\pm$ SD) β_2 -AGONIST USE (puffs/d): not reported

ATOPY (%): not reported

ELIGIBILITY CRITERIA:

- Male or female outpatient
- Age 12 to 70 years
- Treated $\geq$ 3 months before visit 1 with 400 to 1000 μ g of ICS
- Asthma diagnosis
- FEV₁ 50% to 80% of predicted normal
- Show reversibility in FEV₁ $\geq$ 12% and $\geq$ 200 mL after inhalation of 1 mg of terbutaline sulphate
- Smoking history $\leq$ 10 pack-years

In the 7 days before randomisation, $\geq$ 1 of the following:

- Symptom score $\geq$ 1 on 4 days
- Awakening $\geq$ 1 night due to asthma symptoms
- Use of β_2 -agonists $\geq$ 10 puffs as weekly mean

EXCLUSION CRITERIA:

- Respiratory infection
- Clinical obstructive pulmonary disease, or pulmonary dysfunction other than asthma
- Pregnant and lactating women
- Use of long-acting β_2 -agonist within 1 month before visit 1
- Previous use of an LTRA
- Known intolerance to study drugs or inhaled lactose

Interventions

PROTOCOL: LTRA + ICS vs same dose of ICS alone

RUN-IN: not reported

Intervention period: 8 weeks

TEST GROUP: zafirlukast 20 mg twice daily + budesonide 200 mcg twice daily

CONTROL GROUP: budesonide 200 mcg twice daily

DEVICE: Turbuhaler

COMPLIANCE: not reported

CO-TREATMENT: β -agonist as required

SD-004-0216 (Continued)

Outcomes	<p>Modified INTENTION-TO-TREAT ANALYSES (on all participants who received ≥ 1 dose of study medication)</p> <p>OUTCOMES: at endpoint or 8 weeks</p> <p>PULMONARY FUNCTION TESTS:</p> <ul style="list-style-type: none"> Change from baseline in AM PEF_R FEV₁ <p>FUNCTIONAL STATUS: not reported</p> <p>INFLAMMATORY MARKERS: not reported</p> <p>SYMPTOM SCORES</p> <ul style="list-style-type: none"> Asthma diary card data <p>EXACERBATIONS: asthma exacerbations reported</p> <p>ADVERSE EFFECTS: reported</p> <p>WITHDRAWALS: reported</p>
Notes	<p>Summary report from AstraZeneca 2000 (clinicaltrials.gov)</p> <p>Funding: AstraZeneca</p>

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Reported as randomised and provided no further details regarding sequence generation
Allocation concealment (selection bias)	Unclear risk	Allocation concealment not reported
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Reported as double-blinded study
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Double-blind study
Incomplete outcome data (attrition bias) All outcomes	Low risk	Drop-outs are reported at 10% to 30%. Reasons for drop-out not reported. Modified intention-to-treat analysis performed
Selective reporting (reporting bias)	Unclear risk	Unable to assess owing to lack of details regarding selective reporting of outcomes
Other bias	Low risk	No imbalance in baseline characteristics

Shah 2006

Methods	Randomised, double-blind, parallel-group clinical trial
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Shah 2006 (Continued)

Participants	<p>RANDOMISED: 90</p> <ul style="list-style-type: none"> LTRA + ICS: 30 ICS alone: 30 <p>AGE in years: mean years $\pm$ SD (range 18 to 79 years)</p> <ul style="list-style-type: none"> LTRA + ICS: 38.4 ± 11.2 ICS alone: 38.8 ± 12 <p>GENDER (% male):</p> <ul style="list-style-type: none"> LTRA + ICS: 80% ICS alone: 87% <p>SEVERITY: not reported</p> <p>ASTHMA DURATION mean years: not reported</p> <p>BASELINE FEV₁ (% pred) $\pm$SD: not reported</p> <p>MEAN ($\pm$SD) β_2-AGONIST USE (puffs/d):</p> <ul style="list-style-type: none"> LTRA + ICS: 2.7 ± 2.3 ICS alone: 2.8 ± 2.3 <p>ATOPY (%): not reported</p> <p>ELIGIBILITY CRITERIA:</p> <ul style="list-style-type: none"> Age 18 to 60 years Cardinal features of asthma, including paroxysmal wheeze, cough and episodic breathlessness Use of inhaled β_2-agonist and ICS equivalent to or greater than budesonide at daily dose of 400 g/d Reversible airway obstruction with baseline FEV₁ 50% of predicted with a minimum improvement in FEV₁ of 15% after 2 agonist use <p>EXCLUSION CRITERIA:</p> <ul style="list-style-type: none"> Patients with respiratory conditions other than asthma Tobacco smokers Acute exacerbation during run-in period Receiving systemic corticosteroid treatment within 1 month of run-in period Receiving a long-acting antihistamine within 1 week (astemizole within 3 months) of run-in period Receiving long-acting 2-agonist within last 24 hours of the run-in period
Interventions	<p>PROTOCOL: LTRA + ICS vs HIGHER dose of ICS alone</p> <p>RUN-IN: 2 weeks</p> <p>INTERVENTION PERIOD: 8 weeks</p> <p>TEST GROUP: montelukast 10 mg once daily p.o. + budesonide 200 μg twice daily</p> <p>CONTROL GROUP: placebo + budesonide 400 μg twice daily</p> <p>DEVICE: spacer device</p> <p>COMPLIANCE: not reported</p> <p>CO-TREATMENT: β_2-agonists if previously in use</p>

Shah 2006 (Continued)

Outcomes	<p>INTENTION-TO-TREAT ANALYSIS: reported</p> <p>PULMONARY FUNCTION TESTS:</p> <ul style="list-style-type: none"> • Change in morning PEFR • Change in morning FEV₁ <p>FUNCTIONAL STATUS:</p> <ul style="list-style-type: none"> • Change in mean daily use of β_2-agonists • Median nocturnal awakening (% of days) <p>INFLAMMATORY MARKERS: not reported</p> <p>EXACERBATIONS: asthma exacerbations reported</p> <p>ADVERSE EFFECTS: reported (headache, abdominal pain)</p> <p>WITHDRAWALS: reported</p>
Notes	<p>Full-text article (2006)</p> <p>Funding: not reported</p>

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Study was randomised with computerised sequence generation
Allocation concealment (selection bias)	Unclear risk	Allocation concealment not reported
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Mentioned as a double-blinded study
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Double-blinded study. Study reports ensuring blinding of both clinicians and participants
Incomplete outcome data (attrition bias) All outcomes	Low risk	All participants were included in the analysis. No missing data were reported
Selective reporting (reporting bias)	Low risk	Study protocol is not available. Outcomes mentioned in the Methods section are reported in the Results section and are extractable
Other bias	Low risk	No imbalance in baseline characteristics

Shingo 2002

Methods	Randomised, double-blind, placebo-controlled, parallel-group, multi-centre clinical study
Participants	<p>WELL-CONTROLLED PARTICIPANTS</p> <p>RANDOMISED: 22</p>

Shingo 2002 (Continued)

- LTRA + ICS: 10
- ICS alone: 12

AGE in years: mean years $\pm$ SD: not reported

GENDER (% male):

- LTRA + ICS: 60
- ICS alone: 25

SEVERITY: moderate to severe asthma

ASTHMA DURATION mean years: not reported

BASELINE FEV₁ (% pred) $\pm$ SD: not reported

MEAN ($\pm$ SD) β_2 -AGONIST USE (puffs/d): not reported

ATOPY (%): not reported

ELIGIBILITY CRITERIA:

- Non-smoking patients
- Age 15 to 70 years
- Stable asthma
- Pre- β -agonist FEV₁ $\geq$ 75% of predicted
- Improvement in FEV₁ $\geq$ 15% of baseline 20 to 30 minutes after inhaled β_2 -agonist
- Daytime symptom score $\leq$ 7 averaged over run-in period
- Treatment with stable doses of inhaled glucocorticoids for $\geq$ 21 days, namely, BDP (600 to 1600 μ g/d), flunisolide (1000 to 2000 μ g/d) or triamcinolone (1200 to 3200 μ g/d)

EXCLUSION CRITERIA: not reported

Interventions	<p>PROTOCOL: LTRA + ICS vs SAME dose of ICS alone (TAPERING ICS dose)</p> <p>RUN-IN: 7 to 10 days</p> <p>INTERVENTION PERIOD: 8 weeks (ICS dose tapered every 2 weeks)</p> <p>BASELINE DOSE OF ICS: beclomethasone (600 to 1600 μg/d), flunisolide (1000 to 2000 μg/d) or triamcinolone (1200 to 3200 μg/d)</p> <p>LTRA + ICS: montelukast 10 mg daily + beclomethasone (600 to 1600 μg/d), flunisolide (1000 to 2000 μg/d) or triamcinolone (1200 to 3200 μg/d)</p> <p>ICS alone: placebo + beclomethasone (600 to 1600 μg/d), flunisolide (1000 to 2000 μg/d) or triamcinolone (1200 to 3200 μg/d)</p> <p>DEVICE: not specified or flow meters</p> <p>COMPLIANCE: not reported</p> <p>CO-TREATMENT: β_2-agonist as needed</p>
Outcomes	<p>INTENTION-TO-TREAT ANALYSIS: not reported</p> <ul style="list-style-type: none"> • Last tolerated ICS dose as per cent decrease from baseline • Number of tapers to reach minimal effective corticosteroid dose • Number of dose increases required to stabilise participants after worsening • Number of participants discontinued owing to instability <p>PULMONARY FUNCTION TESTS (measured but not reported):</p>

Shingo 2002 (Continued)

- FEV₁
- Change in morning and evening PEFR (L/min)

FUNCTIONAL STATUS (measured but not reported):

- Use of rescue β_2 -agonist (puffs/d)
- Change in daytime symptom score (0 to 6)

ICS DOSE REDUCTION:

- Number of participants tapered off ICS (mcg)

INFLAMMATORY MEDIATORS: not reported

ADVERSE EFFECTS: not reported

WITHDRAWALS: not reported

Notes
Full-text article (2002)
Funding: Merck Research Laboratories

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Study was randomised and provided no further details regarding sequence generation
Allocation concealment (selection bias)	Unclear risk	Allocation concealment not reported
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Mentioned as a double-blinded study.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Double-blinded study
Incomplete outcome data (attrition bias) All outcomes	Low risk	All participants were included in the analysis. No missing data reported
Selective reporting (reporting bias)	Low risk	Study protocol is not available. Outcomes mentioned in the Methods section are reported in the Results section and are extractable
Other bias	Low risk	No imbalance in baseline characteristics

Storms 2004

Methods	Randomised, double-blind, parallel-group, placebo-controlled, multi-centre clinical study
Participants	RANDOMISED: 122 <ul style="list-style-type: none"> • LTRA + ICS: 39 • ICS alone: 44 <p>WITHDRAWALS:</p>

Storms 2004 (Continued)

- LTRA + ICS: 2%
- ICS alone: 8%

AGE in years: mean years $\pm$ SEM

- LTRA + ICS: 33.3
- ICS alone: 30.6

GENDER (% male):

- LTRA + ICS: 28.2
- ICS alone: 45.5

SEVERITY: moderate

ASTHMA DURATION: ≥ 1 year

BASELINE FEV₁ (% pred) $\pm$ SEM

- LTRA + ICS: 87.5 $\pm$ 10.4
- ICS alone: 87.8 $\pm$ 10.6

MEAN ($\pm$ SD) β_2 -AGONIST USE (puffs/d): not reported

- LTRA + ICS: 2.9 $\pm$ 1.5
- ICS alone: 3.1 $\pm$ 2.2

ATOPY (%): not reported

ELIGIBILITY CRITERIA:

- 15 and 45 years old with current ≥ 1 -year history of asthma
- Uncontrolled on ICS ≥ 2 months
- Documentation of EIB within past year showing a decrease in FEV₁ $\geq 15\%$ while receiving ICS (or 20% when not on ICS)
- FEV₁ $\geq 70\%$ of predicted value at rest
- $\geq 12\%$ increase in FEV₁ after β_2 -agonist administration

EXCLUSION CRITERIA:

- Upper respiratory infection (within 3 weeks)
- Emergency care or hospitalisation for asthma within past 3 months
- Systemic corticosteroids not allowed for 1 month before first study visit and throughout the study
- Intake of other antiasthma therapy 2 weeks before first study visit (with the exception of ICS)

Interventions

PROTOCOL: LTRA + ICS vs SAME dose of ICS alone

RUN-IN: 2 weeks

INTERVENTION PERIOD: 4 weeks

TEST GROUP: montelukast 10 mg daily + fluticasone 100 μ g twice daily

CONTROL GROUP: placebo + fluticasone 100 μ g twice daily

DEVICE: inhaler

COMPLIANCE: not reported

CO-TREATMENT: β_2 -agonist as needed

Outcomes

INTENTION-TO-TREAT ANALYSIS: reported

Storms 2004 (Continued)

PULMONARY FUNCTION TESTS:

- Pre-exercise FEV₁ (% predicted)
- Maximum % fall from pre-exercise FEV₁

FUNCTIONAL STATUS: not reported

INFLAMMATORY MARKERS: not reported

ADVERSE EFFECTS: not reported

WITHDRAWALS: reported

Notes	Full-text article 2004
	Funding: Merck and Co Inc

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Study was randomised with computer-generated allocation schedule
Allocation concealment (selection bias)	Unclear risk	Allocation concealment not reported
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Mentioned as a double-blinded study. Matching placebo used for blinding
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Double-blinded study
Incomplete outcome data (attrition bias) All outcomes	Low risk	Missing outcome data < 10%. Reasons for missing data reported and balanced
Selective reporting (reporting bias)	Low risk	Study protocol is not available. Outcomes mentioned in the Methods section are reported in the Results section and are extractable
Other bias	Low risk	No imbalance in baseline characteristics

Tognella 2004

Methods	Randomised, double-dummy, double-blind clinical study
Participants	RANDOMISED: 18 <ul style="list-style-type: none"> • LTRA + ICS: 9 • ICS alone: 9 SEVERITY: mild persistent asthma
Interventions	PROTOCOL: LTRA + ICS vs SAME dose of ICS alone INTERVENTION PERIOD: 6 weeks

Tognella 2004 (Continued)

TEST GROUP: montelukast 10 mg once daily p.o. + fluticasone 250 µg daily

CONTROL GROUP: fluticasone 250 µg daily

Outcomes	OUTCOMES: reported at 6 weeks <ul style="list-style-type: none"> FEV₁ (% predicted) before and after 6 weeks values provided Urinary LTE4
Notes	Conference abstract (2004) Funding: not reported

