

Drug Class Review

Controller Medications for Asthma

Final Report

November 2008

The Agency for Healthcare Research and Quality has not yet seen or approved this report.

The purpose of this report is to make available information regarding the comparative effectiveness and safety profiles of different drugs within pharmaceutical classes. Reports are not usage guidelines, nor should they be read as an endorsement of, or recommendation for, any particular drug, use or approach. Oregon Health & Science University does not recommend or endorse any guideline or recommendation developed by users of these reports.

Daniel E. Jonas, MD, MPH
Katie Kiser, Pharm.D., BCPS
Betsy Bryant Shilliday, Pharm.D., CDE, CPP
Laura C. Morgan, MA
Patricia Thieda, MA
Daniel Reuland, MD, MPH

Produced by
RTI-UNC Evidence-based Practice Center
Cecil G. Sheps Center for Health Services Research
University of North Carolina at Chapel Hill
725 Martin Luther King Jr. Blvd, CB# 7590
Chapel Hill, NC 27599-7590
Tim Carey, M.D., M.P.H., Director

Oregon Evidence-based Practice Center
Oregon Health & Science University
Mark Helfand, MD, MPH, Director

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INTRODUCTION

Asthma is a chronic lung disease characterized by reversible airway obstruction, inflammation, and increased airway responsiveness. As a result of inflammation, individuals with asthma may experience symptoms such as wheezing, difficulty breathing, or coughing. The airway obstruction which occurs with asthma is generally reversible spontaneously or with treatment. Asthma is thought to have a genetic, inheritable component, often begins early in life, and consists of variable symptoms regardless of asthma classification.¹ The Expert Panel of the National Asthma Education and Prevention Program (NAEPP) recently reclassified asthma categories; the mild intermittent category was eliminated (now called intermittent) and the persistent category was subdivided into mild, moderate, or severe.¹ The change was partly done to acknowledge that exacerbations can be severe in any asthma category. Table 1 lists the criteria used to classify asthma severity.

Table 1. Classification of asthma¹

	Daytime symptoms	Nighttime symptoms	Short-Acting Beta-2 Agonist use	Interference with daily activity	FEV ₁ % predicted	FEV ₁ /FVC
Intermittent	≤ 2 days/week	≤ 2 nights/month	≤ 2 days/week	None	> 80%	Normal
Persistent						
Mild	> 2/week but < 1/day	3-4 nights/month	> 2 days/week	Minor	≥ 80%	Normal
Moderate	Daily	> 1 night/week but < 1/night	Daily	Some	> 60% - < 80%	Reduced 5%
Severe	Continual	Frequent	Several times daily	Extreme	≤ 60%	Reduced > 5%

Asthma outcomes have improved over the past several years but the burden remains substantial. Asthma is estimated to affect 300 million individuals worldwide with 22 million of those individuals being in the US.²⁻⁴ It is the cause of 250,000 worldwide deaths annually with 4,000 of them in the US.²⁻⁴ The World Health Organization estimates 15 million disability-adjusted life years (DALYs) lost annually due to asthma.² Based on 2007 data, asthma accounts for 19.7 billion dollars annually in the US with 14.7 billion in direct, 5 billion in indirect, and 6.2 billion in prescription cost. In 2005, there were 488,594 hospital discharges in the US, 12.8 physician office visits, 1.3 million hospital outpatient department visits, and 1.8 million emergency department visits due to asthma in the United States.⁴

Many current medications available to treat persistent asthma target the inflammatory process caused by multiple inflammatory cells and mediators including lymphocytes, mast cells, eosinophils, among others.¹ There are currently two categories of medications used in asthma treatment: controller medications and quick relief (or rescue) medications. Although all patients with persistent asthma should have a short-acting relief medication on hand for treatment of exacerbations and a controller medication for long-term control, this report will focus on the following currently available controller medications: inhaled corticosteroids (ICSs), Long-Acting Beta-2 Agonists (LABAs), leukotriene modifiers, anti-IgE medications, and combination products.

Inhaled corticosteroids are the preferred agents for long-term control of persistent asthma according to expert panel recommendations.¹ The inhaled route of administration serves to directly target the inflammation while minimizing systemic effects which can result from oral administration. These agents act via anti-inflammatory mechanisms and have been approved as first line therapy for asthma control in all stages of persistent asthma.¹ The six ICSs currently available include: beclomethasone dipropionate, budesonide, flunisolide, fluticasone propionate, mometasone furoate, and triamcinolone acetonide. Table 2 lists the trade names, manufacturers, available formulations, and age indications for controller medications for persistent asthma.

Table 2. Long-term controller medication class, trade names, manufacturers, formulations, and indications^{1, 5-10}

Medication class	Generic name	Trade name	Manufacturer	Dosage form/device	Strength	Approved indication in US & Canada
Inhaled corticosteroids	Beclomethasone dipropionate	QVAR [®]	Ivax	HFA	40 mcg/puff 50 mcg/puff* 80 mcg/puff 100 mcg/puff*	Asthma (age ≥ 5)
		Vanceril ^{®++}	Schering	MDI	42 mcg/puff 84 mcg/puff	Asthma (age ≥ 5)
	Budesonide	Pulmicort Flexhaler [®]	AstraZeneca	DPI	90 mcg/dose 180 mcg/dose	Asthma (age ≥ 6)
		Pulmicort Turbuhaler ^{®*}	AstraZeneca	DPI	100 mcg/dose* 200 mcg/dose* 400 mcg/dose*	
Flunisolide	AeroBid [®] AeroBid-M [®]	Forest	Forest	MDI	250 mcg/puff	Asthma (age ≥ 6)
				MDI-menthol		
	AeroSpan [®]	Forest	HFA	80 mcg/puff ⁺		
Fluticasone propionate	Flovent [®]	GlaxoSmithKline	GlaxoSmithKline	HFA	44 mcg/puff 50 mcg/puff* 110 mcg/puff 125 mcg/puff* 220 mcg/puff 250 mcg/puff*	Asthma (age ≥ 4)
					DPI	
	Flovent Rotadisk ^{®++}	GlaxoSmithKline	DPI	50 mcg/dose 100 mcg/dose 250 mcg/dose	Asthma (age ≥ 12)	
	Flovent Diskus ^{®*}	GlaxoSmithKline	DPI	50 mcg/dose ⁺ 100 mcg/dose* 250 mcg/dose* 500 mcg/dose*	Asthma (age ≥ 4 yrs)	
Mometasone	Asmanex	Schering	DPI	110 mcg/dose	Asthma (age ≥ 4)	

Medication class	Generic name	Trade name	Manufacturer	Dosage form/device	Strength	Approved indication in US & Canada
	furoate	Twisthaler®			220 mcg/dose	
	Triamcinolone acetoneide	Azmacort®	Kos	MDI – with spacer mouthpiece	75 mcg/dose	Asthma (age ≥ 6)
Leukotriene modifiers	Montelukast	Singulair®	Merck	Tablets Chewable tablets Granules	10 mg ⁺ 4 mg, 5 mg ⁺ 4 mg/packet ⁺	Asthma (age ≥ 1)
Leukotriene receptor antagonists	Zafirlukast	Accolate®	AstraZeneca	Tablets	10 mg ⁺ 20 mg ⁺	Asthma (age ≥ 5 yrs in US); (age ≥ 12 yrs in Canada)
5-lipoxygenase inhibitor	Zileuton	Zyflo® Zyflo CR®	Critical Therapeutics	Tablets Extended release tablets	600 mg 600 mg	Asthma (age ≥ 12 yrs)
	Arformoterol	Brovana®	Sepracor	Inhalation solution	15 mcg/2ml	Not approved for asthma (COPD only)
		Foradil Aerolizer®	Schering	DPI	12 mcg/capsule ⁺	Asthma (age ≥ 5 yrs)
Long-Acting Beta-2 Agonists	Formoterol fumarate/ Eformoterol	Oxeze Turbuhaler® ⁺	AstraZeneca (Canada)	DPI	6 mcg/capsule* 12 mcg/capsule*	Asthma (age ≥ 6 yrs)
		Oxis Turbuhaler® [#]	Astra Pharmaceuticals	DPI	6 mcg/puff 12 mcg/puff	Asthma (age ≥ 6 yrs)
	Salmeterol xinafoate	Serevent Diskus®	GlaxoSmithKline	DPI	50 mcg/blister ⁺	Asthma (age ≥ 4 yrs)
		Serevent Diskhaler® [*]	GlaxoSmithKline	DPI	50 mcg/blister*	Asthma (age ≥ 4 yrs)
Anti-IgE medications	Omalizumab	Xolair®	Genentech	Powder for subcutaneous injection	202.5 mg (delivers 150 mg/1.2ml)	Asthma (age ≥ 12 yrs)
		Advair Diskus®	GlaxoSmithKline	DPI	100mcg/50mcg ⁺ 250mcg/50mcg ⁺ 500mcg/50mcg ⁺	Asthma (age ≥ 4 yrs)
Combination products	Fluticasone propionate/ Salmeterol xinafoate	Advair HFA®	GlaxoSmithKline	HFA	45mcg/21mcg 115mcg/21mcg 125mcg/25mcg* 230mcg/21mcg 250mcg/25mcg*	Asthma (age ≥ 12 yrs)
		Symbicort®	AstraZeneca	HFA	80mcg/4.5mcg 160mcg/4.5mcg	Asthma (age ≥ 12 yrs)
	Budesonide/ formoterol	Symbicort Turbuhaler® [*]	AstraZeneca (Canada)	DPI	100mcg/6mcg* 200mcg/6mcg*	Asthma (age ≥ 12 yrs)

Abbreviations: DPI = dry powder inhaler; HFA = hydrofluoroalkane propellant; MDI = metered dose inhaler.

*This product is available in Canada only.

+This product is available in the US & Canada.

#This product is not available in the US or in Canada.

++This product has been discontinued by the manufacturer.

Inhaled corticosteroids are delivered through a variety of devices including metered dose inhalers (MDIs), dry powder inhalers (DPIs), or nebulizers. In the past, MDI products contained chlorofluorocarbons (CFCs) which were found to be detrimental to the ozone and have now been banned from use. They were replaced with alternative administration devices including hydrofluoroalkane propellant (HFA) MDIs and dry powder inhalers. The ICSs often have different kinetic and side effect profiles with similar numerical doses depending on the delivery device and the product.¹ Since there are not enough head-to-head trials comparing all of the various ICSs, determining equivalency among products is sometimes difficult. Table 3 lists comparative dosing of the available products based on the recently updated NAEPP guidelines.¹

Long-Acting Beta-2 Agonists (LABAs) are agents used in combination with ICSs to obtain control in persistent asthma. The mechanism of action of these agents is through relaxation of airway smooth muscles to reverse bronchoconstriction.^{1,5} In contrast to short-acting beta-2 agonists, which are used for quick relief of acute symptoms due to their quick onset and short-duration of action, LABAs provide long-acting bronchodilation for 12 hours allowing for twice daily administration.¹ The NAEPP expert panel advocates the use of LABAs as the preferred adjunct therapy with ICSs in individuals ≥ 12 years old for persistent asthma.¹ In addition, LABAs are useful in the prevention of exercise-induced bronchospasm (EIB).^{1,5} These agents are not recommended nor approved for relief of acute asthma symptoms or for use as monotherapy for persistent asthma.¹ Currently there are two available LABAs: formoterol (formerly known as eformoterol in the UK) and salmeterol. Arformoterol is available in the US but is currently approved only for COPD (Table 2). The main clinical difference in the two available agents is that formoterol has a quicker onset of action than salmeterol.¹

The leukotriene modifiers are another class of controller medications used in the treatment of asthma and are comprised of two classes of medications: leukotriene receptor antagonists (montelukast and zafirlukast) and 5-lipoxygenase inhibitors (zileuton) (Table 2). Leukotrienes cause contraction of smooth muscles, mucous secretion, and inflammation contributing to asthma symptoms.^{1,5} The leukotriene receptor antagonists (LTRAs) bind to cell receptors to prevent these actions from occurring.¹ Montelukast is approved for children ≥ 1 year old and zafirlukast for children ≥ 5 years old in the United States and ≥ 12 years old in Canada. They are approved for mild persistent asthma and as adjunct therapy with ICSs.^{1,5} Montelukast is also approved for EIB.⁵ The leukotriene modifiers are the only medications delivered orally in pill-form, rather than as inhalers, for the treatment of persistent asthma.

Zileuton's mechanism of action is through the inhibition of 5-lipoxygenase which is involved in the production of leukotrienes.¹ This medication is indicated for use in children ≥ 12 years old.^{1,5} Metabolism of this drug is through the CYP 450 1A2, 2C9, and 3A4 isoenzymes which are responsible for a variety of drug-drug interactions.⁵ In addition, liver function monitoring is required with zileuton therapy,^{1,5} due to the involvement of the CYP 450 system and potential adverse events, which has limited the use of this product.

The newest class of asthma control medications is the anti-IgE medication class, which currently consist of one agent, omalizumab (Table 2). This agent binds to IgE receptors on mast cells and basophils to decrease sputum production and asthma symptoms.¹ Omalizumab is approved for use in patients ≥ 12 years old who have uncontrolled asthma on inhaled corticosteroids.^{1,5} This agent is an injectable medication (given every two to four weeks)

approved for adjunct therapy with ICSs in moderate to severe persistent asthma as well as for adjunct therapy with high dose ICSs plus LABA in severe persistent asthma.¹

Lastly, the combination controller medications available for the treatment of asthma include fluticasone/salmeterol (FP/SM) and budesonide/formoterol (BUD/FM) (Table 2). These medications are both combinations of an ICS and a LABA and are indicated for use in those patients requiring two agents for control.^{1,5} These combination products can be used when monotherapy with ICS is not adequate or when disease severity warrants treatment with two controller medications. These agents are available as DPI or HFA products (Table 2).

Table 3. Estimated comparative daily dosages for inhaled corticosteroids¹

Drug	Low daily dose			Medium daily dose			High Daily Dose		
	Child 0-4 yrs	Child 5-11 yrs	≥12yrs & adults	Child 0-4 yrs	Child 5-11 yrs	≥12yrs & adults	Child 0-4 yrs	Child 5-11 yrs	≥12yrs & Adults
Beclomethasone CFC[*]		84-336 mcg	168-504 mcg		336-672 mcg	504-840 mcg		> 672 mcg	> 840 mcg/d
42 mcg/puff		2-8 puffs/d	4-12 puffs/d		8-16 puffs/d	13-20 puffs/d		> 16 puffs/d	> 20 puffs/d
84 mcg/puff		1-4 puffs/d	2-6 puffs/d		4-8 puffs/d	7-10 puffs/d		> 8 puffs/d	> 10 puffs/d
Beclomethasone HFA		80-160mcg	80-240mcg		> 160-320 mcg	> 240-480 mcg		> 320 mcg	> 480 mcg
40 mcg/puff		2-4 puffs/d	2-6 puffs/d		4-8 puffs/d	6-12 puffs/d		> 8 puffs/d	> 12 puffs/d
80 mcg/puff		1-2 puffs/d	1-3 puffs/d		2-4 puffs/d	3-6 puffs/d		> 4 puffs/d	> 6 puffs/d
Budesonide CFC[†]		400-800 mcg	400-1200 mcg		800-1600 mcg	1200-2400 mcg		> 1600 mcg	> 2400mcg
200 mcg/dose		2-4 puffs/d	2-6 puffs/d		4-8 puffs/d	6-12 puffs/d		> 8 puffs/d	> 12 puffs/d
Budesonide DPI (Flexhaler)		180-400 mcg	180-600 mcg		> 400-800 mcg	> 600-1200 mcg		> 800 mcg	> 1200 mcg
90 mcg/dose		2-4 puffs/d	2-6 puffs/d		4-8 puffs/d	6-13 puffs/d		> 8 puffs/d	> 13 puffs/d
180 mcg/dose		1-2 puffs/d	1-3 puffs/d		2-4 puffs/d	3-6 puffs/d		> 4 puffs/d	> 6 puffs/d
Budesonide DPI (Turbuhaler)		180-400 mcg	180-600 mcg		> 400-800 mcg	> 600-1200 mcg		> 800 mcg	> 1200 mcg
200 mcg/dose		1-2 puffs/d	1-3 puffs/d		2-4 puffs/d	3-6 puffs/d		> 4 puffs/d	> 6 puffs/d
Budesonide suspension (Respules)	0.25-0.5mg	0.5mg		> 0.5-1mg	1mg		> 1mg	2mg	
0.25 mg/2ml inhalation	2-4 ml/d	4 ml/d		4-8 ml/d	8 ml/d		> 8 ml/d	16 ml/d	
0.5mg/2ml inhalation	1-2ml/d	2ml/d		2-4ml/d	4ml/d		> 4ml/d		
1 mg/2ml inhalation	0.5-1ml/d	1ml/d		1-2ml/d	2 ml/d		> 2 ml/d	4 ml/d	
Flunisolide		500-750 mcg	500-1000 mcg		1000-1250 mcg	>1000-2000 mcg		> 1250 mcg	> 2000 mcg
250 mcg/puff		2-3 puffs/d	2-4 puffs/d		4-5 puffs/d	4-8 puffs/d		> 5 puffs/d	> 8 puffs/d
Flunisolide HFA		160 mcg	320 mcg		320mcg	> 320-640 mcg		≥ 640 mcg	> 640 mcg
80 mcg/puff		2 puffs/d	4 puffs/d		4 puffs/d	4-8 puffs/d		> 8 puffs/d	> 8 puffs/d
Fluticasone MDI	176 mcg	88-176 mcg	88-264 mcg	> 176-352 mcg	> 176-352 mcg	> 264-440 mcg	> 352 mcg	> 352 mcg	> 440 mcg
44 mcg/puff	4 puffs/d	2-4 puffs/d	2-6 puffs/d	6-15 puffs/d	4-10 puffs/d	6-10 puffs/d	> 8 puffs/d	> 8 puffs/d	> 10 puffs/d
110 mcg/puff	1 puff/d	1 puff/d	1-2 puffs/d	2-6 puffs/d	1-4 puffs/d	2-4 puffs/d	> 4 puffs/d	> 4 puffs/d	> 4 puffs/d
220 mcg/puff	NA	NA	1 puff/d	1-3 puffs/d	1-2 puffs/d	1-2 puffs/d	> 1 puffs/d	> 1 puffs/d	> 2 puffs/d

Drug	Child 0-4 yrs	Low daily dose		Medium daily dose		High Daily Dose			
		Child 5-11 yrs	≥12yrs & adults	Child 0-4 yrs	Child 5-11 yrs	≥12yrs & adults	Child 0-4 yrs	Child 5-11 yrs	≥12yrs & Adults
Fluticasone DPI (Rotadisk; Diskus)		100-200 mcg	100-300 mcg		> 200-400 mcg	> 300-500 mcg		> 400 mcg	> 500 mcg
50 mcg/dose DPI		2-4 puffs/d	2-6 puffs/d		4-8 puffs/d	6-10 puffs/d		> 8 puffs/d	> 10 puffs/d
100 mcg/dose DPI		1-2 puffs/d	1-3 puffs/d		2-4 puffs/d	3-5 puffs/d		> 4 puffs/d	> 5 puffs/d
250 mcg/dose DPI		NA	1 puff/d		1 puff/d	1-2 puffs/d		> 1 puff/d	> 2 puffs/d
Mometasone DPI (Asmanex Twisthaler)		100 mcg	200 mcg			400 mcg			> 400 mcg
110 mcg/dose (delivers 100mcg/dose)		1 puff/d	2 puff/d			4 puff/d			> 4 puffs/d
220 mcg/dose (delivers 200mcg/dose)		NA	1 puff/d			2 puffs/d			> 2 puffs/d
Triamcinolone MDI		300-600 mcg	300-750 mcg		> 600-900 mcg	> 750-1500 mcg		> 900 mcg	> 1500 mcg
75 mcg/puff		4-8 puffs/d	4-10 puffs/d		8-12 puffs/d	10-20 puffs/d		> 12 puffs/d	> 20 puffs/d

Abbreviations: HFA = Hydrofluoroalkane propellant; MDI = Metered dose inhaler; DPI = Dry powder inhaler; estimated dosing equivalency from Thorsson et al.¹¹ and Agertoft & Pedersen;¹² CFC = Contains chlorofluorocarbons; substances known to destroy ozone in the upper atmosphere

Purpose and Limitations of Evidence Reports

Systematic reviews, or evidence reports, are the building blocks underlying evidence-based practice. An evidence report focuses attention on the strength and limits of evidence from published studies about the effectiveness of a clinical intervention. The development of an evidence report begins with a careful formulation of the problem. The goal is to select questions that are important to patients and clinicians, then to examine how well the scientific literature answers those questions.

An evidence report emphasizes the patient's perspective in the choice of outcome measures. Studies that measure health outcomes (events or conditions that the patient can feel, such as quality of life, functional status, and fractures) are emphasized over studies of intermediate outcomes (such as changes in bone density). Such a report also emphasizes measures that are easily interpreted in a clinical context. Specifically, measures of absolute risk or the probability of disease are preferred to measures such as relative risk. The difference in absolute risk between interventions is dependent on the numbers of events in both groups, such that the difference (absolute risk reduction) is smaller when there are fewer events. In contrast, the difference in relative risk is fairly constant across groups with different baseline risk for the event, such that the difference (relative risk reduction) is similar across these groups. Relative risk reduction is often more impressive than the absolute risk reduction. Another measure useful in applying the results of a study is the number needed to treat (or harm), the NNT (or NNH). The NNT represents the number of patients who would have to be treated with an intervention for 1 additional patient to benefit (experience a positive outcome or avoid a negative outcome). The absolute risk reduction is used to calculate the NNT.

An evidence report also emphasizes the quality of the evidence, giving more weight to studies that meet high methodological standards that reduce the likelihood of biased results. In general, for questions about the relative benefits of a drug, the results of well-done, randomized controlled trials are regarded as better evidence than results of cohort, case-control, or cross-sectional studies. In turn, these studies are considered better evidence than uncontrolled trials or case series. For questions about tolerability and harms, controlled trials typically provide limited information. For these questions, observational study designs may provide important information that is not available from trials. Within this hierarchy, cohort designs are preferred when well conducted and assessing a relatively common outcome. Case control studies are preferred only when the outcome measure is rare, and the study is well conducted.

An evidence report pays particular attention to the generalizability of *efficacy* studies performed in controlled or academic settings. *Efficacy* studies provide the best information about how a drug performs in a controlled setting that allows for better control over potential confounding factors and bias. However, the results of efficacy studies are not always applicable to many, or to most patients seen in everyday practice. This is because most efficacy studies use strict eligibility criteria that may exclude patients based on their age, sex, medication compliance, or severity of illness. For many drug classes, including antipsychotics, unstable or severely impaired patients are often excluded from trials. Often, efficacy studies also exclude patients who have comorbid diseases, meaning diseases other than the one under study. Efficacy studies may also use dosing regimens and follow-up protocols that may be impractical in other practice settings. They often restrict options, such as combining therapies or switching drugs that are of value in actual practice. They often examine the short-term effects of drugs that in practice are used for much longer periods of time. Finally, efficacy studies tend to use objective measures of effects that do not capture all of the benefits and

harms of a drug or do not reflect the outcomes that are most important to patients and their families.

An evidence report also highlights studies that reflect actual clinical *effectiveness* in unselected patients and community practice settings. *Effectiveness* studies conducted in primary care or office-based settings use less stringent eligibility criteria, assess health outcomes, and have longer follow-up periods than most efficacy studies. The results of effectiveness studies are more applicable to the “average” patient than results from highly selected populations in efficacy studies. Examples of effectiveness outcomes include quality of life, hospitalizations, and the ability to work or function in social activities. These outcomes are more important to patients, family, and care providers than surrogate or intermediate measures such as scores based on psychometric scales.

Efficacy and effectiveness studies overlap. For example, a study might use very narrow inclusion criteria like an efficacy study, but, like an effectiveness study, might examine flexible dosing regimens, have a long follow-up period, and measure quality of life and functional outcomes. For this report we sought evidence about outcomes that are important to patients and would normally be considered appropriate for an effectiveness study. However, many of the studies that reported these outcomes were short-term and used strict inclusion criteria to select eligible patients. For these reasons, it is neither possible nor desirable to exclude evidence based on these characteristics. Labeling each study as an efficacy or effectiveness study, while convenient, is of limited value; it is more useful to consider whether the patient population, interventions, time frame, and outcomes are relevant to one’s practice, or, in the clinical setting, how relevant they are to a particular patient.

Studies across the continuum from efficacy to effectiveness can be useful in comparing the clinical value of different drugs. Effectiveness studies are more applicable to practice, but efficacy studies are a useful scientific standard to determine whether the characteristics of different drugs are related to their effects on disease. An evidence report reviews the efficacy data thoroughly to ensure that decision-makers can assess the scope, quality, and relevance of the available data. This thoroughness is not intended to obscure the fact that efficacy data, no matter how much there is of it, may have limited applicability to practice. Clinicians can judge the relevance of the study results to their practice and should note where there are gaps in the available scientific information.

Unfortunately, for many drugs, there are few or no effectiveness studies and many efficacy studies. As a result, clinicians must make decisions about treatment for many patients who would not have been included in controlled trials and for whom the effectiveness and tolerability of the different drugs are uncertain. An evidence report indicates whether or not there is evidence that drugs differ in their effects in various subgroups of patients, but it does not attempt to set a standard for how results of controlled trials should be applied to patients who would not have been eligible for them. With or without an evidence report, these are decisions that must be informed by clinical judgment.

In the context of developing recommendations for practice, evidence reports are useful because they define the strengths and limits of the evidence, clarifying whether assertions about the value of the intervention are based on strong evidence from clinical studies. By themselves, they do not tell you what to do. Judgment, reasoning, and applying one’s values under conditions of uncertainty must also play a role in decision making. Users of an evidence report must also keep in mind that *not proven* does not mean *proven not*; that is, if the evidence supporting an assertion is insufficient, it does not mean the assertion is not true. The quality of

the evidence on effectiveness is a key component, but not the only component, in making decisions about clinical policies. Additional criteria include acceptability to physicians or patients, the potential for unrecognized harms, the applicability of the evidence to practice, and consideration of equity and justice.

Scope and Key Questions

The purpose of this review is to assist healthcare providers, researchers and policy makers in making clinical decisions, creating formularies, and developing policies regarding long-term asthma control medications based on the most current available literature. We compare the efficacy, effectiveness, and tolerability of controller medications used in the treatment of persistent asthma as well as look for subgroups that may differ in these areas. The Research Triangle Institute International-University of North Carolina Evidence-based Practice Center (RTI-UNC EPC) wrote preliminary key questions, identifying the populations, interventions, and outcomes of interest, and based on these, the eligibility criteria for studies. These were reviewed and revised by representatives of organizations participating in the Drug Effectiveness Review Project (DERP) along with the RTI-UNC EPC, after considering comments received from the public which derived from a draft version posted to the DERP web site. The participating organizations of DERP are responsible for ensuring that the scope of the review reflects the populations, drugs, and outcome measures of interest to both clinicians and patients. The participating organizations approved the following key questions to guide this review:

1. What is the comparative efficacy and effectiveness of controller medications used to treat outpatients with persistent asthma?
2. What is the comparative tolerability and frequency of adverse events for controller medications used to treat outpatients with persistent asthma?
3. Are there subgroups of these patients based on demographics (age, racial groups, gender), asthma severity, comorbidities (drug-disease interactions, including obesity), smoking status, genetics, or pregnancy for which asthma controller medications differ in efficacy, effectiveness, or frequency of adverse events?

Inclusion Criteria

This review includes pediatric or adult outpatients with persistent asthma being treated with any of the following agents: inhaled corticosteroids (beclomethasone, budesonide, flunisolide, fluticasone, triamcinolone, mometasone), Long-Acting Beta-2 Agonists (formoterol, arformoterol, salmeterol), leukotriene modifiers (montelukast, zafirlukast, zileuton), anti-IgE therapy (omalizumab), and combination products (fluticasone propionate/salmeterol xinafoate, budesonide/formoterol). For efficacy and effectiveness outcomes of interest we included randomized controlled trials of at least 6 weeks duration and a sample size of at least 40 which evaluate control of symptoms, functional capacity and quality of life, urgent care services, adherence, hospitalization or mortality. For adverse events outcomes, we also included observational studies of at least 6 months duration and a sample size of at least 100 (Table 4). Dosing equivalency of the agents was based on the 2007 NAEPP Expert Panel publication.¹

Table 4. Outcome measures and study eligibility criteria

Outcome	Outcome measures	Study eligibility criteria
Efficacy / Effectiveness	<ul style="list-style-type: none"> • Asthma control <ul style="list-style-type: none"> - Asthma exacerbations - Days/nights frequency of symptoms - Frequency of rescue medication use - Courses of oral steroids • Quality of life • Ability to participate in work, school, sports, or physical activity • Adherence • Emergency department / urgent medical care visits • Hospitalization • Mortality 	<ul style="list-style-type: none"> • Randomized controlled clinical trials of at least 6 weeks duration and $n \geq 40$ or quality systematic reviews • When sufficient evidence was not available for head-to-head trials within a specific diagnostic group we evaluated placebo-controlled trials
Adverse Events/Safety	<ul style="list-style-type: none"> • Overall adverse event reports • Withdrawals due to adverse effects • Serious adverse event reports • Specific adverse events including: <ul style="list-style-type: none"> • <i>Growth</i> • <i>Bone mineral density</i> • <i>Osteoporosis/fractures</i> • <i>Ocular toxicity</i> • <i>Suppression of HPA axis</i> • <i>Anaphylaxis</i> • <i>Death</i> 	<ul style="list-style-type: none"> • Randomized controlled clinical trials of at least 6 weeks duration and $n \geq 40$ • Observational studies of at least 6 months duration and $n \geq 100$ • When sufficient evidence was not available for head-to-head trials within a specific diagnostic group, we evaluated placebo-controlled trials

METHODS

Literature Search

To identify relevant citations, we searched MEDLINE®, the Cochrane Database of Systematic Reviews®, and the Cochrane Central Register of Controlled Trials® and the International Pharmaceutical Abstracts (through April 2008), using terms for included drugs, indications, and study designs (see Appendix 1 for complete search strategies). We limited the electronic searches to “human” and “English language”. We attempted to identify additional studies through hand searches of reference lists of included studies and reviews. In addition, we searched the FDA’s Center for Drug Evaluation and Research (CDER) and Center for Biologics Evaluation and Research (CBER), the Canadian Agency for Drugs and Technology in Health, and the National Institute for Health and Clinical Excellence web sites for medical and statistical reviews, and technology assessments. Finally, we searched dossiers submitted by pharmaceutical companies for the current review. All citations were imported into an electronic database (Endnote® v. X.02).

Study Selection

All citations were reviewed for inclusion using the criteria shown in Table 5. Two reviewers independently assessed titles and abstracts, where available, of citations identified from

literature searches. If both reviewers agreed that the trial did not meet eligibility criteria, it was excluded. Full-text articles of potentially relevant citations were retrieved and again were assessed for inclusion by two reviewers. Disagreements were resolved by consensus. Results published *only* in abstract form were not included unless adequate details were available for quality assessment.

Table 5. Study inclusion criteria

Populations

- Adult or pediatric outpatients with persistent asthma
- Persistent asthma is defined using the NAEPP classification¹ (see Table 1)

Interventions/Treatments

Inhaled corticosteroids:

- Beclomethasone
- Budesonide
- Flunisolide
- Fluticasone
- Triamcinolone
- Mometasone

Long-Acting Beta-2 Agonists (LABAs)

- Formoterol
- Arformoterol
- Salmeterol

Leukotriene modifiers

- Montelukast
- Zafirlukast
- Zileuton

Anti-IgE therapy

- Omalizumab

Combination products

- Fluticasone propionate/Salmeterol xinafoate
- Budesonide/formoterol

Efficacy and effectiveness outcomes

- Control of symptoms (e.g., days/nights/frequency of symptoms, rate of asthma exacerbations, frequency of rescue medication use, courses of oral steroids)
- Functional capacity and quality of life (missed school and missed work days, ability to participate in work/school/sports/physical activity, activity limitation, improved sleep/sleep disruption)
- Urgent care services (Emergency department visits/urgent medical care visits)
- Adherence
- Hospitalization
- Mortality

Adverse events/safety outcomes

- Overall adverse events
- Withdrawals due to adverse events
- Serious adverse events (e.g., acute adrenal crisis, fractures, mortality)
- Specific adverse events (e.g. growth suppression, bone mineral density/osteoporosis, ocular toxicity, suppression of the HPA axis, tachycardia, anaphylaxis, death)

Study designs

- For efficacy and effectiveness, randomized controlled trials of at least 6 weeks duration (N ≥ 40) and good-quality systematic reviews
-

- For adverse events/safety, randomized controlled trials of at least 6 weeks ($N \geq 40$) and observational studies of at least 6 months duration ($N \geq 100$)
-

We reviewed the literature using a hierarchy of evidence approach, where the best evidence is the focus of our synthesis for each question, population, intervention and outcome addressed. Results from well-conducted, systematic reviews and head-to-head trials provide the strongest evidence to compare drugs with respect to effectiveness, efficacy, and adverse events; head-to-head trials were defined as those comparing one included treatment with another. If sufficient evidence was available from head-to-head trials we did not examine placebo-controlled trials for general efficacy/effectiveness. If no head-to-head evidence was published, as was the case for omalizumab, we reviewed placebo-controlled trials.

A review was considered to be systematic if it presented a systematic approach to reviewing the literature through a comprehensive search strategy, provided adequate data from included studies, and evaluated the methods of included studies (with quality review/critical appraisal).

Data Abstraction

We designed and used a structured data abstraction form to ensure consistency in appraisal for each study. Trained reviewers abstracted data from each study and assigned an initial quality rating. A second reviewer read each abstracted article, evaluated the completeness of the data abstraction, and confirmed the quality rating. Differences in quality ratings were resolved by discussion or involving a third senior reviewer when necessary. We abstracted the following data from included trials: study design, setting, population characteristics (including age, sex, asthma severity, smoking status), inclusion and exclusion criteria, interventions (drugs, dose, delivery device, duration), comparisons, numbers screened/eligible/enrolled, additional medications allowed, outcome assessments, attrition, withdrawals attributed to adverse events, results, and adverse events reported. We recorded intention-to-treat (ITT) results if available.

Validity Assessment (Quality Assessment)

Two independent reviewers assigned quality ratings; they resolved any disagreements by discussion or by consulting a third, senior reviewer. We assessed the internal validity (quality) of trials based on the predefined criteria listed in Appendix C. These criteria are based on the U.S. Preventive Services Task Force and the National Health Service Centre for Reviews and Dissemination (U.K.) criteria.^{13, 14}

Elements of internal validity assessment for trials included, among others, the methods used for randomization, allocation concealment, and blinding; the similarity of compared groups at baseline; maintenance of comparable groups; adequate reporting of dropouts, crossover, adherence, and contamination; overall and differential loss to follow-up; and the use of intention-to-treat analysis.

We assessed observational study designs based on the potential for selection bias (methods of selection of subjects and loss to follow-up), potential for measurement bias (equality, validity, and reliability of ascertainment of outcomes), and control for potential confounders (Appendix C).

Systematic reviews which fulfilled inclusion criteria were rated for quality using predefined criteria (see Appendix C): a clear statement of the questions and inclusion criteria; adequacy of the search strategy; quality assessment of individual trials; the adequacy of information provided; and appropriateness of the methods of synthesis.

Studies that had a fatal flaw were rated “poor quality” and were not included in the evidence report. Trials that met all criteria were rated “good quality”. The remainder received a quality rating of “fair”. This includes studies that presumably fulfilled all quality criteria but did not report their methodologies to an extent that answered all our questions. As the fair-quality category is broad, studies with this rating vary in their strengths and weaknesses: the results of some fair-quality studies are *likely* to be valid, while others are only *probably* valid. A poor-quality trial is not valid—the results are at least as likely to reflect flaws in the study design as the true difference between the compared drugs. A fatal flaw is reflected by failing to meet combinations of items of the quality assessment checklist.

Attrition, or loss to follow-up, was defined as the number of persons randomized who did not reach the endpoint of the study,¹⁵ independent of the reason and the use of intention-to-treat analysis. We adopted no formal cut-off point for loss to follow-up because many studies defined withdrawals due to acute worsening of the disease as an outcomes measure.

Identification of Effectiveness Trials

The first key question addresses both efficacy (i.e., do asthma controller medications differ in their effects under ideal or highly controlled circumstances) and effectiveness. We distinguish between efficacy studies and effectiveness studies. Studies conducted in highly selected populations over shorter periods of time are characterized as efficacy studies. Those conducted in primary care or office-based settings that use less stringent eligibility criteria (i.e., broad range of population characteristics and disease severity) and long follow-up periods (i.e., greater than one year) are characterized as effectiveness studies. The results of effectiveness studies are more applicable to the average patient than results from highly selected populations (i.e., efficacy studies)

Data Synthesis

We constructed evidence tables showing the study characteristics, quality ratings, and results for all included studies. Trials that evaluated one included medication against another provided direct evidence of comparative effectiveness and adverse event rates. These data are the primary focus. In theory, trials that make comparisons with other drug classes or placebos can also provide evidence about effectiveness. This is known as an indirect comparison and can be difficult to interpret for a number of reasons, primarily issues of heterogeneity between trial populations, interventions, and assessment of outcomes. Data from indirect comparisons are used to support direct comparisons, where they exist, and are also used as the primary comparison where no direct comparisons exist. Such indirect comparisons should be interpreted with caution.

In addition to discussion of the findings of the studies overall, quantitative analyses were conducted using meta-analyses on outcomes for which a sufficient number of studies reported and for studies which they were homogeneous enough such that combining their results can be justified. Otherwise, the data are summarized qualitatively. Random effects models were used for the estimation of pooled effects.¹⁶ Forest plots are presented to graphically summarize the study results and the pooled results.¹⁷ The Q-statistic and the I^2 statistic (the proportion of variation in study estimates due to heterogeneity) were calculated to assess heterogeneity between the effects from the studies.^{18,19} Potential sources of heterogeneity were examined with subgroup analysis by factors such as study design, study quality,

variations in interventions, and patient population characteristics. Meta-analyses were conducted using Stata®, version 9.

Overall Strength of Evidence

We summarize the overall strength of evidence for the efficacy/effectiveness of each head-to-head comparison in evidence profiles. The overall strength of evidence for a particular key question reflects the design, quality, consistency, directness, and magnitude of effect of the set of studies relevant to the question. We rate the overall strength of evidence as low, moderate, high, or insufficient using a modified GRADE approach established by the Evidence-based Practice Centers. *High* strength of evidence indicates high confidence in the estimate of effect and that the evidence reflects the true effect; further research is unlikely to change our confidence. *Moderate* strength of evidence indicates moderate confidence that the evidence reflects the true effect; further research may change our confidence in the estimate and may change the estimate. *Low* strength of evidence indicates low confidence that the evidence reflects the true effect; further research is likely to change our confidence in the estimate and is likely to change the estimate. *Insufficient* indicates that evidence is unavailable or does not permit estimation of an effect.

Peer Review and Public Comment

Original DERP reports are independently reviewed and commented upon by three to five peer reviewers. Peer reviewers are identified through a number of sources, including but not limited to: professional society membership, acknowledged expertise in a particular field, prominent authorship in the published literature or recommendation by DERP participating organizations. A listing of individuals who have acted as peer reviewers of DERP reports is available on the DERP website. Peer reviewers have a maximum of three weeks for review and comment. They are asked to submit their comments in a standardized form in order to maintain consistent handling of comments across reports and to allow the DERP team to address all comments adequately. The DERP process allows for a two-week public comment period prior to finalization of the report. Draft reports are posted on the DERP web site and interested individuals or organizations have the ability to review the complete draft report and submit comments.

RESULTS

Overview

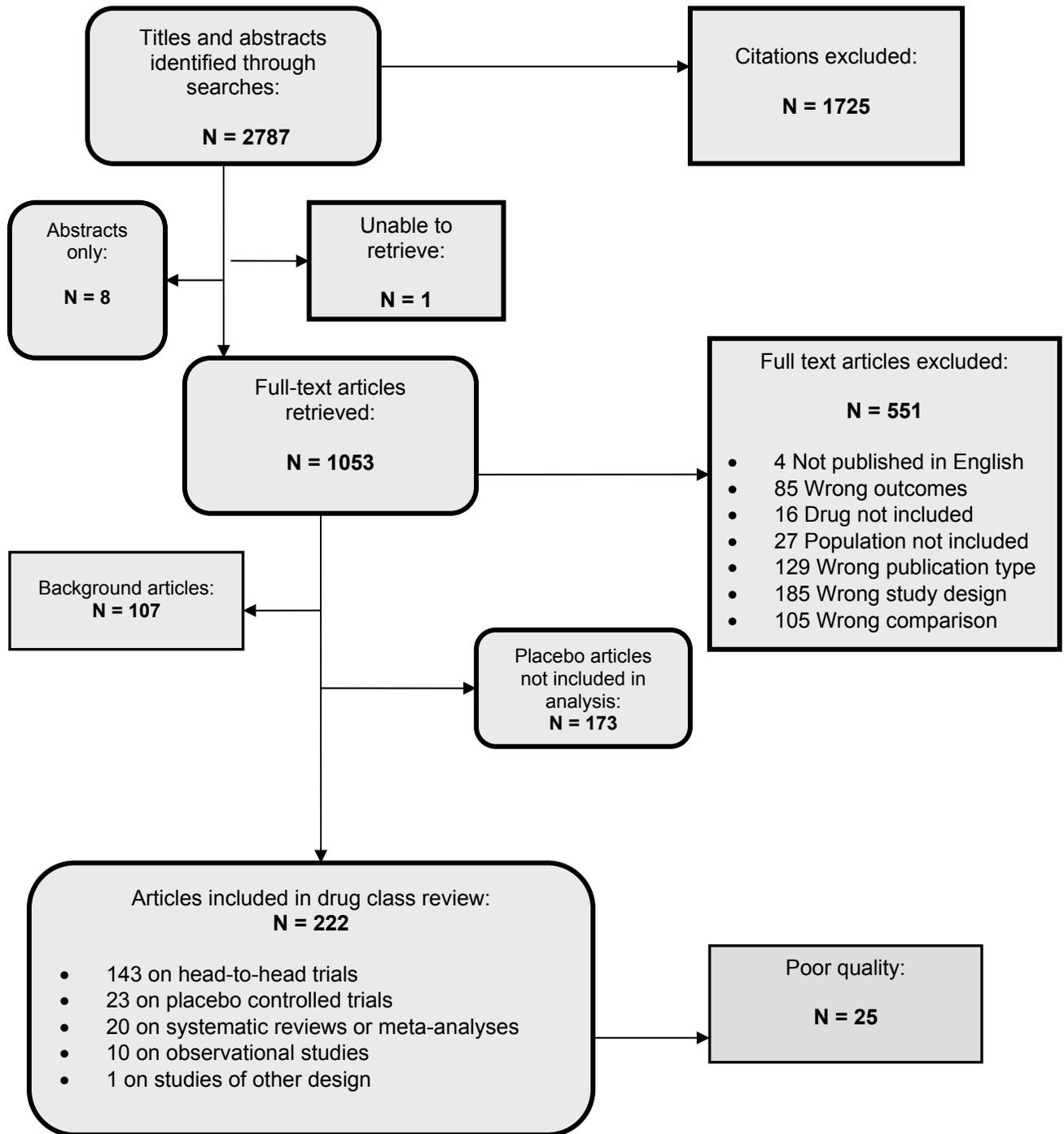
We identified 2,775 citations from searches and reviews of reference lists. We identified nine additional references from dossiers submitted by pharmaceutical companies and three from public comments. The total number of citations in our database was 2,787. In total we included 201 studies (222 articles): 20 systematic reviews with meta-analyses, 146 randomized controlled trials (166 articles), nine observational studies (10 articles), and one study of other design. We retrieved 107 articles for background information.

Reasons for exclusions were based on eligibility or quality criteria (Figure 1, QUORUM Tree). Twenty-five studies that met the eligibility criteria were subsequently rated as poor quality for internal validity (Appendix D).

Of the 201 included studies, 69 percent were financially supported by pharmaceutical companies and 11 percent were funded by government agencies or independent funds. Two

percent were funded by both government and pharmaceutical sources. Five percent did not report the source of funding but at least one author had a primary affiliation with a pharmaceutical company. We could not determine a funding source for 13 percent of the studies included.

Figure 1. Results of Literature Search



Key Question 1. Efficacy and Effectiveness

What is the comparative efficacy and effectiveness of controller medications used to treat outpatients with persistent asthma?

I. Intra-class comparisons (within one class)

A. Inhaled Corticosteroids

Summary of findings

We found 2 systematic reviews with meta-analyses^{20, 21} and 30 head-to-head RCTs (29 publications)²²⁻⁵⁰ (Table 7). Four of the head-to-head RCTs included children < 12^{26, 29, 39, 41} (Table 8). No study was characterized as an effectiveness trial; all included efficacy studies were conducted in narrowly defined populations and/or were limited to less than one year of follow-up.

Overall, efficacy studies provide moderate evidence that ICSs do not differ in their ability to control asthma symptoms, prevent exacerbations, and reduce the need for additional rescue medication at equipotent doses administered through comparable delivery devices (Table 6 Evidence Profile). Relatively few studies reported exacerbations, healthcare utilization (hospitalizations, emergency visits), or quality of life outcomes. Long-term data beyond 12 weeks is lacking for most of the comparisons. In children, head-to-head trials support the conclusion that ICSs do not differ in their impact on health outcomes, but data was only available for three comparisons (two systematic reviews and four RCTs): beclomethasone compared with budesonide, beclomethasone compared with fluticasone, and budesonide compared with fluticasone. We do not include meta-analyses for this section of the report because there were generally too few trials comparing equipotent ICS doses reporting similar outcomes measures.

Table 6. Evidence profile of the comparative efficacy of inhaled corticosteroids

Evidence Profile: Comparative efficacy of inhaled corticosteroids							
No. of Studies (# of subjects)	Design	Quality	Consistency	Directness	Result (for equipotent doses)	Other modifying factors*	Overall Strength of the Evidence
Beclomethasone compared with Budesonide							
1 SR (1174) 2 RCTs (669)	1 SR w/ MA 2 RCTs	Good Fair	Some inconsistency	Direct	No difference for most outcomes	None	Moderate
Beclomethasone compared with Flunisolide							
We did not identify any good or fair quality systematic reviews or head-to-head trials							
Beclomethasone compared with Fluticasone							
1 SR (14,602) 10 RCTs (3,223)	1 SR w/ MA 10 RCTs	Good Good (1), Fair (9)	Some inconsistency	SR not direct (compared FP compared with combined effect of BDP/BUD)	No difference for most outcomes	None	High
Beclomethasone compared with Mometasone							
2 (592)	RCTs	Fair	Consistent	Direct	No difference	None	Moderate

Evidence Profile: Comparative efficacy of inhaled corticosteroids							
No. of Studies (# of subjects)	Design	Quality	Consistency	Directness	Result (for equipotent doses)	Other modifying factors*	Overall Strength of the Evidence
					for all outcomes		
Beclomethasone compared with Triamcinolone							
2 (668)	RCTs	Fair	Some inconsistency	Direct	No difference for most outcomes	No long-term data (both were 8-weeks)	Moderate
Budesonide compared with Flunisolide							
1 (179)	RCT	Fair	NA	Direct	No difference for all outcomes	No long-term data (6-week trail)	Moderate
Budesonide compared with Fluticasone							
1 SR (14,602)	1 SR w/ MA	Good	Consistent	SR not direct (compared FP compared with combined effect of BDP/BUD)	No difference for all outcomes for equipotent comparisons	3 of the 6 RCTs compared equipotent doses and consistently found no difference	High
6 RCTs (2606)	6 RCTs	Fair		RCTs were direct			
Budesonide compared with Mometasone							
2 (992)	RCTs	Fair	Some inconsistency	Direct	No difference for symptoms, MOM > BUD for rescue use	Only 1 RCT included an equipotent comparison	Low
Budesonide compared with Triamcinolone							
1 (945)	RCT	Fair	Consistent	Direct	BUD > TAA for symptoms, rescue med use, and quality of life	starting doses and dose adjustments were left to the discretion of the clinical investigator	Low
Flunisolide compared with Fluticasone							
2 (653)	RCTs	Fair	Consistent	Direct	NA	Both compared nonequipotent doses	Low
Flunisolide compared with Mometasone							
We did not identify any good or fair quality systematic reviews or head-to-head trials							
Flunisolide compared with Triamcinolone							
We did not identify any good or fair quality systematic reviews or head-to-head trials							
Fluticasone compared with Mometasone							
1 (733)	RCT	Fair	NA	Direct	No difference for most outcomes for equipotent comparisons	No long-term data (12-week trail)	Moderate
Fluticasone compared with Triamcinolone							
3 (1275)	RCTs	Fair	Some inconsistency	Direct	FP > TAA for most outcomes for equipotent doses (one 12-week RCT)	2 of the 3 RCTs compared non-equipotent doses	Low

Abbreviations: **BDP** = beclomethasone dipropionate; **BUD** = Budesonide; **FLUN** = Flunisolide; **FP** = Fluticasone Propionate; **ICS** = Inhaled Corticosteroids; **MA**=meta-analysis; **MOM** = Mometasone; **RCT**= randomized controlled trial; **SR**=systematic review; **TAA** = Triamcinolone Acetonide

*Imprecise or sparse data; a strong or very strong association; high risk of reporting bias; dose response gradient; effect of plausible residual confounding

Detailed Assessment

Description of Studies

Of the included studies (Table 7), one systematic review with meta-analysis and two RCTs compared beclomethasone with budesonide; one systematic review with meta-analysis and ten RCTs compared beclomethasone with fluticasone; two RCTs compared beclomethasone with mometasone; two RCTs compared beclomethasone with triamcinolone; one RCT compared budesonide with flunisolide; one meta-analysis and six RCTs compared budesonide with fluticasone; two RCTs compared budesonide with mometasone; one RCT compared budesonide with triamcinolone; one RCT compared flunisolide with fluticasone; one RCT compared fluticasone with mometasone; three RCTs compared fluticasone with triamcinolone.

Based on National Asthma Education and Prevention Program equipotent dose estimates (Table 3), 22 head-to-head RCTs (73%) included equipotent comparisons for some arms (six of these had multiple arms, with both equipotent and non-equipotent comparisons)^{31, 33, 34, 38, 43, 47} and eight RCTs (27%) compared only non-equipotent doses.^{38, 40, 41, 44, 46, 49, 50} Of the 22 head-to-head trials that compared equivalent doses, eight compared high dose to high dose, 13 compared medium dose to medium dose, two compared low dose to low dose (overall sum of these comparisons does not equal the total number of trials because there were several studies with multiple arms). The most commonly used delivery devices were MDIs and DPIs; 12 studies (40%) compared MDI to MDI; nine studies (30%) compared DPI to DPI; seven studies (23%) compared MDI to DPI; one study (3%) compared both MDI to MDI and MDI to DPI;³¹ one study (3%) compared both DPI to DPI and MDI to DPI.²²

Study Populations

The 30 head-to-head RCTs included a total of 11,615 patients. Most studies were conducted in adult populations. Four studies^{26, 29, 39, 41} were conducted primarily in pediatric populations. Ten studies (33%) were conducted in the United States, nine (30%) in Europe, one (3%) in Canada, and 10 (33%) were other multinational combinations often including Europe, Canada, or the US. Asthma severity ranged from mild persistent to severe persistent: five studies (17%) were conducted in patients with mild to moderate persistent asthma, four (13%) in patients with mild to severe persistent asthma, eight (27%) in patients with moderate persistent asthma, five (17%) in patients with moderate to severe persistent asthma, and four (13%) in patients with severe persistent asthma. Four studies did not report the severity or it was unable to be determined.

Smoking status was not reported for eight studies (27%), including the four studies in pediatric populations. Among the others, twelve studies (40%) excluded individuals with a recent or current history of smoking and 10 (33%) allowed participants to smoke. Among the studies that allowed and reported smoking status, 5% to 34% of participants were current smokers.

Other asthma medications were often allowed if maintained at a constant dose; all trials allowed the use of a short-acting beta-agonist. Most trials enrolled patients who were currently being treated with ICS.

Methodologic Quality

The overall quality of the 30 head-to-head trials included in our review was rated fair to good. Most trials received a quality rating of fair. The method of randomization and allocation concealment was rarely reported.

Sponsorship

Of the 30 head-to-head trials, 25 (83%) were funded by pharmaceutical companies; 3 trials (10%) did not report the source of funding but at least one author had a primary affiliation with a pharmaceutical company, and 2 studies (7%) did not report funding sources.

Head-to-head comparisons

1. *Beclomethasone compared with budesonide*

One good systematic review²⁰ and two fair head-to-head RCTs^{22,23} comparing beclomethasone (BDP) to budesonide (BUD) met our inclusion criteria.

The systematic review²⁰ compared included 24 studies (1174 subjects); 18 of these were in adults. Twelve studies (50%) had treatment periods of between two and four weeks, 10 studies (42%) had treatment periods of between six and 12 weeks. The longest study had an effective treatment period of two years. As an inclusion criterion for the review, all studies had to assess equal nominal daily doses of BDP and BUD. Results were distinguished by whether patients were not treated with regular oral corticosteroids (OCS) (20 studies) or were dependent on regular OCS. They further divided studies by parallel and crossover designs. The majority of crossover trials had significant design flaws, so the results should be viewed with caution.

For asthma patients not treated with OCS, crossover studies showed no significant difference between treatments for symptom measures (variety of symptom scores reported) or rescue medication use. There was no significant difference between BDP and BUD for daytime breathlessness, morning breathlessness, and daily symptom scores (6 studies, 256 subjects; standardized mean difference (SMD) 0.06, 95% CI: -0.18, 0.31). Nor was there a significant difference in night-time breathlessness and evening breathlessness scores (3 studies, 134 subjects; SMD -0.09, 95% CI: -0.43, 0.25). Similarly, for asthma patients not treated with OCS, parallel group studies showed no significant differences in rescue medication use or withdrawals due to asthma exacerbations.

For asthma patients treated with OCS, one crossover study assessed OCS-sparing effects and three evaluated other outcomes. The outcomes for those that did not assess OCS-sparing effects were pooled (3 studies, 144 subjects) and found no significant difference between BDP and BUD for daytime or night-time breathlessness scores, sleep disturbance scores, or rescue medication use.

Two fair-rated open-label head-to-head RCTs^{22,23} met the criteria for our review. The first was a 12-week parallel group trial (N = 460) with stratification for LABA use (2:1 yes:no) that compared treatment with three inhaled corticosteroids: BDP extrafine aerosol (Qvar Autohaler 800 mcg/d, N = 149), BUD Turbuhaler (1600 mcg/d, N = 162), and fluticasone Diskus (1000 mcg/d, N = 149).²² It enrolled patients with moderate to severe persistent asthma who were not controlled with a regimen that included ICS, with or without LABAs. Overall asthma control, assessed by the French version of the Juniper asthma control questionnaire, was improved in all groups with no significant difference between groups (mean change from

baseline for BDP compared with BUD: -1.0 compared with -0.8; 95% CI of the difference: -0.29, 0.08). Among the individual components of control included in the questionnaire (nocturnal awakenings, morning discomfort, limitation of activity, dyspnea, wheezing, and consumption of short-acting beta-agonist) there were no significant differences except for improvement in nocturnal awakenings favoring BDP (-1.0 compared with -0.7; 95% CI of difference: -0.43, -0.05; $P = 0.045$).

The other fair-rated RCT (N = 209) compared BDP Autohaler (800 mcg/d) with BUD Turbuhaler (1600 mcg/d)²³ over 8 weeks. Patients were 18-75 years old and had poorly controlled asthma while taking ICS. Subjects treated with BDP had greater improvement in symptoms than those treated with BUD (mean change from baseline in % of days without symptoms: wheeze 26.48 compared with 8.29, $P = 0.01$; shortness of breath 22.68 compared with 11.25, $P = 0.02$; chest tightness 20.71 compared with 6.25, $P = 0.01$; daily asthma symptoms 25.36 compared with 12.22, $P = 0.03$; difference not significant for cough or sleep disturbance). There was no significant difference in beta-agonist use (mean change from baseline % of days used; -23.76 compared with -17.13; P not significant).

2. Beclomethasone compared with flunisolide

We did not identify any good or fair quality systematic reviews or head-to-head trials that compared beclomethasone to flunisolide.

3. Beclomethasone compared with fluticasone

One systematic review and 10 head-to-head RCTs comparing fluticasone (FP) to BDP met our inclusion criteria. The systematic review²¹ included studies comparing FP compared with BDP or BUD. Of the 71 studies included in this review, 33 compared FP to BDP (nine of those 33 were included in our review). Comparisons were stratified by FP:BDP/BUD dose ratios of 1:2 or 1:1. The pooled treatment effect of FP was compared to the pooled treatment effect for BDP and BUD. For the studies conducted at dose ratios of 1:2, pooled estimates indicate that FP-treated patients had fewer symptoms, required less rescue medication, and had a higher likelihood of pharyngitis (see Key Question 2) than those treated with BDP or BUD. There was no difference in exacerbations. For the studies conducted at dose ratios of 1:1, individual studies and pooled estimates suggest no difference in symptoms, rescue medicine use, or the number of asthma exacerbations. Although we rated the quality of this review as good, the comparison of fluticasone to the combined effect of beclomethasone and budesonide limits possible conclusions regarding the *specific* comparison of beclomethasone to fluticasone.

Ten trials, one good-rated²⁸ and nine fair-rated^{22, 24-27, 29-32} head-to-head RCTs, comparing BDP to FP met the inclusion/exclusion criteria for our review. The single good-rated trial compared BDP 400 mcg/day (MDI-HFA) to FP 400 mcg/day (MDI) in 172 adults with mild to severe persistent asthma for 6 weeks; both were medium potency doses.²⁸ The trial was conducted in 30 general practice sites in the United Kingdom and Ireland. There were no significant differences in the improvement of asthma symptoms, sleep disturbance, rescue medicine use, or quality of life (AQLQ mean change from baseline) between the two groups.

Of the nine fair-rated RCTs that compared BDP to FP,^{22, 24-27, 29-32} just two included children and adolescents <12 years of age. One was conducted exclusively in a population of children and adolescents aged 4-11²⁶ and one included children, adolescents, and young adults aged 4-19.²⁹ Asthma severity ranged from mild- to severe-persistent. Doses ranged from low to high; all studies included comparisons of equipotent doses of BDP and FP. Study duration

ranged from 6 to 52 weeks. All but one trial³⁰ assessed asthma symptoms and rescue medicine use.

The majority of trials reported no difference between BDP- and FP-treated patients for the outcomes of interest reported. Four studies found FP to be better than BDP for at least one outcome: symptoms,³² nighttime symptoms,³¹ rescue medicine use—increase in percent of rescue free days²⁹ or mean change in rescue puffs per day,³² or exacerbations.²⁷ One study found BDP-treated patients to have lower daytime symptom scores.³¹

4. Beclomethasone compared with mometasone

Two fair-quality RCTs^{33,34} compared treatment with BDP and mometasone for 12 weeks. Both compared medium-dose BDP MDI (336 mcg/d), multiple doses of mometasone DPI (low-dose 200 mcg/d and medium-dose 400 mcg/d in both studies, and high-dose 800 mcg/d in only one),³³ and placebo in patients at least 12 years old with persistent asthma. Both studies found no statistically significant differences between BDP and mometasone for symptoms, nocturnal awakenings, and rescue medicine use.

5. Beclomethasone compared with triamcinolone

We found two fair-quality multicenter RCTs comparing BDP to triamcinolone (TAA).^{35,36} Both compared medium-dose BDP (336 mcg/d), medium-dose TAA (800 mcg/d), and placebo for eight weeks in adult subjects. Both found no difference between the active treatment groups for rescue medicine use and one found no difference in nighttime awakenings.³⁶ They reported conflicting results for improvement of symptoms: one reported greater improvement with BDP than TAA³⁶ and one reported no difference.³⁵

6. Budesonide compared with flunisolide

We found one fair-quality multicenter RCT comparing BUD (1200 mcg/d) to flunisolide (1500 mcg/d) in adults (N = 154) with moderate persistent asthma for 6 weeks.³⁷ They reported no statistically significant differences between BUD and flunisolide in change from baseline in asthma symptoms, nocturnal awakenings, or rescue medicine use.

7. Budesonide compared with fluticasone

One previously described systematic review and six head-to-head RCTs comparing FP to BUD met our inclusion criteria. The systematic review²¹ included studies comparing FP compared with BDP or BUD. Of the 71 studies included in this review, 37 compared FP to BUD (six of those 37 were included in our review). Comparisons were stratified by FP: BDP/BUD dose ratios of 1:2 or 1:1. The pooled treatment effect of FP was compared to the pooled treatment effect for BDP and BUD. For the studies conducted at dose ratios of 1:2, pooled estimates indicate that FP-treated patients had fewer symptoms, required less rescue medication, and had a higher likelihood of pharyngitis (see Key Question 2) than those treated with BDP or BUD. There was no difference in exacerbations. For the studies conducted at dose ratios of 1:1, individual studies and pooled estimates suggest no difference in symptoms, rescue medicine use, or the number of asthma exacerbations. Although we rated the quality of this review as good, the comparison of FP to the combined effect of beclomethasone and budesonide limits possible conclusions regarding the *specific* comparison of BUD to FP.

Six fair-rated head-to-head RCTs meeting our inclusion criteria compared budesonide to fluticasone.^{22,38-42} Trial duration ranged from six to 24 weeks. Two were conducted in

children and adolescents;^{39,41} five were conducted in patients with moderate and/or severe persistent asthma and one was conducted in patients with mild to moderate persistent asthma.⁴¹ Three trials compared nonequivalent doses with FP given at a higher relative dose than BUD.^{38,40,41} All but one study³⁸ used dry powder formulations of both medications. All six trials evaluated outcomes for asthma symptoms and rescue medicine use.

Overall, the evidence from these studies supports the conclusion that there is no difference between equipotent doses of BUD and FP. Three of the trials^{22,39,42} that compared equipotent doses and one⁴¹ that compared medium- with low-doses of BUD and FP found no difference for symptoms, exacerbations, or rescue medicine use. In addition, one trial³⁸ comparing two high-doses of FP (1000 mcg/d and 2000 mcg/d) with medium-dose BUD (1600 mcg/d) found no difference between the lower of the two high doses and medium-dose BUD for symptoms, exacerbations, and rescue medicine use. The remaining trial⁴⁰ compared non-equivalent doses (relative potency of fluticasone was greater at the doses given) and found FP to be superior to BUD for symptoms, rescue medicine use, and missed days of work, but found no difference in exacerbations.

8. Budesonide compared with mometasone

One fair-rated 12-week RCT⁴³ and one fair-rated 8-week trial⁴⁴ compared BUD and mometasone. Overall, the trials reported no significant differences for equipotent doses for most outcomes of interest, but there were some dose-related differences favoring mometasone over BUD when comparing non-equipotent doses. The 12-week trial randomized 730 persons 12 years and older with moderate persistent asthma to medium dose (800 mcg/day) BUD or low-, medium-, or high-dose (200, 400, 800 mcg/day, respectively) mometasone.⁴³ They found no statistically significant differences between medium-dose BUD and medium-dose mometasone for symptoms or nocturnal awakenings, but patients treated with medium-dose mometasone had a greater decrease in rescue medicine use than those treated with medium-dose BUD (-90.66 mcg/d compared with -33.90 mcg/d; $P < 0.05$). The 8-week trial compared once daily low-dose (400 mcg/day) BUD with once daily medium-dose (440 mcg/day) mometasone in 262 persons 12 years and older with moderate persistent asthma.⁴⁴ The trial reported statistically significant differences in evening asthma symptoms ($P < 0.05$), symptom-free days ($P < 0.01$), and rescue medication use ($P < 0.05$), favoring medium-dose mometasone over low-dose BUD.

9. Budesonide compared with triamcinolone

One fair-rated 52-week RCT⁴⁵ met our inclusion/exclusion criteria for this comparison. The trial randomized 945 adults ≥ 18 with mild, moderate, or severe persistent asthma to BUD DPI (mean dose at start and end: 941.9 and 956.8 mcg/d) or TAA pMDI (1028.2 and 1042.9 mcg/d, respectively). On average, patients were treated with medium doses, but starting doses and dose adjustments were left to the discretion of the clinical investigator. Patients treated with BUD had greater improvements in symptom- and episode-free days ($P < 0.001$), daytime and nighttime asthma symptom scores ($P < 0.001$), and quality of life ($P < 0.001$) than those treated with TAA.

10. Flunisolide compared with fluticasone

We found two RCTs reported in one publication⁴⁶ that compared flunisolide and fluticasone meeting our inclusion/exclusion criteria. Both were fair-quality trials comparing non-

equipotent doses that randomized patients to high-dose FP MDI (500 mcg/d) or medium-dose flunisolide MDI (1000 mcg/d). One was an 8-week double-blind RCT (N = 321) and the other was a 6-week open-label RCT (N = 332). There was a trend toward greater improvement in symptom-free days for patients treated with high-dose FP (P NR for either).

11. Flunisolide compared with mometasone We did not identify any good or fair quality systematic reviews or head-to-head trials that compared beclomethasone to flunisolide.

12. Flunisolide compared with triamcinolone

We did not identify any good or fair quality systematic reviews or head-to-head trials that compared beclomethasone to flunisolide.

13. Fluticasone compared with mometasone

One fair-rated dose-ranging study (N = 733) conducted in 60 study centers compared medium-dose fluticasone (500 mcg/day) to low-, medium-, and high-dose mometasone (200, 400, and 800 mcg/day, respectively) in 733 patients 12 years and older with moderate persistent asthma.⁴⁷ The investigators found no statistically significant differences at endpoint between patients treated with medium-dose fluticasone and those treated with medium- and high-dose mometasone with respect to wheeze and cough scores, nighttime awakenings, or rescue medication use ($P > 0.05$ for all). However, patients treated with medium-dose fluticasone had significantly greater improvement in the number of nighttime awakenings ($P < 0.05$) than did those treated with low-dose mometasone. In addition, patients on medium-dose fluticasone had significantly better morning difficulty breathing scores than did patients on either low- or medium-dose mometasone ($P < 0.05$).

14. Fluticasone compared with triamcinolone

Three fair-rated trials comparing FP to TAA met our inclusion/exclusion criteria.⁴⁸⁻⁵⁰ The only one of the three trials comparing equipotent doses⁴⁸ found greater improvements in subjects treated with FP. The other two trials comparing non-equipotent doses^{49,50} reported greater improvements for FP-treated subjects for some outcomes and no difference for the others.

The trial comparing equipotent doses⁴⁸ was a 12-week, multicenter RCT (N = 680) comparing medium-dose FP MDI (440 mcg/d), medium-dose TAA MDI (1200 mcg/d), and the combination of FP (196 mcg/d) and Salmeterol. Subjects were at least 12 years of age and were poorly controlled on ICS therapy. FP-treated subjects had better improvements in symptoms, nighttime awakenings, and rescue medicine use.

The two comparing non-equipotent doses were similarly designed fair-rated RCTs^{49,50} conducted in 24 outpatient centers. Subjects in both were randomized to medium-dose FP (500 mcg/day by DPI), low-dose TAA (800 mcg/day by MDI with spacer), or placebo for 24 weeks. Both were conducted in subjects 12 years or older previously being treated with ICS. No differences were found in symptom scores or in the percentage of symptom-free days. Subjects treated with FP had greater improvements in rescue medicine requirements in both studies than those treated with TAA. One of the trials reported greater improvement in nighttime awakenings⁵⁰ for those treated with FP, but the other reported no difference.⁴⁹ One reported significantly better improvements in quality of life for FP-treated patients compared to TAA-treated patients.⁵⁰

Table 7. Summary of head-to-head studies comparing inhaled corticosteroids in children and adults

Study	Study Design N Duration	Country Population Setting	Comparison (total daily dose in mcg)	Equivalent dosing	Results	Quality Rating
Beclomethasone compared with budesonide						
Adams et al. 2000 ²⁰	Systematic review with meta-analysis 24 studies (1174 subjects), 5 parallel, 19 cross-over (two had a washout) Range 2 weeks to 2 years; 50% were 2-4 weeks	Majority in Europe 24 trials (6 trials in children, 18 in adults)	BDP compared with BUD all studies assessed equal nominal daily doses of BDP and BUD	Yes	Symptoms: No difference [<i>symptom score</i> (6 cross-over studies): SMD 0.06, 95% CI: -0.18, 0.31, 6 studies; <i>night-time breathlessness</i> (three cross-over studies): SMD -0.09 (95% CI: -0.43, 0.25)] Rescue medicine use: No difference [qualitative summary, no meta-analysis]	Good
Molimard et al. 2005 ²²	RCT, open-label 460 12 weeks	France Age 18-60, moderate to severe persistent, not controlled on ICS, smoking status NR Multicenter, subspecialty clinics (69 pulmonologists)	BDP MDI (800) compared with BUD DPI (1600) compared with FP DPI (1000)	Yes (all high)	Symptoms and Control: No difference [<i>FrACQ</i> , mean change from baseline for BDP compared with BUD: -1.0 compared with -0.8; 95% CI: -0.29, 0.08; all individual components of <i>FrACQ</i> score also NS, except for nocturnal awakenings (below) Nocturnal awakenings: BDP > BUD [nocturnal awakenings component of <i>FRACQ</i> : favoring BDP (-1.0 compared with -0.7; 95% CI of difference: -0.43, -0.05; <i>P</i> = 0.045)] Rescue med use: No difference [consumption of rescue medication component of <i>FRACQ</i> : data NR, <i>P</i> = NS]	Fair

Table 7. Summary of head-to-head studies comparing inhaled corticosteroids in children and adults

Study	Study Design N Duration	Country Population Setting	Comparison (total daily dose in mcg)	Equivalent dosing	Results	Quality Rating
Worth et al. 2001 ²³	RCT, open-label 209 8 weeks	Germany, France, Netherlands Age 18-75, moderate to severe, on ICS, smoking status NR Multicenter (39)	BDP MDI (800) compared with BUD DPI (1600)	Yes (high)	Symptoms: BDP > BUD [mean change from baseline in % of days without symptoms: wheeze 26.48 compared with 8.29, <i>P</i> = 0.01; shortness of breath 22.68 compared with 11.25, <i>P</i> = 0.02; chest tightness 20.71 compared with 6.25, <i>P</i> = 0.01; daily asthma symptoms 25.36 compared with 12.22, <i>P</i> = 0.03; cough (numbers NR, data in graph) <i>P</i> = NS; sleep disturbance (numbers NR, data in graph) <i>P</i> = NS] Rescue medicine use: No difference [mean reduction in % of days on which rescue was used: -23.76 compared with -17.13; <i>P</i> = NS]	Fair
Beclomethasone compared with flunisolide						
No systematic reviews or head-to-head trials found						
Beclomethasone compared with Fluticasone						
Adams et al. 2007 ²¹	Systematic review with meta-analysis 71 trials (14,602 participants), 59 parallel, 14 cross-over (four had a washout) Majority of studies (47) were between 6 weeks and 5 months; 14 were ≤4 weeks	Multinational (most in Europe) Severity ranged from mild to severe persistent	FP compared with BDP (33 trials) FP compared with BUD (37) FP compared with BDP/BUD (2) 38 studies had FP:BDP/BUD dose ratio of 1:2; 22 had dose ratio 1:1; remainder had multiple dose ratio comparisons or ratio was unclear	For some of the included studies	Dose ratio 1:2: Symptoms: FP > BDP/BUD [Change in symptom scores: SMD: -0.19 (95% CI: -0.31, -0.07) 6 studies, N = 1035. Absolute percentage of symptom free days: MD 4.9% (95% CI: -1, 11), two studies, N = 699. Change in percentage of symptom free days: MD 6.43% (95% CI: 0.47, 12.39), two studies, N = 399.] Nocturnal awakenings: No difference [Change in number of awakenings per night: MD: 0.01 (95% CI: -0.04, 0.06), two studies,	Good

Table 7. Summary of head-to-head studies comparing inhaled corticosteroids in children and adults

Study	Study Design N Duration	Country Population Setting	Comparison (total daily dose in mcg)	Equivalent dosing	Results	Quality Rating
					<p>N = 282]</p> <p>Exacerbations: No difference [<i>Withdrawal due to asthma exacerbation: Peto OR 0.77 (95% CI: 0.54, 1.1), 11 studies N = 2824; Participants with an exacerbation: Peto OR 0.74 (95% CI: 0.53, 1.03), four studies N = 1213; Withdrawal due to lack of efficacy: Peto OR 0.6 (95% CI: 0.33, 1.07), seven studies, N = 1781]</i></p> <p>Rescue med use: FP > BDP/BUD [<i>Change in percentage of rescue-free days: MD 6.89% (95% CI: 0.32, 13.46), two studies, N = 399; Change in rescue usage (puffs/day): MD -0.35 puffs (95% CI: -0.63, -0.07), four studies, N = 763; # of participants experiencing rescue-free days and nights: no significant differences were reported, 6 studies reported (data not pooled for several reasons)]</i></p> <p>Dose ratio 1:1: Symptoms: No difference [<i>proportion of symptom-free days: MD 5.54% (95% CI: -0.68, 11.76), two studies, N = 571; daytime symptoms: SMD: -0.10 (95% CI: -0.34, 0.13), two studies, N = 285. Change from baseline in daytime symptoms: SMD -0.03 (95% CI: -0.11, 0.06), three studies, N = 534; change from baseline in</i></p>	

Table 7. Summary of head-to-head studies comparing inhaled corticosteroids in children and adults

Study	Study Design N Duration	Country Population Setting	Comparison (total daily dose in mcg)	Equivalent dosing	Results	Quality Rating
					<p><i>nocturnal symptoms:</i> SMD -0.03 (95% CI: -0.15, 0.09), three studies, N = 537]</p> <p><i>Exacerbations:</i> No difference [<i>Requirement for medication other than beta-agonist:</i> Random Effects OR: 0.70 (95% CI: 0.45, 1.09); <i>One or more exacerbations:</i> Peto OR 0.99 (95% CI: 0.73, 1.33), three studies, N = 1054; <i>Withdrawal due to an exacerbation:</i> Peto OR 0.72 (95% CI: 0.38, 1.35), five studies, N = 978]</p> <p><i>Rescue med use:</i> No difference [<i>Change from baseline, day use:</i> -0.04 puffs/day (95% CI: -0.12, 0.04), two studies, N = 368; <i>change from baseline, night use:</i> -0.03 puffs/day (95% CI: -0.13, 0.08), two studies, N = 368]</p>	
Barnes et al. 1993 ²⁴	RCT, DB 154 6 weeks	Multinational (7 countries worldwide) Age ≥ 18, severe, 20% smokers Multicenter (18 outpatient clinics)	FP MDI (1000) compared with BDP MDI (2000)	Yes (high)	<p>Symptoms: No difference [mean % of <i>symptom free days</i>, baseline and endpoint: 38% and 52% compared with 28% and 37%; <i>P</i> = 0.212; mean % <i>symptom-free nights</i>: 46% and 59% compared with 38% and 50%; <i>P</i> = 0.854]</p> <p>Rescue medicine use: No difference [mean <i>number of uses/day</i>, baseline, endpoint: 13, 10 compared with 14, 11; <i>P</i> = 0.866; mean <i>uses/night</i>: 6, 5 compared with 8, 6; <i>P</i> = 0.875; <i>Rescue-free</i></p>	Fair

Table 7. Summary of head-to-head studies comparing inhaled corticosteroids in children and adults

Study	Study Design N Duration	Country Population Setting	Comparison (total daily dose in mcg)	Equivalent dosing	Results	Quality Rating
					<i>days</i> , mean: 36% compared with 30%; <i>P</i> = 0.733; <i>Rescue-free nights</i> , mean: 53% compared with 47%; <i>P</i> = 0.935]	
Boe et al. 1994 ²⁵	RCT, DB 134 12 weeks	Norway Age ≥ 18, poorly controlled, 34% smokers Multicenter	FP DPI (1600) compared with BDP DPI (2000)	Yes (high)	Symptoms: No difference [mean (SEM) <i>daytime symptom score</i> (0-5); baseline, endpoint: 1.7(0.11), 1.35(0.13) compared with 1.94(0.11), 1.6 (0.12); <i>P</i> = NS; mean <i>nighttime symptom scores</i> : 0.77(0.08), 0.62(0.08) compared with 0.85(0.08), 0.65(0.08); <i>P</i> = NS] Rescue medicine use: No difference [mean <i>daytime puffs</i> ; baseline, endpoint: 2.75(0.24), 2.24(0.24) compared with 2.92(0.24), 2.35(0.25); <i>P</i> = NS; <i>mean nighttime puffs</i> : 0.77(0.12), 0.73(0.14) compared with 0.76(0.11), 0.51(0.09); <i>P</i> = NS]	Fair
de Benedictis et al. 2001 ²⁶	RCT, DB 434 52 weeks	Multinational (7 countries: Holland, Hungary, Italy, Poland, Argentina, Chile, South Africa) Age 4-11, prepubertal, severity and smoking status NR	FP DPI (400) compared with BDP DPI (400)	Yes (medium)	Symptoms: No difference [daytime or nighttime symptom scores (data NR; <i>P</i> = NS)] Exacerbations: No difference [number of exacerbations: 47 compared with 52; <i>P</i> = NS; % of patients: 16% compared with 19%; <i>P</i>	Fair

Table 7. Summary of head-to-head studies comparing inhaled corticosteroids in children and adults

Study	Study Design N Duration	Country Population Setting	Comparison (total daily dose in mcg)	Equivalent dosing	Results	Quality Rating
		Multicenter (32)			= NS]	
					Rescue medicine use: No difference [no significant difference (data NR; p NS)]	
					Objective of the study was to compare long- term effects on growth (see KQ2 section)	
Fabbri et al. 1993 ²⁷	RCT, DB 274 12 months (daily symptom outcomes collected for initial 12 weeks)	Multinational (10 European) Age 12-80, moderate to severe, not controlled on ICS, 11% smokers Multicentre (25)	FP MDI (1500) compared with BDP MDI (1500)	Yes (high)	Symptoms: No difference [mean % of <i>symptom free days</i> during run-in, and over the first 12 weeks: 19%, 38% compared with 22%, 41%; <i>P</i> = NS; mean % <i>symptom free</i> <i>nights</i> : 47%, 61% compared with 50%, 63%; <i>P</i> = NS) Exacerbations: FP > BDP [# (%) of patients that had <i>at least one</i> <i>exacerbation</i> : 23 (16%) of patients compared with 37 (28%); <i>P</i> < 0.05); # (%) of patients that had <i>severe</i> <i>exacerbations</i> : 3 (2 %) compared with 13 (10%); <i>P</i> < 0.02] Rescue medicine use: No difference [mean % rescue free days: run- in, over first 12 weeks: 20%, 29% compared with 13%, 19%; <i>P</i> = NS]	Fair
Fairfax et al. 2001 ²⁸	RCT, DB, DD 172 6 weeks	UK and Ireland Age 18-65, mild to severe, symptomatic on ICS, 24% current smokers Multicenter (30 general practice sites)	BDP MDI (extrafine HFA, 400) compared with FP MDI (CFC, 400)	Yes (medium)	Symptoms: No difference [mean change from baseline in % of <i>days</i> <i>without wheeze</i> : data in graph only, <i>P</i> = NS; mean change from baseline in % of <i>days</i> <i>without cough</i> , <i>shortness of breath</i> , or <i>chest tightness</i> : data in graphs only, <i>P</i> = NS]	Good

Table 7. Summary of head-to-head studies comparing inhaled corticosteroids in children and adults

Study	Study Design N Duration	Country Population Setting	Comparison (total daily dose in mcg)	Equivalent dosing	Results	Quality Rating
					<p>Nocturnal awakenings: No difference [% of nights without sleep disturbance: data in graph only, <i>P</i> = NS]</p> <p>Rescue medicine use: No difference [mean change from baseline in total # of puffs per day: data in graph only, <i>P</i> = NS]</p> <p>Quality of life: No difference [AQLQ overall: mean change from baseline +0.47 compared with +0.41; <i>P</i> = 0.002 for equivalence]</p>	
Gustafsson et al. 1993 ²⁹	RCT, DB 398 6 weeks	Multinational (11 worldwide) Age 4-19, mild to moderate, not controlled on current meds, smoking status NR Multicenter (32)	FP MDI (200) compared with BDP MDI (400)	Yes (medium)	<p>Symptoms: No difference [% of patients with daytime symptoms the same or better: 83% compared with 81%; <i>P</i> NS.; Nighttime symptoms: % same or better: 83% compared with 82%; <i>P</i> NS.; % with symptom-free days or - nights (data NR, <i>P</i> = NS) or changes in median day, night, or exercise symptom scores (data NR, <i>P</i> = NS)]</p> <p>Rescue medicine use: FP > BDP [Increase in % of rescue-free days at week six: 87% compared with 80%, <i>P</i> = 0.01; over the entire six weeks: 80% compared with 73%, <i>P</i> = 0.046]</p>	Fair

Table 7. Summary of head-to-head studies comparing inhaled corticosteroids in children and adults

Study	Study Design N Duration	Country Population Setting	Comparison (total daily dose in mcg)	Equivalent dosing	Results	Quality Rating
Lorentzen et al. 1996 ³⁰	RCT, DB 213 12 months	Multinational (7, Europe) Age 18-77, severe, well controlled on high dose ICS, 19% smokers Multicenter (20 outpatient clinics)	FP MDI (1000) compared with BDP MDI (2000)	Yes (high)	Exacerbations: No difference [61% compared with 52% remained free of exacerbations; 22% compared with 20% experienced one exacerbation; 10% compared with 19% experienced two exacerbations; <i>P</i> = NS for all]	Fair
Lundback et al. 1993 ³¹	RCT, DB 585 6 weeks (N = 489 continued an additional 46 weeks)	Multinational (10) Age 15-90, moderate, not controlled on ICS, smoking status NR Multicenter (47)	FP MDI (500) compared with FP DPI (500) compared with BDP MDI (1000)	No, only for FP MDI compared with BDP MDI (high) ; FP DPI 500 is medium	Symptoms: Mixed results [<i>median daytime symptom score</i> : BDP group had lower scores than either FP group (data NR, <i>P</i> = 0.03); <i>median nighttime symptom score</i> : greater improvement in FP DPI group than BDP group (data NR, <i>P</i> = 0.048), not reported for FP MDI compared with BDP MDI; % of patients with <i>no change or an improvement in daytime symptoms</i> : 88 compared with 90 compared with 92; <i>P</i> = NR; % patients w/ <i>no change or improvement in nighttime symptoms</i> : 92 compared with 89 compared with 90; <i>P</i> = NR; % pts experiencing <i>a change or increase in % of symptom-free days or nights</i> ; <i>P</i> = NS, data NR] Rescue med use: No difference [% pts w/ same or reduced daytime use: 83 compared with 83 compared with 88; <i>P</i> = NR; % pts w/ same or reduced nighttime use: 77 compared with 83 compared with 82; <i>P</i> = NR]	Fair

Table 7. Summary of head-to-head studies comparing inhaled corticosteroids in children and adults

Study	Study Design N Duration	Country Population Setting	Comparison (total daily dose in mcg)	Equivalent dosing	Results	Quality Rating
Molimard et al. 2005 ²²	RCT, open-label 460 12 weeks	France Age 18-60, moderate to severe persistent, not controlled on ICS, smoking status NR Multicenter, subspecialty clinics (69 pulmonologists)	BDP MDI (800) compared with BUD DPI (1600) compared with FP DPI (1000)	Yes (all high)	Symptoms and Control: No difference [FrACQ, mean change from baseline for BDP compared with FP: -1.0 compared with -0.8; 95% CI of the difference: = -0.30, 0.07.; individual components of FrACQ score: morning discomfort, limitation of activity, dyspnea, wheezing, consumption of rescue medication: data NR, <i>P</i> = NS] Nocturnal awakenings: No difference [nocturnal awakenings component of FRACQ: -1.0 compared with -0.8; <i>P</i> = NS] Rescue med use: No difference [consumption of rescue medication component of FRACQ: data NR, <i>P</i> = NS]	Fair
Raphael et al. 1999 ³²	RCT, DB, DD 399 12 weeks	US Age ≥ 12 years, mild to severe, not controlled on ICS, smokers excluded Multicenter, specialty asthma and primary care centers (23)	FP MDI (164) compared with FP MDI (440) compared with BDP MDI (336) compared with BDP MDI (672)	Yes (low, medium, low, medium)	Symptoms: FP > BDP [mean change % <i>days no symptoms</i> : 14.0 compared with 8.7 compared with 4.9 compared with 4.4; <i>P</i> = 0.027; mean change from baseline <i>symptom score</i> (0-3): -0.24 compared with -0.26 compared with -0.05 compared with -0.15; <i>P</i> = 0.024] Nocturnal awakenings: No difference [mean change in <i>night awakenings</i> : -0.03 compared with -0.12 compared with -0.03 compared with -0.07; <i>P</i> = 0.458] Rescue medicine use:	Fair

Table 7. Summary of head-to-head studies comparing inhaled corticosteroids in children and adults

Study	Study Design N Duration	Country Population Setting	Comparison (total daily dose in mcg)	Equivalent dosing	Results	Quality Rating
					Mixed results (FP > BDP for one measure) [mean change from baseline in <i>rescue puffs per day</i> : -0.9 compared with -0.5 compared with 0.0 compared with -0.3; $P = 0.004$; mean change in % of <i>rescue-free days</i> : 15.8 compared with 11.0 compared with 5.0 compared with 7.7; $P = 0.10$]	
					All P values are for the comparison of the combined FP groups compared with BDP groups	
Beclomethasone compared with mometasone						
Bernstein et al. 1999 ³³	RCT, DB, DD 365 12 weeks	US Age ≥12, mild to moderate, on ICS, smokers excluded Multicenter (20)	Mometasone DPI (200) vs. Mometasone DPI (400) vs. Mometasone DPI (800) vs. BDP MDI (336) vs. placebo	No; only for MOM 400 vs. BDP 336 (both medium)	Symptoms: No difference [<i>Change in symptom scores for wheezing</i> : -0.15 vs. -0.22 vs. -0.25 vs. 0.30 ($P < 0.01$ vs. placebo for all; NS MF vs. BDP); <i>change in symptom scores for difficulty breathing</i> : -0.15 vs. -0.31 vs. -0.25 vs. -0.29 vs. 0.39 ($P < 0.01$ vs. placebo for all; NS MF vs. BDP); <i>change in symptom scores for cough</i> : -0.03 vs. -0.05 vs. -0.04 vs. -0.13 vs. 0.36 ($P < 0.01$ vs. placebo for all; NS MF vs. BDP)] Nocturnal awakenings: No difference [Change in <i>number of awakenings</i> : -0.02 vs. -0.08 vs. -0.12 vs. 0.00 vs. 0.31 ($P < 0.01$ vs. placebo for all; NS for MF vs. BDP)] Rescue medicine use: No difference [<i>Albuterol puffs per day</i> , %	Fair

Table 7. Summary of head-to-head studies comparing inhaled corticosteroids in children and adults

Study	Study Design N Duration	Country Population Setting	Comparison (total daily dose in mcg)	Equivalent dosing	Results	Quality Rating
					change from baseline: 22% vs. -21.4% vs. - 2.3% vs. -21.4% vs. 25.3% ($P < 0.01$ vs. placebo for all; NS for MF 400 vs. BDP)]	
Nathan et al. 2001 ³⁴	RCT, DB, DD 227 12 weeks	US Age ≥ 12 , moderate, on ICS, smokers excluded Multicenter (15)	Placebo vs. Mometasone DPI (200) vs. Mometasone DPI (400) vs. BDP MDI (336)	No; only for MF 200 vs. BDP (both low), MF 400 is medium	Symptoms: No difference [<i>change in AM wheezing score:</i> 0.32 vs. -0.14 vs. -0.29 vs. -0.11; <i>change in AM difficulty breathing score:</i> 0.20 vs. -0.22 vs. -0.25 vs. -0.10; <i>change in AM cough score:</i> 0.22 vs. -0.11 vs. -0.05 vs. 0.02; $P < 0.02$ for all active compared with placebo except BDP vs. placebo was NS for AM cough score] Nocturnal awakenings: No difference [mean change from baseline: 0.09 vs. -0.09 vs. -0.18 vs. 0.06; $P = \text{NS}$] Rescue med use: No difference [mean change from baseline, inhalations/day: 1.31 vs. -1.18 vs. -0.94 vs. - 1.05; $P < 0.01$ for all active compared with placebo]	Fair
Beclomethasone compared with triamcinolone						
Berkowitz et al. 1998 ³⁵	RCT, DB, DD 339 8weeks	US Age 18-65, mild to moderate, on ICS, smokers excluded Multicenter (17), asthma/allergy centers	BDP MDI (336) vs. TAA MDI (800) vs. placebo	Yes (medium)	Symptoms: No difference [<i>Symptom Scores (0-3) were significantly improved compared to placebo (P = 0.001) in both treatment groups; $P =$ NS for BDP vs. TAA (data NR)]. Rescue med use: No difference [average daily use (mean) was similar between the two treatment groups: baseline and endpoint:</i>	Fair

Table 7. Summary of head-to-head studies comparing inhaled corticosteroids in children and adults

Study	Study Design N Duration	Country Population Setting	Comparison (total daily dose in mcg)	Equivalent dosing	Results	Quality Rating
					3.24 and 3.45 vs. 3.24 and 3.7 vs. 3.82 and 4.25, <i>P</i> = NR]	
Bronsky et al. 1998 ³⁶	RCT, DB, DD 329 8 weeks	US Age 18-65, mild to severe, on ICS, smokers excluded Multicenter	BDP MDI (336) vs. TAA MDI (800) vs. placebo	Yes (medium)	Symptoms: BDP > TAA [<i>Total symptom score</i> (0 to 3 for four symptoms): Baseline mean (SD), mean change: 3.18 (2.99), -1.37 (2.89) vs. 2.71 (2.63), -0.58 (2.86) vs. 2.77 (2.84), 0.83 (2.97); <i>P</i> = 0.028] Nighttime awakenings: No difference [<i>P</i> = NS, data NR] Rescue med use: No difference [mean <i>puffs/day</i> : 2.86 vs. 3.61 vs. 4.43, <i>P</i> = 0.094]	Fair
Budesonide compared with flunisolide						
Newhouse et al. 2000 ³⁷	RCT 179 6 weeks	Canada Age 18-75, moderate, on ICS, 5% current smokers Multicenter (17)	Flunisolide MDI + AeroChamber (1500) vs. BUD DPI (1200)	Yes (medium)	Symptoms: No difference [change from baseline in mean <i>daily symptom score</i> : 0.1 vs. 0.1; <i>P</i> = 0.92] Nocturnal awakenings: No difference [change from baseline in <i>mean awakenings/night</i> : 0.1 vs. 0.1; <i>P</i> = 0.849] Rescue med use: No difference [change in <i>mean puffs/day</i> from baseline: 0.4 vs. 0.1; <i>P</i> = 0.333]	Fair
Budesonide compared with fluticasone						

Table 7. Summary of head-to-head studies comparing inhaled corticosteroids in children and adults

Study	Study Design N Duration	Country Population Setting	Comparison (total daily dose in mcg)	Equivalent dosing	Results	Quality Rating
Adams et al. 2007 ²¹	Systematic review with meta-analysis 71 trials (14,602 participants), 59 parallel, 14 cross-over (four had a washout) Majority of studies (47) were between 6 weeks and 5 months; 14 were ≤4 weeks	Multinational (most in Europe) Severity ranged from mild to severe persistent	FP vs. BDP (33 trials) FP vs. BUD (37) FP vs. BDP/BUD (2) 38 studies had FP:BDP/BUD dose ratio of 1:2; 22 had dose ratio 1:1; remainder had multiple dose ratio comparisons or ratio was unclear	For some of the included studies	Dose ratio 1:2: Symptoms: FP > BDP/BUD [<i>Change in symptom scores: SMD: -0.19 (95% CI: -0.31, -0.07)</i>] 6 studies, N = 1035. <i>Absolute percentage of symptom free days: MD 4.9% (95% CI: -1, 11), two studies, N = 699.</i> <i>Change in percentage of symptom free days: MD 6.43% (95% CI: 0.47, 12.39), two studies, N = 399.]</i> Nocturnal awakenings: No difference [<i>Change in number of awakenings per night: MD: 0.01 (95% CI: -0.04, 0.06), two studies, N = 282]</i> Exacerbations: No difference [<i>Withdrawal due to asthma exacerbation: Peto OR 0.77 (95% CI: 0.54, 1.1), 11 studies N = 2824; Participants with an exacerbation: Peto OR 0.74 (95% CI: 0.53, 1.03), four studies N = 1213; Withdrawal due to lack of efficacy: Peto OR 0.6 (95% CI: 0.33, 1.07), seven studies, N = 1781]</i> Rescue med use: Mixed, some results suggest FP > BDP/BUD [<i>Change in percentage of rescue-free days: MD 6.89% (95% CI: 0.32, 13.46), two studies, N = 399; Change in rescue usage (puffs/day): MD -0.35 puffs (95% CI: -0.63, -0.07), four studies, N = 763; # of participants experiencing rescue-</i>	Good

Table 7. Summary of head-to-head studies comparing inhaled corticosteroids in children and adults

Study	Study Design N Duration	Country Population Setting	Comparison (total daily dose in mcg)	Equivalent dosing	Results	Quality Rating
					<p><i>free days and nights</i>: no significant differences were reported, 6 studies reported (data not pooled for several reasons)]</p> <p>Dose ratio 1:1: Symptoms: No difference [<i>proportion of symptom-free days</i>: MD 5.54% (95% CI: -0.68, 11.76), two studies, N = 571; <i>daytime symptoms</i>: SMD: -0.10 (95% CI: -0.34, 0.13), two studies, N = 285. <i>Change from baseline in daytime symptoms</i>: SMD -0.03 (95% CI: -0.11, 0.06), three studies, N = 534; <i>change from baseline in nocturnal symptoms</i>: SMD -0.03 (95% CI: -0.15, 0.09), three studies, N = 537]</p> <p>Exacerbations: No difference [<i>Requirement for medication other than beta-agonist</i>: Random Effects OR: 0.70 (95% CI: 0.45, 1.09); <i>One or more exacerbations</i>: Peto OR 0.99 (95% CI: 0.73, 1.33), three studies, N = 1054; <i>Withdrawal due to an exacerbation</i>: Peto OR 0.72 (95% CI: 0.38, 1.35), five studies, N = 978]</p> <p>Rescue med use: No difference [<i>Change from baseline, day use</i>: -0.04 puffs/day (95% CI: -0.12, 0.04), two studies, N = 368; <i>change from baseline, night use</i>: -0.03 puffs/day (95% CI: -</p>	

Table 7. Summary of head-to-head studies comparing inhaled corticosteroids in children and adults

Study	Study Design N Duration	Country Population Setting	Comparison (total daily dose in mcg)	Equivalent dosing	Results	Quality Rating
					0.13, 0.08), two studies, N = 368]	
Ayres et al. 1995 ³⁸	RCT, DB, DD 671 6 weeks	Multinational (13 countries worldwide) Age 18-70, severe, on ICS, smokers excluded Multicenter (66)	FP MDI (1000) vs. FP MDI (2000) vs. BUD MDI (1600)	No (high vs. high vs. medium)	Symptoms: Mixed results, FP > BUD for some measures [% of patients that improved: <i>Day time asthma score:</i> 30% vs. 27% vs. 23% (<i>P</i> = 0.161 FP 1 vs. BUD; 0.029 FP 2 vs. BUD). <i>Night time asthma score:</i> 21% improved vs. 28% vs. 23% (<i>P</i> = 0.058; <i>P</i> = 0.050). <i>Symptom-free days:</i> 50% vs. 51% vs. 44% (<i>P</i> = 0.048; <i>P</i> = 0.101). <i>Symptom-free nights:</i> 44 vs. 52 vs. 46 (<i>P</i> = 0.964, <i>P</i> = 0.116)] Exacerbations: No difference [% of patients experiencing <i>exacerbation:</i> 17 vs. 16 vs. 22 (<i>P</i> = 0.354, <i>P</i> = 0.054); % requiring oral steroids: 7% vs. 4% vs. 10%] Rescue med use: No difference [% improved: <i>rescue free days:</i> 42% improved vs. 44% vs. 46% (<i>P</i> = 0.592 FP1 vs. BUD, <i>P</i> = 0.275 FP2 vs. BUD); <i>frequency of daytime rescue med use:</i> 27% vs. 29% vs. 31% (<i>P</i> = 0.964, <i>P</i> = 0.975)]	Fair
Ferguson	RCT, DB, DD	Multinational (6	FP DPI (400)	Yes (medium)	Symptoms: No	Fair

Table 7. Summary of head-to-head studies comparing inhaled corticosteroids in children and adults

Study	Study Design N Duration	Country Population Setting	Comparison (total daily dose in mcg)	Equivalent dosing	Results	Quality Rating
et al. 1999 ³⁹	333 20 weeks	countries worldwide) Ages 4-12, moderate to severe, on ICS, smoking status NR Multicenter	vs. BUD DPI (800)		difference [daytime ($P = 0.729$) and nighttime ($P = 0.34$) symptom scores (Actual data NR)] Exacerbations: Trend toward fewer with FP [% and number of subjects: 1% (2) vs. 5% (8); $P = NR$] Rescue med use: No difference [albuterol use for daytime ($P = 0.181$) and nighttime ($P = 0.59$) (Actual data NR)]	
Heinig et al. 1999 ⁴⁰	RCT, DB, DD 395 24 weeks	Multinational (Belgium, Canada, Denmark, Netherlands) Age 18-75, severe, not controlled on ICS, 15% current smokers Multicenter (47)	FP DPI (2000) vs. BUD DPI (2000)	No (both are high doses, but relative potency of fluticasone is greater at the given doses)	Symptoms: FP > BUD [mean % of symptom-free days: 31.5 vs. 22.8; $P = 0.02$] Exacerbations: No difference [% of patients having exacerbations: 33.8 vs. 28.4; $P = NS$; % of patients remaining exacerbation free after 180 days: 60 vs. 68; $P = NS$] Rescue med use: FP > BUD [mean % of rescue free days: 42.7 vs. 33.7; $P = 0.02$] Missed days of work: FP > BUD [mean: 4.2 vs. 7.6; $P = 0.012$]	Fair

Table 7. Summary of head-to-head studies comparing inhaled corticosteroids in children and adults

Study	Study Design N Duration	Country Population Setting	Comparison (total daily dose in mcg)	Equivalent dosing	Results	Quality Rating
Hoekx et al, 1996 ⁴¹	RCT, DB, DD 229 8 weeks	Multinational (4: Netherlands, Sweden, Denmark, Finland) Children up to 13, mild to moderate, on ICS, smoking status NR Multicenter (22)	FP DPI (400) vs. BUD DPI (400)	No (medium vs. low)	Symptoms: No difference [no difference in % of symptom free days and nights, % of days with normal activity, and mean symptom or activity scores ($P = NS$, data NR)] Nocturnal awakenings: No difference [sleep disturbance: $P = NS$, actual data NR] Rescue med use: No difference [median % <i>rescue-free days</i> : baseline, endpoint over weeks 1-8: 0, 43 vs. 0, 44; $P = NS$] Missed days of school for children or missed days of work for parents: No difference [$P = NS$, data NR] Parent report of impact of asthma: no difference in sleep or days of missed school or parental work. FP group had significantly less disruption in physical activities after 8 weeks as compared to BUD group ($P = 0.03$)	Fair
Molimard et al. 2005 ²²	RCT, open-label 460 12 weeks	France Age 18-60, moderate to severe persistent, not controlled on ICS, smoking status NR Multicenter, subspecialty clinics (69 pulmonologists)	BDP MDI (800) vs. BUD DPI (1600) vs. FP DPI (1000)	Yes (all high)	Symptoms and Control: No difference [FrACQ, mean change from baseline for BUD vs. FP: -0.8 vs. -0.8, $P = NS$; individual components of FrACQ score, mean changes from baseline: nocturnal awakening (below); morning discomfort (data NR, $P = NS$); limitation of activity (data NR, $p NS$); dyspnea (data NR, $p NS$); wheezing (data	Fair

Table 7. Summary of head-to-head studies comparing inhaled corticosteroids in children and adults

Study	Study Design N Duration	Country Population Setting	Comparison (total daily dose in mcg)	Equivalent dosing	Results	Quality Rating
					NR, p NS); consumption of rescue medication (data NR, p NS)]	
					Nocturnal awakenings: No difference [nocturnal awakenings component of FrACQ: - 0.7 vs. -0.8, P = NS]	
					Rescue med use: No difference [consumption of rescue medication component of FrACQ: data NR, P = NS]	
Ringdal et al. 1996 ⁴²	RCT, DB, DD 518 12 weeks	Multinational Age 18-75, moderate to severe, not controlled on ICS, 19% smokers Multicenter	FP DPI (800) vs. BUD DPI (1600)	Yes (high)	Symptoms: No difference [median % of <i>days with symptom score < 2</i> : baseline, weeks 1-12: 33.3%, 85.7% vs. 33.3%, 88.3%; P = 0.42; median % of <i>symptom free nights</i> : baseline, weeks 1-12: 28.6%, 73.2% vs. 33.3%, %77.5; P = 0.43]	Fair
					Exacerbations: No difference [total # (%) of patients with exacerbations: 41 (16.0%) vs. 51 (19.5%); P = NS]	
					Rescue med use: No difference [% <i>rescue- free days</i> : baseline, weeks 1-12: 0.0, 27.8 vs. 0.0, 16.2; P = 0.12; % <i>rescue-free nights</i> : baseline, weeks 1-12: 26.7, 75.9 vs. 28.6, 74.8; P = 0.32)	
Budesonide compared with mometasone						
Bousquet et al. 2000 ⁴³	RCT, single- blind 730 12 weeks	Multinational (17) Age ≥ 12, moderate, on ICS, smokers excluded	Mometasone DPI (200) vs. Mometasone DPI (400) vs.	No (only for M 400 vs. BUD, both medium)	Symptoms: No difference for equipotent dose comparison (medium compared with medium), high-dose	Fair

Table 7. Summary of head-to-head studies comparing inhaled corticosteroids in children and adults

Study	Study Design N Duration	Country Population Setting	Comparison (total daily dose in mcg)	Equivalent dosing	Results	Quality Rating
		Multicenter (57)	Mometasone DPI (800) vs. Budesonide DPI (800)		MOM (800) > BUD for am wheezing [<i>wheezing am symptom score</i> (mean): baseline, change from baseline: 0.31, -0.07 vs. 0.47, - 0.17 vs. 0.43, -0.27 vs. 0.35, -0.10; <i>P</i> < 0.05 MOM 800 compared with BUD (high compared with med); NS for all other comparisons; <i>difficulty breathing am symptom score</i> (mean): 0.46, - 0.10 vs. 0.59, -0.20 vs. 0.53, -0.24 vs. 0.50, - 0.14; <i>P</i> NS for all comparisons; <i>cough am symptom score</i> (mean): 0.35, -0.10 vs. 0.45, - 0.16 vs. 0.41, -0.19 vs. 0.30, -0.19; <i>P</i> NS for all; results for the p.m. asthma symptoms (wheeze, difficulty breathing, cough) were generally similar to the am results (data not reported)] Nocturnal awakenings: No difference [baseline, change from baseline: 0.36, -0.06 vs. 0.33, - 0.09 vs. 0.41, -0.16 vs. 0.30, -0.07; <i>P</i> = NS for all] Rescue med use: MF 400 > BUD [baseline, change from baseline (mcg/day): 256, -45.86 vs. 282, -90.66 vs. 259, -72.13 vs. 252, -33.90; <i>P</i> < 0.05 MF 400 vs. BUD, medium vs. medium-dose]	
Corren et al. 2003 ⁴⁴	RCT, DB, DD 262 8 weeks	US Age ≥ 12, moderate, on ICS, smokers excluded	Mometasone DPI (400) vs. BUD DPI (320) vs. placebo	No (medium vs. low)	Symptoms: Mixed results, no difference in morning symptoms, MF > BUD for evening symptoms and symptom-free days	Fair

Table 7. Summary of head-to-head studies comparing inhaled corticosteroids in children and adults

Study	Study Design N Duration	Country Population Setting	Comparison (total daily dose in mcg)	Equivalent dosing	Results	Quality Rating
		Multicenter (17)			<p>[<i>morning total asthma score</i>, mean and change from baseline: 1.59 and -0.42 vs. 1.36 and -0.12 vs. 1.42 and 0.16; <i>P</i> = NS MF vs. BUD; <i>evening total asthma score</i>: 1.64 and -0.46 vs. 1.38 and -0.11 vs. 1.23 and 0.24; <i>P</i> < 0.05 MF vs. BUD.</p> <p><i>Symptom-free days</i> (%): 39.7 vs. 26.8 vs. 26.5; <i>P</i> < 0.01 MF vs. BUD.</p> <p>Nocturnal awakenings: No difference (% of patients with no nocturnal awakenings, baseline and endpoint: 68.3 and 78.8 vs. 70.8 and 81.1 vs. 66.7 and 60.8; <i>P</i> NS)</p> <p>Rescue med use: MF > BUD [baseline, change at endpoint inhalations/day: 2.85, -0.91 vs. 2.86, -0.21 vs. 2.46, 1.09; <i>P</i> < 0.05 MF vs. BUD]</p>	
Budesonide compared with triamcinolone						
Weiss et al. 2004 ⁴⁵	RCT 945 52 weeks	US Age ≥ 18, mild to severe, smoking status NR Multicenter, patients from 25 managed care plans	BUD DPI (mean dose at start and end: 941.9 and 956.8 mcg/d) vs. TAA pMDI (1028.2/1042.9 mcg/d)	Yes, on average both are medium, but difficult to assess clearly because starting doses and dose adjustments were left to the discretion of the clinical investigator	Symptoms: BUD > TAA [<i>symptom-free days/month</i> , no. (95% CI): 7.74 (6.81 to 8.66) vs. 3.78 (2.47 to 5.09); <i>P</i> < 0.001. <i>Daytime asthma symptom score</i> , change from baseline (95% CI): -0.37 (-0.43 to -0.31) vs. -0.20 (-0.29 to -0.12); <i>P</i> = 0.001. <i>Nighttime asthma symptom score</i> , change from baseline (95% CI): -0.32 (-0.38 to -0.26) vs. -0.12 (-0.21 to -0.03); <i>P</i> < 0.001. <i>Episode-free days/mo</i> , no. (95% CI): 5.73 (4.90 to 6.56) vs. 2.12 (0.94 to 3.31); <i>P</i> < 0.001]	Fair

Table 7. Summary of head-to-head studies comparing inhaled corticosteroids in children and adults

Study	Study Design N Duration	Country Population Setting	Comparison (total daily dose in mcg)	Equivalent dosing	Results	Quality Rating
					<p>Rescue med use: BUD > TAA [puffs/wk (95% CI): mean use decreased from 4.42 to 2.58 puffs/wk (adjusted mean change, -1.88 puffs/wk [95% CI: -2.17, -1.581]) vs. from 4.56 to 3.68 puffs/wk (adjusted mean change, -0.94 puffs/wk [95% CI: -1.36, -0.52]; $P < 0.001$]</p> <p>Quality of Life: BUD > TAA [AQLQ - overall: baseline and end: 4.6 (1.1) and 0.99 (0.91 to 1.07) vs. 4.5 (1.1) and 0.72 (0.61 to 0.83); $P < 0.001$; AQLQ - symptoms at end: 0.99 (0.91 to 1.08) vs. 0.69 (0.56 to 0.81); $P < 0.001$. AQLQ - environment: 0.81 (0.72 to 0.91) vs. 0.60 (0.46 to 0.74); $P = 0.009$. AQLQ - emotions: 1.12 (1.03 to 1.22) vs. 0.80 (0.66 to 0.94); $P < 0.001$. AQLQ - activities: 1.00 (0.92 to 1.09) vs. 0.75 (0.64 to 0.87); $P < 0.001$. SF-36 General health scores: 6.58 (5.34 to 7.82) vs. 3.03 (1.30 to 4.76), $P = 0.001$. SF-36 Health transition item: baseline and end: 2.7 (1.0) and -0.65 (-0.73 to -0.58) vs. 2.7 (1.0) and -0.29 (-0.40 to -0.18); $P < 0.001$. See evidence tables for data from SF-36 subscores]</p>	
Flunisolide compared with fluticasone						
Volmer et al. 1999 ⁴⁶	Two RCTs (one DB, one open), results reported	Germany Age 18-70, moderate, ICS	FP MDI (500) vs. Flunisolide MDI (1000)	No (high vs. medium)	Symptoms: trend toward FP > Flunisolide [change from baseline in <i>proportion of</i>	Fair

Table 7. Summary of head-to-head studies comparing inhaled corticosteroids in children and adults

Study	Study Design N Duration	Country Population Setting	Comparison (total daily dose in mcg)	Equivalent dosing	Results	Quality Rating
	within a cost-effectiveness analysis publication 321 and 332 8 weeks and 6 weeks	naïve, 26% and 19% smokers Multicenter			<i>symptom-free days</i> : 30.2 vs. 21.1 in study one and 25.7 vs. 20.0 in study two; <i>P</i> = NR for either; <i>Proportion of symptom-free days at study end</i> : 36.4 vs. 28.5 and 35.1 vs. 31.1; <i>P</i> = NR for either study]	
Flunisolide compared with mometasone						
No systematic reviews or head-to-head trials found						
Flunisolide compared with triamcinolone						
No systematic reviews or head-to-head trials found						
Fluticasone compared with mometasone						
O'Connor et al. 2001 ⁴⁷	RCT, DB 733 12 weeks	Multi-national (20) Age ≥12, moderate, on ICS, excluded smokers Multicenter, University hospitals	MF DPI (200) vs. MF DPI (400) vs. MF DPI (800) vs. FP DPI (500)	No (only for medium doses of each: MF 400 vs. FP 500)	Symptoms: Mixed results, no difference for wheeze and cough scores, but FP > MF 200 or 400 for improvement of AM difficulty breathing scores [<i>wheeze and cough scores</i> , change from baseline: -0.01 vs. -0.04 vs. -0.11 vs. -0.13 and -0.07 vs. -0.07 vs. -0.11 vs. -0.12; all <i>P</i> NS). <i>AM difficulty breathing</i> , change from baseline: -0.02 vs. -0.05 vs. -0.11 vs. -0.20; <i>P</i> ≤ 0.05 for FP vs. both MF 200 and MF 400; other <i>P</i> values NS] Nocturnal awakenings: FP > low-dose MF (200), otherwise no differences [change from baseline in # of nocturnal awakenings: 0.07 vs. 0.01 vs. -0.06 vs. 0.14; all <i>P</i> = NS except <i>p</i> ≤0.05 for FP vs. MF 200] Rescue medicine use: No difference [change from baseline (mcg/day): -13.23 vs. -94.84 vs. -38.1 vs. -52.06; <i>P</i> = NS for all]	Fair

Table 7. Summary of head-to-head studies comparing inhaled corticosteroids in children and adults

Study	Study Design N Duration	Country Population Setting	Comparison (total daily dose in mcg)	Equivalent dosing	Results	Quality Rating
Fluticasone compared with triamcinolone						
Baraniuk et al. 1999 ⁴⁸	RCT, DB, triple-dummy 680 12 weeks	US Age ≥12, not controlled on ICS, excluded smokers Multicenter, Pulmonary/allergy medicine clinics (50)	FP MDI (196) + Salmeterol (84) vs. FP MDI (440) vs. TAA MDI (1200)	Yes (medium for both ICS-only arms)	Only data for FP vs. TAA shown here Symptoms: FP > TAA [<i>symptom score</i> , baseline, mean change from baseline(SEM): 1.09, -0.46(0.05) vs. 1.04, -0.31(0.05); P≤0.035; % <i>symptom free days</i> : 11.6, 22.6(2.6) vs. 14.2, 11.9(2.1); P≤0.035] Nighttime awakenings: FP > TAA [<i>nighttime awakenings</i> : 0.47, -0.32(0.04) vs. 0.41, -0.18(0.03); P ≤ 0.035] Rescue medicine use: Mixed results: FP > TAA for puffs/d, no difference in % rescue free days [<i>puffs/day</i> : baseline, mean change from baseline(SEM): 4.9, -2.4(0.2) vs. 4.7, -1.8(0.2); P ≤ 0.035; % of <i>rescue-free days</i> : 12.5, 28.9(2.7) vs. 11.6, 27.4(2.5); P NS]	Fair
Condemni et al. 1997 ⁴⁹	RCT, DB, DD 291 24 weeks	US Age ≥12, persistent asthma, on ICS, excluded smokers Multicenter (24 outpatient centers)	FP DPI (500) vs. TAA MDI (800) vs. placebo	No (medium vs. low)	Symptoms: No difference [<i>overall symptom score</i> , baseline/change: 1.7 (0.1)/-0.3 (0.1) vs. 1.8 (0.1)/-0.1 (0.1) vs. 1.7 (0.1)/0.7 (0.2); p NS for FP vs. TAA; <i>symptom-free days, no. (%)</i> , baseline/change: 33 (4)/14 (5) vs. 23 (3)/12 (3) vs. 25 (3)/-5 (3); p NS FP vs. TAA] Nocturnal awakenings: No difference [baseline/change: 0.09 (0.02)/-0.03 (0.03) vs. 0.10 (0.02)/-0.01 (0.03) vs. 0.08 (0.02)/0.27 (0.05); p NS FP vs.	Fair

Table 7. Summary of head-to-head studies comparing inhaled corticosteroids in children and adults

Study	Study Design N Duration	Country Population Setting	Comparison (total daily dose in mcg)	Equivalent dosing	Results	Quality Rating
					TAA] Rescue medicine use: FP > TAA [puffs per day: baseline/change: 3.0/- 0.9 vs. 3.3/-0.2 vs. 3.2/1.6; <i>P</i> < 0.05, FP vs. TAA; <i>rescue-free days</i> (%): 34/14 vs. 34/1 vs. 32/11; <i>P</i> < 0.05, FP vs. TTA]	
					Withdrawals for lack of efficacy: No difference [% of patients withdrawn for predefined lack-of- efficacy criteria: 17% vs. 27% vs. 60%; <i>P</i> = 0.06 FP vs. TAA]	
Gross et al. 1998 ⁵⁰	RCT, DB, DD 304 24 weeks	US <u>Age ≥12</u> , mild to moderate, on ICS, excluded smokers Multicenter (24 respiratory care or allergy University Clinics)	FP DPI (500) vs. TAA MDI (800) vs. placebo	No (medium vs. low)	Symptoms: No difference [mean overall <i>asthma</i> <i>symptom score</i> (0-9), baseline/change from baseline: 1.7/-0.3 vs. 1.7/-0.1 vs. 1.6/0.8; <i>P</i> = NS; % of <i>symptom-free</i> <i>days</i> , mean baseline/change: 23/18 vs. 32/5 vs. 30/-10; <i>P</i> = NS] Nocturnal awakenings: FP > TAA [mean number per week, baseline/change: 0.09/-0.04 vs. 0.09/0.11 vs. 0.10/0.26; <i>P</i> < 0.016] Rescue medicine use: FP > TAA [mean puffs/day, baseline/change: 3.2/- 0.6 vs. 3.2/0.6 vs. 3.3/1.9; <i>P</i> < 0.018 compared with placebo for both; <i>P</i> < 0.016 for FP compared with TAA; <i>mean % rescue free</i> <i>days</i> , baseline/change: 22/19 vs. 33/1 vs. 32/-	Fair

Table 7. Summary of head-to-head studies comparing inhaled corticosteroids in children and adults

Study	Study Design N Duration	Country Population Setting	Comparison (total daily dose in mcg)	Equivalent dosing	Results	Quality Rating
					12; $P < 0.016$]	
					Quality of life: FP > TAA [AQLQ, mean increase in global score: 0.4 vs. 0.0 vs. -0.5; $P = 0.007$; change in global scores did not reach 0.5, the number thought to be indicative of a clinically meaningful difference]	
					Withdrawals due to unstable asthma: FP > TAA [% patients withdrawn for unstable asthma: 17% vs. 33%; probability of remaining in the study was greater for FP than TAA; $P =$ 0.008]	

Abbreviations: AQLQ = Asthma Quality of Life Questionnaire; BDP = beclomethasone dipropionate; BUD = Budesonide; CI = confidence interval; DB = double-blind; DD = double dummy; DPI = dry powder inhaler; FLUN = Flunisolide; FP = Fluticasone Propionate; FrACQ = French version of the Juniper Asthma Control Questionnaire; ICS = Inhaled Corticosteroids; MA=meta-analysis; MDI = metered dose inhaler; MOM = Mometasone; NR = not reported; NS = not statistically significant; OR= odds ratio; QOL = quality of life; RCT= randomized controlled trial; SMD = standard mean difference; SR=systematic review; TAA = Triamcinolone Acetonide.

Note: "No difference" in the above results section indicates that there was no statistically significant difference between active treatments with ICSs; results are written in the same order as the drugs are entered in the comparison column for each study.

Symbol use: Drug X > Drug Y = statistically significant difference in outcomes favoring Drug X; Drug X > Drug Y trend = point estimate favors Drug X, but the difference is not statistically significant or tests of statistical significance were NR; No difference = no statistically significant difference or tests of statistical significance were not reported and outcomes are similar.

Note: "No difference" in the above results section indicates that there was no statistically significant difference between active treatments with ICSs; results are written in the same order as the drugs are entered in the comparison column for each study.

Note: All results are listed in the same order as the comparison column lists the medications.

Table 8. Summary of head-to-head studies comparing omalizumab with placebo

Study	Study Design N Duration	Study Population	Comparison (total daily dose)	Equivalent dosing	Results	Quality Rating
Beclomethasone compared with budesonide						
Adams, N et al. 2002 ²⁰	Systematic review with meta-analysis	Majority in Europe 24 trials (6 children, 18 in adults)	BDP vs. BUD all studies assessed equal nominal daily doses of BDP and BUD	Yes	Symptoms: No difference [<i>symptom score</i> (6 cross-over studies): SMD 0.06, 95% CI: -0.18, 0.31, 6 studies; <i>night-time breathlessness</i> (three cross-over studies): SMD -0.09 (95% CI: -0.43, 0.25)] Rescue medicine use: No difference [qualitative summary, no meta-analysis]	Good
	Range 2 weeks to 2 years; 50% were 2-4 weeks					

Study	Study Design N Duration	Study Population	Comparison (total daily dose)	Equivalent dosing	Results	Quality Rating
Beclomethasone compared with fluticasone						
Adams, et al. 2007 ²¹	Systematic review with meta-analysis 71 trials (14,602 participants), 59 parallel, 14 cross-over (four had a washout) Majority of studies (47) were between 6 weeks and 5 months; 14 were ≤ 4 weeks	Multinational (most in Europe) Severity ranged from mild to severe persistent	FP vs. BDP (33 trials) FP vs. BUD (37) FP vs. BDP/BUD (2) 38 studies had FP: BDP/BUD dose ratio of 1:2; 22 had dose ratio 1:1; remainder had multiple dose ratio comparisons or ratio was unclear	For some of the included studies	<p>Dose ratio 1:2: Symptoms: FP > BDP/BUD [Change in symptom scores: SMD: -0.19 (95% CI: -0.31, -0.07) 6 studies, N = 1035. Absolute percentage of symptom free days: MD 4.9% (95% CI: -1, 11), two studies, N = 699. Change in percentage of symptom free days: MD 6.43% (95% CI: 0.47, 12.39), two studies, N = 399]</p> <p>Nocturnal awakenings: No difference [Change in number of awakenings per night: MD: 0.01 (95% CI: -0.04, 0.06), two studies, N = 282]</p> <p>Exacerbations: No difference [Withdrawal due to asthma exacerbation: Peto OR 0.77 (95% CI: 0.54, 1.1), 11 studies N = 2824; Participants with an exacerbation: Peto OR 0.74 (95% CI: 0.53, 1.03), four studies N = 1213; Withdrawal due to lack of efficacy: Peto OR 0.6 (95% CI: 0.33, 1.07), seven studies, N = 1781]</p> <p>Rescue med use: FP > BDP/BUD [Change in percentage of rescue-free days: MD 6.89% (95% CI: 0.32, 13.46), two studies, N = 399; Change in rescue usage (puffs/day): MD -0.35 puffs (95% CI: -0.63, -0.07), four studies, N = 763; # of participants experiencing rescue-free days and nights: no significant differences were reported, 6 studies reported (data not pooled for several reasons)]</p> <p>Dose ratio 1:1: Symptoms: No difference [proportion of symptom-free days: MD 5.54% (95% CI: -0.68, 11.76), two studies, N = 571; daytime symptoms: SMD: -0.10 (95% CI: -0.34, 0.13), two studies, N = 285. Change from baseline in daytime symptoms: SMD -0.03 (95% CI: -0.11, 0.06), three studies, N = 534; change from baseline in nocturnal symptoms: SMD -0.03 (95% CI: -0.15, 0.09), three studies, N = 537]</p> <p>Exacerbations: No difference [Requirement for medication other than beta-agonist: Random Effects OR: 0.70 (95% CI: 0.45, 1.09); One or more exacerbations: Peto OR 0.99 (95% CI: 0.73, 1.33), three studies, N = 1054; Withdrawal due to an exacerbation: Peto OR 0.72 (95% CI: 0.38, 1.35), five studies, N = 978]</p>	Good

Study	Study Design N Duration	Study Population	Comparison (total daily dose)	Equivalent dosing	Results	Quality Rating
					Rescue med use: No difference [Change from baseline, day use: -0.04 puffs/day (95% CI: -0.12, 0.04), two studies, N = 368; change from baseline, night use: -0.03 puffs/day (95% CI: -0.13, 0.08), two studies, N = 368]	
De Benedicts et al. 2001 ²⁶	RCT, DB 434 52 weeks	Multinational (7 countries: Holland, Hungary, Italy, Poland, Argentina, Chile, South Africa) Age 4-11, prepubertal, severity and smoking status NR Multicenter (32)	FP DPI (400) vs. BDP DPI (400)	Yes (medium)	Symptoms: No difference [daytime or nighttime symptom scores (data NR; P = NS)] Exacerbations: No difference [number of exacerbations: 47 vs. 52; P = NS; % of patients: 16% vs. 19%; P = NS] Rescue medicine use: No difference [no significant difference (data NR; p NS)] Objective of the study was to compare long-term effects on growth (see KQ2 section)	Fair
Gustafsson et al. 1993 ²⁹	RCT, DB 398 6 weeks	Multinational (11 worldwide) Age 4-19, mild to moderate, not controlled on current meds, smoking status NR Multicenter (32)	FP MDI (200) vs. BDP MDI (400)	Yes (medium)	Symptoms: No difference [% of patients with daytime symptoms the same or better: 83% vs. 81%; P NS.; Nighttime symptoms: % same or better: 83% vs. 82%; P NS.; % with symptom-free days or -nights (data NR, P = NS) or changes in median day, night, or exercise symptom scores (data NR, P = NS)] Rescue medicine use: FP > BDP [Increase in % of rescue-free days at week six: 87% vs. 80%, P = 0.01; over the entire six weeks: 80% vs. 73%, P = 0.046]	Fair
Budesonide compared with Fluticasone						
Adams et al. 2007 ²¹	Systematic review with meta-analysis 71 trials (14,602 participants), 59 parallel, 14 cross-over (four had a washout) Majority of studies (47) were between 6	Multinational (most in Europe) Severity ranged from mild to severe persistent	FP vs. BDP (33 trials) FP vs. BUD (37) FP vs. BDP/BUD (2) 38 studies had FP:BDP/BUD dose ratio of 1:2; 22 had dose ratio 1:1;	For some of the included studies	Dose ratio 1:2: Symptoms: FP > BDP/BUD [Change in symptom scores: SMD: -0.19 (95% CI: -0.31, -0.07) 6 studies, N = 1035. Absolute percentage of symptom free days: MD 4.9% (95% CI: -1, 11), two studies, N = 699. Change in percentage of symptom free days: MD 6.43% (95% CI: 0.47, 12.39), two studies, N = 399.] Nocturnal awakenings: No difference [Change in number of awakenings per night: MD: 0.01 (95% CI: -0.04, 0.06), two	Good

Study	Study Design N Duration	Study Population	Comparison (total daily dose)	Equivalent dosing	Results	Quality Rating
	weeks and 5 months; 14 were ≤ 4 weeks		remainder had multiple dose comparisons or ratio was unclear		<p>studies, N = 282]</p> <p>Exacerbations: No difference [<i>Withdrawal due to asthma exacerbation</i>: Peto OR 0.77 (95% CI: 0.54, 1.1), 11 studies N = 2824; <i>Participants with an exacerbation</i>: Peto OR 0.74 (95% CI: 0.53, 1.03), four studies N = 1213; <i>Withdrawal due to lack of efficacy</i>: Peto OR 0.6 (95% CI: 0.33, 1.07), seven studies, N = 1781]</p> <p>Rescue med use: FP > BDP/BUD [<i>Change in percentage of rescue-free days</i>: MD 6.89% (95% CI: 0.32, 13.46), two studies, N = 399; <i>Change in rescue usage (puffs/day)</i>: MD -0.35 puffs (95% CI: -0.63, -0.07), four studies, N = 763; # of participants experiencing rescue-free days and nights: no significant differences were reported, 6 studies reported (data not pooled for several reasons)]</p> <p>Dose ratio 1:1: Symptoms: No difference [<i>proportion of symptom-free days</i>: MD 5.54% (95% CI: -0.68, 11.76), two studies, N = 571; <i>daytime symptoms</i>: SMD: -0.10 (95% CI: -0.34, 0.13), two studies, N = 285. <i>Change from baseline in daytime symptoms</i>: SMD -0.03 (95% CI: -0.11, 0.06), three studies, N = 534; <i>change from baseline in nocturnal symptoms</i>: SMD -0.03 (95% CI: -0.15, 0.09), three studies, N = 537]</p> <p>Exacerbations: No difference [<i>Requirement for medication other than beta-agonist</i>: Random Effects OR: 0.70 (95% CI: 0.45, 1.09); <i>One or more exacerbations</i>: Peto OR 0.99 (95% CI: 0.73, 1.33), three studies, N = 1054; <i>Withdrawal due to an exacerbation</i>: Peto OR 0.72 (95% CI: 0.38, 1.35), five studies, N = 978]</p> <p>Rescue med use: No difference [<i>Change from baseline, day use</i>: -0.04 puffs/day (95% CI: -0.12, 0.04), two studies, N = 368; <i>change from baseline, night use</i>: -0.03 puffs/day (95% CI: -0.13, 0.08), two studies, N = 368]</p>	
Ferguson et al. 1999 ³⁹	RCT, DB, DD 333 20 weeks	Multinational (6 countries worldwide) Ages 4-12, moderate to severe, on	FP DPI (400) vs. BUD DPI (800)	Yes (medium)	<p>Symptoms: No difference [daytime ($P = 0.729$) and nighttime ($P = 0.34$) symptom scores (Actual data NR)]</p> <p>Exacerbations: Trend toward fewer with FP [% and number of subjects: 1% (2) vs. 5% (8); $P = \text{NR}$]</p>	Fair

Study	Study Design N Duration	Study Population	Comparison (total daily dose)	Equivalent dosing	Results	Quality Rating
		ICS, smoking status NR			Rescue med use: No difference [albuterol use for daytime ($P = 0.181$) and nighttime ($P = 0.59$) (Actual data NR)]	
		Multicenter				
Hoekx et al. 1996 ⁴¹	RCT, DB, DD 229 8 weeks	Multinational (4: Netherlands, Sweden, Denmark, Finland) Children up to 13, mild to moderate, on ICS, smoking status NR Multicenter (22)	FP DPI (400) vs. BUD DPI (400)	No (medium vs. low)	Symptoms: No difference [no difference in % of symptom free days and nights, % of days with normal activity, and mean symptom or activity scores ($P = NS$, data NR)] Nocturnal awakenings: No difference [sleep disturbance: $P = NS$, actual data NR] Rescue med use: No difference [median % rescue-free days: baseline, endpoint over weeks 1-8: 0, 43 vs. 0, 44; $P = NS$] Missed days of school for children or missed days of work for parents: No difference [$P = NS$, data NR] Parent report of impact of asthma: no difference in sleep or days of missed school or parental work. FP group had significantly less disruption in physical activities after 8 weeks as compared to BUD group ($P = 0.03$)	Fair

Abbreviations: AQLQ = Asthma Quality of Life Questionnaire; BDP = beclomethasone dipropionate; BUD = Budesonide; CI = confidence interval; DB = double-blind; DD = double dummy; DPI = dry powder inhaler; FP = Fluticasone Propionate; MA = meta-analysis; MDI = metered dose inhaler; NR = not reported; NS = not statistically significant; OR= odds ratio; QOL = quality of life; RCT= randomized controlled trial; SMD = standard mean difference; SR=systematic review.

Symbol use: Drug X > Drug Y = statistically significant difference in outcomes favoring Drug X; Drug X > Drug Y trend = point estimate favors Drug X, but the difference is not statistically significant or tests of statistical significance were NR; No difference = no statistically significant difference or tests of statistical significance were not reported and outcomes are similar.

Note: All results are listed in the same order as the comparison column lists the medications.

B. Leukotriene Modifiers

Summary of findings

We found just one fair-rated 12-week head-to-head trial comparing one leukotriene modifier with another that met inclusion/exclusion criteria for our review (Table 10).⁵¹ The trial compared montelukast and zafirlukast at recommended doses in adults with mild persistent asthma and reported no statistically significant differences between groups in rescue medicine use and quality of life. We found no head-to-head trials for comparisons of other leukotriene modifiers. In addition, we found no head-to-head trials in children.

Overall, limited head-to-head evidence from one short-term study (12 weeks) does not support a difference between montelukast and zafirlukast in their ability to decrease rescue medicine use or improve quality of life (Table 9 Evidence Profile).

Table 9. Evidence profile of the comparative efficacy of leukotriene modifiers (LMs)

Evidence profile: Comparative efficacy of LM compared with LM							
Number of studies (# of subjects)	Design	Quality	Consistency	Directness	Result and magnitude of effect	Other modifying factors*	Overall Strength of the evidence
Overall total: LM compared with LM							
1 (40)	RCT (12 weeks)	Fair	NA	Direct	No difference	None	Low
Montelukast compared with Zafirlukast							
1 (40)	RCT (12 weeks)	Fair	NA	Direct	No difference	None	Low
Montelukast compared with Zileuton							
We did not identify any systematic reviews or head-to-head trials							
Zafirlukast compared with Zileuton							
We did not identify any systematic reviews or head-to-head trials							

Abbreviations: LM= Leukotriene Modifiers; MA= meta-analysis; RCT= randomized controlled trial; SR= systematic review.

*Imprecise or sparse data; a strong or very strong association; high risk of reporting bias; dose response gradient; effect of plausible residual confounding.

Detailed Assessment

Head-to-head comparisons

1. Montelukast compared with Zafirlukast

One fair-rated 12-week⁵¹ head-to-head trial comparing montelukast to zafirlukast met the inclusion/exclusion criteria for our review. The trial aimed to compare the effect of montelukast (10 mg/day) and zafirlukast (40 mg/day) on quality of life and rescue medication use. The trial enrolled 40 adults with mild persistent asthma from a subspecialty respiratory pathophysiology center in Italy. At endpoint, improvement in beta-agonist use and asthma-related quality of life (AQLQ) were not significantly different between montelukast- and zafirlukast-treated patients.

2. Montelukast compared with Zileuton

We did not identify any good or fair quality systematic reviews or head-to-head trials that compared montelukast to zileuton.

3. Zafirlukast compared with Zileuton

We did not identify any good or fair quality systematic reviews or head-to-head trials that compared zafirlukast to zileuton.

Table 10. Summary of head-to-head studies comparing leukotriene modifiers in children and adults

Study	Study design N Duration	Country Study population Setting	Comparison (total daily dose in mg/day)	Results	Quality rating
Montelukast (ML) compared with zafirlukast					
Riccioni et al. ⁵¹	RCT 40 12 weeks	Italy Age ≥12, mild, smoking status NR Respiratory Pathophysiology Center	ML (10) compared with ZAF (40)	Rescue medicine use: No difference [<i>number of puffs</i> during entire 12 weeks: 25 compared with 27, <i>P</i> = NS] Quality of life: No difference [<i>overall AQLQ and each of</i> <i>the domains</i> (symptoms, environment, emotions, and activities) at 12 weeks: 5.5 compared with 5.7, <i>P</i> = NS (5.7 compared with 5.6; <i>P</i> = NS) (5.3 compared with 5.6; <i>P</i> = NS) (5.3 compared with 5.8; <i>P</i> = NS) (5.9 compared with 5.7; <i>P</i> = NS)]	Fair
Montelukast compared with zileuton					
No systematic reviews or head-to-head trials found					
Zafirlukast compared with zileuton					
No systematic reviews or head-to-head trials found					

Abbreviations: AQLQ = Asthma Quality of Life Questionnaire; ML = Montelukast; NR = not reported; NS = not statistically significant; RCT= randomized controlled trial; ZAF = Zafirlukast.

Symbol use: Drug X > Drug Y = statistically significant difference in outcomes favoring Drug X;

Drug X > Drug Y trend = point estimate favors Drug X, but the difference is not statistically significant or tests of statistical significance were NR;

No difference = no statistically significant difference or tests of statistical significance were not reported and outcomes are similar.

Note: All results are listed in the same order as the comparison column lists the medications.

C. Long-Acting Beta-2 Agonists (LABAs)

Summary of findings

We found three fair RCTs⁵²⁻⁵⁵ that included head-to-head comparisons of one LABA with another LABA meeting our inclusion/exclusion criteria. Two compared eformoterol with salmeterol^{52, 53} and one compared formoterol with salmeterol.^{54, 55} Of note, formoterol was formerly known as eformoterol in the UK and these are generally considered to be the same medicine. We also found one 6-month open-label trial comparing formoterol and salmeterol that we rated poor quality.⁵⁶

Overall, results from three efficacy studies provide moderate evidence that LABAs do not differ in their ability to control asthma symptoms, prevent exacerbations, improve quality of life, and prevent hospitalizations or emergency visits in patients with persistent asthma not controlled on ICSs alone (Table 11 Evidence Profile).

Table 11. Evidence profile of the comparative efficacy of LABAs

Evidence Profile: Comparative efficacy of LABA compared with LABA							
Number of studies (# of subjects)	Design	Quality	Consistency	Directness	Result and magnitude of effect	Other modifying factors*	Overall strength of the evidence
Overall total: LABA compared with LABA							
3 (1107)	RCTs	Fair	Consistent	Direct	No difference	None	Moderate
Eformoterol (eFM) compared with salmeterol (SM)							
2 (625)	RCTs (8-week cross-over; 12-week open-label)	Fair	Consistent	Direct	No difference in health outcomes	None	Moderate
Formoterol (FM) compared with salmeterol (SM)							
1 (482)	RCT (open-label, 6-month trial)	Fair	Consistent	Direct	No difference in health outcomes	None	Moderate
Formoterol (FM) compared with arformoterol (ARF)							
We did not identify any systematic reviews or head-to-head trials that compared FM to ARF							
Salmeterol (SM) compared with arformoterol (ARF)							
We did not identify any systematic reviews or head-to-head trials that compared SM to ARF							

Abbreviations: ARF= Arformoterol; eFM = Eformoterol; FM = Formoterol; LABAs = Long-Acting Beta-2 Agonists;

MA= meta-analysis; RCT= randomized controlled trial; SM= Salmeterol; SR= systematic review.

*Imprecise or sparse data; a strong or very strong association; high risk of reporting bias; dose response gradient; effect of plausible residual confounding.

Detailed Assessment

Description of Studies

Of the 3 trials, two compared eformoterol (eFM) with salmeterol (SM) and one compared formoterol (FM) with SM (Table 12). Study duration ranged from 8 weeks to 6 months. The most commonly used delivery devices were MDIs and DPIs: two studies (66%) compared DPI to DPI; one study (33%) compared DPI to DPI and to MDI (eFM DPI compared with SM DPI compared with SM MDI).⁵³

Study Populations

The three head-to-head RCTs included a total of 1107 subjects. Two were conducted primarily in adult populations.^{52, 54, 55} One study⁵³ was conducted in a pediatric and adolescent population (age 6-17) (Table 12). Two trials (66%) were conducted in the UK and Republic of Ireland^{52, 53} and one was conducted in France, Italy, Spain, Sweden, Switzerland and the UK.^{54, 55} Asthma severity ranged from mild to severe persistent: one study (33%) was conducted in patients with mild to moderate persistent asthma,⁵² one (33%) in patients with moderate persistent,⁵³ and one (33%) in patients with moderate to severe persistent.^{54, 55} All three trials enrolled subjects that were not adequately controlled on ICSs. Smoking status was not reported for the pediatric/adolescent trial.⁵³ The other two studies (66%) allowed smokers and reported that 14 to 24 percent in each group were smokers.

Sponsorship

Of the 3 head-to-head trials, 2 (66%) were funded by pharmaceutical companies; 1 trial (33%) did not report the source of funding but at least one author had a primary affiliation with a pharmaceutical company.

Head-to-head comparisons

1. *Eformoterol (eFM) compared with Salmeterol (SM)*

Two fair-quality RCTs meeting our inclusion/exclusion criteria compared eFM with SM.^{52, 53} Both enrolled patients not adequately controlled on ICSs and were conducted in the UK and Republic of Ireland. The first was an 8-week trial that enrolled 469 adolescents and adults ≥ 12 years of age with mild to moderate persistent asthma.⁵² The other was a 12-week trial that enrolled 156 children and adolescents between six and 17 years of age with moderate persistent asthma.⁵³

Both trials assessed asthma symptoms, nocturnal awakenings, and exacerbations. One trial also reported hospital admission or visits to A&E⁵² while the other study also reported rescue medication use, quality of life, missed work, missed school, and compliance as well.⁵³ The trials found no difference between those treated with eFM and those treated with SM for all outcomes except for rescue medicine use: one trial⁵³ found a greater decrease in rescue medicine use in those treated with eFM than in those treated with SM (Table 12).

2. *Formoterol (FM) compared with Salmeterol (SM)*

One fair-quality open-label 6-month RCT meeting our inclusion/exclusion criteria compared FM with SM in 482 adults ≥ 18 years of age with moderate to severe persistent asthma.^{54, 55} This trial reported symptoms, rescue medicine use, quality of life, missed days of work, ER visits, and hospitalizations. There were no statistically significant differences in these outcomes between those treated with FM than those treated with SM (Table 12).

3. *Formoterol (FM) compared with Arformoterol (ARF)*

We did not identify any systematic reviews or head-to-head trials that compared FM to ARF.

4. *Salmeterol (SM) compared with Arformoterol (ARF)*

We did not identify any systematic reviews or head-to-head trials that compared SM to ARF.

Table 12. Summary of head-to-head studies comparing LABAs in children and adults

Study	Study Design N Duration	Country Study population Setting	Comparison (total daily dose in mcg)	Results	Quality rating
Eformoterol compared with Salmeterol					
Campbell et al. 1999 ⁵²	RCT, cross-over 469 8 weeks	UK & Republic of Ireland Age ≥ 12, mild to moderate, not controlled on ICS, 20-24% current smokers in each group General practice & hospital centres	eFM DPI (24) vs. SM DPI (100) vs. SM MDI (100)	Symptoms: No difference [% of <i>days symptom-free and using no rescue medicine to relieve symptoms</i> : 32.8 vs. 24.1 vs. 28; <i>P</i> = NS] Nocturnal awakenings: No difference [patients in all treatment groups gained an additional 1-1.5 nights undisturbed by asthma per week; <i>P</i> = NS] Exacerbations: No difference [mean (SD) <i>number of episodes of worsening of asthma per patient</i> : 0.12 (0.35) vs. 0.13 (0.36) vs. 0.12 (0.32), <i>P</i> = 0.9144 for eFM vs. SM DPI, <i>P</i> = 0.9041 for eFM vs. SM MDI; % of <i>patients with worsening asthma</i> : 11 vs. 12 vs. 12; <i>P</i> = NR; number of episodes of worsening asthma resulting in short course of oral or nebulised steroids: 13 vs. 5 vs. 11; <i>P</i> = NR] Hospital admission or visit to A&E: No difference [# of admissions/visits: 1 vs. 1 vs. 2; <i>P</i> = NR]	Fair
Everden et al. 2004 ⁵³	RCT, open 156 12 weeks	UK & Republic of Ireland Children and adolescents age 6- 17, moderate persistent, not controlled on ICS, smoking status=NR General practice outpatient clinics	eFM DPI (24) compared with SM DPI (100)	Symptoms: No difference [<i>overall daytime symptom score</i> , mean (SD): -0.70 (0.62) vs. -0.53 (0.57), mean treatment difference (95% CI): -0.17 (-0.36, +0.02), <i>P</i> = 0.052; <i>overall night-time symptom score</i> , mean (SD): -0.50 (0.59) vs. - 0.47 (0.62), mean treatment difference (95% CI): -0.02 (- 0.22,+0.17), <i>P</i> = 0.687; <i>poorly controlled days per patient per 12 week</i> : 12.4 vs. 17.0, ratio 0.73, <i>P</i> = 0.107; <i>median days time to achieve pre-defined criteria for asthma control</i> : 12 vs. 26, <i>P</i> = 0.175] Nocturnal awakenings: No difference [nights per week, mean (SD): -1.03 (1.96) vs. -1.31 (1.94), mean treatment difference (95% CI): +0.28 (-0.36,+0.92), <i>P</i> = 0.632] Exacerbations: No difference [% of <i>patients experiencing a severe exacerbation</i> : 17 vs. 17, <i>P</i> = NS;	Fair

Study	Study Design N Duration	Country Study population Setting	Comparison (total daily dose in mcg)	Results	Quality rating
				<p>frequency of mild exacerbations per patient per 12 weeks: 7.8 vs. 12.2, ratio 0.63, $P = 0.051$]</p> <p>Rescue medication use: eFM > SM [number of puffs per 24 hours, mean change from baseline (SD): -2.45 (2.29) vs. -2.05 (2.5), adjusted mean difference (95% CI): -0.70 (-1.37, -0.03), $P = 0.043$;</p> <p>Daytime # inhalations, mean change from baseline (SD): -1.85 (1.9) vs. -1.72 (2.02), adjusted mean difference (95% CI): -0.46 (-0.97, +0.05), $P = 0.081$;</p> <p>Nighttime # inhalations, mean change from baseline (SD): -0.56 (0.83) vs. -0.39 (0.69), adjusted mean difference (95% CI): -0.17 (-0.42, +0.09), $P = 0.251$;</p> <p>% decrease from baseline in reliever use in 6-11 year age group: 64% vs. 47% and 12-17 year age group: 67% vs. 57%; $P = \text{NR}$]</p> <p>QOL: No difference [PAQLQ: trend towards greater improvement with eFM ($P = \text{NS}$, data NR, shown in figure only)]</p> <p>Missed work: No difference [proportion of days in which parents were unable to attend work or participate in leisure activities because of child's asthma: 0.76% vs. 3.52%, $P = 0.071$]</p> <p>Missed school: No difference [1-2% of days in both groups, $P = \text{NR}$]</p> <p>Compliance: No difference [90% vs. 88% $P = \text{NS}$]</p>	
Formoterol compared with Salmeterol					
Vervloet et al. 1998 ⁵⁴	RCT, open 482	France, Italy, Spain, Sweden, Switzerland & UK	FM DPI (24) compared with SM DPI (100)	Symptoms: No difference [mean (SD) episode-free days per patient per 6 months: 97 (64) compared with 95 (62); $P = \text{NS}$]	Fair
AND Rutten-van Molken et al. 1998 ⁵⁵	6 months	Age ≥ 18 , moderate-severe, not controlled on ICS, 14-16% current smokers Outpatient centres		Rescue med use: No difference [mean (SD) puffs per patient per 6 months: 199 (348) compared with 203 (248); $P = 0.406$]	
				QOL: No difference [percentage of patients reaching a clinically relevant improvement in quality of life (4 or more points	

Study	Study Design N Duration	Country Study population Setting	Comparison (total daily dose in mcg)	Results	Quality rating
				improvement in total SGRQ score) after 6 months of treatment: 64 compared with 62; <i>P</i> = NS]	
				Missed days of work: No difference [mean (SD) days of absence from paid work per patient per 6 months: 3.19 (15.75) compared with 2.64 (16.10); <i>P</i> = 0.144]	
				Emergency Room visits: No difference [mean (SD) per patient per 6 months: 0.027 (0.20) compared with 0.095 (0.78); <i>P</i> = 0.188]	
				Inpatient hospitalization days: No difference [mean (SD) days per patient per 6 months: 0.58 (5.38) compared with 0.43 (3.50); <i>P</i> = 0.996]	

Abbreviations: AQLQ = Asthma Quality of Life Questionnaire; CI = confidence interval; DPI = dry powder inhaler; eFM = Eformoterol; FM = Formoterol; MDI = metered dose inhaler; NR = not reported; NS = not statistically significant; QOL = quality of life; RCT= randomized controlled trial; SM = Salmeterol; SMD = standard mean difference. Symbol use: Drug X > Drug Y = statistically significant difference in outcomes favoring Drug X; Drug X > Drug Y trend = point estimate favors Drug X, but the difference is not statistically significant or tests of statistical significance were NR; No difference = no statistically significant difference or tests of statistical significance were not reported and outcomes are similar.

Note: All results are listed in the same order as the comparison column lists the medications.

Table 13. Summary of head-to-head studies comparing LABAs in children ≤12 years of age

Study	Study design N Duration	Country Study population Setting	Comparison (total daily dose)	Results	Quality rating
Eformoterol compared with Salmeterol					
Everden et al. 2004 ⁵³	RCT, open 156 12 weeks	UK & Republic of Ireland Children and adolescents age 6-17, moderate persistent, not controlled on ICS, smoking status=NR General practice outpatient clinics	eFM DPI (24) compared with SM DPI (100)	Symptoms: No difference [overall daytime symptom score, mean (SD): -0.70 (0.62) compared with -0.53 (0.57), mean treatment difference (95% CI): -0.17 (-0.36, +0.02), <i>P</i> = 0.052; overall night-time symptom score, mean (SD): -0.50 (0.59) compared with -0.47 (0.62), mean treatment difference (95% CI): -0.02 (-0.22, +0.17), <i>P</i> = 0.687; poorly controlled days per patient per 12 week: 12.4 compared with 17.0, ratio 0.73, <i>P</i> = 0.107; median days time to achieve pre-defined criteria for asthma control: 12 compared with 26, <i>P</i> = 0.175]	Fair
				Nocturnal awakenings: No difference [nights per week, mean (SD): -1.03 (1.96) compared with -1.31 (1.94),	

Study	Study design N Duration	Country Study population Setting	Comparison (total daily dose)	Results	Quality rating
				<p>mean treatment difference (95% CI): +0.28 (-0.36,+0.92), $P = 0.632$]</p> <p>Exacerbations: No difference [% of patients experiencing a severe exacerbation: 17 compared with 17, $P = NS$; frequency of mild exacerbations per patient per 12 weeks: 7.8 compared with 12.2, ratio 0.63, $P = 0.051$]</p> <p>Rescue medication use: eFM > SM [number of puffs per 24 hours, mean change from baseline (SD): -2.45 (2.29) compared with -2.05 (2.5), adjusted mean difference (95% CI): -0.70 (-1.37, -0.03), $P = 0.043$; Daytime # inhalations, mean change from baseline (SD): -1.85 (1.9) compared with -1.72 (2.02), adjusted mean difference (95% CI): -0.46 (-0.97,+0.05), $P = 0.081$; Nighttime # inhalations, mean change from baseline (SD): -0.56 (0.83) compared with -0.39 (0.69), adjusted mean difference (95% CI): -0.17 (-0.42,+0.09), $P = 0.251$; % decrease from baseline in reliever use in 6-11 year age group: 64% compared with 47% and 12-17 year age group: 67% compared with 57%; $P = NR$]</p> <p>QOL: no difference [PAQLQ: trend towards greater improvement with eFM ($P = NS$, data NR, shown in figure)]</p> <p>Missed work: No difference [proportion of days in which parents were unable to attend work or participate in leisure activities because of child's asthma: 0.76% compared with 3.52%, $P = 0.071$]</p> <p>Missed school: no difference [1-2%of days in both groups, $P = NR$]</p> <p>Compliance: No difference [90% compared with 88% $P = NS$]</p>	

Abbreviations: CI = confidence interval; DPI= dry powder inhaler; eFM= Eformoterol; LABAs= Long-Acting Beta-2 Agonists; NR = not reported; NS= not statistically significant; PAQLQ= Pediatric Asthma Quality of Life Questionnaire; QOL= quality of life; RCT= randomized controlled trial; SM= Salmeterol.

Symbol use: Drug X > Drug Y = statistically significant difference in outcomes favoring Drug X; Drug X > Drug Y trend = point estimate favors Drug X, but the difference is not statistically significant or tests of statistical significance were NR; No difference = no statistically significant difference or tests of statistical significance were not reported and outcomes are similar.

Note: All results are listed in the same order as the comparison column lists the medications.

D. Anti-IgE Therapy

Summary of findings

Omalizumab is the only available anti-IgE drug approved for the treatment of asthma; therefore, there are no studies of intra-class comparisons. We did not find any head-to-head studies directly comparing omalizumab to ICSs, LABAs, leukotriene modifiers, or combination products. All included trials are placebo comparisons. We found six RCTs (11 publications)⁵⁷⁻⁶⁸ and two systematic reviews with meta-analyses^{69, 70} that met our eligibility criteria. All were of fair or good quality. Only one of the RCTs^{62, 63} enrolled children (6-12 years old); all other RCTs included adolescents and adults ≥ 12 years of age.

Overall, efficacy studies provide consistent evidence favoring omalizumab over placebo for the ability to control asthma symptoms, prevent exacerbations, and reduce the need for additional rescue medication (high strength of evidence, Table 14 Evidence Profile). Data from good and fair quality RCTs and systematic reviews consistently found that omalizumab-treated patients showed significant improvement in asthma-related health outcomes compared to placebo-treated patients. Trials were 28-32 weeks in duration; in addition, two trials conducted optional double-blind extensions providing data for up to 52 weeks. However, only one trial enrolled pediatric subjects. Our meta-analyses showed omalizumab to be statistically significantly superior to placebo for five outcome measures (Appendix G).

Table 14. Evidence profile of the comparative efficacy of omalizumab

Omalizumab compared with placebo							
No. of studies (# of subjects)	Design	Quality	Consistency	Directness	Results and magnitude of effect*	Other modifying factors*	Overall strength of evidence
Overall total: Omalizumab compared with placebo							
2 SRs (5,199)	2 SR w/ MA	Good (1), Fair (1)	Consistent	Direct	OM > placebo	None	High
6 RCTs (2,538)	6 RCTs	Good (2), Fair (4)			Change in # of exacerbations per patient: SMD = -0.231, 95% CI: -0.311, -0.151; $P < 0.001$		
					Decrease in percentage of patients with \geq exacerbation per patient: SMD = -0.273, 95% CI: -0.366, -0.179; $P < 0.001$		
					Increase in AQLQ scores: SMD = 0.303, 95% CI: 0.223, 0.383; $P < 0.001$		
					Proportion of patients achieving a clinically meaningful improvement in overall QOL score (i.e., increase in score of ≥ 0.5 points): SMD = 0.303, 95% CI: 0.223, 0.383; $P < 0.001$		

AQLQ = Asthma Quality of Life Questionnaire; CI = confidence interval; MA=meta-analysis; OM= Omalizumab; RCT= randomized controlled trial; SMD = standard mean difference; SR= systematic review.

*Selected results from our meta-analyses of included RCTs; the complete meta-analyses is in Appendix G.

Detailed Assessment

Description of Studies

All but one of the RCTs were 28 weeks in duration; one trial was 32 weeks in duration⁶⁰ (Table 15). Four trials had 16 weeks of stable ICS dose followed by a 12-16 week phase of ICS tapering. In all included RCTs, subjects continued stable ICS treatment. Subjects were treated with concurrent beclamethosone in four of the six trials,^{57, 61, 62, 64} with concurrent fluticasone in one trial,⁶⁰ and with budesonide in one trial.⁶⁷ In one trial, all patients were also taking LABAs at constant doses throughout the study.⁶¹ In all six RCTs and one systematic review,⁶⁹ omalizumab was administered subcutaneously. One systematic review included studies where omalizumab was administered intravenously or by inhalation (modes that are not approved for use in the US or Canada) as well as by subcutaneous injection.⁷⁰

Study Populations

The six RCTs included a total of 2,538 patients. Five trials were conducted in adolescent and adult populations (ranging from 12 to 75 years of age). Only one study was conducted in a pediatric population (6-12 years of age).⁶² In addition, all patients had moderate to severe asthma with concurrent allergies and/or rhinitis. One trial was conducted in the US and one in the US and UK; the remaining four trials were multinational.

Current smoking status was not reported in the study that enrolled children (age 6-12).⁶² One study explicitly excluded smokers;⁶¹ the remaining four studies had no current smokers enrolled but included previous smokers.

Methodological Quality

The RCTs and systematic reviews were of fair to good quality. One efficacy study that met our eligibility criteria was not included in our analysis because it was rated poor quality for internal validity (Appendix D).

Sponsorship

Of the six included RCTs, five (83%) were funded by pharmaceutical companies; one did not report the source of funding but at least one author had a primary affiliation with a pharmaceutical company.⁶¹

Head-to-head comparisons

We found no head-to-head studies directly comparing the efficacy of omalizumab with another asthma treatment. Omalizumab is the only anti-IgE medication approved in the US or Canada for the treatment of asthma.

Omalizumab compared with placebo

The majority of trials assessed overall asthma symptom scores, exacerbations, use of rescue medication, quality of life, urgent care or ER visits, and hospitalization rates. All trials found greater improvements in omalizumab-treated patients (Table 15). One RCT conducted in children reported nocturnal awakenings.⁶² No studies reported mortality or adherence. We conducted meta-analyses on these outcomes when sufficient data was reported by multiple studies (Appendix G).

The five trials in adolescent and adult populations reported statistically significant differences favoring omalizumab in overall symptom scores. The pediatrics study, however, reported “little change” in scores and “minimal difference” between omalizumab and placebo (data NR).⁶² Two trials reported the proportion of “low symptom days.”^{57, 64, 68} Both studies used the term “asthma-free days” but defined the concept to allow for some daily symptoms and daily use of rescue-medication, which essentially means “low symptom” days. Our meta-analysis found a significant increase (mean increase of 23.2%) in the proportion of low symptom days in omalizumab-treated patients compared to placebo-treated patients (SMD = 0.232, 95% CI: 0.112, 0.353; $P < 0.001$, 2 studies) (Appendix G). There was no significant heterogeneity between studies ($P = 0.3992$).

All studies assessed the change in the number of exacerbations per patient. The results of our meta-analysis show a significant decrease in the number of exacerbations per patient with omalizumab compared to placebo (SMD = -0.231, 95% CI: -0.311, -0.151; $P < 0.001$, 6 studies). Sensitivity analyses indicate no difference in overall meta-analysis conclusions with any single study removed. There was no significant heterogeneity between studies ($P = 0.9871$). In addition, four studies reported the percentage of patients with one or more exacerbations. Our meta-analysis results show a significant decrease in the proportion of patients with at least one exacerbation per patient for omalizumab compared to placebo (SMD = -0.273, 95% CI: -0.366, -0.179; $P < 0.001$, 4 studies). There was no significant heterogeneity between studies ($P = 0.710$).

All studies reported a greater decrease in use of rescue medication for omalizumab. Differences were statistically significant in four of six RCTs. The difference was not significant in one study,⁶¹ and the P value was not reported in one.⁶⁷ We were not able to conduct meta-analyses for rescue medicine use outcomes because too few studies reported sufficient data.

Results of our meta-analyses show greater improvements in quality of life for those treated with omalizumab than for those treated with placebo. Subjects treated with omalizumab had a statistically significantly greater increase in AQLQ scores than subjects treated with placebo (SMD = 0.303, 95% CI: 0.223, 0.383; $P < 0.001$, 6 studies). Sensitivity analyses indicate no difference in overall meta-analysis with single studies removed; there was no significant heterogeneity between studies ($P = 0.2191$). In addition, a greater proportion of omalizumab-treated patients had a significant improvement in quality of life (i.e., increase in score of ≥ 0.5 points) (SMD = 0.217, 95% CI: 0.138, 0.297; $P < 0.001$, 6 studies). There was no significant heterogeneity between studies ($P = 0.5309$).

Two systematic reviews with meta-analyses reported results consistent with our findings. One good systematic review included 14 RCTs (3143 subjects) comparing omalizumab and placebo in children and adults with chronic asthma.⁷⁰ This review included the six RCTs that met our inclusion criteria and eight studies that did not meet our eligibility criteria (e.g., studies with $N < 40$, drug routes of administration not approved in the US or Canada, such as inhaled or intravenous). All patients had a diagnosis of allergic asthma (ranging from mild to severe). A fair quality systematic review conducted a meta-analysis of asthma-related QoL from five RCTs.⁶⁹ We included these trials in our analysis; in addition, we included the INNOVATE trial.⁶¹ Results from this meta-analysis are consistent with our findings.

Table 15. Summary of head-to-head studies comparing omalizumab with placebo

Study design N Duration	Country Population Setting	Dose	Results	Quality rating
Omalizumab compared with placebo				
Busse, et al. 2001 ⁵⁷	RCT DB 525	US and UK	0.016 mg/kg/IgE (IU/mL) per 4 weeks (150 mg or 300 mg every 4 wks or 225 mg, 300 mg, or 375 mg every 2 wks)	Fair
Finn et al. 2003 ⁵⁸	28 weeks (16 weeks followed by 12 weeks tapering ICS dose)	Age 12-75, moderate to severe allergic asthma requiring daily ICS, on stable BDP dose 4 wks prior to randomization and during wks 1-16		
Lanier et al. 2005 ⁵⁹				
+ Unpublished data from FDA ⁶⁸	Optional 24 week DB extension (N = 460)	Multicenter (5)		
			<p>Symptoms: OM > placebo [Median <i>change in total symptom score</i> from baseline to week 16: -1.5 compared with -1.1; $P < 0.05$; <i>daily asthma scores</i> over 28 weeks: significantly improved with OM: data NR; $P < 0.01$; <i>median proportion of low symptom days</i> for 28 week period: 0.03 compared with 0.01 ($P = 0.04$)]</p> <p>Night symptoms: OM > placebo [Median change from baseline to week 16 in nocturnal asthma score: -0.4 compared with -0.2; $P < 0.05$]</p> <p>Exacerbations: OM > placebo [<i>number per patient</i>, weeks 1-16: 0.28 compared with 0.54, $P = 0.006$; <i>% of subjects experiencing 1 or more</i>: 14.6% compared with 23.3%, $P = 0.009$; <i>% of subjects with exacerbations during steroid reduction phase</i>, weeks 17-28: 21.3 compared with 32.3, $P = 0.004$; <i>number per subject</i>, weeks 17-28: 0.39 compared with 0.66, $P = 0.003$]</p> <p>Rescue med use: OM > placebo [Significant difference favoring OM in reduction in daily rescue medication use over 28 weeks (data reported in line graph only; $P < 0.01$)]</p> <p>QoL: OM > placebo [<i>Mean improvement in overall AQLQ score at week 16</i>: 0.93 compared with 0.66, $P < 0.01$; <i>mean improvement in overall AQLQ score at week 28</i>: 0.97 compared with 0.7, $P < 0.01$; <i>proportion of patients achieving a clinically meaningful improvement in overall QoL</i> (i.e., increase in score of ≥ 0.5 points): at 16 weeks, 64.1% compared with 51.7%, $P < 0.01$; at 28 weeks, 66.4% compared with 54.8%, $P < 0.05$]</p> <p>Missed school: OM > placebo [<i>Mean Number (\pm SD) of school days missed</i>: 0.49 (± 2.1) compared with 0.59 (± 1.9), $P = \text{NR}$]</p> <p>Missed work: OM > placebo</p>	

Study design N Duration	Country Population Setting	Dose	Results	Quality rating	
			<p>[Mean (± SD) Number of work days missed: 0.38 (± 1.4) compared with 0.72 (± 3.2), <i>P</i> = NR]</p> <p>ER/Urgent care: No difference [Mean unscheduled medical contacts (± SD): 0.26 (0.65) compared with 0.27 (0.62), <i>P</i> = NR]</p> <p>Hospitalization: No difference [Exacerbations requiring hospitalization 1 (<1%) compared with 2 (<1%), <i>P</i> = NR]</p> <p>EXTENSION PHASE: Exacerbations: OM > placebo [Exacerbations per patient: 0.60 compared with 0.83, <i>P</i> = 0.023]</p> <p>QOL: OM > placebo [improvement in mean overall AQLQ score: 1.19 compared with 0.91, <i>P</i> < 0.01; % of patients achieving a clinically meaningful improvement in overall QoL score at 52 weeks: 74.6 compared with 65.5, <i>P</i> < 0.01]</p> <p>Missed school: OM > placebo [Mean number (± SD) of school days missed: 0.40 (± 2.1) compared with 0.53 (± 1.84), <i>P</i> = NR]</p> <p>Missed work: OM > placebo [Mean number (± SD) of work days missed: 0.39 (± 1.76) compared with 0.33 (± 1.27), <i>P</i> = NR]</p> <p>ER/Urgent care: OM > placebo [Unscheduled medical visits (mean ± SD) : 0.13 (± 0.44) compared with 0.20 (± 0.51) <i>P</i> = NR]</p> <p>Hospitalization: No difference [Exacerbations requiring hospitalization 0 compared with 1, <i>P</i> = NR]</p>		
Holgate et al. 2004 ⁶⁰ + Unpublished data from FDA ⁶⁸	RCT DB 246 32 weeks (16 weeks followed by 16 weeks FP reduction phase)	Multinational Age 12-75, severe asthmatics, optimally controlled, requiring high dose FP (between 1000 and 2000 mcg/day) stabilized for 4 wks prior to randomization;	0.016 mg/kg/IgE (IU/mL) per 4 weeks	<p>Symptoms: OM > placebo [OM led to improvements in symptoms scores over both the stable steroid and stable reduction phases (data NR; <i>P</i> < 0.05 at weeks 16 and 32)]</p> <p>Exacerbations: OM > placebo [OM patients had lower mean number of exacerbations per patient during stable steroid phase (weeks</p>	Good

Study design N Duration	Country Population Setting	Dose	Results	Quality rating
	allergic response (> 1 positive SPT) to aeroallergen(s) Multicenter		1-16): 0.15 compared with 0.23 ($P = 0.57$) and during steroid reduction phase: 0.19 compared with 0.34 ($P = 0.15$) Rescue med use: OM > placebo [OM led to improvements in rescue med use over both phases of study (data NR; $P < 0.05$ at week 16; $P < 0.01$ at week 32)] QOL: OM > placebo Overall, 58% of OM patients compared with 39% of placebo patients had a clinically detectable improvement in mean AQLQ scores ($P < 0.01$); 16% had a large improvement compared to 6% with placebo ($P < 0.05$). These differences were also reflected in various QOL domain scores Mean change in score ≥ 0.5 and ≥ 1.5 taken to represent clinically detectable and large differences in asthma related QoL respectively. Change in overall AQLQ score (0.52 compared with 0.28) at 16 weeks Change in overall AQLQ score (0.68 compared with 0.26) at 32 weeks	
Holgate et al. 2004 ⁶⁰ + Unpublished data from FDA ⁶⁸	RCT DB 246 32 weeks (16 weeks followed by 16 weeks FP reduction phase) Multicenter	Multinational Age 12-75, severe asthmatics, optimally controlled, requiring high dose FP (between 1000 and 2000 mcg/day) stabilized for 4 wks prior to randomization; allergic response (> 1 positive SPT) to aeroallergen(s) Multicenter	0.016 mg/kg/IgE (IU/mL) per 4 weeks Symptoms: OM > placebo [OM led to improvements in symptoms scores over both the stable steroid and stable reduction phases (data NR; $P < 0.05$ at weeks 16 and 32)] Exacerbations: OM > placebo [OM patients had lower mean number of exacerbations per patient during stable steroid phase (weeks 1-16): 0.15 compared with 0.23 ($P = 0.57$) and during steroid reduction phase: 0.19 compared with 0.34 ($P = 0.15$)] Rescue med use: OM > placebo [OM led to improvements in rescue med use over both phases of study (data NR; $P < 0.05$ at week 16; $P < 0.01$ at week 32)] QOL: OM > placebo Overall, 58% of OM patients	Good

Study design N Duration	Country Population Setting	Dose	Results	Quality rating	
			<p>compared with 39% of placebo patients had a clinically detectable improvement in mean AQLQ scores ($P < 0.01$); 16% had a large improvement compared to 6% with placebo ($P < 0.05$). These differences were also reflected in various QOL domain scores</p> <p>Mean change in score ≥ 0.5 and ≥ 1.5 taken to represent clinically detectable and large differences in asthma related QoL respectively.</p> <p>Change in overall AQLQ score (0.52 compared with 0.28) at 16 weeks</p> <p>Change in overall AQLQ score (0.68 compared with 0.26) at 32 weeks</p>		
Humbert et al. 2005 ⁶¹ INNOVATE	RCT DB 482 28 weeks	Multinational Age 12-75, positive SPT to ≥ 1 perennial aeroallergen, severe persistent asthma requiring regular treatment with >1000 mcg BDP or equivalent LABA, continued high dose ICS + LABA throughout study Multicenter (hospital clinics)	0.016 mg/kg per IU/mL of IgE	<p>Symptoms: OM $>$ placebo [Mean change from baseline in total symptom score significantly greater with OM (data NR; $P = 0.039$)]</p> <p>Exacerbations: OM $>$ placebo After adjustment for baseline differences, statistically significant difference in OM group in clinically significant asthma exacerbation rate (0.68 compared with 0.91; $P = 0.042$; rate ratio 0.738 [95% CI: 0.552, 0.998]. Treatment group difference (rate ratio 0.806, $P = 0.153$) did not reach statistical significance in analysis without adjustment for previous exacerbation difference at baseline; however, similar magnitude of effect was seen (19% reduction). NNT for 1 year to save one clinically significant exacerbation is 2.2.</p> <p>Severe exacerbations significantly lower in OM group (0.24 compared with 0.48; $P = 0.002$). NNT for 1 year to save one severe exacerbation was 2.2.</p> <p>Rescue med use: No difference [OM patients used approximately 0.5 puffs/day less of rescue medication compared with placebo at endpoint ($P = NS$)]</p> <p>QoL: OM $>$ placebo [Significantly greater improvements in overall AQLQ score in OM</p>	Fair

Study design N Duration	Country Population Setting	Dose	Results	Quality rating
			<p>patients: (LSM: 0.91 compared with 0.46; LSM difference: 0.45; $P < 0.001$). Significantly greater proportion of OM patients achieved a clinically meaningful (≥ 0.5 point) improvement from baseline (60.8% compared with 47.8%; $P = 0.008$)</p> <p>ER/Urgent care: OM > placebo OM patients had statistically significantly lower rates for total emergency visits [0.24 compared with 0.43; ratio of rates [0.561 (95% CI: 0.325, 0.968); $P = 0.038$]. Rates also lower for OM patients (but not statistically significant) for ER visits [0.04 compared with 0.06; ratio of rates [0.659 (95% CI: 0.208, 2.094); $P = 0.480$], for hospital admissions [0.06 compared with 0.12; ratio of rates [0.540 (95% CI: 0.250, 1.166); $P = 0.117$], and unscheduled doctor visits [0.13 compared with 0.24; ratio of rates [0.546 (95% CI: 0.271, 1.100); $P = 0.090$]</p> <p>Hospitalization: OM > placebo Rate per treatment period [0.6 compared with 0.12; ratio of rates [0.540 (95% CI: 0.250, 1.166); $P = 0.117$]. Hospital admission rate equated to 1 admission/yr of txt for every 8 OM patients compared with every 4 placebo patients</p>	
Milgrom et al. 2001 ⁶² 334 Lemanske et al. 2002 ⁶³ 28 weeks (16 week stable steroid phase followed by 12 week steroid reduction phase) + Unpublished data from FDA ⁶⁸	RCT DB US Age 6-12, moderate to severe allergic asthma of at least 1 year duration that was well controlled with ICSs equivalent to 168-420 mcg/day BDP, positive SP Multicenter	0.016 mg/kg/IgE (IU/mL) every 2 or 4 weeks	<p>Symptoms: No difference “Little change” in asthma symptom scores during either phase; “minimal difference” between treatment groups (data NR)</p> <p>Night symptoms: No difference [Median nocturnal asthma symptom score: lower in OM group but no significant differences between groups during stable steroid phase]</p> <p>Exacerbations: OM > placebo Incidence of exacerbations lower in OM group in both phases; statistical difference in steroid reduction phase % patients with exacerbations: stable phase 15.6% compared with 22.9% ($P = 0.95$); reduction phase: 18.2% compared with 38.5% ($P < 0.001$). Mean number of episodes/patient: stable phase 0.3 compared with 0.4 ($P = 0.093$); reduction phase: 0.42</p>	Fair

Study design N Duration	Country Population Setting	Dose	Results	Quality rating
			<p>compared with 0.72 ($P < 0.001$)</p> <p>Nocturnal awakenings/exacerbations requiring rescue meds on 2 or 3 consecutive nights: 11.6% compared with 21.1%; $P = 0.002$</p> <p>Rescue med use: OM > placebo # of puffs/day of albuterol consistently lower than baseline during both phases in OM group. At week 28, median puffs/day was 0 compared with 0.46 ($P = 0.004$)</p> <p>QoL: OM > placebo Both groups had modest improvement in PAQLQ scores from baseline throughout study. OM showed larger improvement over placebo in all domains at end of stable phase but difference was not statistically significant. At study end, OM patients showed statistically significantly greater improvements from baseline in activities, symptoms and overall score ($P < 0.05$)</p> <p>PAQLQ overall score ≥ 0.5 point increase at week 16: 36.8% compared with 38.5%; at week 28: 46.9% compared with 33.7% ($P < 0.05$)</p> <p>Overall score increase ≥ 1.5 points end of stable phase: 9.5% compared with 6.6% (ns); end of reduction phase: 13.7% compared with 8.1% ($P = 0.2258$)</p> <p>PAQLQ overall change (0.3 compared with 0.2) at 16 weeks, $P = \text{NR}$</p> <p>PAQLQ overall change (0.4 compared with 0.1) at 28 weeks, $P = \text{NR}$</p> <p>Missed school: OM > placebo Over 28 weeks, OM patients missed mean fewer school days (0.65 compared with 1.21; $P = 0.040$)</p> <p>Urgent care/ER: OM > placebo OM patients requiring urgent/unscheduled physician visits significantly lower: 12.9% compared with 30.3%, $P = 0.001$. Mean # (\pm SD)—stable phase: 0.13 (± 0.52)</p>	

Study design N Duration	Country Population Setting	Dose	Results	Quality rating
			<p>compared with 0.23 (\pm 0.74); reduction phase: 0.19 (\pm0.52) compared with 0.38 (\pm 0.75)</p> <p>Hospitalization: OM > placebo [Exacerbations requiring hospitalization 0 compared with 5 (4.6%), P = NR]</p>	
Solèr et al. 2001 ⁶⁴	RCT DB 546	Multinational Age 12-75, Moderate-severe allergic asthma	\geq 0.016 mg/kg per IU/mL of IgE	Good
Buhl et al. 2002 ⁶⁵	28 weeks (16 week stable ICS phase followed by 8 week reduction phase and 4 week stable phase)	Multicenter		
Buhl et al. 2002 ⁶⁶ + Unpublished data from FDA ⁶⁸	24 week DB extension (N = 483)		<p>Symptoms: OM > placebo Change in total asthma symptom scores during stable steroid phase statistically significant compared with placebo (data NR; P < 0.001). Improvement in symptom scores continued during steroid reduction phase (data NR; P < 0.01)</p> <p>Median proportion of low symptom days for 28 week period: OM 0.06 compared with placebo 0 (P < 0.001)</p> <p>Night symptoms: OM > placebo Better improvements in night-time symptom scores in OM patients during both phases of study (data NR; P < 0.01 at week 16 and week 28)</p> <p>Exacerbations: OM > placebo Asthma exacerbations per patient lower in OM patients compared with placebo patients in stable-steroid phase: 0.28 (0.15-0.41) compared with 0.66 (0.49-0.83); P < 0.001 and in steroid reduction phase: 0.36 (0.24-0.48) compared with 0.75 (0.58-0.92); P < 0.001.</p> <p>Percentage of patients with \geq 1 exacerbation significantly lower in OM group compared with placebo group for stable-steroid phase (12.8% compared with 30.5%; P < 0.001) and in steroid reduction phase (15.7% compared with 29.8%; P < 0.001)</p> <p>Rescue med use: OM > placebo Median number of puffs of rescue med lower in OM group than placebo group during both treatment phases (data NR; P < 0.001)</p> <p>QoL: OM > placebo Greater percentage of OM patients achieved a clinically significant</p>	

Study design N Duration	Country Population Setting	Dose	Results	Quality rating
			<p>improvement in overall AQLQ score at week 16 (59% compared with 52%; $P < 0.001$) and at week 28 (65% compared with 55%; $P < 0.001$)</p> <p>Overall AQLQ change (0.83 compared with 0.59) at week 16, $P = \text{NR}$</p> <p>Overall AQLQ change (1.0 compared with 0.64) at week 28, $P = \text{NR}$</p> <p>Missed school: OM > placebo Mean number of school days missed [0.12 (\pm 0.48) compared with 1.25 (\pm 3.88); $P = \text{NR}$] due to asthma lower in OM group</p> <p>Missed work: OM > placebo Mean number (\pm SD) of work days missed [0.51 (\pm 1.7) compared with 0.44 (\pm 1.5); $P = \text{NR}$] due to asthma higher in OM group</p> <p>ER/Urgent care: No difference No significant difference between groups in mean unscheduled medical contacts [0.3 compared with 0.31; $P = \text{NR}$]</p> <p>Hospitalization: No difference Exacerbations resulting in hospitalization 0 compared with 2.2%, $P = \text{NR}$</p> <p>EXTENSION PHASE Exacerbations: OM > placebo OM patients experienced significantly fewer exacerbations per patient during extension phase: 0.48 (0.30-0.66) compared with 1.14 (0.81-1.46); $P < 0.001$</p> <p>Patients with ≥ 1 exacerbation: 24% compared with 40.6%, $P < 0.001$</p> <p>QoL: OM > placebo Mean AQLQ domain and overall scores showed progressive increase throughout 52 weeks of treatment in OM patients. Greater percentage of OM patients achieved a clinically significant improvement in overall AQLQ score at end of extension phase (data NR; $P < 0.001$)</p> <p>Overall AQLQ change 1.10 compared with 0.88 at 52 weeks, $P =$</p>	

Study design N Duration	Country Population Setting	Dose	Results	Quality rating
			<p>NR</p> <p>Missed school: Placebo > OM Mean number (\pm SD) of school days missed: 0.12 (\pm 0.73) compared with 0.0 (\pm 0.0)</p> <p>Missed work: No difference Mean number (\pm SD) of work days missed: 0.42 (\pm 3.26) compared with 0.41 (\pm 1.65)</p> <p>ER/Urgent care: Unscheduled medical visits: 0.17 (\pm 0.59) compared with 0.21 (\pm 0.64) $P = \text{NR}$</p> <p>Hospitalization: Exacerbations requiring hospitalization 0.4% compared with 1.7%, $P = \text{NR}$</p>	

Study design N	Country Population Setting	Dose	Results	Quality rating
Vignola et al. 2004 ⁶⁷ SOLAR	RCT DB 405 28 weeks Multinational Age 12-74, stable on ≥ 400 mcg BUD, continued BUD treatment, allergic asthma and PAR Concomitant asthma and rhinitis Multicenter	≥ 0.016 mg/kg/IgE (IU/mL) per 4 weeks	<p>Symptoms: OM > placebo Significant reduction in Wasserfallen asthma symptom score in OM patients at endpoint (treatment difference -1.8, $P = 0.023$) and total rhinitis symptom score (treatment difference -3.53, $P < 0.001$) compared with placebo</p> <p>Exacerbations: OM > placebo Fewer OM patients experienced at least one exacerbation (20.6% compared with 30.1%; $P = 0.02$)</p> <p>Mean rate of exacerbations lower with OM (0.25 compared with 0.40; $P = 0.02$)</p> <p>Rescue med use: No difference Use (mean puffs/day) of short-acting beta-2 agonists similar between groups during study (1.8 compared with 2.4; $P = \text{NR}$)</p> <p>QoL: OM > placebo Clinically significant (≥ 1.0 point) improvement in AQLQ and RQLQ in 57.7% of OM patients compared with 40.6% placebo patients ($P < 0.001$)</p> <p>AQLQ ≥ 0.5 point improvement: 78.8% compared with 69.8%; $P = 0.50$; ≥ 1.0 improvement: 67.3% compared with 50.0%, $P < 0.001$</p> <p>RQLQ ≥ 0.5 point improvement: 83.7% compared with 71.4%, $P = 0.003$; ≥ 1.0 improvement: 67.3% compared with 52.1%, $P = 0.001$</p> <p>Overall change in AQLQ 1.4 compared with 1.1 at 28 weeks, $P = \text{NR}$</p>	Fair
Niebauer et al. 2006 ⁶⁹	Systematic review with meta-analysis 5 trials (2,056 patients) Multinational Adults and children with asthma; 3 with adult and adolescent patients with moderate to severe asthma, 1 trial of children and adolescents with allergic asthma, 1 with adults and adolescents with asthma and allergic rhinitis; concurrent	0.016 mg/kg/IgE (IU/mL) per 2 or 4 weeks	<p>QoL: OM > placebo All results favored OM. For improvement of > 0.5 for the 3 respective phases: 1.35 (1.11-1.64; $P = 0.003$), 1.69 (1.40-2.05; $P < 0.001$), and 1.50 (1.15-1.95; $P = 0.001$). test of homogeneity was NS ($P = 0.06$ to 0.94) suggesting consistency across trials. For improvement of 1 or more for the 3 phases: 1.61 (1.29-2.00; $P < 0.001$), 2.03 (1.66-2.47; $P < 0.001$), and 1.25 (0.9-1.59; $P = 0.08$). Test of homogeneity NS for first two phases ($P = 0.69$ and 0.51), but evidence of</p>	

Study design N Duration	Country Population Setting	Dose	Results	Quality rating
			<p>OM in order to prevent one exacerbation (NNT(b) = 8, 95% CI: 7, 11)</p> <p>Rescue med use: <i>Stable phase:</i> Moderate to severe adolescent and adult participants required significantly less rescue beta-2 agonist compared with placebo (-0.63 puffs/d (95% CI: -0.90, -0.36; six studies).</p> <p><i>Tapering phase:</i> Change from baseline in rescue medication use: OM treatment enabled participants to use significantly less rescue medication than placebo [WMD-0.74, (95% CI: -1.05, -0.43; Busse 2001; Holgate 2004; Holgate 2004a; Soler 2001).</p> <p>QOL: <i>Stable phase:</i> Change from baseline in quality of life scores: significantly greater improvement in overall AQLQ in favour of OM of 0.32 (95% CI: 0.22, 0.43; five studies).</p> <p><i>Tapering phase:</i> Change from baseline in quality of life scores Unpublished data were used for Holgate 2004: overall change was 0.68 (SD 1.02) for OM compared with 0.26 (SD 0.96) for placebo ($P = \text{NR}$) In severe participants there was a significant difference in the numbers of patients who achieved a clinically relevant improvement in their overall quality of life (an increase of at least 0.5 above baseline) in the OM group (57.5%) compared with the placebo group (38.6%), $P < 0.01$. A greater number of patients in the OM group (16%) than in the placebo group (5.9%) also reported a clinically relevant improvement in their overall quality of life ($P < 0.05$).</p> <p>Hospitalization: Significant reduction in the odds of hospitalization in OM participants compared with treatment with placebo (OR 0.11 (95% CI: 0.03, 0.48), Busse 2001; Milgrom 2001; Soler 2001). This translates to a NNT(b) of 57</p>	

Abbreviations: AQLQ= Asthma Quality of Life Questionnaire; BDP = beclomethasone dipropionate; FP = fluticasone propionate; ICS= inhaled corticosteroid; LSM= least squares mean; NNT= number needed to treat; OM= omalizumab; OR= odds ratio; PAQLQ= Pediatric Asthma Quality of Life Questionnaire; PAR= persistent allergic rhinitis; QOL= quality of life; RCT= randomized controlled trial; RQLQ= Rhinitis Quality of Life Questionnaire; SDM= standard differences in mean; SPT= skin prick test; WMD= weighted mean difference.