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Reported as randomised and provided no further details regarding sequence generation
Allocation concealment (selection bias)	Unclear risk	Allocation concealment not reported
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Reported as double-blinded study
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Double-blinded study
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Details on drop-outs not reported
Selective reporting (reporting bias)	Low risk	Study protocol is not available. Outcomes mentioned in the Methods section are reported in the Results section and are extractable
Other bias	Unclear risk	Unable to assess bias owing to baseline imbalance

Tohda 2002

Methods	Randomised, parallel-group, double-blind, placebo-controlled, multi-centre (16 study sites) clinical study
Participants	WELL-CONTROLLED PARTICIPANTS RANDOMISED: 191 <ul style="list-style-type: none"> LTRA + ICS: 93 ICS alone: 98 WITHDRAWALS, %: <ul style="list-style-type: none"> LTRA + ICS: 15 ICS alone: 20

Tohda 2002 (Continued)

AGE in years: mean years $\pm$ SD

Participants < 39 years of age

- LTRA + ICS: 24 ± 28.6
- ICS alone: 12 ± 14.3

Participants 40 to 59 years of age

- LTRA + ICS: 32 ± 38.1
- ICS alone: 35 ± 41.7

Participants ≥ 60 years of age

- LTRA + ICS: 28 ± 33.3
- ICS alone: 37 ± 44

GENDER (% male):

- LTRA + ICS: 58.3
- ICS alone: 58.3

SEVERITY: moderate to severe bronchial asthma

ASTHMA DURATION mean years:

- LTRA + ICS: < 10 years = 57 (67.9); > 10 years = 27 (32.1)
- ICS alone: < 10 years = 56 (66.7); > 10 years = 28 (33.3)

BASELINE FEV₁ (% pred) $\pm$ SEM

- LTRA + ICS: 87.4 ± 18.4
- ICS alone: 85.6 ± 24.8

MEAN ($\pm$ SD) β_2 -AGONIST USE (puffs/d): not reported

ATOPY (%):

- LTRA + ICS: 36.9
- ICS alone: 35.7

ELIGIBILITY CRITERIA:

- Taking a dose of ICS 800 to 1600 μ g/d
- PEF $\geq 80\%$ of patient's best or predicted
- Diurnal variation PEF no greater than 20%
- Asthma symptom score no greater than 5 points/wk

EXCLUSION CRITERIA:

- Use of following medication 1 month before run-in period
- Antiallergic drugs (disodium cromoglycate, ketotifen or pranlukast)
- Oral corticosteroids at start of the run-in period
- Long-acting corticosteroids (methylprednisone acetate or triamcinolone acetonide)

Interventions

PROTOCOL: LTRA + ICS vs SAME dose of ICS alone (TAPERING ICS dose)

RUN-IN: 4 weeks

INTERVENTION PERIOD: 24 weeks

TEST GROUP: montelukast 10 mg film-coated tablet once daily p.o. + beclomethasone dipropionate 800 to 1600 μ g daily

Tohda 2002 (Continued)

CONTROL GROUP: placebo + beclomethasone dipropionate 800 to 1600 µg daily

DEVICE: not reported

COMPLIANCE: not reported

CO-TREATMENT: β_2 -agonist use as needed

CRITERIA FOR WITHDRAWAL FROM STUDY: not reported

CRITERIA FOR TAPERING:

- Mean PEFR observed during previous 2 weeks in not less than 90% of value in run-in
- Weekly mean symptom score during previous 2 weeks is not 3 points or more higher than score at run-in period
- Mean inhaled β -agonist use during previous 2 weeks is less than twice use at run-in period

CRITERIA FOR MAINTAINING ICS DOSE:

- 2 out of 3 criteria for dose tapering mentioned above

CRITERIA FOR INCREASING ICS DOSE:

- 1 or none of the criteria for dose tapering mentioned above

MINIMAL DOSE OF ICS ALLOWED:

- No minimal dose required

Outcomes

INTENTION-TO-TREAT ANALYSIS: reported

OUTCOMES: reported at 4, 8, 16 and 24 weeks

PULMONARY FUNCTION TESTS:

- % change in morning and evening PEFR
- % change in FVC
- % change in FEV₁
- FEV₁/FVC ratio

SYMPTOM SCORES:

- % change in breathlessness and wheezing (range 0 to 9)
- % change in therapy score (range not reported, based on Japanese Society of Allergology)
- % change in asthmatic score (calculated by combining symptom score with therapy score)

FUNCTIONAL STATUS: not reported

FUNCTIONAL STATUS

- Pre-treatment and post-treatment β_2 -agonist use/wk

INFLAMMATORY MARKERS: not reported

ADVERSE EFFECTS: reported

- Alopecia areata, headache, bitter taste, stomachache, heartburn and asthma in the montelukast group and toxicoderma, papules, headache, diarrhoea, constipation, retching, palpitations and nocturia in the placebo group

WITHDRAWALS: reported

Notes

Full text (2002)

Tohda 2002 (Continued)

Funding: Banyu Pharmaceutical Co Limited (makers of montelukast)

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Study was randomised and provided no further details regarding sequence generation
Allocation concealment (selection bias)	Unclear risk	Allocation concealment not reported
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Mentioned as a double-blinded study.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Double-blinded study
Incomplete outcome data (attrition bias) All outcomes	Low risk	Missing outcome data < 10%. Reasons for missing data reported
Selective reporting (reporting bias)	Low risk	Study protocol is not available. Outcomes mentioned in the Methods section are reported in the Results section and are extractable
Other bias	Low risk	No imbalance in baseline characteristics

Tomari 2001

Methods	Randomised, parallel-group clinical study
Participants	<p>SYMPTOMATIC PARTICIPANTS</p> <p>RANDOMISED: 41</p> <ul style="list-style-type: none"> LTRA + ICS: 21 ICS alone: 20 <p>WITHDRAWALS, %: none</p> <p>AGE in years: mean $\pm$ SEM</p> <ul style="list-style-type: none"> LTRA + ICS: 53.7 $\pm$ 3.1 ICS alone: 56.1 $\pm$ 3.2 <p>GENDER (% male):</p> <ul style="list-style-type: none"> LTRA + ICS: 38 ICS alone: 45 <p>SEVERITY: moderate asthma</p> <p>ASTHMA DURATION mean years: not reported</p> <p>BASELINE FEV₁ (% pred) $\pm$SEM: not reported</p>

Tomari 2001 (Continued)

	<p>MEAN ($\pm$SD) β_2-AGONIST USE (puffs/d): not reported</p> <p>ATOPY (%): not reported</p> <p>ELIGIBILITY CRITERIA:</p> <ul style="list-style-type: none"> • Diagnosis of asthma • Treated with 800 μg/d of BDP • PEFR < 80% of predicted <p>EXCLUSION CRITERIA:</p> <ul style="list-style-type: none"> • Pulmonary or bronchial disease for 2 weeks before study
Interventions	<p>PROTOCOL: LTRA + ICS vs HIGHER dose of ICS alone</p> <p>RUN-IN: 2 weeks</p> <p>INTERVENTION PERIOD: 16 weeks</p> <p>TEST GROUP: pranlukast 450 mg once daily p.o. + beclomethasone dipropionate 800 μg daily</p> <p>CONTROL GROUP: beclomethasone dipropionate 1600 μg daily</p> <p>DEVICE: not reported</p> <p>COMPLIANCE: not reported</p> <p>CO-TREATMENT: theophylline and β_2-agonists if previously in use</p>
Outcomes	<p>INTENTION-TO-TREAT ANALYSES</p> <p>OUTCOMES: reported at 16 weeks</p> <p>PULMONARY TESTS</p> <ul style="list-style-type: none"> • Pre- and post-treatment AM PEFR (%) • Pre- and post-treatment daily variability of PEFR (%) <p>SYMPTOM SCORES</p> <ul style="list-style-type: none"> • Pre- and post-treatment symptom score <p>(sum of 7 symptoms scored from 0 to 3)</p> <p>FUNCTIONAL STATUS</p> <ul style="list-style-type: none"> • Pre- and post-treatment β_2-agonist use/wk <p>INFLAMMATORY MARKERS: not reported</p> <p>ADVERSE EFFECTS: reported</p> <p>WITHDRAWALS: no withdrawals</p>
Notes	<p>Full text 2001</p> <p>Funding: not specified</p>

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Study participants were divided at random and study provided no further details on randomisation or regarding sequence generation

Tomari 2001 (Continued)

Allocation concealment (selection bias)	Unclear risk	Allocation concealment not reported
Blinding of participants and personnel (performance bias) All outcomes	High risk	This is not a double-blinded study
Blinding of outcome assessment (detection bias) All outcomes	High risk	Not a blinded study
Incomplete outcome data (attrition bias) All outcomes	Low risk	No missing outcome data in this study
Selective reporting (reporting bias)	Low risk	Study protocol is not available. Outcomes mentioned in the Methods section are reported in the Results section and are extractable
Other bias	Low risk	No imbalance in baseline characteristics

Ulrik 2010

Methods	Randomised, double-blind, placebo-controlled, parallel-group clinical study
Participants	<p>WELL-CONTROLLED PARTICIPANTS</p> <p>RANDOMISED: 31</p> <ul style="list-style-type: none"> LTRA + ICS: 16 ICS alone: 15 <p>WITHDRAWALS, %: not reported</p> <p>AGE in years: mean years $\pm$ SD (range 18 to 79 years)</p> <ul style="list-style-type: none"> LTRA + ICS: 39 $\pm$ 9 ICS alone: 36 $\pm$ 9 <p>GENDER (% male):</p> <ul style="list-style-type: none"> LTRA + ICS: 50 ICS alone: 40 <p>SEVERITY: mild to moderate asthma</p> <p>ASTHMA DURATION mean years: not reported</p> <p>BASELINE FEV₁ (% pred) $\pm$SD</p> <ul style="list-style-type: none"> LTRA + ICS: 83 $\pm$ 8 ICS alone: 86 $\pm$ 9 <p>MEAN ($\pm$SD) β_2-AGONIST USE (puffs/d): not reported</p> <p>ATOPY (%): not reported</p> <p>ELIGIBILITY CRITERIA</p>

Ulrik 2010 (Continued)

- Males and non-pregnant females aged 18 to 50 years with stable mild to moderate persistent asthma [pre-bronchodilator forced expiratory volume in 1 s (FEV₁) > 70% pred, PD₂₀ < 3.9 mmol methacholine] were eligible provided they were treated with ICS (daily ICS dose similar to ≤ 1000 mg BPD; stable dose ≥ 12 weeks) and short-acting β₂-agonist prn
- Dose–response plateau to inhaled methacholine on 2 pre-study occasions
- In case of seasonal allergy, study was conducted outside the relevant season
- If presenting with recent respiratory tract infection, study enrolment was postponed ≥ 6 weeks

EXCLUSION CRITERIA:

- Current smoking (never smokers or quit smoking × 12 months)
- Cardiovascular disease
- History of malignant disease within preceding 5 years and/or concomitant pulmonary disease

Interventions	<p>PROTOCOL: LTRA + ICS vs SAME dose of ICS alone</p> <p>RUN-IN: 2 weeks</p> <p>INTERVENTION PERIOD: 12 weeks</p> <p>TEST GROUP: 10 mg montelukast once daily + ICS 200 to 1000 µg/d</p> <p>CONTROL GROUP: placebo once daily + ICS 200 to 1000 µg/d</p> <p>DEVICE: not reported</p> <p>COMPLIANCE: not reported</p> <p>CO-TREATMENT: none reported</p>
Outcomes	<p>INTENTION-TO-TREAT ANALYSIS: not reported</p> <p>OUTCOMES: reported at 12 weeks</p> <p>PULMONARY FUNCTION TESTS:</p> <p>Change from baseline levels not reported</p> <p>SYMPTOM SCORE: not reported</p> <p>FUNCTIONAL STATUS: not reported</p> <p>INFLAMMATORY MARKERS: none documented</p> <p>ADVERSE EFFECTS: reported</p> <p>WITHDRAWALS: not reported</p>
Notes	<p>Full text (2010)</p> <p>Funding: in part by MSD, Denmark</p>

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Study was randomised and provided no further details regarding sequence generation
Allocation concealment (selection bias)	Unclear risk	Allocation concealment not reported
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Mentioned as a double-blinded study. Matching placebo given

Ulrik 2010 (Continued)

Blinding of outcome assessment (detection bias) All outcomes	Low risk	Double-blinded study
Incomplete outcome data (attrition bias) All outcomes	Low risk	All participants completed the study
Selective reporting (reporting bias)	Low risk	Study protocol is not available. Outcomes mentioned in the Methods section are reported in the Results section and are extractable
Other bias	Low risk	No imbalance in baseline characteristics

Vaquerizo 2003

Methods	Randomised, placebo-controlled, double-blind, parallel-group, multi-centre (80) clinical study
Participants	<p>WELL-CONTROLLED PARTICIPANTS</p> <p>RANDOMISED: 639</p> <ul style="list-style-type: none"> LTRA + ICS: 326 ICS alone: 313 <p>WITHDRAWALS, %:</p> <ul style="list-style-type: none"> LTRA + ICS: 10% ICS alone: 10% <p>AGE in years: mean years $\pm$ SD (range 18 to 79 years)</p> <ul style="list-style-type: none"> LTRA + ICS: 42 ± 15 ICS alone: 44 ± 16 <p>GENDER (% male):</p> <ul style="list-style-type: none"> LTRA + ICS: 62% ICS alone: 61% <p>SEVERITY: mild to moderate asthma</p> <p>ASTHMA DURATION mean years: not reported</p> <p>BASELINE FEV₁ (% pred) $\pm$SD</p> <ul style="list-style-type: none"> LTRA + ICS: 81 ± 19 ICS alone: 81 ± 21 <p>MEAN ($\pm$SD) β_2-AGONIST USE (puffs/d):</p> <ul style="list-style-type: none"> LTRA + ICS: 3.2 ± 2.5 ICS alone: 3.3 ± 2.3 <p>BASELINE DOSE OF ICS: not reported</p> <p>ATOPY (%): not reported</p> <p>ELIGIBILITY CRITERIA</p> <ul style="list-style-type: none"> Non-smokers

Vaquerizo 2003 (Continued)

- Aged 18 to 70 (*age of participants outside of range*)
- Treated with 400 to 1600 µg/d BUD ≥ 8 weeks
- FEV₁ ≥ 55% of predicted
- Reversible airway obstruction (increase ≥ 12% of baseline FEV₁)
- Minimum total daytime asthma symptom score of 64 during 2-week run-in period
- Using a mean of ≥ 1 puff/d of β₂-agonist during run-in period
- Negative pregnancy test (urine B-human chorionic gonadotropin)
- Use of contraceptive 2 weeks before treatment and 2 weeks after study