Symbol use: Drug X > Drug Y = statistically significant difference in outcomes favoring Drug X; Drug X > Drug Y trend = point estimate favors Drug X, but the difference is not statistically significant or tests of statistical significance were NR; No difference = no statistically significant difference or tests of statistical significance were not reported and outcomes are similar.

Note: All results are listed in the same order as the comparison column lists the medications.

E. Combination Products

1. ICS+LABA compared with ICS+LABA

Summary of findings

We found four fair quality RCTs (five publications)⁷¹⁻⁷⁵ that compared the combination of an ICS plus a LABA with another ICS/LABA combination for controller therapy meeting our inclusion/exclusion criteria (Table 17). All four trials compared fixed doses of the combination of budesonide and formoterol (BUD/FM) to fixed doses of the combination of fluticasone and salmeterol (FP/SM).

Overall, results from large trials up to six months in duration comparing equipotent steroid components support no significant difference in efficacy between combination treatment with BUD/FM and combination treatment with FP/SM when each is administered via a single inhaler. The results of our meta-analysis show no difference in exacerbations between those treated with BUD/FM and those treated with FP/SM (SMD = -0.0286, 95% CI: -0.0872, 0.0299; $P = 0.3378$, 4 studies).

Table 16. Evidence profile of the comparative efficacy of BUD/FM compared with FP/SM

Evidence Profile: Comparative efficacy of BUD/FM compared with FP/SM							
No. of studies (# of subjects)	Design	Quality	Consistency	Directness	Magnitude of effect	Other modifying factors*	Overall strength of evidence
Overall total: BUD/FM compared with FP/SM							
4 (5,818)	RCTs	Good (3); Fair (1)	Consistency among equipotent comparisons and when both BUD/FM and FP/SM delivered via a single inhaler	Direct	No difference; Exacerbations: (SMD = -0.0286, 95% CI: -0.0872, 0.0299)	None	High
BUD/FM compared with FP/SM							
3 (5,390)	RCTs	Good (2); Fair (1)	Consistent	Direct	No difference	None	High
BUD+FM compared with FP/SM							
1 (428)	RCT	Good	NA	Direct	FP/SM > BUD/FM (despite BUD administered at higher dose equivalence than FP)	Compared non-equipotent steroid components, only study that administered BUD+FM in separate inhalers	Low

Abbreviations: BUD = Budesonide; CI = confidence interval; FP = Fluticasone; ICS = Inhaled Corticosteroids; RCT = randomized controlled trial; SM = Salmeterol; SMD = standard mean difference.

Detailed Assessment

Description of Studies

Of the four RCTs we included (Table 17), all four compared the same medications (BUD+FM compared with FP+SM). All but one study administered both of the ICS+LABA combinations in a single inhaler; one trial administered BUD+FM in separate inhalers.⁷⁵ Study duration ranged from 12 weeks⁷⁵ to seven months.⁷¹ All four trials administered the same total daily dose of FP/SM (500/100), which contained a medium-dose ICS. For BUD/FM, total daily doses were similar (in medium-dose ICS range) in three trials (640-800/18-24); one used a two-fold greater dose of BUD (BUD/FM 1600/24, high-dose ICS range).⁷⁵ In three studies all medications were delivered via DPIs; one study compared BUD/FM DPI with FP/SM pMDI.^{73, 74}

Study Populations

The four head-to-head RCTs included a total of 5,818 subjects. All studies were conducted in adolescent and/or adult populations. None included children < 12 years of age. All trials were multinational. All enrolled subjects that were not adequately controlled on current therapy. Three were conducted in subjects with moderate to severe persistent asthma; one did not report the severity classification.^{73, 74} Three trials (75%) excluded smokers with at least a 10 pack-year history; one (25%) allowed some smokers and reported that 5% to 7% of subjects in each group were current smokers.

Sponsorship

Of the four head-to-head trials, 3 (75%) were funded by pharmaceutical companies; 1 trial (25%) did not report the source of funding but at least one author had a primary affiliation with a pharmaceutical company. No trials were funded primarily by a source other than a pharmaceutical company.

Head-to-head comparisons

1. Budesonide/formoterol (BUD/FM) compared with Fluticasone/salmeterol (FP/SM)

All four trials reported asthma symptoms and exacerbations (Table 17). Two trials reported each of the following: nocturnal awakenings,^{73, 75} rescue medicine use,^{72, 73} and hospitalizations or emergency visits.⁷³⁻⁷⁵ One trial reported missed work.^{73, 74} For most of these outcomes, there were no statistically significant differences between the BUD/FM and FP/SM groups. Three of the four trials were relatively consistent in finding no difference between groups. One trial reported fewer symptoms, nocturnal awakenings, exacerbations, hospitalization days, and unscheduled outpatient visits for those treated with FP/SM than for those treated with BUD+FM.⁷⁵ This trial was the smallest (N = 428) and shortest in duration (12 weeks) among the four making this comparison. It was also the only one that administered BUD+FM in separate inhalers and used a two-fold greater dose of BUD than the other trials. The only other included outcomes that were statistically significantly different between treatments were from a 6 month trial. (N = 3,335)^{73, 74} It reported no difference in symptoms, nocturnal awakenings, exacerbations, or missed work, but found mixed results for rescue medicine use and hospitalizations or emergency visits. Specifically, they reported greater improvement in the number of rescue puffs used per day for those treated with FP/SM (mean difference, 95% CI: 0.10, 0.01-0.19) and a lower rate of hospitalizations or emergency visits per 100 patients per six months for those treated with BUD/FM (5 compared with 8, $P = 0.013$) (Table 17).

We conducted meta-analysis for exacerbations, the only outcome reporting sufficient data in multiple studies (Appendix G). All studies assessed exacerbations. The results of our meta-analysis show no difference in exacerbations between those treated with BUD/FM and those treated with FP/SM (SMD = -0.0286, 95% CI: -0.0872, 0.0299; $P = 0.3378$, 4 studies) (Figure 2). Sensitivity analyses indicate no difference in overall meta-analysis conclusions with any single study removed. There was no significant heterogeneity between studies ($P = 0.466$).

Figure 2. Meta-analysis comparing exacerbations for BUD/FM compared with FP/SM

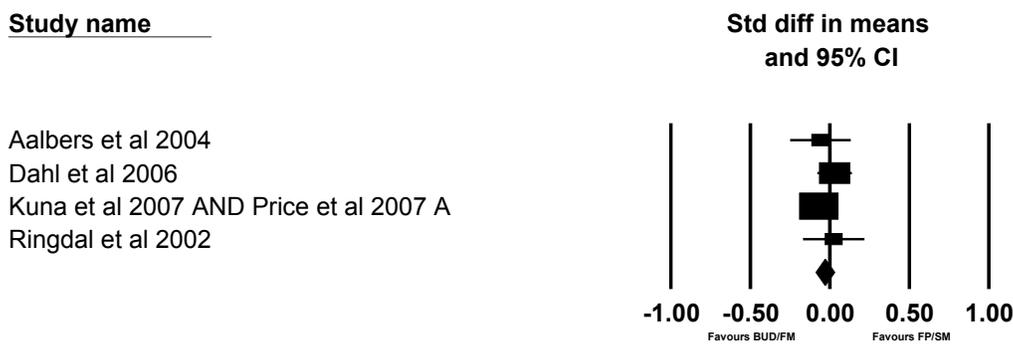


Table 17. Summary of head-to-head studies comparing ICS+LABA compared with ICS+LABA

Study	Study design N Duration	Country Study Population Setting	Comparison (total daily dose)	Results	Quality rating
Budesonide/formoterol (BUD/FM) compared with fluticasone/salmeterol (FP/SM)					
Aalbers et al. 2004 ⁷¹	RCT 658 7 months (1 month double-blind, 6 months open)	Multinational (6: Denmark, Finland, Germany, Norway, Sweden and The Netherlands) Age ≥ 12 years, asthma ≥ 6 months, not controlled on ICS alone, moderate to severe, excluded smokers with ≥ 10 pack-year history Multicenter (93), outpatient clinics	BUD/FM (320-640/9-18) adjustable dose (AD) DPI compared with BUD/FM (640/18) DPI compared with FP/SM (500/100) DPI	Only data for BUD/FM (640/18) compared with FP/SM shown here Symptoms and control: No difference [odds of achieving a well-controlled asthma week for FP/SM compared with BUD/FM: odds ratio 1.289; 95% CI: 0.981, 1.694; <i>P</i> = NS] Exacerbations: No difference [<i># of exacerbations and rate per month per patient.</i> #50 = 0.036/month compared with #59 = 0.041/month; <i>P</i> = NR]	Fair
Dahl et al. 2006 ⁷² EXCEL trial	RCT 1397 24 weeks	Multinational Age ≥ 18 years with asthma for a minimum of 6 months, on 1000-2000 BDP or equivalent, moderate to severe, excluded smokers with ≥ 10 pack-year history Multicenter	BUD/FM (800/24) DPI compared with FP/SM (500/100) DPI	Symptoms: No difference [<i>median % symptom-free days</i> : baseline 0 for both; during treatment: 60 compared with 63, <i>P</i> = NR; <i>median % symptom-free nights</i> : baseline 25 compared with 14; end 86 compared with 85; <i>P</i> = NR] Exacerbations: No difference [Mean rate per patient over 24 weeks: 2.79 compared with 2.69; Ratio 0.96, 95% CI: 0.84, 1.10, <i>P</i> = 0.571] Rescue medicine use: No difference [Median % rescue-free days baseline: 0 for both; during treatment: 81 compared with 82 <i>P</i> = NS]	Good
Kuna et al. 2007 ⁷³ AND Price et al. 2007 ⁷⁴	RCT 3335 6 months	Multinational Age ≥12, not controlled, taking ICS at entry (46-47% also taking LABA at entry), 5-7% were current smokers Multicenter, outpatients	BUD/FM (320/9 + as-needed use) DPI compared with BUD/FM (640/18) DPI compared with FP/SM (500/100) pMDI	Only data for BUD/FM (640/18) compared with FP/SM shown here Symptoms: No difference [<i>Total symptom score</i> (0-6): base, treatment: 1.93, 1.07 compared with 1.93, 1.03; mean difference (95% CI): 0.04 (-0.02 to 0.11) <i>P</i> = NS. <i>Symptom free days %</i> : 8.8, 44.6 compared with 8.6, 46.0; mean difference (95% CI): -1.6 (-4.4 to 1.2) <i>P</i> = NS for all. <i>Asthma control days (%)</i> : 5.9, 42.2 compared with 5.7, 43.7; mean difference (95% CI): -1.9 (-4.7, 1.0); <i>P</i> = NS] Nocturnal awakenings: No difference [% of nights: baseline, treatment: 32.8, 14.6 compared with 31.5, 14.6; mean difference(95% CI): 0.2 (-1.4 to 1.8) <i>P</i> = NS] Exacerbations: No difference [<i>severe: #</i>	Good

Study	Study design N Duration	Country Study Population Setting	Comparison (total daily dose)	Results	Quality rating
				<p>patients (%) having at least one, 126 (11%) compared with 138 (12%), treatment comparison of HR (95% CI): 0.91 (0.72, 1.16), $P = 0.45$; Exacerbation rate in events/100 patients/6 months: 16 compared with 19 (HR 0.85 95% CI: 0.65, 1.04, $P = 0.1$]</p> <p>Rescue medicine use: Mixed, FP/SM >BUD/FM for one measure [total # inhalations/day at baseline, treatment: 2.31, 1.05 compared with 2.33, 0.96, mean difference(95% CI): 0.10 (0.01 to 0.19), $P < 0.05$; Rescue free days (%):8.8, 57.8 compared with 8.8, 59.1; mean difference(95% CI): -1.4 (-4.2 to 1.4), $P = NS$]</p> <p>Missed days of work: No difference [sick leave mean/patient/6 mos: 1.16 compared with 1.11; $P = NR$]</p> <p>Hospitalizations and Emergency room visits: BUD/FM > FP/SM trend [# (%) of patients having at least one visit: 50 (5) compared with 70 (6) Treatment comparison HR (95% CI) 0.71 (0.49, 1.02) $P = 0.066$; rate/100patients/6 months: 5 compared with 8 (HR 0.68, 95% CI: 0.51, 0.92, $P = 0.013$)</p>	
Ringdal et al. 2002 ⁷⁵	RCT 428	Multinational (11 European countries)	BUD (1600) DPI + FM (24) DPI compared with FP/SM (500/100) DPI	<p>Symptoms (nighttime): FP/SM > BUD+FM [FP/SM group had higher median % of nights without symptoms (difference= 2.7; 95% CI: 0.0, 8.4; $P = 0.04$) and with a symptom score <2 (difference=0.0; 95% CI: 0.0,1.2; $P = 0.03$)</p> <p>Nocturnal awakenings: FP/SM > BUD+FM [FP/SM group had higher % of nights with no awakenings: difference = 4.9; 95% CI: 0.0, 12.0; $P = 0.02$]</p> <p>Exacerbations: FP/SM > BUD+FM [mean rate of exacerbations per patient per 84 days of treatment (Poisson model): 0.735 compared with 0.472; 36% reduction with FP/SM; OR = 0.64; 95% CI: 0.51, 0.80; $P < 0.001$; total # of exacerbations: 206 compared with 129; $P = NR$]</p> <p>Hospitalizations and urgent care: FP/SM > BUD+FM trend [# of days on general ward: 18 compared with 7; $P = NR$; unscheduled outpatient visits: 17 compared with 6; $P = NR$]</p>	Good
EDICT trial	12 weeks	Age 16-75 years, moderate to severe persistent asthma, not controlled on ICS, excluded smokers with ≥ 10 pack-year history Primary care and hospital respiratory clinics			

Abbreviations: AD= adjustable dosing; BUD+FM= budesonide and formoterol in separate inhalers; BUD/FM= budesonide and formoterol in one inhaler; CI = confidence interval; DPI= dry powder inhaler; FP = Fluticasone Propionate; FP+SM= fluticasone and salmeterol in separate inhalers; FP/SM= fluticasone and salmeterol in one inhaler; ML= Montelukast; NR = not reported; NS= not statistically significant; QOL = quality of life; pMDI= pressurized metered dose inhaler; RCT= randomized controlled trial

Symbol use: Drug X > Drug Y = statistically significant difference in outcomes favoring Drug X; Drug X > Drug Y trend = point estimate favors Drug X, but the difference is not statistically significant or tests of statistical significance were NR; No difference = no statistically significant difference or tests of statistical significance were not reported and outcomes are similar.

Note: All results are listed in the same order as the comparison column lists the medications.

2. ICS+LABA for both maintenance and as-needed relief vs. ICS+LABA for maintenance with a Short-Acting Beta-Agonist (SABA) for relief

Summary of findings

We found four fair or good quality RCTs (making five relevant comparisons) meeting our inclusion/exclusion criteria (Table 19).^{73, 74, 76-79} All five compared the combination of budesonide (BUD) plus formoterol (FM) *in a single inhaler* for maintenance *and* as-needed relief with a fixed dose ICS/LABA combination plus a Short-Acting Beta-Agonist (SABA) for as-needed relief. Two trials compared BUD/FM for maintenance and relief to BUD/FM for maintenance with a SABA for relief,^{73, 74, 76, 78} three trials compared BUD/FM for maintenance and relief to the combination of fluticasone and salmeterol (FP/SM) for maintenance with a SABA for relief.^{73, 77, 79} Of note, BUD/FM is not approved for acute as-needed relief of asthma symptoms in the United States. It has been approved for maintenance and as-needed relief use in Canada. Several of the trials included in this section significantly reduced the total ICS doses for many of the subjects upon randomization.

Overall, results from large trials up to twelve months in duration found statistically significantly lower exacerbation rates for those treated with BUD/FM for maintenance and relief than for those treated with ICS/LABA for maintenance and a SABA for relief (high strength of evidence, Table 18 Evidence Profile). Our meta-analysis shows a standardized average percent difference in exacerbations of 12% (SMD = -0.1216, 95% CI: -0.1595, -0.0837; 5 comparisons). Results from individual trials for other outcomes were mixed, but generally favored BUD/FM for maintenance and relief or were not different between groups. None of the individual trials found a significant difference in symptoms. Our meta-analysis found no statistically significant differences in symptom-free days (SMD = 0.0026, 95% CI: -0.0397, 0.0449), symptom scores (SMD = -0.0363, 95% CI: -0.0859, 0.0133), nocturnal awakenings (SMD = -0.0533, 95% CI: -0.1220, 0.0154), rescue-free days (SMD = -0.0276, 95% CI: -0.0700, 0.0148), or rescue medicine use (SMD = -0.0656, 95% CI: -0.1337, 0.0026; 5 comparisons). It is difficult to determine the applicability of the results of these trials given the heterogeneity of study designs and dose comparisons. In addition, several of the trials significantly reduced the total ICS doses for many subjects upon randomization (some studies averaged a 75% dose reduction).

Table 18. Evidence profile of the comparative efficacy of BUD+FM for maintenance and as-needed relief compared with ICS+LABA with a Short-Acting Beta-Agonist (SABA) for relief

Evidence Profile: Comparative efficacy of BUD/FM for maintenance and relief compared with ICS/LABA with SABA for relief							
No. of Studies (# of subjects)	Design	Quality	Consistency	Directness	Result and Magnitude of Effect	Other modifying factors	Overall strength of evidence
Overall total: BUD/FM for maintenance and relief compared with ICS/LABA for maintenance with SABA for relief							
4* (10,547)	RCTs	Good (2); Fair (2)	Consistent for symptoms and exacerbations Some inconsistency for other outcomes	Direct	Fewer exacerbations (SMD = -0.1216, 95% CI: -0.1595, -0.0837) with BUD+FM for maintenance and relief No difference in symptom-free days, symptom scores, nocturnal awakenings, rescue-free days, or rescue medicine use	Heterogeneity of study designs and dose comparisons; not always clear amount of FM delivered; trials using lower total ICS doses in BUD+FM for maintenance and relief group reported similar outcomes to other trials	Moderate
BUD/FM for maintenance and relief compared with BUD/FM for maintenance with SABA for relief							
2 (6,095)	RCTs	Good (1); Fair (1)	Consistent for symptoms and exacerbations Some inconsistency for other outcomes	Direct	All trials reported lower exacerbation rates for those treated with BUD+FM for maintenance and relief and no difference in symptom measures		Moderate
BUD/FM for maintenance and relief compared with FP/SM for maintenance with SABA for relief							
3 (7,787)	RCTs	Good (2); Fair (1)	Consistent for symptoms and exacerbations Some inconsistency for other outcomes	Direct	All trials reported lower exacerbation rates for those treated with BUD+FM for maintenance and relief and no difference in symptom measures		Moderate

Abbreviations: BUD = Budesonide; CI = confidence interval; FD=fixed dose; FM = Formoterol; ICS= Inhaled Corticosteroids; LABAs = Long-Acting Beta-2 Agonists; SABA = Short-Acting Beta-Agonist; SMD = standard mean difference-

*The overall total of trials and number of participants do not equal the sum of trials for the two specific comparisons because one trial contributed to both comparisons (BUD/FM maintenance and reliever therapy compared with BUD/FM fixed dose and compared with FP/SM fixed dose).

Detailed Assessment

Description of Studies

Of the four RCTs we included (Table 19), two compared BUD/FM for maintenance and relief to BUD/FM for maintenance and SABA for relief,^{73, 74, 76, 78} and three compared BUD/FM for maintenance and relief to FP/SM for maintenance and SABA for relief. All trials administered the ICS/LABA combinations in a single inhaler. Study duration ranged from 6 months^{73, 77} to 12 months.^{76, 78, 79}

Total daily maintenance ICS components of the BUD/FM for maintenance relief groups ranged from low dose in one study^{76, 78} to medium dose. One study compared low dose (ICS component) BUD/FM for maintenance and reliever therapy with low dose BUD/FM,^{76, 78} one compared low dose with medium dose,⁷³ one compared medium dose with medium dose,⁷⁹ and one compared medium dose with high dose.⁷⁷ In three studies, the mean total dose of ICS administered in the BUD+FM for maintenance and relief group was less than the total daily dose in the ICS+LABA with a SABA for relief group.^{73, 74, 77, 79} Several of the trials significantly reduced the total ICS doses for many of the subjects upon randomization. Some studies reduced the starting doses to levels that could be considered inadequate compared to the subjects' previous dose requirements. In three studies all medications were delivered via DPIs; one study compared BUD/FM DPI with FP/SM pMDI.^{73, 74}

Study Populations

The four head-to-head RCTs included a total of 10,547 subjects. Three studies were conducted in adolescent and/or adult populations. One study included children and adults,⁷⁸ and one publication further described the subset of children four to 11 years of age from the study that included children and adults.⁷⁶ All trials were multinational. All enrolled subjects that were not adequately controlled on current therapy. Two were conducted in subjects with mild to moderate persistent asthma⁷⁶⁻⁷⁸ and two did not report asthma severity classification.^{73, 79} Two trials did not report smoking rates and two allowed some smokers.^{73, 77} Trials enrolling smokers reported that 4% to 7% of subjects in each group were current smokers.

Sponsorship

Of the four head-to-head trials, all four (100%) were funded by pharmaceutical companies.

Head-to-head comparisons

1. BUD/FM for maintenance and relief compared with ICS/LABA for maintenance and SABA for relief

The results of the four RCTs contributing five comparisons (one study compared BUD/FM for maintenance and relief with BUD/FM maintenance and SABA relief and with FP/SM maintenance and SABA relief) are described below under the appropriate drug comparisons. Overall, all five comparisons reported statistically significantly lower rates of exacerbations for those treated with BUD/FM for maintenance and relief, but no differences in symptoms.

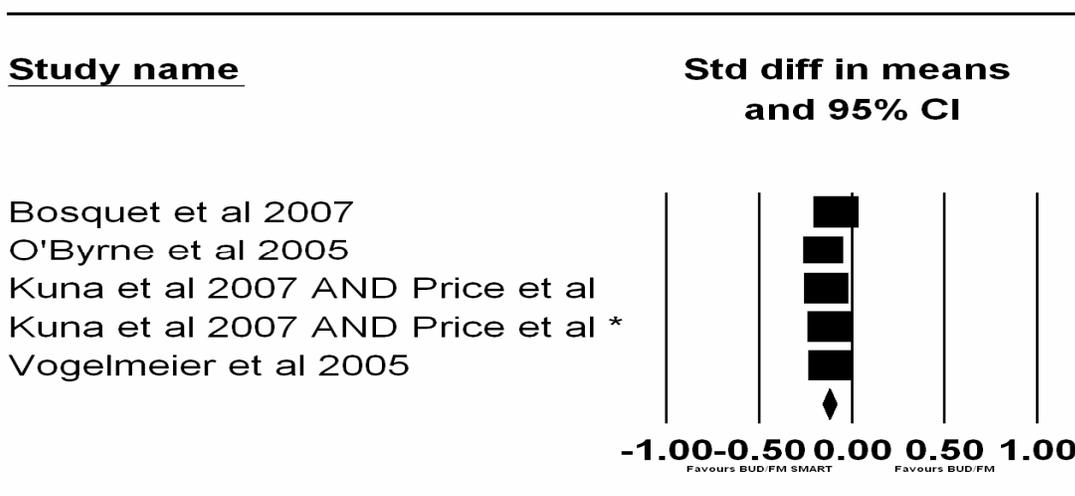
We conducted meta-analyses for six outcomes that were reported with sufficient data in multiple trials (Appendix G). These included symptom-free days, symptom scores, nocturnal awakenings, exacerbations, rescue-free days, and rescue medicine use (puffs/day).

We found no statistically significant differences in symptom-free days (SMD = 0.0026, 95% CI: -0.0397, 0.0449, 3 studies contributing 4 comparisons), symptom scores (SMD = -0.0363, 95% CI: -0.0859, 0.0133, 3 studies contributing 4 comparisons), nocturnal awakenings (SMD = -0.0533, 95% CI: -0.1220, 0.0154, 3 studies contributing 4 comparisons), rescue-free days (SMD = -0.0276, 95% CI: -0.0700, 0.0148, 3 studies contributing 4 comparisons), or rescue medicine use (SMD = -0.0656, 95% CI: -0.1337, 0.0026; 4 studies contributing 5 comparisons). Sensitivity analyses indicate that removing one of the comparisons⁷³ would result in outcomes favoring BUD/FM for maintenance and relief for symptom scores and for rescue medicine use. For the other outcomes sensitivity analyses indicate no difference in overall meta-analysis conclusions with any single study removed. There was no significant

heterogeneity between studies for these outcomes with the exception of nocturnal awakenings ($P = 0.049$) and rescue medicine use ($P = 0.012$).

However, those treated with BUD/FM for maintenance and relief had fewer exacerbations (SMD = -0.1216, 95% CI: -0.1595, -0.0837; 4 studies contributing 5 comparisons) (Figure 3). Sensitivity analyses indicate no difference in overall meta-analysis conclusions with any single study removed. There was no significant statistical heterogeneity between studies ($P = 0.842$).

Figure 3. Meta-analysis comparing exacerbations for BUD/FM for maintenance and relief compared with ICS/LABA for maintenance with SABA relief



Of note, the comparisons that administered scheduled maintenance ICS doses that were lower in the BUD/FM for maintenance and relief group all found statistically significantly lower exacerbation rates for those treated with BUD/FM for maintenance and relief.^{73, 74, 77} In addition, the BUD/FM for maintenance and relief group had a lower mean daily steroid dose (maintenance plus relief) than the ICS/LABA for maintenance with SABA relief in three of the five trials.^{73, 74, 77, 79} Thus, it does not appear that delivering a higher total ICS dose explains the better exacerbations outcomes in the BUD/FM for maintenance and relief group.

2. Budesonide/formoterol (BUD/FM) for maintenance and relief compared with Budesonide/formoterol (BUD/FM) for maintenance and Short-Acting Beta-Agonist (SABA) for relief

We found one good-⁷³ and one fair-quality RCTs^{76, 78} for this comparison. Both trials reported asthma symptoms, nocturnal awakenings, exacerbations, and rescue medicine use (Table 19). One trial also reported missed work, hospitalizations, and emergency visits⁷³ (Table 19). The results are mixed but show a trend favoring the BUD/FM for maintenance and relief for several outcomes. Both reported statistically significant differences in exacerbations favoring BUD/FM for maintenance and relief, but reported no difference in symptoms. One trial reported fewer nocturnal awakenings in those treated with BUD/FM for maintenance and relief.^{76, 78} The single study reporting missed work, hospitalizations, and emergency visits found

no difference between groups.⁷³ None of the trials reported any outcomes favoring the BUD/FM for maintenance and SABA for relief.

3. Budesonide/formoterol (BUD/FM) for maintenance and relief compared with Fluticasone/salmeterol (FP/SM) for maintenance and Short-Acting Beta-Agonist (SABA) for relief

We found two good-^{73,77} and one fair-quality RCTs⁷⁹ comparing these treatments. All three trials reported asthma symptoms, exacerbations, and rescue medicine use (Table 19). Two trials reported nocturnal awakenings and hospitalizations or emergency visits.^{73,77} One trial also reported missed work⁷³ and one reported quality of life.⁷⁹ The results are mixed but show a trend favoring BUD/FM for maintenance and relief for some outcomes. All three trials reported no difference in symptoms or nocturnal awakenings, but statistically significantly lower exacerbation rates in those treated with BUD/FM for maintenance and relief. Outcomes related to rescue medications use were mixed. One trial reported no difference in rescue medicine use or rescue-free days;⁷⁷ one reported no difference in rescue medicine use but a greater percentage of rescue-free days for those treated with FP/SM plus SABA for relief (56% compared with 59.1%, $P < 0.05$);⁷³ one reported less rescue medicine use for those treated with BUD/FM for maintenance and relief (0.58 puffs/day compared with 0.93, $P < 0.001$).⁷⁹ The trials reporting missed work, quality of life, and hospitalizations or emergency visits found no difference between treatment groups.

Of note, the fair-quality trial reduced the starting doses to levels that could be considered inadequate compared to the subjects' previous doses. If randomized to FP/SM subjects were stepping down in their level of control and did not have the possibility to adjust the dose for 4 weeks. The BUD/FM maintenance and relief group could increase their dose with as needed BUD/FM. This initial possible under-treatment may have biased the study in favor of the BUD/FM maintenance and relief group.

Table 19. Summary of head-to-head studies comparing BUD/FM for maintenance and relief compared with ICS/LABA for maintenance and Short-Acting Beta-Agonist (SABA) for relief

Study	Study Design N Duration	Country Study Population Setting	Comparison (total daily dose)	Results	Quality rating
BUD/FM for maintenance and relief compared with BUD/FM for maintenance and SABA for relief or compared with FP/SM for maintenance and SABA for relief					
Bisgaard et al. 2006 ⁷⁶	RCT, DB 341 12 months	Multinational (12) Age 4-11, mild-moderate persistent asthma, not controlled on ICS, smoking status NR Multicenter (41)	BUD/FM (80/4.5 + SABA as-needed) vs. BUD/FM (80/4.5 + as-needed) vs. BUD (320) All given via DPI	Only data for BUD/FM (80/4.5 + SABA as-needed) compared with BUD/FM (80/4.5 + as-needed) shown here Symptoms and control: No difference [Symptom-free days, mean %, base and treatment, 36.4, 68.0 compared with 35.3, 63.4 $P = 0.31$; Symptom Score (0-6): baseline and endpoint 1.1, 0.54 compared with 1.1, 0.60, $P = 0.53$; asthma control days, mean %, base and treatment: 14.0, 60.6	Fair
Note: this publication describes the pediatric subset of the population in the O'Byrne et al. 2005 trial below. ⁷⁸ Thus it is not a separate trial and is not included in meta-analyses, to avoid					

Table 19. Summary of head-to-head studies comparing BUD/FM for maintenance and relief compared with ICS/LABA for maintenance and Short-Acting Beta-Agonist (SABA) for relief

Study	Study Design N Duration	Country Study Population Setting	Comparison (total daily dose)	Results	Quality rating
double counting subjects			BUD/FM (80/4.5 + as- needed) group: overall mean daily dose including rescue use 126/7.1	<p>compared with 12.5, 57.0, $P = 0.60$]</p> <p>Nocturnal awakenings: BUD/FM (80/4.5 + as-needed) > BUD/FM (+ SABA) [% of nights: 12.8, 4.4 compared with 10.8, 2.4; $P = 0.0039$]</p> <p>Exacerbations: BUD/FM (80/4.5 + as-needed) > BUD/FM (+ SABA) [Patients with exacerbations, 38% compared with 14%, $P < 0.001$; Exacerbations per patient 0.76 compared with 0.41, $P = 0.017$]</p> <p>Rescue med use: Mixed results BUD/FM (80/4.5 + as-needed) > BUD/FM (+ SABA) for some [Baseline and endpoint; <i>mean # puffs/24 hours</i>: 1.6, 0.76 compared with 1.7, 0.58 $P = 0.038$; <i>mean daytime as needed # puffs</i>: 0.59 compared with 0.49, $P = 0.066$; <i>mean nighttime as needed # puffs</i>: 0.17 compared with 0.09 $P = 0.024$; % of <i>rescue-free days</i>, mean: 17.2, 67.5 compared with 15.3, 69.4; $P = 0.48$]</p>	

Table 19. Summary of head-to-head studies comparing BUD/FM for maintenance and relief compared with ICS/LABA for maintenance and Short-Acting Beta-Agonist (SABA) for relief

Study	Study Design N Duration	Country Study Population Setting	Comparison (total daily dose)	Results	Quality rating
Bousquet et al. 2007 ⁷⁷	RCT 2309 6 months	Multinational Age ≥ 12, uncontrolled on ICS or ICS+LABA, moderate persistent asthma, 4-5% were current smokers Multicenter (246 centers)	BUD/FM (640/18 + as- needed) DPI vs. FP/SM (1000/100 + as-needed SABA) DPI BUD/FM (640/18 + as- needed) group: overall mean daily BUD dose including rescue use 792	Symptoms: No difference [<i>Symptom free days (%)</i> at baseline, endpoint: 10.7, 47.2 compared with 11.2, 48.1; Treatment comparison (95% CI): -0.50 (-3.3, 2.3), <i>P</i> = 0.73; <i>total symptom score</i> (0-6): 1.87, 0.98 compared with 1.89, 0.98, Treatment comparison (95% CI): 0.00 (-0.06, 0.07), <i>P</i> = 0.92; ACQ-5: 1.84, 1.08 compared with 1.89, 1.12; <i>P</i> = 0.59] Nocturnal awakenings: No difference [% of nights with awakenings: 32.1, 12 compared with 32.2, 13.3; Treatment comparison (95% CI): -1.30 (-2.8 to 0.3); <i>P</i> = 0.11] Exacerbations: BUD/FM (640/18 + as-needed) > FP/SM (+ as-needed SABA) for rate [<i>severe exacerbations /100 patients/year</i> : 25 compared with 31, % reduction in rate with BUD/FM: 21%, 95% CI: 1, 37, <i>P</i> = 0.039; # patients (%) having event: 108 (9.4) compared with 130 (11.3), % reduction with BUD/FM: 18%, 95% CI: -5, 37, <i>P</i> = 0.12] Hospitalizations or ER visits: BUD/FM (640/18 + as-needed) > FP/SM (+ as-needed SABA) [Rate, events/100 patients/year: 9 compared with 13; % reduction with BUD/FM (95% CI): 31 (1, 51); <i>P</i> = 0.046] Rescue medicine use: No difference [% of rescue free days: base and endpoint: 10.3 and 58.2 compared with 9.3 and 58.4; Treatment comparison (95% CI) -0.80 (-3.6 to 1.9), <i>P</i> = 0.56; <i>total inhalations daily</i> : 2.23, 0.95 compared with 2.29, 1.01, Treatment comparison (95% CI) -0.04 (-0.12, 0.04), <i>P</i> = 0.36]	Fair

Table 19. Summary of head-to-head studies comparing BUD/FM for maintenance and relief compared with ICS/LABA for maintenance and Short-Acting Beta-Agonist (SABA) for relief

Study	Study Design N Duration	Country Study Population Setting	Comparison (total daily dose)	Results	Quality rating
O'Byrne et al. 2005 ⁷⁸ AND Bisgaard et al. 2006 ⁷⁶	RCT, DB 2760 1 year	Multinational (22 countries) Age 4-80, uncontrolled on ICS, moderate persistent asthma, smoking status NR Multicenter (246 centers)	BUD/FM (160/9 + as- needed) vs. BUD/FM (160/9 + SABA as-needed) vs. BUD (320) All delivery devices = DPIs	Only data for BUD/FM (160/9 + as- needed) compared with BUD/FM (160/9 + SABA as-needed) shown here Symptoms: No difference [mean daytime symptom score (0-3), endpoint: 0.48 compared with 0.50 P = 0.12; mean nighttime symptom score (0-3): 0.31 compared with 0.36, P = 0.01; symptom-free days (%):23.1, 54 compared with 24.0, 53 P = 0.52; asthma control days (%):5.4, 45 compared with 5.9, 44 P = 0.64] Nocturnal awakenings: BUD/FM (160/9 + as-needed) > BUD/FM (+ SABA as-needed) [% of nights: 21.8, 9 compared with 20.2, 12, P < 0.001] Exacerbations: BUD/FM (160/9 + as- needed) > BUD/FM (+ SABA as- needed) [patients with severe exacerbations resulting in medical intervention, %: 11 compared with 21, P < 0.001; events/ patient/ year: 0.19 compared with 0.40, P < 0.001] Rescue med use: BUD/FM (160/9 + as-needed) > FD for some [% rescue- free days: 8.2, 55 compared with 8.3, 54 P = 0.6; mean Inhalations/day, base and endpoint,: 1.74, 0.73 compared with 1.69, 0.84, P < 0.001; inhalations/ night: 0.72, 0.28 compared with 0.73, 0.37 P < 0.001]	Fair

Table 19. Summary of head-to-head studies comparing BUD/FM for maintenance and relief compared with ICS/LABA for maintenance and Short-Acting Beta-Agonist (SABA) for relief

Study	Study Design N Duration	Country Study Population Setting	Comparison (total daily dose)	Results	Quality rating
Kuna et al. 2007 ⁷³ AND Price et al. 2007 ⁷⁴	RCT 3335 6 months	Multinational Age ≥12, not controlled, taking ICS at entry (46-47% also taking LABA at entry), 5-7% were current smokers Multicenter, outpatients	BUD/FM (320/9 + as- needed) pMDI vs. BUD/FM (640/18 + SABA as- needed) pMDI vs. FP/SM (500/100 + SABA as- needed) DPI BUD/FM (320/9 + as- needed) group: overall mean daily BUD/FM dose including rescue use 483/13.6	Only data for BUD/FM (320/9 + as- needed) compared with FP/SM (+ SABA as-needed) shown here Symptoms: No difference [<i>Total symptom score</i> (0-6): base, treatment: 1.91, 1.06 compared with 1.93, 1.03; mean difference(95% CI): 0.04 (-0.03 to 0.10) <i>P</i> = NS. <i>Symptom free days</i> %: 9.3, 44.2 compared with 8.6, 46.0; mean difference(95% CI): - 2.5 (-5.3 to 0.3) <i>P</i> = NS; <i>Asthma control days</i> (%): 5.8, 41.3 compared with 5.7, 43.7; mean difference (95% CI): -2.6 (-5.4 to 0.2); <i>P</i> = NS] Nocturnal awakenings: No difference [% of nights: baseline, treatment: 33.7, 14.1 compared with 31.5, 14.0; mean difference(95% CI): -0.8 (-2.4 to 0.9) <i>P</i> = NS] Exacerbations: BUD/FM (320/9 + as- needed) > FP/SM (+ SABA as- needed) [severe: # patients (%) having at least one, 94 (9%) compared with 138 (12%), treatment comparison of HR (95% CI): 0.67 (0.52, 0.87) <i>P</i> = 0.003; Exacerbation rate in events/100 patients/6 months: 12 compared with 19 (HR 0.61 95% CI: 0.49, 0.76, <i>P</i> < 0.001] Rescue medicine use: Mixed results [<i>total # inhalations/day</i> at baseline, treatment: 2.29, 1.02 compared with 2.33, 0.96, mean difference(95% CI): 0.07 (-0.02 to 0.16) <i>P</i> = NS; <i>Rescue free days</i> (%): 8.9, 56.0 compared with 8.8, 59.1; mean difference(95% CI): -3.2 (-6.0 to -0.5), <i>P</i> < 0.05] Missed days of work: No difference [sick leave mean/patient/6 mos: 1.11 compared with 0.93; <i>P</i> = NR] Hospitalizations and Emergency room visits: BUD/FM (320/9 + as-needed) > FP/SM (+ SABA as-needed) [# (%) of patients having at least one visit: 48 (4) compared with 70 (6), Treatment comparison HR (95% CI) 0.69 (0.48, 0.99) <i>P</i> = 0.047; rate/100patients/6 months: 5 compared with 8 (HR 0.61 (0.44, 0.83) <i>P</i> = 0.0015]	Good

Table 19. Summary of head-to-head studies comparing BUD/FM for maintenance and relief compared with ICS/LABA for maintenance and Short-Acting Beta-Agonist (SABA) for relief

Study	Study Design N Duration	Country Study Population Setting	Comparison (total daily dose)	Results	Quality rating
Kuna et al. 2007 ⁷³ AND Price et al. 2007 ⁷⁴	RCT 3335 6 months	Multinational Age ≥12, not controlled, taking ICS at entry (46-47% also taking LABA at entry), 5-7% were current smokers Multicenter, outpatients	BUD/FM (320/9 + as- needed) pMDI vs. BUD/FM (640/18 + SABA as- needed) pMDI vs. FP/SM (500/100 + SABA as- needed) DPI BUD/FM (320/9 + as- needed) group: overall mean daily BUD/FM dose including rescue use 483/13.6	Only data for BUD/FM (320/9 + as- needed) compared with BUD/FM (640/18 + SABA as-needed) Symptoms: No difference [<i>Total symptom score</i> (0-6): base, treatment: 1.91, 1.06 compared with 1.93, 1.07; mean difference(95% CI): 0.00 (-0.07 to 0.06) <i>P</i> = NS; <i>Symptom free days</i> %: 9.3, 44.2 compared with 8.8, 44.6; mean difference(95% CI): - 0.8 (-3.6 to 2.0) <i>P</i> = NS; <i>Asthma control days</i> (%): 5.8, 41.3 compared with 5.9, 42.2; mean difference (95% CI): -0.7 (-3.6 to 2.1); <i>P</i> = NS] Nocturnal awakenings: No difference [% of nights: baseline, treatment: 33.7, 14.1 compared with 32.8, 14.6; mean difference(95% CI): -1.0 (-2.6 to 0.7) <i>P</i> = NS] Exacerbations: BUD/FM (320/9 + as- needed) > BUD/FM (640/18 + SABA as-needed) [severe: # patients (%) having at least one, 94 (9%) compared with 126 (11%), treatment comparison of HR (95% CI): 0.74 (0.56, 0.96) <i>P</i> = 0.026; Exacerbation rate in events/100 patients/6 months: 12 compared with 16 (HR 0.72 95% CI: 0.57, 0.90, <i>P</i> = 0.0048] Rescue medicine use: No difference [<i>total # inhalations/day</i> at baseline, treatment: 2.29, 1.02 compared with 2.31, 1.05, mean difference(95% CI): -0.03 (0.12 to 0.06) <i>P</i> = NS; <i>Rescue free days</i> (%): 8.9, 56.0 compared with 8.8, 57.8; mean difference (95% CI): -1.8 (-4.6 to 1.0), <i>P</i> = NS] Missed days of work: No difference [<i>sick leave mean/patient/6 mos</i> : 0.93 compared with 1.16; <i>P</i> = NR] Hospitalizations and Emergency room visits: No difference [# (%) of patients having at least one visit: 48 (4) compared with 50 (5), Treatment comparison HR (95% CI) 0.97 (0.65, 1.44), <i>P</i> = 0.87; rate/100patients/6 months: 5 compared with 5 (HR 0.88 (0.63, 1.24) <i>P</i> = 0.47]	Good

Table 19. Summary of head-to-head studies comparing BUD/FM for maintenance and relief compared with ICS/LABA for maintenance and Short-Acting Beta-Agonist (SABA) for relief

Study	Study Design N Duration	Country Study Population Setting	Comparison (total daily dose)	Results	Quality rating
Vogelmeier, et al. ⁷⁹	RCT 2143 12 months	Multinational Age ≥12, not controlled, taking ICS at entry (38% also taking LABA at entry), smoking status NR Multicenter, primary care	BUD/FM (640/18 + as- needed) DPI vs. FP/SM (500/100 + as- needed SABA) DPI BUD/FM (640/18 + as- needed) group: overall mean daily BUD dose including as-rescue use about 650	Symptoms: No difference [ACQ5 score, mean change from baseline: -0.64 compared with -0.58; $P =$ 0.069] Exacerbations: BUD/FM (640/18 + as- needed) > FP/SM (+ as-needed SABA) [all severe exacerbations, # of patients (%): 159 (15) compared with 204 (19), $P = 0.0076$; Severe exacerbations excluding unscheduled clinic visits, # of patients (%): 132 (12) compared with 167 (6), $P = 0.025$] Rescue medicine use: BUD/FM (640/18 + as-needed) > FP/SM (+ as- needed SABA) [mean puffs per 24 hrs. : baseline, end: 2.6, 0.58 compared with 2.7, 0.93; $P < 0.001$] ER visits and hospitalizations: No difference [ER visits/hospitalizations due to severe exacerbations, # of patients (%): 31 (3%) compared with 46 (4%); $P = 0.18$] Quality of Life: No difference (AQLQ, overall score, mean change from baseline: 0.60 compared with 0.57; P = 0.51)	Good

Abbreviations: AQLQ = Asthma Quality of Life Questionnaire; BUD = Budesonide; CI = confidence interval; DB = double-blind; DPI = dry powder inhaler; FD= fixed dose; FM = Formoterol; FP = Fluticasone Propionate; HR= hazard ratio; ICS = Inhaled Corticosteroids; LABAs = Long-Acting Beta-2 Agonists; NR = not reported; NS = not statistically significant; QOL = quality of life; pMDI= pressurized metered dose inhaler; RCT= randomized controlled trial; SABA = Short-Acting Beta-Agonist; SM = Salmeterol
> Symbol use: Drug X > Drug Y = statistically significant difference in outcomes favoring Drug X; Drug X > Drug Y trend = point estimate favors Drug X, but the difference is not statistically significant or tests of statistical significance were NR; No difference = no statistically significant difference or tests of statistical significance were not reported and outcomes are similar.

AQLQ = Asthma Quality of Life Questionnaire; BUD = Budesonide; CI = confidence interval; DB = double-blind; DPI = dry powder inhaler; FD= fixed dose; FM = Formoterol; FP = Fluticasone Propionate; HR= hazard ratio; ICS = Inhaled Corticosteroids; LABAs = Long-Acting Beta-2 Agonists; NR = not reported; NS = not statistically significant; QOL = quality of life; pMDI= pressurized metered dose inhaler; RCT= randomized controlled trial; SABA = Short-Acting Beta-Agonist; SM = Salmeterol

Note: total daily doses for BUD/FM maintenance and reliever groups only include the total scheduled maintenance dose, they do not include reliever use of the medication

Note: All results are listed in the same order as the comparison column lists the medications.

II. Inter-class comparisons (Between classes)

A. Monotherapy

1. Inhaled Corticosteroids (ICSs) compared with Leukotriene modifiers (LMs)

Summary of findings

We found two systematic reviews with meta-analyses^{80, 81} and 21 RCTs⁸²⁻¹⁰⁴ (Table 21). Thirteen of the RCTs were in adolescents and adults ≥ 12 years of age and eight were in children < 12 .^{96-102, 104}

Overall, efficacy studies up to 56 weeks in duration provide consistent evidence favoring ICSs over LTRAs for the treatment of asthma as monotherapy for both children and adults (high strength of evidence, Table 20 Evidence Profile). Those treated with LTRAs had a significantly higher occurrence of exacerbations than those treated with ICSs (SMD = 0.216, 95% CI: 0.127, 0.305, 12 studies). The standardized average improvement with ICSs was 21.6% compared to LTRAs. In addition, our meta-analyses found statistically significant differences in favor of ICSs over LTRAs in measures of symptoms, rescue medicine use, and quality of life.

Table 20. Evidence profile of the comparative efficacy of of ICSs compared with LTRAs

Evidence Profile: Comparative efficacy of ICSs compared with LTRAs							
Number of studies (# of subjects)	Design	Quality	Consistency	Directness	Results (magnitude of effect)	Other modifying factors	Overall strength of evidence
Overall total of trials: ICS compared with LTRA							
21 (9,467)	RCTs	Fair	Consistent	Direct	ICS > LTRA; had less rescue medicine use (% rescue free days: SMD -0.232; $P < 0.001$; rescue medicine use per day: SMD -0.214, $P = 0.001$), fewer symptoms (% symptom free days: SMD -0.216, $P < 0.001$; lower symptom score: SMD -0.243, $P < 0.001$), less frequent exacerbations (SMD 0.216, $P < 0.001$), and increase in quality of life (AQLQ scores: SMD -0.153, $P < 0.001$)	None	High
ICS compared with LTRA systematic reviews							
2 (14,378)	SR w/ MA	Good (1) Fair (1)	Consistent	Direct	ICS > LTRA: less rescue medicine use (puffs/day: WMD= 0.28, 95% CI: 0.20, 0.36 and rescue-free days: WMD= -14%, 95% CI: -18, -10), fewer symptoms (symptom scores: SMD = 0.29, 95% CI: 0.21, 0.37,	None	High

Evidence Profile: Comparative efficacy of ICSs compared with LTRAs							
Number of studies (# of subjects)	Design	Quality	Consistency	Directness	Results (magnitude of effect)	Other modifying factors	Overall strength of evidence
					symptom-free days: WMD = -12, 95% CI: -16, -7, and nocturnal awakenings: SMD=0.21, 95% CI: 0.13, 0.30), higher exacerbations with LTRA (risk of exacerbation requiring systemic steroids: RR 1.65, 95% CI: 1.36, 2.00), and ICS improved Quality of Life: WMD= -0.3, 95% CI: -0.4, -0.2		
FP compared with ML							
9 (3,864)	RCTs	Fair	Consistent	Direct	FP > ML; had less rescue medicine use (% rescue medicine free days: SMD -0.232, $P < 0.001$), less symptoms (% symptom-free days: SMD -0.258, $P < 0.001$; lower symptom score: SMD -0.244, $P < 0.001$), fewer exacerbations (SMD 0.151, $P < 0.001$), and greater improvement in quality of life (AQLQ scores: SMD -0.123, $P = 0.019$)	None	High
BDP compared with ML							
5 (3,417)	RCTs	Fair	Consistent	Direct	BDP > ML; had less rescue medicine use (% rescue free days: SMD -0.108, $P = 0.034$) and a trend toward fewer symptoms (% symptom-free days: SMD -0.118, $P = 0.073$)	None	Moderate
BUD compared with ML							
3 (520)	RCTs	Fair	Some inconsistency	Direct	Mixed results: reported outcomes either not significantly different or favored BUD	None	Moderate
FP compared with zafirlukast							
4 (1,666)	RCTs	Fair	Consistent	Direct	FP > zafirlukast; less rescue medicine use (rescue medicine free days: SMD -0.307, 95% CI: -0.408, -0.207); fewer symptoms (% symptom free days: SMD -0.291, 95% CI: -0.391, -0.191; greater improvement in symptom score: SMD -0.298, 95% CI: -0.451, -0.145), and fewer exacerbations (SMD 0.207, 95% CI: 0.107, 0.307)	None	High

Abbreviations: AQLQ = Asthma Quality of Life Questionnaire; BDP = beclomethasone dipropionate; BUD = Budesonide; CI = confidence interval; FP = Fluticasone Propionate; ICS = Inhaled Corticosteroids; LTRAs = Leukotriene receptor antagonists; MA=meta-analysis; RCT= randomized controlled trial; SMD = standard mean difference; SR = systematic review; ZAF = Zafirlukast.

Detailed Assessment

Description of Studies

Of the 21 RCTs (Tables 21 and 22), five RCTs compared montelukast with beclomethasone; nine RCTs compared montelukast with fluticasone; four compared zafirlukast with fluticasone; and three RCTs compared montelukast with budesonide. Study duration ranged from six weeks to 56 weeks.

Study Populations

The 21 RCTs included a total of 9,459 patients. Most studies were conducted in adult populations. Eight studies^{96-102, 104} were conducted primarily in pediatric populations. Thirteen studies (62%) were conducted in the United States, two (10%) in Europe, and six (29%) were other multinational combinations often including Europe, Canada, or the US. Asthma severity ranged from mild persistent to severe persistent: six studies (29%) were conducted in patients with mild persistent asthma, eleven (52%) in patients with mild to moderate persistent asthma, two (10%) in patients with mild to severe persistent asthma, and two (10%) did not report the severity or it was unable to be determined.

Methodologic Quality

The 21 RCTs included in our review were rated fair quality for internal validity. The method of randomization and allocation concealment was rarely reported.

Sponsorship

Of the 21 RCTs, 16 (76%) were funded by pharmaceutical companies; only three studies (14%) were funded primarily by sources other than pharmaceutical companies; 2 studies (10%) did not report any source of funding

Head-to-head comparisons

1. Inhaled Corticosteroids (ICSs) compared with Leukotriene Receptor Antagonists (LTRAs)

We conducted meta-analyses for six outcomes that were reported with sufficient data in multiple trials (Appendix G). Those treated with ICSs had a greater increase in the proportion of days free from rescue medication (SMD -0.232, 95% CI: -0.286, -0.177, $P < 0.001$, 11 studies), greater reduction in rescue medicine use per day (SMD -0.214, 95% CI: -0.289, -0.139, $P = 0.001$, 12 studies), greater increase in percent of symptom free days (SMD -0.216, 95% CI: -0.276, -0.157, $P < 0.001$, 13 studies, Figure 5), greater improvement in symptom score (SMD -0.243, 95% CI: -0.310, -0.176, $P < 0.001$, 7 studies), less frequent exacerbations (SMD 0.216, 95% CI: 0.127, 0.305, $P < 0.001$, 12 studies, Figure 4), and a greater increase in quality of life (AQLQ scores; SMD -0.153, 95% CI: -0.234, -0.072, $P < 0.001$, 7 studies) than those treated with leukotriene modifiers. For all six meta-analyses, sensitivity analyses indicate no difference in overall meta-analysis conclusions with any single study removed. In addition, there was no significant heterogeneity between studies (Appendix G).

Figure 4. Meta-analysis comparing percentage of exacerbations for ICSs compared with LTRAs

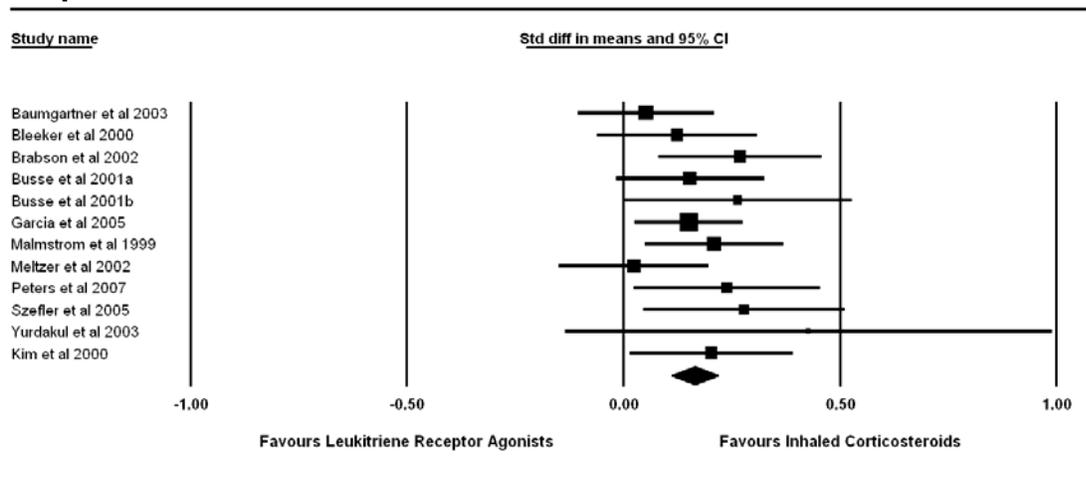
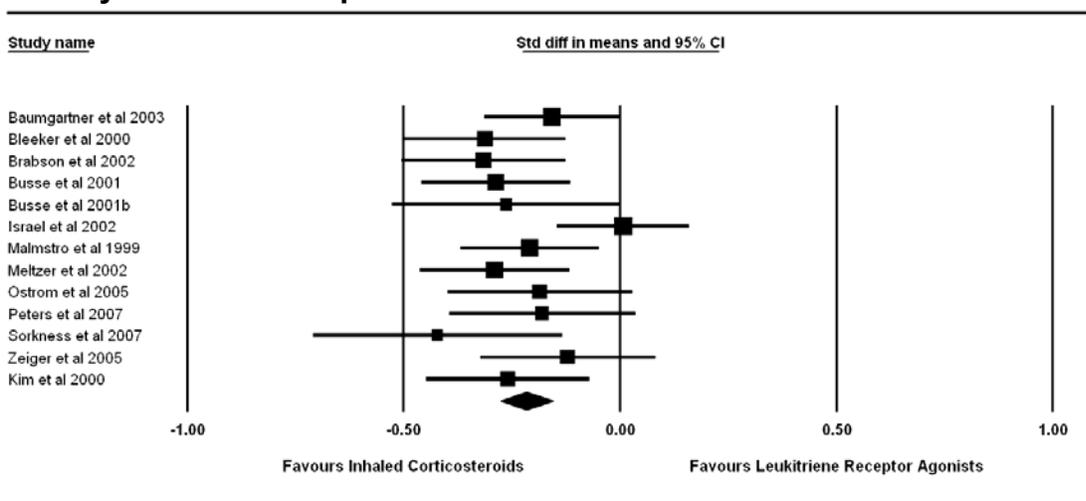


Figure 5. Meta-analysis comparing improvement in the percentage of symptom-free days for ICSs compared with LTRAs



When looking at montelukast alone compared with ICSs, our meta-analysis again shows that patients treated with ICSs had a greater increase in the proportion of days free from rescue medication use (SMD -0.202, 95% CI: -0.267, -0.137, $P < 0.001$), greater reduction in rescue medicine use per day (SMD -0.160, 95% CI: -0.258, -0.063, $P = 0.001$), greater increase in the proportion of symptom free days (SMD -0.189, 95% CI: -0.265, -0.113, $P < 0.001$), greater improvement in symptom score (SMD -0.230, 95% CI: -0.304, -0.156, $P < 0.001$), fewer exacerbations (SMD 0.216, 95% CI: 0.127, 0.305, $P < 0.001$), and greater improvement in quality of life (AQLQ score: SMD -0.141, 95% CI: -0.227, -0.055, $P < 0.001$) than those treated with montelukast (Appendix G).

When looking at zafirlukast alone compared with ICSs, our meta-analysis again shows that patients treated with ICSs had a greater increase of the proportion of days free from rescue

medication use (SMD -0.307, 95% CI: -0.408, -0.207, $P < 0.001$), greater increase of the proportion of symptom free days (SMD -0.291, 95% CI: -0.391, -0.191, $P < 0.001$), greater change in symptom score (SMD -0.298, 95% CI: -0.451, -0.145, $P < 0.001$), and fewer exacerbations (SMD 0.207, 95% CI: 0.107, 0.307, $P < 0.001$) than those treated with zafirlukast (Appendix G).

A previously published good quality systematic review with meta-analysis compared licensed doses of LTRAs with ICSs.⁸⁰ It included 3 trials testing a higher ICS dose; 3 trials testing a lower ICS dose; and the 21 remaining trials using equal nominal daily doses of ICS. It included 27 studies (9100 subjects); 3 of these in children and 24 in adults. Nine of these included trials also met our inclusion criteria.^{82-87, 90, 92-95} Eighteen of the included studies in this systematic review did not meet our inclusion/exclusion criteria. Duration of studies varied but ranged from 4-8 weeks, 12-16 weeks, and 24 to 37 weeks. The intervention drugs included montelukast (5 to 10 mg) and zafirlukast (20 mg twice daily). The ICS dose was uniform across 21 trials; seven of those used BDP 400 mcg/day, one used BDP 400-500 mcg/day, and 11 used FP 200 mcg/day. Three trials tested a high dose of ICS (BUD 800 mcg/day), one trial failed to report the dose used, and three trials used low dose BDP or equivalent. Eight trials enrolled patients who had mild asthma; 19 enrolled patients with moderate asthma; 3 trials did not report baseline FEV1.

Eighteen trials contributed to the primary outcome showing a 65% increased risk of exacerbations requiring systemic steroids for any LTRA (10 trials in montelukast and 5 trials in zafirlukast) compared to any ICS dosing regimen. The pediatric trials (3) could not be pooled due to a lack of exacerbations. However, 5 trials were pooled for exacerbations requiring hospitalization and there was no significant difference. Data at 12 weeks was pooled according to outcome and found ICS significantly improved change in symptom score (6 trials, SMD 0.29, 95% CI: 0.21 to 0.37), nocturnal awakenings (6 trials, SMD 0.21, 95% CI: 0.13 to 0.30), daily use of B2-agonists (6 trials, WMD 0.28 puffs/day, 95% CI: 0.20 to 0.36), symptom-free days (3 trials, WMD -12, 95% CI: -16 to -7), rescue-free days (3 trials, WMD -14%, 95% CI: -18, -10), and quality of life (2 trials, WMD -0.3, 95% CI: -0.4, -0.2). Similarly, ICS significantly improved asthma control days (3 trials, WMD -8 %, 95% CI: -15, -1]) and rescue-free days (2 trials, WMD -9%, 95% CI: -14, -03). LTRAs significantly increased the risk of withdrawal (19 trials, RR 1.3, 95% CI: 1.1, 1.6) which was attributable to poor asthma control (17 trials, RR 2.6, 95% CI: 2.0, 3.4).

Another fair-rated meta-analysis compared LTRAs to ICSs.⁸¹ It included 6 studies (5278 subjects); 5 retrospective cohort studies and 1 prospective trial. None of these 6 studies met our inclusion criteria. The analysis included trials of subjects with a diagnosis of asthma, without restriction to severe asthma patients or children. Duration of trials was at least 6 months. The pooling of the 6 trials showed a significantly higher annual rate of emergency department visits in the LTRA group ($P < 0.005$). The rate of hospitalizations was shown to decrease significantly with the use of ICSs compared to LTRAs (2.23% compared with 4.3%; $P < 0.05$).

2. Fluticasone (FP) compared with Montelukast (ML)

We found nine fair quality RCTs that compared ML with FP^{86-89, 97-102} that met our inclusion criteria. Our meta-analyses of outcomes from these trials show that patients treated with FP had a greater increase in the proportion of days free from rescue medication use (SMD -0.232, 95% CI: -0.307, -0.157, $P < 0.001$, 6 studies), greater reduction in rescue medicine use per day

(SMD -0.204, 95% CI: -0.317, -0.091, $P < 0.001$), greater increase in the proportion of symptom-free days (SMD -0.258, 95% CI: -0.336, -0.180, $P < 0.001$, 7 studies) (Figure 7), greater improvement in symptom score (SMD -0.244, 95% CI: -0.337, -0.151, $P < 0.001$, 4 studies), fewer exacerbations (SMD 0.151, 95% CI: -0.225, -0.021, $P < 0.001$, 5 studies) (Figure 6), and greater improvement in quality of life (AQLQ scores: SMD -0.123, 95% CI: -0.225, -0.021, $P = 0.019$, 5 studies) than those treated with ML (Appendix G).

Figure 6. Meta-analysis comparing percentage of exacerbations for FP compared with ML

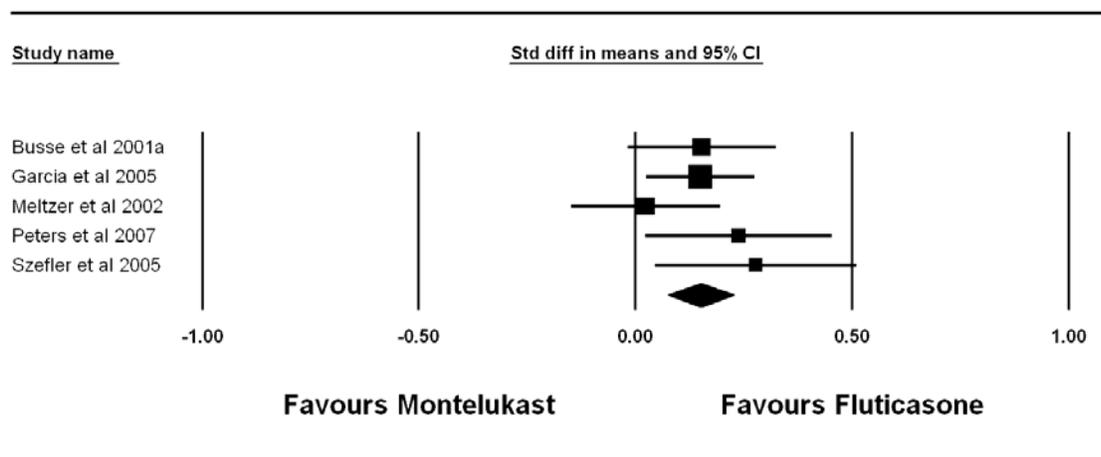
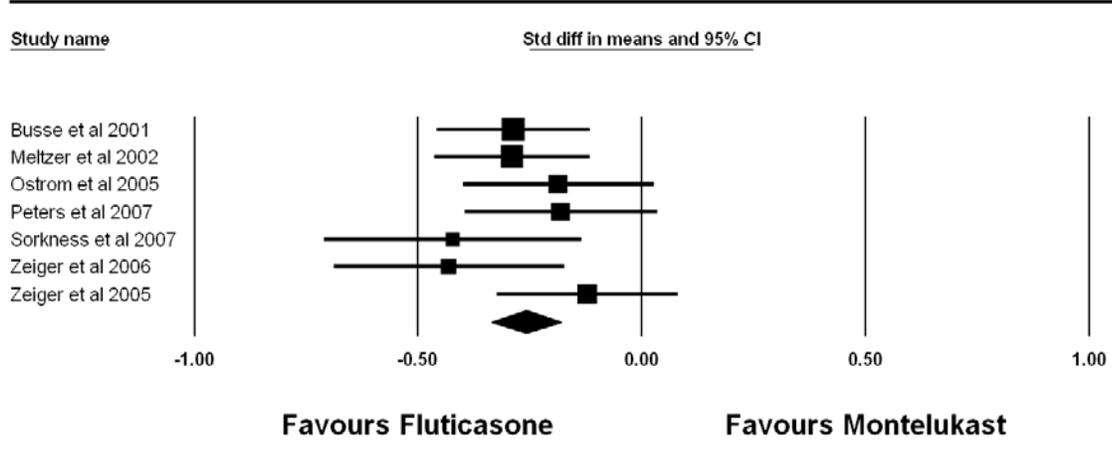


Figure 7. Meta-analysis comparing improvement in the percentage of symptom-free days for FP compared with ML



Details of the nine individual RCTs^{86-89, 97-102} are summarized in Table 21.

3. Beclomethasone (BDP) compared with Montelukast (ML)

Five fair quality RCTs^{82-85, 90, 96} meeting our inclusion criteria compared montelukast with beclomethasone (Table 21). Most of the outcomes reported favored BDP over ML or found no

difference between groups. In general, the results comparing BDP with ML appear to be consistent with the overall results comparing ICSs with LTRAs. Our meta-analyses of outcomes reported with sufficient data in multiple trials shows those treated with BDP had a greater proportion of rescue free days than those treated with ML (SMD -0.108, 95% CI: -0.208, -0.008, $P = 0.034$) and a trend toward a greater proportion of symptom-free days that did not reach statistical significance (SMD -0.118, 95% CI: -0.247, -0.011, $P = 0.073$) (Appendix G).

Details of the individual RCTs are summarized in Tables 21 and 22. We provide further description of the only trial enrolling children < 12 years of age.⁹⁶ The trial was a fair-rated multinational, multi-center RCT in children (N = 360) comparing ML 5 mg/day (N = 120) compared with medium dose BDP 400 mcg/day (N = 119) compared with placebo (N = 121) for 56 weeks. Subjects with mild persistent asthma, age 6.4 – 9.4 for boys and 6.4 – 8.4 for girls were enrolled worldwide (from most continents). The primary objective of the trial was to assess the effects of ML and BDP on linear growth, however some of our primary outcomes of interest were also reported. Fewer subjects treated with ML or BDP had asthma reported as an adverse experience compared to those treated with placebo, but the difference between groups was not statistically significant (36.7% compared with 42.9% compared with 50.4%, $P = NS$ for ML compared with BDP). There were no statistically significant differences in the percentage of patients requiring oral steroids (25% compared with 23.5%), the percentage requiring more than one course of oral steroids (5.8% compared with 5.9%), or the percentage of days of b-agonist use (10.55% compared with 6.65%) between those treated with ML and those treated with BDP.

4. Budesonide (BUD) compared with Montelukast (ML)

We found three fair quality RCTs comparing BUD with ML^{91, 103, 104} that met our inclusion criteria (Tables 21 and 22). Too few studies reported sufficient data for meta-analysis of our included outcomes. Of the three RCTs, one enrolled adult populations, one¹⁰³ enrolled children and adolescents ages 6-18, and one¹⁰⁴ enrolled children ages 2-8. Most subjects in these trials had mild persistent asthma. Study duration ranged from 12 weeks to 52 weeks. The reported outcomes of interest were either not statistically significantly different between the two groups or favored BUD. For symptoms, two trials^{91, 103} reported no statistically significant difference between groups. Two trials reporting exacerbations found more favorable results for those treated with BUD than those treated with ML.^{91, 104} The single trial reporting quality of life found no difference between the treatments for overall quality of life measures.¹⁰⁴

5. Fluticasone (FP) compared with Zafirlukast

We found four fair quality RCTs comparing FP with zafirlukast⁹²⁻⁹⁵ that met our inclusion criteria. All four trials show similar results favoring FP over zafirlukast for symptoms, rescue medicine use, and quality of life. Our meta-analyses again show that subjects treated with FP had a greater increase in days free from rescue medication use (SMD -0.307, 95% CI: -0.408, -0.207, $P < 0.001$, 4 studies), greater increase of the proportion of symptom free days (SMD -0.291, 95% CI: -0.391, -0.191, $P < 0.001$, 4 studies), greater improvement in symptom score (SMD -0.298, 95% CI: -0.451, -0.145, $P < 0.001$, 2 studies), and fewer exacerbations (SMD 0.207, 95% CI: 0.107, 0.307, $P < 0.001$, 4 studies) (Figure 8) than those treated with zafirlukast (Appendix G).