EXCLUSION CRITERIA: not reported

Interventions

PROTOCOL: LTRA + ICS vs SAME dose of ICS alone

RUN-IN: 2 weeks

INTERVENTION PERIOD: 16 weeks

TEST GROUP: montelukast 10 mg once daily p.o. + budesonide 400 to 1600 µg/d

CONTROL GROUP: placebo once daily p.o. + budesonide 400 to 1600 µg/d

DEVICE: Turbuhaler

COMPLIANCE: not reported

CO-TREATMENT: none reported (use of β₂-agonist as needed)

Outcomes

INTENTION-TO-TREAT ANALYSIS

OUTCOMES: reported at 16 weeks

PULMONARY FUNCTION TESTS

- % change from baseline in FEV₁ % of predicted
- % change from baseline in morning PEFR (L/min)

SYMPTOM SCORE

- % change from baseline in daily daytime symptom score

FUNCTIONAL STATUS

- % change from baseline in mean daily use of β₂-agonist (puffs/d)
- Change from baseline in asthma-specific quality of life

INFLAMMATORY MARKERS: none documented

ADVERSE EFFECTS

- Influenza, headache, URI, worsening asthma, epigastric pain, urinary tract infections, rhinitis, pharyngitis, bronchitis

WITHDRAWALS: reported

Notes

Full text (2003)

Funding: Merck Sharpe and Dohme, Spain

Risk of bias
Bias
Authors' judgement
Support for judgement

Vaquerizo 2003 (Continued)

Random sequence generation (selection bias)	Low risk	Study was randomised with computerised sequence generation
Allocation concealment (selection bias)	Unclear risk	Allocation concealment not reported
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Mentioned as a double-blinded study. Participants, investigators, clinical monitors and data co-ordinators were reported as blinded
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Mentioned as double-blinded. Participants, investigators, clinical monitors and data co-ordinators were reported as blinded
Incomplete outcome data (attrition bias) All outcomes	Low risk	Missing outcome data < 10%. Reasons for missing data reported
Selective reporting (reporting bias)	Low risk	Study protocol is not available. Outcomes mentioned in the Methods section are reported in the Results section and are extractable
Other bias	Low risk	No imbalance in baseline characteristics

Virchow 2000

Methods	Randomised, parallel-group, double-blind, double-dummy, multi-centre (82 centres) clinical study
Participants	<p>SYMPTOMATIC PARTICIPANTS RANDOMISED: 368</p> <ul style="list-style-type: none"> LTRA + ICS: 180 ICS alone: 188 <p>WITHDRAWALS:</p> <ul style="list-style-type: none"> LTRA + ICS: 7.7% ICS alone: 9.5% <p>AGE in years: mean $\pm$ SD</p> <ul style="list-style-type: none"> ICS alone: 49.2 $\pm$ 12.9 LTRA + ICS: 47.4 $\pm$ 12.6 <p>GENDER (% male):</p> <ul style="list-style-type: none"> LTRA + ICS: 53 ICS alone: 48 <p>SEVERITY: not reported</p> <p>ASTHMA DURATION mean years: not reported</p> <p>BASELINE FEV₁ $\pm$ SD (% pred):</p> <ul style="list-style-type: none"> ICS alone: 64.3 $\pm$ 7.5 LTRA + ICS: 63.5 $\pm$ 8.0

Virchow 2000 (Continued)

MEAN ($\pm$ SD) β_2 -AGONIST USE (puffs/d):

- ICS alone: 5.3 ± 0.4
- LTRA + ICS: 6.1 ± 0.4

ATOPY (%): not reported

ELIGIBILITY CRITERIA

- 50% to 75% FEV₁ pred
- ICS dose ≥ 1200 μ g/d beclomethasone-equivalent
- Mean FEV₁/PEFR reversibility $\geq 15\%$ after inhalation of < 400 mcg albuterol
- Symptomatic asthma
- No smoking in preceding 6 months

Interventions	<p>PROTOCOL: LTRA + ICS vs SAME dose of ICS alone</p> <p>Run-in period: 2 weeks INTERVENTION PERIOD: 6 weeks</p> <p>TEST GROUP: zafirlukast 80 mg twice daily + beclomethasone 1000 to 4000 μg/d</p> <p>CONTROL GROUP: placebo + beclomethasone 1000 to 4000 μg/d</p> <p>DEVICE: not reported</p> <p>COMPLIANCE:</p> <ul style="list-style-type: none"> • ICS alone: 94% • LTRA + ICS: 95% <p>CO-TREATMENT: none reported</p>
Outcomes	<p>INTENTION-TO-TREAT ANALYSIS (some per-protocol (PP) analyses)</p> <p>Outcomes reported at 6 weeks</p> <p>PULMONARY FUNCTION TESTS - ITT</p> <p>**Change from baseline morning PEFR</p> <p>**Change from baseline evening PEFR</p> <p>FUNCTIONAL STATUS - ITT</p> <p>Change from baseline in mean symptom scores</p> <ul style="list-style-type: none"> • Change from baseline in mean daily use of rescue β_2-agonist (puffs/d) • Change from baseline in nocturnal awakening per week <p>INFLAMMATORY MARKERS: not reported</p> <p>ADVERSE EFFECTS: reported</p> <ul style="list-style-type: none"> • Elevated liver enzymes, headache, nausea, death, worsening asthma, rhinitis, etc. <p>WITHDRAWALS: reported (** denotes primary outcomes)</p>
Notes	<p>Full text (2000)</p> <p>Funding: AstraZeneca Pharmaceuticals, UK</p>

Risk of bias

Virchow 2000 (Continued)

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Study was randomised and provided no further details regarding sequence generation
Allocation concealment (selection bias)	Unclear risk	Allocation concealment not reported
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Mentioned as a double-blinded study
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Double-blinded study
Incomplete outcome data (attrition bias) All outcomes	Low risk	Missing outcome data < 10%. Reasons for missing data reported
Selective reporting (reporting bias)	Low risk	Study protocol is not available. Outcomes mentioned in the Methods section are reported in the Results section and are extractable
Other bias	Low risk	No imbalance in baseline characteristics

Xiang 2001

Methods	Randomised clinical study
Participants	<p>RANDOMISED: 52</p> <ul style="list-style-type: none"> LTRA + ICS: 25 ICS alone: 27 <p>AGE in years: mean $\pm$ SD:</p> <ul style="list-style-type: none"> ICS alone: 35 $\pm$ 8 LTRA + ICS: 33 $\pm$ 5 <p>GENDER (% male):</p> <ul style="list-style-type: none"> LTRA + ICS: 48 ICS alone: 56 <p>SEVERITY: mild to moderate asthma</p> <p>ASTHMA DURATION mean years: not reported</p> <p>BASELINE FEV₁ $\pm$ SD (% pred): not reported</p> <p>MEAN ($\pm$SD) β_2-AGONIST USE (puffs/d): not reported</p> <p>ATOPY (%): not reported</p> <p>ELIGIBILITY CRITERIA: not reported</p>
Interventions	PROTOCOL: LTRA + ICS vs HIGHER dose of ICS alone

Xiang 2001 (Continued)

RUN-IN: not reported

INTERVENTION PERIOD: 4 weeks

TEST GROUP: zafirlukast 20 mg twice daily + inhaled half quantity of the Budelade of Global Initiative for Asthma (GINA) standard quantity

CONTROL GROUP: inhaled standard quantity of Budelade of Global Initiative for Asthma (GINA)

DEVICE: not reported

COMPLIANCE: not reported

CO-TREATMENT: aminophylline 0.2 g twice daily (use of β_2 -agonist as needed)

Outcomes	<p>INTENTION-TO-TREAT ANALYSIS: not reported</p> <p>PULMONARY FUNCTION TESTS:</p> <ul style="list-style-type: none"> • Delta PEFR % • Morning and evening PEFR <p>FUNCTIONAL STATUS</p> <ul style="list-style-type: none"> • Quality of life scores <p>INFLAMMATORY MARKERS: not reported</p> <p>ADVERSE EFFECTS: not reported</p> <p>WITHDRAWALS: not reported</p>
Notes	<p>Full-text article (2001)</p> <p>Funding: not reported</p>

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Reported as randomised and provided no further details regarding sequence generation
Allocation concealment (selection bias)	Unclear risk	Allocation concealment not reported
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Blinding and methods of blinding not reported
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Blinding of outcome assessment not reported
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Details on drop-outs not reported
Selective reporting (reporting bias)	Unclear risk	Unable to assess owing to lack of details regarding selective reporting of outcomes

Xiang 2001 (Continued)

Other bias	Unclear risk	Unable to assess bias owing to baseline imbalance
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Ye 2015

Methods	Randomised, open-label, parallel-designed trial
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Participants

RANDOMISED: 140

- LTRA + ICS: 70
- ICS alone: 70

WITHDRAWALS: 12

- LTRA + ICS: 5
- ICS alone: 7

AGE in years: mean $\pm$ SD

- LTRA + ICS: 68.2. $\pm$ 5.5
- ICS alone: 67.3 $\pm$ 5.1

GENDER (% male):

- LTRA + ICS: 44
- ICS alone: 46

SEVERITY: well-controlled asthma

ASTHMA DURATION: longer than 6 months

BASELINE FEV₁ (% pred) $\pm$ SEM:

- LTRA + ICS: 95.5 $\pm$ 26.5
- ICS alone: 95.7 $\pm$ 21.3

MEAN ($\pm$ SD) β_2 -AGONIST USE (puffs/d): not reported

BASELINE DOSE OF ICS: budesonide 400 μ g/d or equivalent

ATOPY (%): not reported

ELIGIBILITY CRITERIA

Participants ranged in age from 60 to 75 years and had been diagnosed with asthma more than 6 months before enrolment in the study on the basis of clinical symptoms (such as cough, wheezing, breathlessness, chest tightness and dyspnoea), airway reversibility (defined by an increase in forced expiratory volume in one second (FEV₁) > 12% and 200 mL from pre-bronchodilator use) and airway hyperresponsiveness (PC₂₀ < 16 mg/mL of methacholine). Current treatment was ICS (budesonide 400 μ g/d or equivalent) or a combination of low-dose inhaled budesonide and LABA (Seretide® 250 μ g/d or equivalent) for over 1 month before participation in this study. To be eligible for this study, patients were required to have normal results on complete blood count, routine chemistry, urinalysis and electrocardiogram at screening

EXCLUSION CRITERIA

- Other acute diseases within 28 days before administration of trial medications
- History of hypersensitivity to montelukast or budesonide
- Current or former smokers with a smoking history > 10 pack-years

Ye 2015 (Continued)

- Required administration of any medications that may affect asthma control, such as systemic steroids and immunomodulatory drugs (cyclosporine, omalizumab, etc.) for diseases other than asthma

Interventions	<p>PROTOCOL: LTRA + ICS vs HIGHER dose of ICS alone</p> <p>RUN-IN: 4 weeks</p> <p>INTERVENTION PERIOD: 12 weeks</p> <p>TEST GROUP: montelukast 10 mg O.D. + budesonide 400 µg/d</p> <p>CONTROL GROUP: budesonide 800 µg/d</p> <p>DEVICE: inhalers</p> <p>COMPLIANCE: not reported</p> <p>CO-TREATMENT: β₂-agonist use was permitted</p>
Outcomes	<p>ANALYSIS: NO INTENTION-TO-TREAT ANALYSIS reported</p> <p>OUTCOMES: reported as change from baseline values</p> <p>PULMONARY FUNCTION TEST: changes in PFT measured</p> <p>FUNCTIONAL STATUS:</p> <ul style="list-style-type: none"> • Quality of life reported <p>EXACERBATIONS:</p> <ul style="list-style-type: none"> • Exacerbation measures <p>INFLAMMATORY MARKERS:</p> <ul style="list-style-type: none"> • *Change from baseline sputum eosinophil (%) reported • Sputum inflammatory markers reported <p>ADVERSE EFFECTS: reported</p> <p>WITHDRAWALS: reported</p>
Notes	<p>This study was supported by a grant provided by the Korean Health Technology R&D Project, Ministry of Health & Welfare, Republic of Korea (HI14C1061), and was supported in part by a research grant from the Investigator-Initiated Studies Program of Merck Sharp & Dohme Corp</p>

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Balanced block design with centrally generated randomisation code stratified by centre
Allocation concealment (selection bias)	High risk	No allocation concealment owing to open-label study
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open-label study
Blinding of outcome assessment (detection bias)	High risk	Open-label study

Addition of anti-leukotriene agents to inhaled corticosteroids for adults and adolescents with persistent asthma (Review)

104

Ye 2015 (Continued)

All outcomes

Incomplete outcome data (attrition bias) All outcomes	Low risk	Balanced withdrawals and reasons for withdrawals were reported
Selective reporting (reporting bias)	Low risk	Primary outcome was clearly defined
Other bias	Unclear risk	Open-label study with inadequate information for judgement

Yildirim 2004

Methods	Randomised, parallel-group clinical study
Participants	<p>SYMPTOMATIC PARTICIPANTS</p> <p>RANDOMISED: 30</p> <p>WITHDRAWALS, %: not reported</p> <p>AGE in years: mean years $\pm$ SD:</p> <ul style="list-style-type: none"> ICS group: 36.93 ± 2.98 LTRA + ICS: 35.67 ± 2.64 <p>GENDER (% male): 33.3%</p> <ul style="list-style-type: none"> LTRA + ICS: 20 ICS alone: 46.6 <p>SEVERITY: moderate persistent asthma</p> <p>ASTHMA DURATION mean years: ≥ 6 months</p> <p>BASELINE FEV₁ (% pred) $\pm$SD: not reported</p> <p>MEAN ($\pm$SD) β_2-AGONIST USE (puffs/d):</p> <ul style="list-style-type: none"> ICS group: 0.39 ± 0.12 LTRA + ICS: 0.54 ± 0.22 <p>ATOPY (%): not reported</p> <p>ELIGIBILITY CRITERIA:</p> <ul style="list-style-type: none"> Patients with moderate persistent asthma (diagnosed according to American Thoracic Society criteria) ≥ 6 months <p>EXCLUSION CRITERIA:</p> <ul style="list-style-type: none"> Respiratory tract infection Had taken oral corticosteroids or had been hospitalised with an asthma attack within previous 3 months Other active disease states Had entered any other research studies in previous 3 months
Interventions	<p>PROTOCOL: LTRA + ICS vs HIGHER dose of ICS alone</p> <p>RUN-IN: 2 weeks</p>

Yildirim 2004 (Continued)

INTERVENTION PERIOD: 6 weeks

TEST GROUP: montelukast 10 mg once daily + budesonide 400 µg daily

CONTROL GROUP: budesonide 800 µg daily

DEVICE: not reported

COMPLIANCE: not reported

CO-TREATMENT: none reported (use of β_2 -agonist as needed)

Outcomes	<p>ANALYSES: NOT BY INTENTION-TO-TREAT</p> <p>OUTCOMES: reported at 16 weeks</p> <p>PULMONARY FUNCTION TEST: FEV₁ and PEFR reported as absolute values. Change from baseline values in FVC not reported SYMPTOM SCORES: reported as absolute values. Change from baseline values not reported FUNCTIONAL STATUS: not reported INFLAMMATORY MEDIATORS: reported as absolute values. Change from baseline values not reported</p> <p>ADVERSE EFFECTS: headache and nausea reported WITHDRAWALS: not reported</p>
Notes	<p>Full text (2004) Funding: not reported</p>

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Study was randomised and provided no further details regarding sequence generation
Allocation concealment (selection bias)	Unclear risk	Allocation concealment not reported
Blinding of participants and personnel (performance bias) All outcomes	High risk	Not a double-blinded study
Blinding of outcome assessment (detection bias) All outcomes	High risk	Not a double-blinded study
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Inadequate information reported
Selective reporting (reporting bias)	Low risk	Study protocol is not available. Outcomes mentioned in the Methods section are reported in the Results section and are extractable
Other bias	Low risk	No imbalance in baseline characteristics

Abbreviations: ATS: American Thoracic Society; BHR: bronchial hyperresponsiveness; BDP: beclomethasone; BUD: budesonide; ED: emergency department; ER: emergency room; FEF_{25%–75%}: forced expiratory flow between 25% and 75% of FVC; FEV₁: forced expiratory volume in 1 second; FP: fluticasone; FVC: forced vital capacity; GINA: Global Initiative for Asthma; ICS: inhaled corticosteroids; ITT: Intention-

to-treat analysis; LABA: long-acting β_2 -agonist; LTE4: leukotriene E4; LTRA: leukotriene receptor antagonist (anti-leukotriene agent); NIH: National Institutes of Health; NO: nitric oxide; PC₂₀: provocative concentration of methacholine causing a 20% fall in FEV₁; PD₂₀: dose of methacholine causing a 20% fall in forced expiratory volume in 1 second (FEV₁) from baseline; PEFR: peak expiratory flow rate; PFT: pulmonary function test; PP: per protocol; QOL: quality of life; SABA: short-acting β_2 -agonist; SD: standard deviation; SEM: standard error of mean; SGRQ: St George's Respiratory Questionnaire; TAA: triamcinolone acetonide; URTI: upper respiratory tract infection.

Characteristics of excluded studies [ordered by study ID]

Study	Reason for exclusion
Baba 1999	This is not an RCT
Bateman 2016	This is a cross-over trial
Boom 2011	This study included patients with chronic cough and asthma
Canino 2016	This study was conducted in a paediatric population
Chapman 2016	No LTRA + ICS group in this study
Chen 2014	This study was conducted in a paediatric population
Colombo 2016	This is a cross-over trial
Contraffato 2007	This is a cross-over trial
Cronin 2016	No LTRA + ICS group in this study
Dahl 2015	No LTRA + ICS group in this study
Dekhuijzen 2002	Not an RCT
Dempsey 2002	Treatment period is less than 4 weeks
Green 2003	This is a cross-over trial
Green 2006	This is a cross-over trial
Hamelmann 2016	All participants did not receive LTRA + ICS
Harada 2016	No LTRA + ICS group in this study
Horiguchi 2003	Dose of ICS was not maintained throughout the study duration
Ichinose 2015	No LTRA + ICS group in this study
Irvin 2007	All participants did not receive ICS. Participants also received anticholinergic drugs
Jayaram 2005	Participants were given inhaled corticosteroids and prednisone
Kalberg 1998	No LTRA + ICS group in this study
Kowal 2006	No LTRA + ICS group in this study
Li 2001	Dose of ICS was not consistent for all participants throughout the study

Study	Reason for exclusion
Mastruzzo 2010	Treatment period is less than 4 weeks
Nagao 2016	This study was conducted in a paediatric population
Nakaji 2013	Study participants took non-permitted drugs like LABA
Narmadha 2011	Study participants took formoterol in addition to ICS and LTRA
Nishimura 1999	This is a cross-over study
Nomani 2016	This is a cross-over study
O'Sullivan 2003	This is a cross-over trial
Pasaoglu 2008	This is not an RCT
Paulo 2004	Participants are children
Perng 2004	Study participants were given a new diagnosis of asthma
Pezato 2016	This is not an RCT
Philip 2011	This is a cross-over study
Price 2001	No ICS alone group included in this study for comparison
Price 2011a	This is a pragmatic cross-over trial
Price 2011b	No LTRA + ICS group in this study
Price 2012	No LTRA + ICS group in this study
Price 2013	No LTRA + ICS group in this study
Sims 2008	No ICS alone group. This is a pragmatic equivalence trial
Storror 2016	This is a study protocol; study is ongoing
Swenson 2003	This is a cross-over study
Tachimoto 2016	This study was conducted in a paediatric population
Tamaoki 1997	Study participants took anticholinergics
Tomita 1999	No LTRA + ICS group in this study
Trofor 2002	This study is not an RCT
Tsuchida 2005	No ICS alone group included for comparison
Uribe 2007	This is not an RCT; steroid-naïve patients were included
Vandewalker 2015	No LTRA + ICS group in this study
Wilson 1999	Treatment period is less than 4 weeks

Study	Reason for exclusion
Wilson 2010	No ICS alone group included in this study for comparison
Yaldiz 2000	This study is not an RCT
Yin 2016	No LTRA + ICS group in this study
Yoo 2001	No ICS alone group included for comparison. Some participants did not take ICS. This is a mon-telukast vs placebo trial

Abbreviations: ICS: inhaled corticosteroids; LABA: long-acting β_2 -agonist; LTRA: leukotriene receptor antagonist (anti-leukotriene agent); RCT: randomised controlled trial.

Characteristics of studies awaiting assessment *[ordered by study ID]*

[Farzan 2016](#)

Methods	Randomised, double-blind, controlled study
Participants	<p>Patients with mild to moderate persistent early-onset asthma taking inhaled corticosteroids</p> <p>RANDOMISED: not reported</p> <ul style="list-style-type: none"> LTRA + ICS: not reported ICS alone: not reported <p>WITHDRAWALS: not reported</p> <ul style="list-style-type: none"> LTRA + ICS: not reported ICS alone: not reported <p>AGE in years: mean $\pm$ SD</p> <ul style="list-style-type: none"> LTRA + ICS: not reported ICS alone: not reported <p>GENDER (% male):</p> <ul style="list-style-type: none"> LTRA + ICS: not reported ICS alone: not reported <p>SEVERITY: mild to moderate asthma</p> <p>ASTHMA DURATION years: not reported</p> <p>MEAN ($\pm$SEM) β_2-AGONIST USE (puffs/d):</p> <ul style="list-style-type: none"> LTRA + ICS: not reported ICS alone: not reported <p>MEAN ($\pm$SEM) MEAN BASELINE FEV₁ (% predicted):</p> <ul style="list-style-type: none"> LTRA + ICS: not reported ICS alone: not reported <p>BASELINE DOSE OF ICS: not reported</p> <p>ATOPY (%): not reported</p> <p>ELIGIBILITY CRITERIA:</p>

Farzan 2016 (Continued)

	<ul style="list-style-type: none"> Patients with mild to moderate persistent early-onset asthma taking inhaled corticosteroids
Interventions	<p>PROTOCOL: LTRA + ICS vs same dose of ICS alone</p> <p>RUN-IN: not reported</p> <p>Intervention period: 24 weeks</p> <p>TEST GROUP: montelukast + ICS</p> <p>CONTROL GROUP: ICS</p> <p>DEVICE: not reported</p> <p>COMPLIANCE: not reported</p> <p>CO-TREATMENT: not reported</p> <p>CRITERIA FOR WITHDRAWAL FROM STUDY: not reported</p>
Outcomes	<p>INTENTION-TO-TREAT ANALYSIS: not reported</p> <p>PULMONARY FUNCTION TEST:</p> <ul style="list-style-type: none"> Spirometric measures, total ICS dose <p>FUNCTIONAL STATUS:</p> <ul style="list-style-type: none"> % rescue-free days <p>EXACERBATIONS: not reported</p> <p>INFLAMMATORY MARKERS:</p> <ul style="list-style-type: none"> Exhaled nitric oxide Serum leptin Urinary leukotriene E4 <p>ADVERSE EFFECTS: not reported</p> <p>WITHDRAWALS: not reported</p>
Notes	<p>Conference abstract</p> <p>Funding: not reported</p>

DATA AND ANALYSES

Comparison 1. Anti-leukotrienes and inhaled corticosteroids versus SAME dose of inhaled corticosteroids

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Patients with ≥ 1 exacerbations requiring oral corticosteroids	4	815	Risk Ratio (M-H, Random, 95% CI)	0.50 [0.29, 0.86]
1.1 Montelukast	2	423	Risk Ratio (M-H, Random, 95% CI)	0.54 [0.28, 1.06]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.2 Zafirlukast	2	392	Risk Ratio (M-H, Random, 95% CI)	0.42 [0.17, 1.08]
2 Primary outcome: sub-group for funding	4	815	Risk Ratio (M-H, Random, 95% CI)	0.50 [0.29, 0.86]
2.1 Funding from pharmaceutical company	2	761	Risk Ratio (M-H, Random, 95% CI)	0.47 [0.26, 0.82]
2.2 No funding or not reported	2	54	Risk Ratio (M-H, Random, 95% CI)	1.0 [0.15, 6.59]
3 Participants with exacerbations requiring hospital admission	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
3.1 Montelukast	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
4 Participants with ≥ 1 exacerbations leading to emergency department visit	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
4.1 Zafirlukast	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
5 Change from baseline in morning PEFR (L/min)	4	1489	Mean Difference (IV, Random, 95% CI)	8.36 [3.64, 13.07]
5.1 Montelukast	3	1121	Mean Difference (IV, Random, 95% CI)	6.56 [2.60, 10.53]
5.2 Zafirlukast	1	368	Mean Difference (IV, Random, 95% CI)	17.2 [6.94, 27.46]
6 Change from baseline in evening PEFR (L/min)	3	864	Mean Difference (IV, Random, 95% CI)	7.87 [-0.54, 16.29]
6.1 Montelukast	2	496	Mean Difference (IV, Random, 95% CI)	4.00 [-1.28, 9.28]
6.2 Zafirlukast	1	368	Mean Difference (IV, Random, 95% CI)	15.1 [4.71, 25.49]
7 Change from baseline FEV ₁ (L)	3	760	Mean Difference (IV, Random, 95% CI)	0.11 [0.03, 0.19]
7.1 Montelukast	2	496	Mean Difference (IV, Random, 95% CI)	0.10 [-0.05, 0.24]
7.2 Zafirlukast	1	264	Mean Difference (IV, Random, 95% CI)	0.1 [0.01, 0.19]
8 Change from baseline in FEV ₁ % of predicted	3		Mean Difference (IV, Random, 95% CI)	Subtotals only
8.1 Montelukast	3	1121	Mean Difference (IV, Random, 95% CI)	1.84 [-1.08, 4.77]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
9 Change from baseline in mean asthma symptom score (daytime)	3	1386	Std. Mean Difference (IV, Random, 95% CI)	-0.15 [-0.26, -0.05]
9.1 Montelukast	2	1018	Std. Mean Difference (IV, Random, 95% CI)	-0.13 [-0.25, -0.00]
9.2 Zafirlukast	1	368	Std. Mean Difference (IV, Random, 95% CI)	-0.22 [-0.43, -0.02]
10 Change from baseline mean daily daytime use of β_2 -agonists (puffs/d)	1		Mean Difference (IV, Random, 95% CI)	Totals not selected
10.1 Zafirlukast	1		Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]
11 Change in night-time awakenings (episodes/wk)	2	761	Mean Difference (IV, Random, 95% CI)	-0.56 [-1.02, -0.10]
11.1 Montelukast	1	393	Mean Difference (IV, Random, 95% CI)	-0.59 [-1.14, -0.04]
11.2 Zafirlukast	1	368	Mean Difference (IV, Random, 95% CI)	-0.5 [-1.33, 0.33]
12 Change from baseline in rescue-free days (%)	1		Mean Difference (IV, Random, 95% CI)	Totals not selected
12.1 Montelukast	1		Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]
13 Change in quality of life	1		Mean Difference (IV, Random, 95% CI)	Totals not selected
13.1 Montelukast	1		Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]
14 Patients' global evaluation	1		Mean Difference (IV, Random, 95% CI)	Totals not selected
14.1 Montelukast	1		Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]
15 Physicians' global evaluation	1		Mean Difference (IV, Random, 95% CI)	Totals not selected
15.1 Montelukast	1		Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]
16 Overall withdrawals	9	1912	Risk Ratio (M-H, Random, 95% CI)	0.98 [0.75, 1.29]
16.1 Montelukast	4	1218	Risk Ratio (M-H, Random, 95% CI)	0.89 [0.63, 1.25]
16.2 Zafirlukast	5	694	Risk Ratio (M-H, Random, 95% CI)	1.17 [0.72, 1.89]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
17 Withdrawals due to adverse effects	3	1400	Risk Ratio (M-H, Random, 95% CI)	0.90 [0.48, 1.68]
17.1 Montelukast	2	1032	Risk Ratio (M-H, Random, 95% CI)	1.32 [0.25, 6.84]
17.2 Zafirlukast	1	368	Risk Ratio (M-H, Random, 95% CI)	0.82 [0.38, 1.76]
18 Withdrawals due to poor asthma control/exacerbations	6	1571	Risk Ratio (M-H, Random, 95% CI)	0.68 [0.34, 1.37]
18.1 Montelukast	3	1135	Risk Ratio (M-H, Random, 95% CI)	0.49 [0.13, 1.78]
18.2 Zafirlukast	3	436	Risk Ratio (M-H, Random, 95% CI)	0.85 [0.35, 2.12]
19 Number of participants with serious adverse events	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
19.1 Zafirlukast	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
20 Overall adverse effects	3	1024	Risk Ratio (M-H, Random, 95% CI)	1.06 [0.92, 1.22]
20.1 Montelukast	2	656	Risk Ratio (M-H, Random, 95% CI)	1.09 [0.91, 1.31]
20.2 Zafirlukast	1	368	Risk Ratio (M-H, Random, 95% CI)	1.01 [0.81, 1.26]
21 Headache	3	1386	Risk Ratio (M-H, Random, 95% CI)	1.22 [0.93, 1.60]
21.1 Montelukast	2	1018	Risk Ratio (M-H, Random, 95% CI)	1.20 [0.90, 1.59]
21.2 Zafirlukast	1	368	Risk Ratio (M-H, Random, 95% CI)	1.44 [0.59, 3.49]
22 Upper respiratory tract infections	2		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
22.1 Montelukast	2	1018	Risk Ratio (M-H, Random, 95% CI)	0.90 [0.71, 1.14]
23 Rhinitis	2	993	Risk Ratio (M-H, Random, 95% CI)	0.88 [0.42, 1.83]
23.1 Montelukast	1	625	Risk Ratio (M-H, Random, 95% CI)	0.81 [0.25, 2.63]
23.2 Zafirlukast	1	368	Risk Ratio (M-H, Random, 95% CI)	0.93 [0.37, 2.35]
24 Elevated liver enzymes	2	754	Risk Ratio (M-H, Random, 95% CI)	1.22 [0.30, 5.04]
24.1 Montelukast	1	386	Risk Ratio (M-H, Random, 95% CI)	0.86 [0.27, 2.77]
24.2 Zafirlukast	1	368	Risk Ratio (M-H, Random, 95% CI)	5.22 [0.25, 108.01]
25 Nausea	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
25.1 Zafirlukast	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
26 Cough	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
26.1 Zafirlukast	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
27 Abdominal pain	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
27.1 Montelukast	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
28 Influenza	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
28.1 Montelukast	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
29 Pharyngitis	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
29.1 Montelukast	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
30 Bronchitis	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
30.1 Montelukast	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
31 Death	2	761	Risk Ratio (M-H, Random, 95% CI)	0.35 [0.01, 8.49]
31.1 Montelukast	1	393	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
31.2 Zafirlukast	1	368	Risk Ratio (M-H, Random, 95% CI)	0.35 [0.01, 8.49]
32 Change from baseline eosinophil counts	1		Mean Difference (IV, Random, 95% CI)	Totals not selected
32.1 Montelukast	1		Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]

Analysis 1.1. Comparison 1 Anti-leukotrienes and inhaled corticosteroids versus SAME dose of inhaled corticosteroids, Outcome 1 Patients with ≥ 1 exacerbations requiring oral corticosteroids.