Figure 8. Meta-analysis comparing percentage of exacerbations for zafirlukast compared with fluticasone

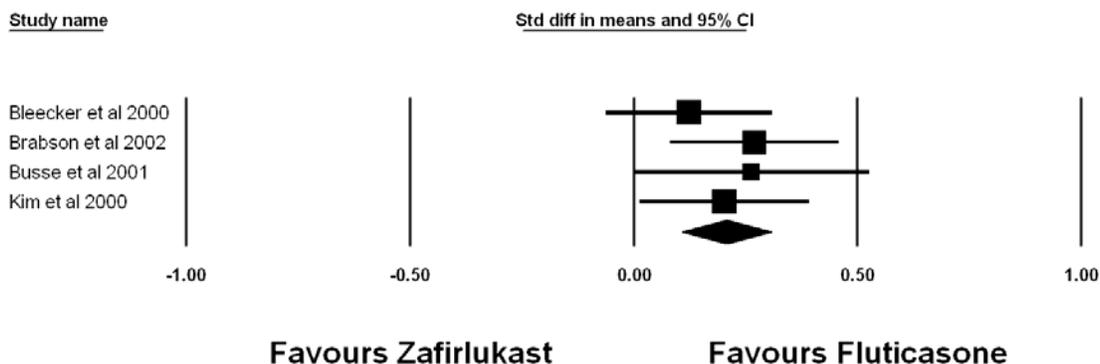


Table 21. Summary of head-to-head studies comparing ICSs compared with LTRAs in children and adults

Study	Study design N Duration	Country Study population Setting	Comparison (total daily dose)	Results	Quality rating
Inhaled corticosteroids (ICSs) compared with leukotriene receptor antagonists (LTRAs)					
Ducharme et al. 2004 ⁸⁰	Systematic review with meta-analysis 27 studies (91,00 subjects)	3 trials in children, 24 trials in adults;	Licensed doses of LTRA compared with ICS (3 trials tested a higher dose; 3 trials tested a lower dose; remaining tested equal to baseline daily doses of ICS)	<p>Symptoms: ICS > LTRA [symptom scores: 6 trials, SMD = 0.29, 95% CI: 0.21, 0.37; symptom-free days: 3 trials, WMD = -12, 95% CI: -16, -7; and nocturnal awakenings: 6 trials, SMD = 0.21, 95% CI: 0.13, 0.30].</p> <p>Exacerbations: ICS > LTRA for some [65% increased risk of exacerbation requiring systemic steroids for any LTRA: relative risk 1.65 (1.36 - 2.00); No significant difference in exacerbations requiring hospitalization [relative risk 1.62 (0.64 – 4.15)]</p> <p>Rescue medicine use: ICS > LTRA [daily use of B2-agonists: 6 trials, WMD = 0.28 puffs/day, 95% CI: 0.20, 0.36; rescue-free days: 3 trials, WMD = -14%, 95% CI: -18, -10]</p> <p>Quality of Life: ICS > LTRA [quality of life: 2 trials: WMD = -0.3, 95% CI: -0.4, -0.2].</p>	Good

Table 21. Summary of head-to-head studies comparing ICSs compared with LTRAs in children and adults

Study	Study design N Duration	Country Study population Setting	Comparison (total daily dose)	Results	Quality rating
				Missed work or school: No difference [<i>days off from school/work</i> : 2 trials, WMD= 0.06 days, -0.03 to 0.15].	
Halpern et al. 2003 ⁸¹	Meta-analysis 6 studies (5278 subjects)	5 retrospective cohort, 1 prospective trial; United States	ICS compared with LTRA	Urgent care services: LTRA > ICS [<i>annual rates of ED visits</i> ; $P < 0.005$] Hospitalizations: ICS > LTRA [<i>decrease in rate</i> ; 2.23% compared with 4.3%; $P < 0.05$]	Fair
Fluticasone (FP) compared with Montelukast (ML)					
Busse et al. 2001 ⁸⁶	RCT 533 24 weeks	United States Age 15 and older, moderate to severe persistent asthma, excluded current smokers within the past year and those with ≥ 10 pack-year history Multicenter (52)	FP (176 mcg) compared with ML (10 mg) Low dose ICS	Symptoms: FP > ML [% of <i>symptom free days</i> ; 32 compared with 18.4; $P < 0.001$; <i>change in symptom score</i> ; -0.85 compared with -0.60; $P < 0.001$]. Exacerbations: no difference [4% compared with 8%; $P = \text{NS}$, NR] Rescue medicine use: FP > ML [<i>puffs/day, change</i> ; -3.1 compared with -2.31; $P < 0.001$; % <i>rescue free days, change</i> ; -45.9% compared with -31.2%; $P < 0.001$] Quality of Life: FP > ML [global and individual domain AQLQ scores; $P < 0.001$; however only the symptoms and emotional domains were clinically significant with a > 0.5 point difference] Compliance: No difference [mean values for compliance were $\geq 91.4\%$]	Fair
Garcia et al. 2005 ⁹⁷	RCT 994 52 weeks	Multinational (24 including Asia, Africa, North and South America) Children age 6 – 14, mild persistent asthma, smoking status NR	FP (200 mcg) via MDI compared with ML (5 mg) Medium to Low (12-14 years of age) dose ICS	Exacerbations: FP > ML [% of <i>exacerbations</i> ; 25.6% compared with 32.2%; RR 1.26; 95% CI: 1.04, 1.52; Courses of steroids; 10.5% compared with 17.8%; $p \leq 0.001$] Rescue medicine use: FP >	Fair

Table 21. Summary of head-to-head studies comparing ICSs compared with LTRAs in children and adults

Study	Study design N Duration	Country Study population Setting	Comparison (total daily dose)	Results	Quality rating
		Multicenter (104) Primary care		<p>ML [% rescue use per day; -25.4% compared with -22.7%; $P = 0.003$; % rescue free days; 25.2% compared with 22.4%; 95% CI: -4.7, -0.9]</p> <p>Quality of Life: FP > ML [overall <i>Pediatric AQLQ</i> score; 1.05 compared with 0.92; $P = 0.036$]</p> <p>Missed work or school: No difference [≥ 1 day lost from school during the 4 weeks prior to the 12 month visit; 6.2% compared with 8.8%; $P = \text{NR}$; > 3 lost days of school; 2.1% compared with 1.9%; $P = \text{NR}$; parents lost ≥ 1 day of work; 2% compared with 2.9%; $P = \text{NR}$; lost > 3 days; 0.2% compared with 0.4%; $P = \text{NR}$]</p> <p>Compliance: No difference [98% compared with 98.1%]</p>	
Meltzer et al. 2002 ⁸⁷	RCT 522 24 weeks	United States Age 15 and older, moderate to severe persistent asthma, excluded current smokers within the past year and those with ≥ 10 pack-year history Multicenter	FP (176 mcg) compared with ML (10 mg) Low dose ICS	<p>Symptoms: FP > ML [change in asthma symptom score; -0.91 compared with -0.57; $P < 0.001$; % of symptom free days; 34.3% compared with 20.2%; $P < 0.001$; % nights with awakenings; -72% compared with -47.1%; $P = 0.01$].</p> <p>Exacerbations: 7% compared with 8%; $P = \text{NR}$.</p> <p>Rescue medicine use: FP > ML [puffs/day; -3.21 compared with -2.25; $P < 0.001$; % rescue free days; 45.6% compared with 33.4%; $P < 0.001$]</p> <p>Quality of Life: FP > ML [AQLQ overall score and individual components of symptoms, environment, emotions, and activities;</p>	Fair

Table 21. Summary of head-to-head studies comparing ICSs compared with LTRAs in children and adults

Study	Study design N Duration	Country Study population Setting	Comparison (total daily dose)	Results	Quality rating
				(1.3 vs. 1.0, $P < 0.001$) (1.4 vs. 1.0, $P < 0.001$) (1.2 vs. 0.9, $P < 0.01$) (1.3 vs. 0.9, $P < 0.001$) (1.3 vs. 1.0, $P < 0.001$)	
				Compliance: No difference [patient reported compliance was 92% or more compared with 93.3% or more]	
Ostrom et al. 2005 ⁹⁸	RCT 342 12 weeks	United States Children age 6-12, mild to moderate persistent asthma, smoking status NR Multicenter (46) Outpatient clinics	FP (100 mcg) compared with ML (5 mg) Low dose ICS	Symptoms: Mixed results [daytime asthma symptom score; -0.81 vs. -0.75; $P = 0.202$; % symptom free days; 37.7% vs. 31.3%; $P = 0.087$; nighttime asthma symptom score; -0.40 vs. -0.19; $P < 0.001$; % symptom free nights; 45.1% vs. 35%; $P = 0.002$]. Rescue medicine use: Mixed results [puffs/day; -1.43 vs. -1.23; $P = 0.18$; puffs during daytime; -1.01 vs. -0.92; $P = 0.1$; puffs during nighttime; -0.39 vs. -0.21; $P < 0.001$]. Hospitalizations: 0 vs. 1; $P = \text{NR}$	Fair
Peters et al. 2007 ⁹⁹	RCT 500 16 weeks	United States Age 6 and older, mild to moderate asthma, smoking status NR Multicenter	FP (200 mcg) compared with FP (200 mcg)/ SM (100 mcg) compared with ML (5 – 10mg) Low dose ICS	Symptoms: Mixed results [% symptom free days; 85.8% vs. 78.7%; $P = 0.1$ for FP vs. ML; Asthma Symptom Utility Index; 0.89 vs. 0.89; $P = \text{NS}$; % with nocturnal awakenings; 16.7% vs. 25.4%; $P = 0.04$]. Exacerbations: FP > ML [% with treatment failure; 20.2% vs. 30.3%; $P = 0.03$]. Rescue medicine use: no difference [% days with rescue med use; 18.2% vs. 22.9%; $P = 0.09$ for FP vs. ML] Quality of Life: No difference [Mini-AQLQ; 5.8 vs. 5.8; $P = \text{NS}$]. FP > ML	Fair

Table 21. Summary of head-to-head studies comparing ICSs compared with LTRAs in children and adults

Study	Study design N Duration	Country Study population Setting	Comparison (total daily dose)	Results	Quality rating
				[ACQ; 0.73 vs. 0.82; $P = 0.02$ for FP vs. ML] Adherence: good for all groups; FP 93.2% and ML 90.5%.	
Sorkness et al. 2007 ¹⁰⁰ Pediatric Asthma Controlled Trial (PACT)	RCT 285 48 weeks	United States Children age 6-14, mild to moderate persistent asthma, excluded current smokers within the past year Childhood Asthma Research and Education Centers	FP (200 mcg) compared with FP (100 mcg)/ SM (50 mcg) plus SM (50 mg) compared with ML (5 mg) Low dose ICS	Symptoms: FP > ML [% <i>asthma control days</i> ; 64.2% compared with 52.5%; $P = 0.004$; % <i>change from baseline of asthma control days</i> ; 32.2% compared with 22.3%; $P = 0.023$] Quality of Life: FP > ML [<i>change in ACQ score from baseline</i> ; -0.69 compared with -0.45; $P = 0.018$] Adherence: estimated to be 90% for Diskus inhaler and 86% for tablets.	Fair
Szeffler et al. 2005 ¹⁰¹	RCT 144 16 weeks	United States Children age 6-17, mild to moderate persistent asthma, smoking status NR University Clinics	FP (200 mcg) compared with ML (5 – 10mg) Low dose ICS	Exacerbations: FP > ML [% of exacerbations; 2% compared with 8%; $P = 0.019$] Adherence: both groups comparable; 94% by Diskus counter and 97% by tablet count and 92% by eDEM	Fair
Zeiger et al. 2005 ^{88, 89} MIAMI Trial	RCT 400 12 weeks with 36 week open label extension	United States Age 15 – 85, mild persistent asthma, smoking status NR Multicenter (39)	ML (10mg) compared with FP (176 mcg) Low dose ICS	Symptoms: mixed results [<i>change from baseline in daytime asthma symptom frequency (scale 3 – 15)</i> ; -1.3 vs. -1.5; $P = 0.27$], [<i>symptom free days</i> ; +6.3 vs. +7.3; $P = 0.24$; <i>asthma control scale score</i> ; -0.4 vs. -0.5; $P = 0.09$; <i>change in nighttime asthma symptom frequency</i> ; -1.4 vs. -2; $P = 0.04$] Exacerbations: no difference [<i>use of oral steroids</i> ; 2.6% vs. 2.1%; $P = NS$] Rescue medicine use: no difference [<i>change from baseline in puffs/day</i> ; -0.4 vs. -0.4; $P = 0.32$; % <i>rescue</i>	Fair

Table 21. Summary of head-to-head studies comparing ICSs compared with LTRAs in children and adults

Study	Study design N Duration	Country Study population Setting	Comparison (total daily dose)	Results	Quality rating
				<p><i>free days</i>; 73.1% vs. 74.9%; <i>P</i> = NS]</p> <p>Quality of Life: no difference [<i>change in AQLQ score from baseline</i>; 0.7 vs. 0.8; <i>P</i> = 0.2]</p> <p>Adherence: patient-reported adherence was high in both treatment groups (98.4%; 94.7%)</p>	
Zeiger et al. 2006 ¹⁰² CARE Network Trial	RCT 144 (127 in analysis) 16wk total (8wk, crossover, 8wk); additionally, only included data from the last 4wk of each treatment period	United States Children age 6-17, mild to moderate persistent asthma, smoking status NR Multicenter	FP (200 mcg) compared with ML (5 – 10mg) Low dose ICS	<p>Symptoms: FP > ML [<i>asthma control days per week</i>; 5 compared with 4.3; <i>P</i> < 0.0001]</p> <p>Rescue medicine use: FP > ML [<i>puffs/week</i>]; 3.1 compared with 4.4; <i>P</i> = 0.0305].</p> <p>Quality of Life: ML > FP [<i>ACQ scores</i>]; 0.59 compared with 0.76; <i>P</i> = 0.0009].</p> <p>Adherence: > 85% for both groups</p>	Fair
Beclomethasone (BDP) compared with Montelukast (ML)					
Baumgartner et al. 2003 ⁸²	RCT 730 6 weeks	Multinational (Canada and South America) Age 15 and older, mild to severe persistent asthma, excluded current smokers within past year and those with > 7 pack-year history Multicenter (16)	BDP (400 mcg) compared with ML (10mg) compared with placebo Medium Dose ICS	<p>Symptoms: BDP > ML [<i>% asthma control days</i>]; 57.9% vs. 50.7% vs. 40%; <i>P</i> < 0.05 for BDP vs. ML].</p> <p>Exacerbations: 4, 7, and 18 in the groups, respectively; <i>P</i> = NR. BDP and ML > placebo [<i>% of patients with asthma attacks</i>]; 3.9% vs. 5.5% vs. 14.9%; <i>P</i> = NS for ML vs. BDP]</p> <p>Rescue medicine use: BDP > ML [<i>% use during 24 hours</i>]; -45.7% vs. -35.7% vs. -15.7%; <i>P</i> < 0.05 for BDP vs. ML]</p> <p>Compliance: high for all three groups respectively; 98.1%, 98.4%, and 98%.</p>	Fair

Table 21. Summary of head-to-head studies comparing ICSs compared with LTRAs in children and adults

Study	Study design N Duration	Country Study population Setting	Comparison (total daily dose)	Results	Quality rating
Becker et al. 2006 ⁹⁶	RCT 360 56 weeks	Multinational (North and South America, Europe, Asia, Africa) Boys age 6.4-9.4 and girls age 6.4-8.4 years, mild to moderate persistent asthma, smoking status NR Multicenter (30)	ML (5mg) compared with BDP (400 mcg) compared with placebo High dose ICS	Exacerbations: ML > BDP trend [% exacerbations; 36.7% vs. 42.9% vs. 50.4%; ML vs. BDP $P = NR$; % requiring oral steroids [25% vs. 23.5% vs. 34.7%; $P > 0.05$; % who required more than one course of oral steroids; 5.8% vs. 5.9% vs. 15.7%, $P = 0.02$] Rescue medicine use: No difference [% of days of rescue use; 10.55% vs. 6.65% vs. 14.58%; $P = 0.17$ for ML vs. BDP].	Fair
Israel et al. 2002 ⁸³	RCT 782 6 weeks	United States Age 15 and older, mild to severe persistent asthma, excluded current smokers within the past year and those with > 7 pack-year history Multicenter (64)	ML (10 mg) compared with BDP (400 mcg) compared with placebo Medium dose ICS	Symptoms: No difference [% days of asthma control; 41.4%, 41.1%, 26.8%; ML vs. BDP $P = 0.929$]. Exacerbations: No difference [% without an asthma attack; 97% vs. 96.1% vs. 91.9%; $P = NS$ for ML vs. BDP; % without rescue steroids; 97.3% vs. 96.4% vs. 92.8%; $P = NS$ for ML vs. BDP]. Rescue medicine use: No difference [puffs/24 hours; -30.3 vs. -31.9 vs. -9.7; $P < 0.001$; ML vs. BDP $P = 0.621$]	Fair
Lavolette et al. 1999 ⁹⁰	RCT 642 16 weeks	Multinational (18 including Europe, Asia, Africa, Australia, North America) Age 15 and older, mild to severe persistent asthma, excluded current or former smoker Multicenter (70)	BDP (400 mcg) plus ML (10 mg) vs. BDP (400 mcg) vs. ML (10mg) vs. placebo Low dose ICS	Symptoms: BDP > ML [mean change in daytime symptoms score in BDP group (-0.09; 95% CI: -0.20, 0.002) compared to ML group (0.27; 95% CI: 0.17, 0.38)] Compliance: high with both inhaled (94.6%, 92.4%, 94%, 96.5%) and oral (98.6%, 98.7%, 98.7%, 99%) in groups respectively	Fair
Malmstrom et al. 1999 ^{84, 85}	RCT 895 (436 in extension) 12weeks plus a	Multinational (19 in Europe, Africa, Australia, Central and South America)	ML (10mg) compared with BDP (400 mcg) compared with placebo	Symptoms: BDP > ML [% asthma control days; 40.1% vs. 48.9% vs. 27.4%; BDP vs. ML $P < 0.01$; daytime symptom scores; -0.41 vs. -	Fair

Table 21. Summary of head-to-head studies comparing ICSs compared with LTRAs in children and adults

Study	Study design N Duration	Country Study population Setting	Comparison (total daily dose)	Results	Quality rating
	3week placebo washout period where patients were switched from treatment to placebo. (Double-blind extension phase =37 weeks)	Age 15 and older, mild to severe persistent asthma, excluded current or former smokers Multicenter (36), clinical centers	(extension: ML compared with BDP in pre-assigned groups) Medium dose ICS	0.62 vs. -0.17; BDP vs. ML $P < 0.01$ Nocturnal awakenings: BDP > ML [change from baseline: -1.7 vs. -2.4 vs. -0.5; BDP vs. ML $P < 0.01$]. Exacerbations: BDP > ML [% of days with an asthma exacerbation; 15.2% vs. 9.7% vs. 26.1%; BDP vs. ML $P < 0.01$; % with asthma attacks; 15.6% vs. 10.1% vs. 27.3%; BDP vs. ML $P = 0.01$] Rescue medicine use: BDP > ML trend [change in % of use during 24 hours; 23.9% vs. -40% vs. 0%] Quality of Life: BDP > ML [increase in overall AQLQ scores; 0.62 vs. 0.83 vs. 0.25; BDP vs. ML $P < 0.01$] Compliance: inhaled study medication was 87.6%, 88.6%, and 89.6%; oral study medication was 99.8%, 99.3%, and 99.6% in groups respectively.	
Budesonide (BUD) vs. Montelukast (ML)					
Stelmach et al. 2005 ¹⁰³	RCT 51 24 weeks	Poland Children age 6-18, newly diagnosed asthma with sensitivity to house dust mites, smoking status NR University clinics	BUD (400 mcg) vs. BUD (800 mcg) vs. ML (5 – 10 mg) Low to Medium Dose ICS	Symptoms: No difference [all significantly improved mean clinical score (daytime and nighttime symptoms and rescue use) compared to baseline; 1.9 vs. 2.2 vs. 1.9; $P = NS$ between groups]	Fair
Szeffler et al. 2007 ¹⁰⁴	RCT, open label 395 52 weeks	United States Children 2-8, mild persistent asthma, smoking status NR Multicenter	BUD inhalation suspension (BIS) (0.5mg) vs. ML (4 or 5mg) Low dose ICS	Exacerbations: BUD > ML [number of exacerbations per year; 1.23 vs. 1.63; $P = 0.034$; length of time to require additional medication for asthma worsening; $P < 0.05$] QOL: No difference [overall,	Fair

Table 21. Summary of head-to-head studies comparing ICSs compared with LTRAs in children and adults

Study	Study design N Duration	Country Study population Setting	Comparison (total daily dose)	Results	Quality rating
				<p><i>activity limitations, and emotional function domains of the PACQLQ; 0.91 vs. 0.92; P = 0.866; 1.22 vs. 1.17; P = 0.651; and 0.77 vs. 0.81; P = 0.677]</i></p> <p>Compliance: 82.9% and 82.8%, respectively.</p>	
Yurdakul et al. 2003 ⁹¹	RCT 74 12 weeks	Turkey Adults age 23 – 45, mild persistent asthma, excluded smokers Research hospital	BUD (400 mcg) vs. ML (10mg) Low dose ICS	<p>Symptoms: No difference [<i>daytime symptom score; 0.5 vs. 0.6; P > 0.05; nighttime symptom score; 0.2 vs. 0.3; P > 0.05]</i></p> <p>Exacerbations: BUD > ML trend [zero vs. 4; P = NR].</p> <p>Rescue medicine use: No difference [<i>puffs/24 hours; 0.1 vs. 0.1; P > 0.05]</i>.</p>	Fair
Fluticasone (FP) compared with Zafirlukast (ZAF)					
Bleecker et al. 2000 ⁹²	RCT 451 12 weeks	Multinational Age 12 and older, mild to severe persistent asthma, excluded current smokers within the past year and those with ≥ 10 pack-year history Multicenter (41)	FP (176 mcg) compared with Zafirlukast (40mg) Low dose ICS	<p>Symptoms: FP > ZAF [<i>% symptom free days; 28.5% compared with 15.6%, P < 0.001]</i></p> <p>Nocturnal awakenings: FP > ZAF [<i>-0.28 compared with -0.15, P < 0.001]</i>.</p> <p>Exacerbations: No difference [4% compared with 6%, P = 0.191]</p> <p>Rescue medicine use: FP > ZAF [<i>change in puffs/day; -2.39 compared with -1.45, P < 0.001; % rescue free days; 40.4% compared with 24.2%, P < 0.001]</i>.</p> <p>Compliance: MDI and oral capsule were 92% in both groups</p>	Fair
Brabson et al. 2002 ⁹³	RCT 440 6 weeks	United States Age 12 and older, mild to moderate persistent asthma, smoking status NR Multicenter (44)	FP (176 mcg) compared with Zafirlukast (40mg) Low dose ICS	<p>Symptoms: FP > ZAF [<i>% symptom free days; 22% vs. 8%, SMD 14%; P < 0.001; % nights with uninterrupted sleep; 0 vs. -5; SDM 5; P < 0.006; change in asthma symptom score; -0.16 vs. -0.01; SDM</i></p>	Fair

Table 21. Summary of head-to-head studies comparing ICSs compared with LTRAs in children and adults

Study	Study design N Duration	Country Study population Setting	Comparison (total daily dose)	Results	Quality rating
				-0.17; $P = 0.001$	
				Exacerbations: FP > ZAF [Percent of patients: 1% vs. 6%; $P = 0.005$; number of patients required oral steroids; 1 vs. 10; $P = 0.005$]	
				Rescue medicine use: FP > ZAF [change in puffs/day; -0.6 vs. 0.1; SDM -0.7; $P < 0.001$; % rescue free days; 23% vs. 10%; SDM 13; $P = 0.002$]	
				Compliance: both groups reported $\geq 88\%$	
Busse et al. 2001 ⁹⁴	RCT 338 12 weeks	United States Age 15 and older, mild to severe persistent asthma, excluded current smokers within the past year and those with ≥ 10 pack-year history Multicenter 50% primary care	FP (176 mcg) compared with zafirlukast (40mg) compared with placebo Low dose ICS	Symptoms: FP > ZAF [% symptom free days; 28.8% vs. 18.7% vs. 6.9%; $P < 0.05$; symptom score; -0.65 vs. -0.36 vs. -0.43; $P < 0.05$; number of days of work or school with symptoms; 1.8 vs. 3.8 vs. 4.4; $P \leq 0.03$] Nocturnal awakenings: FP > ZAF [number per night of awakenings, change; -0.32 vs. -0.23 vs. -0.17; $P < 0.05$] Exacerbations: No difference [% exacerbations; 4% vs. 12% vs. 10%; $P = NS$] Rescue medicine use: FP vs. ZAF [change in puffs/day; -2.8 vs. -1.9 vs. -1.3, $P < 0.05$; % rescue free days; 48.9% vs. 37.5% vs. 19%; $P < 0.05$] QOL: FP > ZAF [AQLQ overall and individual domains (symptoms, environment, emotion, activities) scores; 0.6 vs. 0.3 vs. NR; 0.8 vs. 0.3 vs. NR; 0.5 vs. 0.2 vs. NR; 0.6 vs. 0.1 vs. NR; 0.4 vs. 0.3]	Fair

Table 21. Summary of head-to-head studies comparing ICSs compared with LTRAs in children and adults

Study	Study design N Duration	Country Study population Setting	Comparison (total daily dose)	Results	Quality rating
				vs. NR; $p \leq 0.033$ FP vs. zafirlukast]	
				Compliance: 93% in both groups with inhaled and oral medications	
Kim et al. 2000 ⁹⁵	RCT 437 6 weeks	United States Age 12 and older, mild to severe persistent asthma, excluded current smokers within the past year and those with ≥ 10 pack-year history Multicenter Allergy and Asthma centers	FP (176 mcg) vs. zafirlukast (40mg) Low dose ICS	Symptoms: FP > ZAF [<i>% symptom free days at endpoint</i> (SE); 16.2% (2.4) compared with 7.1% (2.9); $P = 0.007$; <i>mean asthma symptom scores</i> were low at baseline for wheeze, shortness of breath, chest tightness, and cough. At endpoint, mean scores improved for each individual symptom in FP group, but increased in the zafirlukast group; $P < 0.004$] Nocturnal awakenings: FP > ZAF [<i>% awakening free nights at endpoint</i> ; 96% compared with 88%; $P < 0.001$]. Exacerbations: FP > ZAF [<i>exacerbations requiring treatment with oral or IV steroids</i> ; 5 compared with 14; $P = 0.035$]. Rescue medicine use: FP > ZAF [<i>mean puffs/day at endpoint</i> (SE); -0.66 (0.11) compared with 0.27 (0.13); $P < 0.001$; <i>mean change in % rescue-free days at endpoint</i> ; 23.4% (2.5) compared with 9.3% (2.4); $P < 0.001$] QOL: FP > ZAF [FP increased AQLQ scores by ~0.5 points in the global as well as the activity, symptoms, emotional, and environmental individual domains; ZAF did not result in a 0.5 increase for the global score or for any of the domain scores. Mean difference between groups	Fair

Table 21. Summary of head-to-head studies comparing ICSs compared with LTRAs in children and adults

Study	Study design N Duration	Country Study population Setting	Comparison (total daily dose)	Results	Quality rating
				in global score and in all domain scores at endpoint, $P < 0.001$	
				Compliance: Patient self reported compliance was 88% for both groups.	

Abbreviations: AQLQ = Asthma Quality of Life Questionnaire; BDP = beclomethasone dipropionate; BUD = Budesonide; CI = confidence interval; FP = Fluticasone Propionate; ICS = Inhaled Corticosteroids; LTRAs = Leukotriene receptor antagonists; ML = Montelukast; NR = not reported; NS = not statistically significant; QOL = quality of life; WMD = weighted mean difference; ZAF = Zafirlukast.

Symbol use: Drug X > Drug Y = statistically significant difference in outcomes favoring Drug X; Drug X > Drug Y trend = point estimate favors Drug X, but the difference is not statistically significant or tests of statistical significance were NR; No difference = no statistically significant difference or tests of statistical significance were not reported and outcomes are similar.

Note: All results are listed in the same order as the comparison column lists the medications.

Table 22. Summary of head-to-head studies comparing ICSs with LTRAs in children < 12

Study	Study design N Duration	Study population	Comparison (total daily dose)	Results	Quality rating
Fluticasone compared with montelukast					
Garcia et al. 2005 ⁹⁷	RCT 994	Multinational (24 including Asia, Africa, North and South America)	FP (200 mcg) via MDI compared with ML (5mg)	Exacerbations: FP > ML [% of exacerbations; 25.6% compared with 32.2%; RR 1.26; 95% CI: 1.04, 1.52; Courses of steroids; 10.5% compared with 17.8%; $P \leq 0.001$]	Fair
MOSAIC Study	52 weeks	Children age 6 – 14, mild persistent asthma, smoking status NR Multicenter (104) Primary care	Medium to Low (12-14 years of age) dose ICS	Rescue medicine use: FP > ML [% <i>rescue use per day</i> ; -25.4% compared with -22.7%; $P = 0.003$; % <i>rescue free days</i> ; 25.2% compared with 22.4%; 95% CI: -4.7, -0.9] Quality of Life: FP > ML [<i>overall Pediatric AQLQ score</i> ; 1.05 compared with 0.92; $P = 0.036$] Missed work or school: No difference [≥ 1 day lost from school during the 4 weeks prior to the 12 month visit; 6.2% compared with 8.8%; $P = \text{NR}$; > 3 lost days of school; 2.1% compared with 1.9%; $P = \text{NR}$; parents lost ≥ 1 day of work; 2% compared with 2.9%; $P = \text{NR}$; lost > 3 days; 0.2% compared with 0.4%; $P = \text{NR}$]	
				Compliance: No difference [98% compared with 98.1%]	

Study	Study design N Duration	Study population	Comparison (total daily dose)	Results	Quality rating
Ostrom et al. 2005 ⁹⁸	RCT 342 12 weeks	United States Children age 6-12, mild to moderate persistent asthma, smoking status NR Multicenter (46) Outpatient clinics	FP (100 mcg) compared with ML (5mg) Low dose ICS	Symptoms: Mixed results [<i>daytime asthma symptom score</i> ; -0.81 compared with -0.75; $P = 0.202$]; % <i>symptom free days</i> ; 37.7% vs. 31.3%; $P = 0.087$; <i>nighttime asthma symptom score</i> ; -0.40 vs. -0.19; $P < 0.001$; % <i>symptom free nights</i> ; 45.1% vs. 35%; $P = 0.002$]. Rescue medicine use: Mixed results [-1.43 vs. -1.23; $P = 0.18$; <i>puffs during daytime</i> ; -1.01 vs. -0.92; $P = 0.1$; <i>puffs during nighttime</i> ; -0.39 vs. -0.21; $P < 0.001$]. Hospitalizations: 0 vs. 1; $P = \text{NR}$	Fair
Peters et al. 2007 ⁹⁹	RCT 500 16 weeks	United States Age 6 and older, mild to moderate asthma, smoking status NR Multicenter	FP (200 mcg) compared with FP (200mcg)/SM (100 mcg) compared with ML (5 – 10mg) Low dose ICS	Symptoms: Mixed results [% <i>symptom free days</i> ; 85.8% vs. 78.7%; $P = 0.1$ for FP vs. ML; <i>Asthma Symptom Utility Index</i> ; 0.89 vs. 0.89; $P = \text{NS}$; % <i>with nocturnal awakenings</i> ; 16.7% vs. 25.4%; $P = 0.04$] Exacerbations: FP > ML [% <i>with treatment failure</i> ; 20.2% vs. 30.3%; $P = 0.03$] Rescue medicine use: no difference [% <i>days with rescue med use</i> ; 18.2% vs. 22.9%; $P = 0.09$ for FP vs. ML] Quality of Life: Mixed results [<i>Mini-AQLQ</i> ; 5.8 vs. 5.8; $P = \text{NS}$; <i>ACQ</i> ; 0.73 vs. 0.82; $P = 0.02$ for FP vs. ML] Adherence: good for all groups; FP 93.2% and ML 90.5%.	Fair
Sorkness et al. 2007 ¹⁰⁰ Pediatric Asthma Controller Trial (PACT)	RCT 285 48 weeks	United States Children age 6-14, mild to moderate persistent asthma, excluded current smokers within the past year Childhood Asthma Research and Education Centers	FP (200 mcg) compared with FP (100 mcg)/SM (50 mcg) plus SM (50mg) compared with ML (5 mg) Low dose ICS	Symptoms: FP > ML [% <i>asthma control days</i> ; 64.2% compared with 52.5%; $P = 0.004$; % <i>change from baseline of asthma control days</i> ; 32.2% compared with 22.3%; $P = 0.023$] Quality of Life: FP > ML [<i>change in ACQ score from baseline</i> ; -0.69 compared with -0.45; $P = 0.018$] Adherence: estimated to be 90% for Diskus inhaler and 86% for tablets.	Fair
Szeffler et al. 2005 ¹⁰¹	RCT 144 16 weeks	United States Children age 6-17, mild to moderate persistent asthma,	FP (200 mcg) compared with ML (5 – 10 mg)	Exacerbations: FP > ML [% of <i>exacerbations</i> ; 2% compared with 8%; $P = 0.019$] Adherence: both groups comparable;	Fair

Study	Study design N Duration	Study population	Comparison (total daily dose)	Results	Quality rating
		smoking status NR University Clinics	Low dose ICS	94% by Diskus counter and 97% by tablet count and 92% by eDEM	
Zeiger et al. 2006 ¹⁰²	RCT	United States	FP (200 mcg) compared with ML (5 – 10mg)	Symptoms: FP > ML [<i>asthma control days per week</i> ; 5 compared with 4.3; $P < 0.0001$;] Rescue medicine use: FP > ML [<i>puffs/week</i> ; 3.1 compared with 4.4; $P = 0.0305$]. Quality of Life: ML > FP [ACQ scores; 0.59 compared with 0.76; $P = 0.0009$]. Adherence: > 85% for both groups	Fair
CARE Network Trial	144 (127 in analysis) 16wk total (8wk, crossover, 8wk); additionally, only included data from the last 4wk of each treatment period	Children age 6-17, mild to moderate persistent asthma, smoking status NR Multicenter	Low dose ICS		
Beclomethasone compared with montelukast					
Becker et al. 2006 ⁹⁶	RCT 360 56 weeks	Multinational (North and South America, Europe, Asia, Africa) Boys age 6.4-9.4 and girls age 6.4-8.4 years, mild to moderate persistent asthma, smoking status NR Multicenter (30)	ML (5mg) compared with BDP (400 mcg) compared with placebo High dose ICS	Exacerbations: ML > BDP trend [<i>% exacerbations</i> ; 36.7% vs. 42.9% vs. 50.4%; ML vs. BDP $P = \text{NR}$; % <i>requiring oral steroids</i> 25% vs. 23.5% vs. 34.7%; $P > 0.05$]. ML and BDP > placebo; % <i>who required more than one course of oral steroids</i> ; 5.8% vs. 5.9% vs. 15.7%, $P = 0.02$ Rescue medicine use: No difference [<i>% of days of rescue use</i> ; 10.55% vs. 6.65% vs. 14.58%; $P = 0.17$ for ML vs. BDP]	Fair
Budesonide compared with Montelukast					
Szeffler et al. 2007 ¹⁰⁴	RCT, open label 395 52 weeks	United States Children 2-8, mild persistent asthma, smoking status NR Multicenter	BUD inhalation suspension (BIS) (0.5mg) compared with ML (4 or 5mg) Low dose ICS	Exacerbations: BUD > ML [<i>number of exacerbations per year</i> ; 1.23 compared with 1.63; $P = 0.034$; <i>length of time to require additional medication for asthma worsening</i> ; $P < 0.05$] Quality of Life: No difference [<i>overall, activity limitations, and emotional function domains of the PACQLQ</i> ; 0.91 vs. 0.92; $P = 0.866$; 1.22 vs. 1.17; $P = 0.651$; and 0.77 vs. 0.81; $P = 0.677$] Compliance: 82.9% and 82.8%, respectively	Fair

Abbreviations: AQLQ = Asthma Quality of Life Questionnaire; BIS = Budesonide inhalation suspension; BDP = beclomethasone dipropionate; BUD = Budesonide; CI = confidence interval; FP = Fluticasone Propionate; MDI = metered dose inhaler; ML = Montelukast; NR = not reported; NS = not statistically significant; PAQLQ = Pediatric Asthma Quality of Life Questionnaire; QOL = quality of life; RCT = randomized controlled trial; RR = relative risk.

Symbol use: Drug X > Drug Y = statistically significant difference in outcomes favoring Drug X; Drug X > Drug Y trend = point estimate favors Drug X, but the difference is not statistically significant or tests of statistical significance were NR; No difference = no statistically significant difference or tests of statistical significance were not reported and outcomes are similar.

Note: All results are listed in the same order as the comparison column lists the medications.

2. Inhaled Corticosteroids (ICSs) compared with Long-Acting Beta-2 Agonists (LABAs)

Summary of findings

We found 11 fair or good quality RCTs¹⁰⁵⁻¹¹⁷ that included head-to-head comparisons of one ICS with one LABA meeting our inclusion/exclusion criteria. Seven of these were multi-arm trials that compared an ICS/LABA combination product with the individual ICS and LABA components.¹⁰⁵⁻¹¹²

Overall, efficacy studies up to 12 months in duration provide consistent evidence favoring ICSs over LABAs for the treatment of asthma as monotherapy for children and adults (high strength of evidence, Table 23 Evidence Profile). Those treated with LABAs had a significantly higher occurrence of exacerbations than those treated with ICSs (SMD = 0.221, 95% CI: 0.025, 0.417; $P = 0.027$, 6 studies). The standardized average percent increase was 22.1%. Although our meta-analyses found no statistically significant difference in measures of symptoms or rescue medicine use, the majority of individual RCTs included in this review reported no differences or favorable results for those treated with ICSs compared to those treated with LABAs for almost all outcomes. Of note, LABAs are not recommended nor approved for use as monotherapy for persistent asthma.¹

Table 23. Evidence profile of the comparative efficacy of of ICSs compared with LABAs for monotherapy

Evidence Profile: Comparative efficacy of ICSs compared with LABAs for monotherapy							
Number of studies (# of subjects)	Design	Quality	Consistency	Directness	Results, magnitude of effect	Other modifying factors*	Overall strength of evidence
ICS compared with LABA for monotherapy							
11 (3356)	RCTs	Good (1) Fair (10)	Some inconsistency	Direct	LABAs had a significantly higher occurrence of exacerbations than ICSs (SMD = 0.221, 95% CI: 0.025, 0.417; $P = 0.027$, 6 studies); no statistically significant difference found in meta-analyses of other outcomes	None	High
FP compared with SM							
6 (1902)	RCTs	Fair	Some inconsistency	Direct	Fewer exacerbations with FP than SM; mixed results for other outcomes, but trials generally reported no differences or better outcomes for those treated with FP than with SM	None	High
BDP compared with SM							
3 (694)	RCTs	Fair	Some inconsistency	Direct	Mixed results, but trials generally reported no differences or better	None	High

Evidence Profile: Comparative efficacy of ICSs compared with LABAs for monotherapy							
Number of studies (# of subjects)	Design	Quality	Consistency	Directness	Results, magnitude of effect	Other modifying factors*	Overall strength of evidence
					outcomes for those treated with BDP than with SM		
TAA compared with SM							
1 (164)	RCT (16 weeks)	Good	NA	Direct	Fewer patients having exacerbations with TAA (7% compared with 20%, $P = 0.04$) and lower treatment failure rate (6% compared with 24%, $P=0.004$); no difference in symptoms, rescue use, or QOL	None	Moderate
BUD compared with FM							
1 (596)	RCT (12 weeks)	Fair	NA	Direct	Trend toward fewer symptoms, nocturnal awakenings, and exacerbations (4.6% compared with 13.8%, $P = \text{NR}$); trend toward less rescue use	None	Moderate

Abbreviations: BDP = beclomethasone dipropionate; BUD = Budesonide; CI = confidence interval; FM = Formoterol; FP = Fluticasone Propionate; ICS = Inhaled Corticosteroids; LABAs = Long-Acting Beta-2 Agonists; NR = not reported; QOL = quality of life; RCT= randomized controlled trial; SM = Salmeterol; SMD = standard mean difference; TAA = triamcinolone acetonide.

**Imprecise or sparse data; a strong or very strong association; high risk of reporting bias; dose response gradient; effect of plausible residual confounding.

The selected results are from our meta-analyses of included RCTs; the complete meta-analyses are in Appendix G.

Detailed Assessment

Description of Studies

Of the 11 trials, six (55%) compared fluticasone with salmeterol, three (27%) compared beclomethasone with salmeterol, one (9%) compared triamcinolone with salmeterol, and one (9%) compared budesonide with formoterol (Table 24). Study duration ranged from 12 weeks to 12 months. LABAs were compared with low-dose ICSs in five trials (45%) and with medium-dose ICSs in six (55%). The most commonly used delivery devices were MDIs and DPIs; six studies (55%) compared DPI to DPI; four studies (36%) compared MDI to MDI, and one study (9%) compared pMDI to DPI.

Study Populations

The 11 head-to-head RCTs included a total of 3356 subjects. Most were conducted primarily in adult populations. Two studies^{116, 117} were conducted in pediatric and adolescent populations. Seven trials (64%) were conducted in the United States, one in Canada, one in Sweden, one in the Netherlands, and one across North America. Asthma severity ranged from mild to severe persistent but was most commonly not reported: two studies (18%) were conducted in patients with mild to moderate persistent asthma, two (18%) in patients with moderate to severe persistent, and the severity was not reported in eight (73%) trials.

Smoking status was not reported for the two pediatric/adolescent trials. Among the others, eight (73%) excluded current smokers or those with a recent history of smoking and one (9%) allowed smokers and reported that 12-17% in each group were smokers.

Sponsorship

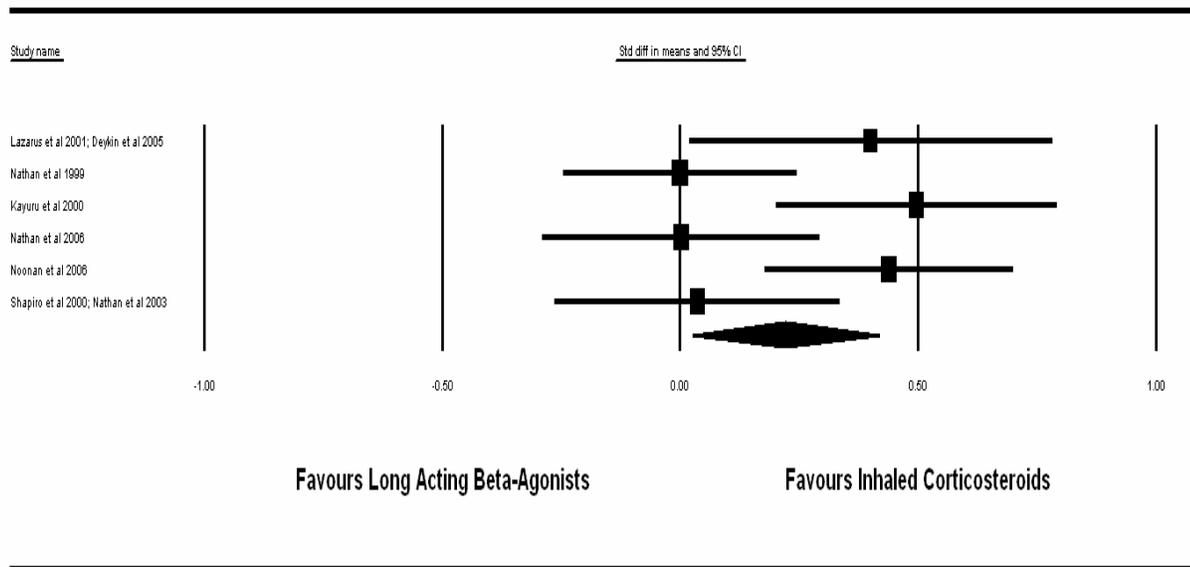
Of the 11 head-to-head trials, 10 (91%) were funded by pharmaceutical companies; only one study (9%) was funded primarily by a source other than a pharmaceutical companies.

Head-to-head comparisons

1. ICS (any) compared with LABA (any) for monotherapy

We conducted meta-analyses for five outcomes that were reported with sufficient data in multiple trials (Appendix G). These included percentage improvement in symptom-free days, change in symptom scores, exacerbations, percentage improvement in rescue-free days, and change in rescue medicine use. We found no statistically significant differences in the percentage improvement in symptom-free days (SMD = -0.069, 95% CI: -0.521, 0.383; *P* = 0.765, 6 studies), change in symptom scores (SMD = -0.140, 95% CI: -0.482, 0.203; *P* = 0.425, 5 studies), percentage improvement in rescue-free days (SMD = 0.257, 95% CI: -0.110, 0.624; *P* = 0.171, 5 studies), and change in rescue medicine use (SMD = -0.134, 95% CI: -0.687, 0.419; *P* = 0.634, 5 studies). However, we found that those treated with LABAs had a significantly higher occurrence of exacerbations than those treated with ICSs (SMD = 0.221, 95% CI: 0.025, 0.417; *P* = 0.027, 6 studies) (Figure 9). The standardized average percent increase between LABA and ICS was 22.1%.

Figure 9. Meta-analysis of exacerbations for ICSs compared with LABAs for monotherapy



2. Fluticasone (FP) compared with Salmeterol (SM)

Six fair-quality RCTs compared FP with SM for monotherapy.^{105-109, 111, 112} None included children ≤ 12 years of age. All six also included comparisons with an FP/SM combination product. Study duration was 12-weeks for five trials and 12 months for one.¹⁰⁶ Three compared SM with low-dose FP and three compared SM with medium-dose FP. Five of the six were conducted in the United States; one was conducted in Sweden.¹⁰⁶

The majority of trials assessed asthma symptoms, nocturnal awakenings, exacerbations, and rescue medicine use. One trial¹¹¹ reported quality of life. The majority of trials found no difference or a trend toward better outcomes in those treated with FP than those treated with SM (Table 24).

3. Beclomethasone (BDP) compared with Salmeterol (SM)

Three fair-quality RCTs compared BDP with SM.¹¹⁵⁻¹¹⁷ One¹¹⁵ enrolled adolescents and adults ≥ 12 years of age; the other two studies enrolled children and adolescents aged 6-14¹¹⁶ or 6-16.¹¹⁷ Study duration ranged from 26 weeks to 12 months. All three compared SM with medium-dose BDP.

All three trials reported exacerbations and rescue medicine use; two reported symptoms^{115, 117} and nocturnal awakenings;^{115, 116} one reported missed school.¹¹⁶ With the exception of one trial that reported greater improvement in the percentage of rescue-free days for those treated with SM (36% compared with 28%, $P = 0.016$),¹¹⁵ all three trials reported no differences or better outcomes for those treated with BDP than for those treated with SM (Table 24).

4. Triamcinolone (TAA) compared with Salmeterol (SM)

One good-rated 16-week multicenter RCT^{113, 114} (SOCS Trial) compared TAA with SM in 164 adolescents and adults aged 12-65. The trial reported fewer exacerbations and a lower treatment failure rate for those treated with TAA, but no statistically significant difference in symptoms, rescue medicine use, or quality of life (Table 24).

5. Budesonide (BUD) compared with Formoterol (FM)

One fair-rated 12-week multicenter RCT¹¹⁰ compared BUD with FM in 596 adolescents and adults aged ≥ 12 . The results showed trends toward fewer exacerbations and greater improvements in symptoms, nocturnal awakenings, and rescue medicine use for those treated with BUD (Table 24). Whether these trends were statistically significantly different was not reported (the study focused on comparing FM/BUD with the other treatments).

Table 24. Summary of head-to-head studies comparing ICS compared with LABA

Study	Study Design N Duration	Country Study Population Setting	Comparison (total daily dose, steroid dosing range)	Results	Quality Rating
ICS compared with LABA monotherapy					
Fluticasone (FP) compared with Salmeterol (SM)					
Kavuru et al. 2000 ¹⁰⁵	RCT, DB 356	US Age ≥ 12 yr, patients	Placebo compared with FP/SM DPI	Only data for SM compared with FP reported here*	Fair

Table 24. Summary of head-to-head studies comparing ICS compared with LABA

Study	Study Design N Duration	Country Study Population Setting	Comparison (total daily dose, steroid dosing range)	Results	Quality Rating
	12 weeks	well controlled on current therapy (stratified into 2 eligible groups: group 1 had to be on ICS for ≥3 months; group 2 was taking SM for ≥1 week), severity NR, smokers excluded Multicenter (42)	(200/100) compared with SM DPI (100) compared with FP DPI (200, low)	Symptoms: No difference [<i>symptom score, mean change from baseline</i> (SE): -0.1 (0.1) compared with -0.2 (0.09), <i>P</i> = NR; % <i>symptom-free days</i> , mean change (SE): 8.0 (3.29) compared with 7.2 (4.09), <i>P</i> = NR; Nocturnal awakenings: FP > SM trend [% of <i>nights with no awakenings</i> , mean change from baseline (SE): -5.3 (2.57) compared with 2.4 (2.34), <i>P</i> = NR] Exacerbations: FP > SM [% of <i>patients withdrawn due to worsening asthma</i> : 35 compared with 11, <i>P</i> = NR] Rescue medicine use: No difference [<i>Puffs/day</i> , mean change from baseline (SE): -0.3 (0.26) compared with -0.4 (0.21), <i>P</i> = NR]	
Lundback et al. 2006 ¹⁰⁶	RCT, DB 282 12 months	Sweden Age ≥18, mild or moderate persistent, uncontrolled on current medication (68% were on ICS), 12-17% smokers in each group Patients recruited from ~4000 individuals with asthma who had participated in large epidemiologic studies	FP/SM DPI (500/100) compared with FP DPI (500, medium) compared with SM DPI (100)	Only data for FP compared with SM reported here Symptoms: FP > SM [median % <i>symptom-free days</i> : 67.9 compared with 44.5, <i>P</i> < 0.05; median % <i>symptom-free nights</i> : 100 compared with 92.3, <i>P</i> < 0.001] Exacerbations : FP > SM [% of <i>patients with ≥ 2 exacerbations</i> : 17.4 compared with 40.0, <i>P</i> < 0.001; % of <i>patients requiring medication adjustment/ increase</i> (usually for having ≥ 2 exacerbations): 34.8 compared with 61.1, <i>P</i> < 0.001] Rescue medicine use: FP > SM [median % <i>rescue-free days</i> : 85.7 compared with 60, <i>P</i> < 0.05; median % of <i>patients with rescue-free nights</i> : 100 compared with 100]	Fair
Murray et al. 2004 ¹⁰⁷	RCT, DB 267 12 weeks	US Age ≥12yr, asthma ≥6 months, not controlled with SABAs, severity NR, smokers	SM DPI (100) compared with FP DPI (200, low) compared with FP/SM DPI (200/100)	Only data for SM compared with FP reported here* Symptoms: No difference [<i>symptom score</i> (0-5), mean change from baseline (SE): -0.9 (0.1) compared with -0.9 (0.1), <i>P</i> = NR; % <i>symptom-</i>	Fair

Table 24. Summary of head-to-head studies comparing ICS compared with LABA

Study	Study Design N Duration	Country Study Population Setting	Comparison (total daily dose, steroid dosing range)	Results	Quality Rating
		excluded Multicenter (33 sites)		<i>free days</i> , mean change (SE) from baseline: 25.6 (3.9) compared with 24.6 (4.1); <i>P</i> = NR] Nocturnal awakenings: SM > FP trend [<i>% nights with none</i> , mean change from baseline (SE): 26.4 (3.4) compared with 21.1 (3.2); <i>P</i> = NR] Rescue medicine use: SM > FP trend [<i>puffs/day</i> , mean change from baseline (SE): -2.6 (0.28) compared with -1.8 (0.23)]	
Nathan et al. 2006 ¹⁰⁸	RCT, DB 365 12 weeks	US Age ≥12yr, not controlled on ICS, severity NR, smokers excluded Multicenter (45)	FP/SM MDI (440/84) vs. FP MDI (440, medium) vs. SM MDI (84) vs. placebo	Only data for FP compared with SM reported here* Symptoms: No difference [<i>symptom score(0-5)</i> , mean change (SE): -0.2 (0.09) compared with -0.3 (0.12), <i>P</i> = NR; <i>% symptom-free days</i> , mean change (SE): 15.0 (3.3) compared with 14.0 (4.1); <i>P</i> = NR] Nocturnal awakenings: No difference [<i>% nights without awakenings</i> , mean change (SE): -0.6 (2.1) compared with -0.5 (2.4), <i>P</i> = NR] Exacerbations: FP > SM trend [<i>% of patients withdrawn due to exacerbations</i> : 11 compared with 24, <i>P</i> = NR] Rescue medicine use: SM > FP trend [<i>puffs/day</i> , mean change (SE): -0.5 (0.2) compared with -0.9 (0.3), <i>P</i> = NR; <i>% of rescue-free days</i> , mean change (SE): 13.1 (3.3) compared with 23.3 (4.3); <i>P</i> = NR]	Fair
Nelson et al. 2003 ¹⁰⁹	RCT, DB 283 12 weeks	US Age ≥12, persistent asthma not controlled with SABA, severity NR, smokers excluded Multicenter (33)	FP/SM MDI (88/42) vs. FP MDI (88, low) vs. SM MDI (42)	Only data for FP compared with SM shown here Symptoms: No difference [<i>Symptom score</i> , mean change (SE) from baseline: -0.8 (0.09) compared with -0.8 (0.10), <i>P</i> = NS; <i>% symptom-free days</i> , mean change (SE): 24.9 (3.71) compared with 29.6 (4.06), <i>P</i> = NS] Nocturnal awakenings: No difference [<i>% nights with no awakenings</i> , mean change (SE): 20.5 (3.26) compared	Fair

Table 24. Summary of head-to-head studies comparing ICS compared with LABA

Study	Study Design N Duration	Country Study Population Setting	Comparison (total daily dose, steroid dosing range)	Results	Quality Rating
				with 17.2 (3.39), $P = NS$]	
				Rescue medicine use: No difference [<i>puffs/24 hour period</i> , mean change from baseline (SE): -1.8 (0.21) compared with -1.6 (0.20), $P = NS$; % <i>rescue-free days</i> , mean change (SE): 26.5 (3.74) compared with 34.3 (4.18); $P = NS$]	
Shapiro et al. 2000 ¹¹¹	RCT, DB 349	US	Placebo vs. FP/SM DPI (500/100)	Only data for SM compared with FP shown here*	Fair
AND Nathan et al. 2003 ¹¹²	12 weeks	Age ≥ 12 , previously treated with low to medium ICS, severity NR, smokers excluded Multicenter (42 Research Centers/ Allergy and Asthma Centers)	vs. SM DPI (100) vs. FP DPI (500, medium)	Symptoms: FP > SM trend [<i>Symptom Score (0-5)</i> , mean change from baseline (SEM): 0.1 (0.1) compared with -0.4 (0.09), $P = NR$; % <i>symptom-free days</i> , change from baseline (SEM): 2.1 (3.6) compared with 15.4 (4.2), $P = NR$] Nocturnal awakenings: FP > SM trend [% <i>awakening-free nights</i> , change from baseline (SEM): -8.0 (3.6) compared with 2.8 (2.4), $P =$ NR] Exacerbations: FP > SM trend [% of <i>patients having a clinical</i> <i>exacerbation</i> : 12 compared with 7, P = NR; Probability of remaining in the study without being withdrawn due to worsening asthma (survival analysis): % of <i>patients remaining</i> : 48 compared with 73, $P = NR$] Rescue medicine use: FP > SM trend [<i>puffs/day</i> , mean change from baseline (SEM): 0 (0.3) compared with -0.9 (0.2), $P = NR$] Quality of life: FP > SM trend [<i>activities limitation</i> , measured by the activities domain of the AQLQ (11 items): -0.003 (0.14) compared with 0.62 (0.10)]	
Beclomethasone (BDP) compared with Salmeterol (SM)					
Nathan et al. 1999 ¹¹⁵	RCT, DB, DD 386 26 weeks	US Age ≥ 12 yr, on SABAs only, severity NR, smokers excluded	SM MDI (84) compared with BDP MDI (336, medium) compared with placebo	Symptoms: Mixed results [% <i>symptom-free days</i> , mean change: data NR, shown in figure, BDP had greater improvement than SM or placebo, $P < 0.032$ for BDP compared with either comparison; % <i>symptom-free nights</i> , mean change:	Fair

Table 24. Summary of head-to-head studies comparing ICS compared with LABA

Study	Study Design N Duration	Country Study Population Setting	Comparison (total daily dose, steroid dosing range)	Results	Quality Rating
		Multicenter (25)		41 compared with 34 compared with 41, <i>P</i> = NS for SM compared with BDP] Nocturnal awakenings: No difference [% of nights without awakenings, mean increase: 18 vs. 17 vs. 7; <i>P</i> = NS for SM vs. BDP] Exacerbations : No apparent difference [% of patients experiencing ≥ 1 : 16-17% for all groups (exact numbers NR); <i>P</i> = NS; # exacerbations treated with oral steroids: 17 vs. 13 vs. 17; <i>P</i> = NR] Rescue medicine use: Mixed results [% of rescue free days, mean change: 36 vs. 28 vs. 16; <i>P</i> = 0.016 for SM compared with BDP; % rescue-free nights, mean increase: 23 vs. 23 vs. 9; <i>P</i> = NS for SM vs. BDP]	
Simons et al. 1997 ¹¹⁶	RCT, DB 241 12 months	Canada Age 6-14, not currently on ICS, severity NR, smoking status NR Multicenter	BDP DPI (400, medium) vs. SM DPI (100) vs. placebo	Nocturnal awakenings: No difference [% of nights: 1 vs. 1 vs. 1; <i>P</i> = NR] Exacerbations: trend favoring BDP > SM [courses of prednisone: 10 vs. 15 vs. 17; <i>P</i> = NR] Rescue medicine use: trend favoring BDP > SM [% of rescue-free days and nights: 92 vs. 88 vs. 83; <i>P</i> NR for BDP vs. SM; <i>P</i> < 0.001 for BDP vs. placebo; % of children requiring no rescue albuterol: 95 vs. 91 vs. 84; <i>P</i> = NR for BDP vs. SM; <i>P</i> = 0.03 for BDP vs. placebo] Missed school: No difference [No school missed due to asthma, % of children: 81 vs. 88 vs. 66; <i>P</i> = NS]	Fair
Verberne et al. 1997 ¹¹⁷	RCT, DB 67 52 weeks	Netherlands Age 6-16, on ICS ≥ 3 months, mild to moderate persistent asthma, smoking status NR Multicenter, Hospital pediatric outpatient clinics	SM DPI (100) vs. BDP DPI (400, medium dose)	Symptoms: BDP > SM [Daytime and nighttime symptoms: fewer symptoms BDP-treated patients; <i>P</i> significant at some time point (data NR); % of children reporting no symptoms during 2-week period at baseline and at endpoint: 3% and 36% vs. 6% and 55%, <i>P</i> = NR] Exacerbations requiring courses of steroids: BDP > SM [# of steroid	Fair

Table 24. Summary of head-to-head studies comparing ICS compared with LABA

Study	Study Design N Duration	Country Study Population Setting	Comparison (total daily dose, steroid dosing range)	Results	Quality Rating
				<p><i>courses: 17 vs. 2, P = NR; # of patients receiving a steroid course: 15 vs. 2, P = NR]</i></p> <p>Rescue med use: BDP > SM [<i>median number of inhalations per day: 0.44 vs. 0.07, P = 0.0001]</i>]</p>	
Triamcinolone (TAA) compared with Salmeterol (SM)					
Lazarus et al. 2001 ^{113, 114}	RCT, triple-blind, DD 164	North America Age 12-65, well controlled on TAA, severity NR, smokers excluded	TAA MDI (800, low) vs. SM MDI (84)	Symptoms : No difference [symptom score : data NR, shown in figure ; P = NS for TAA vs. SM]	Good
SOCS Trial	16 weeks	Multicenter, six University-based ambulatory care centers	vs. placebo	<p>Exacerbations: TAA > SM [<i>number (%) patients: 4 (7%) vs. 11(20%) vs. 16 (29%); P = 0.04 for TAA vs. SM and P = 0.003 for TAA vs. placebo]</i>]</p> <p>Rescue med use: No difference [data NR, shown in figure only; P = NS]</p> <p>Quality of Life: No difference [AQLQ – <i>overall: actual data NR, shown in figure; P = NS for TAA vs. SM; P < 0.001 for either vs. placebo]</i>]</p> <p>Treatment failure rate: TAA > SM [<i>% patients (n): 6% (3/54) vs. 24% (13/54) vs. 36%; P = 0.004 for TAA vs. SM; P < 0.001 TAA vs. placebo; P = 0.18 SM vs. placebo]</i>]</p>	
Budesonide (BUD) compared with Formoterol (FM)					
Noonan et al. 2006 ¹¹⁰	RCT; DB, DD 596 12 weeks	US Age ≥12, moderate to severe persistent asthma not controlled, on ICS for ≥4 weeks, smokers excluded Multicenter (84), respiratory or allergy specialty clinics	BUD/FM pMDI (320/9) vs. BUD pMDI (320, low) vs. FM DPI (9) vs. BUD pMDI + FM DPI (320/9) vs. placebo	<p>Only data for BUD compared with FM shown here*</p> <p>Symptoms: BUD > FM trend [<i>Daytime symptom score, mean change from baseline: -0.19 compared with -0.05, P = NR; Nighttime symptom score, mean change from baseline: -0.10 compared with -0.04, P = NR; % of symptom-free days, mean change from baseline: 9.50 compared with 2.85, P = NR]</i>]</p> <p>Nocturnal awakenings: BUD > FM trend [<i>% awakening-free nights, mean change from baseline: 15.10 compared with 9.36, P = NR]</i>]</p> <p>Exacerbations: BUD > FM trend [<i>n (%) patients with exacerbation: 5</i>]</p>	Fair

Table 24. Summary of head-to-head studies comparing ICS compared with LABA

Study	Study Design N Duration	Country Study Population Setting	Comparison (total daily dose, steroid dosing range)	Results	Quality Rating
				(4.6) compared with 17 (13.8), $P =$ NR; <i>withdrawal due to predefined event</i> , n (%) patients: 22 (20.2) compared with 44 (35.8), $P =$ NR]	
				Rescue medicine use: BUD > FM trend [<i>inhalations/day</i> , mean change from baseline: -0.78 compared with -0.26, $P =$ NR]	

Abbreviations: AQLQ = Asthma Quality of Life Questionnaire; BDP = beclomethasone dipropionate; BUD = Budesonide; DD= double dummy; DPI = dry powder inhaler; FM = Formoterol; FP = Fluticasone Propionate; ICS = Inhaled Corticosteroids; LABAs = Long-Acting Beta-2 Agonists; MA=meta-analysis; MDI = metered dose inhaler; NR = not reported; NS = not statistically significant; QOL = quality of life; RCT= randomized controlled trial; SM = Salmeterol; SR=systematic review; TAA = Triamcinolone Acetonide > Symbol use: Drug X > Drug Y = statistically significant difference in outcomes favoring Drug X; Drug X > Drug Y trend = point estimate favors Drug X, but the difference is not statistically significant or tests of statistical significance were NR; No difference = no statistically significant difference or tests of statistical significance were not reported and outcomes are similar.

*No P values reported for this comparison; study focused on comparing FP/SM or FM/BUD with the other treatments

Note: All results are listed in the same order as the comparison column lists the medications.

3. Leukotriene modifiers compared with Long-Acting Beta-2 Agonists (LABAs) for monotherapy

Summary of findings

We found two fair quality RCTs^{118, 119} that included head-to-head comparisons of one leukotriene modifier with one LABA meeting our inclusion/exclusion criteria. One trial compared montelukast with salmeterol¹¹⁸ and one compared montelukast with eformoterol.¹¹⁹

Overall, two small trials do not provide sufficient evidence to draw any firm conclusions about the comparative efficacy of leukotriene modifiers and LABAs for use as monotherapy for persistent asthma (low strength of evidence, Table 25 Evidence Profile). Of note, LABAs are not recommended nor approved for use as monotherapy for persistent asthma.¹

Table 25. Evidence profile of the comparative efficacy of leukotriene modifiers and LABAs for monotherapy

Evidence profile: Comparative efficacy of leukotriene modifiers compared with LABAs for monotherapy							
Number of studies (# of subjects)	Design	Quality	Consistency	Directness	Results, magnitude of effect	Other modifying factors*	Overall strength of evidence
Montelukast compared with salmeterol							
1 (191)	RCT (8 weeks)	Fair	NA	Direct	zero compared with one death ($P = \text{NR}$)	None	Low
Montelukast compared with eformoterol							
1 (58)	RCT; cross-over with unusual design; 12 weeks contributing to this comparison	Fair, unclear if one-week washout sufficient	NA	Direct	Those treated with eFM had fewer symptoms (% of symptom-free days: 23 compared with 0; $P = 0.01$; symptom scores: 1.2 compared with 1.6; $P = 0.02$), less rescue medicine use (% of rescue-free days: 40 compared with 30; $P = 0.008$), and better quality of life (QOL score: 0.4 compared with 0.6; $P = 0.001$)	None	Low

*Imprecise or sparse data; a strong or very strong association; high risk of reporting bias; dose response gradient; effect of plausible residual confounding.

LABAs = Long-Acting Beta-2 Agonists; NR = not reported; QOL = quality of life; RCT= randomized controlled trial.

Detailed Assessment

Description of Studies

We found two fair quality RCTs^{118,119} that included head-to-head comparisons of one leukotriene modifier with one LABA meeting our inclusion/exclusion criteria (Table 26). One 8-week trial compared montelukast with salmeterol¹¹⁸ and one 18-week trial compared montelukast with eformoterol.¹¹⁹

Study Populations

The two RCTs included a total of 249 subjects. Both were conducted primarily in adult populations. One was conducted in the United States;¹¹⁸ one was conducted in Australia.¹¹⁹ Asthma severity was not reported in one trial;¹¹⁸ patients had mild to moderate persistent asthma in the other trial.¹¹⁹ Both trials excluded current smokers or those with more than a 10 to 15 pack-year history.

Sponsorship

One trial was funded by a pharmaceutical company;¹¹⁸ one trial was funded by a combination of industry and federal government sources.¹¹⁹

Head-to-head comparisons

1. Montelukast compared with Salmeterol

One fair-rated RCT (N = 191) compared ML 10 mg/day (N = 97) compared with SM 100 mcg/day (N = 94) as monotherapy for 8 weeks.¹¹⁸ Subjects with chronic asthma and evidence of exercise-induced bronchoconstriction age 15 to 45 were enrolled from multiple centers in

the United States. The trial was designed to evaluate exercise-induced bronchoconstriction and most of the outcomes reported were intermediate outcomes that are not included in our report. The trial also reported mortality as an outcome, with no deaths in the ML group and one in the SM group ($P = \text{NR}$).

2. Montelukast compared with Eformoterol

One fair-rated cross-over RCT ($N = 58$) compared eformoterol 24 mcg/day with ML 10 mg/day (six weeks of treatment, one-week washout, six weeks of treatment with the other medication, one-week washout, then all subjects received fluticasone 500 mcg/day for six weeks).¹¹⁹ Subjects age 16 to 75 with mild to moderate persistent asthma previously treated with or without ICS were enrolled from multiple research centers in Australia. We only report results of the ML and eFM comparison because the fluticasone portion of the study does not have a comparison. Over the 12 weeks of treatment, subjects treated with eFM had fewer symptoms (percentage of symptom-free days: 23 compared with 0; $P = 0.01$; symptom scores: 1.2 compared with 1.6; $P = 0.02$), less rescue medicine use (percentage of rescue-free days: 40 compared with 30; $P = 0.008$), and better quality of life (QOL score: 0.4 compared with 0.6; $P = 0.001$) compared to those treated with ML.

Table 26. Summary of head-to-head studies comparing leukotriene modifiers compared with LABAs for monotherapy

Study	Study design N Duration	Country study population setting	Comparison (total daily dose)	Results	Quality rating
Montelukast compared with salmeterol					
Edelman et al. ¹¹⁸	RCT 191 8 weeks	United States Age 15-45, severity NR, excluded current smokers and those with ≥15 pack-year history Multicenter (17), research centers	ML (10mg) compared with SM (100 mcg)	Mortality: 0 compared with 1, <i>P</i> = NR Most reported results were intermediate outcomes evaluating exercise-induced bronchoconstriction	Fair
Montelukast compared with formoterol					
Jenkins et al. 2005 ¹¹⁹	RCT, cross-over 58 20 weeks (eFM and ML were compared for first 13 weeks, with 1 week washout in between 6 week treatment periods)	Australia Age 16-75, mild to moderate persistent asthma, excluded current smokers and those with ≥10 pack-year history Research centers	eFM DPI (24 mcg) compared with ML (10 mg) After the first 14 weeks, all subjects were treated with FP 500 mcg/day plus placebo	Symptoms: eFM > ML [% symptom free days: 23% compared with 0%; <i>P</i> = 0.01; nighttime symptom score (0-4): 0 compared with 1; <i>P</i> < 0.0001; daytime symptom scores(0-4): 1.2 compared with 1.6; <i>P</i> = 0.02] Rescue medicine use: eFM > ML [% rescue free days: 40% compared with 30%, <i>P</i> = 0.008] Quality of Life: eFM > ML [QOL score (0-4 scale with 0 being least impaired): 0.4 compared with 0.6; <i>P</i> = 0.001] Compliance: 98% for ML and NR for eFM	Fair

Abbreviations: eFM = eFormoterol; ML = Montelukast; NR = not reported; NS = not statistically significant; QOL = quality of life; SM = Salmeterol.

Symbol use: Drug X > Drug Y = statistically significant difference in outcomes favoring Drug X; Drug X > Drug Y trend = point estimate favors Drug X, but the difference is not statistically significant or tests of statistical significance were NR; No difference = no statistically significant difference or tests of statistical significance were not reported and outcomes are similar.

Note: All results are listed in the same order as the comparison column lists the medications.

B. Combination therapy

1. ICS+LABA compared with ICS (same dose) as first line therapy

Summary of findings

We found one good systematic review¹²⁰ and six fair RCTs^{107, 109, 121-124} that compared the combination of an ICS plus a LABA with an ICS alone (same dose) for first line therapy in patients with persistent asthma meeting our inclusion/exclusion criteria (Table 28). Four trials

compared fluticasone plus salmeterol with fluticasone alone and two compared budesonide plus formoterol with budesonide alone.

Overall, meta-analyses of results from large trials up to twelve months in duration found mixed results and do not provide sufficient evidence to support the use of combination therapy rather than ICS alone as first line therapy. Meta-analyses found statistically significantly greater improvements in symptoms and rescue medicine use, but no difference in exacerbations for adolescents and adults treated with ICS+LABA than for those treated with ICS alone for initial therapy (Table 27 Evidence Profile). Results were consistent for estimates in differences in symptoms between our meta-analysis and a previously published meta-analysis.¹²⁰ However, limited data was available for exacerbations and further research may change our confidence in the estimate of effect for this outcome. We found no studies for this comparison that enrolled children < 12 years of age. Of note, according to FDA labeling, ICS+LABA combination products are only indicated for patients not adequately controlled on other asthma-controller medications (e.g., low- to medium-dose inhaled corticosteroids) or whose disease severity clearly warrants initiation of treatment with two maintenance therapies.

Table 27. Evidence profile of the comparative efficacy of ICS + LABA compared with ICS alone as first line therapy

Evidence profile: Comparative efficacy of ICS + LABA compared with ICS alone as first line therapy								
Number of studies (# of subjects)	Design	Quality	Consistency	Directness	Result (magnitude of effect)	Other modifying factors	Overall strength of evidence	
Overall total: ICS + LABA compared with ICS alone as first line therapy								
1 SR (1061) 6 RCTs (2098)	1 SR w/ MA 6 RCTs	Good Fair	Some inconsistency	Direct	greater improvement in the % of symptom-free days (SMD = 0.262, 95% CI: 0.123, 0.40), symptom scores (SMD = 0.347, 95% CI: 0.174, 0.521), % rescue medicine-free days, and rescue medicine use for those treated with ICS+LABA* No difference in exacerbations (RR 1.19, 95% CI: 0.75, 1.88) **	None	Moderate	
Fluticasone + salmeterol compared with fluticasone								
4 (1062)	RCTs	Fair	Consistent	Direct	Mixed results: reported outcomes found no differences or favored FP+SM	None	Moderate	
Budesonide + formoterol compared with budesonide								
2 (1036)	RCTs	Fair	Some inconsistency	Direct	Mixed results: reported outcomes found no differences or favored BUD+FM	None	Moderate	

Abbreviations: BUD = Budesonide; CI = confidence interval; FM = Formoterol; FP = Fluticasone Propionate; ICS = Inhaled Corticosteroids; LABAs = Long-Acting Beta-2 Agonists; MA=meta-analysis; RCT= randomized controlled trial; RR = relative risk; SM = Salmeterol; SMD = standard mean difference; SR=systematic review.

*The remainder of our meta-analysis results are in Appendix G.

**This result is from a previously published meta-analysis.¹²⁰

BUD = Budesonide; CI = confidence interval; FM = Formoterol; FP = Fluticasone Propionate; ICS = Inhaled Corticosteroids; LABAs = Long-Acting Beta-2 Agonists; MA=meta-analysis; RCT= randomized controlled trial; RR = relative risk; SM = Salmeterol; SMD = standard mean difference; SR=systematic review

Detailed Assessment

Description of Studies

The systematic review¹²⁰ included eight trials with sufficient data for analysis. Three of those trials met our inclusion/exclusion criteria,^{109, 123, 124} three were excluded for wrong study design (two were < 6 weeks), and two were excluded for not reporting any of our included outcomes. We included three trials^{107, 121, 122} that were not in the systematic review (they were published after the review).

Of the six RCTs we included (Table 28), four compared fluticasone + salmeterol with fluticasone alone^{107, 109, 121, 122} and two compared budesonide + formoterol with budesonide alone.^{123, 124}

Study duration was 12 weeks for four trials, 24 weeks for one trial,¹²² and one year for one trial.¹²⁴ Five trials used low doses of ICSs and one trial used medium doses.¹²¹ In five studies all medications were delivered via DPIs; only one used MDIs.¹⁰⁹ Four studies tested the combination of a LABA and an ICS administered in a single inhaler and two used separate inhalers.^{123, 124}

Study Populations

The six head-to-head RCTs included a total of 2,098 subjects. All studies were conducted in adolescent and/or adult populations. None included children < 12 years of age. Two trials were multinational,^{121, 124} two were conducted in the United States,^{107, 109} one in Denmark,¹²² and one in Russia.¹²³ The subjects generally had mild to moderate persistent asthma, were steroid naïve, and were only taking short-acting beta-agonists prior to enrollment. Asthma severity ranged from mild to moderate persistent: one study was conducted in patients with mild asthma,¹²⁴ one in patients with mild to moderate asthma,¹²³ and one in patients with moderate asthma.¹²¹ Severity classification was not reported in three studies.^{107, 109, 122}

Two trials (33%) excluded current smokers or those with a recent history of smoking,^{107, 109} three (50%) allowed some smokers, and one (17%) did not report any information about smoking status.¹²⁴ Among those that allowed some smokers, two^{121, 123} only allowed those with less than a 10 pack-year smoking history and one¹²² reported that 32-46% of subjects in each group were current smokers.

Sponsorship

Of the six head-to-head trials, all six (100%) were funded by pharmaceutical companies.

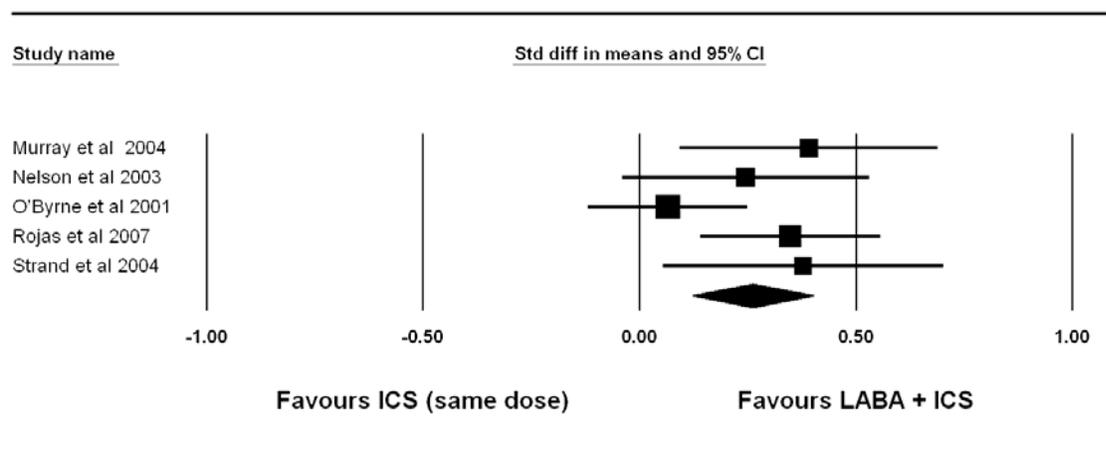
Head-to-head comparisons

1. ICS+LABA compared with ICS

The results of the six individual trials are described below under the appropriate drug comparisons. We conducted meta-analyses for outcomes that were reported with sufficient data in multiple trials (Appendix G). These included symptom-free days, symptom scores, rescue medicine-free days, and rescue medicine use (puffs/day). We found statistically significant differences favoring those treated with ICS+LABA for all four outcomes. Those treated with ICS+LABA had greater improvement in the percentage of symptom-free days (SMD = 0.262, 95% CI: 0.123, 0.40; $P < 0.001$, 5 studies) (Figure 10), greater improvement in symptom scores (SMD = 0.347, 95% CI: 0.174, 0.521; $P < 0.001$, 3 studies), greater improvement in the

percentage of rescue-free days (SMD = 0.076, 95% CI: 0.198, 0.496; $P < .001$, 3 studies), and greater reduction in rescue medicine use (SMD = 0.074, 95% CI: 0.23, 0.52 ; $P < 0.001$, four studies). For all four meta-analyses, sensitivity analyses indicate no difference in overall meta-analysis conclusions with any single study removed. In addition, there was no significant heterogeneity between studies.

Figure 10. Meta-analysis comparing improvement in the percentage of symptom-free days for ICS+LABA compared with ICS alone as first line therapy



2. Fluticasone (FP)+Salmeterol (SM) compared with Fluticasone (FP)

Four fair-quality RCTs (1,062 subjects) compared FP+SM with FP alone^{107, 109, 121, 122} (Table 28). All four compared the combination of FP and SM administered in a single inhaler with FP alone. Three of the four used low dose FP; one used medium dose FP.¹²¹ Three were 12-week trials and one was a 24-week trial.¹²² All were conducted in populations of ≥ 12 or 18 years of age.

All four trials reported outcome measures for symptoms and rescue medicine use, two trials reported nocturnal awakenings,^{107, 109} and one reported exacerbations.¹²² Three trials reported greater improvements in symptoms for those treated with FP/SM combination products than for those treated with FP alone. Just one trial found no difference in symptoms.¹⁰⁹ All four trials reported statistically significantly better outcomes for most measures of rescue medicine use (puffs/day, % of rescue-free days, % of rescue-free nights, episodes of use) for those treated with FP/SM. Just one trial reported no statistically significant difference for one of its measures of rescue medicine use, but there was a trend toward greater improvement for those treated with FP/SM (mean improvement in puffs/24 hours: -2.4 compared with -1.8).¹⁰⁹ The trials reporting nocturnal awakenings and exacerbations found no difference between groups (Table 28).

3. Budesonide (BUD)+Formoterol (FM) compared with Budesonide (BUD)

Two fair-quality RCTs (1,036 subjects) compared BUD+FM with BUD alone.^{123, 124} Both compared BUD+FM administered in separate inhalers with low-dose BUD alone. One was a

12-week Russian trial that enrolled 338 adults.¹²³ The other was a 1-year multinational trial that enrolled 1970 adolescents and adults ≥ 12 years of age.¹²⁴ The two trials reported some conflicting results. The 12-week trial reported better improvement in symptoms and rescue medicine use for subjects treated with BUD+FM, but no difference in quality of life. The 1-year trial reported no statistically significant differences between the two groups for symptoms, nocturnal awakenings, exacerbations, or rescue medicine use.

Table 28. Summary of head-to-head studies comparing ICS+LABA compared with ICS alone as first line therapy in children and adults

Study	Study design N Duration	Country Study population Setting	Comparison (total daily dose)	Results	Quality rating
ICS + LABA compared with ICS alone (same dose) as <i>first line therapy</i>					
Ni Chroinin et al. 2004 ¹²⁰	Systematic review with meta- analysis 8 RCTs with sufficient data (1061 subjects) Trial duration ranged from 4 to 52 weeks	Multinational Age ≥ 2 yr; persistent asthma, any severity; no ICS for at least 1month prior to enrollment	ICS + LABA compared with ICS alone (same dose)	Symptoms: LABA + ICS > ICS [<i>reduction in symptom score</i> : SMD (95% CI) -0.31 (-0.48, -0.13); N = 4 trials; <i>improvement in % of symptom- free days</i> : WMD (95% CI) 10.74% (1.86, 19.62); N = 3 trials] Exacerbations: No difference [# of patients with ≥ 1 exacerbation requiring systemic oral corticosteroids: RR 1.19 95% CI: 0.75, 1.88; data from 3 trials (N = 514)] Rescue medicine use: No difference [use of rescue Short-Acting Beta- Agonist [N = 5 trials; WMD (95% CI) -0.39 puffs/day (-0.88, 0.11) puff/d] Withdrawals: No difference [overall risk of withdrawals, RR (95% CI) 0.89 (0.64, 1.23); N = 6 trials; withdrawals due to poor asthma control, RR (95% CI) 1.28 (0.48, 3.42); N = 6 trials]	Good
Fluticasone + salmeterol compared with fluticasone					
Murray et al. 2004 ¹⁰⁷	RCT, DB 267 12 weeks	US Age ≥ 12 yr, uncontrolled on SABAs alone, severity NR, smokers excluded Multicenter (33 sites)	SM DPI (100) vs. FP DPI (200, low) vs. FP/SM DPI (200/100)	Only data for FP vs. FP/SM shown here Symptoms: FP/SM > FP [<i>symptom Score</i> (0-5), mean change (SE) from baseline: -0.9 (0.1) vs. -1.3 (0.1); $P \leq$ 0.01; % <i>symptom-free days</i> , mean change (SE) from baseline: 24.6 (4.1) vs. 40.6 (4.7); $P \leq 0.01$] Nocturnal awakenings: No difference (% of nights with no awakening, mean change (SE) from baseline: 21.1 (3.2) vs. 29.8 (3.7); ($P = NS$) Rescue medicine use: FP/SM > FP	Fair

Study	Study design N Duration	Country Study population Setting	Comparison (total daily dose)	Results	Quality rating
				[mean (SE) change in puffs/d: -1.8 (0.23) vs. -2.8 (0.31); $P \leq 0.01$]	
Nelson et al. 2003 ¹⁰⁹	RCT, DB 283 12 weeks	US Age ≥ 12 , uncontrolled on SABAs alone, severity NR, smokers excluded Multicenter (33)	FP/SM MDI (176/84) vs. FP MDI (176, low) vs. SM MDI (84)	Only data for FP/SM vs. FP shown here Symptoms: No difference [<i>Symptom score</i> , mean change (SE) from baseline: -1.0 (0.11) vs. -0.8 (0.09), $P = \text{NS}$; % <i>symptom-free days</i> , mean change (SE): 30.3 (4.27) vs. 24.9 (3.71), $P = \text{NS}$] Nocturnal awakenings: No difference [% nights with no awakenings, mean change (SE): 19.6 (3.15) vs. 20.5 (3.26), $P = \text{NS}$] Rescue medicine use: Mixed results [<i>puffs/24 hour period</i> , mean change from baseline (SE): -2.4 (0.31) vs. -1.8 (0.21), $P = \text{NS}$; % <i>rescue-free days</i> , mean change (SE): 40.0 (4.49) vs. 26.5 (3.74); $P = 0.028$]	Fair
Rojas et al. 2007 ¹²¹	RCT, DB 362 12 weeks	Multinational (9) Age 12-80, initiating therapy for moderate persistent asthma, symptomatic on SABAs only, allowed smokers if < 10 pack-year history Multicenter (52)	FP/SM DPI (500/100) vs. FP DPI (500, medium) FP/SM N = 182 FP N = 180	Symptoms: FP/SM > FP [median % of <i>symptom-free days</i> , baseline and during treatment: 0 and 78 vs. 0 and 61 (difference 7%, 95% CI: 1, 16; $P = 0.004$); median % of <i>symptom-free nights</i> : 0 and 91 vs. 0 and 75 (difference 5%, 95% CI: 1, 12; $P = 0.001$)] Exacerbations: [The calculated mean annual exacerbation rate was 0.1 vs. 0.2] Rescue med use: FP/SM > FP [median % of <i>rescue-free days</i> , baseline and during treatment: 0 and 91 vs. 0 and 73 (difference 6%, 95% CI: 2, 13; $P < 0.001$); median % of <i>rescue-free nights</i> , baseline and during treatment: 23 and 95 vs. 14 and 84 (difference 5%, 95% CI: 1, 11; $P < 0.001$)]	Fair
Strand et al. 2004 ¹²²	RCT, DB 150 24 weeks	Denmark Age ≥ 18 , persistent asthma for ≥ 3 months, uncontrolled with SABA only, severity NR, smokers allowed (32% of SM/FP group and 46% of FP group)	FP/SM DPI (200/100) vs. FP DPI (200, low) Steroid dose range: low	Symptoms: FP/SM > FP [Baseline and during treatment means: % <i>symptom-free days</i> : 25, 66 vs. 31, 57; $P = 0.022$; % <i>symptom-free nights</i> : 56, 83 vs. 61, 80; $P = 0.18$; <i>daytime symptom score</i> : 1.4, 0.5 vs. 1.3, 0.7, $P = 0.0047$; <i>nighttime symptom score</i> : 0.6, 0.2 vs. 0.5, 0.2; $P = 0.27$; % symptom-free 'day + night's: 20, 64 vs. 25, 51, treatment	Fair

Study	Study design N Duration	Country Study population Setting	Comparison (total daily dose)	Results	Quality rating
		Multicenter (44 general practices and 1 hospital)		<p>difference 13.2% in favor of SM/FP, $P = 0.035$ (when adjusted for baseline, $P = 0.008$)</p> <p>Exacerbations: No difference [# of patients having exacerbation during study: 1 vs. 1, $P = NS$]</p> <p>Rescue med use: FP/SM > FP [% rescue-free days (24 hours): 22, 71 vs. 25, 63, $P = 0.0497$; # of episodes of rescue-medicine use (24 hours): 2.3, 1.1 vs. 2.1, 1.3; $P = 0.14$]</p>	
Budesonide + formoterol compared with budesonide					
Chuchalin et al. 2002 ¹²³	RCT, DB, DD 338	Russia adults ≥ 18 , mild to moderate persistent asthma, allowed smokers if < 10 pack-year history	FM DPI (24) + BUD DPI (400) vs. BUD DPI (400, low) vs. "investigator's choice of non-corticosteroid treatment"	<p>Symptoms: FM + BUD > BUD [Symptom score (0-3 for each) reduction from baseline, mean (+/- 95% CI): <i>cough</i>: 0.57 (+/-0.10) vs. 0.52 (+/-0.14); <i>wheeze when resting</i>: 0.59 (+/-0.11) vs. 0.46 (+/-0.11); <i>wheeze on activity</i>: 0.72 (+/-0.12) vs. 0.58 (+/-0.13); <i>sleep disturbance</i>: 0.56 (+/-0.11) vs. 0.41 (+/-0.11); <i>problems with normal daily activities</i>: 0.57 (+/-0.12) vs. 0.39 (+/-0.12); authors state that differences in all these variables were greater for the FM + BUD group than the BUD alone group, thus unclear if $P = NR$ or $P = NS$]</p> <p>Exacerbations: Unclear if significant difference [aggravation or exacerbation of asthma or treatment not effective, # of patients reporting: 1 vs. 4; $P = NR$]</p> <p>Rescue medicine use: FM + BUD > BUD [mean improvement in puffs/day (+/-95% CI): 2.51 (+/-0.36) vs. 1.64 (+/-0.30); $P = 0.0001$]</p> <p>Quality of Life: No difference [AQLQ: Improvements the overall score and in each domain were greater in the FM + BUD group than BUD alone, except for the emotional domain, but none were statistically significantly greater ($P = NS$), data shown in figure only; SF-36: Increases in individual domain scores were greater in the FM + BUD group than BUD alone (except the physical domain), but none were statistically significantly greater ($P = NS$), data shown in figure only]</p>	Fair
And Chuchalin et al. 2002 ¹²⁵	12 weeks	pulmonology center			

Study	Study design N Duration	Country Study population Setting	Comparison (total daily dose)	Results	Quality rating
O'Byrne et al. 2001 ¹²⁴	RCT, DB 1970 (698 in group A) 1 year	Multinational: Eastern Europe, Canada, Spain Age ≥ 12, mild, uncontrolled persistent asthma, smoking status NR Multicenter (198)	Group A (N = 698 ICS-free, had used no ICS for ≥ 3 months): Placebo vs. BUD (200, low) vs. FM (9) + BUD (200)	Only data for Group A shown here (Group B was not ICS naïve) Symptoms: No difference (% of days with symptoms, adjusted mean: Group A: 29.4 vs. 23.1 vs. 21.5; <i>P</i> = 0.48 for BUD vs. FM + BUD) Nocturnal awakenings: No difference (% nights with awakenings, adjusted mean: Group A: 7.0 vs. 2.5 vs. 3.1; <i>P</i> = 0.52 for BUD vs. FM + BUD) Exacerbations: No difference (yearly rate severe exacerbations, adjusted mean: Group A: 0.77 vs. 0.29 vs. 0.34; <i>P</i> = 0.50 for BUD vs. FM + BUD) Rescue medicine use: No difference (# rescue inhalations per day, adjusted mean: Group A: 0.75 vs. 0.51 vs. 0.51; D2 vs. D3 <i>P</i> = 0.97)	Fair

Abbreviations: AQLQ = Asthma Quality of Life Questionnaire; BUD = Budesonide; CI = confidence interval; DB = double-blind DPI = dry powder inhaler; FM = Formoterol; FP = Fluticasone Propionate; ICS = Inhaled Corticosteroids; LABAs = Long-Acting Beta-2 Agonists; MA=meta-analysis; MDI = metered dose inhaler; NR = not reported; NS = not statistically significant; QOL = quality of life; RCT= randomized controlled trial; RR = relative risk; SM = Salmeterol; SR=systematic review; WMD = weighted mean difference.