Analysis 1.2. Comparison 1 Anti-leukotrienes and inhaled corticosteroids versus SAME dose of inhaled corticosteroids, Outcome 2 Primary outcome: subgroup for funding.

Analysis 1.3. Comparison 1 Anti-leukotrienes and inhaled corticosteroids versus SAME dose of inhaled corticosteroids, Outcome 3 Participants with exacerbations requiring hospital admission.

Analysis 1.4. Comparison 1 Anti-leukotrienes and inhaled corticosteroids versus SAME dose of inhaled corticosteroids, Outcome 4 Participants with ≥ 1 exacerbations leading to emergency department visit.

Analysis 1.5. Comparison 1 Anti-leukotrienes and inhaled corticosteroids versus SAME dose of inhaled corticosteroids, Outcome 5 Change from baseline in morning PEFR (L/min).

Analysis 1.6. Comparison 1 Anti-leukotrienes and inhaled corticosteroids versus SAME dose of inhaled corticosteroids, Outcome 6 Change from baseline in evening PEFR (L/min).

Analysis 1.7. Comparison 1 Anti-leukotrienes and inhaled corticosteroids versus SAME dose of inhaled corticosteroids, Outcome 7 Change from baseline FEV₁ (L).

Analysis 1.8. Comparison 1 Anti-leukotrienes and inhaled corticosteroids versus SAME dose of inhaled corticosteroids, Outcome 8 Change from baseline in FEV₁ % of predicted.

Analysis 1.9. Comparison 1 Anti-leukotrienes and inhaled corticosteroids versus SAME dose of inhaled corticosteroids, Outcome 9 Change from baseline in mean asthma symptom score (daytime).

Analysis 1.10. Comparison 1 Anti-leukotrienes and inhaled corticosteroids versus SAME dose of inhaled corticosteroids, Outcome 10 Change from baseline mean daily daytime use of β_2 -agonists (puffs/d).

Analysis 1.11. Comparison 1 Anti-leukotrienes and inhaled corticosteroids versus SAME dose of inhaled corticosteroids, Outcome 11 Change in night-time awakenings (episodes/wk).

Analysis 1.12. Comparison 1 Anti-leukotrienes and inhaled corticosteroids versus SAME dose of inhaled corticosteroids, Outcome 12 Change from baseline in rescue-free days (%).

Analysis 1.13. Comparison 1 Anti-leukotrienes and inhaled corticosteroids versus SAME dose of inhaled corticosteroids, Outcome 13 Change in quality of life.

Analysis 1.14. Comparison 1 Anti-leukotrienes and inhaled corticosteroids versus SAME dose of inhaled corticosteroids, Outcome 14 Patients' global evaluation.

Analysis 1.15. Comparison 1 Anti-leukotrienes and inhaled corticosteroids versus SAME dose of inhaled corticosteroids, Outcome 15 Physicians' global evaluation.

Study or subgroup	LTRA+ICS		ICS alone		Mean Difference Random, 95% CI	Mean Difference Random, 95% CI
	N	Mean(SD)	N	Mean(SD)		
Laviolette 1999	193	2 (1.5)	200	2.4 (1.4)		-0.45[-0.74,-0.16]

Analysis 1.16. Comparison 1 Anti-leukotrienes and inhaled corticosteroids versus SAME dose of inhaled corticosteroids, Outcome 16 Overall withdrawals.

Study or subgroup	LTRA+ICS n/N	ICS alone n/N	Risk Ratio		Weight	Risk Ratio
			M-H, Random, 95% CI			M-H, Random, 95% CI
1.16.1 Montelukast						
Djukanovic 2010	6/50	8/53			7.64%	0.8[0.3,2.13]
Laviolette 1999	16/193	22/200			19.76%	0.75[0.41,1.39]
Storms 2004	0/39	1/44			0.74%	0.38[0.02,8.95]
Vaquerizo 2003	34/326	32/313			35.52%	1.02[0.65,1.61]
Subtotal (95% CI)	608	610			63.66%	0.89[0.63,1.25]
Total events: 56 (LTRA+ICS), 63 (ICS alone)						
Heterogeneity: Tau ² =0; Chi ² =0.96, df=3(P=0.81); I ² =0%						
Test for overall effect: Z=0.66(P=0.51)						
1.16.2 Zafirlukast						
Huang 2003	3/20	4/18			4.04%	0.68[0.17,2.62]
Riccioni 2001	2/12	1/12			1.45%	2[0.21,19.23]
Riccioni 2002	1/15	1/15			1.04%	1[0.07,14.55]
SD-004-0216	19/118	9/116			13.17%	2.08[0.98,4.4]
Virchow 2000	14/180	18/188			16.64%	0.81[0.42,1.58]
Subtotal (95% CI)	345	349			36.34%	1.17[0.72,1.89]
Total events: 39 (LTRA+ICS), 33 (ICS alone)						
Heterogeneity: Tau ² =0.02; Chi ² =4.25, df=4(P=0.37); I ² =5.95%						
Test for overall effect: Z=0.63(P=0.53)						
Total (95% CI)	953	959			100%	0.98[0.75,1.29]
Total events: 95 (LTRA+ICS), 96 (ICS alone)						
Heterogeneity: Tau ² =0; Chi ² =6.08, df=8(P=0.64); I ² =0%						
Test for overall effect: Z=0.13(P=0.9)						
Test for subgroup differences: Chi ² =0.81, df=1 (P=0.37), I ² =0%						

Favours LTRA+ICS

0.010.1110100

Favours ICS alone

Analysis 1.17. Comparison 1 Anti-leukotrienes and inhaled corticosteroids versus SAME dose of inhaled corticosteroids, Outcome 17 Withdrawals due to adverse effects.

Study or subgroup	LTRA+ICS n/N	ICS alone n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
1.17.1 Montelukast					
Laviolette 1999	4/193	1/200		8.11%	4.15[0.47,36.76]
Vaquerizo 2003	6/326	8/313		33.2%	0.72[0.25,2.05]
Subtotal (95% CI)	519	513		41.31%	1.32[0.25,6.84]
Total events: 10 (LTRA+ICS), 9 (ICS alone)					
Heterogeneity: Tau ² =0.79; Chi ² =2.04, df=1(P=0.15); I ² =50.98%					
<div><div></div><div>Favours LTRA+ICS</div><div>0.010.116100</div><div></div><div>Favours ICS alone</div></div>

Analysis 1.18. Comparison 1 Anti-leukotrienes and inhaled corticosteroids versus SAME dose of inhaled corticosteroids, Outcome 18 Withdrawals due to poor asthma control/exacerbations.

Analysis 1.19. Comparison 1 Anti-leukotrienes and inhaled corticosteroids versus SAME dose of inhaled corticosteroids, Outcome 19 Number of participants with serious adverse events.

Analysis 1.20. Comparison 1 Anti-leukotrienes and inhaled corticosteroids versus SAME dose of inhaled corticosteroids, Outcome 20 Overall adverse effects.

Analysis 1.21. Comparison 1 Anti-leukotrienes and inhaled corticosteroids versus SAME dose of inhaled corticosteroids, Outcome 21 Headache.

Analysis 1.22. Comparison 1 Anti-leukotrienes and inhaled corticosteroids versus SAME dose of inhaled corticosteroids, Outcome 22 Upper respiratory tract infections.

Analysis 1.23. Comparison 1 Anti-leukotrienes and inhaled corticosteroids versus SAME dose of inhaled corticosteroids, Outcome 23 Rhinitis.

Analysis 1.24. Comparison 1 Anti-leukotrienes and inhaled corticosteroids versus SAME dose of inhaled corticosteroids, Outcome 24 Elevated liver enzymes.

Analysis 1.25. Comparison 1 Anti-leukotrienes and inhaled corticosteroids versus SAME dose of inhaled corticosteroids, Outcome 25 Nausea.

Analysis 1.26. Comparison 1 Anti-leukotrienes and inhaled corticosteroids versus SAME dose of inhaled corticosteroids, Outcome 26 Cough.

Analysis 1.27. Comparison 1 Anti-leukotrienes and inhaled corticosteroids versus SAME dose of inhaled corticosteroids, Outcome 27 Abdominal pain.

Analysis 1.28. Comparison 1 Anti-leukotrienes and inhaled corticosteroids versus SAME dose of inhaled corticosteroids, Outcome 28 Influenza.

Analysis 1.29. Comparison 1 Anti-leukotrienes and inhaled corticosteroids versus SAME dose of inhaled corticosteroids, Outcome 29 Pharyngitis.

Analysis 1.30. Comparison 1 Anti-leukotrienes and inhaled corticosteroids versus SAME dose of inhaled corticosteroids, Outcome 30 Bronchitis.

Analysis 1.31. Comparison 1 Anti-leukotrienes and inhaled corticosteroids versus SAME dose of inhaled corticosteroids, Outcome 31 Death.

Analysis 1.32. Comparison 1 Anti-leukotrienes and inhaled corticosteroids versus SAME dose of inhaled corticosteroids, Outcome 32 Change from baseline eosinophil counts.

Comparison 2. Anti-leukotrienes and inhaled corticosteroids versus HIGHER dose of inhaled corticosteroids

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Participants with ≥ 1 exacerbation requiring oral corticosteroids	4	1779	Risk Ratio (M-H, Random, 95% CI)	0.90 [0.58, 1.39]
1.1 Montelukast	2	945	Risk Ratio (M-H, Random, 95% CI)	0.77 [0.45, 1.33]
1.2 Zafirlukast	2	834	Risk Ratio (M-H, Random, 95% CI)	1.19 [0.57, 2.46]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
2 Primary outcome: subgroup for dose of daily ICS	4	1779	Risk Ratio (M-H, Random, 95% CI)	0.90 [0.58, 1.39]
2.1 ≥ 800 $\mu\text{g/d}$ HFA beclomethasone equ	1	60	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
2.2 < 800 $\mu\text{g/d}$ HFA beclomethasone equ	3	1719	Risk Ratio (M-H, Random, 95% CI)	0.90 [0.58, 1.39]
3 Primary outcome: subgroup for funding by pharmaceutical company	4	1779	Risk Ratio (M-H, Random, 95% CI)	0.90 [0.58, 1.39]
3.1 Funded by pharmaceutical company	3	1719	Risk Ratio (M-H, Random, 95% CI)	0.90 [0.58, 1.39]
3.2 No funding	1	60	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
4 Participants with ≥ 1 exacerbation requiring hospital admission	3	1719	Risk Ratio (M-H, Random, 95% CI)	1.49 [0.06, 36.47]
4.1 Montelukast	1	885	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
4.2 Zafirlukast	2	834	Risk Ratio (M-H, Random, 95% CI)	1.49 [0.06, 36.47]
5 Change from baseline in morning PEFR (L/min)	5	952	Mean Difference (IV, Random, 95% CI)	10.38 [-1.32, 22.08]
5.1 Montelukast	3	152	Mean Difference (IV, Random, 95% CI)	18.18 [6.54, 29.82]
5.2 Zafirlukast	2	800	Mean Difference (IV, Random, 95% CI)	2.94 [-10.01, 15.89]
6 Change from baseline in evening PEFR (L/min)	1		Mean Difference (IV, Random, 95% CI)	Totals not selected
6.1 Montelukast	1		Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]
7 Change from baseline in mean diurnal variation in PEFR	2		Mean Difference (IV, Random, 95% CI)	Subtotals only
7.1 Zafirlukast	2	738	Mean Difference (IV, Random, 95% CI)	-1.42 [-2.94, 0.10]
8 Change from baseline FEV ₁ (L)	4	958	Mean Difference (IV, Random, 95% CI)	0.06 [-0.01, 0.13]
8.1 Montelukast	2	100	Mean Difference (IV, Random, 95% CI)	0.12 [0.06, 0.19]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
8.2 Zafirlukast	2	858	Mean Difference (IV, Random, 95% CI)	0.0 [-0.05, 0.05]
9 Change from baseline mean daily use of β_2 -agonists (puffs/d)	4	1398	Mean Difference (IV, Random, 95% CI)	-0.01 [-0.20, 0.19]
9.1 Montelukast	2	834	Mean Difference (IV, Random, 95% CI)	-0.04 [-0.25, 0.18]
9.2 Zafirlukast	2	564	Mean Difference (IV, Random, 95% CI)	0.12 [-0.35, 0.59]
10 Change from baseline mean symptom scores	3	1539	Std. Mean Difference (IV, Random, 95% CI)	-0.02 [-0.13, 0.08]
10.1 Montelukast	1	860	Std. Mean Difference (IV, Random, 95% CI)	0.01 [-0.12, 0.15]
10.2 Zafirlukast	2	679	Std. Mean Difference (IV, Random, 95% CI)	-0.08 [-0.24, 0.08]
11 Change in nocturnal awakenings per week	1		Mean Difference (IV, Random, 95% CI)	Totals not selected
12 Change in quality of life	1		Mean Difference (IV, Random, 95% CI)	Totals not selected
12.1 Montelukast	1		Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]
13 Overall withdrawals	6	1899	Risk Ratio (M-H, Random, 95% CI)	0.94 [0.61, 1.43]
13.1 Montelukast	3	1024	Risk Ratio (M-H, Random, 95% CI)	0.71 [0.42, 1.21]
13.2 Zafirlukast	2	834	Risk Ratio (M-H, Random, 95% CI)	1.18 [0.59, 2.36]
13.3 Pranlukast	1	41	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
14 Withdrawals due to adverse effects	3	1723	Risk Ratio (M-H, Random, 95% CI)	1.34 [0.57, 3.16]
14.1 Montelukast	1	889	Risk Ratio (M-H, Random, 95% CI)	0.79 [0.31, 1.98]
14.2 Zafirlukast	2	834	Risk Ratio (M-H, Random, 95% CI)	2.18 [0.83, 5.74]
15 Withdrawals due to poor asthma control/exacerbations	3	1723	Risk Ratio (M-H, Random, 95% CI)	0.59 [0.25, 1.38]
15.1 Montelukast	1	889	Risk Ratio (M-H, Random, 95% CI)	0.28 [0.06, 1.35]
15.2 Zafirlukast	2	834	Risk Ratio (M-H, Random, 95% CI)	0.80 [0.29, 2.21]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
16 Participants with serious adverse health events	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
16.1 Montelukast	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
17 Overall adverse effects	6	1899	Risk Ratio (M-H, Random, 95% CI)	0.96 [0.89, 1.03]
17.1 Montelukast	3	1024	Risk Ratio (M-H, Random, 95% CI)	0.89 [0.78, 1.01]
17.2 Zafirlukast	2	834	Risk Ratio (M-H, Random, 95% CI)	0.99 [0.91, 1.09]
17.3 Pranlukast	1	41	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
18 Headache	5	1813	Risk Ratio (M-H, Random, 95% CI)	1.13 [0.85, 1.50]
18.1 Montelukast	3	979	Risk Ratio (M-H, Random, 95% CI)	1.22 [0.77, 1.95]
18.2 Zafirlukast	2	834	Risk Ratio (M-H, Random, 95% CI)	1.08 [0.75, 1.54]
19 Nausea	4	1753	Risk Ratio (M-H, Random, 95% CI)	1.11 [0.55, 2.24]
19.1 Montelukast	2	919	Risk Ratio (M-H, Random, 95% CI)	1.15 [0.19, 6.98]
19.2 Zafirlukast	2	834	Risk Ratio (M-H, Random, 95% CI)	1.29 [0.49, 3.38]
20 Elevated liver enzymes	3	1687	Risk Ratio (M-H, Random, 95% CI)	1.61 [0.36, 7.21]
20.1 Montelukast	1	853	Risk Ratio (M-H, Random, 95% CI)	0.54 [0.18, 1.61]
20.2 Zafirlukast	2	834	Risk Ratio (M-H, Random, 95% CI)	3.60 [0.97, 13.38]
21 Oral moniliasis	2		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
21.1 Zafirlukast	2	834	Risk Ratio (M-H, Random, 95% CI)	0.30 [0.11, 0.81]
22 Hoarseness of voice	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
23 Abdominal pain	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
23.1 Montelukast	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
24 Death	3		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
24.1 Montelukast	1	889	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
24.2 Zafirlukast	2	834	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]

Analysis 2.1. Comparison 2 Anti-leukotrienes and inhaled corticosteroids versus HIGHER dose of inhaled corticosteroids, Outcome 1 Participants with ≥ 1 exacerbation requiring oral corticosteroids.

Analysis 2.2. Comparison 2 Anti-leukotrienes and inhaled corticosteroids versus HIGHER dose of inhaled corticosteroids, Outcome 2 Primary outcome: subgroup for dose of daily ICS.

Study or subgroup	LTRA+ICS n/N	ICS alone n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
Test for overall effect: $Z=0.46(P=0.64)$					
Test for subgroup differences: Not applicable					
<div style="display: flex; justify-content: space-between;"> Favours LTRA+ICS 0.2 0.5 1 2 5 Favours ICS alone </div>					

Analysis 2.3. Comparison 2 Anti-leukotrienes and inhaled corticosteroids versus HIGHER dose of inhaled corticosteroids, Outcome 3 Primary outcome: subgroup for funding by pharmaceutical company.

Study or subgroup	LTRA+ICS n/N	ICS alone n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
2.3.1 Funded by pharmaceutical company					
Nayak 1998	13/264	7/130		23.64%	0.91[0.37,2.24]
Price 2003	22/446	28/439		64.24%	0.77[0.45,1.33]
Ringdal 1999	12/294	3/146		12.12%	1.99[0.57,6.93]
Subtotal (95% CI)	1004	715		100%	0.9[0.58,1.39]
Total events: 47 (LTRA+ICS), 38 (ICS alone)					
Heterogeneity: $\tau^2=0$; $\chi^2=1.85$, $df=2(P=0.4)$; $I^2=0\%$					
Test for overall effect: $Z=0.46(P=0.64)$					
2.3.2 No funding					
Shah 2006	0/30	0/30			Not estimable
Subtotal (95% CI)	30	30			Not estimable
Total events: 0 (LTRA+ICS), 0 (ICS alone)					
Heterogeneity: Not applicable					
Test for overall effect: Not applicable					
Total (95% CI)	1034	745		100%	0.9[0.58,1.39]
Total events: 47 (LTRA+ICS), 38 (ICS alone)					
Heterogeneity: $\tau^2=0$; $\chi^2=1.85$, $df=2(P=0.4)$; $I^2=0\%$					
Test for overall effect: $Z=0.46(P=0.64)$					
Test for subgroup differences: Not applicable					
<div style="display: flex; justify-content: space-between;"> Favours LTRA+ICS 0.2 0.5 1 2 5 Favours ICS alone </div>					

Analysis 2.4. Comparison 2 Anti-leukotrienes and inhaled corticosteroids versus HIGHER dose of inhaled corticosteroids, Outcome 4 Participants with ≥ 1 exacerbation requiring hospital admission.

Study or subgroup	LTRA+ICS n/N	ICS alone n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
2.4.1 Montelukast					
Price 2003	0/446	0/439			Not estimable
Subtotal (95% CI)	446	439			Not estimable
Total events: 0 (LTRA+ICS), 0 (ICS alone)					
Heterogeneity: Not applicable					
Test for overall effect: Not applicable					
2.4.2 Zafirlukast					
Nayak 1998	0/264	0/130			Not estimable
Ringdal 1999	1/294	0/146		100%	1.49[0.06,36.47]
<div style="display: flex; justify-content: space-between;"> Favours LTRA+ICS 0.001 0.1 1 10 100 Favours ICS alone </div>

Analysis 2.5. Comparison 2 Anti-leukotrienes and inhaled corticosteroids versus HIGHER dose of inhaled corticosteroids, Outcome 5 Change from baseline in morning PEFR (L/min).

Analysis 2.6. Comparison 2 Anti-leukotrienes and inhaled corticosteroids versus HIGHER dose of inhaled corticosteroids, Outcome 6 Change from baseline in evening PEFR (L/min).

Analysis 2.7. Comparison 2 Anti-leukotrienes and inhaled corticosteroids versus HIGHER dose of inhaled corticosteroids, Outcome 7 Change from baseline in mean diurnal variation in PEFr. **Analysis 2.8. Comparison 2 Anti-leukotrienes and inhaled corticosteroids versus HIGHER dose of inhaled corticosteroids, Outcome 8 Change from baseline FEV₁ (L).** **Analysis 2.9. Comparison 2 Anti-leukotrienes and inhaled corticosteroids versus HIGHER dose of inhaled corticosteroids, Outcome 9 Change from baseline mean daily use of β_2 -agonists (puffs/d).**

Analysis 2.10. Comparison 2 Anti-leukotrienes and inhaled corticosteroids versus HIGHER dose of inhaled corticosteroids, Outcome 10 Change from baseline mean symptom scores.

Analysis 2.11. Comparison 2 Anti-leukotrienes and inhaled corticosteroids versus HIGHER dose of inhaled corticosteroids, Outcome 11 Change in nocturnal awakenings per week.

Analysis 2.12. Comparison 2 Anti-leukotrienes and inhaled corticosteroids versus HIGHER dose of inhaled corticosteroids, Outcome 12 Change in quality of life.

Study or subgroup	LTRA+ICS		ICS alone		Mean Difference Random, 95% CI	Mean Difference Random, 95% CI
	N	Mean(SD)	N	Mean(SD)		
2.12.1 Montelukast						
Barnes 2007	37	0.7 (0.8)	38	0.5 (0.9)		0.25[-0.14,0.64]

Analysis 2.13. Comparison 2 Anti-leukotrienes and inhaled corticosteroids versus HIGHER dose of inhaled corticosteroids, Outcome 13 Overall withdrawals.

Study or subgroup	LTRA+ICS n/N	ICS alone n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
2.13.1 Montelukast					
Barnes 2007	1/37	5/38		3.9%	0.21[0.03,1.68]
Price 2003	20/448	26/441		31.31%	0.76[0.43,1.34]
Shah 2006	2/30	2/30		4.73%	1[0.15,6.64]
Subtotal (95% CI)	515	509		39.94%	0.71[0.42,1.21]
Total events: 23 (LTRA+ICS), 33 (ICS alone)					
Heterogeneity: Tau²=0; Chi²=1.53, df=2(P=0.47); I²=0%					
Test for overall effect: Z=1.26(P=0.21)					
2.13.2 Zafirlukast					
Nayak 1998	37/264	21/130		36.32%	0.87[0.53,1.42]
Ringdal 1999	32/294	9/146		23.75%	1.77[0.87,3.6]
Subtotal (95% CI)	558	276		60.06%	1.18[0.59,2.36]
Total events: 69 (LTRA+ICS), 30 (ICS alone)					
Heterogeneity: Tau²=0.16; Chi²=2.62, df=1(P=0.11); I²=61.88%					
Test for overall effect: Z=0.47(P=0.64)					
2.13.3 Pranlukast					
Tomari 2001	0/21	0/20			Not estimable
Subtotal (95% CI)	21	20			Not estimable
Total events: 0 (LTRA+ICS), 0 (ICS alone)					
Heterogeneity: Not applicable					
Test for overall effect: Not applicable					
Total (95% CI)	1094	805		100%	0.94[0.61,1.43]
Total events: 92 (LTRA+ICS), 63 (ICS alone)					
Heterogeneity: Tau²=0.07; Chi²=5.69, df=4(P=0.22); I²=29.65%					
Test for overall effect: Z=0.3(P=0.76)					
Test for subgroup differences: Chi²=1.28, df=1 (P=0.26), I²=22.14%					

Analysis 2.14. Comparison 2 Anti-leukotrienes and inhaled corticosteroids versus HIGHER dose of inhaled corticosteroids, Outcome 14 Withdrawals due to adverse effects.

Analysis 2.15. Comparison 2 Anti-leukotrienes and inhaled corticosteroids versus HIGHER dose of inhaled corticosteroids, Outcome 15 Withdrawals due to poor asthma control/exacerbations.

Analysis 2.16. Comparison 2 Anti-leukotrienes and inhaled corticosteroids versus HIGHER dose of inhaled corticosteroids, Outcome 16 Participants with serious adverse health events.

Study or subgroup	LTRA+ICS n/N	ICS alone n/N	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
2.16.1 Montelukast				
Barnes 2007	0/37	0/38		Not estimable
			Favours LTRA+ICS 0.01 0.1 1 10 100 Favours ICS alone	

Analysis 2.17. Comparison 2 Anti-leukotrienes and inhaled corticosteroids versus HIGHER dose of inhaled corticosteroids, Outcome 17 Overall adverse effects.

Study or subgroup	LTRA+ICS n/N	ICS alone n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
2.17.1 Montelukast					
Barnes 2007	28/37	33/38		11.98%	0.87[0.7,1.09]
Price 2003	166/448	182/441		21.63%	0.9[0.76,1.06]
Shah 2006	3/30	4/30		0.29%	0.75[0.18,3.07]
Subtotal (95% CI)	515	509		33.9%	0.89[0.78,1.01]
Total events: 197 (LTRA+ICS), 219 (ICS alone)					
Heterogeneity: Tau ² =0; Chi ² =0.11, df=2(P=0.95); I ² =0%					
Test for overall effect: Z=1.79(P=0.07)					
2.17.2 Zafirlukast					
Nayak 1998	172/264	90/130		27.88%	0.94[0.81,1.09]
Ringdal 1999	217/294	104/146		38.21%	1.04[0.92,1.17]
Subtotal (95% CI)	558	276		66.1%	0.99[0.91,1.09]
Total events: 389 (LTRA+ICS), 194 (ICS alone)					
Heterogeneity: Tau ² =0; Chi ² =0.99, df=1(P=0.32); I ² =0%					
Test for overall effect: Z=0.11(P=0.92)					
2.17.3 Pranlukast					
Tomari 2001	0/21	0/20			Not estimable
Subtotal (95% CI)	21	20			Not estimable
Total events: 0 (LTRA+ICS), 0 (ICS alone)					
Heterogeneity: Not applicable					
Test for overall effect: Not applicable					
Total (95% CI)	1094	805		100%	0.96[0.89,1.03]
Total events: 586 (LTRA+ICS), 413 (ICS alone)					
Heterogeneity: Tau ² =0; Chi ² =3.12, df=4(P=0.54); I ² =0%					
Test for overall effect: Z=1.13(P=0.26)					
Test for subgroup differences: Chi ² =1.95, df=1 (P=0.16), I ² =48.59%					
			Favours LTRA+ICS 0.2 0.5 1 2 5 Favours ICS alone		

Analysis 2.18. Comparison 2 Anti-leukotrienes and inhaled corticosteroids versus HIGHER dose of inhaled corticosteroids, Outcome 18 Headache.

Analysis 2.19. Comparison 2 Anti-leukotrienes and inhaled corticosteroids versus HIGHER dose of inhaled corticosteroids, Outcome 19 Nausea.

Analysis 2.20. Comparison 2 Anti-leukotrienes and inhaled corticosteroids versus HIGHER dose of inhaled corticosteroids, Outcome 20 Elevated liver enzymes.

Analysis 2.21. Comparison 2 Anti-leukotrienes and inhaled corticosteroids versus HIGHER dose of inhaled corticosteroids, Outcome 21 Oral moniliasis.

Analysis 2.22. Comparison 2 Anti-leukotrienes and inhaled corticosteroids versus HIGHER dose of inhaled corticosteroids, Outcome 22 Hoarseness of voice.

Study or subgroup	LTRA+ICS n/N	ICS alone n/N	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
Yildirim 2004	0/15	1/15		0.33[0.01,7.58]
Favours LTRA+ICS 0.01 0.1 1 10 100 Favours ICS alone				

Analysis 2.23. Comparison 2 Anti-leukotrienes and inhaled corticosteroids versus HIGHER dose of inhaled corticosteroids, Outcome 23 Abdominal pain.