Symbol use: Drug X > Drug Y = statistically significant difference in outcomes favoring Drug X; Drug X > Drug Y trend = point estimate favors Drug X, but the difference is not statistically significant or tests of statistical significance were NR; No difference = no statistically significant difference or tests of statistical significance were not reported and outcomes are similar.

*The data is only reported for comparisons relevant to this section.

Note: All results are listed in the same order as the comparison column lists the medications.

2. ICS+LABA compared with higher dose ICS (addition of LABA to ICS compared with increasing the dose of ICS)

Summary of findings

We found two systematic reviews with meta-analysis^{126, 127} and 27 RCTs^{48, 76, 78, 99, 124, 128-152} that included head-to-head comparisons between an ICS+LABA with a higher dose ICS meeting our inclusion/exclusion criteria (Table 30). These trials compared the addition of a LABA to an ICS with increasing the dose of the ICS. Fifteen of the 27 (56%) administered the ICS and LABA in a single inhaler and twelve (44%) administered the ICS and LABA in separate inhalers. Although four trials^{76, 78, 99, 144} included children, just one enrolled an exclusively pediatric population under 12 years of age.⁷⁶

Overall, results from large trials up to twelve months in duration support greater efficacy with the addition of a LABA to an ICS than with a higher dose ICS for adults and adolescents with persistent asthma (high strength of evidence, Table 29 Evidence Profile). Our

meta-analysis shows statistically significantly greater improvement in symptom-free days (SMD = 0.177, 95% CI: 0.130, 0.224), symptom scores (SMD = 0.158, 95% CI: 0.048, 0.268), rescue-free days (SMD = 0.186, 95% CI: 0.115, 0.256), and rescue medicine use (SMD = 0.201, 95% CI: 0.151, 0.250) for subjects treated with ICS+LABA. Despite a trend toward fewer subjects with exacerbations in the ICS+LABA group, the difference was not statistically significant in our analysis (SMD = -0.039, 95% CI: -0.091, 0.013; $P = 0.147$, 17 studies contributing 18 comparisons). Just one trial exclusively enrolled children under 12 (four included some subjects < 12) and results are not necessarily generalizable to pediatric populations.

Table 29. Evidence profile of the comparative efficacy of ICS + LABA compared with higher dose ICS

Evidence profile: Comparative efficacy of ICS + LABA compared with higher dose of ICS							
Number of studies (# of subjects*)	Study design (# using 1 inhaler for ICS+ LABA**)	Quality	Consistency	Directness	Result, magnitude of effect*	Other modifying factors	Overall strength of evidence
Overall total: ICS + LABA compared with higher dose of ICS							
27 ¹ (13,734)	27 RCTs	Good (1) Fair (26)	Some inconsistency	Direct	ICS+LABA had greater improvement in the percentage of symptom-free days (SMD = 0.177, 95% CI: 0.130, 0.224), symptom scores (SMD = 0.158, 95% CI: 0.048, 0.268), rescue-free days (SMD = 0.186, 95% CI: 0.115, 0.256), rescue medicine use (SMD = 0.201, 95% CI: 0.151, 0.250) No statistically significant difference in the percentage of subjects with exacerbations, but trend favors those treated with ICS+LABA (SMD = -0.039, 95% CI: -0.091, 0.013)	None	High
ICS + LABA compared with higher dose of ICS (previously published meta-analyses)							
1 (9,509)	1 SR w/ MA	Good	Some inconsistency	Direct	ICS+LABA > ICS for some symptoms measures**: <i>improvement in symptom-free days</i> : WMD =11.90%, 95% CI: 7.37, 16.44; N = 8 No statistically significant difference in exacerbations requiring OCS**: RR 0.88, 95% CI: 0.77, 1.02, N = 15 Rescue medicine use**: ICS+LABA > ICS for some outcome measures Quality of life**: No difference [change from baseline in AQLQ score: N = 25, WMD=0.18 (95%	None	High

Evidence profile: Comparative efficacy of ICS + LABA compared with higher dose of ICS							
Number of studies (# of subjects*)	Study design (# using 1 inhaler for ICS+ LABA**)	Quality	Consistency	Directness	Result, magnitude of effect* CI: [-0.14, 0.51]]	Other modifying factors	Overall strength of evidence
1 (5,680)	1 SR w/ MA	Good	Some inconsistency	Direct	Fewer exacerbations with ICS+LABA: RR 0.86; 95% CI: 0.76, 0.96; 10 studies]***		Moderate
FP+SM compared with FP							
10 (4,025)	RCTs (7)	Fair	Some inconsistency	Direct	no difference in the percentage of subjects with exacerbations, but the point estimate favors FP+SM (SMD = -0.0922, 95% CI: -0.1946, 0.0102)		High
meta-analyses for symptom-free days, symptom scores, rescue-free days, and rescue medicine use show a trend toward results similar to those in the overall meta-analysis for ICS+LABA compared with higher dose ICS							
BUD+FM compared with BUD							
6 (5,752)	RCTs (4)	Fair	Some inconsistency	Direct	Meta-analyses shows trends consistent with the overall ICS+LABA compared with higher dose ICS meta-analyses		High
BDP+SM compared with BDP							
6 (2,574)	RCTs (0)	Fair	Some inconsistency	Direct	greater reduction in rescue medicine use (SMD = 0.179, 95% CI: 0.048) and trend toward greater improvement in the percentage of symptom-free days with BDP+SM	None	High
No difference in exacerbations (SMD = -0.0185, 95% CI: -0.095, 0.058)							
BDP+FM compared with BDP							
2 (337)	RCT (1)	Fair	Consistent	Direct	Better symptom and rescue medicine use outcomes for BDP+FM in both trials; one also found a trend toward fewer exacerbations with BDP+FM	None	Moderate
FP+SM compared with BUD							
2 (702)	RCTs (2)	Fair (1) Good (1)	Some inconsistency	Direct	Mixed results between studies; No difference in exacerbations for both; other outcomes show no difference or favor FP+SM	None	Moderate
BUD+FM compared with FP							
1 (344)	RCT (1)	Fair	NA	Direct	no difference in symptoms or nocturnal awakenings, but fewer exacerbations and less rescue medicine for BUD+FM	None	Moderate
FP+SM compared with TAA							
1 (680)	RCT (0)	Fair	NA	Direct	greater improvement in symptoms, nocturnal awakenings, and rescue	None	Moderate

Evidence profile: Comparative efficacy of ICS + LABA compared with higher dose of ICS

Number of studies (# of subjects*)	Study design (# using 1 inhaler for ICS+ LABA**)	Quality	Consistency	Directness	Result, magnitude of effect* medicine use for FP+SM	Other modifying factors	Overall strength of evidence
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Abbreviations: AQLQ = Asthma Quality of Life Questionnaire; BDP = beclomethasone dipropionate; BUD = Budesonide; CI = confidence interval; FP = Fluticasone Propionate; ICS = Inhaled Corticosteroids; LABAs = Long-Acting Beta-2 Agonists; MA=meta-analysis; OCS = oral corticosteroids; QOL = quality of life; RCT= randomized controlled trial; RR = relative risk; SM = Salmeterol; SMD = standard mean difference; SR=systematic review; TAA = Triamcinolone Acetonide; WMD = weighted mean difference.

* This is the total number of asthma subjects randomized in the trial. Some subjects may have received other treatments as several trials had multiple treatment arms.

** This is the number of trials that administered the ICS/LABA in 1 inhaler for this comparison.

▲ This includes the selected results of meta-analyses presented; see Appendix G and text for complete results.

▲▲ These are selected results from a previously published meta-analysis; ¹²⁶ see Table 30 below for more complete results.

▲▲▲ These results are from a previously published meta-analysis. ¹²⁷

† The total number # of studies and subjects are less than the sum of the trials and subjects for each comparison because some trials included multiple comparisons.

Detailed Assessment

Description of Studies

One large systematic review with meta-analysis¹²⁶ (N = 9,509 subjects) compared the addition of any LABA to any ICS (ICS+LABA) with increasing the ICS dose. The review included 30 trials (3 of them in pediatric populations). Twenty-one of those trials met our inclusion/exclusion criteria. We included six additional trials^{76, 78, 99, 128, 133, 134} that were not in the systematic review (they were published after the review).

Of the 27 RCTs we included (Table 30), 10 (37%) compared fluticasone + salmeterol compared with fluticasone; six (22%) compared budesonide + formoterol compared with budesonide, six (22%) compared beclomethasone + salmeterol compared with beclomethasone, two (7%) compared beclomethasone + formoterol compared with beclomethasone, two (7%) compared fluticasone + salmeterol compared with budesonide, one (4%) compared budesonide + formoterol compared with fluticasone, and one (4%) compared fluticasone + salmeterol compared with triamcinolone (the total number of comparisons, 28, does not equal the number of trials because one trial contributed comparisons to both FP+SM compared with FP and to FP+SM compared with TAA).⁴⁸

Study duration ranged from 12 weeks (11 trials, 41%) to 12 months (six trials, 22%). The most commonly used delivery devices were DPIs: 18 studies (67%) delivered all medicines via DPIs, seven studies (26%) delivered all via MDIs, and two studies (7%) used MDIs for the ICSs in both groups and DPIs for the LABAs.^{140, 148} Fifteen of the 27 (56%) administered the ICS and LABA in a single inhaler and twelve (44%) administered the ICS and LABA in separate inhalers.

Study Populations

The 27 head-to-head RCTs included a total of 13,734 subjects (Table 30). Most were conducted primarily in adult populations. Four studies (15%) included pediatric populations under 12 years of age.^{76, 78, 99, 144} Fourteen trials (52%) were multinational, six (22%) were conducted in the United States, three in the Netherlands, and one each in Germany, Greece, Australia, and the United Kingdom.

Asthma severity ranged from mild to severe persistent: two studies (7%) were conducted in patients with mild persistent asthma, six (22%) in patients with mild to moderate persistent asthma, four (15%) in patients with moderate persistent asthma, three (11%) in patients with moderate to severe persistent, and the severity was not reported in 12 (44%) trials. Smoking status was not reported for 10 trials (37%). Nine (33%) excluded current smokers or those with greater than a 10 pack-year history. Eight (30%) allowed active smokers and reported that between five and 33% of subjects were active smokers

Almost all trials required use of ICS prior to randomization for all subjects. There were two exceptions: one trial enrolled previously steroid naïve patients that achieved good control on FP/SM¹²⁸ and one trial enrolled patients that were uncontrolled on previous therapy (80% had been on ICS).¹⁵¹ The vast majority enrolled subjects that were not controlled on ICS therapy. Just four trials enrolled subjects that were described as controlled on ICS therapy.^{99, 130, 133, 144}

Sponsorship

Of the 27 head-to-head trials, 25 (92%) were funded by pharmaceutical companies; one trial (4%) did not report the source of funding but at least one author had a primary affiliation with a pharmaceutical company. Only one study (4%) was funded primarily by a source other than a pharmaceutical company.

Head-to-head comparisons

1. ICS + LABA compared with higher dose ICS

Using data from the 27 head-to-head RCTs that met our inclusion criteria, we conducted meta-analyses for five outcomes that were reported with sufficient data in multiple trials (Appendix G). These included symptom-free days, symptom scores, exacerbations, rescue-free days, and rescue medicine use (puffs/day). Subjects treated with ICS+LABA had greater improvement in the percentage of symptom-free days (SMD = 0.191, 95% CI: 0.133, 0.248; $P < 0.001$, 16 studies contributing 17 comparisons) (Figure 11), greater improvement in symptom scores (SMD = 0.176, 95% CI: 0.066, 0.287; $P = 0.002$, 10 studies contributing 11 comparisons), greater improvement in the percentage of rescue-free days (SMD = 0.214, 95% CI: 0.114, 0.301; $P < 0.001$, 9 studies contributing 10 comparisons), and greater reduction in rescue medicine use (SMD = 0.196, 95% CI: 0.138, 0.253; $P < 0.001$, 15 studies contributing 16 comparisons) than those treated with a higher dose ICS alone. However, there was no statistically significant difference in the percentage of subjects with exacerbations, but the point estimate favors those treated with ICS+LABA (SMD = -0.042, 95% CI: -0.095, .010; $P = 0.111$, 18 studies contributing 19 comparisons) (Figure 12). For all five meta-analyses, sensitivity analyses indicate no difference in overall meta-analysis conclusions with any single study removed. There was no significant heterogeneity between studies for these outcomes (Appendix G). Additional sensitivity analyses removing all five studies enrolling subjects that were well controlled on current therapy^{99, 128, 130, 133, 144} found no difference in overall meta-analysis conclusions (Appendix G).

Figure 11. Meta-analysis comparing improvement in the percentage of symptom-free days for ICS+LABA compared with higher dose ICS

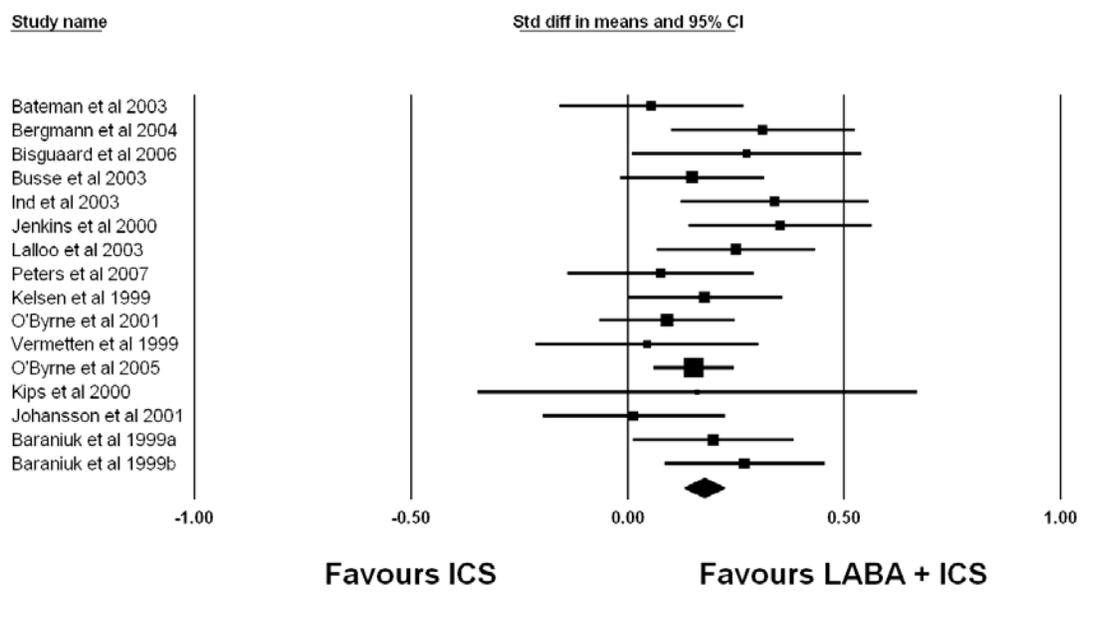
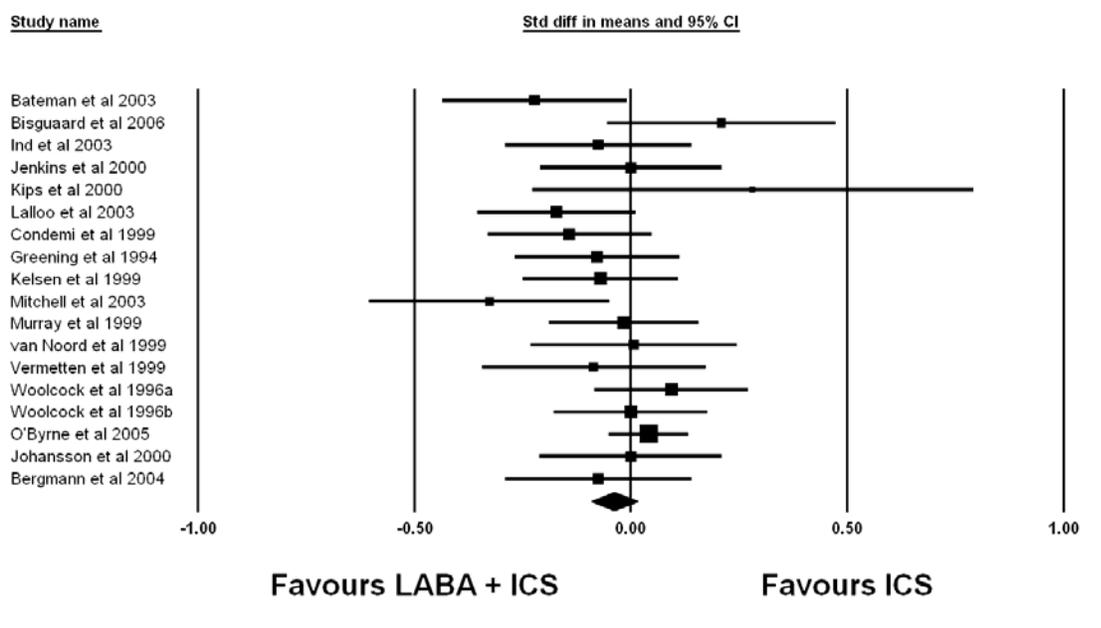


Figure 12. Meta-analysis comparing percentage of exacerbations for ICS+LABA compared with higher dose ICS



One good systematic review¹²⁶ compared the addition of any LABA to any ICS (ICS+LABA) with increasing the ICS dose (Table 30). The review included 30 trials (3 of

them in pediatric populations) that included a total of 9,509 subjects. Trial duration ranged from four to 54 weeks. Most studies ($N = 26$) were less than or equal to 24 weeks. All but one study required subjects to be taking ICS for some time prior to randomization. Eight examined ICSs+LABAs delivered via a single device and 22 tested the combination therapy delivered by separate devices. The systematic review reported no significant difference between groups for the primary outcome, the rate of patients with exacerbations requiring systemic corticosteroids (RR 0.88, 95% CI: 0.77, 1.02, $N = 15$). They also reported no significant difference in nocturnal awakenings, quality of life, and some measures of symptoms (daytime symptoms at endpoint, nighttime symptoms, % of symptom-free nights at endpoint, and nighttime awakenings) and rescue medicine use (number of daytime rescue inhalations, nighttime rescue inhalations, % overall rescue-free days, or change in nighttime inhalations). However, they reported more favorable results for some measures of symptoms (daytime symptom score, overall 24 hour symptom score, % symptom-free days at endpoint), rescue medicine use (change in daytime rescue inhalations, rescue inhalations over 24 hours), and withdrawals for those treated with ICSs+LABAs (Table 30).

Another good systematic review with meta-analysis¹²⁷ compared the impact of numerous asthma therapies on exacerbations. They found that combination therapy with ICSs+LABAs was associated with fewer exacerbations than was increasing the dose of ICSs (RR 0.86; 95% CI: 0.76, 0.96; $P = 0.65$ for heterogeneity; 10 studies) (Table 30).

2. Fluticasone (FP) + Salmeterol (SM) compared with Fluticasone (FP)

Ten fair-quality RCTs (4,025 subjects) compared FP+SM with a higher dose of FP^{48, 99, 128-135} (Table 30). Seven administered FP+SM in a single inhaler device^{99, 128-130, 132-134} and three tested the combination delivered by separate inhalers. Only one study⁹⁹ included any children ≤ 12 years of age. Study duration was 12 weeks for five trials, 16 weeks for one trial, and 24 weeks for four trials.

The majority of trials assessed asthma symptoms (all 10 trials) and rescue medicine use (nine trials). Five trials also reported exacerbations and two reported quality of life. For these outcomes, all 10 trials either reported no difference or outcomes favoring FP+SM combination therapy over the increased dose of FP. No trial reported a statistically significant difference in favor of FP alone for any of these outcomes. For subjects treated with FP+SM compared to those treated with FP alone, six trials reported fewer symptoms or better improvement in symptoms,^{128, 129, 131, 132, 134, 135} seven trials reported a greater decrease or less frequent use of rescue medicine,^{48, 128-132, 135} one trial reported a trend toward fewer exacerbations,¹²⁹ and one trial reported greater improvement in nocturnal awakenings.¹³¹ The two trials reporting quality of life found no statistically significant difference in overall quality of life measures^{99, 134} (Table 30).

Meta-analyses of these 10 trials shows no statistically significant difference in the percentage of subjects with exacerbations, but the point estimate favors those treated with FP+SM (SMD = -0.0922, 95% CI: -0.1946, 0.0102; $P = 0.0776$, 5 studies). Sensitivity analyses indicate that removing one study¹³⁵ would have resulted in a statistically significant difference in favor of FP+SM ($P = 0.0473$). There was no significant heterogeneity between studies ($P = 0.770$). Additional meta-analyses for symptom-free days, symptom scores, rescue-free days, and rescue medicine use are presented in Appendix G. These results show a trend toward results similar to those in the overall meta-analysis for ICS+LABA compared with higher dose ICS.

3. Budesonide (BUD) + Formoterol (FM) compared with Budesonide (BUD)

Six fair quality RCTs (5,752 subjects) compared BUD+FM with a higher dose of BUD^{76, 78, 124, 136-139} (Table 30). Four administered BUD+FM in a single inhaler device^{76, 78, 136, 137} and two tested the combination delivered by separate inhalers. Two of the trials^{76, 78} included children ≤ 12 years of age. One enrolled children with mild to moderate persistent asthma between the ages of four and 11.⁷⁶ The other enrolled subjects with moderate persistent asthma between the ages of four and 80.⁷⁸ Study duration was 12 months for five trials and 12 weeks for one trial.¹³⁷

All trials assessed asthma symptoms, exacerbations, and rescue medicine use. Four trials also reported nocturnal awakenings. For these outcomes, the majority of trials reported no difference or outcomes favoring BUD+FM combination therapy. For subjects treated with BUD+FM compared to those treated with BUD alone, four of six trials reported fewer symptoms or better improvement in symptoms,^{76, 78, 137-139} one trial (of five reporting) found greater reduction in nocturnal awakenings,¹³⁷ and three trials reported a greater decrease or less frequent use of rescue medicine.^{78, 137-139} Four trials found no difference in exacerbations.^{76, 78, 136, 137} The remainder of trials reported no difference for these outcomes except for one trial reporting a trend toward fewer exacerbations in subjects treated with the increased dose of BUD than those treated with BUD+FM^{138, 139} (Table 30).

Meta-analyses of these six trials found trends consistent with the overall ICS+LABA compared with higher dose ICS meta-analyses. Subjects treated with BUD+FM had greater improvement in the percentage of symptom-free days (SMD = 0.164, 95% CI: 0.094, 0.233 ; $P < 0.001$, 5 studies), greater improvement in symptom scores (SMD = 0.176, 95% CI: 0.283, 0.070; $P = 0.001$, 2 studies), greater improvement in the percentage of rescue-free days (SMD = 0.149, 95% CI: 0.063, 0.235; $P = 0.01$, 2 studies), and greater reduction in rescue medicine use (SMD = 0.153, 95% CI: 0.037, 0.269; $P < 0.01$, 5 studies) than those treated with a higher dose BUD alone. There was no statistically significant difference in the percentage of subjects with exacerbations (SMD = 0.063, 95% CI: -0.248, 0.375; $P = 0.69$, 4 studies) (Appendix G).

4. Beclomethasone (BDP) + Salmeterol (SM) compared with Beclomethasone (BDP)

Six fair quality RCTs (2,574 subjects) compared BDP+SM with a higher dose of BDP¹⁴⁰⁻¹⁴⁶ (Table 30). All six administered BDP+SM in separate inhalers. One trial¹⁴⁴ enrolled children and adolescents between the ages of four and 18. The remainder were conducted in populations ≥ 12 years of age. Study duration was 12 weeks for one trial,¹⁴⁵ 21-24 weeks for four,^{140-143, 146} and one year for one.¹⁴⁴

All trials assessed asthma symptoms, exacerbations, and rescue medicine use. Four trials also reported nocturnal awakenings and two reported quality of life outcomes. For each of these outcomes, the majority of trials reported no difference or outcomes favoring BDP+SM combination therapy; none reported a statistically significantly greater improvement for those treated with BDP alone. For symptoms, three trials reported no difference^{140, 141, 144, 145} and three found results favoring BDP+SM.^{142, 143, 146} For nocturnal awakenings, one trial reported no difference¹⁴³ and three found results favoring BDP+SM.^{140-142, 146} For exacerbations, five trials reported no difference^{140-143, 145, 146} and one reported a trend toward fewer exacerbations requiring steroids for those treated with BDP alone.¹⁴⁴ All but one trial^{140, 141} reported a greater decrease or less frequent use of rescue medicine for those treated with BDP+SM than for those treated with BDP alone. The two trials reporting quality of life found no significant difference between the groups^{140, 141, 145} (Table 30).

Meta-analyses of these six trials showed trends consistent with the overall ICS+LABA compared with higher dose ICS meta-analyses. Subjects treated with BDP+SM had statistically significantly greater reduction in rescue medicine use (SMD = 0.179, 95% CI: 0.048, 0.31; $P < 0.007$, 4 studies; $P = 0.290$ for heterogeneity) and trended toward greater improvement in the percentage of symptom-free days (SMD = 0.136, 95% CI: -0.011, 0.282 ; $P = 0.07$, 2 studies) than those treated with a higher dose BDP alone. There was no statistically significant difference in the percentage of subjects with exacerbations (SMD = -0.0185, 95% CI: -0.095, 0.058; $P = 0.64$, 5 studies contributing 6 comparisons; $P = 0.768$ for heterogeneity) (Appendix G).

5. *Beclomethasone (BDP) + Formoterol (FM) compared with Beclomethasone (BDP)*

Two fair RCTs (337 subjects) meeting our inclusion/exclusion criteria compared BDP+FM with a higher dose of BDP alone.^{147, 148} Both enrolled adults ≥ 18 that were not controlled on ICSs. One compared BDP+FM in a single inhaler device¹⁴⁷ and one tested the combination delivered by separate inhalers.¹⁴⁸ Both reported statistically significantly better symptom and rescue medicine use outcomes for subjects treated with BDP+FM than those treated with FM alone (Table 30). One also found a trend toward fewer exacerbations in those treated with BDP+FM (number (%) experiencing at least one exacerbation: 34 (34) compared with 51 (51), $P = \text{NR}$).¹⁴⁸

6. *Fluticasone (FP) + Salmeterol (SM) compared with Budesonide (BUD)*

One good 12-week RCT (N = 349)¹⁵¹ and one fair 24-week RCT (N = 353)^{149, 150} meeting our inclusion/exclusion criteria compared FP+SM with a higher relative dose of BUD alone. The 12-week trial compared FP/SM (200/100) with BUD (800) and the 24-week trial compared FP/SM (500/100) with BUD (1600). Both were multinational trials that enrolled subjects ≥ 12 years of age. Both administered FP/SM in a single inhaler device. The two trials reported some conflicting results. The 12-week trial found no statistically significant difference between treatment groups in symptoms, exacerbations, or rescue medicine use. The 24-week trial reported fewer symptoms, less rescue medicine use, and greater improvement in quality of life for those treated with FP+SM than those treated with BUD alone, but no significant difference in exacerbations (Table 30).

7. *Budesonide (BUD) + Formoterol (FM) compared with Fluticasone (FP)*

One 12-week fair RCT meeting our inclusion/exclusion criteria compared BUD+FM in a single inhaler with a higher relative dose of FP alone in 344 adults with moderate persistent asthma.¹⁵² The trial reported no statistically significant difference in symptoms or nocturnal awakenings. But, those treated with BUD+FM had fewer exacerbations and required less rescue medicine compared to those treated with FP alone (Table 30).

8. *Fluticasone (FP) + Salmeterol (SM) compared with Triamcinolone (TAA)*

We found one fair RCT meeting our inclusion/exclusion criteria that compared FP+SM (in separate inhalers) with a higher relative dose of TAA alone.⁴⁸ This trial is also included above in this section for the FP+SM compared with FP comparison because there was an FP-only arm as well. It enrolled 680 adults and adolescents ≥ 12 years of age with persistent asthma not adequately controlled on ICS. They reported greater improvement in symptoms, nocturnal

awakenings, and rescue medicine use for those treated with FP+SM than for those treated with TAA alone (Table 30).

Table 30. Summary of head-to-head studies comparing ICS+LABA compared with higher dose ICS

Study	Study design N Duration	Country Study population Setting	Comparison (total daily dose)	Results	Quality rating
ICS+LABA (in one or separate inhalers) compared with higher dose ICS					
Greenstone et al. ¹²⁶	Systematic review with meta-analysis 9509 adults and children (3 pediatric and 27 adult studies) duration ≤ 24wk in 26 studies	Multinational adults and children with asthma	ICS+LABA compared with higher dose of ICS	<p>Symptoms: ICS+LABA > ICS for some outcomes [<i>change in daytime symptom score</i>: N = 4, SMD -0.19 (95% CI: -0.30, -0.09)]; <i>change in overall (24 hour) symptom score</i>: N = 5, SMD = -0.23 (95% CI: -0.41, -0.05); <i>improvement in symptom-free days</i> (N = 8, WMD (95% CI) = 11.90% (7.37, 16.44)); % of <i>symptom-free days</i>: N = 5, WMD (95% CI) = 5.22% (-1.58, 12.02); % of <i>symptom-free nights</i>: N = 2, WMD (95% CI) = -2.10% (-7.98, 3.79)]</p> <p>Nocturnal awakenings: No difference [change from baseline in nighttime awakenings: N = 4, SMD (95% CI) = 0.01 (-0.08, 0.10)]</p> <p>Exacerbations: No difference [exacerbations requiring OCS (<i>primary outcome</i>): RR 0.88 (95% CI: 0.77, 1.02), N = 15; exacerbations requiring hospitalization RR 0.73 (95% CI: 0.36, 1.49), N = 11]</p> <p>Rescue medicine use: ICS+LABA > ICS for some outcomes [<i>change in daytime puffs/day</i>: N = 4, WMD (95% CI) = -0.99 (-1.41, -0.58)]; <i>improvement in puffs/24 hours</i>: N = 8, SMD = -0.22 (95% CI: -0.29, -0.14); % of <i>rescue-free days</i>: N = 2, WMD = 5.14% (95% CI: -2.79, 13.08)]</p> <p>Quality of life: No difference [change from baseline in AQLQ score: N = 25, WMD = 0.18 (95% CI: -0.14, 0.51)]</p> <p>Withdrawals: ICS+LABA > ICS [withdrawals due to poor asthma control: N = 20, RR (95% CI) = 0.69 (0.52, 0.93); withdrawals overall: N = 23, RR (95% CI) = 0.92 (0.82, 1.03)]</p>	Good
Sin et al. ¹²⁷	Systematic review with meta-	Multinational	ICS+LABA compared with	Exacerbations: ICS+LABA > higher dose ICS [RR 0.86; 95% CI: 0.76,	Good

Table 30. Summary of head-to-head studies comparing ICS+LABA compared with higher dose ICS

Study	Study design N Duration	Country Study population Setting	Comparison (total daily dose)	Results	Quality rating
	analysis N = 5680 for ICS+LABA compared with higher dose ICS	Adults with asthma	Higher dose ICS	0.96; <i>P</i> = 0.65 for heterogeneity; 10 studies]	
Fluticasone + salmeterol compared with fluticasone					
Baraniuk et al. 1999 ⁴⁸	RCT, DB, triple- dummy 680 12 weeks	US Age ≥ 12, uncontrolled with low-dose ICS, severity NR, smokers excluded Pulmonary/allergy medicine clinics (50)	FP MDI (196) + SM (84) compared with FP MDI (440) compared with TAA MDI (1200) (steroid dosing ranges: low, medium, medium)	Only data for FP+SM compared with FP shown here Symptoms: No difference [<i>Mean change in overall symptom score (SEM): -0.44 (0.05) compared with - 0.46 (0.05); P = NS; % symptom free days, change from baseline (SEM): 29.2 (2.9) compared with 22.6 (2.6); P = NS]</i> Nocturnal awakenings: No difference [<i>mean change from baseline (SEM): -0.31 (0.04) compared with -0.32 (0.04); P = NS]</i> Rescue medicine use: SM + FP > FP [<i>mean change from baseline, puffs/d (SEM): -2.9 (0.2) compared with -2.4 (0.2); P ≤ 0.033; % rescue free days, mean change from baseline (SEM): 45.0 (2.9) compared with 28.9 (2.7); P ≤ 0.033]</i>	Fair
Bateman et al. 2006 ¹²⁸	RCT, DB 484 12 weeks	Multinational Age 12 to 80, previously steroid naïve patients that achieved good control on FP/SM (500/100), smokers excluded Multicenter	FP/SM (200/100) compared with FP (500) All delivery devices=DPIs	Symptoms: FP/SM > FP [<i>daytime symptom score, adjusted mean change from baseline (SE): 0.03 (0.02) compared with 0.09 (0.02), P = 0.042; nighttime symptom score adjusted mean change from baseline (SE): 0.05 (0.01) compared with 0.06 (0.01), P = 0.348; number (%) of patients with 100% symptom- free days and nights: 139 (57) and 179 (74) compared with 108 (46) and 140 (60), P = 0.004 and 0.001]</i> Rescue med use: FP/SM > FP [<i>number of daytime uses, adjusted mean change from baseline (SE): 0.02 (0.02) compared with 0.09 (0.02), P = 0.016 Number of nighttime uses adjusted mean change from baseline (SE): 0.03 (0.02) compared with 0.07 (0.02), P = 0.065; number (%) of patients with 100% rescue-free days</i>	Fair

Table 30. Summary of head-to-head studies comparing ICS+LABA compared with higher dose ICS

Study	Study design N Duration	Country Study population Setting	Comparison (total daily dose)	Results	Quality rating
				and nights: 150 (62) and 172 (71) compared with 126 (54) and 144 (62), $P = 0.021$ and 0.019]	
Bergmann et al. 2004 ¹²⁹	RCT, DB 365 12 weeks	Germany Age 18-70, moderate persistent asthma, poorly controlled on ICS, smokers excluded Multicenter, private practice and outpatient clinics	FP/SM DPI (500/100) compared with FP DPI (1000)	Symptoms: FP/SM > FP [<i>symptom score</i> , mean change from baseline (SD): -1.5 (1.4) compared with -1.0 (1.5), adjusted difference between groups (95% CI) = -0.5 (- 0.78, -0.22), $P = 0.005$; % of <i>symptom free days</i> , mean increase: 49 (38) compared with 38 (40), adjusted difference (95% CI) = 12.6 (4.0, 20.7), $P = 0.0038$] Exacerbations: FP/SM > FP trend [Number: 1 compared with 4, $P =$ NR] Rescue medicine use: FP/SM > FP [mean change in <i>puffs per day</i> : -1.6 (1.9) compared with -1.0 (2.2), adjusted difference (95% CI) = -0.84 (-1.13, -0.37), $P = 0.0015$]	Fair
Busse et al. 2003 ¹³⁰	RCT, DB 558 24 weeks	US Age ≥ 12 , mild to moderate persistent asthma, had to be controlled on FP (500) during the third run-in, smoking status NR multicenter	FP/SM DPI (200/100) compared with FP DPI (500)	Symptoms: No difference [% of <i>symptom-free days</i> , mean change from baseline (SEM): 11.6 (3.0) compared with 6.2 (2.9), $P = 0.078$; <i>symptom score</i> : -0.22 (0.06) compared with -0.14 (0.06), $P =$ 0.137] Nocturnal awakenings: No difference [mean change from baseline in number: -0.37 (0.05) compared with - 0.43 (0.09), $P = 1.00$] Rescue medicine use: FP/SM > FP [<i>puffs/24 hours</i> , mean change from baseline to 24 weeks -0.43 (0.11) compared with -0.21 (0.07), $P =$ 0.022; % <i>rescue free days</i> , mean change from baseline: 14.9 (3.2) compared with 8.3 (2.7), $P = 0.032$]	Fair
Conдеми et al. 1999 ¹³¹	RCT, DB, DD 437 24 weeks	US age ≥ 12 , uncontrolled on ICS, severity NR, smokers excluded Multicenter (36)	FP MDI (196) +SM MDI (84) compared with FP MDI (440)	Symptoms: FP+SM > FP [<i>combined symptom score</i> , mean change from baseline (SE): -0.43 (0.04) vs. -0.26 (0.04), $P < 0.001$; <i>wheezing score</i> : - 0.40 (0.04) vs. -0.26 (0.05), $P =$ 0.015; <i>shortness of breath score</i> : - 0.52 (0.05) vs. -0.25 (0.05), $P <$ 0.001; <i>chest tightness</i> : -0.55 (0.05) vs. -0.29 (0.04), $P = 0.002$; <i>cough</i> : -	Fair

Table 30. Summary of head-to-head studies comparing ICS+LABA compared with higher dose ICS

Study	Study design N Duration	Country Study population Setting	Comparison (total daily dose)	Results	Quality rating
				<p>0.25 (0.04) vs. -0.23 (0.05), $P = 0.858$; improvement in % <i>symptom-free days</i> greater for SM + FP ($P \leq 0.014$, actual data NR)]</p> <p>Nocturnal awakenings: FP+SM > FP [<i>number of</i>, mean change (SE): -0.22 (0.03) vs. -0.11 (0.03), $P < 0.001$; % <i>awakening-free nights</i>, mean change (SE): 14.9 (1.9) vs. 10.1 (1.8), $P = 0.008$]</p> <p>Exacerbations: No difference [<i>n (%) of patients with at least one</i>: 21 (10) compared with 31 (14), $P = 0.140$; <i>n (%) of patients with more than one</i>: 4 (2) compared with 7 (3), $P = 0.377$]</p> <p>Rescue medicine use: FP+SM > FP [<i>Number of puffs/day</i>, mean change from baseline (SE): -2.51 (0.17) compared with -1.55 (0.15), $P < 0.001$]</p>	
Ind et al. 2003 ¹³²	RCT, DB, DD 502 24 weeks	Multinational (UK, Italy, Canada, Denmark, Iceland, Republic of Ireland) Age 16 to 75, moderate to severe persistent asthma, uncontrolled on ICS, 13-24% smokers in each group Multicenter (100) - Hospitals and primary care centers	FP/SM MDI (500/100) vs. FP MDI (500) vs. FP MDI (1000)	<p>Only data for FP/SM compared with FP 1000 shown here</p> <p>Symptoms: FP/SM > FP [% <i>symptom free days</i>, median change from baseline: 21 compared with 1.5, $P = 0.002$; % <i>symptom free nights</i>, median change from baseline: 15 compared with 2, $P < 0.002$]</p> <p>Exacerbations: No difference [<i>severe exacerbations/patient/year</i> 0.05 compared with 0.23, $P = NS$; <i>moderate exacerbations/patient/year</i> 0.77 compared with 0.95, $P = NS$; % <i>of patients experiencing a severe exacerbation</i>: 3 compared with 6, $P = 0.16$; % <i>of patients experiencing at least 1 moderate or severe exacerbation</i>: 27 compared with 31, $P = NS$]</p> <p>Rescue med use : FP/SM > FP [<i>rescue-free days</i>, median % of days: 53 compared with 9, $P \leq 0.001$; <i>rescue-free nights</i>, median % of nights: 90 compared with 77, $P \leq 0.001$]</p>	Fair
Jarjour et al. 2006 ¹³³	RCT, DB 88	Multinational (US, Canada, UK)	FP/SM DPI (200/100) compared with	Symptoms: No difference [<i>daily asthma symptom score (0-5)</i> , mean change from baseline (SE): -	Fair

Table 30. Summary of head-to-head studies comparing ICS+LABA compared with higher dose ICS

Study	Study design N Duration	Country Study population Setting	Comparison (total daily dose)	Results	Quality rating
	24 weeks Note: the subjects in this study were a subset of the subjects in Busse et al. 2003 ¹³⁰ and thus were not included in meta-analyses to avoid double-counting.	Age≥18, well controlled during final run-in on FP (500), excluded smokers with > 10 pack-year history Multicenter	FP DPI (500)	0.23 (0.09) compared with -0.20 (0.12), treatment difference (95% CI) 0.05 (-0.26 to 0.36), <i>P</i> = NS; % of symptom-free days, mean change from baseline (SE): 16.1 (5.1) compared with 12.1 (5.1), treatment difference (95% CI) 0.3 (-14.8 to 15.4); <i>P</i> = NS] Exacerbations: No difference [# (%) of subjects: 5 (13%) compared with 9 (19%) <i>P</i> = NS] Rescue med use: No difference, [puffs/24 hours, mean change from baseline (SE): -0.24 (0.11) compared with -0.29 (0.23), treatment difference (95% CI) -0.21 (-0.72 to 0.30), <i>P</i> = NS; % of rescue-free days, mean change from baseline (SE): 16.9 (5.8) compared with 12.0 (4.6), treatment difference (95% CI) 5.4 (-9.1 to 20.0), <i>P</i> = NS]	
Peters et al. 2007 ⁹⁹	RCT, DB 500 16 weeks	US Age ≥6, controlled on FP (200), severity NR, 10-18% were former smokers Multicenter	FP/SM (100/50) vs. FP (200, low) vs. ML (5-10) All delivery devices=DPIs	Only data for FP/SM compared with FP shown Symptoms and control: No difference [Treatment failure (primary outcome): number (%) of patients with: 33 (20.4) compared with 34 (20.2), hazard ratio (95% CI) 1.0 (0.6-1.6), <i>P</i> = 0.99; % of days symptom-free, mean (95% CI) 82.7 (78.9-86.6) compared with 85.8 (82.8-89.6), <i>P</i> = 0.48; Asthma Control Questionnaire (ACQ) Score: mean (SD) at baseline and mean (95% CI) at endpoint: 0.72 (0.38) and 0.71 (0.65-0.76) compared with 0.67 (0.38) and 0.73 (0.67-0.78), <i>P</i> = 0.58] Nocturnal awakenings: No difference [number (%) of patients reporting ≥ one: 28 (17.3) compared with 28 (16.7); <i>P</i> = 0.92] Rescue med use : No difference [% of days with use, mean (95% CI): 17.1 (12.8-21.3) compared with 18.2 (14.1-22.3) <i>P</i> = 0.69] Quality of life: No difference [Mini-AQLQ score (range 1 to 7), mean at baseline (SD) and mean	Fair

Table 30. Summary of head-to-head studies comparing ICS+LABA compared with higher dose ICS

Study	Study design N Duration	Country Study population Setting	Comparison (total daily dose)	Results	Quality rating
				(95% CI) at endpoint: <i>For patients age ≥15</i> : 5.90 (0.79) and 5.8 (5.7-6.0) compared with 5.74 (0.89) and 5.8 (5.7-5.9), <i>P</i> = 0.66; <i>For age 6-14</i> : 6.14(0.73) and 6.6 (6.4-6.8) compared with 6.48(0.57) and 6.6(6.4-6.8), <i>P</i> = 0.82; ASUI (range 0 to 1): mean at endpoint (95% CI): 0.89 (0.88-0.90) compared with 0.89 (0.88-0.90), <i>P</i> = 0.85]	
Schermer et al. 2007 ¹³⁴	RCT, DB 177 (137 with asthma and 40 with COPD, results presented separately) 12 weeks	Netherlands Age ≥12, on ICS for at least 3 months, NR whether controlled or not, severity NR, enrolled smokers (17% compared with 37%) Multi-site, patients recruited by 41 Family Practice physicians	FP/SM (200 or 500/100) compared with FP (500 or 1000, low to medium) All delivery devices=DPIs	Symptoms: FP/SM > FP [FP/SM-treated asthma patients had 1.1 more symptom-free days per week (<i>P</i> = 0.044) than FP-treated] Quality of life: No difference overall [AQLQ total and domain scores: no differences (data NR, <i>P</i> = NS) except for a difference on the symptoms domain of 0.24 points in favor of FP/SM [0.38 (SD 0.58) points compared with 0.14 (SD 0.62); <i>P</i> = 0.039] Note: majority of data reported only in figures or combining the asthma and COPD populations	Fair
van Noord et al. 1999 ¹³⁵	RCT, DB 274 12 weeks	Netherlands Age ≥18, mild or moderate persistent, uncontrolled on ICS, smoking status NR Multi-center (27)	Addition of SM compared with doubling ICS dose Low Dose: FP (200) + SM (100) vs FP (400) High Dose: FP (500) + SM (100) vs FP (1000) All given by DPI	Results presented as odds ratio for increased dose FP compared with FP+SM Symptoms: FP+SM > FP [<i>days with symptoms</i> , OR (95% CI): 1.52 (1.01, 2.28) <i>P</i> = 0.04] Exacerbations: No difference [OCS use, <i>n</i> (%) <i>patients receiving ≥1 course</i> : 16 (12) compared with 15 (11), <i>P</i> = NS] Rescue med use: FP+SM > FP [<i>daytime use</i> : OR (95% CI): 2.19 (1.42, 3.40), <i>P</i> < 0.001; <i>nighttime use</i> : OR (95% CI): 1.47 (1.04, 2.10) <i>P</i> = 0.03]	Fair
Budesonide + formoterol compared with budesonide					
Bisgaard et al. 2006 ⁷⁶	RCT, DB 341 12 months	Multinational (12) Age 4-11, mild-moderate persistent asthma, not controlled on ICS,	SMART [BUD/FM (80/4.5) +BUD/FM as needed] vs	Only data for BUD/FM (80/4.5) compared with BUD (320) shown here Symptoms: BUD/FM > BUD [mean % <i>symptom-free days</i> , 68.0	Fair

Table 30. Summary of head-to-head studies comparing ICS+LABA compared with higher dose ICS

Study	Study design N Duration	Country Study population Setting	Comparison (total daily dose)	Results	Quality rating
		smoking status NR Multicenter (41)	BUD/FM (80/4.5) compared with BUD (320, low) All given via DPI	<p>compared with 56.2, $P = 0.041$; <i>symptom score</i> (0-6): mean treatment value: 0.54 compared with 0.81, $P = 0.024$; <i>asthma control days</i>, mean %: 60.6 compared with 50.8, $P = 0.047$]</p> <p>Nocturnal awakenings: No difference [mean % of nights: 4.4 compared with 4.6, $P = 0.87$]</p> <p>Exacerbations: No difference [number (%) of patients with exacerbations : 44 (38) vs. 28 (26), $P = 0.12$; exacerbations per patient 0.76 vs. 0.48, $P = 0.073$; number (%) of patients with <i>exacerbation requiring medical intervention</i>: 36 (31) vs. 21 (20), $P = 0.098$]</p> <p>Rescue med use: No difference [mean # puffs/24 hours: 0.76 vs. 0.74, $P = 0.72$; mean daytime as needed # puffs: 0.59 vs. 0.59 $P = 0.71$; mean nighttime as needed # puffs: 0.17 vs. 0.15; $P = 0.73$; % of rescue-free days, mean: 67.5 vs. 64.0, $P = 0.39$]</p>	
Kips et al. 2000 ¹³⁶	RCT, DB 60 1 year	Multinational (Canada, UK and Belgium) Age 18-70, on ICS, controlled for at least 10 days out of the 1 month run-in, moderate, smoking status NR Multicenter (3 University clinics)	BUD/FM DPI (200/24) compared with BUD DPI (800, medium)	<p>Symptoms: No difference [% of episode-free days, mean (SEM): 41.3 (7.0) compared with 30.4 (6.0) $P = NS$; morning and evening symptom scores were lower in the BUD+FM group, but data NR and $P = NS$]</p> <p>Nocturnal awakenings: No difference [data NR, $P = NS$]</p> <p>Exacerbations: No difference [<i>mild exacerbations</i>, number and rate=n/pt/yr (SEM): 339, 18.3 (6.92) compared with 348, 14.6 (5.42), $P = NS$; <i>severe exacerbations</i>, number and rate=n/pt/yr (SEM): 8, 0.29 (0.14) compared with 12, 0.47 (0.24), $P = NS$]</p> <p>Rescue medicine use: No difference [data NR, $P = NS$]</p>	Fair
Laloo et al. 2003 ¹³⁷	RCT, DB 467	Multinational (Czech Republic, Hungary, Norway, Poland, South	BUD/FM DPI (160/9) compared with BUD DPI	Symptoms: BUD/FM > BUD [improvement in % of asthma control days: 17 compared with 10; between group difference 8% (95% CI: 3,	Fair

Table 30. Summary of head-to-head studies comparing ICS+LABA compared with higher dose ICS

Study	Study design N Duration	Country Study population Setting	Comparison (total daily dose)	Results	Quality rating
	12 weeks	Africa, United Kingdom Age \geq 18, mild to moderate, uncontrolled on ICS, smokers excluded Multicenter (51) University Hospitals	(400)	13%); $P = 0.002$; Improvement in % of symptom free days: 16 compared with 10; between group difference 6% (95% CI: 2, 11%); $P = 0.007$; symptom score, % reduction from baseline: 24 compared with 6, $P = \text{NR}$ Nocturnal awakenings: BUD/FM > BUD trend [<i>nights with awakenings</i> , % reduction from baseline: 23 compared with 14%, $P = \text{NR}$; <i>number of patients having repeated nighttime awakenings</i> : 75 compared with 105, $P = \text{NR}$] Exacerbations: No difference for severe, BUD/FM > BUD for mild [No difference in <i>time to first severe exacerbation</i> , $P = \text{NR}$; % of patients with severe exacerbations: 7 compared with 7, $P = \text{NS}$; patients in BUD group had shorter <i>time to first mild exacerbation</i> ($P = 0.02$); number (%) of patients with <i>at least one mild asthma exacerbation</i> : 110 (48) compared with 136 (57), $P = \text{NR}$] Rescue med use: BUD/FM > BUD [number of inhalations/24 hours, mean change from baseline: -0.33 compared with -0.1, $P = 0.025$]	
O'Byrne et al. 2001 ¹²⁴	RCT, DB 1970	Multinational (Eastern Europe, Canada, Spain)	Group A (used no ICS for ≥ 3 months): Placebo compared with BUD (200) compared with BUD+FM (200+9)	Only data for BUD (200)+ FM (9) compared with BUD (400) from Group B shown here Symptoms: No difference [<i>% of days with symptoms</i> , adjusted mean: 27.4 compared with 29.7; $P = 0.25$] Nocturnal awakenings: No difference [<i>% nights with awakenings</i> , adjusted mean: 5.4 compared with 6.0; $P = 0.43$]	Fair
OPTIMA trial	(698 in Group A, 1272 Group B) 1 year	Age ≥ 12 , uncontrolled, mild persistent asthma (Group A ICS naïve, Group B on ICS), smoking status NR multicenter (198)	Group B (taking ICS for ≥ 3 months): BUD (200) vs. BUD(200)	Exacerbations: FM +BUD > BUD [<i>yearly rate (#/patient/year) of severe exacerbations</i> , adjusted mean: 0.56 compared with 0.96; $P = 0.0001$; <i>risk</i>	

Table 30. Summary of head-to-head studies comparing ICS+LABA compared with higher dose ICS

Study	Study design N Duration	Country Study population Setting	Comparison (total daily dose)	Results	Quality rating
			+FM (9) vs. BUD (400, low) vs. FM + BUD (9/400) All delivery devices=DPIs	<i>of a severe exacerbation day by adding FM [RR (95% CI) 0.71 (0.52, 0.96)]; risk of a poorly controlled asthma day by adding FM [RR (95% CI) 0.81 (0.66, 0.99)], and risk of severe exacerbations when adding FM [RR (95% CI) 0.58 (0.44, 0.76), P = 0.001]</i> Rescue med use: No difference [<i># puff/day</i> , adjusted mean: 0.66 compared with 0.75, P = 0.17]	
O'Byrne et al. 2005 ⁷⁸	RCT, DB 2760 1 year	Multinational (22 countries) Age 4-80, uncontrolled on ICS, moderate persistent asthma, smoking status NR Multicenter (246 centers)	BUD/FM (160/9) (+ SABA for relief) compared with BUD/FM (160/9) (maintenance & relief) compared with BUD (320, low) Drug 1: 909 Drug 2: 925 Drug 3: 926 All delivery devices=DPIs	Only data for BUD/FM (+SABA for relief) compared with BUD shown here; mean values over 12 months of treatment Symptoms: BUD/FM > BUD [<i>daytime symptom score (0-3)</i> : 0.50 compared with 0.59, P < 0.001; <i>nighttime symptom score (0-3)</i> : 0.36 compared with 0.42, P = 0.01; <i>symptom-free days (%)</i> : 53 compared with 46, P < 0.001; <i>asthma control days (%)</i> : 44 compared with 37, P < 0.001] Nocturnal awakenings: No difference [<i>% of nights</i> : 12 compared with 12, P = 0.60] Exacerbations: No difference [<i>patients with severe exacerbations resulting in medical intervention, %</i> : 21 compared with 19, P = 0.37; <i>events/patient/year</i> : 0.40 compared with 0.35, P = 0.11] Rescue med use: BUD/FM > BUD [<i>rescue-free days</i> : 54 compared with 45, P < 0.001; <i>Inhalations/day</i> , mean: 0.84 compared with 1.03, P < 0.001; <i>Inhalations/night</i> : 0.37 compared with 0.43, P = 0.003]	Fair
Pauwels, et al. 1997 ¹³⁸ AND Juniper, et al. 1999 ¹³⁹ FACET	RCT, DB, DD 852 (470 in quality of life evaluation) 12 months	Multinational (9: Belgium, Canada, Netherlands, Israel, Italy, Luxembourg, Norway, Spain, and UK) Age 18-70, uncontrolled on ICS, severity NR,	BUD (200, low) compared with BUD (200)+ FM (24) compared with BUD (800, medium) compared with BUD (800)+	Only data for BUD (200) + FM (24) compared with BUD (800) described here (no P values reported for this comparison as study focused on comparing addition of FM to BUD compared with same dose of BUD) Symptoms: BUD+FM > BUD trend [<i>mean daytime symptom score (0-3)</i> at endpoint: 0.46 compared with	Fair

Table 30. Summary of head-to-head studies comparing ICS+LABA compared with higher dose ICS

Study	Study design N Duration	Country Study population Setting	Comparison (total daily dose)	Results	Quality rating
(Formoterol And Corticosteroids Establishing Therapy) International study group		smoking status NR Multicenter (71)	FM (24) All administered via DPI	0.53, <i>P</i> = NR; <i>mean nighttime symptom score</i> : 0.31 compared with 0.38, <i>P</i> = NR; <i>episode-free days</i> , mean % of the year: 51.1 compared with 45.7; <i>P</i> = NR] Exacerbations : BUD > BUD+FM trend [<i>severe exacerbations</i> , #/patient/yr: 0.67 compared with 0.46, <i>P</i> = NR; reduction in rate of severe exacerbations: 26% compared with 49%, <i>P</i> = NR; <i>mild exacerbations</i> , #/patient/yr: 21.3 compared with 22.3, <i>P</i> = NR; % <i>patients without severe exacerbation</i> : 70.3 compared with 71.8, <i>P</i> = NR] Rescue med use: BUD+FM > BUD trend [<i>rescue med use day</i> , mean #puffs: 0.57 compared with 0.82, <i>P</i> = NR; <i>rescue med use night</i> , mean #puffs: 0.18 compared with 0.20, <i>P</i> = NR]	
Beclomethasone + salmeterol compared with beclomethasone					
Greening et al. 1994 ¹⁴⁰ AND Hyland, 1995 ¹⁴¹	RCT, DB, DD 429 21 weeks	UK Age ≥ 18 with uncontrolled asthma on low-dose ICS, severity NR, enrolled 26-27% smokers in each group General practice Centers (99)	BDP MDI (400) + SM DPI (100) compared with BDP MDI (1000)	Symptoms : No difference [<i>proportion of days with symptoms from LWAQ</i> , median change from baseline: -0.35 compared with -0.26, <i>P</i> = NS ; % of days with symptoms, baseline, endpoint: 87, 56 compared with 87, 61; <i>P</i> = NS] Nocturnal awakenings: BDP+SM > BDP [<i>proportion of nights</i> , median change from baseline: -0.20 compared with -0.14, <i>P</i> = 0.02] Exacerbations : No difference [<i>rate of exacerbations</i> , #/person/28 days: 0.21 compared with 0.29, <i>P</i> = 0.42] Rescue medicine use: No difference [<i>mean daytime use</i> , baseline, endpoint (# puffs): 3.0, 2.1 compared with 3.3, 2.4, <i>P</i> = 0.553; <i>mean nighttime use</i> : 0.7, 0.4 compared with 0.6, 0.5, <i>P</i> = 0.086] Quality of life: No difference [LWAQ <i>two domains</i> : Functional limitation domain: median change from baseline: -0.04 compared with -0.06, <i>P</i> = NS; Distress domain: 0.00 compared with 0.00, <i>P</i> = NS]	Fair

Table 30. Summary of head-to-head studies comparing ICS+LABA compared with higher dose ICS

Study	Study design N Duration	Country Study population Setting	Comparison (total daily dose)	Results	Quality rating
Kelsen et al. 1999 ¹⁴²	RCT, DB, DD 483 24 weeks	US Age ≥18 with uncontrolled on ICS, severity NR, smokers excluded 34 outpatient clinical sites	BDP MDI (336) + SM (84) MDI compared with BDP MDI (672)	<p>Symptoms: BDP+SM > BDP [symptom scores, mean change: <i>wheezing</i>: -0.35 compared with -0.22, $P \leq 0.05$; <i>shortness of breath</i>: -0.48 compared with -0.28, $P \leq 0.05$; <i>chest tightness</i>: -0.45 compared with -0.26, $P \leq 0.05$; <i>cough</i>: data NR, $P = \text{NS}$; % <i>symptom-free days</i>, mean increase: 23.6 compared with 12.5, $P \leq 0.05$]</p> <p>Nocturnal awakenings: BDP+SM > BDP [<i># awakenings/night</i>, mean change (SE): -0.26 (0.03) compared with -0.20 (0.03), $P = 0.009$; % <i>awakening-free nights</i>, mean change (SE): 18.8 (1.7) compared with 13.4 (1.6), $P = 0.001$; <i>lost sleep, minutes/night</i>, mean change (SE): -5.55 (0.77) compared with -4.4 (1.20), $P = 0.003$]</p> <p>Exacerbations : No difference [<i>number (%) of patients</i> : 38 (16%) compared with 44 (18%); $P = \text{NS}$; <i>total number of exacerbations</i>: 52 compared with 58; $P = \text{NS}$]</p> <p>Rescue medicine use: BDP + SM > BDP [% <i>rescue-free days</i>: greater improvement with SM + BDP ($P \leq 0.011$), data shown in figure; <i>puffs/day</i>: greater improvement with SM + BDP ($P \leq 0.011$), data shown in figure; <i>puffs/night</i>, mean change (SE): -0.52 (0.06) compared with -0.44 (0.08), $P = 0.007$; % <i>rescue-free nights</i>, mean change (SE): 23.2 (2.0) compared with 14.7 (1.9), $P \leq 0.05$]</p>	Fair
Murray et al. 1999 ¹⁴³	RCT, DB, DD 514 24 weeks	US Age ≥18, uncontrolled on ICS, severity NR, smoking status NR Multicenter (35)	BDP MDI (336) + SM MDI (84) compared with BDP MDI (672, medium)	<p>Symptoms: BDP+SM > BDP [<i>symptom scores (0-4), mean decrease from baseline</i>: ratings of wheeze, SOB, and chest tightness: 0.49, 0.71, and 0.62 compared with 0.27, 0.25, and 0.33; $P \leq 0.05$ for all; <i>combined symptom score</i> and % <i>symptom-free days</i>, mean changes: greater improvements with BDP + SM, $P \leq 0.05$, data NR]</p> <p>Nocturnal awakenings: No difference [$P = \text{NS}$, data NR]</p> <p>Exacerbations: No difference</p>	Fair

Table 30. Summary of head-to-head studies comparing ICS+LABA compared with higher dose ICS

Study	Study design N Duration	Country Study population Setting	Comparison (total daily dose)	Results	Quality rating
				<p><i>[% of patients having at least one: 17 compared with 18, P = NR; total # of exacerbations: 52 compared with 56, P = NR]</i></p> <p>Rescue medicine use: BDP+SM > BDP [mean <i>daytime rescue med use</i> (puffs/day), % of <i>rescue-free days</i>, and % of <i>rescue-free nights</i>: greater improvement with BDP + SM, P≤0.05, data NR; mean <i>nighttime use</i> (puffs/night): P > 0.05, data NR]</p>	
Verberne et al. 1998 ¹⁴⁴	RCT, DB 177 1 year	Multinational (Netherlands, UK) Children and adolescents age 4-18, mild to moderate asthma, on ICS ≥3 months, stable asthma for ≥1 month prior to run-in, smoking status NR Multicenter (outpatient clinics of 9 hospitals, 6 university hospitals, and 3 general hospitals)	BDP (400) + SM (100) vs. BDP (800) vs. BDP (400) All given by DPI	<p>Only data for BDP+SM compared with BDP (800) described here</p> <p>Symptoms: No difference <i>[% of children reporting no symptoms</i>, baseline and endpoint: 3, 34 compared with 13, 39; P = NS]</p> <p>Exacerbations: BDP > BDP+SM trend [<i>patients requiring OCS for exacerbations, total # of prednisolone courses (# of patients)</i>: 13 (10) compared with 8 (7), P = NR]</p> <p>Rescue med use: BDP+SM > BDP trend [<i>median # additional inhalations per day</i>: 0.19 compared with 0.33; P = NR]</p>	Fair
Vermetten et al. 1999 ¹⁴⁵	RCT, DB 233 12 weeks	Netherlands Age 18-66, on ICS for ≥ 6 weeks, mild persistent asthma, enrolled 33% smokers Primary care	BDP (400)+ SM (100) compared with BDP (800) All given by DPI	<p>Symptoms: No difference [mean <i>proportion of days with symptoms</i> (SE), baseline, endpoint: 0.56 (0.04), 0.37 (0.04) compared with 0.54 (0.03), 0.38 (0.04); P = NS; mean <i>proportion of nights with symptoms</i> (SE): 0.43 (0.04), 0.33 (0.04) compared with 0.41 (0.03), 0.34 (0.04); P = NS]</p> <p>Exacerbations: No difference <i>[% of patients reporting</i>: 8 compared with 14, P = NS]</p> <p>Rescue med use: BDP+SM > BDP [mean <i>number of blisters/day</i> (SE), baseline, endpoint: 0.88 (0.09), 0.48 (0.07) compared with 0.84 (0.09), 0.61 (0.10), P < 0.05; Mean <i>number of blisters/ night</i> (SE): 0.47 (0.06), 0.30 (0.06) compared with 0.47 (0.05), 0.37 (0.06); P = NS]</p>	Fair

Table 30. Summary of head-to-head studies comparing ICS+LABA compared with higher dose ICS

Study	Study design N Duration	Country Study population Setting	Comparison (total daily dose)	Results	Quality rating
				Quality of life: No difference [Hyland Quality of life questionnaire: data NR, <i>P</i> = NS]	
Woolcock et al. 1996 ¹⁴⁶	RCT, DB 738 24 weeks	Multinational (14 countries) Age ≥ 17, uncontrolled on ICS, severity NR, 13-19% smokers in each group Multicenter (72)	BDP (1000) + SM (100) vs. BDP (1000) + SM (200) vs. BDP (2000) All given by MDI	Symptoms: BDP+SM > BDP [median % <i>symptom-free days</i> and median % <i>of symptom-free nights</i> : greater improvement in both SM + BDP groups, <i>P</i> < 0.001 for both comparisons, data in figure only] Nocturnal awakenings: BDP+SM > BDP [% <i>awakening-free nights</i> , baseline, endpoint: 43, 100 compared with 43, 100 compared with 29, 86; <i>P</i> ≤ 0.001 for both SM + BDP compared with BDP comparisons] Exacerbations: No difference [% of <i>patients experiencing</i> ≥ 1 <i>exacerbation</i> : 20 compared with 16 compared with 20, <i>P</i> = NS between all groups; # of <i>patients requiring</i> <i>OCS or increased ICS</i> : 35 compared with 30 compared with 39; <i>P</i> = NR] Rescue med use: BDP+SM > BDP [median % <i>rescue-free days</i> and median % of <i>rescue-free nights</i> : greater improvement in both SM + BDP groups, <i>P</i> < 0.001 for both comparisons, data in figure only]	Fair
Beclomethasone + formoterol compared with beclomethasone					
Bouros et al. 1999 ¹⁴⁷	RCT, open 134 3 months	Greece Age ≥ 18, poorly controlled on ICS, severity NR, smoking status NR Multicenter (11)	BDP/FM pMDI (500/24) compared with BDP pMDI (1000)	Symptoms: BDP/FM > BDP [<i>symptom scores</i> : greater decrease in <i>daytime</i> (<i>P</i> = 0.001) and <i>nighttime</i> <i>scores</i> (<i>P</i> < 0.001) for BDP/FM, actual data NR, shown in figures] Rescue medicine use: BDP/FM > BDP [greater improvement in <i>daytime puffs/day</i> (<i>P</i> < 0.001) and <i>nighttime puffs/day</i> (<i>P</i> = 0.003) for BDP/FM group, actual data NR, shown in figures]	Fair
Mitchell et al. 2003 ¹⁴⁸	RCT, DB, DD 203 12 weeks	Australia Age ≥ 18, moderate to severe, uncontrolled on ICS, 8-10% smokers in each group	BDP MDI (1000) + FM DPI (24) compared with BDP MDI (2000)	Symptoms: BDP+FM > BDP [<i>daytime symptom score</i> at endpoint, mean (SD): 0.49 (0.71) compared with 0.99 (0.76), <i>P</i> = 0.001; <i>nighttime</i> <i>symptom score</i> at endpoint, mean (SD): 0.34 (0.65) compared with 0.50 (0.57), <i>P</i> = 0.001]	Fair

Table 30. Summary of head-to-head studies comparing ICS+LABA compared with higher dose ICS

Study	Study design N Duration	Country Study population Setting	Comparison (total daily dose)	Results	Quality rating
		Multicenter (16), outpatients		Exacerbations: BDP+FM > BDP trend [<i>number (%) experiencing at least one exacerbation</i> : 34 (34) compared with 51 (51), <i>P</i> = NR] Rescue med use: FM + BDP > BDP [<i>number of inhalations during daytime</i> , mean (SD): 0.93 (1.38) compared with 2.43 (2.43), <i>P</i> = 0.001; <i>inhalations during nighttime</i> , mean (SD): 0.69 (1.27) compared with 1.43 (1.56), <i>P</i> = 0.001]	
Fluticasone + salmeterol compared with budesonide					
Jenkins et al. 2000 ¹⁴⁹	RCT, DB, DD 353 (subanalysis 113 for AQLQ)	Multinational (Australia, Finland, Sweden)	FP/SM DPI (500/100) compared with BUD DPI (1600)	Symptoms: FP/SM > BUD [Increase in median % <i>symptom-free days</i> : 60 compared with 34, <i>P</i> < 0.001; median % <i>symptom-free nights</i> (weeks 1-24): 86 compared with 79, <i>P</i> = NS]	Fair
AND Juniper et al. 2002 ¹⁵⁰	24 weeks	Age ≥12, moderate to severe persistent asthma, uncontrolled on ICS, excluded smokers with > 10 pack-year smoking history Multicenter (44)		Exacerbations: No difference [% <i>patients with ≥ 1 exacerbation</i> : 30 compared with 30, <i>P</i> = NS] Rescue medicine use: FP/SM > BUD [% of <i>rescue-free days</i> : higher % in SM/FP group, data NR, <i>P</i> ≤ 0.001; % of <i>rescue-free nights</i> : 90 compared with 82, <i>P</i> = 0.029, 95% CI: 0, 4] Quality of life: FP/SM > BUD [AQLQ <i>overall</i> , mean change from baseline (SEM): 0.89 (0.11) compared with 0.44 (0.10), difference 0.45 (0.14), 95% CI: 0.17, 0.72, <i>P</i> = 0.002; AQLQ <i>symptoms</i> : 1.11 (0.13) compared with 0.58 (0.13), <i>P</i> = 0.002 AQLQ <i>environment</i> : 0.93 (0.13) compared with 0.52 (0.12), <i>P</i> = 0.014 ; AQLQ <i>emotions</i> : 0.75 (0.14) compared with 0.24 (0.13), <i>P</i> = 0.004 ; AQLQ <i>activities</i> : 0.69 (0.12) compared with 0.36 (0.11), <i>P</i> = 0.032]	
Johansson et al. 2001 ¹⁵¹	RCT, DB, DD 349 12 weeks	Multinational (6: Canada, Greece, Israel, Italy, S Africa, and Sweden) Age ≥ 12, mild to moderate persistent asthma, uncontrolled on	FP/SM DPI (200/100) compared with BUD DPI (800)	Symptoms: No difference [% of <i>days when symptom score <2</i> (SD): 79 (30) compared with 79 (27), <i>P</i> = NS; % of <i>symptom-free days</i> (SD): 53 (38) compared with 55 (38), <i>P</i> = NS; % <i>nights when symptom score <2</i> (SD): 91 (18) compared with 92 (18), <i>P</i> = NS; % <i>symptom-free nights</i> (SD): 68 (36) compared with 72 (33),	Good

Table 30. Summary of head-to-head studies comparing ICS+LABA compared with higher dose ICS

Study	Study design N Duration	Country Study population Setting	Comparison (total daily dose)	Results	Quality rating
		previous therapy (~80% ICS), excluded smokers or those with > 10 pack-year smoking history		<i>P</i> = NS]	
		Multicenter		Exacerbations: No difference [Patients with no exacerbations (%): 86 compared with 86, <i>P</i> = NR; Patients with one or more exacerbations (%): 14 compared with 14, <i>P</i> = NR]	
				Rescue medicine use: No difference [% of rescue-free days (SD): 64 (37) compared with 63 (38), <i>P</i> = NS; % rescue-free nights (SD): 78 (30) compared with 79 (29), <i>P</i> = NS]	
Budesonide + formoterol compared with fluticasone					
Bateman et al. 2003 ¹⁵²	RCT, DB, DD 344 12 weeks	Multinational (6: Germany, Greece, Israel, Netherlands, Portugal, S. Africa) Age ≥ 18; moderate persistent asthma, previous use of constant dose of ICS > 30 days, 5-7% smokers in each group Multicenter (37)	BUD/FM DPI (320/9) compared with FP DPI (500)	Symptoms: No difference [% of symptom-free days: 60.4 compared with 55.5; difference (95% CI) = 4.9 (11.1-10.9), <i>P</i> = NS; % of asthma control days: 57.8 compared with 52.4; difference (95% CI) = 5.4 (-1.0-11.8), <i>P</i> = NS] Nocturnal awakenings: No difference [Night-time awakenings due to asthma (%): 7.9 compared with 9.6; difference (95% CI) = 1.7(-4.6-1.2), <i>P</i> = NS] Exacerbations: BUD/FM > FP [% of patients experiencing 1 or more: 29.8% (N = 50) compared with 42.0% (N = 74); length of time to first exacerbation was longer in BUD/FM group (survival analysis), <i>P</i> = 0.04] Rescue medicine use: BUD/FM > FP [Reduction in puffs/day : 0.31 compared with 0.13 <i>P</i> = 0.04; % of reliever free days: 75.5 compared with 66.4; <i>P</i> < 0.001]	Fair
Fluticasone + salmeterol compared with triamcinolone					
Baraniuk et al. 1999 ⁴⁸	RCT, DB, triple-dummy 680 12 weeks	US Age ≥ 12, uncontrolled with low-dose ICS, severity NR, smokers excluded Pulmonary/allergy medicine clinics (50)	FP MDI (196) + SM (84) vs. FP MDI (440) vs. TAA MDI (1200) (steroid dosing ranges: low,	Only data for FP+SM compared with TAA shown here Symptoms: FP+SM > TAA [Mean change in overall symptom score (SEM): -0.44 (0.05) compared with -0.31 (0.05); <i>P</i> ≤ 0.004; % symptom free days, change from baseline (SEM): 29.2 (2.9) compared with 11.9 (2.1); <i>P</i> ≤ 0.004]	Fair
This study is also listed above under FP+SM compared					

Table 30. Summary of head-to-head studies comparing ICS+LABA compared with higher dose ICS

Study	Study design N Duration	Country Study population Setting	Comparison (total daily dose)	Results	Quality rating
with FP section			medium, medium)	Nocturnal awakenings: FP+SM > TAA [<i>mean change from baseline</i> (SEM): -0.31 (0.04) compared with -0.18 (0.03); $P \leq 0.004$] Rescue medicine use: FP+SM > TAA [<i>mean change from baseline, puffs/d</i> (SEM): -2.9 (0.2) compared with -1.8 (0.2); $P \leq 0.004$ % rescue free days, <i>mean change from baseline</i> (SEM): 45.0 (2.9) compared with 27.4 (2.5); $P \leq 0.004$]	

Abbreviations: AQLQ = Asthma Quality of Life Questionnaire; BDP = beclomethasone dipropionate; BUD = Budesonide; CI = confidence interval; FP = Fluticasone Propionate; ICS = Inhaled Corticosteroids; LABAs = Long-Acting Beta-2 Agonists; MA=meta-analysis; OCS = oral corticosteroids; QOL = quality of life; RCT= randomized controlled trial; RR = relative risk; SM = Salmeterol; SMD = standard mean difference; SR=systematic review; TAA = Triamcinolone Acetonide; WMD = weighted mean difference.

Symbol use: Drug X > Drug Y = statistically significant difference in outcomes favoring Drug X; Drug X > Drug Y trend = point estimate favors Drug X, but the difference is not statistically significant or tests of statistical significance were NR; No difference = no statistically significant difference or tests of statistical significance were not reported and outcomes are similar.

Note: All results are listed in the same order as the comparison column lists the medications.

3. ICS+LABA compared with ICS (same dose) (addition of LABA to ICS compared with continuing same dose ICS)

Summary of findings

We found one systematic review with meta-analysis¹⁵³ and 26 RCTs (28 publications)^{105, 106, 108, 110-112, 124, 132, 138, 139, 144, 154-170} that included head-to-head comparisons between an ICS+LABA with the same dose ICS meeting our inclusion/exclusion criteria (Table 32). These trials compared the addition of a LABA to an ICS with continuing the same dose of the ICS. Thirteen of the 26 (50%) administered the ICS and LABA in a single inhaler, nine (35%) administered them in separate inhalers, and four studies (15%) administered them both as a single inhaler and in separate inhalers to different study groups.

Overall, results from large trials up to one year in duration support greater efficacy with the addition of a LABA to an ICS over continuing the current dose of ICS alone for patients with poorly controlled persistent asthma (high strength of evidence, Table 31 Evidence Profile). Our meta-analysis shows statistically significantly greater improvement in rescue medication-free days (SMD 0.271, 95% CI: 0.195, 0.347), rescue medicine use (SMD -0.324, 95% CI: -0.389, -0.259), symptom free days (SMD 0.260, 95% CI: 0.206, 0.314), symptom scores (SMD -0.298, 95% CI: -0.360, -0.235), and quality of life (AQLQ scores; SMD 0.206, 95% CI: 0.083, 0.328). Results were generally consistent with a previously published meta-analysis¹⁵³ which also reported fewer exacerbations in those treated with the addition of a LABA to ICS (RRR 19% with LABA).

Table 31. Evidence profile of the comparative efficacy of addition of LABA to ICS compared with continuing same dose ICS

Evidence profile: Comparative efficacy of ICS + LABA compared with same dose of ICS (addition of LABA to ICS compared with continuing same dose ICS)							
Number of studies (# of subjects*)	Study design (# using single combo inhaler**)	Quality	Consistency	Directness	Result (magnitude of effect)	Other modifying factors	Overall strength of evidence
ICS + LABA compared with same dose of ICS							
26 (11,839)	RCTs	Good (2), Fair (24)	Consistent	Direct	ICS+LABA > ICS for symptom free days (SMD 0.260, 95% CI: 0.206, 0.314), symptom scores (SMD -0.298, 95% CI: -0.360, -0.235), rescue medicine use, and quality of life (AQLQ scores; SMD 0.206, 95% CI: 0.083, 0.328)*	None	High
ICS + LABA compared with same dose of ICS							
1 (8,147)	1 SR w/ MA	Good	Consistent	Direct	Exacerbation requiring OCS: RRR 19% with LABA [RR 95% CI) 0.81 (0.73, 0.90) ^{††}	None	High
BUD+FM (or eFM) compared with BUD							
13 (7,881)	RCTs (10) [†]	Good (2) Fair (11)	Consistent	Direct	BUD+FM > BUD	None	High
FP+SM compared with FP							
7 (2,405)	RCTs (7)	Fair	Consistent	Direct	FP+SM > FP	None	High
ICS+SM compared with ICS							
3 (835)	RCTs (0)	Fair	Consistent	Direct	ICS+SM > ICS for symptoms and rescue medicine use in all trials	None	High
ICS+FM compared with ICS							
2 (541)	RCTs (0)	Fair	Some inconsistency	Direct	ICS+FM > ICS for some outcomes and no difference for others	None	Low
BDP+SM compared with BDP							
1 (177)	RCT (0)	Fair	NA	Direct	No difference in symptoms, exacerbations, or rescue medicine use	None	Low

Abbreviations: AQLQ = Asthma Quality of Life Questionnaire; BDP = beclomethasone dipropionate; BUD = Budesonide; CI = confidence interval; eFM = Eformoterol; FM = Formoterol; FP = Fluticasone Propionate; ICS = Inhaled Corticosteroids; LABAs = Long-Acting Beta-2 Agonists; MA=meta-analysis; OCS= oral corticosteroids; RCT= randomized controlled trial; RR = relative risk; SM = Salmeterol; SMD = standard mean difference; SR=systematic review.

* Total number of asthma subjects randomized in the trial. Some subjects may have received other treatments as several trials had multiple treatment arms.

** Number of trials for this comparison that administered the ICS/LABA in 1 inhaler.

[†] Five trials had an arm with BUD+FM in single inhaler and an arm with them in separate inhalers.

^{††} Results from previously published meta-analysis.

♣ See Appendix G for complete results of meta-analyses.

Detailed Assessment

Description of Studies

Of the included studies (Table 32), the systematic review with meta-analysis¹⁵³ compared the addition of any LABA to any ICS (ICS+LABA) with the addition of placebo and continuing the same dose of the ICS. The review included 26 trials (eight of them in pediatric populations). Fifteen of those trials met our inclusion/exclusion criteria. We included eleven additional trials^{106, 108, 110, 154, 157, 159-162, 169, 170} that were not in the systematic review.

Of the 26 RCTs that met our inclusion/exclusion criteria, 13 (50%) compared budesonide + formoterol compared with budesonide (one used eformoterol), seven (27%) compared fluticasone + salmeterol compared with fluticasone, three (12%) compared an ICS (not specified) + salmeterol compared with an ICS, two (8%) compared an ICS (not specified) + formoterol compared with an ICS, and one (4%) compared beclomethasone + salmeterol compared with beclomethasone.

Study duration ranged from 12 weeks (17 trials, 65%) to 12 months (five trials, 19%). The most commonly used delivery devices were DPIs: 17 studies (65%) delivered all study medicines via DPIs, four studies (15%) delivered all via MDIs, and five studies (19%) used both MDIs and DPIs. Thirteen of the 26 (50%) administered the ICS and LABA in a single inhaler, nine (35%) administered them in separate inhalers, and four studies (15%) administered them both as a single inhaler and in separate inhalers to different study groups.

Study Populations

The 26 head-to-head RCTs included a total of 11,839 subjects (Table 32). Most were conducted primarily in adult populations. Six studies (23%) included pediatric populations under 12 years of age.^{144, 162, 164, 165, 168, 169} The majority of trials were multinational (15 trials, 58%); six (23%) were conducted in the United States, two (8%) were conducted in the UK, and one in each of the following: Canada, Sweden, and the Netherlands.

All subjects were poorly controlled on ICS therapy prior to randomization in all but three trials.^{105, 106, 163} One of the three enrolled subjects that were initially symptomatic on ICS (about 67%) or SABA alone, but re-randomized those that were well controlled during the initial 4 weeks (N = 505) and followed them for the remainder of the 32 week study.¹⁶³ Another enrolled subjects that were well controlled on current therapy (either ICS or ICS+SM).¹⁰⁵ The last one enrolled subjects uncontrolled on current medication, but only 68% were on ICSs.¹⁰⁶

Sponsorship

Of the 26 head-to-head trials, 23 (88%) were funded by pharmaceutical companies; only two studies (8%) were funded primarily by sources other than pharmaceutical companies; one study (4%) did not report any source of funding.

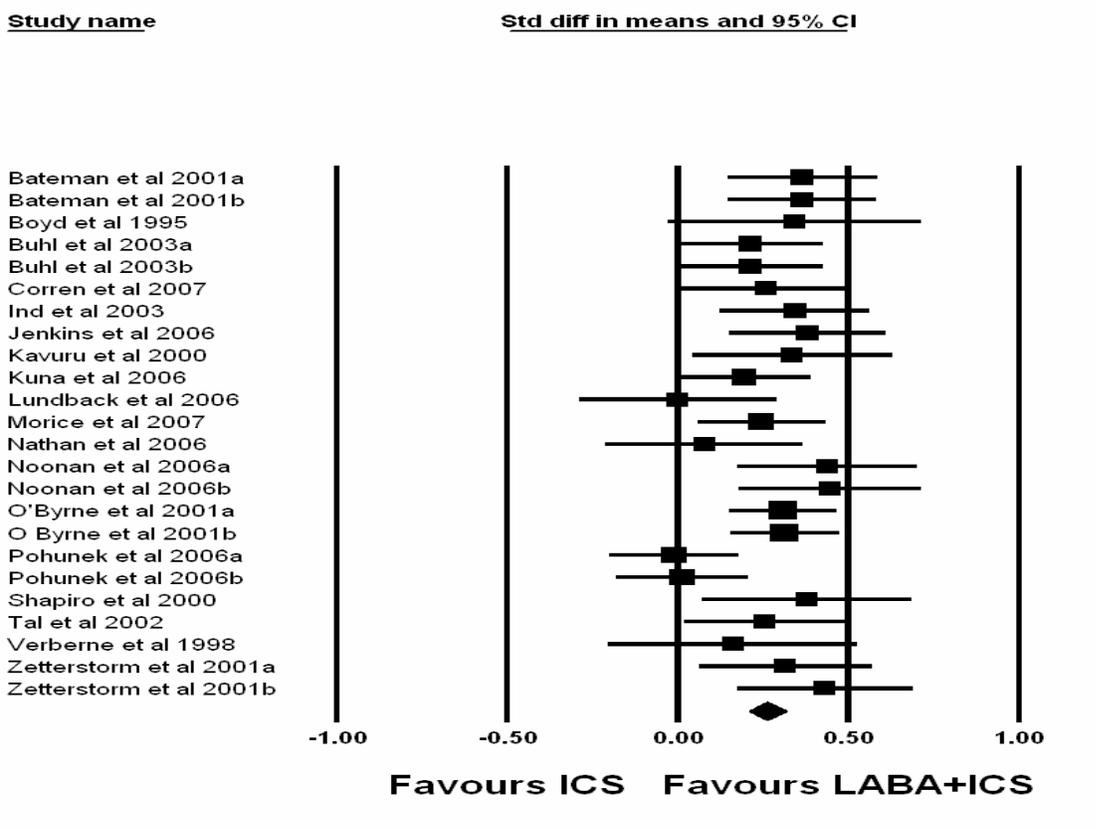
Head-to-head comparisons

1. ICS+LABA compared with ICS (same dose)

We conducted meta-analyses for five outcomes that were reported with sufficient data using similar measures in multiple trials (Appendix G). Those treated with ICS+LABA had a greater increase in the proportion of days free from rescue medication (SMD 0.271, 95% CI: 0.195, 0.347, $P < 0.001$, 17 comparisons), greater reduction in rescue medicine use per day (SMD -0.324, 95% CI: -0.389, -0.259, $P < 0.001$, 17 comparisons), greater increase in percentage of

symptom free days (SMD 0.260, 95% CI: 0.206, 0.314, $P < 0.001$, 24 comparisons) (Figure 13), greater improvement in symptom score (SMD -0.298, 95% CI: -0.360, -0.235, $P < 0.001$, 15 comparisons), and a greater increase in quality of life (AQLQ scores; SMD 0.206, 95% CI: 0.083, 0.328, $P = 0.001$, 4 comparisons) than those treated with ICS alone. For all five meta-analyses, sensitivity analyses indicate no difference in overall meta-analysis conclusions with any single study removed. In addition, there was no significant heterogeneity between studies (Appendix G).