Study or subgroup	LTRA+ICS n/N	ICS alone n/N	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
2.23.1 Montelukast				
Shah 2006	2/30	1/30		2[0.19,20.9]
Favours LTRA+ICS 0.01 0.1 1 10 100 Favours ICS alone				

Analysis 2.24. Comparison 2 Anti-leukotrienes and inhaled corticosteroids versus HIGHER dose of inhaled corticosteroids, Outcome 24 Death.

Study or subgroup	LTRA+ICS n/N	ICS alone n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
2.24.1 Montelukast					
Price 2003	0/448	0/441			Not estimable
Subtotal (95% CI)	448	441			Not estimable
Total events: 0 (LTRA+ICS), 0 (ICS alone)					
Heterogeneity: Not applicable					
Test for overall effect: Not applicable					
2.24.2 Zafirlukast					
Nayak 1998	0/264	0/130			Not estimable
Ringdal 1999	0/294	0/146			Not estimable
Subtotal (95% CI)	558	276			Not estimable
Total events: 0 (LTRA+ICS), 0 (ICS alone)					
Heterogeneity: Not applicable					
Test for overall effect: Not applicable					
Favours LTRA+ICS 0.01 0.1 1 10 100 Favours ICS alone					

Comparison 3. Anti-leukotrienes and inhaled corticosteroids versus TAPERING dose of inhaled corticosteroids

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 % Change from baseline ICS dose	4	930	Mean Difference (IV, Random, 95% CI)	-3.05 [-8.13, 2.03]
1.1 Montelukast	2	359	Mean Difference (IV, Random, 95% CI)	-8.25 [-18.19, 1.68]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.2 Zafirlukast	2	571	Mean Difference (IV, Random, 95% CI)	-0.23 [-5.97, 5.50]
2 Participants with ≥ 1 exacerbation requiring oral corticosteroids	5	542	Risk Ratio (M-H, Random, 95% CI)	0.46 [0.20, 1.04]
2.1 Montelukast	4	280	Risk Ratio (M-H, Random, 95% CI)	0.44 [0.17, 1.16]
2.2 Zafirlukast	1	262	Risk Ratio (M-H, Random, 95% CI)	0.50 [0.10, 2.41]
3 Participants with ≥ 1 exacerbation requiring hospital admission	2	231	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
3.1 Montelukast	2	231	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
4 Participants with change from baseline dose of ICS required to maintain control	3		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
4.1 Montelukast	3	112	Risk Ratio (M-H, Random, 95% CI)	0.98 [0.85, 1.13]
5 Participants who completely tapered off ICS	3	607	Risk Ratio (M-H, Random, 95% CI)	1.17 [0.95, 1.46]
5.1 Montelukast	2	248	Risk Ratio (M-H, Random, 95% CI)	1.38 [0.97, 1.96]
5.2 Zafirlukast	1	359	Risk Ratio (M-H, Random, 95% CI)	1.06 [0.81, 1.40]
6 Participants with $\geq 50\%$ reduction from baseline ICS dose	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
6.1 Montelukast	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
7 Change from baseline in morning PEFR (L/min)	2		Mean Difference (IV, Random, 95% CI)	Subtotals only
7.1 Montelukast	2	218	Mean Difference (IV, Random, 95% CI)	-2.45 [-10.96, 6.06]
8 Change from baseline in evening PEFR (L/min)	1		Mean Difference (IV, Random, 95% CI)	Totals not selected
8.1 Montelukast	1		Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]
9 Change from baseline FEV ₁ (L)	1		Mean Difference (IV, Random, 95% CI)	Totals not selected
9.1 Montelukast	1		Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
10 Change in PC ₂₀	1		Mean Difference (IV, Random, 95% CI)	Totals not selected
10.1 Montelukast	1		Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]
11 Change from baseline in mean daytime asthma symptom score	1		Mean Difference (IV, Random, 95% CI)	Totals not selected
11.1 Montelukast	1		Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]
12 Change from baseline in mean night-time asthma symptom score	1		Mean Difference (IV, Random, 95% CI)	Totals not selected
12.1 Montelukast	1		Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]
13 Change from baseline in mean daily use of β_2 -agonists (puffs/d)	1		Mean Difference (IV, Random, 95% CI)	Totals not selected
13.1 Montelukast	1		Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]
14 Overall withdrawals	7	1150	Risk Ratio (M-H, Random, 95% CI)	0.80 [0.62, 1.04]
14.1 Montelukast	5	529	Risk Ratio (M-H, Random, 95% CI)	0.67 [0.46, 0.98]
14.2 Zafirlukast	2	621	Risk Ratio (M-H, Random, 95% CI)	0.93 [0.66, 1.33]
15 Withdrawals due to adverse effects	6	1110	Risk Ratio (M-H, Random, 95% CI)	0.87 [0.42, 1.81]
15.1 Montelukast	4	489	Risk Ratio (M-H, Random, 95% CI)	0.49 [0.23, 1.05]
15.2 Zafirlukast	2	621	Risk Ratio (M-H, Random, 95% CI)	1.63 [0.71, 3.74]
16 Withdrawals due to poor asthma control/exacerbations	7	1150	Risk Ratio (M-H, Random, 95% CI)	0.61 [0.41, 0.92]
16.1 Montelukast	5	529	Risk Ratio (M-H, Random, 95% CI)	0.60 [0.39, 0.93]
16.2 Zafirlukast	2	621	Risk Ratio (M-H, Random, 95% CI)	0.71 [0.19, 2.58]
17 Serious adverse events	2	621	Risk Ratio (M-H, Random, 95% CI)	2.44 [1.52, 3.92]
17.1 Zafirlukast	2	621	Risk Ratio (M-H, Random, 95% CI)	2.44 [1.52, 3.92]
18 Overall adverse effects	6	1100	Risk Ratio (M-H, Random, 95% CI)	0.95 [0.83, 1.08]
18.1 Montelukast	4	479	Risk Ratio (M-H, Random, 95% CI)	0.82 [0.54, 1.25]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
18.2 Zafirlukast	2	621	Risk Ratio (M-H, Random, 95% CI)	0.98 [0.89, 1.09]
19 Headache	7	1140	Risk Ratio (M-H, Random, 95% CI)	0.79 [0.54, 1.15]
19.1 Montelukast	5	519	Risk Ratio (M-H, Random, 95% CI)	0.66 [0.34, 1.27]
19.2 Zafirlukast	2	621	Risk Ratio (M-H, Random, 95% CI)	0.89 [0.47, 1.67]
20 Nausea	6	1100	Risk Ratio (M-H, Random, 95% CI)	1.32 [0.59, 2.97]
20.1 Montelukast	4	479	Risk Ratio (M-H, Random, 95% CI)	1.72 [0.34, 8.76]
20.2 Zafirlukast	2	621	Risk Ratio (M-H, Random, 95% CI)	1.21 [0.47, 3.10]
21 Elevated liver enzymes	6	1099	Risk Ratio (M-H, Random, 95% CI)	1.58 [0.82, 3.04]
21.1 Montelukast	4	478	Risk Ratio (M-H, Random, 95% CI)	1.31 [0.61, 2.79]
21.2 Zafirlukast	2	621	Risk Ratio (M-H, Random, 95% CI)	2.81 [0.74, 10.64]
22 Pharyngitis	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
22.1 Montelukast	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
23 Abdominal pain	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
23.1 Montelukast	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
24 Vomiting	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
24.1 Montelukast	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
25 Diarrhoea	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
26 Death	6	1100	Risk Ratio (M-H, Random, 95% CI)	3.1 [0.13, 75.10]
26.1 Montelukast	4	479	Risk Ratio (M-H, Random, 95% CI)	3.1 [0.13, 75.10]
26.2 Zafirlukast	2	621	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
27 Change from baseline exhaled NO concentration (ppb)	1		Mean Difference (IV, Random, 95% CI)	Totals not selected
27.1 Montelukast	1		Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]
28 Change from baseline in sputum eosinophil counts	1		Mean Difference (IV, Random, 95% CI)	Totals not selected
28.1 Montelukast	1		Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
29 Change from baseline in serum eosinophils at lowest tolerated dose	2		Mean Difference (IV, Random, 95% CI)	Subtotals only
29.1 Montelukast	2	167	Mean Difference (IV, Random, 95% CI)	0.18 [-1.13, 1.50]

Analysis 3.1. Comparison 3 Anti-leukotrienes and inhaled corticosteroids versus TAPERING dose of inhaled corticosteroids, Outcome 1 % Change from baseline ICS dose.

Analysis 3.2. Comparison 3 Anti-leukotrienes and inhaled corticosteroids versus TAPERING dose of inhaled corticosteroids, Outcome 2 Participants with ≥ 1 exacerbation requiring oral corticosteroids.

Analysis 3.3. Comparison 3 Anti-leukotrienes and inhaled corticosteroids versus TAPERING dose of inhaled corticosteroids, Outcome 3 Participants with ≥ 1 exacerbation requiring hospital admission.

Analysis 3.4. Comparison 3 Anti-leukotrienes and inhaled corticosteroids versus TAPERING dose of inhaled corticosteroids, Outcome 4 Participants with change from baseline dose of ICS required to maintain control.

Analysis 3.5. Comparison 3 Anti-leukotrienes and inhaled corticosteroids versus TAPERING dose of inhaled corticosteroids, Outcome 5 Participants who completely tapered off ICS.

Analysis 3.6. Comparison 3 Anti-leukotrienes and inhaled corticosteroids versus TAPERING dose of inhaled corticosteroids, Outcome 6 Participants with ≥ 50% reduction from baseline ICS dose.

Analysis 3.7. Comparison 3 Anti-leukotrienes and inhaled corticosteroids versus TAPERING dose of inhaled corticosteroids, Outcome 7 Change from baseline in morning PEFR (L/min).

Analysis 3.8. Comparison 3 Anti-leukotrienes and inhaled corticosteroids versus TAPERING dose of inhaled corticosteroids, Outcome 8 Change from baseline in evening PEFR (L/min).

Analysis 3.9. Comparison 3 Anti-leukotrienes and inhaled corticosteroids versus TAPERING dose of inhaled corticosteroids, Outcome 9 Change from baseline FEV₁ (L).

Analysis 3.10. Comparison 3 Anti-leukotrienes and inhaled corticosteroids versus TAPERING dose of inhaled corticosteroids, Outcome 10 Change in PC₂₀.

Analysis 3.11. Comparison 3 Anti-leukotrienes and inhaled corticosteroids versus TAPERING dose of inhaled corticosteroids, Outcome 11 Change from baseline in mean daytime asthma symptom score.

Analysis 3.12. Comparison 3 Anti-leukotrienes and inhaled corticosteroids versus TAPERING dose of inhaled corticosteroids, Outcome 12 Change from baseline in mean night-time asthma symptom score.

Study or subgroup	LTRA+ICS		ICS alone		Mean Difference	Mean Difference
	N	Mean(SD)	N	Mean(SD)	Random, 95% CI	Random, 95% CI
Kanniess 2002	26	0.1 (0.4)	24	0.2 (0.3)		-0.08[-0.26,0.1]
					Favours LTRA+ICS	Favours ICS alone

Analysis 3.13. Comparison 3 Anti-leukotrienes and inhaled corticosteroids versus TAPERING dose of inhaled corticosteroids, Outcome 13 Change from baseline in mean daily use of β_2 -agonists (puffs/d).

Study or subgroup	LTRA+ICS		ICS alone		Mean Difference	Mean Difference
	N	Mean(SD)	N	Mean(SD)	Random, 95% CI	Random, 95% CI
3.13.1 Montelukast						
Kanniess 2002	26	0.5 (2)	24	0.7 (2.2)		-0.21[-1.36,0.94]
					Favours LTRA+ICS	Favours ICS alone

Analysis 3.14. Comparison 3 Anti-leukotrienes and inhaled corticosteroids versus TAPERING dose of inhaled corticosteroids, Outcome 14 Overall withdrawals.

Study or subgroup	LTRA+ICS n/N	ICS alone n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
3.14.1 Montelukast					
Kanniess 2002	3/26	2/24		2.28%	1.38[0.25,7.59]
Lofdahl 1999	18/113	31/113		24.48%	0.58[0.35,0.98]
Riccioni 2005	2/20	3/20		2.34%	0.67[0.12,3.57]
Shingo 2002	1/10	1/12		0.94%	1.2[0.09,16.84]
Tohda 2002	14/93	20/98		17.08%	0.74[0.4,1.37]
Subtotal (95% CI)	262	267		47.12%	0.67[0.46,0.98]
Total events: 38 (LTRA+ICS), 57 (ICS alone)					
Heterogeneity: Tau ² =0; Chi ² =1.27, df=4(P=0.87); I ² =0%					
Test for overall effect: Z=2.06(P=0.04)					
3.14.2 Zafirlukast					
Bateman 1993	47/242	26/117		36.47%	0.87[0.57,1.34]
Laitinen 1993	26/175	12/87		16.41%	1.08[0.57,2.03]
Subtotal (95% CI)	417	204		52.88%	0.93[0.66,1.33]
Total events: 73 (LTRA+ICS), 38 (ICS alone)					
Heterogeneity: Tau ² =0; Chi ² =0.29, df=1(P=0.59); I ² =0%					
Test for overall effect: Z=0.39(P=0.7)					
Total (95% CI)	679	471		100%	0.8[0.62,1.04]
Total events: 111 (LTRA+ICS), 95 (ICS alone)					
Heterogeneity: Tau ² =0; Chi ² =3.08, df=6(P=0.8); I ² =0%					
Test for overall effect: Z=1.7(P=0.09)					
Test for subgroup differences: Chi ² =1.52, df=1 (P=0.22), I ² =34.22%					
			Favours LTRA+ICS		Favours ICS alone

Analysis 3.15. Comparison 3 Anti-leukotrienes and inhaled corticosteroids versus TAPERING dose of inhaled corticosteroids, Outcome 15 Withdrawals due to adverse effects.

Analysis 3.16. Comparison 3 Anti-leukotrienes and inhaled corticosteroids versus TAPERING dose of inhaled corticosteroids, Outcome 16 Withdrawals due to poor asthma control/exacerbations.

Analysis 3.17. Comparison 3 Anti-leukotrienes and inhaled corticosteroids versus TAPERING dose of inhaled corticosteroids, Outcome 17 Serious adverse events.

Analysis 3.18. Comparison 3 Anti-leukotrienes and inhaled corticosteroids versus TAPERING dose of inhaled corticosteroids, Outcome 18 Overall adverse effects.

Analysis 3.19. Comparison 3 Anti-leukotrienes and inhaled corticosteroids versus TAPERING dose of inhaled corticosteroids, Outcome 19 Headache.

Analysis 3.20. Comparison 3 Anti-leukotrienes and inhaled corticosteroids versus TAPERING dose of inhaled corticosteroids, Outcome 20 Nausea.

Analysis 3.21. Comparison 3 Anti-leukotrienes and inhaled corticosteroids versus TAPERING dose of inhaled corticosteroids, Outcome 21 Elevated liver enzymes.

Analysis 3.22. Comparison 3 Anti-leukotrienes and inhaled corticosteroids versus TAPERING dose of inhaled corticosteroids, Outcome 22 Pharyngitis.

Analysis 3.23. Comparison 3 Anti-leukotrienes and inhaled corticosteroids versus TAPERING dose of inhaled corticosteroids, Outcome 23 Abdominal pain.

Analysis 3.24. Comparison 3 Anti-leukotrienes and inhaled corticosteroids versus TAPERING dose of inhaled corticosteroids, Outcome 24 Vomiting.

Analysis 3.25. Comparison 3 Anti-leukotrienes and inhaled corticosteroids versus TAPERING dose of inhaled corticosteroids, Outcome 25 Diarrhoea.

Analysis 3.26. Comparison 3 Anti-leukotrienes and inhaled corticosteroids versus TAPERING dose of inhaled corticosteroids, Outcome 26 Death.

Analysis 3.27. Comparison 3 Anti-leukotrienes and inhaled corticosteroids versus TAPERING dose of inhaled corticosteroids, Outcome 27 Change from baseline exhaled NO concentration (ppb).

Analysis 3.28. Comparison 3 Anti-leukotrienes and inhaled corticosteroids versus TAPERING dose of inhaled corticosteroids, Outcome 28 Change from baseline in sputum eosinophil counts.

Analysis 3.29. Comparison 3 Anti-leukotrienes and inhaled corticosteroids versus TAPERING dose of inhaled corticosteroids, Outcome 29 Change from baseline in serum eosinophils at lowest tolerated dose.

ADDITIONAL TABLES

Table 1. Summary of study characteristics for same dose of ICS comparison

Anti-leukotrienes and ICS versus same dose of ICS									
Trial ID	ICS alone		Combination of anti-leukotriene and ICS				Weeks of treatment	Asthma severity	Funding source
	Drug	Dose	Drug	Dose	Drug	Dose			
Cakmak 2004	BUD	400 µg/d	ZAF	40 mg/d	BUD	400 µg/d	6	Mild to moderate	NR
Demuro-Mercon 2001	FLU	100 µg twice daily	MON	10 mg/d	FLU	100 µg twice daily	4	Chronic	NR
Djukanovic 2010	FLU	100 µg twice daily	MON	10 mg/d	FLU	100 µg twice daily	12	Mild to moderate	GlaxoSmithKline
Huang 2003	BUD	At least 400 µg/d	ZAF	20 mg twice daily	BUD	At least 400 µg/d	4	Moderate persistent	NR
Korzh 2004	BUD	400 µg/d	MON	10 mg/d	BUD	400 µg/d	8	Mild to moderate	NR
Laviolette 1999	BDP	200 µg twice daily	MON	10 mg/d	BDP	200 µg twice daily	16	NR	Merck Research Laboratories
Riccioni 2001	BUD	800 µg/d	ZAF	20 mg twice daily	BUD	800 µg/d	8	Mild persistent	NR
Riccioni 2002	BUD	800 µg/d	MON	10 mg/d	BUD	800 µg/d	16	Mild persistent	NR
Sano 2008	BDP	800 µg/d	PRA	450 mg/d	BDP	800 µg/d	260	Mild to moderate	NR
SD-004-0216	BUD	200 µg twice daily	ZAF	20 mg twice daily	BUD	200 µg twice daily	8	NR	AstraZeneca
Storms 2004	FLU	100 µg twice daily	MON	10 mg/d	FLU	100 µg twice daily	4	Moderate	Merck
Tognella 2004	FLU	250 µg/d	MON	10 mg/d	FLU	250 µg/d	6	Mild persistent	NR

Table 1. Summary of study characteristics for same dose of ICS comparison (Continued)

Ulrik 2010	ICS	200 to 1000 µg/d BDP equivalent	MON	10 mg/d	ICS	200 to 1000 µg/d BDP equivalent	12	Mild to moder- ate	Merck
Vaquerizo 2003	BUD	400 to 1600 µg/d	MON	10 mg/d	BUD	400 to 1600 µg/d	16	Mild to moder- ate	Merck, Sharpe and Dohme, Spain
Virchow 2000	ICS	1000 to 4000 µg/d	ZAF	80 mg twice daily	ICS	1000 to 4000 µg/d	6	NR	AstraZeneca Pharmaceu- ticals, UK
Riccioni 2003*	BUD	800 µg/d	MON	10 mg/d	BUD	800 µg/d	12	Mild persistent	NR

*Three-arm study

BDP: beclomethasone; BUD: budesonide; FLU: fluticasone; ICS: inhaled corticosteroids; MDI: metered dose inhaler; MON: montelukast; NR: not reported; PRA: pranlukast; TRI: triamcinolone; ZAF: zafirlukast.

Table 2. Summary of study characteristics for higher dose of ICS comparison

Anti-leukotrienes and ICS vs higher dose of ICS									
Trial ID	ICS alone		Combination of anti-leukotriene and ICS				Weeks of treatment	Asthma severity	Funding source
	Drug	Dose	Drug	Dose	Drug	Dose			
Riccioni 2003a	BUD	800 µg/d	MON	10 mg/d	BUD	1600 µg/d	12	Mild persis- tent	NR
Barnes 2007	BUD	800 µg/d	MON	10 mg/d	BUD	1600 µg/d	12	NR	Merck, Sharpe and Dohme Ltd, UK
Bilancia 2000	BUD	400 µg twice daily	MON	10 mg/d	BUD	800 µg twice daily	12	Mild to mod- erate	NR
Chlumský 2000	ICS	400 to 1000 µg/ d	ZAF	40 mg twice daily	ICS	800 to 2000 µg/d	6	Moderate to severe	NR
Kirishi 2013	ICS	NR	MON	10 mg/d	ICS	NR	12	NR	Ministry of Education, Science and

Table 2. Summary of study characteristics for higher dose of ICS comparison *(Continued)*

									Culture, Japan
Nayak 1998*	BDP	336 µg/d	ZAF	40 mg twice daily	BDP	672 µg/d	13	NR	AstraZeneca
Nayak 1998a	BDP	336 µg/d	ZAF	80 mg twice daily	BDP	672 µg/d	13	NR	AstraZeneca
Nsouli 2000	BDP	168 to 500 µg/d	MON	10 mg/d	BDP	336 to 1000 µg/d	12	NR	NR
Price 2003	BUD	800 µg/d	MON	10 mg/d	BUD	800 µg twice daily	12	NR	Merck
Ringdal 1999*	BDP	400 to 500 µg/d	ZAF	20 mg twice daily	BDP	800 to 1000 µg/d	12	Mild to moderate	AstraZeneca
Ringdal 1999a	BDP	400 to 500 µg/d	ZAF	80 mg twice daily	BDP	800 to 1000 µg/d	12	Mild to moderate	AstraZeneca
Shah 2006	BUD	200 µg twice daily	MON	10 mg/d	BUD	400 µg twice daily	8	NR	NR
Tomari 2001	BDP	800 µg/d	PRA	450 mg/d	BDP	1600 µg/d	16	Moderate	NR
Xiang 2001	BUD	NR	ZAF	20 mg twice daily	BUD	NR	4	Mild to moderate	NR
Yildirim 2004	BUD	200 µg twice daily	MON	10 mg/d	BUD	400 µg twice daily	6	Moderate persistent	NR
Beg 2014	FLU	125 µg twice daily	MON	10 mg/d	FLU	250 µg twice daily	12	Moderate persistent	No support
Ye 2015	BUD	400 µg/d	MON	10 mg/d	BUD	800 µg/d	12	NR	Merck

* Three-arm study

BDP: beclomethasone; BUD: budesonide; FLU: fluticasone; ICS: inhaled corticosteroids; MON: montelukast; NR, not reported; PRA: pranlukast; TRI: triamcinolone; ZAF: zafirlukast.

Table 3. Summary of study characteristics for tapering dose of ICS in both groups

Anti-leukotrienes and ICS versus tapering dose of ICS	
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Table 3. Summary of study characteristics for tapering dose of ICS in both groups (Continued)

Trial ID	ICS alone		Combination of anti-leukotriene and ICS				Weeks of treatment	Asthma severity	Funding source
	Drug	Dose	Drug	Dose	Drug	Dose			
Kanniess 2002	BDP	800 µg/d	MON	10 mg/d	BDP	800 µg/d	6	Moderate	Merck
Lofdahl 1999	ICS	Tapering or increased doses of ICS	MON	10 mg/d	ICS	Tapering or increased doses of ICS	12	Chronic	Merck
Riccioni 2005	BUD	400 µg twice daily: tapered to half at 4, 8 and 12 weeks	MON	10 mg/d	BUD	400 µg twice daily: tapered to half at 4, 8 and 12 weeks	12	Mild to moderate persistent	NR
Tohda 2002	BDP	800 to 1600 µg/d tapered to half every 8 weeks	MON	10 mg/d	BDP	800 to 1600 µg/d tapered to half every 8 weeks	24	Moderate to severe	Banyu Pharmaceutical Co Ltd
Shingo 2002	ICS	BDP (600 to 1600 µg/d), FLN (1000 to 2000 µg/d) or TRI (1200 to 3200 µg/d)	MON	10 mg/d	ICS	BDP (600 to 1600 µg/d), FLN (1000 to 2000 µg/d) or TRI (1200 to 3200 µg/d)	8	Moderate to severe	Merck Research Laboratories
Bateman 1993	ICS	400 to 750 µg/d	ZAF	20 mg twice daily	ICS	400 to 750 µg/d	20	Mild	AstraZeneca
Laitinen 1993	ICS	800 to 2000 µg/d	ZAF	20 mg twice daily	ICS	800 to 2000 µg/d	12	Moderate	AstraZeneca

* Three-arm study

BDP: beclomethasone; BUD: budesonide; FLN: flunisolide; ICS: inhaled corticosteroids; MON: montelukast; NR, not reported; TRI: triamcinolone; ZAF: zafirlukast.

APPENDICES

Appendix 1. Search strategy for Cochrane Airways Group Register of Trials

#1 AST:MISC1

#2 MeSH DESCRIPTOR Asthma Explode All

#3 asthma*:ti,ab

#4 #1 or #2 or #3

#5 MeSH DESCRIPTOR Leukotriene Antagonists

#6 leukotriene*

#7 leucotriene*

#8 anti-leukotriene*

#9 anti-leucotriene*

#10 montelukast

#11 singulair

#12 zafirlukast

#13 accolate

#14 pranlukast

#15 azlaire

#16 LTRA

#17 #5 or #6 or #7 or #8 or #9 or #10 or #11 or #12 or #13 or #14 or #15 or #16

#18 (steroid* or corticosteroid* or glucocorticoid*) AND (inhal*)

#19 fluticasone

#20 beclomethasone

#21 budesonide

#22 triamcinolone

#23 flunisolide

#24 ciclesonide

#25 flixotide or flovent

#26 becotide or beclofort or becodisk or QVAR or vanceril

#27 pulmicort

#28 kenalog or azmacort

#29 bronalide

#30 Alvesco

#31 #18 or #19 or #20 or #21 or #22 or #23 or #24 or #25 or #26 or #27 or #28 or #29 or #30

#32 #4 and #17 and #31

Note: The Airways Group Register is maintained in specialist software developed for Cochrane: the Cochrane Register of Studies (CRS)

MISC1 denotes the field in the CRS reference record where the record has been coded for condition, in this case, asthma.

Appendix 2. Sources and search methods for the Cochrane Airways Group Specialised Register (CAGR)

Electronic searches: core databases

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

Handsearches: core respiratory conference abstracts

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

MEDLINE search strategy used to identify trials for the CAGR

Asthma search

1. exp Asthma/
2. asthma\$.mp.
3. (antiasthma\$ or anti-asthma\$).mp.
4. Respiratory Sounds/

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

Filter to identify RCTs

1. exp "clinical trial [publication type]"/
2. (randomised or randomised).ab,ti.
3. placebo.ab,ti.
4. dt.fs.
5. randomly.ab,ti.
6. trial.ab,ti.
7. groups.ab,ti.
8. or/1-7
9. Animals/
10. Humans/
11. 9 not (9 and 10)
12. 8 not 11

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

WHAT'S NEW

Date	Event	Description
3 April 2017	Amended	Corrected typo in plain language summary.

CONTRIBUTIONS OF AUTHORS

Dr. Bhupendrasinh Chauhan updated the protocol, updated the literature review from 2004 to 2015, reviewed citations for selection screening, extracted data from included papers, prepared summary of findings tables, updated the manuscript, prepared the response to peer reviewers' comments and approved the final version.

Dr. Maya Jeyaraman reviewed citations from the updated literature review for eligibility, extracted baseline characteristics and outcome data from included papers, assessed the methodological quality of included studies, entered all study data into RevMan, analysed and interpreted results and contributed to updating the manuscript.

Dr. Amrinder Mann contributed to extracting baseline characteristics and assessed the methodological quality of a few included studies.

Dr. Justin Lys contributed to extracting baseline characteristics, prepared summary of findings tables and assessed the methodological quality of a few included studies.

Dr. Ahmed Abou-Setta provided methodological expertise, acted as an expert to resolve conflicts and contributed to updating the manuscript.

Dr. Ryan Zarychanski provided methodological expertise.

Prof Francine Ducharme wrote the initial protocol, conducted and published the original review and supervised the update, reviewed the analysis and interpretation of data and edited the final manuscript.

DECLARATIONS OF INTEREST

Prof Francine Ducharme has received a travel support, research funds and honoraria for advisory boards, consultation and speaking from GlaxoSmithKline, Novartis, Takeda and Merck Frosst Inc.

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Internal sources

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

External sources

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

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

We planned to determine the homogeneity of effect sizes between studies pooled with the DerSimonian and Laird method, with an I^2 statistic > 40% used as the cut-off level for significance. In the case of heterogeneity, we proposed to use a random-effects model for these summary estimates. However, considering the high heterogeneity between included studies, we used a random-effects model to analyse summary estimates for all outcomes.

INDEX TERMS

Medical Subject Headings (MeSH)

Administration, Inhalation; Adrenal Cortex Hormones [*administration & dosage] [adverse effects]; Anti-Asthmatic Agents [*administration & dosage] [adverse effects]; Asthma [*drug therapy]; Disease Progression; Drug Therapy, Combination; Forced Expiratory Volume [drug effects]; Leukotriene Antagonists [*administration & dosage] [adverse effects]; Numbers Needed To Treat; Peak Expiratory Flow Rate [drug effects]; Randomized Controlled Trials as Topic

MeSH check words

Adolescent; Adult; Humans