Figure 13. Meta-analysis comparing improvement in the percentage of symptom-free days for ICS+LABAs compared with ICS (same dose)



One previously published good systematic review¹⁵³ compared the addition of any LABA to any ICS (ICS+LABA) with continuing the same dose of ICS. The review included 26 trials (eight of them in pediatric populations) that contributed information (N = 8,147 subjects). Trial duration ranged from four to 54 weeks. Most studies (N = 13) were 12 to 16 weeks. Six trials examined ICSs+LABAs delivered via a single device. The systematic review reported that the addition of a LABA to an ICS reduced the risk of exacerbations requiring systemic steroids by 19% (RR 0.81, 95% CI: 0.73 to 0.90) compared to ICS alone. In addition, the addition of LABA resulted in greater improvement in symptoms, rescue medicine use, and quality of life. They found no difference in nocturnal awakenings (Table 32).

2. *Budesonide (BUD) + Formoterol (FM) compared with Budesonide (BUD)*

Two good^{157, 167} and 11 fair RCTS^{110, 124, 138, 156, 160-163, 165, 169, 170} (7,881 subjects total) compared the addition of FM to BUD with continuing the same dose of BUD (Table 32). One of these trials reported using eformoterol (eFM).¹⁶³ Five trials administered BUD+FM in a single inhaler device,^{156, 161, 165, 169, 170} three tested the combination delivered by separate inhalers,^{124, 138, 163} and five administered them both as a single inhaler and in separate inhalers to different study groups.^{110, 157, 160, 162, 167}

Three trials included children ≤ 12 years of age.^{162, 165, 169} Study duration was 12 weeks for ten trials, 32 weeks for one trial,¹⁶³ and one year for two trials.^{124, 138}

The majority of trials assessed asthma symptoms (all 13 trials), nocturnal awakenings (11 trials), exacerbations (eight trials), and rescue medicine use (all 13 trials). Four trials also assessed quality of life and one assessed missed work or school. For these outcomes, all 13 trials either reported no difference or outcomes favoring BUD+FM combination therapy over the same dose of BUD. No trial reported a statistically significant difference in favor of BUD alone for any of these outcomes. For subjects treated with BUD+FM compared to those treated with BUD alone, nine trials (69%) reported fewer symptoms or better improvement in symptoms,^{105, 106, 108, 110-112, 124, 132, 138, 139, 144, 154-161, 163, 164, 166-168} six trials (of seven reporting the outcome) reported fewer exacerbations or a lower risk exacerbations,^{124, 138, 156, 163, 165, 170} and nine trials (69%) reported a greater decrease or less frequent use of rescue medicine.^{105, 106, 108, 111, 112, 124, 132, 138, 139, 144, 154-161, 163-168} For three of the eleven trials reporting nocturnal awakenings, results favored the BUD+FM group.^{156, 157, 161} The other eight reported no difference.^{110, 124, 160, 162, 165, 167, 169, 170} Three^{162, 163, 169} of the four trials reporting quality of life found no statistically significant difference in overall quality of life measures and one¹⁶¹ reported greater improvement in those treated with BUD+FM. The single trial reporting missed work or school found no significant difference between groups (Table 32).¹⁶³

3. *Fluticasone (FP)+Salmeterol (SM) compared with Fluticasone (FP)*

Seven fair quality RCTs (2,405 subjects) compared the addition of SM to FP with continuing the same dose of FP^{105, 106, 108, 111, 132, 154, 159} (Table 32). All seven administered FP+SM in a single inhaler device.^{105, 106, 108, 111, 132, 154, 159} None tested the combination delivered by separate inhalers. None of the trials included children ≤ 12 years of age. Study duration was 12 weeks for four trials,^{105, 108, 111, 154} 24 weeks for one trial,¹³² and 12 months for two trials.^{106, 159}

The majority of trials assessed asthma symptoms (all trials), exacerbations (five trials), and rescue medicine use (all trials). Three trials also reported nocturnal awakenings and one reported quality of life. For these outcomes, all seven trials either reported no difference or outcomes favoring FP+SM combination therapy over the same dose of FP. No trial reported a statistically significant difference in favor of FP alone for any of these outcomes. For subjects treated with FP+SM compared to those treated with FP alone, five trials (71%) reported fewer symptoms or better improvement in symptoms,^{105, 111, 132, 154, 159} three trials (of five reporting) reported fewer patients having exacerbations or withdrawn due to exacerbations,^{105, 106, 111} and six trials (86%) reported a greater decrease or less frequent use of rescue medicine.^{105, 108, 111, 132, 154, 159} Two of the three trials reporting nocturnal awakenings found no difference between groups,^{105, 108} one reported a higher percentage of awakening-free nights for the FP+SM group.¹¹¹ The single trial reporting quality of life measures reported a trend toward better scores on the activities limitation domain of the AQLQ, but no difference in other domains (*activities limitation*: 1.0 compared with 0.62, $P = \text{NR}$)¹¹¹ (Table 32).

4. *ICS+Salmeterol (SM) compared with ICS*

Three fair quality RCTs (835 subjects) compared the addition of SM to any ICS with continuing the same dose of ICS (plus placebo)^{155, 158, 164} (Table 32). All three administered ICS+SM by separate inhalers. One trial included children, enrolling 210 subjects between the ages of 4 and 16.¹⁶⁴ Study duration was 12 weeks for two trials^{155, 164} and 14 weeks for one.¹⁵⁸

All three trials reported symptoms and rescue medicine use, one reported exacerbations,¹⁵⁵ and one reported quality of life measures.¹⁵⁸ In all three trials, those treated with ICS+SM had greater improvements in symptoms (in one trial the difference was only statistically significant for nighttime symptoms)¹⁵⁵ and rescue medicine use. The single trial reporting exacerbations found no statistically significant difference in the number of patients requiring a course of oral steroids (19 compared with 15, $P = 0.19$).¹⁵⁵ The trial reporting quality of life found no statistically significant difference in overall quality of life, but there was a trend toward greater improvement in the ICS+SM group (AQLQ global score, mean change from baseline: 1.08 compared with 0.61, $P = 0.47$).¹⁵⁸

5. *ICS+Formoterol (FM) compared with ICS*

Two fair quality RCTs (541 subjects) compared the addition of FM to any ICS with continuing the same dose of ICS (plus placebo)^{166, 168} (Table 32). Both administered ICS+FM by separate inhalers. One was a 6 month trial that enrolled 239 adults with mild to moderate persistent asthma that were not adequately controlled on ICSs.¹⁶⁶ The other was a 12-week trial that enrolled 302 children (ages 6-11) not adequately controlled on ICSs.¹⁶⁸ The 6 month trial in adults found greater improvement in symptoms and rescue medicine use in those treated with ICS+FM, but no difference in exacerbations.¹⁶⁶ The 12-week trial in children found no statistically significant difference in symptoms, rescue medicine use, or quality of life¹⁶⁸ (Table 32).

6. *Beclomethasone (BDP) + Salmeterol (SM) compared with Beclomethasone (BDP)*

One 12-month fair quality RCT meeting our inclusion/exclusion criteria compared BDP+SM in a separate inhalers with the same dose of BDP alone in 177 children and adolescents (age 6-16) with mild to moderate persistent asthma.¹⁴⁴ The trial reported no statistically significant difference in symptoms, exacerbations, or rescue medicine use (Table 32).

Table 32. Summary of head-to-head studies comparing ICS+LABA compared with same dose ICS

Study	Study design N Duration	Country Study population Setting	Comparison (total daily dose)	Results	Quality rating
ICS + LABA compared with same dose ICS (addition of LABA to ICS compared with continuing same dose ICS)					

Table 32. Summary of head-to-head studies comparing ICS+LABA compared with same dose ICS

Study	Study design N Duration	Country Study population Setting	Comparison (total daily dose)	Results	Quality rating
Ni Chroinin et al. 2005 ¹⁵³	Systematic review with meta- analysis of RCTs comparing addition of LABA compared with placebo to ICS 26 trials (N = 8,147) 4-8 weeks in 6 trials, 12-16 weeks in 13 trials, and 24-54 weeks in 7 trials	Multinational Adults and children age ≥ 2 with chronic asthma who had been taking ICS ≥ 30 days prior to enrollment Numerous settings	LABA + ICS compared with placebo +ICS (addition of LABA compared with placebo to ICS) SM (100) in 14 comparisons, FM (12 or 24) in 17 (In three trials a higher than usual dose of SM (100 mcg BID) or FM (24 mcg BID) were used. Of the 23 comparisons reporting a fixed dose, 12 tested the addition of LABA to low- dose ICSs, 8 added LABA to a medium dose of ICS, and 3 comparisons used a high dose of ICS 11 trials failed to specify the ICS used	Symptoms: LABA + ICS > placebo + ICS [LABA use significantly reduced <i>daytime symptoms</i> [N = 5, SMD (95% CI) -0.34 (-0.44, -0.23)], <i>night- time symptoms</i> [N = 2, SMD (95% CI) -0.18 (-0.31, -0.05)], and <i>overall 24-hour symptoms</i> [(N = 2, SMD (95% CI) -0.28 (-0.45, -0.11) while increasing % <i>symptom-free days</i> during the observation period [(N = 4, SMD (95% CI) 0.32 (0.02, 0.62)], the <i>change from baseline in % symptom-free day</i> [N = 6, WMD (95% CI) 17.21 (12.06, 22.36)], in <i>symptom-free nights</i> [N = 4, SMD (95% CI) 0.51 (0.28, 0.74)], and the <i>change in % asthma-control days</i> [N = 2, WMD (95% CI) 15.61 (8.51, 22.70)] Nocturnal awakenings: No difference [% <i>nights with no awakening</i> [N = 2, WMD (95% CI) -1.37 (-2.75, 0.02)]; <i>changes in % nights with no awakening</i> [N = 2, WMD (95% CI) 3.24 (-0.89, 7.38)]; <i>night-time awakening</i> [N = 3, WMD (95% CI) - 0.22 (-2.24, 1.81)] Exacerbations: LABA + ICS > placebo + ICS [patients <i>experiencing ≥1 exacerbation requiring OCS</i> , RRR 19% with LABA [RR 95% CI) 0.81 (0.73, 0.90)]; <i>Risk of exacerbation decreased from 27% to 22% with the addition of LABA</i> , with ARR (95% CI)=5% (3%, 8%), and NNT (95% CI) with LABA to prevent 1 exacerbation over 1yr is 18 (13, 33); <i>overall withdrawals</i> [N = 26 comparisons, RR (95% CI) 0.87 (0.77, 0.97), RD (95% CI) -0.02, (- 0.04, 0.00)]; <i>withdrawals due to poor asthma control</i> (N = 22 comparisons, RR (95% CI) 0.50 (0.36, 0.70), RD (95% CI) -0.02 (-0.03, -0.01)] Rescue med use: LABA + ICS > placebo + ICS [<i>daytime use at endpoint</i> [N = 2, WMD (95% CI) - 0.73 (-1.24, -0.22)puffs/d] <i>night-time use at endpoint</i> [N = 2, WMD (95% CI) -0.44 (-0.81, -0.07) puffs/night]; <i>change in overall 24-hour use</i> (N = 8, WMD (95% CI) -0.81 (-1.17, -0.44) puffs/d], <i>change in nighttime use</i> [N = 6, WMD (95% CI) -0.33 (-0.57,-0.1) puffs/night], <i>change in daytime use</i> [N = 9, WMD (95% CI) -0.82 (-1.17, - 0.44)], <i>change in % rescue-free days</i> [N = 2, WMD (95% CI) 19.1 (12.19, 26.01)]	Good

Table 32. Summary of head-to-head studies comparing ICS+LABA compared with same dose ICS

Study	Study design N Duration	Country Study population Setting	Comparison (total daily dose)	Results	Quality rating
Budesonide + formoterol compared with budesonide					
Buhl et al. 2003 ¹⁵⁶	RCT, DB, DD 523 12 weeks	Multinational (9: Argentina, Belgium, Czech Repub, Germany, Mexico, Russia, Spain, Netherlands) Age ≥ 18, moderate persistent asthma, not controlled on ICS Multicenter (56)	BUD/FM (320/9 given once daily) compared with BUD/FM (320/9 divided into two doses) compared with BUD (400)* All given by DPI	Symptoms: BUD/FM > BUD [% of Symptom-free days, mean during treatment: 58.6 vs. 58.2 vs. 51.3; <i>P</i> < 0.05 for both; % of asthma control days: 55.2 vs. 53.5 vs. 47.6; <i>P</i> < 0.05 for both; Total asthma symptom score (0-6) 0.76 vs. 0.78 vs. 0.90, <i>P</i> < 0.05 and <i>P</i> = NS] Nocturnal awakenings: BUD/FM > BUD [% of nights with awakenings: 9.9 vs. 12.1 vs. 14.1%, <i>P</i> < 0.01 and <i>P</i> = NS] Exacerbations: BUD/FM > BUD [RR of having a mild exacerbation: 38% lower for BUD/FM once daily compared with BUD (hazard ratio 0.62; 95% CI: 0.46-0.84; <i>P</i> < 0.001), 35% lower for the BUD/FM twice daily than BUD (hazard ratio 0.65; 95% CL 0.49-0.88; <i>P</i> < 0.002); median # of days remaining exacerbation-free: 80 vs. 78 vs. 42 (<i>P</i> < 0.001 for both); % of patients having severe exacerbations: 8 vs. 9 vs. 11, <i>P</i> = NR; % having mild exacerbations: 42 vs. 45 vs. NR) Rescue med use: BUD/FM > BUD [change in # of inhalations/day: -0.37 vs. -0.45 vs. -0.10; <i>P</i> < 0.01 and <i>P</i> < 0.001; % of rescue-free days: 68.6 vs. 70.7 vs. 59.7; <i>P</i> < 0.01 and <i>P</i> < 0.001] <i>P</i> = BUD/FM (320/9 given once daily) vs. BUD and BUD/FM (320/9 divided in two) vs. BUD	Fair
Corren et al. 2007 ¹⁷⁰	RCT, DB, DD 480 12 weeks	US Age ≥ 12, uncontrolled on ICS, mild to moderate persistent asthma Multicenter (56)	BUD/FM pMDI (320/18) vs. BUD pMDI (320) vs. FM DPI (18) vs. Placebo	Only data for BUD/FM vs. BUD shown here Symptoms: No difference [% symptom-free days: change from baseline, mean (SD): 26.47 (39.46) vs. 29.77 (38.19); mean difference between groups (95% CI): -2.66(-12.26 to 6.93); Daytime symptom score: change from baseline, mean (SD): -0.41 (0.52) vs. -0.44 (0.58); mean difference between groups (95% CI): 0.04 (-0.10 to 0.18); Night time symptom score: change from	Fair

Table 32. Summary of head-to-head studies comparing ICS+LABA compared with same dose ICS

Study	Study design N Duration	Country Study population Setting	Comparison (total daily dose)	Results	Quality rating
				<p>baseline, mean: -0.48 vs. -0.48; mean difference between groups (95% CI): 0.01(-0.13 to 0.15)]</p> <p>Nocturnal awakenings: No difference [% awakening free nights; change from baseline: 21.63 (24.08) vs. 22.15 (24.63); mean difference between groups (95% CI): 0.61(-4 to 5.23)]</p> <p>Exacerbations: BUD/FM > BUD [0.8% vs. 2.5%; Odds Ratio (95% CI): Bud/FM minus BUD: 0.32 (0.03 to 3.14)]</p> <p>Rescue med use: No difference [<i>Inhalations/day</i>; change from baseline, mean: -2.01 (2.36) vs. -1.86 (2.59); mean difference between groups(95% CI): -0.23(-0.80 to 0.34)]</p>	
Jenkins et al. 2006 ¹⁵⁷	RCT, DB, DD 456 12 weeks	Multinational (6) Age ≥ 12, uncontrolled on ICS, mild to moderate persistent asthma Multicenter (54)	BUD/FM DPI (1280/36) vs. BUD MDI (1600) + FM (36) vs. BUD MDI (1600)* All given by MDI	<p>Symptoms: BUD/FM (both combinations) > BUD [% of <i>symptom-free days</i>, mean change from baseline: 31.2 vs. 32.2 vs. 15.6, $P < 0.001$ for both; <i>total asthma symptom score</i>, mean change from baseline: -0.62 vs. -0.66 vs. -0.36; $P < 0.01$ for both; % of asthma control days, mean change from baseline: 32.4 vs. 32.2 vs. 16.3, $P < 0.001$ for both (baseline % asthma control days: 10 vs. 9 vs. 7)]</p> <p>Exacerbations: BUD/FM > BUD [<i>time to first mild exacerbation</i>: longer in BUD/FM group than BUD group; <i>instantaneous risk of a mild exacerbation</i>: 36% lower for BUD/FM than for BUD group (Kaplan-Meier curve, $P = 0.0032$), data NR for BUD + FM vs. BUD]</p> <p>Rescue med use: BUD/FM (both combinations) > BUD [% <i>rescue-free days</i>, mean change from baseline: 36.1 vs. 38.6 vs. 17.2, $P < 0.001$ for both (baseline % rescue-free days: 30 vs. 28 vs. 25)]</p> <p>P values reported for BUD/FM vs. BUD and for BUD + FM vs. BUD</p>	Good
Kuna et	RCT, DB, DD	Multinational (8)	BUD/FM	Symptoms: BUD/FM > BUD	Fair

Table 32. Summary of head-to-head studies comparing ICS+LABA compared with same dose ICS

Study	Study design N Duration	Country Study population Setting	Comparison (total daily dose)	Results	Quality rating
al. 2006 ¹⁶⁰	617 12 weeks	Age ≥18, mild or moderate persistent, uncontrolled on ICS Multicenter (61)	(160/9 give once daily) vs. BUD+FM (160/9 divided twice daily) vs. BUD (200)* All given by DPI	[% <i>symptom-free days</i> , baseline and treatment mean (95% CI) = 37.8, 50.0 (46.0, 54.0) vs. 36.1, 50.3 (46.3, 54.3) vs. 38, 43.4 (39.4, 47.3), <i>P</i> < 0.05 for both; % <i>asthma control days</i> , baseline and treatment mean (95% CI)= 33.9, 47.3 (43.4, 51.3) vs. 32.5, 47.3 (43.3, 51.1) vs. 35.1, 40.0 (36.2, 43.9), <i>P</i> < 0.01] Nocturnal awakenings: No difference [% <i>night-time awakenings due to asthma</i> , baseline and treatment mean (95% CI) = 15.8, 11.3 (9.0, 13.6) vs. 14.6, 9.9 (7.7, 12.2) vs. 17.9, 12.0 (9.8, 14.3), <i>P</i> = NS for both] Rescue med use: BUD/FM > BUD [% <i>rescue-free days</i> , treatment mean (95% CI): 61.8 (58.1, 65.4) vs. 66.3 (62.7, 69.9) vs. 55.5 (52.0, 59.1), <i>P</i> < 0.05 and <i>P</i> < 0.001] <i>P</i> values reported are BUD/FM once daily vs. BUD and BUD/FM divided vs. BUD	
Morice et al. 2007 ¹⁶¹	RCT, DB, DD 680 12 weeks	Multinational (8 countries) Age ≥12, asthma for at least 6 months, uncontrolled on ICS alone Multicenter (62 centers)	BUD pMDI (800) vs. BUD/FM DPI (640/18) vs. BUD/FM pMDI (640/18)	Symptoms: BUD/FM > BUD [% of <i>symptom-free days</i> , mean change from baseline: 19.1 vs. 34.2 vs. 28.0; <i>P</i> < 0.001 and <i>P</i> < 0.01 (baseline data: 10 vs. 12 vs. 12); <i>total symptom score</i> (0-6), mean change from baseline: -0.44 vs. -0.84 vs. -0.70, <i>P</i> < 0.001 for both (baseline data: 2.1 vs. 2.0 vs. 1.9); % <i>asthma control days</i> , mean change from baseline: 18.3 vs. 33.1 vs. 26.5, <i>P</i> < 0.001 and <i>P</i> < 0.01 (baseline: 8 vs. 10 vs. 10)] Nocturnal awakenings: BUD/FM > BUD [% of <i>nights</i> , mean change from baseline: -9.7 vs. -15.5 vs. -16.5, <i>P</i> < 0.01 and <i>P</i> < 0.001 (baseline: 33.1 vs. 32.1 vs. 29.2)] Rescue med use: BUD/FM > BUD [% <i>Inhalations/24 hours</i> , mean change from baseline: -0.35 vs. -0.92* vs. -0.94* <i>P</i> < 0.001 for both (baseline: 2.0 vs. 1.8 vs. 2.1); % <i>rescue free days</i> ,	Fair

Table 32. Summary of head-to-head studies comparing ICS+LABA compared with same dose ICS

Study	Study design N Duration	Country Study population Setting	Comparison (total daily dose)	Results	Quality rating
				<p>mean change from baseline: 17.9 vs. 31.1 vs. 30.8, $P < 0.001$ for both (baseline: 29 vs. 34 vs. 29)]</p> <p>Quality of life: BUD/FM > BUD [AQLQ (S) overall score, adjusted mean increase: 0.37 vs. 0.76 vs. 0.65, $P < 0.001$ and $P = 0.002$ (baseline means: 4.8 vs. 4.62 vs. 4.70); % of patients having clinically relevant increase of ≥ 0.5 units: 35 vs. 56 vs. 52, $P = \text{NR}$]</p> <p>P values reported are for BUD/FM DPI vs. BUD and BUD/FM pMDI vs. BUD</p>	
Morice et al. 2008 ¹⁶⁹	RCT, DB, DD 622 12 weeks	Multinational (8) Age 6-11, not controlled, on ICS Multicenter (53)	BUD pMDI (400) vs. BUD/FM DPI (320/18) vs. BUD/FM pMDI (320/18)	<p>Symptoms: No difference [Total asthma symptom score (0-6): -0.69 vs. -0.77 vs. -0.68; symptom free days (%): 35.2 vs. 37.4 vs. 34.9; asthma control days (%): 35.8 vs. 37.6 vs. 35.2]</p> <p>Nocturnal awakenings: No difference [Nights w/awakenings (%): -7.5 vs. -8.2 vs. -7.9]</p> <p>Rescue med use: No difference [inhalations/24 hr period: -0.42 vs. -0.54 vs. -0.50]</p> <p>Quality of life: No difference [PAQLQ score, adjusted mean increase: 0.49 vs. 0.60 vs. 0.47]</p> <p>All values are adjusted mean change from baseline; all p values NS</p>	Fair
Noonan et al. 2006 ¹¹⁰	RCT, DB, DD 596 12 weeks	US Age ≥ 12 , moderate to severe persistent asthma not controlled, on ICS for ≥ 4 weeks Multicenter	BUD/FM pMDI (320/9) vs. BUD pMDI (320) vs. FM DPI (9) vs. BUD pMDI (320) + FM (9) DPI vs. placebo	<p>Only data for BUD/FM vs. BUD vs. BUD + FM shown here (no P values reported for BUD vs. BUD + FM as study focused on comparing BUD/FM with all other arms)</p> <p>Symptoms: BUD/FM > BUD [Daytime symptom score, mean change from baseline: -0.32 vs. -0.19 vs. -0.35, difference between groups (95% CI): -0.17 (-0.30, -0.05), $P \leq 0.01$; Nighttime symptom score, mean change from baseline: -0.22 vs. -0.10 vs. -0.27, difference between groups (95% CI): -0.15 (-0.28, -0.03), $P \leq 0.05$; % of symptom-free days, mean change from</p>	Fair

Table 32. Summary of head-to-head studies comparing ICS+LABA compared with same dose ICS

Study	Study design N Duration	Country Study population Setting	Comparison (total daily dose)	Results	Quality rating
				<p>baseline: 23.14 vs. 9.50 vs. 21.80, difference between groups (95% CI): 15.47 (7.19, 23.74), $P \leq 0.001$]</p> <p>Nocturnal awakenings: No difference [% <i>awakening-free nights</i>, mean change from baseline: 12.67 vs. 15.10 vs. 13.44, difference between groups (95% CI): -2.16 (-7.38, 3.06), $P = \text{NS}$]</p> <p>Exacerbations: Mixed, BUD/FM > BUD for some measures [<i>n</i> (%) <i>patients with clinical exacerbation</i>: 7 (5.6) vs. 5 (4.6) vs. 6 (5.2), OR (95% CI) between groups: 1.25 (0.38, 4.04), $P = \text{NS}$; <i>n</i> (%) <i>of patients with ≥ 1 predefined event meeting criteria for worsening asthma</i> : 37 (29.8) vs. 48 (44.0) vs. 24 (20.9), OR (95% CI) between groups: 0.54 (0.32, 0.93), $P \leq 0.05$; <i>withdrawal due to predefined event</i>, <i>n</i> (%) <i>patients</i>: 13 (10.5) vs. 22 (20.2) vs. 13 (11.3), OR (95% CI) between groups: 0.46 (0.22, 0.97), $P \leq 0.05$; <i>time to withdrawal due to worsening asthma</i>: longer for BUD/FM vs. BUD ($P = 0.047$, survival analysis)</p> <p>Rescue medicine use: No difference [<i>inhalations/day</i>, mean change from baseline: -1.00 vs. -0.78 vs. -1.50, difference between groups (95% CI): -0.51 (-1.05, 0.03), $P = \text{NS}$]</p> <p>All between group differences and P values shown are BUD/FM vs. BUD</p>	
O'Byrne et al. 2001 ¹²⁴	RCT, DB 1970	Multinational (Eastern Europe, Canada, Spain)	Group A (used no ICS for ≥ 3 months): Placebo vs. BUD (200 mcg/d) vs. FM + BUD (9/200 mcg/d)	Only data for BUD (200) vs. BUD (200) + FM (9) and for BUD (400) vs. BUD (400)+ FM (9) from Group B shown here	Fair
OPTIMA trial	(698 in Group A, 1272 Group B) 1 year	Age ≥ 12 , Group B was not controlled with ICS Multicenter (198)	Group B (taking ICS for ≥ 3 months): BUD (200) vs.	Symptoms: BUD+FM > BUD [% <i>of days with symptoms</i> , adjusted mean: 32.8 vs. 27.4 vs. 29.7 vs. 25.1; $P = 0.0001$ BUD vs. BUD+FM (both strengths)	
				Nocturnal awakenings: No difference [% <i>nights with awakenings</i> , adjusted mean: 6.0 vs. 5.4 vs. 6.0 vs. 4.5; $P = 0.061$]	

Table 32. Summary of head-to-head studies comparing ICS+LABA compared with same dose ICS

Study	Study design N Duration	Country Study population Setting	Comparison (total daily dose)	Results	Quality rating
			BUD (200)+ FM (9) vs. BUD (400) vs. BUD (400)+ FM (9) All delivery devices=DPIs	Exacerbations: BUD+FM > BUD [<i>yearly rate severe exacerbations</i> , adjusted mean: 0.92 vs. 0.56 vs. 0.96 vs. 0.36; $P = 0.0001$ BUD vs. BUD+FM (both strengths); <i>reduction</i> <i>in risk of the first asthma</i> <i>exacerbation</i> by adding FM = 43% [RR (95% CI) 0.57 (0.46, 0.72)]; <i>rate</i> <i>of poorly controlled asthma days</i> <i>reduced</i> by 30% by adding FM [RR (95% CI) 0.70 (0.60 to 0.82)]; <i>reduction</i> <i>in the rate of severe</i> <i>exacerbations</i> by adding FM = 52% [RR (95% CI) 0.48 (0.39, 0.59)] Rescue med use: BUD+FM > BUD [# <i>rescue inhalations per day</i> , adjusted mean: 0.89 vs. 0.66 vs. 0.75 vs. 0.63; $P = 0.0001$ BUD vs. BUD+FM (both strengths)]	
Pauwels et al. 1997 ¹³⁸	RCT, DB, DD 852	Multinational (9: Belgium, Canada, Netherlands, Israel, Italy, Luxembourg, Norway, Spain, and UK)	BUD (200) vs. BUD (200) + FM (24) vs. BUD (800) vs. BUD (800) + FM (24)	Symptoms: BUD+FM > BUD [<i>mean daytime symptom score</i> : 0.57 vs. 0.46 vs. 0.53 vs. 0.33, $P < 0.001$; <i>Mean nighttime symptom score</i> : 0.37 vs. 0.31 vs. 0.38 vs. 0.20, $P <$ 0.001; <i>episode-free days</i> , mean % of the year: 41.7 vs. 51.1 vs. 45.7 vs. 54.8, $P = 0.001$]	Fair
Juniper et al. 1999 ¹³⁹	12 months	Age 18-70 with uncontrolled asthma on ICS	All administered via DPI	Exacerbations : BUD+FM > BUD [#/ <i>patient/yr of severe</i> : 0.91 vs. 0.67 vs. 0.46 vs. 0.34, $P = 0.01$; #/ <i>patient/</i> <i>year of mild</i> : 35.4 vs. 21.3 vs. 22.3 vs. 13.4, $P < 0.001$; % <i>patients</i> <i>without severe exacerbation</i> : 61.4 vs. 70.3 vs. 71.8 vs. 80.8, $P = \text{NR}$] Rescue med use: BUD+FM > BUD [#/ <i>puffs/day</i> : 0.91 vs. 0.57 vs. 0.82 vs. 0.44, $P < 0.001$; #/ <i>puffs/night</i> : 0.29 vs. 0.18 vs. 0.20 vs. 0.11, $P < 0.001$] P values reported for combined BUD vs. combined BUD + FM groups	
Pohunek et al. 2006 ¹⁶²	RCT, DB, DD 630 12 weeks	Multinational (Austria, Belgium, the Czech Republic, France, Hungary, Poland, Spain and Switzerland)	BUD (400) vs. BUD (400) + FM (18) vs. BUD/FM (320/18)	Symptoms: No difference [<i>baseline mean and mean over 12-</i> <i>week treatment: symptom score</i> (0– 6): 1.4 and 0.8 vs. 1.5 and 0.8 vs. 1.5 and 0.8, $P = \text{NS}$; % of <i>symptom-free</i> <i>days</i> : 20.8 and 52.8 vs. 17.7 and 50.6 vs. 19.5 and 52.5, $P = \text{NS}$] Nocturnal awakenings: No difference [<i>baseline mean and mean over 12-</i>	Fair
		Age 4-11, treated with ICS for at least	All given by DPI		

Table 32. Summary of head-to-head studies comparing ICS+LABA compared with same dose ICS

Study	Study design N Duration	Country Study population Setting	Comparison (total daily dose)	Results	Quality rating
		3 months, symptomatic mild to severe persistent asthma, uncontrolled		week treatment, <i>nighttime awakenings</i> (%): 16.9 and 6.6 vs. 17.0 and 7.1 vs. 18.4 and 6.8, <i>P</i> = NS]	
		Multicenter (80), outpatients		Rescue med use: No difference [baseline mean and mean over 12-week treatment, <i>inhalations/24 hours</i> : 0.82 and 0.36 vs. 0.88 and 0.41 vs. 0.96 and 0.37, <i>P</i> = NS; % <i>rescue-free days</i> : 54.8 and 78.2 vs. 53.8 and 77.0 vs. 52.4 and 79.4, <i>P</i> = NS]	
				Quality of life: No difference [baseline mean and mean at endpoint, PAQLQ(S) score (range 1–7): 5.8 and 6.2 vs. 5.8 and 6.2 vs. 5.7 and 6.2, <i>P</i> = NS; PAQLQ(S) score adjusted mean changes: 0.501 vs. 0.494 vs. 0.437, <i>P</i> = NS]	
Price et al. 2002 ¹⁶³	RCT, DB	UK and Ireland	BUD DPI (800) + eFM	Only data from Part II shown here	Fair
FLOW research group	663 (505 for second randomization) 32 weeks (Part I = 4 weeks, Part II = well controlled subjects were re-randomized for 28 more weeks)	Age > 12, asthma > 3 months, symptomatic on ICS (about 67%) or SABA alone, subject that were well controlled during initial 4 weeks (N = 505) were re-randomized to the same treatments	DPI (18) vs. BUD DPI (800) + placebo	Symptoms: BUD + eFM > BUD [frequency of poorly controlled days, days/patient/6months: 10.0 vs. 14.2, frequency ratio 0.70 (95% CI: 0.52 to 0.95; <i>P</i> = 0.02); # of symptom-free days: 89.0 vs. 71.6, difference 17.4 (95% CI: 6.4, 28.7; <i>P</i> = 0.002) Exacerbations: BUD + eFM > BUD [Frequency of mild exacerbations per patient: 7.2 vs. 10.5 per 6 months, frequency ratio 0.69 (95% CI: 0.49, 0.96; <i>P</i> = 0.03) Rescue med use: BUD + eFM > BUD [Day and nighttime use: lower in BUD + eFM group (data NR, <i>P</i> < 0.001); # of rescue-free days: 77.4 vs. 57.1, difference 20.3 (95% CI: 9.4, 31.4; <i>P</i> < 0.001) Quality of life: No difference [improvement in overall QoL score: 0.23 vs. 0.03, difference between treatments = 0.20, <i>P</i> = 0.1] Missed work or school: No difference [% of days taken off work or school because of asthma (<i>P</i> = NS, data	

Table 32. Summary of head-to-head studies comparing ICS+LABA compared with same dose ICS

Study	Study design N Duration	Country Study population Setting	Comparison (total daily dose)	Results	Quality rating
Tal et al. 2002 ¹⁶⁵	RCT, DB, DD 286 12 weeks	Multi-national (Belgium, Czech Republic, Hungary, Israel, South Africa, Spain, UK) Age 4-17, suboptimal lung function despite treatment with ICS, moderate persistent Multicenter (48), University Hospitals	BUD/FM DPI (320/9) vs. BUD DPI (400) BUD/FM N = 148 BUD N = 138	<p>NR]]</p> <p>Symptoms: No difference [mean % <i>symptom-free days</i>, baseline and treatment: 65, 77.5 vs. 70, 75.1, between group difference = -2.3 (95% CI: -2.4, 7; <i>P</i> = NS); <i>mean total asthma symptom score</i> (0-6), baseline and endpoint: 0.67, 0.45 vs. 0.58, 0.48, between group difference = -0.04 (95% CI: -0.16, 0.08; <i>P</i> = NS)]</p> <p>Nocturnal awakenings: No difference [% <i>nights with awakenings at baseline</i>: 7.2% vs. 8.5%; Mean night time awakenings during treatment, %: 5.5 vs. 6.6, between group difference = -1.1 (95% CI: -3.6, 1.3; <i>P</i> = NS)]</p> <p>Exacerbations: BUD/FM > BUD trend [<i>N (%) of patients with asthma aggravations</i>: 8 (5.4) vs. 4 (2.9), <i>P</i> = NR]</p> <p>Rescue med use: No difference [<i>Inhalations/24 hour period</i>, baseline and mean change during 24 hour period: 0.71, -0.11 vs. 0.5, -0.09, between group difference = -0.03 (95% CI: -0.19, 0.14; <i>P</i> = NS)]</p>	Fair
Zetterstrom et al. 2001 ¹⁶⁷	RCT, DB, DD 362 12wk	Multinational (Finland, Germany, Ireland, Norway, Spain, and Sweden) Age ≥ 18yr, mild to severe persistent asthma, not controlled with ICS alone Multicenter (59), University hospitals	BUD/FM (640/18) vs. BUD (800) + FM (18) vs. BUD (800)* All given by DPI	<p>Symptoms: BUD/FM > BUD; BUD+FM > BUD [<i>total asthma symptom score</i> (0-6), mean change from baseline (95% CI): -0.52 (-0.65, -0.39) vs. -0.44 (-0.57, -0.31) vs. - 0.20 (-0.33, -0.7), <i>P</i> < 0.01 for both; % <i>symptom-free days</i>, increase from baseline (95% CI): 25 (19.5, 30.6) vs. 22.3 (16.6, 28.0) vs. 8 (2.4, 13.6), <i>P</i> < 0.001 for both; % of <i>asthma control days</i>, increase from baseline (95% CI): 28.5 (22.8, 34.2) vs. 26.9 (21.1, 32.8) vs. 12.1 (6.3, 17.9), <i>P</i> < 0.001 for both]</p> <p>Nocturnal awakenings: No difference [% of <i>nights with awakenings due to asthma</i>, change from baseline (95% CI): -8.4 (-11.4, -5.4) vs. -5.6 (-8.7, -2.5) vs. -5.8 (-8.8, -2.7), <i>P</i> = NS]</p> <p>Exacerbations: No difference</p>	Good

Table 32. Summary of head-to-head studies comparing ICS+LABA compared with same dose ICS

Study	Study design N Duration	Country Study population Setting	Comparison (total daily dose)	Results	Quality rating
				<p>[severe exacerbations, n (%) of patients: 8 (6.5) vs. 11 (9.6) vs. 11 (8.9); $P = \text{NS}$]</p> <p>Rescue med use: BUD/FM > BUD; BUD + FM > BUD [Inhalations per day, mean change from baseline (95% CI): -0.99 (-1.29, -0.69) vs. -1.13 (-1.43, -0.28) vs. -0.44 (-0.74, -0.13), $P < 0.01$ for both; % rescue-free days, mean increase from baseline (95% CI): 31.9 (26.3, 37.5) vs. 31.9 (26.2, 37.6) vs. 12.8 (7.1, 18.4), $P < 0.001$ for both]</p> <p>P values reported are for BUD/FM vs. BUD and BUD + FM vs. BUD</p>	
Fluticasone + salmeterol compared with fluticasone					
Bateman et al. 2001 ¹⁵⁴	RCT, DB, DD 497 12 weeks	Multinational (10) Age ≥ 12, mild-moderate persistent asthma, not controlled on ICS Multicenter (69)	FP/SM MDI (200/100) vs. FP/SM DPI (200/100) vs. FP MDI (200)	<p>Symptoms: FP/SM > SM [% symptom-free days during treatment, median: 55 vs. 52 vs. 25, $P = 0.001$; % symptom-free nights during treatment, median: 71 vs. 78 vs. 53, $P = 0.063$]</p> <p>Rescue med use: FP/SM > SM [% rescue-free days during treatment, median: 73 vs. 75 vs. 58, $P = 0.003$; median % rescue-free nights during treatment: 90 vs. 93 vs. 80, $P = 0.033$]</p> <p>All P values are FP/SM MDI vs. FP; no P values were reported for FP/SM DPI vs. FP</p>	Fair
Ind et al. 2003 ¹³²	RCT, DB, DD 502 24 weeks	Multinational (UK, Italy, Canada, Denmark, Iceland, Republic of Ireland) Age 16 to 75, moderate to severe, not controlled on ICS Multicenter (100) - Hospitals and primary care centers	FP/SM MDI (500/100) vs. FP MDI (500) vs. FP MDI (1000)	<p>Only data for FP/SM vs. FP 500 shown here</p> <p>Symptoms: FP/SM > FP [% symptom free days, median change from baseline: 21 vs. 0, $P = 0.002$; % symptom free nights, median change from baseline: 15 vs. 0, $P < 0.002$]</p> <p>Exacerbations: No difference [severe exacerbations/patient/year 0.05 vs. 0.16, $P = \text{NS}$; moderate exacerbations/patient/year 0.77 vs. 0.95, $P = \text{NS}$; % of patients experiencing a severe exacerbation: 3 vs. 8, $P = 0.059$; % of patients experiencing at least 1 moderate or</p>	Fair

Table 32. Summary of head-to-head studies comparing ICS+LABA compared with same dose ICS

Study	Study design N Duration	Country Study population Setting	Comparison (total daily dose)	Results	Quality rating
				severe exacerbation: 27 vs. 35, $P =$ NS] Rescue med use : FP/SM > FP [<i>rescue-free days</i> , median % of days: 53 vs. 15, $P \leq 0.00$; <i>rescue-free nights</i> , median % of nights: 90 vs. 78, $P \leq 0.001$]	
Kavuru et al. 2000 ¹⁰⁵	RCT, DB 356 12 weeks	US Age ≥ 12 yr, patients well controlled on current therapy (stratified into 2 eligible groups: group 1 had to be on ICS for ≥ 3 months; group 2 was taking SM for ≥ 1 week), severity NR Multicenter	Placebo vs. FP/SM DPI (200/100) vs. SM DPI (100) vs. FP DPI (200)	Only data for FP/SM vs. FP reported here Symptoms: FP/SM > FP [<i>symptom score</i> , mean change from baseline (SE): -0.7 (0.11) vs. -0.2 (0.09), $P \leq 0.025$; % <i>symptom-free days</i> , mean change (SE): 22.6 (4.59) vs. 7.2 (4.09), $P \leq 0.025$] Nocturnal awakenings: No difference [% of nights with no awakenings, mean change from baseline (SE): 4.6 (1.73) vs. 2.4 (2.34), $P =$ NS] Exacerbations: FP/SM > FP [% of patients withdrawn due to worsening asthma: 3 vs. 11; SM/FP group had greater probability of remaining in the study without being withdrawn due to worsening asthma ($P \leq 0.02$, survival analysis)] Rescue medicine use: FP/SM > FP [<i>puffs/day</i> , mean change from baseline (SE): -1.9 (0.26) vs. -0.4 (0.21), $P \leq 0.025$]	Fair
Koopmans et al. 2006 ¹⁵⁹	RCT, DB 54 1 year	The Netherlands Age 18-60, mild-moderate persistent allergic asthma, not controlled on ICS Outpatient, Academic Medical Center	FP/SM (500/100) vs. FP (500) All given by DPI	Symptoms: FP/SM > FP [<i>Day time symptom score</i> (0-4): mean difference (SE) : -0.1 (0.1), $P = 0.02$; <i>Night time symptom score</i> (0-5): mean difference (SE): -0.2 (0.1) $P = 0.01$] Rescue med use: FP/SM > FP [<i>puffs/day</i> , mean difference (SE) -0.9 (0.3), $P < 0.001$]	Fair
Lundback et al. 2006 ¹⁰⁶	RCT, DB 282 12 months	Sweden Age ≥ 18 , mild or moderate persistent, uncontrolled on current medication (68% were on ICS)	FP/SM DPI (500/100) vs. FP DPI (500) vs. SM DPI (100)	Only data for FP/SM vs. FP reported here Symptoms: No apparent difference [median % <i>symptom-free days</i> : 66.7 vs. 67.9, $P =$ NR; median % <i>symptom-free nights</i> : 100 vs. 100, $P =$ NR]	Fair

Table 32. Summary of head-to-head studies comparing ICS+LABA compared with same dose ICS

Study	Study design N Duration	Country Study population Setting	Comparison (total daily dose)	Results	Quality rating
		Patients recruited from ~4000 individuals with asthma who had participated in large epidemiologic studies		Exacerbations : FP/SM > FP [% patients with ≥ 2 exacerbations: 4.2 vs. 17.4, $P < 0.01$; % of patients requiring medication adjustment (usually for having ≥ 2 exacerbations): 10.5 vs. 34.8, $P < 0.001$] Rescue medicine use: No difference [median % rescue-free days: 85.7 vs. 85.7, $P = \text{NR}$; median % of patients with rescue-free nights: 100 vs. 100, $P = \text{NR}$]	
Nathan et al. 2006 ¹⁰⁸	RCT, DB 365 12 weeks	US Age ≥ 12 yr, not controlled on ICS, severity NR Multicenter (45)	FP/SM MDI (440/84) vs. FP MDI (440) vs. SM MDI (84) vs. placebo	Only data for FP/SM vs. FP reported here Symptoms: No difference [symptom score(0-5), mean change from baseline (SE): -0.5 (0.11) vs. -0.2 (0.09); $P = \text{NS}$; % Symptom-free days, mean change (SE): 18.5 (3.9) compared with 15.0 (3.3); $P = \text{NS}$] Nocturnal awakenings: No difference [% nights without awakenings, mean change (SE): 4.1 (1.4) compared with -0.6 (2.1), $P = \text{NS}$] Exacerbations: No difference [% of patients withdrawn due to exacerbations: 7 compared with 11, $P = \text{NS}$] Rescue medicine use: FP/SM > FP [puffs/day, mean change (SE): -1.6 (0.3) vs. -0.5 (0.2), $P < 0.001$; % of rescue-free days, mean change (SE): 32.5 (4.5) vs. 13.1 (3.3), $P \leq 0.005$]	Fair
Shapiro et al. 2000 ¹¹¹ AND Nathan et al. 2003 ¹¹²	RCT, DB 349 12 weeks	US Age ≥ 12 , previously treated with low to medium ICS for at least 12 weeks Multicenter (42 Research Centers/ Allergy and Asthma Centers)	Placebo vs. FP/SM DPI (500/100) vs. SM DPI (100) vs. FP DPI (500)	Only data for FP/SM compared with FP shown here Symptoms: FP/SM > FP [Symptom Score (0-5), mean change from baseline (SEM): -0.8 (0.12) vs. -0.4 (0.09), $P \leq 0.015$; symptom score, % improvement from baseline: 57 vs. 25, $P \leq 0.015$; % symptom-free days, change from baseline (SEM): 33.8 (4.6) vs. 15.4 (4.2), $P \leq 0.015$] Nocturnal awakenings: FP/SM > FP	Fair

Table 32. Summary of head-to-head studies comparing ICS+LABA compared with same dose ICS

Study	Study design N Duration	Country Study population Setting	Comparison (total daily dose)	Results	Quality rating
				<p>[% <i>awakening-free nights</i>, change from baseline (SEM): 7.2 (1.9) compared with 2.8 (2.4), $P \leq 0.015$]</p> <p>Exacerbations: FP/SM > FP [% of patients having a clinical exacerbation: 2 compared with 7; probability of remaining in the study without being withdrawn due to worsening asthma (survival analysis): % of patients remaining: 84 compared with 73; $P \leq 0.002$]</p> <p>Rescue medicine use: FP/SM > FP [<i>puffs/day</i>, mean change from baseline (SEM): -2.3 (0.4) compared with -0.9 (0.2), $P \leq 0.015$]</p> <p>Quality of life: Unclear [<i>activities limitation</i>, measured by the activities domain of the AQLQ (11 items): 1 (0.13) compared with 0.62 (0.10); $P = \text{NR}$ for comparison; $P < 0.001$ within each group]</p>	
ICS + salmeterol compared with ICS					
Boyd et al. 1995 ¹⁵⁵	RCT, DB 119 12 weeks	UK Age ≥ 18 , uncontrolled on ICS ($\geq 1,500$ mcg of BDP or equivalent), under consideration for maintenance oral corticosteroid therapy Multicenter (15 out-patient departments)	ICS + SM DPI (200) compared with ICS + placebo Subjects continued their current ICS and were randomized to SM compared with placebo	<p>Symptoms: ICS+SM > ICS+placebo for nighttime symptoms, trend for daytime [<i>Daytime symptom scores</i>, mean (SD): baseline: 0.94 (0.23) vs. 0.94 (0.22); during treatment: 0.74 (0.45) vs. 0.82 (0.39); change from baseline: -0.21 (0.41) vs. -0.12 (0.32), $P = 0.24$; <i>Nighttime symptom scores</i>, mean (SD): baseline: 0.91 (0.28) vs. 0.73 (0.44); treatment: 0.45 (0.50) vs. 0.58 (0.50); change from baseline: -0.45 (0.49) vs. -0.15 (0.48); $P = 0.002$ <i>Proportion of symptom-free days</i>, mean (SD): baseline: 0.08 (0.17) vs. 0.07 (0.19); treatment: 0.30 (0.36) vs. 0.20 (0.31); change from baseline: 0.22 (0.30) vs. 0.13 (0.22); $P = 0.07$; <i>Proportion of symptom-free nights</i>, mean (SD): baseline: 0.20 (0.25) vs. 0.29 (0.33); treatment: 0.53 (0.38) vs. 0.42 (0.38); change from baseline: 0.33 (0.32) vs. 0.13 (0.26), $P = 0.001$]</p> <p>Exacerbations: No difference [# of patients requiring short course of oral steroids: 19 vs. 15, $P = 0.19$]</p>	Fair

Table 32. Summary of head-to-head studies comparing ICS+LABA compared with same dose ICS

Study	Study design N Duration	Country Study population Setting	Comparison (total daily dose)	Results	Quality rating
				Rescue med use: ICS+SM > ICS + placebo [<i>Puffs/24 hours</i> , mean (SD): baseline: 11.3 (6.0) vs. 9.7 (4.0); treatment: 6.3 (6.2) vs. 7.2 (4.9); change from baseline: -5.1 (4.7) vs. -2.5 (4.0), <i>P</i> = 0.002]	
Kemp et al. 1998 ¹⁵⁸	RCT, DB 506 14 weeks	US Age ≥12yr, used a SABA on a daily basis, symptomatic despite using fixed and approved dose of ICS Multicenter (44)	ICS + SM MDI (84) compared with ICS + placebo Subjects continued their current ICS and were randomized to SM compared with placebo	Symptoms: ICS+SM > ICS+placebo [<i>Daytime symptom score</i> , mean change from baseline (SEM): -0.55 (0.03) vs. -0.30 (0.03); <i>P</i> < 0.001; <i>Nighttime symptom score</i>): -0.65 (0.04) vs. -0.26 (0.04); <i>P</i> < 0.001] Rescue med use: ICS+SM > ICS+ placebo [<i>Puffs/day</i> , mean change from baseline (SEM): -2.73 (0.16) vs. -1.06 (0.12), <i>P</i> < 0.001; <i>Puffs/night</i> , mean change from baseline (SEM): -0.75 (0.07) vs. -0.18 (0.07), <i>P</i> < 0.001; % <i>rescue-free days</i> , mean change: 38.1 (2.3) vs. 13.6 (1.8), <i>P</i> < 0.001; % <i>rescue-free nights</i> , mean change: 29.2 (2.4) vs. 9.5 (1.8), <i>P</i> < 0.001] Quality of life: No difference, trend toward ICS+SM > ICS + placebo [<i>AQLQ global score</i> : baseline mean (SEM): 4.30 (0.06) vs. 4.27 (0.06); mean change from baseline (SEM): 1.08 (0.08) vs. 0.61 (0.07), <i>P</i> = 0.47; <i>AQLQ activity limitation</i> : 4.64 (0.07) vs. 4.57 (0.07); mean change: 0.91 (0.07) vs. 0.54 (0.07), <i>P</i> = 0.37; <i>AQLQ asthma symptoms</i> : 4.07 (0.07) vs. 4.05 (0.06); mean change: 1.28 (0.08) vs. 0.71 (0.08), <i>P</i> = 0.57; <i>AQLQ emotional function</i> : 3.96 (0.09) vs. 4.02 (0.09); mean change 1.17 (0.10) vs. 0.65 (0.09), <i>P</i> = 0.52; <i>AQLQ environmental exposure</i> : 4.50 (0.09) vs. 4.45 (0.09); mean change: 0.84 (0.09) vs. 0.47 (0.08), <i>P</i> = 0.37]	Fair
Russell et al. 1995 ¹⁶⁴	RCT, DB 210 12 weeks	UK Age 4-16, uncontrolled on high-dose ICS (≥ 400 BDP daily or equivalent), moderate to severe persistent asthma	ICS + SM DPI (100) compared with ICS + placebo DPI Subjects continued their current	Symptoms: ICS+SM > ICS + placebo [<i>median % of symptom-free days</i> : baseline: 15 vs. 8; median % symptom-free days at weeks 9-12: 60 vs. 26, <i>P</i> = 0.008; <i>median change from baseline</i> : favors SM group, data in figure, <i>P</i> = 0.008; <i>median % of symptom-free nights</i> : baseline: 57 vs. 38; median change from baseline: favors SM group during	Fair

Table 32. Summary of head-to-head studies comparing ICS+LABA compared with same dose ICS

Study	Study design N Duration	Country Study population Setting	Comparison (total daily dose)	Results	Quality rating
		Multicenter (78 hospitals)	ICS and were randomized to SM compared with placebo	first 4 weeks ($P = 0.013$), other data NR] Rescue med use: ICS+SM > ICS+ placebo for daytime [# blisters/day used, baseline: 2 vs. 2; median change from baseline in rescue med use to weeks 9-12 (#blisters/day): 0.8 vs. 0.3, $P = 0.032$; nighttime use, #blisters/night: baseline: 0.4 vs. 0.5; decrease in use: 0.1 vs. 0.1, $P = NR$]	
ICS + formoterol compared with ICS					
van der Molen et al. 1997 ¹⁶⁶	RCT, DB 239 6 months	Netherlands and Canada Adults, uncontrolled on ICS, mild to moderate persistent asthma Multicenter (16), general practitioners and outpatient hospitals	ICS + FM DPI (48) compared with ICS + placebo DPI ICS + FM N = 125 ICS + placebo N = 114 Subjects continued their current ICS and were randomized to FM compared with placebo	Symptoms: ICS+FM > ICS + placebo [Improvement in symptom score from baseline: 1.28 compared with 0.64, between group difference=0.64, $P = 0.039$] Exacerbations: No difference [# (%) of subjects requiring courses of oral prednisolone: 33 (26.4%) compared with 32 (28.1%), difference between groups $P = NS$; # of courses of prednisolone: 58 compared with 55; $P = NS$] Rescue med use: ICS+FM > ICS + placebo [decrease in mean daytime # inhalations: 1.5 (from 2.4 at baseline to treatment mean 0.9) compared with 0.4, between group difference= -1.1 (95% CI: -1.4, -0.7; $P < 0.001$); decrease in mean nighttime # inhalations: 0.9 (from 1.5 at baseline to treatment mean 0.6) compared with 0.2, between group difference== -0.8 (95% CI: -1.1, -0.5; $P < 0.001$)]	Fair
Zimmerman et al. 2004 ¹⁶⁸	RCT, DB 302 12 weeks	Canada Age 6-11, not controlled on ICS alone Multicenter (27)	ICS + FM DPI (18) vs. ICS + FM DPI (9) vs. ICS + placebo Subjects continued their current ICS and were randomized to FM (18) vs. FM (9) vs. placebo	Symptoms: No difference [Total symptom score: baseline mean (range): 1.32 (0.0–4.0) vs. 1.58 (0.1–4.2) vs. 1.50 (0.0–4.0); treatment mean (range): 1.02 (0.0–3.3) vs. 1.28 (0.0–4.2) vs. 1.23 (0.0–4.4); adjusted mean change from baseline: -0.37 vs. -0.28 vs. -0.27, $P = NS$] Rescue med use: No difference [mean #inhalations/day: baseline mean (range): 0.74 (0.0–5.6) vs. 1.04 (0.0–5.4) vs. 1.36 (0.0–9.2); treatment mean (range): 0.72	Fair

Table 32. Summary of head-to-head studies comparing ICS+LABA compared with same dose ICS

Study	Study design N Duration	Country Study population Setting	Comparison (total daily dose)	Results	Quality rating
				(0.0–5.2) vs. 0.73 (0.0–8.4) vs. 0.95 (0.0–7.7); adjusted mean change from baseline: -0.13 vs. -0.27 vs. -0.21, <i>P</i> = NS]	
				Quality of life: No difference [<i>PAQLQ total score</i> : baseline mean (range): 5.33 (2.4–6.9) vs. 5.13 (2.5–7.0) vs. 5.09 (1.6–6.9); treatment mean (range): 5.80 (3.4–7.0) vs. 5.72 (2.7–7.0) vs. 5.76 (2.2–7.0); adjusted mean change from baseline: 0.49 vs. 0.52 vs. 0.57]	

Beclomethasone + salmeterol compared with beclomethasone

Verberne et al. 1998 ¹⁴⁴	RCT, DB 177 1 year	Multinational (Netherlands, UK) Age 6-16, on ICS for at least 3 months, mild to moderate asthma Multicenter (outpatient clinics of 9 hospitals, 6 university hospitals, and 3 general hospitals)	BDP (400) + SM (100) vs. BDP (800) vs. BDP (400) All given by DPI	Only data for BDP+SM vs. BDP (400) shown here Symptoms: No difference [% of children reporting no symptoms, baseline and endpoint: 3, 34 vs. 11, 35; <i>P</i> = NS] Exacerbations: No difference [patients requiring OCS for exacerbations, total # of prednisolone courses (# of patients): 13 (10) vs. 13 (10), <i>P</i> = NR] Rescue med use: No difference [median # additional inhalations per day: 0.19 vs. 0.15, <i>P</i> = NS]	Fair
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Abbreviations: AQLQ = Asthma Quality of Life Questionnaire; BDP = beclomethasone dipropionate; BUD = Budesonide; CI = confidence interval; DB = double-blind; DD = double dummy; DPI = dry powder inhaler; eFM = Eformoterol; FM = Formoterol; FP = Fluticasone Propionate; ; ICS = Inhaled Corticosteroids; LABAs = Long-Acting Beta-2 Agonists; MA=meta-analysis; MDI = metered dose inhaler; NR = not reported; NS = not statistically significant; OCS= oral corticosteroids; QOL = quality of life; pMDI= pressurized metered dose inhaler; RCT= randomized controlled trial; RR = relative risk; SM = Salmeterol; SMD = standard mean difference; SR=systematic review; WMD = weighted mean difference.

Symbol use: Drug X > Drug Y = statistically significant difference in outcomes favoring Drug X; Drug X > Drug Y trend = point estimate favors Drug X, but the difference is not statistically significant or tests of statistical significance were NR; No difference = no statistically significant difference or tests of statistical significance were not reported and outcomes are similar.

*Doses of ICS in this study are considered equivalent: differences in the number are explained by labeling changes for new inhaled drugs, which require the delivered dose rather than metered dose to be reported.

Note: All results are listed in the same order as the comparison column lists the medications.

4. ICS+LTRA compared with ICS

Summary of findings

We found one systematic review with meta-analysis¹⁷¹ and four RCTs^{90, 172-175} meeting our inclusion/exclusion criteria (Table 34). Three of the RCTs were in adolescents and adults ≥ 12 years of age and one was in children < 12.¹⁷⁵

Overall, the addition of LTRAs to ICSs compared to continuing the same dose of ICSs resulted in improvement in rescue medicine use and a non-statistically significant trend toward fewer exacerbations requiring systemic steroids. There is no apparent difference in other health outcomes between those treated with ICSs plus LTRAs compared to those treated with increasing the dose of ICSs. There were some conflicting results and further research may alter the results (Table 3 Evidence Profile).

Table 33. Evidence profile of the comparative efficacy of ICS + LTRA compared with ICS

Evidence profile: Comparative efficacy of ICS + LTRA compared with ICS							
Number of studies (# of subjects)	Design	Quality	Consistency	Directness	Result, magnitude of effect*	Other modifying factors*	Overall strength of evidence
LTRA + ICS compared with ICS same dose							
1 (5,871)	1 SR w/ MA	Good	Some inconsistency	Direct	Exacerbations: non-statistically significant reduction in the risk of exacerbations requiring systemic steroids: RR 0.64, 95% CI: 0.38, 1.07 Symptoms: No difference Rescue medicine use: LTRA+ICS > ICS [SMD -0.15, 95% CI: -0.24, -0.05] Quality of Life: No difference [WMD 0.08, 95% CI: -0.03, 0.20]	Few trials tested licensed doses of LTRAs: just 4 trials did so for the primary outcome: exacerbations requiring systemic steroids	Low
BUD + ML compared with BUD same dose							
1 (639)	RCT (16 weeks)	Fair	Some inconsistency	Direct	Mixed results: BUD+ML > BUD for most outcome measures; no difference for some	None	Low
BDP + ML compared to BDP same dose							
1 (642)	RCT (16 weeks)	Fair	Some inconsistency	Direct	Mixed results: BDP+ML > BDP for most outcome measures; no difference for some	None	Low
LTRA + ICS compared with ICS increased dose							
1 (5,871)	1 SR w/ MA	Good	Some inconsistency	Direct	Symptoms: No difference [change from baseline in symptoms score (WMD 0.01, 95% CI: -0.09, 0.10)] Exacerbations: No difference [risk of exacerbation requiring systemic steroids: RR 0.92, 95% CI: 0.56, 1.51] Rescue medicine use: No difference	Only 3 trials in the MA compared licensed doses of LTRAs with increasing the dose of ICSs Power of the MA is insufficient to confirm	Moderate

Evidence profile: Comparative efficacy of ICS + LTRA compared with ICS							
Number of studies (# of subjects)	Design	Quality	Consistency	Directness	Result, magnitude of effect*	Other modifying factors* the equivalence	Overall strength of evidence
BUD + ML compared with BUD increased dose							
2 (960)	RCTs (12-16 weeks)	Fair	Some inconsistency	Direct	No difference for most outcomes (one trial); One trial reported fewer exacerbations with increased dose BUD	None	Low

Abbreviations: BUD = Budesonide; CI = confidence interval; ICS = Inhaled Corticosteroids; LTRAs = Leukotriene receptor antagonists; MA=meta-analysis; ML = Montelukast; QOL = quality of life; RCT= randomized controlled trial; RR= Risk Ratio; SMD = standard mean difference; SM = Salmeterol; SR=systematic review; WMD = weighted mean difference.

Detailed Assessment

Description of Studies

We found one systematic review with meta-analysis¹⁷¹ and four RCTs^{90, 172-175} meeting our inclusion/exclusion criteria (Table 34). Three compared budesonide plus montelukast with budesonide alone. Two studies^{90, 174} compared the combination of an ICS plus LTRA with the same dose ICS and two studies^{172, 173, 175} compared the combination with an increased dose of ICS.

Study Populations

The four RCTs included a total of 2,241 patients. Most studies were conducted in adolescent and adult populations; one study enrolled a pediatric population ages six to 14.¹⁷⁵ One was conducted in Europe, one in India, and two were other multinational combinations. Asthma severity ranged from mild persistent to severe persistent. One enrolled patients with mild to moderate persistent asthma; two enrolled patients with mild to severe persistent asthma; one enrolled patients with moderate persistent asthma.

Methodologic Quality

The four included RCTs were fair quality studies. The method of randomization and allocation concealment was rarely reported.

Head-to-head comparisons

1. ICS+LTRA compared with ICS

One good systematic review with meta-analysis¹⁷¹ compared LTRA plus ICS with the same dose of ICS, same dose of ICS with taper, or increased doses of ICS. The systematic review included 27 studies (5871 subjects); two of the studies were in children and 25 were in adults. Sixteen of the 27 trials reported data in a way that allowed meta-analysis. Three of these included trials met our inclusion criteria.^{90, 172-174} Many were excluded for wrong medication (pranlukast) or short duration (less than six weeks). Thirteen of the studies (two in children) compared an LTRA plus an ICS with the same doses of an ICS; seven studies compared an LTRA plus an ICS with increased doses of an ICS; and seven studies compared an LTRA plus an ICS with the same doses of ICS with tapering. The LTRAs included montelukast,

zafirlukast, and pranlukast. Many trials used higher than licensed doses of LTRAs. Most trials used BDP with a dosing range from low (≤ 400 mcg/day BDP or equivalent) to high (> 800 mcg/day BDP or equivalent) potency, with each trial ensuring same ICS dosing for both groups.

ICS+LTRA compared with same dose ICS. For ICS plus LTRA compared with the same dose of ICS, the systematic review reported a non-significant reduction in the risk of exacerbations requiring systemic steroids (RR 0.64, 95% CI: 0.38 to 1.07), the primary outcome. Just four trials using licensed doses of LTRAs contributed data to the primary outcomes. The systematic review found no significant difference in symptom score (WMD = -0.10, 95% CI: -0.24, 0.03) or nocturnal awakenings (WMD -6.25, 95% CI: -12.72, 0.23). Higher than licensed doses of LTRA did show a significant difference in improvement from baseline in asthma symptom scores (SMD = -0.46, 95% CI: -0.25, -0.66). Those treated with both licensed and higher than licensed doses of LTRAs had a significant decrease in beta-agonists use compared to those treated with same dose ICSs (SMD -0.15, 95% CI: -0.24, -0.05) and SMD -0.43, 95% CI: -0.22, -0.63). There was no significant difference in quality of life (WMD 0.08, 95% CI: -0.03, 0.20).

ICS+LTRA compared with increased ICS. For ICS plus LTRA compared with increased doses of ICS, only 3 of the trials included in the systematic review compared licensed doses of LTRAs with increasing the dose of ICSs. The meta-analyses found no significant difference in any outcomes including the following: change from baseline in symptoms score with licensed (WMD 0.01, 95% CI: -0.09, 0.10) or higher than licensed doses of LTRA (WMD -0.06, 95% CI: -0.16, 0.03); risk of experiencing an asthma exacerbation requiring systemic steroids with licensed doses (RR 0.92, 95% CI: 0.56, 1.51) or higher than licensed doses of LTRA (RR 1.05 95% CI: 0.55, 2.00); withdrawals due to poor asthma control with licensed (RR 0.49, 95% CI: 0.15, 1.63) or higher than licensed doses of LTRA (RR 0.72 95% CI: 0.29, 1.76); and change from baseline in use of rescue beta-agonists with licensed (WMD -0.03 95% CI: -0.24, 0.18) nor higher than licensed doses of LTRA (WMD 0.00 95% CI: -0.37, 0.37).

ICS+LTRA compared with same ICS (tapering). For ICS plus LTRA compared with the same ICS dose with tapering (seven studies), the systematic review found no significant difference in final symptom scores (WMD -0.06, 95% CI: -0.17 to 0.05), number of patients with exacerbations requiring systemic steroids (RR 0.47, 95% CI: 0.20, 1.09), difference in final beta-agonist use (WMD -0.2 puffs/day, 95% CI: -0.7 to 0.3), or change from baseline in beta-agonist use (WMD -0.15 puffs/week; 95% CI: -0.91, 0.61). There was a significant reduction in rate of withdrawals due to poor asthma control for those treated with ICS plus LTRA (RR 0.63, 95% CI: 0.42 to 0.95), however this was not significant when only the trials using intention to treat analysis were considered (RR 0.63, 95% CI: 0.42, 0.95).

2. Budesonide (BUD)+ Montelukast (ML) compared with Budesonide (BUD) same dose

We found one fair RCT¹⁷⁴ comparing the combination of BUD+ML with the same dose of BUD (Table 34). This fair-rated RCT (N = 639), the CASIOPEA study, compared low to high dose BUD (400 to 1600 mcg/day) plus placebo (N = 313) with low to high dose BUD (400 to 1600 mcg/day) + ML 10 mg/day (N = 326) for 16 weeks.¹⁷⁴ Subjects age 18 to 70 with poorly controlled mild to severe asthma currently being treated with a stable dose of ICS for at least 8 weeks were enrolled from hospital centers in Spain. At endpoint, there were no statistically

significant differences in asthma symptom scores or quality of life. However, those treated with BUD+ML had fewer nocturnal awakenings, more asthma free days, fewer days with exacerbations, and greater decrease in rescue medicine use. The differences were reportedly independent of BUD dose.

3. *Beclomethasone (BDP) + Montelukast (ML) compared to Beclomethasone (BDP) same dose*

We found one trial (N = 642) which compared four treatments for 16 weeks:⁹⁰ low dose BDP (400 mcg/day) + ML (10 mg/day) (N = 193) compared with low dose BDP 400 mcg/day (N = 200) compared with ML 10mg/day (N = 201) compared with placebo (N = 48). Subjects with uncontrolled mild to moderate asthma treated with ICS who were age 15 or greater were enrolled from 18 countries and 70 different centers. At endpoint, those treated with BDP+ML had greater improvement in daytime asthma symptom scores (-0.13 compared with -0.02; $P = 0.041$), nights per week with awakenings (-1.04 compared with -0.45; $P = 0.01$), and percentage of days with an exacerbation (13.37% compared with 17.92%; $P = 0.041$) compared to BDP. BDP+ML showed no significant difference in % of patients with an asthma attack or difference in total puffs/day compared to BDP. Compliance was high with both inhaled and oral groups respectively.

4. *Budesonide (BUD)+ Montelukast (ML) compared with Budesonide (BUD) increased dose*

We found two fair RCTs^{172, 173, 175} comparing the combination of BUD+ML with an increased dose of BUD (Table 34). One fair multinational trial (N = 889) compared medium dose BUD (800 mcg/day) plus ML (10 mg/day) (N = 448) compared with high dose BUD (1600 mcg/day) (N = 441) for 16 weeks.^{172, 173} The trial enrolled subjects age 15 to 75 with uncontrolled asthma treated with medium dose ICS. At endpoint, there were no statistically significant differences between those treated with BUD+ML and those treated with BUD for percentage of asthma free days, daytime symptom score, percentage of nights with awakenings, percentage of days with an exacerbation, percentage of patients requiring oral steroids or hospitalization, rescue medicine use, or quality of life. Adherence was high for both the tablets and inhalers, with over 95% of days fully compliant.

The other trial¹⁷⁵ (N = 71) compared low dose BUD (400 mcg/day) (N = 33) compared with low dose BUD (200 mcg/day) plus ML (5 mg/day) (N = 30) for 12 weeks. Subjects with moderate persistent asthma age 6 to 14 were enrolled from a Pediatric Asthma Clinic in India. At endpoint, those treated with increased dose of BUD had fewer exacerbations compared to BUD+ML (9.1% compared with 33.3%; $P < 0.01$). Adherence was high in both groups with only one patient declaring non-adherence.

Table 34. Summary of head-to-head studies comparing ICS + LTRA compared with ICS

Study	Study design N Duration	Country Study population Setting	Comparison (total daily dose)	Results	Quality rating
ICS + LTRA compared with ICS same dose					
Ducharm et al. 2004 ¹⁷¹	Systematic Review with meta-analysis 27 studies (5871 subjects)	2 trials in children; 25 in adults	LTRA plus ICS vs. ICS same dose, ICS same dose tapering, or ICS increased dose.	<p>LTRA + ICS vs. Same ICS: Symptoms: No difference [change in <i>symptom score</i> (WMD = -0.10, 95% CI: -0.24, 0.03) or <i>nocturnal awakenings</i> (WMD -6.25, 95% CI: -12.72, 0.23) with licensed doses of LTRAs]</p> <p>Exacerbations: LTRA+ICS > ICS trend [<i>reduction in the risk of exacerbations requiring systemic steroids</i>: RR 0.64, 95% CI: 0.38, 1.07]</p> <p>Rescue medicine use: LTRA+ICS > ICS [change from baseline in <i>beta- agonists use</i> (SMD -0.15, 95% CI: -0.24, -0.05)]</p> <p>QOL: No difference [(WMD 0.08, 95% CI: -0.03, 0.20)]</p>	Good
Budesonide + montelukast compared with budesonide same dose					
Vaquerizo et al. 2003 ¹⁷⁴	RCT 639	Spain Age 18 – 70	BUD (400 – 1600) + placebo vs. BUD (400 – 1600) + ML (10) Low to High dose ICS	<p>Symptoms: Mixed results, some favor BUD+ML [<i>asthma symptom score</i>: mean of scores (0-6), mean change from baseline: -0.24 (0.06) vs. -0.34 (0.06); <i>P</i> = 0.07; <i>median % asthma free days</i> (95% CI): 42.3% (32.7 to 51.2) vs. 66.1% (57.4 to 73.8); <i>P</i> = 0.001]</p> <p>Nocturnal awakenings: BUD+ML > BUD [<i>mean % of nocturnal awakenings</i> (95% CI): 32.2% (25.9 to 38.5) vs. 25.6% (19.3 to 31.9); <i>P</i> = 0.01]</p> <p>Exacerbations: BUD+ML > BUD [<i>median % asthma exacerbation days</i>: 4.8% (3.5 to 6.3) vs. 3.1% (2.0 to 4.2); <i>P</i> = 0.03]</p> <p>Rescue medicine use: BUD+ML > BUD [mean % change from baseline in <i>rescue med use per day</i>: -4.92% (7.56) vs. -17.26% (7.5); <i>P</i> < 0.05]</p> <p>QOL: No difference [mean change from baseline in <i>AQLQ score</i> (SE): 0.52 (0.05) vs. 0.60 (0.05); <i>P</i> = 0.34]</p>	Fair
Beclomethasone + montelukast compared with beclomethasone same dose					

Study	Study design N Duration	Country Study population Setting	Comparison (total daily dose)	Results	Quality rating
Lavolette et al. 1999 ⁹⁰	RCT 642 16 weeks	Multinational Age ≥ 15 multicenter	BDP (400) + ML (10) vs. BDP (400) vs. ML (10) vs. placebo Low dose ICS	Symptoms: BDP+ML > BDP [<i>daytime asthma symptom score</i> (- 0.13 vs. -0.02; <i>P</i> = 0.041)] Nocturnal awakenings: BDP+ML > BDP [<i>nights/week with awakenings</i> : - 1.04 vs. -0.45; <i>P</i> = 0.01] Exacerbation: BDP+ML > BDP [% of <i>days with an exacerbation</i> : 13.37% vs. 17.92%; <i>P</i> = 0.041; % <i>patients</i> <i>with an asthma attack</i> (6.2% vs. 12%; <i>P</i> = 0.055] Rescue medicine use: No difference [<i>total puffs/day</i> , change: -5.51% vs. - 6.04; <i>P</i> = 0.08] Compliance: high with both inhaled (94.6%, 92.4%, 94%, 96.5%) and oral (98.6%, 98.7%, 98.7%, 99%) in groups respectively	Fair
ICS + LTRA compared with ICS increased dose					
Ducharm et al. 2004 ¹⁷¹	Systematic Review with meta-analysis 27 studies (5871 subjects)	2 trials in children; 25 in adults	LTRA plus ICS vs. ICS same dose, ICS same dose tapering, or ICS increased dose.	LTRA+ICS vs. Increased ICS : Symptoms: No difference [change from baseline in <i>symptoms</i> <i>score</i> (WMD 0.01, 95% CI: -0.09, 0.10)] Exacerbations: No difference [<i>risk of</i> <i>exacerbation requiring systemic</i> <i>steroids</i> : RR 0.92, 95% CI: 0.56, 1.51; withdrawals due to poor asthma control: RR 0.49, 95% CI: 0.15, 1.63] Rescue medicine use: No difference [change from baseline in <i>use of</i> <i>rescue beta-agonists</i> : WMD -0.03 95% CI: -0.24, 0.18]	Good
Budesonide (BUD)+Montelukast (ML) compared with Budesonide (BUD) increased dose					
Jat et al. 2006 ¹⁷⁵	RCT 71 12 weeks	India Age 6-14 Pediatric Asthma Clinic	BUD (400) vs. BUD (200) + ML (5) Low dose ICS	Exacerbations: BUD+ML > BUD [<i>exacerbations</i> (9.1% vs. 33.3%; <i>P</i> < 0.01] Adherence: high in both groups. Only one patient declared non-adherence.	Fair
Price et al. 2003 ^{172, 173} COMPACT	RCT 889 16 weeks	Multinational Age 15 – 75 Multicenter	ML (10) + BUD (800) vs. BUD (1600) Medium to High dose ICS	Symptoms: No difference [% asthma <i>free days</i> : 86.7% vs. 82.2%; <i>P</i> = 0.371; <i>daytime symptom score</i> : -0.34 vs. -0.35; <i>P</i> = 0.908] Nocturnal awakenings: No difference [% of <i>nights with awakenings</i> : 2.3% vs. 3.9%; <i>P</i> = 0.353]	Fair

Study	Study design N Duration	Country Study population Setting	Comparison (total daily dose)	Results	Quality rating
				<p>Exacerbations: no difference [% of days with an exacerbation: 6.7% vs. 6.3%, $P = 0.781$; % of patients requiring oral steroids or hospitalization: 1.6% vs. 2.3%; $P =$ 0.472]</p> <p>Rescue medicine use: No difference [puffs/day: -0.78 vs. -0.75; $P = 0.51$]</p> <p>QOL: No difference [overall AQLQ score: +0.71 vs. +0.59; $P = 0.091$]</p> <p>Adherence: high for both the tablet and inhaler with > 95% of days fully compliant</p>	

Abbreviations: AQLQ = Asthma Quality of Life Questionnaire; BUD = Budesonide; CI = confidence interval;; FM = Formoterol; FP = Fluticasone Propionate; ICS = Inhaled Corticosteroids; LABAs = Long-Acting Beta-2 Agonists; LTRAs = Leukotriene receptor antagonists; MA=meta-analysis; ML = Montelukast; NR = not reported; NS = not statistically significant; OR = odds ratio; QOL = quality of life; RCT= randomized controlled trial; SM = Salmeterol; SMD = standard mean difference; SR = systematic review; WMD = weighted mean difference.

Symbol use: Drug X > Drug Y = statistically significant difference in outcomes favoring Drug X; Drug X > Drug Y trend = point estimate favors Drug X, but the difference is not statistically significant or tests of statistical significance were NR; No difference = no statistically significant difference or tests of statistical significance were not reported and outcomes are similar.

Note: All results are listed in the same order as the comparison column lists the medications.

5. Combination products compared with Leukotriene Modifiers

Summary of findings

We found four RCTs^{99, 100, 176, 177} meeting our inclusion/exclusion criteria for this comparison (Table 36). All four compared low dose fluticasone plus salmeterol with montelukast. Two of the RCTs were in adolescents and adults, one enrolled subjects over the age of six⁹⁹ (~15% of subjects < 12 years of age), and one enrolled children ages 6-14.¹⁰⁰

Overall, our meta-analysis and results from four RCTs find the combination of fluticasone plus salmeterol to be more efficacious than montelukast for the treatment of persistent asthma (Table 35 Evidence Profile).

Table 35. Evidence profile of the comparative efficacy of LABA + ICS compared with LTRA

Evidence Profile: Comparative efficacy of fluticasone plus salmeterol compared with montelukast							
Number of studies (# of subjects)	Design	Quality	Consistency	Directness	Magnitude of effect	Other modifying factors*	Overall strength of evidence
Overall total: ML compared with FP + SM							
4 (1,640)	RCTs (12 to 48 weeks)	Good (1) Fair (3)	Consistent	Direct	FP+SM > ML Greater improvement in symptom-free days (SMD -0.256, 95% CI: -0.392, -0.120) and percentage of rescue medicine-free days (SMD -0.289, 95% CI: -0.403, -0.174) Fewer exacerbations (SMD 0.227, 95% CI: 0.109, 0.344)	None	High

Abbreviations: CI = confidence interval; FP = Fluticasone Propionate; ICS = Inhaled Corticosteroids; LABAs = Long-Acting Beta-2 Agonists; LTRAs = Leukotriene receptor antagonists; ML = Montelukast; RCT= randomized controlled trial; SM = Salmeterol; SMD=standard mean difference.

Symbol use: Drug X > Drug Y = statistically significant difference in outcomes favoring Drug X; Drug X > Drug Y trend = point estimate favors Drug X, but the difference is not statistically significant or tests of statistical significance were NR; No difference = no statistically significant difference or tests of statistical significance were not reported and outcomes are similar.

Detailed Assessment

Description of Studies

We found four RCTs^{99, 100, 176, 177} meeting our inclusion/exclusion criteria (Table 36). Of the included studies, all four compared montelukast with low dose fluticasone plus salmeterol.

Study Populations

The four RCTs included a total of 1,640 patients. Two studies were conducted in adult populations; two studies^{99, 100} included children < 12 years of age. All four studies were conducted in the United States. Asthma severity ranged from mild persistent to severe persistent: two studies enrolled subjects with mild to moderate persistent asthma; two studies enrolled subjects with any severity of persistent asthma.

Methodologic Quality

Three trials were rated fair quality; one was rated good quality.

Sponsorship

Of the four RCTs, 3 (75%) were funded by pharmaceutical companies; only one study (25%) was funded primarily by sources other than pharmaceutical companies.

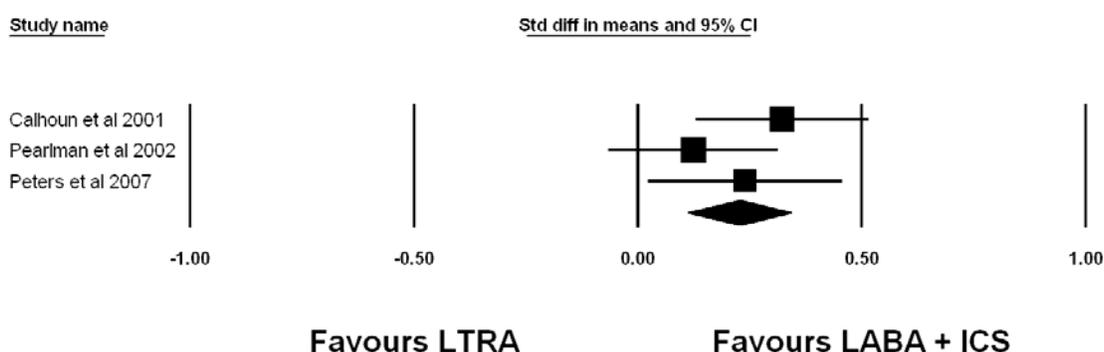
Head-to-head comparisons

1. Fluticasone (FP)+Salmeterol (SM) compared with Montelukast (ML)

The four included studies are described below. We conducted meta-analyses for outcomes that were reported with sufficient data in multiple trials (Appendix G). These included symptom-

free days, rescue medicine-free days, and exacerbations. We found statistically significant differences favoring those treated with FP+SM for all three outcomes. Those treated with FP+SM had greater improvement in the percentage of symptom-free days (SMD -0.256, 95% CI: -0.392, -0.120, $P < 0.001$), greater improvement in the percentage of rescue medicine-free days (SMD -0.289, 95% CI: -0.403, -0.174, $P < 0.001$), and fewer exacerbations (SMD 0.227, 95% CI: 0.109, 0.344, $P < 0.001$) (Figure 14). For all these meta-analyses, sensitivity analyses indicate no difference in overall meta-analysis conclusions with any single study removed. In addition, there was no significant heterogeneity between studies (Appendix G).

Figure 14. Meta-analysis comparing percentage of exacerbations for FP+SM compared with ML



The four studies included one good quality RCT¹⁷⁶ and three fair quality RCTs (Table 36).^{99, 100, 177} The good-rated RCT (N = 432) compared low dose FP/SM (200 mcg/100 mcg daily) (N = 216) compared with ML (10 mg/day) (N = 216) as monotherapy for 12 weeks.¹⁷⁶ Subjects with uncontrolled asthma treated with oral or inhaled short-acting beta-agonist age 15 and older were enrolled from 51 different centers in the United States. At endpoint those treated with FP/SM showed a greater improvement in all outcomes compared to ML including a decrease in the combined asthma symptom score (-1 compared with -0.7; $P \leq 0.001$), increase from baseline in % symptom free days (+40.3% compared with +27%; $P \leq 0.001$), increase from baseline in % of awakening free nights (+29.8% compared with +19.6%; $P = 0.011$), decrease from baseline in nights/ week with awakenings (-2.2 compared with -1.6; $P \leq 0.001$), decrease in puffs/day (-3.6 compared with -2.2; $P \leq 0.001$), increase in % of rescue free days (53.4% compared with 26.7%; $P \leq 0.001$), and increase in quality of life (AQLQ overall score, increase: 1.7 compared with 1.2; $P < 0.001$). Exacerbations occurred less frequently in the FP/SM group (3% compared with 6%; $P = \text{NR}$). Compliance was approximately 99% in both groups.

The first fair-rated RCT (N = 423) also compared low dose FP/SM (200 mcg/100mcg daily) (N = 211) compared with ML (10mg/day) (N = 212) for 12 weeks.¹⁷⁷ Subjects with uncontrolled asthma treated with oral or inhaled short-acting beta-agonist age 15 or older were enrolled from multiple centers in the United States. At endpoint, results were similar to those in the good quality RCT described above¹⁷⁶ with significant differences for all outcomes favoring

FP/SM over ML: including decrease in symptoms, rescue medicine use, and exacerbations (0%, 5%; $P < 0.001$) (Table 36).

The other two fair-rated RCTs showed some mixed results, with some outcomes favoring FP/SM and others finding no difference. The first ($N = 500$) compared low dose FP (200 mcg/day) ($N = 169$) compared with low dose FP (100 mcg/day) plus SM (50 mcg/day) (delivered once daily at night) ($N = 165$) compared with ML (5-10 mg/day) ($N = 166$) for 16 weeks.⁹⁹ Subjects were age six and older, had mild to moderate asthma controlled on ICS, and were enrolled from multiple American Lung Association Asthma Clinical Research Centers in the United States. At endpoint, there were no significant differences between FP plus SM and ML in symptom-free days or rescue medicine use. But, there were significant differences in the percentage of patients with treatment failure (20.4% compared with 30.3%; $P = 0.03$) and asthma control (ACQ: 0.71 compared with 0.82; $P = 0.004$) favoring FP plus SM. Adherence was good for all groups (FP/SM 93.3% compared with ML 90.5%).

The last fair-rated RCT ($N = 285$), the Pediatric Asthma Controller Trial (PACT), compared low dose FP 200 mcg/day via DPI ($N = 96$) compared with ML 5 mg/day ($N = 95$) compared with low dose FP 100 mcg/day plus SM 100 mcg/day via DPI (FP 100 mcg plus SM 50 mcg in the morning plus SM 50 mcg in the evening) ($N = 94$) for 48 weeks.¹⁰⁰ Of note, the dose of FP/SM used was outside of the product label recommendation. Subjects with mild to moderate asthma age 6 to 14 were enrolled from Childhood Asthma Research and Education Centers in the United States. At endpoint, the trial found no significant difference in the overall percentage of asthma control days (52.5% compared with 59.6%; $P = 0.08$), but found favorable results for FP/SM in the change in the percentage of asthma control days from baseline (33.3% compared with 22.3%; $P = 0.011$). There was no significant difference in asthma control as measured by change in ACQ score from baseline (-0.45 compared with 0.55; $P = 0.42$). Adherence was similar between groups (86% compared with 90%; $P = \text{NR}$).

Table 36. Summary of head-to-head studies comparing ICS+LABA compared with leukotriene modifiers

Study	Study design N Duration	Study population	Comparison (total daily dose)	Results	Quality rating
Montelukast compared with fluticasone plus salmeterol					
Pearlman et al. 2002 ¹⁷⁶	RCT 432 12 weeks	United States Age 15 and older, mild to severe persistent asthma, smoking status NR Multicenter (51)	FP/SM (200 mcg/100 mcg) vs. ML (10 mg) Low dose ICS	Symptoms: FP/SM > ML [combined <i>asthma symptom</i> <i>score</i> : -1 vs. -0.7; $P =$ 0.001, % <i>symptom free</i> <i>days</i> change from baseline: +40.3% vs. +27%; $P =$ 0.001, % of <i>awakening free</i> <i>nights</i> change from baseline: +29.8% vs. +19.6%; $P = 0.011$, <i>nights/</i> <i>week with awakenings</i> change from baseline: -2.2 vs. -1.6; $P = 0.001$]. Exacerbations: occurred in 3% and 6% of groups respectively, $P = \text{NR}$.	Good

Study	Study design N Duration	Study population	Comparison (total daily dose)	Results	Quality rating
Montelukast compared with fluticasone plus salmeterol					
				<p>Rescue medicine use: FP/SM > ML [change in <i>puffs/day</i>: -3.6 vs. -2.2; $P = 0.001$, % of <i>rescue free days</i>: 53.4% vs. 26.7%; $P = 0.001$].</p> <p>Quality of Life: FP/SM > ML [AQLQ overall score: 1.7 vs. 1.2; $P < 0.001$, individual components symptoms, environment, emotions, and activities: 1.9 vs. 1.4; $P < 0.001$, 1.5 vs. 1.1; $P < 0.001$, 1.8 vs. 1.2, $P < 0.001$, 1.4 vs. 1.1, $P < 0.001$].</p> <p>Compliance: approximately 99% in both groups.</p>	
Calhoun et al. ¹⁷⁷	RCT 423 12 weeks	United States Age 15 and older, mild to severe persistent asthma, smoking status NR Multicenter	FP/SM (200 mcg/100 mcg) vs. ML (10 mg) Low dose ICS	<p>Symptoms: FP/SM > ML [symptom score change from baseline: -1, -0.6; $P \leq 0.001$, % of symptoms free days: 48.9, 21.7; $P \leq 0.001$, nights/week with awakenings: -1.7, -1.3; $P \leq 0.001$, % of nights with no awakenings: 23, 15.5; $P \leq 0.001$].</p> <p>Exacerbations: FP/SM > ML [0%, 5%; $P < 0.001$].</p> <p>Rescue medicine use: FP/SM > ML [<i>puffs/day</i> -3.3, -1.9; $P \leq 0.001$, % of <i>rescue free days</i>: 53, 26.2; $P < 0.001$].</p> <p>Compliance: similar between groups at 98% for Diskus and 99% for capsules.</p>	Fair
Peters et al. 2007 ⁹⁹	RCT 500 16 weeks	United States Age 6 and older, mild to moderate asthma, smoking status NR Multicenter	FP (200 mcg) vs. FP/SM (100 mcg/50 mcg) vs. ML (5 – 10 mg) Low dose ICS	<p>Symptoms: mixed results [% symptom free days: 82.7% vs. 78.7%; $P = 0.35$; [Asthma Symptom Utility Index: 0.89 vs. 0.89; $P = \text{NS}$; % with nocturnal awakenings: 25.4% vs. 17.3%, $P = 0.06$]; ACQ: 0.71 vs. 0.82; $P = 0.004$]</p> <p>Exacerbations: FP/SM > ML</p>	Fair

Study	Study design N Duration	Study population	Comparison (total daily dose)	Results	Quality rating
Montelukast compared with fluticasone plus salmeterol					
				<p>[% with treatment failure: 20.4% vs. 30.3%, $P = 0.03$]</p> <p>Rescue medicine use: No difference [% days with rescue medicine use: 17.1% vs. 22.9%; $P = 0.06$]</p> <p>Quality of Life: No difference [mini-AQLQ: 5.8 vs. 5.8; $P = NS$].</p> <p>Adherence: good for all groups; 93.3% vs. 90.5%.</p>	
Sorkness et al. 2007 ¹⁰⁰ Pediatric Asthma Controller Trial (PACT)	RCT 285 48 weeks	United States Children age 6-14, mild to moderate persistent asthma, excluded current smokers within the past year	FP (200 mcg) vs. FP/SM (100 mcg/50 mcg) once in the morning plus SM (50 mcg) in the evening vs. ML (5 mg)	<p>Symptoms: No statistically significant difference, trend favors FP/SM [% asthma control days: 59.6% vs. 52.5%, $P = 0.08$; % change from baseline of asthma control days: 33.3% vs. 22.3%; $P = 0.011$].</p> <p>QOL: No difference [change in AQLQ score from baseline: -0.55 vs. -0.45, P $= 0.42$].</p> <p>Adherence: estimated to be 90% for Diskus inhaler and 86% for tablets.</p>	Fair

Abbreviations: AQLQ = Asthma Quality of Life Questionnaire; BUD = Budesonide; CI = confidence interval;; FM = Formoterol; FP = Fluticasone Propionate; ICS = Inhaled Corticosteroids; LABAs = Long-Acting Beta-2 Agonists; LTRAs = Leukotriene receptor antagonists; MA=meta-analysis; ML = Montelukast; NR = not reported; NS = not statistically significant; OR= odds ratio; QOL = quality of life; RCT= randomized controlled trial; SM = Salmeterol; SR=systematic review.

Symbol use: Drug X > Drug Y = statistically significant difference in outcomes favoring Drug X; Drug X > Drug Y trend = point estimate favors Drug X, but the difference is not statistically significant or tests of statistical significance were NR; No difference = no statistically significant difference or tests of statistical significance were not reported and outcomes are similar.

Note: All results are listed in the same order as the comparison column lists the medications.

6. ICS+LABA vs ICS+LTRA

(addition of LABAs compared with LTRAs as add-on therapy to ICSs)

Summary of findings

We found one systematic review with meta-analysis¹⁷⁸ and seven RCTs¹⁷⁹⁻¹⁸⁵ meeting our inclusion/exclusion criteria that compared the addition of a LABA with the addition of an LTRA for patients poorly controlled on ICS therapy (Table 38). All seven of the RCTs were in adolescents and adults ≥ 12 years of age.

Overall, results from a good quality systematic review with meta-analysis and seven RCTs provide strong evidence that the addition of a LABA to ICS therapy is more efficacious than the addition of an LTRA to ICS therapy for adolescents and adults with persistent asthma

(Table 37 Evidence Profile). We found no RCTs enrolling children < 12 years of age; the systematic review included just one trial in children (that did not contribute data to the meta-analysis). Thus, there is insufficient evidence to draw conclusions in children < 12 years of age.

Table 37. Evidence profile of the comparative efficacy of LTRA + ICS compared with LABA + ICS

Evidence profile: Comparative efficacy of LTRA plus ICS compared with LABA plus ICS							
Number of studies (# of subjects)	Design	Quality	Consistency	Directness	Magnitude of effect	Other modifying factors*	Overall strength of evidence
Overall total: LTRA plus ICS compared with LABA plus ICS							
1 (6,030)	1 SR w/ MA	Good	Consistent	Direct	ICS+LABA > ICS+LTRA	None	High
7 (5,277)	7 RCTs	Good (1); Fair (6)			Exacerbation requiring systemic steroids (RR 0.83; 95% CI: 0.71, 0.97)*		
ML + FP compared with SM + FP							
6 (5,229)	RCTs	Good (1) Fair (5)	Consistent	Direct	ICS+LABA > ICS+LTRA for most reported outcomes	None	High
ML + BUD compared with FM + BUD							
1 (48)	RCT	Fair	NA	Direct	FM+BUD > ML+BUD	None	Moderate

Abbreviations: BUD = Budesonide; CI = confidence interval;; FM = Formoterol; FP = Fluticasone Propionate; ICS = Inhaled Corticosteroids; LABAs = Long-Acting Beta-2 Agonists; LTRAs = Leukotriene receptor antagonists; MA=meta-analysis; RCT= randomized controlled trial; SM = Salmeterol; SR=systematic review.

Detailed Assessment

Description of Studies

We found one systematic review with meta-analysis¹⁷⁸ and seven RCTs.¹⁷⁹⁻¹⁸⁵ Of the included studies (Table 38), six RCTs compared montelukast plus fluticasone with salmeterol plus fluticasone, one RCT¹⁸⁵ compared montelukast plus budesonide with formoterol plus budesonide. All but one of the included RCTs¹⁸³ were included in the systematic review and meta-analysis.¹⁷⁸

Study Populations

The seven RCTs included a total of 5,277 patients. All studies were conducted in adult populations. Three studies (43%) were conducted in the United States, two (29%) in Europe, and two (29%) were other multinational combinations often including Europe, Canada, or the US. Asthma severity ranged from mild persistent to severe persistent: one study (14%) was conducted in patients with mild to moderate persistent asthma, two (29%) in patients with mild to severe persistent asthma, one (14%) in patients with moderate persistent asthma, and two (29%) in patients with moderate to severe persistent asthma. One study did not report the severity or it was unable to be determined.

Methodologic Quality

The overall quality of the seven RCTs included in our review was rated fair to good. Most trials received a quality rating of fair. The method of randomization and allocation concealment was rarely reported.

Sponsorship

Of the seven RCTs, six (86%) were funded by pharmaceutical companies and one trial (14%) did not report the source of funding.

Head-to-head comparisons

1. ICS+LABA compared with ICS+LTRA

One good quality systematic review with meta-analysis including 6,030 subjects (11 of 15 included trials contributed to the analyses) compared LABAs with LTRAs as add-on therapy to ICSs.¹⁷⁸ The included trials compared salmeterol (100 mcg/day) or formoterol (24 mcg/day) plus ICS compared with montelukast (10 mg/day) or zafirlukast (40 mg/day) plus ICS. The ICS dose average was 400 to 560 mcg/day of beclomethasone or equivalent.¹⁷⁸ Of the fifteen trials the met inclusion criteria, a total of 80 subjects were children. Of the 11 trials that contributed to the analyses, 10 were in adults and one was in children. Six of the included trials met our inclusion criteria.^{179-182, 184, 185} Five of the studies included in the analysis did not meet our inclusion criteria.

The systematic review included randomized controlled trials conducted in adults or children with persistent asthma where a LABA or LTRA was added to ICS for 4 to 48 weeks. Inhaled Short-Acting Beta-2 Agonists and short courses of oral steroids were permitted as rescue medications. Subjects had to be on a stable dose of ICSs throughout the trials.

The meta-analysis reported that LABA plus ICS was significantly better than LTRA plus ICS for all observed outcomes.¹⁷⁸ Six trials contributed to the primary outcome showing a significant decrease in risk of exacerbation requiring systemic steroids for those treated with LABAs (RR 0.83; 95% CI: 0.71, 0.97). The type of LTRA used did not impact the results. The reported number of patients who must be treated with the combination of LABA and ICS instead of LTRA and ICS to prevent one exacerbation over 48 weeks was 38 (95% CI: 23, 247).

Subjects treated with LABA+ICS had greater improvement in the percentage of symptom-free days (WMD 6.75%; 95% CI: 3.11, 10.39, 5 studies), daytime symptom scores (SMD -0.18; 95% CI: -0.25, -0.12, 5 studies), nighttime awakenings (WMD -0.12; 95% CI: -0.19, -0.06, 4 studies), percentage of rescue-free days (WMD 8.96%; 95% CI: 4.39, 13.53, 4 studies), rescue medication use per day (WMD -0.49 puffs/day; 95% CI: -0.75, -0.24, 7 studies), overall asthma-related quality of life (WMD 0.11; 95% CI: 0.05, 0.17, 3 studies). There was significant heterogeneity in one of the analyses (percentage of rescue-free days; $I^2 = 61%$; $P < 0.05$).

The seven RCTs meeting the inclusion/exclusion criteria for our review are summarized in Table 38. Six of the seven trials were included in the systematic review with meta-analysis¹⁷⁸ described above. The other fair-rated RCT,¹⁸³ the SOLTA study, compared low dose FP (200 mcg/day) plus SM (100 mcg/day) (N = 33) compared with low dose FP (200 mcg/day) plus ML 10 mg/day (N = 33) for 12 weeks in 66 adults (age 18 to 50) with uncontrolled mild to moderate asthma. The ICS/LABA combination was delivered via a single inhaler. Patients being treated with medium dose ICSs were enrolled from multiple centers in the United Kingdom. At endpoint, there were no statistically significant differences in asthma

symptoms, but the trends in direction of the effect sizes favored the ICS/LABA combination (symptoms-free days: mean difference in change from baseline: 13.2%, 95% CI: -1.9%, -32.9%; $P = 0.064$; symptom-free nights: mean difference in change from baseline: 13.3%, 95% CI: -1.5%, -34.5%; $P = 0.055$). There was no significant difference in daytime rescue use (median % rescue free days at endpoint 73% compared with 70%; $P = \text{NS}$), but there was a difference in rescue use at night favoring FP/SM (median rescue free nights at endpoint: 93% compared with 82%; $P = 0.01$).

We do not describe all of the other included RCTs in detail because they generally found results consistent with the overall conclusions of the meta-analysis. For all of our outcomes of interest, most trials reported favorable results for subjects treated with ICS+LABA; the others reported no statistically significant differences (Table 38).

Table 38. Summary of head-to-head studies comparing ICS+LABA compared with leukotriene modifiers

Study	Study design N Duration	Study population	Comparison (total daily dose)	Results	Quality rating
LTRA plus ICS compared with LABA plus ICS					
Ducharme et al. 2006 ¹⁷⁸	Systematic Review with meta-analysis 11 studies (6,030 subjects) included in meta-analysis	1 trial in children; 10 in adults	LABA (salmeterol 100 mcg or formoterol 24 mcg) plus ICS vs. LTRA (montelukast 10 mg, zafirlukast 40 mg) plus ICS ICS was average 400 to 560 mcg/day of BDP or equivalent (medium to high dose ICS)	Symptoms: LABA + ICS > LTRA + ICS [% <i>symptom free days</i> : 6.75%; 95% CI: 3.11, 10.39, improvement in <i>daytime symptom score</i> : -0.18; 95% CI: -0.25, -0.12, <i>decrease in nighttime awakenings</i> : -0.12; 95% CI: -0.19, -0.06, <i>increase in % awakening-free nights per week</i> : 6.89%; 95% CI: 2.87, 10.91]. Exacerbations: LABA + ICS > LTRA + ICS [<i>risk of exacerbation requiring systemic steroids</i> : RR 0.83; 95% CI: 0.71, 0.97; regardless of LABA used, <i>risk of exacerbation requiring hospital admission</i> : RR 1.31; 95% CI: 0.58, 2.98]. Rescue medicine use: LABA + ICS > LTRA + ICS [<i>increase in % rescue free days</i> : 8.96%; 95% CI: 4.39, 13.53, but there was significant heterogeneity in this pooled estimate with a significant difference between the two subgroups $P < 0.05$]. QOL: LABA + ICS > LTRA	Good

Study	Study design N Duration	Study population	Comparison (total daily dose)	Results	Quality rating
				+ ICS [increase (improvement) in <i>Global Asthma Quality of Life</i> score: 0.11; 95% CI: 0.05, 0.17]. Mortality: no difference ($P = \text{NR}$)	
Montelukast plus fluticasone compared with salmeterol plus fluticasone					
Bjermer et al. ¹⁷⁹	RCT 1490	Multinational (37 countries - eastern Europe)	ML (10mg) plus FP (200 mcg) vs. SM (100 mcg) plus FP (200 mcg)	Symptoms: no difference [mean days per week with <i>nocturnal awakenings</i> compared to baseline: -1.68 vs. -1.74, $P < = 0.001$; NS between groups]. Exacerbations: no difference [% with at least one exacerbation: 20.1% vs. 19.1%, Risk Ratio 1.05, 95% CI: 0.86, 1.29, number of courses of steroids over 48 weeks: 118 vs. 107, Risk Ratio 1.10, 95% CI: 0.86, 1.40]. QOL: no difference [mean overall AQLQ compared to baseline: 0.71 vs. 0.76, $p \leq 0.001$; NS between groups]. Urgent care services: no difference [number of emergency room visits: 21 vs. 21; Risk Ratio 0.99, 95% CI: 0.55, 1.81, number of urgent care visits: 82 vs. 80; Risk Ratio 1.02, 95% CI: 0.76, 1.36]. Hospitalizations: no difference [hospitalizations: 5 vs. 7; Risk Ratio 0.71, 95% CI: 0.21, 2.22]. Mortality: 1 death in the SM/FP group due to a severe asthma attack; $P = \text{NR}$	Good
IMPACT	48 weeks	Age 15 – 72, mild to severe persistent asthma currently uncontrolled on low dose ICS, smoking status NR Multicenter (148)	Same Low dose ICS		
Fish et al. 2001 ¹⁸⁰	RCT 948 12 weeks	United States and Puerto Rico Age 15 and older, moderate to severe persistent asthma despite low to high	SM (100 mcg) plus baseline ICS vs. ML plus baseline ICS (10mg) Same Low to High	Symptoms: SM + ICS > ML + ICS [% symptom free days: 24% vs. 16%; $P < 0.001$, nighttime awakening: -1.42 vs. -1.32; $P = 0.015$, nights per week with awakenings: -1.06 vs. -0.93;	Fair

Study	Study design N Duration	Study population	Comparison (total daily dose)	Results	Quality rating
		dose ICS, smoking status NR Multicenter (71)	dose ICS	<p>$P = 0.007$, symptoms of shortness of breath, chest tightness, and all symptoms: -0.59 vs. -0.44; $P = 0.044$; -0.60 vs. -0.42; $P = 0.008$; -0.55 vs. -0.41; $P = 0.039$; wheezing: -0.47 vs. -0.37; $P = 0.403$].</p> <p>Exacerbations: no difference [6% vs. 5%; $P = \text{NR}$].</p> <p>Rescue medicine use: SM + ICS > ML + ICS [% rescue free days: 27% vs. 22%; $P = 0.002$, puffs/day: -1.9 vs. -1.66; $P = 0.004$, puffs during daytime: -1.51 vs. -1.31; $P = 0.010$, puffs during nighttime: -0.39 vs. -0.35; $P = 0.012$].</p>	
Ilowite et al. 2004 ¹⁸¹	RCT 1473 48 weeks	United States Age 14 – 73, mild to severe persistent asthma uncontrolled on ICS, smoking status NR Multicenter (132)	SM (84 mcg) plus FP (220 mcg) vs. ML (10 mg) plus FP (220 mcg) Unspecified whether ICS dose changed from baseline to study low dose ICS	<p>Symptoms: SM + FP > ML + FP [daytime symptoms scores: -0.66 vs. -0.48, mean difference -0.18; 95% CI: 0.10, 0.26, nights of awakening: -1.02 vs. -0.79, mean difference -0.23; 95% CI: 0.10, 0.36, symptom free days per week: 1.69 vs. 1.15, mean difference 0.54; 95% CI: -0.76, -0.32].</p> <p>Exacerbations: no difference [courses of steroids: 14.2% vs. 16.8%, relative risk 1.18; 95% CI: 0.93, 1.5, asthma attacks: 120 vs. 147, relative risk 1.2; $P = \text{NS}$].</p> <p>Rescue medicine use: SM + FP > ML + FP [puffs/day: -1.66 vs. -1.15, mean difference -0.52; 95% CI: 0.36, 0.68].</p> <p>QOL: SM + FP > ML + FP [overall AQLQ score: 0.9 vs. 0.78; mean difference 0.12; 95% CI: -0.22, -0.02].</p> <p>Urgent care services: no difference [emergency room visits: 2.2% vs. 2%, relative risk 0.92, 95% CI: 0.46,</p>	Fair

Study	Study design N Duration	Study population	Comparison (total daily dose)	Results	Quality rating
				<p>1.84, <i>urgent care visits</i>: 10.3% vs. 14.6%, relative risk 1.41; 95% CI: 1.07, 1.87].</p> <p>Hospitalizations: no difference [0.7% vs. 0.4%, relative risk 0.59; 95% CI: 0.14, 2.45].</p>	
Nelson et al. 2000 ¹⁸²	RCT 447 12 weeks	United States Age 15 and older, moderate to severe persistent asthma uncontrolled on low dose ICS, smoking status NR Multicenter	FP (200 mcg) / SM (100 mcg) vs. FP (200 mcg) plus ML (10 mg) Same Low dose ICS	<p>Symptoms: no difference [change from baseline in <i>daytime symptom scores</i>: -0.49 vs. -0.41; p 0.199]; <i>shortness of breath score</i>: -0.56 vs. -0.40; <i>P</i> = 0.017; <i>chest tightness or wheeze scores</i>: -0.49 vs. -0.43; <i>P</i> = 0.521, -0.41 vs. -0.38; <i>P</i> = 0.279].</p> <p>Exacerbations: SM + FP > ML + FP [<i>exacerbations</i>: 2 vs. 6; <i>P</i> = 0.031].</p> <p>Rescue medicine use: SM + FP > ML + FP [<i>puffs/day</i>: -1.55 vs. -1.14, <i>P</i> = 0.014, % <i>rescue free days</i>: 26.3% vs. 19.1%; <i>P</i> = 0.032].</p> <p>Urgent care services: zero vs. one emergency room visits in the groups respectively; <i>P</i> = NR</p> <p>Compliance with both the oral and inhaled DPI was high at 96 - 97%.</p>	Fair
Pavord et al. 2007 ¹⁸³	RCT SOLTA Study Group 66 12 weeks	United Kingdom Age 18 – 50, mild to moderate persistent asthma uncontrolled on medium dose ICS, excluded smokers Multicenter	FP (200 mcg) / SM (100 mcg) vs. FP (200 mcg) plus ML (10 mg) Decrease to Low dose ICS	<p>Symptoms: No difference [<i>% symptoms free days</i> mean change from baseline: 13.2%; 95% CI: -1.9, 32.9; <i>P</i> = 0.064, <i>symptom free night</i> change from baseline: 13.3%; 95% CI: -1.5, 34.5; <i>P</i> = 0.055].</p> <p>Rescue medicine use: Mixed results [<i>median % rescue free days at endpoint</i>: 73% vs. 70%; <i>P</i> = NS; <i>median % rescue free nights at endpoint</i>: 93% vs. 82%; % difference 16.5%; 95% CI: 1.4, 36.1; <i>P</i> = 0.01].</p>	Fair

Study	Study design N Duration	Study population	Comparison (total daily dose)	Results	Quality rating
Ringdal et al. 2003 ¹⁸⁴	RCT 805 12 weeks	Multinational (19 – Europe, Middle East, Africa) Age 15 and older, mild to severe persistent asthma on low to high dose ICS at baseline, excluded patients with a 10 pack-year history of smoking Multicenter (114)	FP (200 mcg) / SM (100 mcg) vs. FP (200 mcg) plus ML (10 mg) Decreased to Low dose ICS and had to remain uncontrolled.	Symptoms: SM + FP > ML + FP [% <i>symptom free days</i> : 50% vs. 38.5%; OR 1.32; <i>P</i> < 0.05, % <i>symptom free nights</i> : 78.6% vs. 71.4%; OR 1.28; <i>P</i> < 0.05]. Exacerbations: SM + FP > ML + FP [% <i>asthma exacerbations</i> : 9.6% vs. 14.6%; <i>P</i> < 0.05]. Rescue medicine use: SM + FP > ML + FP [% <i>rescue free days</i> : 71.4% vs. 66.7%; OR 1.29; <i>P</i> = 0.03; <i>rescue free nights</i> : 92.9% vs. 85.7%; OR 1.15; <i>P</i> = 0.26]. Compliance: high in both groups; 96% with inhaled medication and 97% with tablets	Fair

Montelukast plus budesonide compared with formoterol plus budesonide

Ceylan et al. 2004 ¹⁸⁵	RCT 48 8 weeks	Turkey Age 15 – 60, moderate persistent asthma uncontrolled on unspecified ICS dose, excluded smokers University based clinics	BUD (400 mcg) plus FM (18 mcg) vs. BUD (400 mcg) plus ML (10 mg) Unspecified change from baseline to Low dose ICS	Symptoms: FM + BUD > ML + BUD [<i>morning symptoms scores</i> : -2.6 vs. -0.8; <i>P</i> < 0.0001, <i>number of asymptomatic days</i> : <i>P</i> < 0.0001]. Rescue medicine use: FM + BUD > ML + BUD [<i>puffs/day</i> : -1.9 vs. -0.5; <i>P</i> < 0.0001].	Fair
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Abbreviations: BUD = Budesonide; CI = confidence interval; DPI= Dry Powder Inhaler; FM = Formoterol; FP = Fluticasone Propionate; ICS = Inhaled Corticosteroids; LABAs = Long-Acting Beta-2 Agonists; LTRAs = Leukotriene receptor antagonists; MA=meta-analysis; ML = Montelukast; NR = not reported; NS = not statistically significant; OR= odds ratio; QOL = quality of life; RCT= randomized controlled trial; SM = Salmeterol;; SR=systematic review.

Symbol use: Drug X > Drug Y = statistically significant difference in outcomes favoring Drug X; Drug X > Drug Y trend = point estimate favors Drug X, but the difference is not statistically significant or tests of statistical significance were NR; No difference = no statistically significant difference or tests of statistical significance were not reported and outcomes are similar.

Note: All results are listed in the same order as the comparison column lists the medications.

7. LTRA+LABA compared with ICS+LABA

Summary of findings

We found one fair quality RCT comparing LTRA plus LABA with ICS plus LABA (Evidence Profile Table 39 and Table 40).¹⁸⁶ The fair-rated, placebo-controlled, multi-center RCT (N = 192) compared ML (10mg/day) plus SM (100 mcg/day) plus placebo ICS (N = 98) compared with low dose BDP (160 mcg/day) plus SM (100 mcg/day) plus placebo LTRA (N = 92) for 14 weeks, washout for 4 weeks, then crossover for another 14 weeks.¹⁸⁶ Subjects age 12 to 65 with moderate asthma were enrolled from multiple sites in the United States. There was a 4-week

run-in period that involved a single-blind treatment with both BDP (160 mcg/day) and ML (10 mg/day). The primary objective of the study was to assess time until treatment failure. The trial was terminated early because the Data and Safety Monitoring Board determined that the primary research question had been answered. Those treated with LTRA+LABA had significantly shorter time to treatment failure than those treated with ICS+LABA ($P = 0.0008$).

Table 39. Evidence profile of the comparative efficacy of ICS + LABA compared with LTRA + LABA

Evidence profile: Comparative efficacy of ICS+LABA compared with LTRA+LABA							
Number of studies (# of subjects)	Design	Quality	Consistency	Directness	Result (magnitude of effect)	Other modifying factors	Overall strength of evidence
Montelukast plus Salmeterol compared with Beclomethasone plus Salmeterol							
1 (192)	RCT, cross-over	Fair	NA	Direct	ICS+LABA > LTRA+LABA	Composite outcome	Moderate

Abbreviations: ICS = Inhaled Corticosteroids; LABAs = Long-Acting Beta-2 Agonists; LTRAs = Leukotriene receptor antagonists; RCT= randomized controlled trial.

Table 40. Summary of head-to-head studies comparing ICS+LABA compared with LTRA+LABA

Study	Study design N Duration	Country Study population Setting	Comparison (total daily dose)	Results	Quality rating
Montelukast plus salmeterol compared with beclomethasone plus salmeterol					
Deykin et al. 2007 ¹⁸⁶	RCT 192 14 weeks, washout for 4 weeks, then crossover for 14 weeks	United States Age 12 to 65 Multicenter	ML (10mg) + SM (100 mcg) plus placebo ICS vs. BDP (160 mcg) + SM (100 mcg) plus placebo LTRA	Exacerbations/treatment failure: ICS+LABA > LTRA+LABA [Significantly more subjects had a shorter time to treatment failure* while using LTRA plus LABA as compared to ICS plus LABA ($P = 0.0008$)]	Fair
Low dose ICS					

Abbreviations: BDP = Beclomethasone dipropionate; ICS = Inhaled Corticosteroids; LABAs = Long-Acting Beta-2 Agonists; LTRAs = Leukotriene receptor antagonists; ML = Montelukast; RCT= randomized controlled trial; SM = Salmeterol.

Symbol use: Drug X > Drug Y = statistically significant difference in outcomes favoring Drug X; Drug X > Drug Y trend = point estimate favors Drug X, but the difference is not statistically significant or tests of statistical significance were NR; No difference = no statistically significant difference or tests of statistical significance were not reported and outcomes are similar.

*Treatment failure defined as increased as-needed albuterol, persistent asthma symptoms or drop in PEF despite rescue use, use of oral, parenteral, or non-study related ICS, emergency department therapy with steroids, drop in FEV1 or PEF, or physician clinical judgment for safety.

Note: All results are listed in the same order as the comparison column lists the medications.

Key Question 2. Adverse Events

What is the comparative tolerability and frequency of adverse events for controller medications used to treat outpatients with persistent asthma?

I. Intra-class Evidence (within one class)

A. Inhaled Corticosteroids

Summary of Findings

We found seven systematic reviews,^{20, 21, 187-191} 35 RCTs^{22-28, 30-45, 47-50, 192-199} and 11 observational studies²⁰⁰⁻²⁰⁹ reporting the tolerability or frequency of adverse events for inhaled corticosteroids meeting our inclusion/exclusion criteria (Tables 41-44). Few RCTs were designed to assess adverse events as primary outcomes; most published studies designed to assess adverse events were observational studies.

The overall incidence of adverse events and withdrawals due to adverse events are similar for equipotent doses of ICSs; results from 32 head-to-head RCTs suggest no significant differences between ICSs (moderate strength of evidence). Overall summaries for specific adverse events are described below in the specific adverse events section. Most of the data for specific adverse events comes from placebo-controlled trials or observational studies, rather than from head-to-head comparisons.

Detailed Assessment

Description of Studies

Most studies (93%, 28 of 30) that examined the efficacy of one ICS relative to another (described in Key Question 1) also reported tolerability and adverse events. Four head-to-head RCTs that did not report efficacy met our inclusion/exclusion criteria for tolerability or adverse events.¹⁹²⁻¹⁹⁵ Four of the head-to-head RCTs included children < 12.^{26, 39, 41, 192} Placebo-controlled RCTs and observational studies are described below in their respective specific adverse event sections.

Methods of adverse events assessment differed greatly. Few studies used objective scales such as the adverse reaction terminology from the World Health Organization (WHO). Most studies combined patient-reported adverse events with a regular clinical examination by an investigator. Often it was hard to determine if assessment methods were unbiased and adequate; many trials reported only those adverse events considered to be related to treatment. Rarely were adverse events prespecified and defined. Short study durations and small sample sizes limited the validity of adverse events assessment in many trials. Many studies excluded eligible participants that did not tolerate treatment during the run-in period, limiting the generalizability of adverse event assessment. Few RCTs were designed to assess adverse events as primary outcomes; most published studies were post hoc analyses or retrospective reviews of databases.

A. Overall adverse events, tolerability, and common adverse events

Of the 32 head-to-head studies reviewed for this section (Appendix F), most reported frequency of adverse events without tests of statistical significance. The vast majority of studies reported similar results for equipotent ICS doses. Only three studies reported a

difference of greater than 5% in overall adverse events for equipotent doses.^{32, 35, 37} Only one study reported a statistically significant difference in overall adverse events between two ICSs (overall AEs (%): 20 compared with 5, $P < 0.001$ for FP compared with TAA, but the study did not compare equipotent doses.⁵⁰ Three studies reported a difference of greater than 5% in withdrawals due to AEs for equipotent doses.^{25, 36, 194} No trial reported a statistically significant difference in withdrawals due to AEs.

Most head-to-head trials reported specific adverse events (Appendix F). Oral candidiasis, rhinitis, cough, sore throat, hoarseness, headache, and upper respiratory infection were among the most commonly reported adverse events. In most head-to-head trials oral candidiasis, rhinitis, cough, sore throat, hoarseness, and bronchitis were reported in fewer than 10 percent of ICS-treated patients. Upper respiratory tract infections were reported by 3 to 32% of study participants. For common specific adverse events, just two trials reported a statistically significant difference between equipotent doses of different ICSs.^{30, 36} One reported a greater incidence of headache in those treated with BDP than those treated with FP (7% compared with < 1%, $P = 0.03$)³⁰ and one reported a greater incidence of upper respiratory tract infection with TAA than with BDP (10.4% compared with 2.7%, $P = 0.027$).³⁶

B. Specific adverse events

When we found direct evidence for patients with asthma, we did not include studies of mixed populations (e.g., asthma + COPD) unless they reported results independently for subjects with asthma. Only for the section on ocular hypertension and open-angle glaucoma were we unable to find direct evidence for patients with asthma; thus we included two studies that included more broad populations of subjects taking ICSs.

I. Bone density/osteoporosis

We found two fair quality systematic reviews with meta-analyses that studied the effect of ICSs on markers of bone function and metabolism.^{187, 188} One included 14 studies (2,302 subjects) of patients with asthma or COPD (both RCTs and prospective cohort studies) assessing BMD.¹⁸⁷ The other included six studies of asthmatic subjects with median duration of ICS use of at least three years.¹⁸⁸ Pooled results from both meta-analyses showed no statistically significant difference in BMD between patients taking ICSs and controls. The one that included patients with asthma and COPD reported that asthma patients treated with ICSs showed a slight increase in BMD (0.13%) whereas COPD patients showed a slight decrease (-0.42%); however, neither change was statistically significant.¹⁸⁷

Our review includes eight studies: three of the trials^{194, 195, 200} in the systematic reviews, as well as five additional studies.^{196, 198, 199, 201-203} We excluded the remainder of studies from these two reviews because of wrong population (COPD patients), insufficient sample size, and/or poor quality. In total we include one good-rated RCT,^{198, 199} three fair-rated RCTs,¹⁹⁴⁻¹⁹⁶ one fair prospective cohort study,²⁰⁰ one fair case-control study,²⁰¹ one fair retrospective cohort study,²⁰² and one fair cross-sectional study.²⁰³

All eight studies assessed BMD, fracture risk, or both (Table 41). In total, three studies evaluated the risk of fracture^{195, 201, 202} and six measured BMD as an intermediate outcome of osteoporosis.^{194-196, 198-200, 203} Two studies compared one ICS to another,^{194, 195} three compared one ICS to placebo,^{196, 198, 199, 203} and three studies compared one ICS or any ICS to a population that did not use an ICS.²⁰⁰⁻²⁰² Most studies evaluated the risk of bone weakening over two to six years; no study was designed specifically to assess lifetime or long-term cumulative ICS exposure.

Two of the trials were head-to-head RCTs comparing one ICS with another ICS in adult subjects.^{194, 195} One 24-month open-label trial measuring BMD and vertebral fractures randomized 374 adult patients with asthma to beclomethasone, budesonide, or placebo.¹⁹⁵ Patients were titrated to the minimal effective dose following a pre-specified management plan; subjects who required more than three courses of oral corticosteroids were withdrawn. At two years, no significant differences in BMD were reported between the three treatment groups. A smaller trial reporting BMD randomized 69 asthmatic patients to medium and high doses of beclomethasone or fluticasone.¹⁹⁴ At one year, no significant differences in bone mass or metabolism were noted between the two treatment groups.

Six studies (two of them in pediatric populations) comparing an ICS-treated population to a population not treated with ICSs provided mixed evidence of an association between ICS use and loss of BMD or osteoporosis;^{196, 198-203} two of these studies measured bone fractures.^{201, 202} Both of the studies conducted in pediatric populations reported no difference in BMD between ICS- and placebo-treated subjects.^{198, 199, 203} Of the remaining studies, one reported a dose-related decline in BMD with ICS-treated subjects,²⁰⁰ one reported a dose-related increase in the risk of vertebral and nonvertebral fractures with ICS,²⁰² and two reported no difference in nonvertebral fracture²⁰¹ or BMD¹⁹⁶ between ICS-treated subjects and controls (Table 41).

Table 41. Summary of studies on bone density or fractures

Author Year	N	Design	Population	Results	Quality rating
Adult populations					
Israel et al. 2001 ²⁰⁰	109	Prospective cohort	premenopausal women with asthma (age 18-45)	TAA associated with dose-related decline in BMD (total hip and trochanter) of 0.00044 g/cm ² per puff/year	Fair
Johannes et al. 2005 ²⁰¹	18,942	Nested case-control	Asthma & COPD (adults)	No ICS-related increase in the risk of nonvertebral fracture over 1 year for the total group of subjects or for either of the separate respiratory disease categories (asthma or COPD)	Fair
Kemp et al. 2004 ¹⁹⁶	160	RCT	Asthma (adult)	No difference in BMD between placebo-treated patients and patients treated with low to high doses of FP	Fair
Medici et al. 2000 ¹⁹⁴	69	RCT	Asthma (adult)	No difference in BMD between BDP- and FP-treated patients over 1 year	Fair
Tattersfield et al. 2001 ¹⁹⁵	374	RCT (open label)	Asthma (adult)	No difference in BMD/fractures between BDP, BUD, and placebo over 2 years	Fair
Van Staa et al. 2001 ²⁰²	450,422	Retrospective cohort	Asthma & COPD (adult)	Statistically significant dose-related increase in risk of vertebral and nonvertebral fractures with ICS	Fair
Pediatric populations					
Childhood Asthma Management Program Research Group, 2000 ^{198, 199}	1041	RCT	Asthma (pediatric)	No difference in bone density between BUD- and placebo-treated patients	Good
Agertoft & Pedersen, 1998 ²⁰³	157	Cross-sectional	Asthma (pediatric)	No difference between BUD and placebo (3-6 years use) in BMD	Fair

Abbreviations: BDP = beclomethasone dipropionate; BUD = Budesonide; COPD= chronic obstructive pulmonary disease; ICS = Inhaled Corticosteroids; NA= not applicable; RCT= randomized controlled trial; TAA = Triamcinolone Acetonide.

Symbol use: Drug X > Drug Y = statistically significant difference in outcomes favoring Drug X; Drug X > Drug Y trend = point estimate favors Drug X, but the difference is not statistically significant or tests of statistical significance were NR; No difference = no statistically significant difference or tests of statistical significance were not reported and outcomes are similar.

II. Growth

Three head-to-head RCTs comparing fluticasone to beclomethasone²⁶ or fluticasone to budesonide^{39, 192} assessed differences in growth. A fair 1-year multinational head-to-head trial determined differences in growth velocity comparing a medium dose of fluticasone (400 mcg/day) to a medium dose of beclomethasone (400 mcg/day) in 343 pre-pubertal children with asthma.²⁶ ITT analysis revealed that adjusted mean growth velocity was significantly greater in fluticasone than in beclomethasone-treated patients (+0.70 cm/year; 95% CI: 0.13 to 1.26; $P < 0.02$). Another fair RCT compared growth velocity in 60 children treated with either a low dose of fluticasone (200 mcg/day) or a low dose of budesonide (400 mcg/day) over one year.¹⁹² Fluticasone-treated children had less reduction in growth velocity than the budesonide-treated group (height standard deviation score: 0.03 compared with 0.23; $P < 0.05$); the authors did not provide absolute numbers in centimeters of differences in growth. The third RCT compared differences in growth velocity in 333 children treated with a medium dose of fluticasone (400 mcg/day) or a medium dose of budesonide (800 mcg/day) over 20 weeks.³⁹ Linear growth velocity was greater for fluticasone-treated children compared to those treated with budesonide (adjusted mean increase in height: 2.51 cm compared with 1.89; difference 6.2 mm (95% CI: 2.9-9.6, $P = 0.0003$).

Four additional studies provide general evidence of growth retardation for ICSs (Table 42). These included two meta-analyses^{189, 190} and three RCTs.^{96, 197-199} A good quality meta-analysis assessed differences in short-term growth velocity in 273 children with mild to moderate asthma treated with either beclomethasone (mean 400 mcg/day) or placebo for 7 to 12 months.¹⁸⁹ The meta-analysis reported a statistically significant decrease in linear growth velocity of children treated with beclomethasone (-1.54 cm per year; 95% CI: -1.15, -1.94) compared to the placebo group. Another good-quality meta-analysis assessed short-term growth velocity in 855 children treated with beclomethasone or fluticasone compared to placebo. Growth velocity was statistically significantly reduced in those treated with beclomethasone (1.51 cm/year; 95% CI: 1.15, 1.87; four studies) and in those treated with fluticasone (0.43cm/year; 95% CI: 0.1, 0.85; 1 study) compared to placebo.¹⁹⁰

The best longer-term evidence of linear growth delay comes from the Childhood Asthma Management Program (CAMP) study, a good quality RCT with median follow-up of 4.3 years that randomized 1,041 asthmatic children to budesonide, nedocromil, or placebo.^{198, 199} The mean increase in height was significantly less in budesonide-treated patients than in placebo-treated patients (-1.1 cm; 22.7 cm compared with 23.8 cm; $P = 0.005$). This analysis was performed on an intent-to-treat basis, providing a more conservative than an “as treated” analysis. The differences in growth occurred, however, primarily during the first year of treatment. After two years of treatment growth velocity was approximately the same between groups.

Another placebo controlled trial assessing growth velocity under low-dose fluticasone treatment (100 mcg/day; 200 mcg/d) did not find any significant differences in linear growth compared to placebo after one year of treatment.^{197, 210} One additional fair quality RCT (N = 360) compared linear growth rates in prepubertal children treated with montelukast,

beclomethasone, or placebo over 56 weeks and found that the mean growth rate of subjects treated with beclomethasone was 0.78 cm less than that of subjects treated with placebo and 0.81 cm less than that of subjects treated with montelukast ($P < 0.001$ for both).⁹⁶

Table 42. Summary of studies on growth retardation

Author Year	N	Design	Population	Duration	Results	Quality rating
Head-to-head comparisons of ICS compared with ICS						
De Benedictis et al. 2001 ²⁶	343	RCT	Pre-pubertal children with asthma	1 year	Greater growth velocity in FP than in BDP group	Fair
Ferguson et al, 1999 ³⁹	333	RCT	Children with asthma	20 weeks	Greater growth velocity in FP than in BUD group	Fair
Kannisto et al. 2000 ¹⁹²	75	RCT	Children with asthma	1 year	Greater growth velocity in FP than in BUD group	Fair
General evidence from ICS-treated subjects compared with non-ICS treated controls						
Sharek et al. 1999 ¹⁸⁹	273	Meta-analysis	Children with asthma	More than 3 months	Reduction in growth for BDP compared to placebo	Good
Sharek et al. 2000 ¹⁹⁰	855	Meta-analysis	Children with asthma	7 months to 54 weeks	Reduction in growth of 0.43 and 1.51 cm/year for BDP and FP, respectively, vs. placebo	Good
Childhood Asthma Management Program Research Group, 2000 ^{198, 199}	1041	RCT	Children with asthma	4.3 years	Reduction in growth (1.1 cm) for BUD-treated children	Good
Allen et al. 1998 ¹⁹⁷	268	RCT	Children with asthma	1 year	No differences in height and growth velocity between FP and placebo	Fair
Becker et al. 2006 ⁹⁶	360	RCT	Children with asthma	56 weeks	Reduction in growth for BDP-treated children	Fair

Abbreviations: BDP = beclomethasone dipropionate; BUD = Budesonide; FP = Fluticasone Propionate; ICS = Inhaled Corticosteroids; RCT= randomized controlled trial; SR=systematic review.

III. Acute adrenal crisis

The use of ICSs includes the risk of altered hypothalamic-pituitary axis (HPA axis) functioning and the rare possibility of resultant adrenal suppression. We did not find any studies meeting our inclusion/exclusion criteria reporting on the comparative frequency of clinical adrenal insufficiency in patients treated with ICSs. However, multiple studies report on adrenal suppression during ICS therapy using urinary or serum cortisol levels and results of stimulation tests as intermediate outcomes. It is unclear to what extent results from sensitive studies of HPA axis suppression can be extrapolated to assess differences in risks for clinically significant adrenal suppression.

Various case reports indicate that acute adrenal crisis is an extremely rare but potentially fatal adverse event of ICS treatment.²¹¹⁻²¹³ However, in most cases dosing was likely outside approved labeling. These case reports did not meet eligibility criteria for this report.

IV. Cataracts

Systemic corticosteroid-induced cataracts typically are located on the posterior side of the lens and are referred to as posterior subcapsular cataracts (PSC); we reviewed studies that compared the risk of PSC in ICS-treated populations to non-ICS-treated populations (Table 43).

No study compared the risk of developing PSC between one ICS and another. One placebo-controlled trial^{198, 199} and five observational studies²⁰⁴⁻²⁰⁸ evaluated the risk of developing cataracts between ICS- and non-ICS-treated patients. One RCT^{198, 199} and one observational study²⁰⁴ compared budesonide to placebo; the other studies all compared nonspecific ICS use to no ICS use. Two studies were conducted in pediatric populations,^{198, 199, 204} one in a mixed population of children and adults,²⁰⁷ and three evaluated adult populations (≥ 40 years).^{205, 206, 208}

Both trials conducted in children reported no significant differences in the development of PSC between budesonide-treated patients and placebo or matched controls.^{198, 199, 204} One of these was the CAMP study, a good quality RCT with median follow-up of 4.3 years that allocated 1,041 asthmatic children to budesonide, nedocromil, or placebo.^{198, 199} The single study that included a mixed population of adults and children reported no increase in the risk of developing cataracts between ICS-treated patients and controls in persons younger than 40 years; a dose-, duration-, and age-related increase in risk was observed for persons older than 40 years of age.²⁰⁷

Consistent evidence from two case-control studies^{206, 208} and one cross-sectional study²⁰⁵ conducted in adult populations reported an increased risk of cataracts for ICS-treated patients compared to controls. Both case-control studies found the risk of cataracts increased at higher ICS doses and longer duration of treatment; one study reported a higher relative risk for ICS doses greater than 1,600 mcg/day²⁰⁸ and one study reported a higher relative risk for budesonide or beclomethasone doses greater than 1,000 mcg/day.²⁰⁶

Most studies did not control for or did not report previous exposure to systemic corticosteroids, a known cause of cataracts. Only one observational study controlled for previous exposure to systemic corticosteroids; controlling for systemic corticosteroid use and other potential confounders had little effect on the magnitude of the associations in this study.²⁰⁵

Table 43. Summary of studies on posterior subcapsular cataracts

Author Year	N	Design	Population	Results	Quality rating
Childhood Asthma Management Program Research Group, 2000 ^{198, 199}	1041	RCT	Children	No significant differences in PSC between BUD-, nedocromil-, or placebo-treated children	Good
Agertoft et al., 1998 ²⁰⁴	268	Prospective cohort	Children (age 5-16)	No significant differences in PSC between BUD-treated children and matched controls	Fair
Cumming et al. 1997 ²⁰⁵	3654	Cross-sectional	Adults (age 49-97)	Increased risk of nuclear and PSC among ICS users	NA
Garbe et al. 1998 ²⁰⁶	25,545	Case-control	RAMQ age ≥ 70 years	Increased risk of cataract extraction for ICS users only at high dose and duration	Good
Jick et al. 2001 ²⁰⁷	201,816 (3,581)	Cohort + case-control	GPRD (age 3-90)	Dose-, duration-, and age-related increased risk of cataracts among ICS users; no increase in risk for age < 40	Good
Smeeth et al. 2003 ²⁰⁸	30,958	Case-control	GPRD age ≥ 40 years	Dose- and duration-related increased risk of cataracts among ICS users	Fair

Abbreviations: BUD = Budesonide; GPRD= general practice research database; ICS = Inhaled Corticosteroids; RCT= randomized controlled trial; PSC= posterior subcapsular cataracts; RAMQ= regi de l'assurance maladie du Quebec database

No difference = no statistically significant difference or tests of statistical significance were not reported and outcomes are similar.

V. Ocular hypertension and open-angle glaucoma

No study compared one ICS to another for the risk of ocular hypertension or open-angle glaucoma. One fair-rated case-control study of 48,118 Canadians age 66 years and older²⁰⁶ and one cross-sectional population-based study of 3,654 Australians 49 to 97 years of age²⁰⁹ compared the risk of increased intraocular pressure or open-angle glaucoma between ICS- and non-ICS-treated patients. The populations in these studies were not limited to asthmatics. Both studies reported a dose-related increase in the risk of open-angle glaucoma for ICS-treated patients compared to patients that had not used an ICS. In one study this relationship was observed only among current users of high doses of ICSs prescribed regularly for three or more months (OR 1.44; 95% C.I. 1.01 to 2.06).²⁰⁶ The other study found an association between ever using ICSs and findings of elevated intraocular pressure or glaucoma only in subjects with a glaucoma family history (OR 2.8; 95% CI: 1.2 to 6.8).²⁰⁹ Both studies adjusted for age, sex, oral steroid use, history of diabetes, and history of hypertension (Table 44).

Table 44. Summary of studies on ocular hypertension or open-angle glaucoma

Author Year	N	Design	Population	Results	Quality rating
Garbe et al. 1997 ²⁰⁶	48,118	Case-control	RAMQ age ≥ 66 years	≥ 3 months of high-dose ICS associated with an increased risk of open-angle glaucoma and ocular hypertension	Fair
Mitchell et al. 1999 ²⁰⁹	3654	Cross-sectional	Adults (age 49-97)	Dose-related increased risk of elevated IOP and open-angle glaucoma for ICS users with glaucoma family history	Fair

Abbreviations: ICS = Inhaled Corticosteroids; IOP – intraocular pressure; N/A= not applicable; RAMQ= regi de l'assurance maladie du Quebec database.

Summary of the evidence

Osteoporosis/fractures/bone density

Overall, the evidence of an association between ICSs and significant changes in bone mineral density is mixed. For adults, the strongest evidence comes from three studies that assessed fractures.^{195, 201, 202} Two of these studies, one RCT (N = 374)¹⁹⁵ and one case-control study (N = 18,942)²⁰¹ reported no increased risk of fractures in those treated with ICSs. The other, a retrospective cohort study (N = 450,422), reported a dose-related increase in fracture risk.²⁰² Of four studies reporting BMD in adult subjects, three RCTs reported no difference between ICS-treated subjects and controls¹⁹⁴⁻¹⁹⁶ and one small prospective cohort study (N = 109) reported a small dose-related decline in BMD in premenopausal women treated with ICSs.²⁰⁰ For children, one good quality RCT and one cross-sectional study reported no difference in BMD between those treated with BUD and those treated with placebo. We view BMD as an intermediate outcome measure of osteoporosis; although a causal relationship exists between loss of BMD and risk of fractures due to osteoporosis, the clinical significance of small changes in BMD is uncertain.

Growth retardation

Three head-to-head trials provide fair evidence that short-term growth velocity is reduced less with fluticasone than with beclomethasone²⁶ or budesonide.^{39, 192} In addition, two meta-analyses report a reduction in growth velocity for beclomethasone or fluticasone compared to placebo.^{189, 190} Most studies of growth only address ICS treatment duration up to about one year. The best longer-term evidence is from the CAMP study, which followed subjects for an average of 4.3 years and found a 1.1 cm difference in mean increase in height ($P = 0.005$) between budesonide-treated patients and placebo-treated patients.^{198, 199} The differences in growth occurred primarily during the first year of treatment, suggesting that the small decrease in growth velocity with ICSs occurs early in treatment and is not progressive. Insufficient evidence exists to determine if long-term treatment with ICSs lead to a reduction in final adult height.

Acute adrenal crisis

Evidence from randomized trials and observational studies is insufficient to draw conclusions regarding the risk of rare but potentially fatal adverse events such as acute adrenal crisis. Nonetheless, multiple case reports have indicated that high-dose ICS treatment is associated

with acute adrenal crisis, especially in children.²¹¹⁻²¹³ Evidence from intermediate outcomes can not be extrapolated reliably to form conclusions about the comparative frequency of acute adrenal crisis for ICSs.

Cataracts

No study compared the risk of developing PSC between one ICS and another. General evidence of an association between ICS use and PSC is fair. No significant differences have been reported in the risk of PSC in children, adolescents, and adults less than 40 years of age between ICS users and controls. In older adults, however, an increase in the risk of developing cataracts was reported among individuals who took ICSs; increased risk was related to dose and duration of treatment. No study evaluated the link between childhood ICS use and risk of cataracts in older age.

Ocular hypertension and open-angle glaucoma

No study compared the risk of ocular hypertension or open-angle glaucoma between one ICS and another. Two observational studies provide consistent evidence of a dose-related increase in risk for ICS-treated patients. Overall, existing evidence of an association between ICS use and increased intraocular pressure or open-angle glaucoma is fair to poor.

B. Leukotriene Modifiers

Summary of findings

There is insufficient head-to-head data (one trial) to determine differences in tolerability or overall adverse events between any of the leukotriene modifiers using direct evidence. Indirect evidence from placebo-controlled trials and large safety databases suggests that zileuton has an increased risk of liver toxicity compared with either montelukast or zafirlukast.

Direct Evidence

We found just one fair-rated 12-week head-to-head trial comparing one leukotriene modifier with another that met inclusion/exclusion criteria for our review.⁵¹ The trial compared quality of life outcomes between montelukast and zafirlukast at recommended doses in adults with mild persistent asthma and did not report any adverse events in either group. We found no head-to-head trials for comparisons of other leukotriene modifiers. In addition, we found no head-to-head trials in children.

Indirect Evidence

Placebo-controlled trials and post-marketing surveillance provide further information on the comparative safety of leukotriene modifiers.¹⁰

Liver toxicity

Evidence from placebo-controlled trials of zileuton reported an increased risk of hepatic toxicity with increased frequency of elevated liver transaminases (ALT elevations of ≥ 3 times the upper limit of normal: 1.9% compared with 0.2% for zileuton compared with placebo).¹⁰ In patients treated for up to 12 months with zileuton in addition to their usual asthma care, 4.6% developed an ALT of at least three times the upper limit of normal, compared with 1.1% of

patients receiving their usual asthma care.¹⁰ Due to the increased risk, monitoring of liver function tests is required with zileuton therapy.¹

Rare cases of liver toxicity have been reported with montelukast (cholestatic hepatitis, hepatocellular liver injury, and mixed-pattern liver injury) and zafirlukast (fulminant hepatitis, hepatic failure, liver transplantation, and death have been reported).¹⁰ Data from safety databases and placebo-controlled trials suggest numerically similar rates of increased transaminases between montelukast (increased ALT: 2.1% compared with 2%; increased AST 1.6% compared with 1.2%) or zafirlukast (increased ALT: 1.5% compared with 1.1%) and placebo.¹⁰

Table 45. Summary of head-to-head studies comparing tolerability and overall adverse events of leukotriene modifiers

Study	Study design N Duration	Country Study population Setting	Comparison (total daily dose in mg/day)	Results	Quality rating
Montelukast (ML) compared with zafirlukast					
Riccioni et al. 2004 ⁵¹	RCT 40 12 weeks	Italy Age ≥12, mild, smoking status NR Respiratory Pathophysiology Center	ML (10) vs. ZAF(40)	No AEs reported	NA
Montelukast compared with zileuton					
No systematic reviews or head-to-head trials found					
Zafirlukast compared with zileuton					
No systematic reviews or head-to-head trials found					

Abbreviations: AE= adverse events; NR = not reported; RCT= randomized controlled trial; ZAF = Zafirlukast.

Note: All results are listed in the same order as the comparison column lists the medications.

C. Long-Acting Beta-2 Agonists (LABAs)

Formoterol and salmeterol, the two LABAs currently available for the treatment of asthma, are both selective beta2-adrenergic receptor agonists. At high doses, both can produce clinically important sympathomimetic adverse effects including tremor and hyperglycemia.

Of greater concern are reports that regular use of LABAs may be associated with an increased risk of severe asthma exacerbations, both life-threatening and fatal.²¹⁴ Subgroup analysis from one study²¹⁴ has suggested this risk may be significantly higher in African Americans (see Key Question 3). These concerns have resulted in an FDA boxed warning (also referred to as a “black box warning”) for products that contain formoterol or salmeterol. A boxed warning is a type of warning that the FDA requires on the labels of prescription drugs that may cause serious adverse effects, and it signifies that clinical studies have indicated that the drug carries a significant risk of serious or even life-threatening side effects. Experts recommend strongly against using LABAs as monotherapy for long-term control of persistent asthma.¹

Potential mechanisms by which LABAs could increase the risk of life-threatening asthma exacerbations include: (1) a direct tachyphylactic effect on airway smooth muscle, leading to more severe obstruction after a bronchoconstrictive stimulus, and/ or (2) transient maintenance of bronchodilation (and symptom control) even in the face of worsening airways inflammation, leading eventually to a sudden and severe increase in obstruction and/or to patients' delaying in seeking medical attention for a severe exacerbation.

For this review, we sought evidence of comparative safety of formoterol and salmeterol with respect to these severe adverse events as well as for common side effects.

Summary of findings

We found four RCTs that met our inclusion criteria and provided direct evidence regarding the relative safety of formoterol and salmeterol (Table 46). We rated three studies^{52, 54-56} as fair quality for assessment of adverse events. The fourth⁵³ was rated as "poor" quality for assessment of adverse events. However, since it was the only head-to-head trial performed specifically in children, we describe it in this section. In general, these trials were of relatively short duration, with none lasting more than 24 weeks. All were designed primarily to assess efficacy. Adverse events were typically collected via spontaneous reports from patients or "general questioning" by the investigators, though study withdrawals and reasons for withdrawals were reported. In these trials, all patients were taking ICS at the time of enrollment, and severe adverse events were rare.

We also identified four systematic reviews with meta-analysis of placebo-controlled studies of LABAs that provided some indirect evidence regarding the relative safety of LABAs as well as more robust evidence of their safety (as a class) when compared with placebo.^{120, 153, 215, 216}

Overall, limited direct evidence from head-to-head trials and indirect evidence from systematic reviews provides no evidence of a difference in tolerability or adverse events between formoterol and salmeterol.

Detailed Assessment

Direct Evidence

Of the four included head to head trials, two were conducted only in adults,^{55, 56} one enrolled adults and adolescents⁵² and one enrolled only children and adolescents between 5-18 years old.⁵³ All four trials compared FM (12 mcg twice daily) with SM (50 mcg twice daily) (Table 46). Only one⁵² of the four trials was blinded. Detailed descriptions of these RCTs are provided in the Key Question 1 section of this report with the exception of one study that was included for this section but not for efficacy outcomes.⁵⁶

One open-label RCT conducted in the United States⁵⁶ compared formoterol (24 mcg/day) to salmeterol (50 mcg/day) in 528 adult asthmatics who were already taking low dose ICSs. The duration of the study was 24 weeks and the investigator found similar numbers of total withdrawals (14.5% compared with 11.3%) and withdrawals due to adverse events (5.7% compared with 3.4%).

One trial^{52, 217} randomized 469 patients to blinded eFM via DPI, SM via DPI, or SM via MDI. They found similar rates of hospital admission and ED visits and total study withdrawals. Another trial⁵⁴ compared FM administered via DPI with SM given via DPI in 482 adult asthmatics. The trial found comparable rates of hospitalizations, study withdrawals, withdrawals due to adverse events, and drug-related adverse events. The only trial enrolling

children and adolescents⁵³ randomized subject (N = 156) to FM or SM and also found similar rates of study withdrawals and withdrawals due to adverse events.

Indirect evidence

Among the systematic reviews with meta-analysis we included for this section, the most recent was published in 2007.²¹⁶ Their review aimed to examine both efficacy and safety outcomes of studies comparing LABAs to placebo in “real world” asthmatic populations in which only some patients were using regular ICSs at baseline. They included 67 studies randomizing a total of 42,333 participants. Salmeterol was used as a long-acting agent in 50 studies and formoterol in 17. The treatment and monitoring period was relatively short (4 -9 weeks) in 29 studies, and somewhat longer (12 -52 weeks) in 38 studies. The systematic review reported that LABAs were generally effective in reducing asthma symptoms in this population, but they noted safety concerns for patients not using ICSs and for African Americans, based on data from the Salmeterol Multicenter Asthma Research Trial (SMART), described below.²¹⁴ From a post-hoc analysis of SMART, their estimate for the relative risk of asthma-related death for those taking ICSs at baseline did not show an increased risk (RR 1.34, 95% CI: 0.30 to 5.97). However, those not taking ICSs at baseline had an increased risk of asthma-related death (RR 18.98, 95% CI: 1.1 to 326). In addition, other asthma-related serious adverse events were increased in LABA-treated patients (OR 7.46, 95% CI: 2.21 to 25.16). For respiratory-related death, they found an increased risk in the total population (RR 2.18, 95% CI: 1.07 to 4.05), but no difference between subgroups of subjects using ICS compared with those not using ICS at baseline (test for interaction $P = 0.84$). Among their findings regarding less severe side effects, they noted that tremor was more common in LABA treated patients (OR 3.86, 95% CI: 1.91 to 7.78).

Of the four included systematic reviews with meta-analysis (Table 46), one²¹⁵ was designed specifically to examine risks for life-threatening or fatal asthma exacerbations associated with LABA. The majority of subjects (about 80%) in the studies included in this review were treated with salmeterol. The meta-analyses found that the risk of hospitalization was increased in LABA treated patients (OR 2.6, CI: 1.6 to 4.3). The estimated risk difference for hospitalization attributed to LABA was 0.7% (CI: 0.1% to 1.3%) over 6 months. Notably, the investigators assessed separately the associations between SM and FM and risk for this outcome. They found an increased risk for hospitalization associated with both salmeterol (OR, 1.7 [CI: 1.1 to 2.7]) and with formoterol (OR, 3.2 [CI: 1.7 to 6.0]). They also estimated the risk for life-threatening asthma attacks and found it to be increased for LABA-treated patients (OR 1.8, CI: 1.1 to 2.9, risk difference 0.12%, CI: 0.01% to 0.3% over 6 months). Lastly, they examined the risk for asthma-related deaths in these studies and found it to be increased for LABA treated patients: (OR 3.5, 95% CI: 1.3 to 9.3; risk difference 0.07%, CI: 0.01% to 0.1% over 6 months).

There was significant overlap between the two meta-analyses described above.^{215, 216} Twelve of 14 (86%) published studies included in the 2006 meta-analysis²¹⁵ were also included in the 2007 meta-analysis.²¹⁶ The 2007 analysis included studies of shorter duration, which partially accounted for the greater number of included studies.

An older systematic review¹⁵³ evaluated RCTs in which the addition of LABAs to ICS was compared with adding placebo to ICS. They found no differences in overall adverse effects, serious adverse events, or in specific side effects. Comparative safety was examined secondarily, and only one included study reported deaths, with three deaths reported overall.

Further, the Salmeterol Multicenter Asthma Research Trial (SMART),²¹⁴ a large 28-week randomized study of the safety of LABAs was categorized as “awaiting assessment” at the time this systematic review was published.

SMART included 26,355 subjects and was terminated due to findings in African Americans and difficulties in enrollment.²¹⁴ The trial found no statistically significant difference between those treated with salmeterol and those treated with placebo for the primary outcome, respiratory-related deaths, or life-threatening experiences was low and not significantly different for salmeterol compared with placebo (50 compared with 36; RR 1.40; 95% CI: 0.91 to 2.14). However, the trial reported statistically significant increases in respiratory-related deaths (24 compared with 11; RR 2.16; 95% CI: 1.06 to 4.41) and asthma-related deaths (13 compared with 3; RR 4.37; 95% CI: 1.25 to 15.34), and in combined asthma-related deaths or life-threatening experiences (37 compared with 22; RR 1.71; 95% CI: 1.01 to 2.89) for subjects receiving salmeterol compared to those receiving placebo. In addition, subgroup analyses suggest the risk may be greater in African Americans compared with Caucasian subjects. The increased risk was thought to be largely attributable to the African-American subpopulation: respiratory-related deaths or life-threatening experiences (20 compared with 5; RR 4.10; 95% CI: 1.54 to 10.90) and combined asthma-related deaths or life-threatening experiences (19 compared with 4; RR 4.92; 95% CI: 1.68 to 14.45) in subjects receiving salmeterol compared to those receiving placebo.²¹⁴

Finally, another systematic review with meta-analysis¹²⁰ examined the efficacy and safety of *initiating* LABA with ICS compared with ICS alone in steroid naïve asthmatics. They found no differences in rates of any adverse effects or in withdrawals due to adverse effects. They did find an increased risk for tremor associated with LABA (RR 5.05; 95% CI: 1.33 to 19.17).

Table 46. Summary of head to head studies comparing tolerability and overall adverse events of LABAs

Study	Study design N Duration	Country Study population Setting	Comparison (total daily dose)	Results	Quality rating
Direct evidence (formoterol compared with salmeterol)					
Campbell et al. 1999 ⁵²	RCT, cross-over 469 8 weeks	UK & Republic of Ireland Age ≥ 12, mild to moderate, not controlled on ICS, 20-24% current smokers in each group General practice & hospital centers	eFM DPI (24) vs. SM DPI (100) vs. SM MDI (100)	Hospital admission or ED visit, number (%): 1 (4) vs. 1 (7) vs. 2 (15) Withdrawals due to AE: Not reported	Fair

Study	Study design N Duration	Country Study population Setting	Comparison (total daily dose)	Results	Quality rating
Condemni et al. 2001 ⁵⁶	RCT; open-label N = 528 24 wks (monthly visits in which pts could volunteer adverse events); symptom diaries collected only for first 4 weeks.	USA Adults with moderate to moderately severe asthma already taking low dose ICS (400ug/day or FP 200 ug/d) smoking status=NR Multi-center, outpatient practices	FM (24) vs. SM (100)	Withdrawals due to AE: FM 5.7% vs. SM 3.4% No. (%) with at least 1 adverse event 202 (77.1) vs. 201 (75.6)	Fair
Everden et al. 2004 ⁵³	RCT; open; N = 156 12wk	UK & Republic of Ireland Children and adolescents age 6-17, moderate persistent, not controlled on ICS, smoking status=NR General practice outpatient clinics	eFM DPI (24) vs. SM DPI (100)	Withdrawals due to AE no. (%): 4 (5.1) vs. 2 (2.6) Overall adverse events reported (%): 55 vs. 59	Poor
Vervolet et al. 1998 ⁵⁴ and Rutten-van Molken 1998 ⁵⁵	RCT, open label N = 482 6 mo.	France, Italy, Spain, Sweden, Switzerland & UK Age ≥ 18, moderate-severe, not controlled on ICS, 14-16% current smokers Outpatient centers	FM DPI (24) vs. SM DPI (100)	Hospitalizations (mean inpatient days): 0.58 vs. 0.43 <i>P</i> = 0.996 Withdrawals due to AEs (%) (4.6) vs. (5.0) Drug related AEs (%) 32 (13%) vs. 21 (9%) (headache most common)	Fair
Indirect evidence (LABA compared with placebo)					
Ni Chroinin et al. 2004 ¹²⁰	Systematic review and meta-analysis N = 1061 Duration: at least 30 d.	Multinational Adults and/or children aged two years and above with persistent asthma of any severity and who were steroid-naïve. 18 trials met the inclusion criteria; 9 (N = 1061 adults) contributed sufficient data to be analyzed.	Initiating combined ICS+LABA vs. ICS alone at same (or equivalent).	Any adverse effects (N = 5 trials: RR 1.09; 95% CI: 0.81 to 1.48). Withdrawals due to AEs (N = 3 trials: RR 1.71; 95% CI: 0.68 to 4.27), Specific side effects: Oral candidiasis (N = 2 trials: RR 0.43; 95% CI: 0.07 to 2.84). Headache (N = 2 trials: RR 1.92; 95% CI: 0.54 to 6.85). Tremor (N = 2 trials: RR 5.05; 95% CI: 1.33 to 19.17).	Good
Ni Chroinin et al. 2005 ¹⁵³	Systematic review and meta-analysis N = 8147	Multinational RCTs conducted in adults or children aged 2 or above in whom LABA were added to	addition LABA to ICS vs. placebo added to ICS	Overall adverse effects: no difference (N = 11, RR 0.98, 95% CI: 0.92 to 1.05), Serious adverse events: no difference (N = 4 studies, RR	Good

Study	Study design N Duration	Country Study population Setting	Comparison (total daily dose)	Results	Quality rating
	26 RCTs Duration: at least 30 days (most less than 4 mo.)	ICS.		1.16, 95% CI: 0.30 to 4.42) or Specific side effects: headache (N = 12, RR 1.13, 95% CI: 0.92 to 1.41); hoarseness (N = 3 comparisons, RR 0.71, 95% CI: 0.16 to 3.18, random-effects model); oral thrush (N = 4, RR 1.04, 95% CI: 0.35 to 3.06); tachycardia or palpitations (N = 5, RR 2.13, 95% CI: 0.77 to 5.88); cardiovascular adverse effects such as chest pain (N = 3, RR 0.90, 95% CI: 0.32 to 2.54); tremor (N = 7, RR 2.48, 95% CI: 0.78 to 7.89). Effect on growth, adrenal function and methacholine challenge could not be aggregated due to insufficient number of trials (fewer than 2) reporting these outcomes. Only one study reported deaths, with three deaths reported overall. Withdrawals due to adverse effects: no difference (N = 19, RR 1.29, 95% CI: 0.96 to 1.75).	
Salpeter et al. 2006 ²¹⁵	Systematic review with meta-analysis 19 RCTs (N = 33826) Duration: at least 3 mo.	Adults and children with asthma Mean age 37 years; 51% men; 15% African American. 53% of subjects on ICS.	LABA vs. placebo	Hospitalization: OR 2.6 (CI: 1.6 to 4.3). Risk difference attributed to LABA 0.7% (CI: 0.1% to 1.3%) over 6 months. Risk increased in children (OR, 3.9 [CI: 1.7 to 8.8]) and in adults (OR, 2.0 [CI: 1.0 to 3.9]). Risk increased with SM (OR, 1.7 [CI: 1.1 to 2.7]) and with FM (OR, 3.2 [CI: 1.7 to 6.0]) Life-threatening asthma attacks: OR 1.8 (CI: 1.1 to 2.9). Risk difference 0.12% (CI: 0.01% to 0.3%) over 6 months. Asthma-related deaths: (OR, 3.5 [CI: 1.3 to 9.3]). Pooled risk difference of 0.07% (CI: 0.01% to 0.1%)	Good
Walters et al. 2007 ²¹⁶	Systematic review with meta-analysis 67 RCTs (N = 42,333). Duration: at	Multinational Adults and children with asthma who were not uniformly on ICS. (Studies in which all subjects were uniformly taking ICS excluded	Regular inhaled LABA (either salmeterol or formoterol) administered twice daily vs. placebo.	Asthma-related death: for those taking ICS at baseline RR 1.34 (95% CI: 0.30 to 5.97). For those not taking ICS at baseline the Relative Risk is 18.98 (95% CI: 1.1 to 326). Respiratory-related death: RR	Good

Study	Study design N Duration	Country Study population Setting	Comparison (total daily dose)	Results	Quality rating
	least 4 wks.	from this review.) 11 studies included children under 12 yrs. Asthma severity: of 67 RCTs, number with mild -moderate asthma, 28; mild asthmatics, 9; moderate - severe disease, 1; persistent or symptomatic disease, 11; unknown disease severity, 18.		<p>for total population of 2.18 (95% CI: 1.07 to 4.05), N = 26355. No difference between subgroups using ICS vs. not using ICS at baseline (test for interaction $P = 0.84$).</p> <p>All-cause mortality: no significant difference (RR 1.33, 95% CI: 0.76 to 2.35; three studies using the non-ICS subgroup from SMART, N = 14534 and RR 1.37, 95% CI: 0.87 to 2.14 using all participants from SMART, N = 26799).</p> <p>Serious adverse events: Increased odds of asthma-related serious AE with LABA (OR 7.46, 95% CI: 2.21 to 25.16; three studies, N = 895). However, OR for life-threatening AE from SMART for both mixed and ICS - treated populations were not significantly different. LABA treatment led to a significant increase in the odds of serious AE where this was reported for 'total events' in three pediatric studies (OR 2.11, 1.03 to 4.31; N = 973). Total AE: No difference between LABA and placebo (OR 1.15, 95% CI: 0.99 to 1.33; 18 studies, N = 3447).</p> <p>Drug-related AE: more in LABA groups (OR 1.37, 95% CI: 1.01 to 1.87; seven studies, N = 2130),</p> <p>Specific side effects: "Nervousness": (OR 5.11, 95% CI: 1.72 to 15.22; two studies, N = 546). Tremor: (OR 3.86, 95% CI: 1.91 to 7.78; eight studies, 2257 participants), Headache: (OR 1.28, 95% CI: 1.04 to 1.57; 23 studies, N = 5667). Throat irritation (OR 1.68, 95% CI: 1.10 to 2.56; eight studies, N = 1170).</p> <p>Other AEs: NS difference for pharyngitis, cough, cramps, myalgia/ fatigue, insomnia, upper respiratory infection, musculo-skeletal pain or palpitations.</p>	

Study	Study design N Duration	Country Study population Setting	Comparison (total daily dose)	Results	Quality rating
				Withdrawal (due to AE): NS (OR 1.11, 95% CI: 0.93 to 1.32; 21 studies, N = 30943).	

Abbreviations: AE = adverse events; CI = confidence interval; DPI = dry powder inhaler; eFM = Eformoterol; FM = Formoterol; ICS = Inhaled Corticosteroids; LABAs = Long-Acting Beta-2 Agonists; MDI = metered dose inhaler; NS = not statistically significant; OR= odds ratio; RCT= randomized controlled trial.

No difference = no statistically significant difference or tests of statistical significance were not reported and outcomes are similar.

Note: All results are listed in the same order as the comparison column lists the medications.

D. Anti-IgE Therapy

Summary of findings

The prescription information for omalizumab has a boxed (or “black box”) warning for anaphylaxis which includes bronchospasm, hypotension, syncope, urticaria, and/or angioedema of the throat or tongue.¹⁰ A boxed warning is a type of warning that the FDA requires on the labels of prescription drugs that may cause serious adverse effects, and it signifies that clinical studies have indicated that the drug carries a significant risk of serious or even life-threatening side effects. According to the boxed warning for omalizumab, there have been reports of anaphylaxis as early as after the first dose of omalizumab, but anaphylaxis has also occurred more than one year after the start of regular treatment with omalizumab. Some of these events were life-threatening.

Omalizumab prescription information also contains a warning for a potential increased risk of malignancy. In clinical studies, malignant neoplasms were seen in 0.5% of omalizumab-treated patients compared with 0.2% of control patients. The majority of patients in these studies were observed for less than one year; consequently, longer-term studies are needed to better determine the impact of longer exposure to omalizumab.

As previously noted, omalizumab is the only available anti-IgE drug approved for the treatment of asthma; therefore, there are no studies of intra-class comparisons. We did not find any head-to-head studies directly comparing omalizumab to ICSs, LABAs, leukotriene modifiers. All included trials are placebo comparisons. We found six fair to good quality RCTs^{57, 59-62, 64, 65, 67} and one systematic review with meta-analysis⁷⁰ that met our eligibility criteria.

Overall, tolerability and adverse events were similar in omalizumab- and placebo-treated patients with the exception of injection site reactions which were greater in omalizumab-treated patients. As noted above, omalizumab has a boxed warning for anaphylaxis.¹⁰ Further studies, including those in pediatric populations, are needed to determine the impact of long-term treatment.

Detailed Assessment

Of the six included RCTs, only one⁶² focused on children (6-12 years old); all other RCTs included adolescents and adults ≥ 12 years of age. The systematic review included all six RCTs (Table 47). These studies are described in detail in the Key Question 1 section of this report.

A good quality systematic review with meta-analysis found no difference in headache, urticaria, number of patients with any adverse events, and withdrawals due to adverse events between subcutaneous omalizumab and placebo.⁷⁰ However, injection site reactions were significantly greater in omalizumab patients (OR 2, 95% CI: 1.37 to 2.92).

When looking at the individual studies, we found wide variation in incidence of injection site reaction across studies. Most studies reported the occurrence of injection site reaction as less than 10%. One study, however, reported that the frequency of occurrence was greater than 35% in both the omalizumab and placebo groups. Wide variance in the occurrence of injection site reaction across studies may be explained by the fact that one study interpreted this term more broadly to encompass one or more of a number of symptoms (e.g., burning, itching, warmth, bruising, redness, hive formation, rashes). Other studies limited the term to denote severe reactions, and some studies do not describe how they apply the term. The package insert for omalizumab used a broader definition (injection site reactions of any severity) and reported occurrence rates of 45% and 43% for omalizumab and placebo, respectively.¹⁰

Withdrawals attributed explicitly to adverse events were similar in adult and pediatric patients. However, in the pediatric study, 1.8% of omalizumab- and 1.8% of placebo-treated patients withdrew because of pain or fear of injection.⁶²

Table 47. Summary of tolerability and adverse events for omalizumab compared with placebo

Study	Study design N Duration	Country Population Setting	Comparison (total daily dose)	Results	Quality rating
Omalizumab compared with placebo					
Walker et al. 2006 ⁷⁰	Systematic review with meta-analysis 14 DB RCTs (15 group comparisons; 3,143 patients) Trials of any duration were included	Multinational Adults and children with chronic asthma	OM (SQ, IV or inhaled)	Overall AEs: No difference Withdrawals: No difference Injection site reaction: Significantly greater in OM patients (OR: 2 [95% CI: 1.37-2.92]); NNT(h) = 21 Other: No difference in headache, urticaria	Good
Busse et al. 2001 ⁵⁷	RCT DB 525 28 weeks (16 weeks followed by 12 weeks tapering ICS dose)	US and UK Adolescents and adults age 12-75; moderate to severe allergic asthma requiring daily ICS; on stable BDP dose 4 wks prior to randomization and during wks 1-16	0.016 mg/kg/IgE (IU/mL) per 4 weeks (150 mg or 300 mg every 4 wks or 225 mg, 300 mg, or 375 mg every 2 wks)	Overall AEs: 89.2% vs. 89.1% Withdrawals: 0.7% vs. 0% Injection site reaction: 8.6% vs. 6.5%	Fair
Lanier et al. 2005 ⁵⁹ + unpublished data ⁶⁸	Optional 24 week DB extension (N = 460)	Multicenter (5)		EXTENSION PHASE Overall AEs: 82.9% vs. 82.5% Withdrawals: 0 vs. 0 Injection site reaction: NR	
Holgate et	RCT DB	Multinational	0.016	Overall AEs: 76.2% vs. 82.5%	Fair

Study	Study design N Duration	Country Population Setting	Comparison (total daily dose)	Results	Quality rating
al. 2004 ⁶⁰ + Unpublished data ⁶⁸	246 32 weeks (16 weeks followed by 16 weeks FP reduction phase) Subgroup analysis from FDA data	Adolescents and adults age 12-75; severe asthmatics; optimally controlled; requiring high dose FP (between 1000 and 2000 mcg/day for symptom control stabilized for 4 wks prior to randomization; allergic response (> 1 positive SPT) to aeroallergen(s) Multicenter	mg/kg/IgE (IU/mL) per 4 weeks	Withdrawals: 0% vs. 1.7% Injection site reaction: 20.4% vs. 10.3%	
INNOVAT E Humbert et al. 2005 ⁶¹	RCT DB 482 28 weeks	Multinational Patients age 12-75; positive SPT to ≥ 1 perennial aeroallergen; severe persistent asthma requiring regular treatment with > 1000 mcg BDP or equivalent LABA; continued usual care (high dose ICS + LABA) throughout study Multicenter (hospital clinics)	0.016 mg/kg per IU/mL of IgE	Overall AEs: 72.2% vs. 75.5% Withdrawals: 5% vs. 2% Injection site reaction: 5.3% vs. 1.3%	Fair
Milgrom et al. 2001 ⁶²	RCT DB 334 28 weeks (16 week stable steroid phase followed by 12 week steroid reduction phase)	US Children aged 6-12; moderate to severe allergic asthma of at least 1 year duration that was well controlled with ICSs equivalent to 168-420 mcg/day BDP; positive SP Multicenter	0.016 mg/kg/IgE (IU/mL) every 2 or 4 weeks	Overall AEs: 89.3% vs. 87.2% Withdrawals: <1% vs. <1% Injection site reaction: 37.5% vs. 36.6%	Fair
Solèr et al. 2001 ⁶⁴ Buhl et al. 2002 ⁶⁵ + unpublish ed data ⁶⁸	RCT DB 546 28 weeks (16 week stable ICS phase followed by 8 week reduction phase and 4 week stable phase)	Multinational Patients age 12-75; Moderate-severe allergic asthma Multicenter	≥0.016 mg/kg per IU/mL of IgE	Overall AEs: No difference (data NR, <i>P</i> = 0.504) Withdrawals: 0% vs. 1.8% Injection site reaction: 11.8% vs. 7.7%	Fair

Study	Study design N Duration	Country Population Setting	Comparison (total daily dose)	Results	Quality rating
	24 week DB extension (N = 483)			EXTENSION PHASE Overall AEs: 63.4% vs. 65.9%, <i>P</i> = 0.548 Withdrawals: 0.8% vs. 0 Injection site reaction: 5.3% vs. 4.3%	
SOLAR Vignola et al. 2004 ⁶⁷	RCT DB 405 28 weeks	Multinational Patients age 12-74; stable on ≥ 400 mcg BUD; continued BUD treatment; allergic asthma and PAR Concomitant asthma and rhinitis Multicenter	≥ 0.016 mg/kg/IgE (IU/mL) per 4 weeks	Overall AEs: 78.5% vs. 68.9% Withdrawals: NR Injection site reaction: 7.7% vs. 4.6%	Fair

Abbreviations: AE= adverse events; BDP = beclomethasone dipropionate; BUD= Budesonide; DB = double-blind; FP = Fluticasone Propionate; ICS = Inhaled Corticosteroids; NNT(h)= number needed to treat/harm;; NR = not reported; OM= Omalizumab; OR= odds ratio; PAR= persistent allergic rhinitis; RCT= randomized controlled trial; SPT= skin prick test.

No difference = no statistically significant difference or tests of statistical significance were not reported and outcomes are similar

Note: All results are listed in the same order as the comparison column lists the medications.

E. Combination Products ICS+LABA compared with ICS+LABA

Summary of findings

We found four head-to-head RCTs comparing budesonide/formoterol (BUD/FM) with fluticasone/salmeterol (FP/SM)⁷¹⁻⁷⁵ for maintenance therapy. In addition, we found two head-to-head RCTs^{73, 74, 78} comparing BUD/FM for maintenance and as-needed relief with BUD/FM or FP/SM for maintenance and a Short-Acting Beta-Agonist (SABA) for relief reporting tolerability or frequency of adverse events (Table 48).

Overall, data from four large head-to-head trials (5,818 subjects) provides no evidence of a difference in tolerability or overall adverse events between BUD/FM and FP/SM for maintenance therapy in adults and adolescents. There is insufficient evidence to draw conclusions in children ≤ 12.

Detailed Assessment

Description of Studies

Most studies that examined the efficacy of one combination treatment relative to another (described in Key Question 1) also reported tolerability and adverse events. All trials included adolescents and adults; one trial also included children.⁷⁸ Study duration ranged from 12 weeks to one year; most trials were six months or greater. Methods of adverse events assessment differed greatly. Few studies used objective scales such as the adverse reaction terminology from the World Health Organization (WHO). Most studies combined patient-reported adverse events with a regular clinical examination by an investigator. Often it was hard to determine if assessment methods were unbiased and adequate; many trials reported only those adverse events considered to be related to treatment. Rarely were adverse events prespecified and defined.

A. Overall adverse events, tolerability, and common adverse events

Overall adverse events and withdrawals due to adverse events were commonly reported (Table 48). Most combination trials reported specific adverse events. Oral candidiasis, rhinitis, cough, sore throat, hoarseness, headache, and upper respiratory infection were among the most commonly reported adverse events (see Evidence Tables). Frequency of adverse events was similar between those treated with BUD/FM and those treated with FP/SM.

Table 48. Summary of head-to-head studies comparing tolerability and adverse events for combination products (BUD/FM and FP/SM)

Study	Study design N Duration	Study population Country Setting	Comparison (total daily dose)	Results	Quality rating
Budesonide/formoterol (BUD/FM) compared with fluticasone/salmeterol (FP/SM)					
Aalbers et al. 2004 ⁷¹	RCT 658 7 months, 1 month double-blind, 6 months open	Age ≥ 12 years, asthma for a minimum of 6 months, not controlled on ICS alone Multinational (6: Denmark, Finland, Germany, Norway, Sweden and The Netherlands) Multicenter (93), outpatient clinics	BUD/FM (320-640/9-18) adjustable dose (AD) DPI vs. BUD/FM (640/18) DPI vs. FP/SM (500/100) DPI	Only data for BUD/FM (640/18) vs. FP/SM shown here Adverse events caused withdrawal (%): 5 vs. 4 Overall adverse events reported (%): 58 vs. 66	Fair
Dahl et al. 2006 ⁷²	RCT 1397 24 weeks	Male or female; aged ≥ 18 years with asthma for a minimum of 6 months	BUD/FM (800/24) DPI vs. FP/SM(500/100) DPI	Overall adverse events reported (%): 55 vs. 54 Adverse events caused withdrawal (%): 1.9 vs. 1.4	Good

Study	Study design N Duration	Study population Country Setting	Comparison (total daily dose)	Results	Quality rating
		Moderate/severe			
		Multinational			
		Multicenter			
Kuna et al. 2007 ⁷³	RCT 3335	Outpatients aged 12 years or more, with persistent asthma	BUD/FM (320/9 + as-needed use)	Only data for BUD/FM (640/18) vs. FP/SM shown here	Good
AND	6 months	Not or poorly controlled	DPI	Adverse events caused withdrawal (%): 1 vs. 1	
Price et al. 2007 ⁷⁴		Multinational	BUD/FM (640/18) DPI	Overall adverse events reported (%): NR	
		Multicenter	vs. FP/SM (500/100) pMDI		
Ringdal et al. 2002 ⁷⁵	RCT 428	Aged 16-75 years with a clinical history of asthma	BUD (1600) DPI + FM (24) DPI	Adverse events caused withdrawal (%): 4.2 vs. 4.2	Good
	12 weeks	Moderate/severe and not or poorly controlled	vs. FP/SM (500/100) DPI	Overall adverse events reported (%): 78 vs. 91	
		Multinational (11 European countries)		Hospitalizations: days on general ward: 18 vs. 7	
		Primary care and hospital respiratory clinics		Urgent care use: unscheduled outpatient visits: 17 vs. 6	
BUD/FM for maintenance and relief compared with BUD/FM for maintenance and SABA relief or compared with FP/SM for maintenance and SABA relief					
O'Byrne et al. 2005 ⁷⁸	RCT 2760	Outpatients aged 4 to 80 years with asthma treated with 400 to 1,000 mcg/day of ICS for adults and 200 to 500 mcg/day for children (4–11 years) with a history of one or more asthma exacerbation in the last year	BUD/FM (160/9 + as-needed) vs. BUD/FM (160/9 + SABA as-needed)	Only data for BUD/FM (160/9 + as-needed) vs. BUD/FM (160/9 + SABA as-needed) shown here	
	1 year		BUD/FM (160/9 + SABA as-needed) vs. BUD (320)	Overall adverse events reported (%): 54 vs. 52	
		Multinational	All delivery devices=DPIs		
		Multicenter			
Kuna et al. 2007 ⁷³	RCT 3335	Outpatients aged 12 years or more, with persistent asthma	BUD/FM (320/9 + as-needed) DPI	Only data for BUD/FM (320/9 + as-needed) vs. FP/SM (+ SABA as-needed) shown here	Good
AND	6 months	Not or poorly controlled	vs. BUD/FM (640/18) DPI	Adverse events caused withdrawal (%): 1 vs. 1	
Price et al.					

Study	Study design N Duration	Study population Country Setting	Comparison (total daily dose)	Results	Quality rating
2007 ⁷⁴		Multinational Multicenter	vs. FP/SM (500/100) pMDI	Missed days of work: sick leave mean/patient/6 mos: 1.11 vs. 0.93; <i>P</i> = NR Hospitalizations and Emergency room visits: 48 (4) vs. 70 (6); Treatment comparison (95% CI) 0.69 (0.48, 0.99) <i>P</i> = 0.047	
Kuna et al. 2007 ⁷³	RCT 3335	Outpatients aged 12 years or more, with persistent asthma	BUD/FM (320/9 + as- needed) DPI	Only data for BUD/FM (320/9 + as- needed) vs. BUD/FM (640/18 + SABA as-needed)	Good
AND Price et al. 2007 ⁷⁴	6 months	Not or poorly controlled Multinational Multicenter	vs. BUD/FM (640/18 + SABA as- needed) DPI vs. FP/SM (500/100 + SABA as- needed) pMDI	Adverse events caused withdrawal (%): 1 vs. 1 Hospitalizations and Emergency room visits: 48 (4) vs. 50 (5) Treatment comparison (95% CI) 0.97 (0.65, 1.44) <i>P</i> = 0.87	

Abbreviations: AE = adverse events; BUD = Budesonide; DPI = dry powder inhaler; FD= fixed dose; FM = Formoterol; FP = Fluticasone Propionate; NR = not reported; pMDI= pressurized metered dose inhaler; RCT= randomized controlled trial; SABA = Short-Acting Beta-Agonist; SM = Salmeterol.

Note: All results are listed in the same order as the comparison column lists the medications.

II. Inter-class comparisons (between classes)

A. Monotherapy

1. Inhaled Corticosteroids (ICSs) compared with Leukotriene modifiers (LMs)

Summary of findings

We found one systematic review with meta-analyses⁸⁰ and 15 RCTs^{82, 84-89, 91-99, 104} (Table 49). These were described in the Key Question 1 section of this report.

Overall, data from one good quality systematic review and numerous head-to-head RCTs provides no evidence of a difference in tolerability or overall adverse events between ICSs and leukotriene modifiers. Trials were generally not designed to compare tolerability and adverse events.

Detailed Assessment

Most studies that examined the efficacy of ICSs compared to leukotriene modifiers (described in Key Question 1) also reported tolerability and adverse events. Study duration ranged from six weeks to 56 weeks. Methods of adverse events assessment differed greatly. Few studies used objective scales such as the adverse reaction terminology from the World Health Organization (WHO). Most studies combined patient-reported adverse events with a regular clinical examination by an investigator. Often it was hard to determine if assessment methods

were unbiased and adequate; many trials reported only those adverse events considered to be related to treatment. Rarely were adverse events prespecified and defined.

Direct Evidence

One good quality systematic review with meta-analysis⁸⁰ provides the best evidence for overall adverse events and tolerability. The meta-analysis found no significant difference in the risk of experiencing any adverse effects (N = 15 trials, RR 0.99, 95% CI: 0.93 to 1.04) or of specific adverse events including elevation of liver enzymes, headaches, nausea, or oral candidiasis (Table 49). In addition, treatment with leukotriene modifiers was associated with a 30% increased risk of overall withdrawals (N = 19 trials, RR 1.3, 95% CI: 1.1 to 1.6), which appeared to be due to poor asthma control (N = 17 trials, RR 2.6, 95% CI: 2.0 to 3.4) rather than due to adverse effects (N = 14 trials, RR 1.2, 95% CI: 0.9 to 1.6).

Overall tolerability and adverse events from individual head-to-head trials are summarized in Table 49. Most studies did not find a significant difference between ICSs and leukotriene modifiers for overall tolerability and adverse events. Specific adverse events reported with ICSs (see Key Question 2 section on ICSs above), such as cataracts and decreased growth velocity, were not found among patients taking LTRAs. One fair quality head-to-head RCT (N = 360) compared linear growth rates in prepubertal children treated with montelukast, beclomethasone, or placebo.⁹⁶ The mean growth rate of subjects treated with beclomethasone was 0.81 cm less than that of subjects treated with montelukast.

Indirect Evidence

Indirect evidence from placebo-controlled trials is described in other sections of this report (see Key Question 2, Inhaled Corticosteroids and Leukotriene Modifiers sections). Evidence from placebo-controlled trials and observational studies suggest that ICSs may increase the risk of cataracts and may decrease short term growth velocity and bone mineral density.

Table 49. Summary of head-to-head studies comparing tolerability and overall adverse events between ICSs and LTRAs in children and adults

Study	Study design N Duration	Study population Country Setting	Comparison (total daily dose)	Results	Quality rating
Leukotriene receptor antagonist compared with ICS					
Ducharme et al. 2004 ¹⁷⁸	Systematic review with meta-analysis 27 studies (9100 subjects)	3 trials in children, 24 trials in adults;	Licensed doses of LTRA vs. ICS (3 trials tested a higher dose; 3 trials tested a lower dose; remaining tested equal to baseline daily doses of ICS)	Overall adverse events: No significant difference in the number of patients who experienced any adverse effects, [N = 15 trials, RR 0.99, 95% CI: 0.93 to 1.04] Specific adverse events: No significant difference in elevation of liver enzymes, [N = 6 trials, RR 1.3, 95% CI: 0.7 to 2.3], headaches [N = 16 trials, RR 0.9, (95% CI: 0.8 to 1.1], nausea [N = 12 trials, RR 1.0, 95% CI: 0.7 to 1.5)], or oral	Good

Study	Study design N Duration	Study population Country Setting	Comparison (total daily dose)	Results	Quality rating
				candidiasis [N = 2 trials, RR 0.15, 95% CI: 0.02 to 1.18] Withdrawals due to adverse events: LTRA were associated with a 30% increased risk of overall withdrawals [N = 19 trials, RR 1.3, 95% CI: 1.1 to 1.6], which appeared to be due to poor asthma control [N = 17 trials, RR 2.6, 95% CI: 2.0 to 3.4] and not due to adverse effects [N = 14 trials, RR 1.2, 95% CI: 0.9 to 1.6]	
Montelukast compared with beclomethasone					
Baumgartner et al. 2003 ⁸²	RCT 730 6 weeks	Multinational Age 15 and older Multicenter	BDP (400 mcg/day) vs. ML (10mg/day) vs. placebo Medium Dose ICS	Overall adverse events: 42% vs. 39% vs. 54%; <i>P</i> = NR Specific adverse events: ALT elevations were the most frequent adverse experience: 0.3% vs. 1.3% vs. 0%; <i>P</i> = NR Withdrawal due to adverse events: 1% vs. 0% vs. 2.9%; <i>P</i> = NR	Fair
Becker et al. 2006 ⁹⁶	RCT 360 56 weeks	Multinational Boys 6.4-9.4 and girls 6.4-8.4 years Multicenter	ML (5mg/day) vs. BDP (400 mcg/ day) vs. placebo High dose ICS	Withdrawal due to adverse events: 0% vs. 0%; <i>P</i> = NR Growth: linear growth rate (cm/year); at baseline, endpoint : 5.96, 5.67 vs. 5.74, 4.86 vs. 5.72, 5.64; mean differences (95%CI): ML vs placebo 0.03 (-0.26, 0.31); BDP vs placebo -0.78 (-1.06, -0.49), <i>P</i> < 0.001; ML vs BDP 0.81 (0.53, 1.09), <i>P</i> < 0.001	Fair
Malmstrom et al. 1999 (and Williams et al. 2001) ^{84, 85}	RCT 895 (436 in extension) 12weeks plus a 3week placebo washout period where patients were switched from treatment to placebo. (Double-blind extension)	Multinational Age 15 and older Multicenter	ML (10mgday) vs. BDP (400 mcg/day) vs. placebo (extension: ML vs. BDP in pre-assigned groups) Medium dose ICS	Withdrawal due to adverse events: 2% vs. 2% vs. 4% (including asthma exacerbations); <i>P</i> = NR	Fair

Study	Study design N Duration	Study population Country Setting	Comparison (total daily dose)	Results	Quality rating
	phase =37 weeks)				
Montelukast compared with fluticasone					
Busse et al. 2001 ⁸⁶	RCT 533 24 weeks	United States Age 15 and older Multicenter	FP (176 mcg/day) vs ML (10mg/day) Low dose ICS	Overall adverse events: 71% vs. 68%; <i>P</i> = NR Withdrawal due to adverse events: 4% vs. 2%, <i>P</i> = NR	Fair
Garcia et al. 2005 ⁹⁷	RCT 994 52 weeks	Multinational Children 6 – 14 Multicenter in primary care	FP (200 mcg/day) via MDI vs. ML (5mg/day) Medium to Low (12-14 years of age) dose ICS	Overall adverse events: 3.2% vs. 4.4%; <i>P</i> = NR Withdrawal due to adverse events: 0.2% vs. 1.2%; <i>P</i> = NR	Fair
Meltzer et al. 2002 ⁸⁷	RCT 522 24 weeks	United States Age 15 and older Multicenter	FP (176 mcg/day) vs. ML (10 mg/day) Low dose ICS	Overall adverse events: NR; <i>P</i> = NS Specific adverse events: Significant difference in oral candidiasis (3% vs. 0%; <i>P</i> = 0.008) and hoarseness (3% vs. 0%; <i>P</i> = 0.002) Withdrawal due to adverse events: 2% vs. 2%; <i>P</i> = NR	Fair
Ostrom et al. 2005 ⁹⁸	RCT 342 12 weeks	United States Children 6-12 Multicenter	FP (100 mcg/day) vs. ML (5 mg/day) Low dose ICS	Overall adverse events: 69% vs. 71%; <i>P</i> = NR Withdrawal due to adverse events: 2% vs. 2%; <i>P</i> = NR	Fair
Peters et al. 2007 ⁹⁹	RCT 500 16 weeks	United States Age 6 and older Multicenter	FP (200 mcg/day) vs. FP (200 mcg/day)/ SM (100 mcg/day) vs. ML (5 – 10 mg/day) Low dose ICS	Withdrawal due to adverse events: 0.5% vs. 0% vs. 0.6%; <i>P</i> = NR Specific adverse events: ML caused significantly less upper respiratory tract infections: 37.5% vs. 38.5% vs. 26.7%; <i>P</i> = 0.03 for ML vs. FP; <i>P</i> = 0.02 for ML vs. FP / SM	Fair
Zeiger et al. 2005 (and Rand et al., 2007) ^{88, 89}	RCT 400 12 weeks with 36 week open label extension	United States Age 15 – 85 Multicenter	ML (10 mg/day) vs. FP (176 mcg/day) Low dose ICS	Withdrawal due to adverse events: 0.5% vs. 2.1%; <i>P</i> = NR	Fair
MIAMI Trial					

Study	Study design N Duration	Study population Country Setting	Comparison (total daily dose)	Results	Quality rating
Montelukast compared with budesonide					
Szeffler et al. 2007 ¹⁰⁴	RCT, open label 395 52 weeks	United States Children 2-8 Multicenter	BUD inhalation suspension (BIS) (0.5mg/day) vs. ML (4 or 5mg/day) Low dose ICS	Withdrawal due to adverse events: 1% vs. 2.5%; <i>P</i> = NR	Fair
Yurdakul et al. 2003 ⁹¹	RCT 74 12 weeks	Turkey Adults 23 – 45 Research hospital	BUD (400 mcg/day) vs. ML (10 mg/day) Low dose ICS	Overall adverse events: 12% vs. 16%; <i>P</i> = NR	Fair
Zafirlukast compared with fluticasone					
Bleecker et al. 2000 ⁹²	RCT 451 12 weeks	Multinational Age 12 and older Multicenter	FP (176 mcg/day) vs. Zafirlukast (40mg/day) Low dose ICS	Overall adverse events: 10% vs. 10%; <i>P</i> = NR Withdrawal due to adverse events: 5% vs. 3%; <i>P</i> = NR	Fair
Brabson et al. 2002 ⁹³	RCT 440 6 weeks	United States; Age 12 and older Multicenter	FP (176 mcg/day) vs. Zafirlukast (40mg/day) Low dose ICS	Overall adverse events: 7% vs. 4%; <i>P</i> = 0.14 Withdrawal due to adverse events: <1% vs. 2%; <i>P</i> = NR	Fair
Busse et al. 2001 ⁹⁴	RCT 338 12 weeks	United States Age 15 and older Multicenter primary care	FP (176 mcg/day) vs. zafirlukast (40mg/day) vs. placebo Low dose ICS	Withdrawal due to adverse events: #2, #1, #1; <i>P</i> = NR	Fair
Kim et al. 2000 ⁹⁵	RCT 437 6 weeks	United States Age 12 and older Multicenter	FP (176 mcg/day) vs. zafirlukast (40 mg/day) Low dose ICS	Overall adverse events: 14% vs. 7%; <i>P</i> = 0.027 Withdrawal due to adverse events: 3% vs. 4%; <i>P</i> = NR	Fair

Abbreviations: BDP = beclomethasone dipropionate; CI = confidence interval; FP = Fluticasone Propionate; ICS= Inhaled Corticosteroids; LTRAs = Leukotriene receptor antagonists; MA=meta-analysis; ML = Montelukast; NR = not reported; NS = not statistically significant; RCT= randomized controlled trial; RR = relative risk; SM = Salmeterol; SR=systematic review; ZAF = Zafirlukast.

No difference = no statistically significant difference or tests of statistical significance were not reported and outcomes are similar;

Note: All results are listed in the same order as the comparison column lists the medications.

2. Inhaled Corticosteroids (ICSs) compared with Long-Acting Beta-2 Agonists (LABAs)

Summary of findings

LABAs are not recommended nor approved for use as monotherapy for persistent asthma because they may increase the risk of asthma-related death.¹ The indirect evidence comparing LABAs (with or without ICSs) with placebo reporting this increased risk is described earlier in this report (Key Question 2, Long-Acting Beta-Agonists) and contributes to the conclusion that ICSs are safer than LABAs for use as monotherapy (high strength of evidence).

Direct Evidence

We found 11 fair or good quality RCTs¹⁰⁵⁻¹¹⁷ that included head-to-head comparisons of one ICS with one LABA reporting tolerability or overall adverse events. These trials are described in the Key Question 1 section of this report.

Overall tolerability and adverse events from individual head-to-head trials are summarized in Table 50. Rates of overall adverse events and withdrawals due to adverse events were similar for those treated with ICSs and those treated with LABAs.

Indirect Evidence

Indirect evidence from placebo-controlled trials is described in other sections of this report. Evidence from several systematic reviews suggests that LABAs may increase the risk of asthma-related death (see Key Question 2, Long-Acting Beta-Agonists section). Evidence from placebo-controlled trials and observational studies suggest that ICSs may increase the risk of cataracts and may decrease short term growth velocity and bone mineral density (see Key Question 2, Inhaled Corticosteroids section)

Table 50. Summary of head-to-head studies comparing tolerability and overall adverse events between ICSs and LABAs as monotherapy

Study	Study design N Duration	Country Study population Setting	Comparison (total daily dose, steroid dosing range)	Results	Quality rating
Fluticasone compared with salmeterol					
Kavuru et al. 2000 ¹⁰⁵	RCT, DB 356 12 weeks	US Age ≥ 12yr, patients well controlled on current therapy (stratified into 2 eligible groups: group 1 had to be on ICS for ≥3 months; group 2 was taking SM for ≥1 week), severity NR, smokers excluded Multicenter (42)	Placebo vs. FP/SM DPI (200/100) vs. SM DPI (100) vs. FP DPI (200, low)	Overall adverse events: NR Withdrawal due to adverse events (%): 1 vs. 0 vs. 2 vs. 1 Oral candidiasis- thrush (%): 0 vs. 1 vs. 0 vs. 2 Sore throat (%): 1 vs. 4 vs. 1 vs. 2 Headache (%): 0 vs. 2 vs. 0 vs. 0 Hoarseness (%): 0 vs. 3 vs. 1 vs. 1	Fair
Lundback et al. 2006 ¹⁰⁶	RCT, DB 282 12 months	Sweden Age ≥18, mild or moderate persistent, uncontrolled on current medication (68% were on ICS), 12-17% smokers in each group	FP/SM DPI (500/100) vs. FP DPI (500, medium) vs. SM DPI (100)	Overall adverse events: NR Withdrawal due to adverse events (%): 2 vs. 2 vs. 1 Overall adverse events reported number (%): 92 (97) vs. 88 (96) vs. 90 (95) Oral candidiasis- thrush (%): 6 vs. 0 vs. 1	Fair

Study	Study design N Duration	Country Study population Setting	Comparison (total daily dose, steroid dosing range)	Results	Quality rating
		Patients recruited from ~4000 individuals with asthma who had participated in large epidemiologic studies		Dysphonia (%): 11 vs. 9 vs. 2 Cough (%): 2 vs. 3 vs. 7 Headache (%): 2 vs. 7 vs. 8 Respiratory infection (%): 74 vs. 78 vs. 55 gastroenterities (%): 12 vs. 5 vs. 5	
Murray et al. 2004 ¹⁰⁷	RCT, DB 267 12 weeks	US Age ≥ 12yr, asthma ≥ 6 months, not controlled with SABAs, severity NR, smokers excluded Multicenter (33 sites)	SM DPI (100) vs. FP DPI (200, low) vs. FP/SM DPI (200/100)	Overall adverse events: NR Withdrawal due to adverse events (%): 2 vs. 1 vs. 0 Overall adverse events reported (%): drug related: 12 vs. 13 vs. 17 Oral candidiasis- thrush (%): 0 vs. 3 vs. 5 Sore throat (%): 2 vs. 4 vs. 1 Headache (%): 4 vs. 2 vs. 3	Fair
Nathan et al. 2006 ¹⁰⁸	RCT, DB 365 12 weeks	US Age ≥ 12yr, not controlled on ICS, severity NR, smokers excluded Multicenter (45)	FP/SM MDI (440/84) vs. FP MDI (440, medium) vs. SM MDI (84) vs. placebo	Overall adverse events (%): 69 vs. 69 vs. 66 vs. 60 Withdrawal due to adverse events (%): 1.1 vs. 2.2 vs. 4.4 vs. 2.2 Sore throat (%): 7 vs. 13 vs. 7 vs. 6 vs. 1-2 Headache (%): 15 vs. 16 vs. 21 vs. 12 vs. 1-4 Upper respiratory tract infection (%): 24 vs. 15 vs. 19 vs. 12 Viral respiratory infection (%): 5 vs. 5 vs. 5 vs. 4 sinusitis (%): 4 vs. 5 vs. 2 vs. 6	Fair
Nelson et al. 2003 ¹⁰⁹	RCT, DB 283 12 weeks	US Age ≥ 12, persistent asthma not controlled with SABA, severity NR, smokers excluded	FP/SM MDI (88/42) vs. FP MDI (88, low) vs. SM MDI (42)	Overall adverse events(%): 17% vs. 16% vs. 15% Withdrawal due to adverse events Adverse events caused withdrawal (%): 3 vs. 5 vs. 2	Fair

Study	Study design N Duration	Country Study population Setting	Comparison (total daily dose, steroid dosing range)	Results	Quality rating
Multicenter (33)					
Shapiro et al. 2000 ¹¹¹	RCT, DB 349	US	Placebo vs. FP/SM DPI (500/100)	Overall adverse events: NR Withdrawal due to adverse events (%): 0 vs. 0 vs. 2 vs. 0	Fair
AND Nathan et al. 2003 ¹¹²	12 weeks	Age ≥ 12, previously treated with low to medium ICS, severity NR, smokers excluded	SM DPI (100) vs. FP DPI (500, medium)	Oral candidiasis- thrush (%): 0 vs. 4 vs. 0 vs. 2 Cough (%): 0 vs. 2 vs. 1 vs. 0 candidiasis(%): 0 vs. 2 vs. 0 vs. 4	
Multicenter (42 Research Centers/ Allergy and Asthma Centers)					
Beclomethasone compared with salmeterol					
Nathan et al. 1999 ¹¹⁵	RCT, DB, DD 386 26 weeks	US Age ≥ 12yr, on SABAs only, severity NR, smokers excluded	SM MDI (84) vs. BDP MDI (336, medium) vs. placebo	Overall adverse events reported, at least one potentially drug related event, number (%): 14 (11%) vs. 17 (13%) vs. 7 (5%) Withdrawal due to adverse events: NR Cough (%): 4 vs. 1 vs. NR chest tightness after inhaler use (%): 1 vs. 2 vs. 2	Fair
Multicenter (25)					
Simons et al. 1997 ¹¹⁶	RCT, DB 241 12 months	Canada Age 6-14, not currently on ICS, severity NR, smoking status NR	BDP DPI (400, medium) vs. SM DPI (100) vs. placebo	Overall adverse events: NR Withdrawal due to adverse events (%): 4 vs. 5 vs. 4 Growth: height increase: 3.96 cm vs. 5.4 cm vs. 5.04 cm; BDP vs. placebo P = 0.018; BDP vs. SM P = 0.004	Fair
Multicenter					
Verberne et al. 1997 ¹¹⁷	RCT, DB 67 52 weeks	Netherlands Age 6-16, on ICS ≥ 3 months, mild to moderate persistent asthma, smoking status NR	SM DPI (100) vs. BDP DPI (400, medium dose)	Overall adverse events reported (%): 94 vs. 89 Withdrawal due to adverse events (%): 3 vs. 0 Cough (%): 9 vs. 23 Sore throat (%): 6 vs. 9 Headache (%): 19 vs. 31 Upper respiratory tract infection (%): 9 vs. 14 Rhinitis (%): 28 vs. 14 fever(%): 25 vs. 11	Fair
Multicenter, Hospital pediatric outpatient clinics					

Study	Study design N Duration	Country Study population Setting	Comparison (total daily dose, steroid dosing range)	Results	Quality rating
				nausea/vomiting (%): 22 vs. 11 fatigue(%): 13 vs. 29	
Triamcinolone compared with salmeterol					
Lazarus et al. 2001 ^{113, 114}	RCT, triple-blind, DD 164	North America Age 12-65, well controlled on TAA, severity NR, smokers excluded	TAA MDI (800, low) vs. SM MDI (84)	Withdrawal due to adverse events (%): 0 vs. 2 vs. 0	Good
SOCS Trial	16 weeks	Multicenter, six University-based ambulatory care centers	vs. placebo		
Budesonide compared with formoterol					
Noonan et al. 2006 ¹¹⁰	RCT; DB, DD 596 12 weeks	US Age ≥ 12, moderate to severe persistent asthma not controlled, on ICS for ≥ 4 weeks, smokers excluded Multicenter (84), respiratory or allergy specialty clinics	BUD/FM pMDI (320/9) vs. BUD pMDI (320, low) vs. FM DPI (9) vs. BUD pMDI + FM DPI (320/9) vs. placebo	Overall adverse events: NR Adverse events caused withdrawal (%): 6.5 vs. 3.7 vs. 4.1 vs. 7.8 vs. 3.2 Oral candidiasis- thrush (%): 3.2 vs. 0 vs. 0 vs. 0.9 vs. 0 Cough (%): 0 vs. 0 vs. 0.8 vs. 0.9 vs. 1.6 Sore throat (%): 1.6 vs. 0 vs. 0 vs. 0.9 vs. 0.8 Headache (%): 0 vs. 0 vs. 1.6 vs. 1.7 vs. 0.8 Tremor (%): 0 vs. 0.9 vs. 1.6 vs. 0.9 vs. 0	Fair

Abbreviations: BDP = beclomethasone dipropionate; BUD = Budesonide; DB = double-blind; DD = double dummy; DPI = dry powder inhaler; FM = Formoterol; FP = Fluticasone Propionate; ICS= Inhaled Corticosteroids; MDI = metered dose inhaler; NR = not reported; pMDI = pressurized metered dose inhaler; RCT= randomized controlled trial; SM = Salmeterol; TAA = Triamcinolone Acetonide.

Note: All results are listed in the same order as the comparison column lists the medications.

3. Leukotriene modifiers compared with Long-Acting Beta-2 Agonists (LABAs) for monotherapy

Summary of findings

Overall, two small trials do not provide sufficient direct evidence to draw conclusions about the comparative tolerability and adverse events of leukotriene modifiers and LABAs for use as monotherapy for persistent asthma. Of note, LABAs are not recommended nor approved for use as monotherapy for persistent asthma because they may increase the risk of asthma-related

death.¹ The indirect evidence comparing LABAs (with or without ICSs) with placebo reporting this increased risk is described earlier in this report (Key Question 2, Long-Acting Beta-Agonists) and provides a high strength of evidence that leukotriene modifiers are safer than LABAs for use as monotherapy.

Detailed Assessment

Direct Evidence

We found two fair quality RCTs^{118,119} that included head-to-head comparisons of one leukotriene modifier with one LABA. In both trials, overall adverse events and/or withdrawals due to adverse events were similar between those treated with leukotriene modifiers and those treated with LABAs (Table 51).

Indirect Evidence

Indirect evidence from placebo-controlled trials is described in other sections of this report. Evidence from several systematic reviews suggests that LABAs may increase the risk of asthma-related death (see Key Question 2, Long-Acting Beta-Agonists section).

Table 51. Summary of head-to-head studies comparing tolerability and overall adverse events between leukotriene modifiers and LABAs

Study	Study design N Duration	Study population Country Setting	Comparison (total daily dose)	Results	Quality rating
Montelukast compared with salmeterol (monotherapy)					
Edelman et al. 2000 ¹¹⁸	RCT 191 8 weeks	United States Age 15-45, severity NR, excluded current smokers and those with ≥ 15 pack-year history Multicenter (17), research centers	ML (10mg) vs. SM (100 mcg)	Overall adverse events: 41% vs. 40%; <i>P</i> = NR Withdrawal due to adverse events: 1% vs. 5%; <i>P</i> = NR	Fair
Montelukast compared with formoterol (monotherapy)					
Jenkins et al. 2005 ¹¹⁹	RCT, cross-over 58 20 weeks (eFM and ML were compared for first 13 weeks, with 1 week washout in between 6 week treatment periods)	Australia Age 16-75, mild to moderate persistent asthma, excluded current smokers and those with ≥ 10 pack-year history Research centers	eFM DPI (24 mcg) vs. ML (10 mg) After the first 14 weeks, all subjects were treated with FP 500 mcg/day plus placebo	Withdrawal due to adverse events: eFM 3% vs. ML 0%; <i>P</i> = NR	Fair

Abbreviations: DPI = dry powder inhaler; eFM = Eformoterol; FP = Fluticasone Propionate; NR = not reported; RCT= randomized controlled trial; SM = Salmeterol.
Note: All results are listed in the same order as the comparison column lists the medications.

B. Combination therapy

1. ICS+LABA compared with ICS (same dose) as first line therapy

Summary of findings

We found one good systematic review¹²⁰ and five fair RCTs^{107, 109, 121-123} that compared the combination of an ICS plus a LABA with an ICS alone (same dose) for first line therapy in patients with persistent asthma meeting our inclusion/exclusion criteria. Four trials compared fluticasone plus salmeterol with fluticasone alone and one compared budesonide plus formoterol with budesonide alone.

Overall, results from a good quality systematic review with meta-analysis and five RCTs found no difference in overall adverse events or withdrawals due to adverse events between subjects treated with ICSs plus LABAs and subjects treated with ICSs alone as first line therapy. Trials were 12-24 weeks in duration and were generally not designed to compare tolerability and adverse events. Indirect evidence from meta-analysis of placebo-controlled trials suggests that the potential increased risk of asthma-related death for those taking LABAs may be confined to patients not taking ICSs at baseline. We found no studies for this comparison that enrolled children < 12 years of age. Thus, there is insufficient evidence to draw conclusions in children < 12 years of age. Of note, according to FDA labeling, ICS+LABA combination products are only indicated for patients not adequately controlled on other asthma-controller medications (e.g., low- to medium-dose inhaled corticosteroids) or whose disease severity clearly warrants initiation of treatment with two maintenance therapies.

Detailed Assessment

Direct evidence

We found one good systematic review¹²⁰ and five fair RCTs^{107, 109, 121-124} (Table 52). Four trials compared fluticasone plus salmeterol with fluticasone alone and two compared budesonide plus formoterol with budesonide alone. The trials are described in the Key Question 1 section of the report.

The systematic review reported no significant differences between treatments in overall adverse events (RR 1.1, 95% CI: 0.8, 1.5, 5 trials), withdrawals due to adverse events (RR 1.71, 95% CI: 0.68, 4.27, 3 trials), overall withdrawals (RR 0.9; 95% CI: 0.6 to 1.2, 6 trials), or in any of the specific adverse events (including headache, oral candidiasis, or tremor).¹²⁰ The authors note that the upper confidence interval was high for some adverse events, ruling out complete reassurance that there is no increased risk. The overall adverse events, withdrawals due to adverse events, and common adverse events reported in the head-to-head trials are summarized in Table 52. The results appear similar for those treated with ICS+LABA and those treated with ICS alone.

Indirect evidence

Indirect evidence described previously in the Key Question 2 Long-Acting Beta-2 Agonists (LABAs) section of this report describes the evidence suggesting the increased risk of asthma-related death in patients treated with LABAs.²¹⁴⁻²¹⁶ Of note, the most current (2007) systematic review included a post-hoc analysis of data from the the Salmeterol Multicenter Asthma Research Trial (SMART) that did not show a statistically significantly increased risk of asthma-related death for those taking ICSs at baseline (RR 1.34, 95% CI: 0.30 to 5.97). But, those not taking ICSs at baseline had an increased risk of asthma-related death (RR 18.98, 95% CI: 1.1 to 326).

Table 52. Summary of head-to-head studies comparing ICS+LABA compared with ICS alone as first line therapy in children and adults

Study	Study design N Duration	Country Study population Setting	Comparison (total daily dose)	Results	Quality rating
ICS + LABA compared with ICS alone (same dose) as <i>first line therapy</i>					
Ni Chroinin et al. 2004 ¹²⁰	Systematic review with meta- analysis 8 RCTs with sufficient data (1061 subjects) Trial duration ranged from 4 to 52 weeks	Multinational Age ≥ 2yr; persistent asthma, any severity; no ICS for at least 1month prior to enrollment	ICS + LABA vs. ICS alone (same dose)	Overall adverse events: No difference (RR 1.1, 95% CI: 0.8, 1.5) Withdrawal due to adverse events: No difference (RR 1.71, 95% CI: 0.68, 4.27, 3 trials) Overall risk of withdrawals: No difference (RR 0.9; 95% CI: 0.6 to 1.2) Withdrawals due to poor asthma control: No difference (N = 6 trials: RR1.3; 95% CI: 0.5 to 3.4)	Good
Fluticasone + salmeterol compared with fluticasone					
Murray et al. 2004 ¹⁰⁷	RCT, DB 267 12 weeks	US Age ≥ 12yr, uncontrolled on SABAs alone, severity NR, smokers excluded Multicenter (33 sites)	FP DPI (200, low) vs. SM DPI (100) vs. FP/SM DPI (200/100)	Overall adverse events: NR Withdrawal due to adverse events (%): 2 vs. 1 vs. 0 Overall adverse events reported (%): drug related: 12 vs. 13 vs. 17 Oral candidiasis- thrush (%): 0 vs. 3 vs. 5 Sore throat (%): 2 vs. 4 vs. 1 Headache (%): 4 vs. 2 vs. 3	Fair
Nelson et al. 2003 ¹⁰⁹	RCT, DB 283 12 weeks	US Age ≥ 12, uncontrolled on SABAs alone, severity NR, smokers excluded Multicenter (33)	FP/SM MDI (88/42) vs. FP MDI (88, low) vs. SM MDI (42)	Overall adverse events (%): 17% vs. 16% vs. 15% vs. Withdrawal due to adverse events (%): 3 vs. 5 vs. 2	Fair
Rojas et al. 2007 ¹²¹	RCT, DB 362 12 weeks	Multinational (9) Age 12-80, initiating therapy for moderate persistent asthma, symptomatic on SABAs only, allowed smokers if < 10 pack-year history	FP/SM DPI (500/100) vs. FP DPI (500, medium) FP/SM N = 182 FP N = 180	Overall adverse events: Total AEs: 19 vs. 26 Withdrawal due to adverse events (%): 0 vs. < 1 Oral candidiasis- thrush (%): 2 vs. <1 Cough (%): 2 vs. 3 Headache (%): 3 vs. 3	Fair

Study	Study design N Duration	Country Study population Setting	Comparison (total daily dose)	Results	Quality rating
		Multicenter (52)		Hoarseness (%): 1 vs. <1	
Strand et al. 2004 ¹²²	RCT, DB 150 24 weeks	Denmark Age ≥ 18, persistent asthma for ≥ 3 months, uncontrolled with SABA only, severity NR, smokers allowed (32% of SM/FP group and 46% of FP group)	FP/SM DPI (200/100) vs FP DPI (200, low) Steroid dose range: low	Overall adverse events(%): 62 vs. 58 Withdrawal due to adverse events (%): 1 vs. 3 Oral candidiasis- thrush (%): 1 vs. 1	Fair
		Multicenter (44 general practices and 1 hospital)			
Budesonide + formoterol compared with budesonide					
Chuchalin et al. 2002 ¹²³	RCT, DB, DD 338 12 weeks	Russia adults ≥ 18, mild to moderate persistent asthma, allowed smokers if < 10 pack-year history	FM DPI (24) + BUD DPI (400) vs. BUD DPI (400, low) vs. "investigator's choice of non-corticosteroid treatment"	Overall adverse events reported (%): 36.0 vs. 35.1 Withdrawal due to adverse events (%): 1 vs. 1 common cold (%): ~ 40% vs. ~ 40% Tremor (%): 10 vs. 2	Fair
Chuchalin ¹²⁵ 2002		pulmonology center			

Abbreviations: BUD = Budesonide; CI = confidence interval; DB = double-blind; DPI = dry powder inhaler; FM = Formoterol; FP = Fluticasone Propionate; ICS= Inhaled Corticosteroids; LABAs = Long-Acting Beta-2 Agonists; MA=meta-analysis; MDI = metered dose inhaler; RCT= randomized controlled trial; RR = relative risk; SM = Salmeterol; SR = systematic review.

No difference = no statistically significant difference or tests of statistical significance were not reported and outcomes are similar.

Note: All results are listed in the same order as the comparison column lists the medications.

2. ICS+LABA compared with higher dose ICS (addition of LABA to ICS compared with increasing the dose of ICS)

Summary of findings

We found one systematic review with meta-analysis¹²⁶ and 27 RCTs^{48, 76, 78, 99, 124, 128-152} that included head-to-head comparisons between an ICS+LABA with a higher dose ICS meeting our inclusion/exclusion criteria. Although four trials^{76, 78, 99, 144} included children, just one enrolled an exclusively pediatric population under 12 years of age.⁷⁶

Overall, results from a good quality systematic review with meta-analysis and numerous RCTs found no difference in overall adverse events or withdrawals between subjects treated with ICSs plus LABAs and subjects treated with an increased dose of ICSs. Those treated with ICSs plus LABAs had an increased rate of tremor (N = 10, RR 2.96, 95% CI: 1.60, 5.45). Indirect evidence from meta-analysis of placebo-controlled trials suggests that the

potential increased risk of asthma-related death for those taking LABAs may be confined to patients not taking ICSs at baseline. Just one of the RCTs enrolled an exclusively pediatric population < 12 years of age (four included some subjects < 12) and results are not necessarily applicable to pediatric populations.

Detailed Assessment

Direct Evidence

We found one systematic review with meta-analysis¹²⁶ and 27 RCTs^{48, 76, 78, 99, 124, 128-152} that included head-to-head comparisons between an ICS+LABA with a higher dose ICS meeting our inclusion/exclusion criteria. These trials compared the addition of a LABA to an ICS with increasing the dose of the ICS. Fifteen of the 27 (56%) administered the ICS and LABA in a single inhaler and twelve (44%) administered the ICS and LABA in separate inhalers. Although four trials^{76, 78, 99, 144} included children, just one enrolled an exclusively pediatric population under 12 years of age.⁷⁶ The trials are described in the Key Question 1 section of the report.

The systematic review reported no difference in overall withdrawals (all reasons) (N = 23, RR 0.92, 95% CI: 0.82, 1.03), overall adverse events (N = 15, RR 0.93, 95% CI: 0.84, 1.03), or specific side effects, with the exception of a three-fold increase rate of tremor in the LABA group (N = 10, RR 2.96, 95% CI: 1.60, 5.45). The rate of withdrawals due to poor asthma control favored the combination of LABA and ICS (N = 20, RR 0.69, 95% CI: 0.52, 0.93). The overall adverse events, withdrawals due to adverse events, and specific adverse events for the included RCTs appear consistent with these findings (Evidence Tables with full details in separate document).

Indirect evidence

Indirect evidence described previously in the Key Question 2 Long-Acting Beta-2 Agonists (LABAs) section of this report describes the evidence suggesting the increased risk of asthma-related death in patients treated with LABAs.²¹⁴⁻²¹⁶ Of note, the most current (2007) systematic review included a post-hoc analysis of data from the the Salmeterol Multicenter Asthma Research Trial (SMART) that did not show a statistically significantly increased risk of asthma-related death for those taking ICSs at baseline (RR 1.34, 95% CI: 0.30 to 5.97). But, those not taking ICSs at baseline had an increased risk of asthma-related death (RR 18.98, 95% CI: 1.1 to 326).

3. ICS+LABA compared with ICS (same dose) (addition of LABA to ICS compared with continuing same dose ICS)

Summary of findings

We found one systematic review with meta-analysis¹⁵³ and 27 RCTs (29 publications)^{105, 106, 108, 110-112, 124, 132, 138, 139, 144, 154-170, 218} that included head-to-head comparisons between an ICS+LABA with the same dose ICS meeting our inclusion/exclusion criteria. Seven studies (26%) included pediatric populations under 12 years of age.^{144, 162, 164, 165, 168, 169, 218}

Overall, results from a good quality systematic review with meta-analysis and numerous RCTs found no difference in overall adverse events or withdrawals between subjects treated with ICSs plus LABAs and subjects treated with the same dose of ICSs. Although not statistically significantly different, the upper limits of the confidence intervals for tachycardia

or palpitations (N = 5, RR 2.13, 95% CI: 0.77, 5.88) and tremor (N = 7, RR 2.48, 95% CI: 0.78, 7.89) were relatively high, suggesting that these may be more frequent in patients treated with ICSs plus LABAs. Indirect evidence from meta-analysis of placebo-controlled trials suggests that the potential increased risk of asthma-related death for those taking LABAs may be confined to patients not taking ICSs at baseline.

Detailed Assessment

Direct Evidence

We found one systematic review with meta-analysis¹⁵³ and 27 RCTs (29 publications)^{105, 106, 108, 110-112, 124, 132, 138, 139, 144, 154-170, 218} that included head-to-head comparisons between an ICS+LABA with the same dose ICS meeting our inclusion/exclusion criteria. These trials compared the addition of a LABA to an ICS with continuing the same dose of the ICS.

Fourteen of the 27 (52%) administered the ICS and LABA in a single inhaler, nine administered them in separate inhalers, and four studies administered them both as a single inhaler and in separate inhalers to different study groups. Seven studies (26%) included pediatric populations under 12 years of age.^{144, 162, 164, 165, 168, 169, 218} The trials are described in greater detail in the Key Question 1 section of the report.

The systematic review reported no difference between treatments in the risk of overall adverse effects (N = 11, RR 0.98, 95% CI: 0.92 to 1.05), withdrawals due to adverse effects (N = 19, RR 1.29, 95% CI: 0.96 to 1.75), serious adverse events (N = 4 comparisons, RR 1.16, 95% CI: 0.30 to 4.42), or in any of the reported specific side effects including headache (N = 12, RR 1.13, 95% CI: 0.92 to 1.41), hoarseness (N = 3 comparisons, RR 0.71, 95% CI: 0.16 to 3.18), oral thrush (N = 4, RR 1.04, 95% CI: 0.35 to 3.06), tachycardia or palpitations (N = 5, RR 2.13, 95% CI: 0.77 to 5.88), cardiovascular adverse effects such as chest pain (N = 3, RR 0.90, 95% CI: 0.32 to 2.54), or tremor (N = 7, RR 2.48, 95% CI: 0.78 to 7.89). However, the upper confidence interval for some adverse events was high (for example tachycardia, palpitations and tremor). The overall adverse events, withdrawals due to adverse events, and specific adverse events for the included RCTs appear consistent with these findings (Evidence Tables with full details in separate document).

Indirect evidence

Indirect evidence described previously in the Key Question 2 Long-Acting Beta-2 Agonists (LABAs) section of this report describes the evidence suggesting the increased risk of asthma-related death in patients treated with LABAs.²¹⁴⁻²¹⁶ Of note, the most current (2007) systematic review included a post-hoc analysis of data from the the Salmeterol Multicenter Asthma Research Trial (SMART) that did not show a statistically significantly increased risk of asthma-related death for those taking ICSs at baseline (RR 1.34, 95% CI: 0.30 to 5.97). But, those not taking ICSs at baseline had an increased risk of asthma-related death (RR 18.98, 95% CI: 1.1 to 326).

4. ICS+LTRA compared with ICS

Summary of findings

We found one good systematic review with meta-analysis¹⁷¹ and two RCTs¹⁷²⁻¹⁷⁴ meeting our inclusion/exclusion criteria. Both RCTs were in adolescents and adults ≥ 12 years of age.

Overall, the addition of LTRAs to ICSs compared to continuing the same dose of ICSs or to increasing the dose of ICSs resulted in no significant differences in overall adverse events or withdrawals due to adverse events. Trials were generally not designed to compare tolerability and adverse events and many used higher than licensed doses of LTRAs. Evidence in children < 12 years of age is limited. Just two of the 27 trials in the systematic review enrolled children.

Detailed Assessment

Direct Evidence

We found one good systematic review with meta-analysis¹⁷¹ and two RCTs¹⁷²⁻¹⁷⁴ meeting our inclusion/exclusion criteria (Table 53). These are described in the Key Question 1 section of the report. The systematic review included 27 studies (5871 subjects); two of the studies were in children and 25 were in adults.

ICS+LTRA compared with same dose ICS

For ICS plus LTRA compared with the same dose of ICS, the systematic review reported no significant differences in overall adverse events (2 trials, RR 1.01, 95% CI: 0.88 to 1.15), specific adverse events (including elevated liver enzymes, headache, and nausea), or withdrawals due to adverse effects (3 trials, RR 0.63, 95% CI: 0.29 to 1.37) among trials using licensed doses of LTRAs (Table 53).

One fair 16 week trial¹⁷⁴ (N = 639) reported similar rates of overall adverse events (41% compared with 44%; $P = \text{NR}$) and withdrawals due to adverse events (2% compared with 3%; $P = \text{NR}$) in those treated with BUD and those treated with BUD+ML.

ICS+LTRA compared with increased ICS

For ICS plus LTRA compared with increased doses of ICS, the systematic review reported no significant differences in overall adverse events (2 trials, RR 0.95, 95% CI: 0.84 to 1.06), risk of elevated liver enzymes (2 trials, RR 0.8 95% CI: 0.34 to 1.92), headache (2 trials, RR 1.07, 95% CI: 0.76 to 1.52), nausea (2 trials, RR 0.63 95% CI: 0.25 to 1.60), or withdrawals due to adverse events (2 trials, RR 1.14, 95% CI: 0.55 to 2.37) among trials using licensed doses of LTRAs. The trials that used two to four-fold higher than licensed doses of LTRA had a five-fold increased risk of liver enzyme elevation (3 trials, RR 4.97 95% CI: 1.45 to 17) (Table 53).

One fair 16 week trial^{172, 173} (N = 889) reported similar rates of overall adverse events (37.1% compared with 41.3%; $P = \text{NR}$) between groups, but found a slightly increased rate of respiratory infections (11.6% compared with 16.6%; $P < 0.05$) in those treated with BUD compared to those treated with BUD+ML.

Table 53. Summary of head-to-head studies comparing tolerability and overall adverse events between ICS+LTRA compared with ICS

Study	Study design N Duration	Study population Country Setting	Comparison (total daily dose)	Results	Quality rating
Leukotriene antagonist plus ICS compared with ICS					
Ducharme et al. 2004 ¹⁷¹	Systematic Review with meta-analysis; 27 studies (5871 subjects)	2 trials in children; 25 in adults	LTRA plus ICS vs. ICS same dose, ICS same dose tapering, or ICS increased dose.	<p>LTRA plus ICS vs. Same ICS: Overall adverse events: No significant difference in overall adverse events (2 trials, RR 1.01, 95% CI: 0.88, 1.15). For two trials that used higher than licensed doses of pranlukast or zafirlukast: there was no significant difference in overall adverse effects (RR 1.02, 95% CI: 0.81, 1.27)</p> <p>Specific adverse events: No significant difference in elevated liver enzymes (2 trials, RR 1.02, 95% CI: 0.36, 2.88), headache (3 trials, RR 1.15, 95% CI: 0.89, 1.49), and nausea (2 trials, RR 0.45, 95% CI: 0.19, 1.07).</p> <p>Withdrawals due to adverse events: No significant differences in risk of withdrawals due to adverse effects (3 trials, RR 0.63, 95% CI: 0.29, 1.37). For two trials that used higher than licensed doses of pranlukast or zafirlukast: there was no significant difference in risk of withdrawals due to adverse effects (RR 0.73, 95% CI: 0.28 to 1.88).</p> <p>LTRA plus ICS vs. Increased ICS : Overall adverse events: No significant difference in risk of overall adverse effects (2 trials, RR 0.95, 95% CI: 0.84 to 1.06). The trials that used two to four-fold the licensed doses of LTRA showed no difference in overall adverse events (3 trials, RR 0.98 95% CI: 0.89 to 1.07)</p>	Good

Study	Study design N Duration	Study population Country Setting	Comparison (total daily dose)	Results	Quality rating
				<p>Specific adverse events: No significant difference in risk of elevated liver enzymes (2 trials, RR 0.8 95% CI: 0.34 to 1.92), headache (2 trials, RR 1.07, 95% CI: 0.76 to 1.52), and nausea (2 trials, RR 0.63 95% CI: 0.25 to 1.60). The trials that used two to four-fold the licensed doses of LTRA showed this was associated with a five-fold increased risk of liver enzyme elevation (3 trials, RR 4.97 95% CI: 1.45 to 17). However, there was no difference in headache (3 trials, RR 1.14 95% CI: 1.14 to 1.63) and nausea (3 trials, RR 1.77 95% CI: 0.79 to 3.95).</p> <p>Withdrawals due to adverse events: No significant difference in risk of withdrawal due to adverse events (2 trials, RR 1.14, 95% CI: 0.55 to 2.37). The trials that used two to four-fold the licensed doses of LTRA showed no difference for withdrawals due to adverse events (3 trials, RR 2.27 95% CI: 0.95 to 5.45).</p>	
Montelukast plus budesonide compared with budesonide					
Price et al. 2003 ¹⁷²	RCT 889	Multinational Age 15 – 75	ML (10) + BUD (800) vs. BUD (1600)	Overall adverse events: 37.1% vs. 41.3%; <i>P</i> = NR	Fair
COMPACT	16 weeks	Multicenter	Medium to High dose ICS	Specific adverse events: Respiratory infections: 11.6% vs. 16.6%; <i>P</i> < 0.05	
Vaquerizo et al. 2003 ¹⁷⁴	RCT 639	Spain Age 18 – 70	BUD (400 – 1600) + placebo vs. BUD (400 – 1600) + ML (10)	Overall adverse events: 41% vs. 44%; <i>P</i> = NR	Fair
CASIOPEA	16 weeks	Hospital centers	Low to High dose ICS	Withdrawal due to adverse events: 2% vs. 3%; <i>P</i> = NR	

Abbreviations: AQLQ = Asthma Quality of Life Questionnaire; BUD = Budesonide; CI = confidence interval; ICS= Inhaled Corticosteroids; LTRAs = Leukotriene receptor antagonists; MA=meta-analysis; ML = Montelukast; NR = not reported; NS = not statistically significant; QOL = quality of life; RCT= randomized controlled trial; RR = relative risk; SMD = standard mean difference; SR=systematic review; WMD = weighted mean difference.

No difference = no statistically significant difference or tests of statistical significance were not reported and outcomes are similar.

Note: All results are listed in the same order as the comparison column lists the medications.

5. Combination products compared with Leukotriene Modifiers

Summary of findings

We found three RCTs^{99, 176, 177} meeting our inclusion/exclusion criteria for this comparison (Table 54). All three compared low dose fluticasone plus salmeterol with montelukast. Two of the RCTs were in adolescents and adults; one enrolled subjects over the age of six⁹⁹ (~15% of subjects were < 12 years of age).

Overall, ICS/LABA combinations and leukotriene modifiers have similar rates of overall adverse events and withdrawals due to adverse events based on limited direct evidence from three short-term trials.

Detailed Assessment

Direct Evidence

We found three RCTs^{99, 176, 177} comparing low dose fluticasone plus salmeterol with montelukast. Two of the RCTs were in adolescents and adults; one enrolled subjects over the age of six⁹⁹ (~15% of subjects were < 12 years of age). The trials are described in the Key Question 1 section of the report. All three trials reported similar overall rates of withdrawals due to adverse events between those treated with ML and those treated with FP/SM. The two trials reporting overall adverse events also reported similar rates between groups (Table 54). One trial reported a greater incidence of upper respiratory tract infections for those treated with FP/SM than those treated with ML.

Table 54. Summary of head-to-head studies comparing tolerability and overall adverse events between ICS+LABA compared with LTRA

Study	Study design N Duration	Study population Country Setting	Comparison (total daily dose)	Results	Quality rating
Fluticasone plus salmeterol compared with montelukast					
Pearlman et al. 2002 ¹⁷⁶	RCT 432 12 weeks	United States Age 15 and older, mild to severe persistent asthma, smoking status NR Multicenter (51)	FP (200 mcg/day)/ SM (100 mcg/day) vs. ML (10 mg/day) Low dose ICS	Overall adverse events: 62% vs. 62%; <i>P</i> = NR Withdrawal due to adverse events: 2% vs. 3%; <i>P</i> = NR	Good
Calhoun et al. 2001 ¹⁷⁷	RCT 423 12 weeks	United States Age 15 and older, mild to severe persistent asthma, smoking status NR Multicenter	FP (200 mcg/day)/ SM (100 mcg/day) vs. ML (10 mg/day) Low dose ICS	Overall adverse events: 61% vs. 62%; <i>P</i> = NR Withdrawal due to adverse events: 3% vs. 4%; <i>P</i> = NR	Fair
Peters et al. 2007 ⁹⁹	RCT 500 16 weeks	United States Age 6 and older,	FP (200 mcg) vs. FP (200 mcg)/ SM (100	Withdrawal due to adverse events: 0.5% vs. 0% vs. 0.6%; <i>P</i> = NR	Fair

Study	Study design N Duration	Study population Country Setting	Comparison (total daily dose)	Results	Quality rating
		mild to moderate asthma, smoking status NR	mcg) vs. ML (5 – 10 mg)	Specific adverse events: upper respiratory tract infections: 37.5% vs. 38.5% vs. 26.7%; <i>P</i> = 0.03 for ML vs. FP; <i>P</i> = 0.02 for ML vs. FP / SM	
		Multicenter	Low dose ICS		

Abbreviations: FP = Fluticasone Propionate; ICS= Inhaled Corticosteroids; ML = Montelukast; NR = not reported; RCT= randomized controlled trial; SM = Salmeterol.

Note: All results are listed in the same order as the comparison column lists the medications.

6. ICS+LABA compared with ICS+LTRA (addition of LABA compared with LTRA to ongoing ICS therapy)

Summary of findings

We found one systematic review with meta-analysis¹⁷⁸ and six RCTs¹⁷⁹⁻¹⁸⁴ that compared the addition of a LABA with the addition of an LTRA for patients poorly controlled on ICS therapy. All six of the RCTs were in adolescents and adults ≥ 12 years of age.

Overall, results from a good quality systematic review with meta-analysis and six RCTs provide moderate evidence that there is no difference in overall adverse events or withdrawals due to adverse events between subjects treated with ICS plus LABA therapy and subjects treated with ICS plus LTRA therapy. Trials were generally not designed to compare tolerability and adverse events. We found no RCTs enrolling children < 12 years of age; the systematic review included just one trial in children (that did not contribute data to the meta-analysis). Thus, there is insufficient evidence to draw conclusions in children < 12 years of age.

Detailed Assessment

Direct Evidence

We found one systematic review with meta-analysis¹⁷⁸ and six RCTs.¹⁷⁹⁻¹⁸⁴ All six of the RCTs were in adolescents and adults ≥ 12 years of age. Of the included studies (Table 55), all six compared montelukast plus fluticasone with salmeterol plus fluticasone. The trials are described in the Key Question 1 section of the report.

The systematic review reported no significant differences in overall adverse events (8 studies, RR 1.03, 95% CI: 0.99, 1.07), withdrawals due to adverse events (10 studies, RR 1.02, 95% CI: 0.80, 1.32), headache (10 studies, RR 1.07, 95% CI: 0.9, 1.26), cardiovascular events (5 studies, RR 1.09, 95% CI: 0.77, 1.52), and elevated liver enzymes (1 study, *P* = NS, NR). There was a statistically significant difference in risk of oral moniliasis (6 studies, 1% for LABA compared with 0.5% for LTRA; risk difference 0.01; 95% CI: 0, 0.01). All but one of the six RCTs meeting our inclusion criteria were included in the systematic review and they reported findings consistent with the conclusions of the meta-analysis (Table 55).

Table 55. Summary of head-to-head studies comparing tolerability and overall adverse events between ICS+LABA compared with ICS+LTRA

Study	Study design N Duration	Study population Country Setting	Comparison (total daily dose)	Results	Quality rating
ICS+LABA compared with ICS+LTRA					
Ducharme et al. 2006 ¹⁷⁸	Systematic Review with meta-analysis; 11 studies (6,030 subjects) included in meta-analysis	1 trial in children; 10 in adults	LABA (salmeterol 50 mcg twice daily or formoterol 12 mcg twice daily) plus ICS vs. LTRA (montelukast 10mg daily, zafirlukast 20mg twice daily) plus ICS ICS was average 400 to 560 mcg/day of BDP or equivalent (medium to high dose ICS)	Overall adverse events: No significant difference in risk of overall adverse events (8 studies, RR 1.03; 95% CI: 0.99 to 1.07). Specific adverse events: No significant difference in headache (10 studies, RR 1.07; 95% CI: 0.9, 1.26), cardiovascular events (5 studies, (RR 1.09; 95% CI: 0.77 to 1.52), and elevated liver enzymes (1 study, <i>P</i> = NS, NR). There was a significant difference in risk of oral moniliasis (6 studies, 1% for LABA vs. 0.5% for LTRA; risk difference 0.01; 95% CI: 0 to 0.01). Withdrawals due to adverse events: No significant difference in withdrawals due to adverse events (10 studies, RR 1.02; 95% CI: 0.80 to 1.32).	Good
Montelukast plus fluticasone compared with salmeterol plus fluticasone					
Bjermer et al. 2003 ¹⁷⁹	RCT 1490 48 weeks	Multinational (Eastern Europe) Age 15 – 72, Uncontrolled on low dose ICS Multicenter	ML (10mg/day) plus FP (200 mcg/day) vs. SM (100 mcg/day) plus FP (200 mcg/day) Same Low dose ICS	Overall adverse events: 71% vs. 72.4%; <i>P</i> = NR Withdrawal due to adverse events: 5.1% vs. 5%; <i>P</i> = NR	Good
Fish et al. 2001 ¹⁸⁰	RCT 948 12 weeks	United States and Puerto Rico Age 15 and older, Symptomatic on low to high dose ICS Multicenter	SM (100 mcg/day) plus baseline ICS vs. ML (10mg/day) plus baseline ICS Same Low to High dose ICS	Overall adverse events: 7% vs. 6%; <i>P</i> = NR Withdrawal due to adverse events: 3% vs. 3%; <i>P</i> = NR	Fair
Ilowite et al. 2004 ¹⁸¹	RCT 1473 48 weeks	United States Age 14 – 73, uncontrolled on ICS Multicenter	SM (84 mcg/day) plus FP (220 mcg/day) vs. ML (10 mg/day) plus FP (220 mcg/day) Unspecified whether ICS dose changed from baseline to study low	Withdrawal due to adverse events: 1.2% vs. 2.4%; <i>P</i> = 0.06	Fair

Study	Study design N Duration	Study population Country Setting	Comparison (total daily dose)	Results	Quality rating
Nelson et al. 2000 ¹⁸²	RCT 447 12 weeks	United States Age 15 and older, uncontrolled on low dose ICS Multicenter	dose ICS FP (200 mcg/day) / SM (100 mcg/day) vs. FP (200 mcg/day) plus ML (10 mg/day) Same Low dose ICS	Withdrawal due to adverse events: 2.7% vs. 1.8%; <i>P</i> = NR	Fair
Pavord et al. 2007 ¹⁸³ SOLTA Study Group	RCT 66 12 weeks	United Kingdom Age 18 – 50, uncontrolled on medium dose ICS Multicenter	FP (200 mcg/day) / SM (100 mcg/day) vs. FP (200 mcg/day) plus ML (10 mg/day) Decrease to Low dose ICS	Overall adverse events: 58% vs. 64%; <i>P</i> = NR Withdrawal due to adverse events: 6% vs. 12%; <i>P</i> = NR	Fair
Ringdal et al. 2003 ¹⁸⁴	RCT 805 12 weeks	Multinational Age 15 and older, low to high dose at baseline Multicenter	FP (200 mcg/day) / SM (100 mcg/day) vs. FP (200 mcg/day) plus ML (10 mg/day) Decreased to Low dose ICS and had to remain uncontrolled.	Overall adverse events: 44% vs. 42%; <i>P</i> = NR	Fair

Abbreviations: BDP = beclomethasone dipropionate; CI = confidence interval; FP = Fluticasone Propionate; ICS = Inhaled Corticosteroids; LABAs = Long-Acting Beta-2 Agonists; LTRAs = Leukotriene receptor antagonists; NR = not reported; RCT= randomized controlled trial; RR = relative risk; SM = Salmeterol.

No difference = no statistically significant difference or tests of statistical significance were not reported and outcomes are similar.

Note: All results are listed in the same order as the comparison column lists the medications.

Key Question 3.

Are there subgroups of these patients based on demographics (age, racial groups, gender), asthma severity, comorbidities (drug-disease interactions, including obesity), other medications (drug-drug interactions), smoking status, genetics, or pregnancy for which asthma controller medications differ in efficacy, effectiveness, or frequency of adverse events?

Summary of findings

We did not find any studies that directly compared the efficacy or adverse events of our included drugs between subgroups and the general population. In head-to-head comparisons, few subgroups based on age, racial groups, sex, other medications, or comorbidities were evaluated (Table 56). We did not find any studies meeting our inclusion/exclusion criteria that directly compared our included medications and found a difference in the comparative efficacy, tolerability, or adverse events.

Detailed assessment

I. Demographics

A. Age

Differences in efficacy, tolerability, and adverse events between children < 12 years of age and adolescents or adults ≥ 12 are described in the body of the report (Key Questions 1 and 2) in the appropriate sections. These differences are also noted in the overall summary table. Therefore, they are not discussed here.

Only a few trials have studied the efficacy and safety of asthma medications in very young children (less than three years). Budesonide inhalation suspension is the only ICS that is approved for use in children down to 12 months of age (see Introduction, Table 2). We found no head-to-head studies comparing the efficacy or safety of our included drugs in very young children with older children, adolescents, or adults. Long-term clinical trials have shown ICS treatment to be effective in this population.¹ Some evidence from placebo-controlled trials suggests that montelukast may be effective in children ages two to five; however, one trial reported that montelukast did not reduce the need for oral systemic corticosteroids to control exacerbations.¹ Most recommendations for treatment are based on limited data and extrapolations from studies in older children and adults.¹ This data, as well as expert opinion, supports the use of ICSs for the treatment for asthma in young children.¹

B. Racial groups

We did not find any head-to-head studies that directly compared the efficacy and tolerability of our included drugs between one ethnic population and another. Two studies performed subgroup analyses; results may provide indirect evidence of differences between racial groups (Table 56).

A good systematic review examined both efficacy and safety outcomes of studies comparing LABAs to placebo in “real world” asthmatic populations in which only some patients were using regular ICSs at baseline.²¹⁶ This study is described in detail in the Key Question 2 section of this report. A post-hoc subgroup analysis indicated that African Americans may be more likely to experience respiratory-related death and life threatening adverse events than Caucasians (Relative Risk Increase 3.9; 95% CI: 1.29, 11.84). There was, however, no significant difference found in asthma-related deaths between African Americans and Caucasians; results from life table analyses were not significantly different between African Americans (7 compared with 1; RR 7.26; 95% CI: 0.89, 58.94), and Caucasians (6 compared with 1; RR 5.82; 95% CI: 0.70, 48.37).

The Salmeterol Multicenter Asthma Research Trial (SMART),²¹⁴ a large 28-week randomized, double-blind study assessed the safety of salmeterol MDI (42 mcg twice/day) compared with placebo. This study is described in detail in Key Question 2. The trial found no statistically significant difference between those treated with salmeterol and those treated with placebo for the primary outcome, respiratory-related deaths or life-threatening experiences (50 compared with 36; RR 1.40; 95% CI: 0.91, 2.14). However, the trial reported statistically significant increases in respiratory-related deaths (24 compared with 11; RR 2.16; 95% CI: 1.06, 4.41), asthma-related deaths (13 compared with 3; RR 4.37; 95% CI: 1.25, 15.34), and in combined asthma-related deaths or life-threatening experiences (37 compared with 22; RR, 1.71; 95% CI: 1.01, 2.89) for subjects receiving salmeterol compared to those receiving placebo.

Subgroup analyses suggest the risk may be greater in African Americans compared with Caucasian subjects. The increased risk was thought to be largely attributable to the African-American subpopulation: respiratory-related deaths or life-threatening experiences (20 compared with 5; RR, 4.10; 95% CI: 1.54, 10.90) and combined asthma-related deaths or life-threatening experiences (19 compared with 4; RR, 4.92; 95% CI: 1.68, 14.45) in subjects receiving salmeterol compared to those receiving placebo.²¹⁴

The FDA released a safety alert based on the results of the trial, reporting that there were no significant differences in asthma-related events between salmeterol and placebo in Caucasian patients; however, in African Americans, there was a statistically significantly greater number of asthma-related events, including deaths, in salmeterol- compared with placebo-treated patients.²¹⁹

One fair quality multicenter trial compared montelukast (10 mg/d plus salmeterol (100 mcg/d plus placebo ICS) with low dose BDP (160 mcg/d plus salmeterol 100 mcg/d plus placebo LTRA) for 14 weeks, washout for 4 weeks, then crossover for another 14 weeks.¹⁸⁶ This study is described in detail in Key Question 1. The LTRA plus LABA combination led to significantly more subjects having a shorter time to treatment failure compared to ICS plus LABA (29 compared with 8; $P = 0.0008$). Subgroup analysis found no difference between races. The proportion of Caucasian subjects with preferential protection against treatment failure while using an ICS + LABA (relative to an LTRA/LABA) was not significantly different from the proportion of African-American subjects ($P = 1.0$).

C. Gender

We did not find any study that directly compared the efficacy and tolerability of our included medications between males and females.

One prospective cohort study (described in detail in Key Question 2) evaluated the risk of osteoporosis in premenopausal women using triamcinolone and found a dose-related decline in BMD.²⁰⁰ Although several other studies conducted in mixed populations of men and women found no relationship between ICS use and BMD, evidence is insufficient to support a differential decline in BMD between male and female patients treated with ICSs.

II. Comorbidities

We did not find any study that directly compared the efficacy, effectiveness, or tolerability of our included drugs in populations with specific comorbidities. Because mixed evidence supports an increased risk of osteoporotic fractures, cataracts, and glaucoma in ICS-treated patients (especially at high doses), ICSs should be used with care in populations at increased risk for these conditions. No evidence reflects different risks between one ICS and another.

One study assessed differences in efficacy of montelukast, beclomethasone and placebo in patients with differing BMI (normal, overweight and obese).²²⁰ This study did not meet our eligibility criteria; it was a pooled data analysis that was not based on a systematic literature search. Data were pooled from four trials (3 that are described in detail in Key Question 1 and 1 that was reported as an abstract only) to compare the efficacy of montelukast and beclomethasone in patients with differing BMI. Pooled data included 3,073 patients. Patients with normal BMI treated with placebo had a higher percentage of asthma control days than patients who were overweight or obese (33.91% compared with 25.04% for overweight, $P = 0.002$; 25.80% for obese, $P = 0.026$). The effect of montelukast on asthma control days was

similar across all three BMI categories; however, the effect of beclomethasone decreased with increasing BMI.

III. Other medications

We did not find any studies meeting our inclusion/exclusion criteria that examined the impact of other medications on the comparative efficacy, tolerability, or adverse events of our included medications.

Although little documentation supports the clinical relevance of this interaction, the product labeling for budesonide, fluticasone, and mometasone does mention the potential for interaction between ICSs and inhibitors of the cytochrome P450 isoenzyme 3A4 (CYP3A4). Because beclomethasone, flunisolide, and triamcinolone also are metabolized by CYP3A4, the potential for interaction with drugs that inhibit this isoenzyme likely applies to all ICSs. Drugs known to inhibit CYP3A4 include amiodarone, cimetidine, clarithromycin, delavirdine, diltiazem, dirithromycin, disulfiram, erythromycin, fluoxetine, fluvoxamine, indinavir, itraconazole, ketoconazole, nefazodone, nevirapine, propoxyphene, quinupristin-dalfopristin, ritonavir, saquinavir, telithromycin, verapamil, zafirlukast, and zileuton. However, the clinical significance of these “potential” interactions is questionable.

IV. Smoking status

We found one cross-over study comparing asthmatic smokers and nonsmokers.²²¹ In this study, 44 nonsmokers (total lifetime smoking history of less than 2 pack-years and no smoking for at least one year) and 39 “light” smokers (currently smoking 10-40 cigarettes/day and a 2-15 pack-year history) were randomized to BDP (320 mcg/d) or montelukast (10 mg/d) for eight weeks of active treatment, an eight week washout, and then eight weeks of active treatment with the other medication. Both smokers and non-smokers showed some improvement in change in average quality of life scores (AQOL). However, the change from baseline was only statistically significant in montelukast-treated non-smokers. Average change was greater in montelukast-treated non-smokers compared with smokers than it was in BDP-treated non-smokers compared with smokers. The difference was not based on a direct statistical comparison between the ML and BDP groups and further studies are needed to determine if there are differences in the response to ML and/or BDP based on smoking status.

V. Pregnancy

Maintaining adequate control of asthma during pregnancy is important for the health and well-being of both the mother and her baby. Inadequate control of asthma during pregnancy has been associated with higher rates of premature birth, intrauterine growth retardation, lower birth weight, perinatal death, and preeclampsia.^{1, 222, 223} Expert opinion recommends ICSs as the preferred treatment for long-term control of asthma symptoms in pregnancy.¹ This preference is based on favorable efficacy data in both non-pregnant and pregnant women and also on safety data in pregnant women; results do not show an increased risk of adverse perinatal outcomes.¹

FDA approved labeling classifies medications by the potential for risk during pregnancy. Budesonide is the only ICS labeled as a pregnancy category B – i.e., no well-controlled studies have been conducted in women but animal studies have found little to no risk. Other ICS products are pregnancy category C.– i.e., no well-controlled studies have been conducted in women but animal studies have shown harmful effects on the fetus. Currently,

ICS product labeling recommends the use of an ICS in pregnancy only when anticipated benefits outweigh potential risk.¹⁰

In general, budesonide is the preferred ICS because more data are available on its use during pregnancy than other ICSs. Minimal published data are available on the efficacy and safety of LTRAs or LABAs during pregnancy, but there is theoretical justification for expecting the safety profile of LABAs to resemble that of albuterol, for which there are data related to safety during pregnancy.¹

We found one systematic review and one database review focusing on ICS use in pregnant asthmatics. We did not identify any studies assessing the efficacy or safety of LABAs, LTSIs, or anti-IgE therapy during pregnancy. We found one observational study that reported perinatal outcomes for a small sample (N = 96) of pregnant women who took LTRAs compared with women who took only short-acting beta2-agonists.²²⁴ The latter study was rated poor for internal validity primarily due to the small sample size (inadequate to detect differences in the adverse events of interest).

One systematic review with meta-analysis showed that ICSs did not increase the rates of any adverse obstetrical outcomes.²²⁵ Studies were eligible for inclusion in this analysis if the included women were exposed to any therapeutic dosage of any fluticasone, beclomethasone, budesonide, triamcinolone or flunisolide during pregnancy. Studies were excluded if either did not have a control group or had a control group comprised of non-asthmatic women. Four studies met inclusion criteria. The summary OR for major malformations in two studies was 0.96 (95% CI: 0.51, 1.83; $P = 0.9582$). The summary OR for preterm delivery in three studies was 0.99 (95% CI: 0.8, 1.22; $P = 0.9687$). The summary OR for low birth weight delivery in two studies was 0.89 (95% CI: 0.7, 1.14; $P = 0.4013$). The summary OR for pregnancy-induced hypertension in three studies was 0.97 (95% CI: 0.84, 1.2; $P = 0.9932$). Tests for heterogeneity ($P = 0.9249$, $P = 0.2521$, $P = 0.6146$ and $P = 0.0013$, respectively) indicated that the studies for major malformation, preterm delivery and low birth weight were not significantly heterogeneous and could be combined. ICSs do not increase the risk of major malformations, preterm delivery, low birth weight and pregnancy-induced hypertension.

The database review reported no significant differences were observed between ICS- and non-ICS-treated mothers.²²⁶ Compared with infants whose mothers did not use an ICS, infants born to mothers treated with an ICS had no significant differences in gestational age, birth weight, and length. Additionally, the rates of preterm delivery, congenital malformation, and stillbirth were similar for ICS- and non-ICS-treated patients.

Insufficient data exists to determine if risks associated with ICSs differ among ICSs or among other medications included in this review.

VI. Genetics

Several genes (coding for LTRA, ICS, or beta-agonist receptors), have been associated with response to medications used in the treatment of asthma.^{1, 101, 227-231} To date, there is not sufficient evidence to draw conclusions about whether testing for variants in these genes has any clinical utility (insufficient strength of evidence). Multiple studies have investigated the impact of polymorphisms of the Beta-2 adrenoreceptor gene (ADRB2) on response to beta-agonist therapy, but none have demonstrated clinical validity or clinical utility of testing for ADRB2 polymorphisms.^{1, 227, 228, 231}

Table 56. Summary of studies evaluating subgroups of patients for which asthma controller medications may differ in efficacy or frequency of adverse events

Study	Study design N Duration	Country Population Setting	Comparison (total daily dose)	Results	Quality rating
Racial groups					
Walters et al. 2007 ²¹⁶	Systematic review with meta-analysis 67 RCTs (N = 42,333) Duration: ≥ 4 weeks	Multinational Adults and children with asthma who were not uniformly on ICS. (Studies in which all subjects were uniformly taking ICS excluded from this review.) 11 studies included children under 12 yrs. Asthma severity: of 67 RCTs, number with mild -moderate asthma, 28; mild asthmatics, 9; moderate - severe disease, 1; persistent or symptomatic disease, 11; unknown disease severity, 18.	Regular inhaled LABA (either SM or FM) administered twice daily vs. placebo.	Composite endpoint of respiratory-related death and life threatening adverse events (intubation and mechanical ventilation): Greater in African-Americans than Caucasians (Relative Risk Increase 3.9; 95% CI: 1.29, 11.84).	Good
Deykin et al. 2007 ¹⁸⁶	RCT 192 14 weeks, washout for 4 weeks, then crossover for 14 weeks	US Ages 12-65 No current smokers Multicenter	ML (10 mg/d) + SM (100 mcg/d) + placebo ICS vs. BDP (160 mcg/d) + SM (100 mcg/d) + placebo LTRA Low dose ICS	Exacerbations/treatment failure: ICS + LABA > LTRA + LABA [Significantly more subjects had a shorter time to treatment failure* while using LTRA plus LABA as compared to ICS plus LABA ($P = 0.0008$)] Subgroup analysis: Treatment failure in ICS + LABA > LTRA + LABA No difference in proportion of Caucasian subjects with preferential* protection against treatment failure while using ICS + LABA (relative to an LTRA/LABA) as vs. that in the African-American subjects ($P = 1.0$) [In Caucasian, significantly more subjects had a shorter time to treatment failure* while using LTRA plus LABA as compared to ICS plus LABA (10 vs. 2, $P = 0.039$)]	Fair

Study	Study design N Duration	Country Population Setting	Comparison (total daily dose)	Results	Quality rating
				[In African American subgroup, significantly more subjects had a shorter time to treatment failure* while using LTRA plus LABA as compared to ICS plus LABA (15 vs. 3, $P = 0.0075$)]	
Nelson et al. 2006 ²¹⁴	DB Randomized	US	SM (84 mcg/d) vs. placebo	Respiratory-related deaths or life threatening experiences: no significant difference between SM and placebo (50 vs. 36; RR 1.4; 95% CI: 1.25, 15.34)	Fair
SMART	Observational study 26,355 28 weeks	Age ≥ 12 , asthma severity=NR; smoking status=NR Multicenter		Respiratory-related deaths: significant increase with SM compared to placebo (24 vs. 11; RR 2.16; 95% CI: 1.06, 4.41) Asthma-related deaths: significant increase with SM vs. placebo (13 vs. 3; RR 4.37; 95% CI: 1.25 to 15.34) Combined asthma-related deaths or life-threatening experiences: significant increase with SM vs. placebo (37 vs. 22; RR 1.71; 95% CI: 1.01, 2.89) Subgroup analysis, African American participants: Respiratory-related deaths or life threatening experiences: significant increase in SM vs. placebo (20 vs. 5; RR 4.10; 95% CI: 1.54 to 10.90) Combined asthma-related deaths or life-threatening experiences: significant increase in SM vs. placebo (19 vs. 4; RR 4.92; 95% CI: 1.68, 14.45)	
Smoking status					
Lazarus et al. 2007 ²²¹	RCT, DB, DD crossover 83	US Age 18-50	Smokers vs. non-smokers	Change in AQOL average score: ML /Non-smoker 0.23 (0.04, 0.42 ; $P = 0.02$) ML smoker 0.07 (-0.19, 0.32; $P = NS$) BDP Non-smoker 0.13 (-0.06, 0.32; $P = NS$) BDP Smoker 0.12 (-0.13, 0.37; $P = NS$)	Fair
SMOG study	24 weeks (16 weeks with 8 week washout between)	Multicenter			
Pregnancy					
Norjavaara	Database	Pregnant asthmatic	BUD vs.	No difference in gestational age,	Fair

Study	Study design N Duration	Country Population Setting	Comparison (total daily dose)	Results	Quality rating
& Gerhardsso n de Verdier, 2003 ²²⁶	review 293,948	women (Swedish)	control (no BUD exposure during pregnancy)	birth weight, length, rate of stillbirths, or multiple births for children born to BUD-treated mothers. Rate of caesarean birth was higher in women taking BUD early in pregnancy ($P < 0.05$)	
Rahimi et al. 2006 ²²⁵	Systematic review with meta-analysis (SR)	Pregnant asthmatic women	Any therapeutic dosage of any ICS (FP, BDP, BUD, TAA, flunisolide) vs. no ICS exposure	ICSs did not increase the rates of any obstetrical outcomes. Major malformations: Summary (2 studies) OR=0.96 (95% CI: 0.51, 1.83); $P = 0.9582$ Preterm delivery: Summary (3 studies) OR = 0.99 (95% CI: 0.8, 1.22); $P = 0.9687$ Low birth weight delivery: Summary (2 studies) OR = 0.89 (95% CI: 0.7, 1.14); $P = 0.4013$ Pregnancy-induced hypertension: Summary (3 studies) OR = 0.97 (95% CI: 0.84, 1.2); $P = 0.9932$ Tests for heterogeneity ($P = 0.9249$, $P = 0.2521$, $P = 0.6146$ and $P =$ 0.0013 , respectively) indicated that the studies for major malformation, preterm delivery and low birth weight were not significantly heterogeneous and could be combined.	Fair

Abbreviations: BUD = Budesonide; CI = confidence interval; DPI= Dry Powder Inhaler; FM = Formoterol; FP = Fluticasone Propionate; ICS = Inhaled Corticosteroids; LABAs = Long-Acting Beta-2 Agonists; LTRAs = Leukotriene receptor antagonists; MA=meta-analysis; ML = Montelukast; NR = not reported; NS = not statistically significant; OR= odds ratio; QOL = quality of life; RCT= randomized controlled trial; RR = relative risk; SM = Salmeterol;; SR=systematic review.

*Treatment failure defined as increased as-needed albuterol, persistent asthma symptoms or drop in PEF despite rescue use, use of oral, parenteral, or non-study related ICS, emergency department therapy with steroids, drop in FEV1 or PEF, or physician clinical judgment for safety.

SUMMARY

The results are summarized in Table 57.

Table 57. Summary of the evidence by key question for controller medications for the treatment of persistent asthma in adolescents/adults \geq 12 years of age and children $<$ 12 years of age

Key Question	Strength of evidence	Conclusions
Key Question 1. What is the comparative efficacy and effectiveness of controller medications used to treat outpatients with persistent asthma?	Moderate $(\geq 12 \text{ years})$	Inhaled Corticosteroids (ICSs) compared with ICSs: Efficacy studies provide moderate evidence that ICSs do not differ in their ability to control asthma symptoms, prevent exacerbations, and reduce the need for additional rescue medication at equipotent doses administered through comparable delivery devices. Relatively few studies reported exacerbations, healthcare utilization (hospitalizations, emergency visits), or quality of life outcomes. Long-term data beyond 12 weeks is lacking for most of the comparisons.
	Moderate $(< 12 \text{ years})$	In children, the body of evidence supports the above conclusion, but data was only available for three comparisons (two systematic reviews and four RCTs): beclomethasone compared with budesonide, beclomethasone compared with fluticasone, and budesonide compared with fluticasone.
	Low $(\geq 12 \text{ years})$	Leukotriene Modifiers (LMs) compared with LMs: Limited head-to-head evidence from one short-term study (12 weeks) in adults and adolescents ≥ 12 years of age does not support a difference between montelukast and zafirlukast in their ability to decrease rescue medicine use or improve quality of life.
	Insufficient $(< 12 \text{ years})$	We found no head to head trials in children < 12 years of age.
	Moderate $(\geq 12 \text{ years})$	Long-Acting Beta-2 Agonists (LABAs) compared with LABAs: Results from three efficacy studies provide moderate evidence that LABAs do not differ in their ability to control asthma symptoms, prevent exacerbations, improve quality of life, and prevent hospitalizations or emergency visits in patients with persistent asthma not controlled on ICSs alone. Large systematic reviews comparing LABAs with other treatments provide some indirect evidence supporting this conclusion.
	Moderate $(< 12 \text{ years})$	In children, direct evidence is limited to one fair trial enrolling children and adolescents age 6-17. The trial reported no difference in symptoms, exacerbations, quality of life, missed work, or

Table 57. Summary of the evidence by key question for controller medications for the treatment of persistent asthma in adolescents/adults ≥ 12 years of age and children < 12 years of age

Key Question	Strength of evidence	Conclusions
		missed school, but found a greater decrease in rescue medicine use in subjects treated with eformoterol compared to those treated with salmeterol.
	<p>High (≥ 12 years)</p> <p>Low (< 12 years)</p>	<p>Anti-IgE Therapy (Omalizumab): Meta-analyses and efficacy studies provide consistent evidence favoring omalizumab over placebo for the ability to control asthma symptoms, prevent exacerbations, and reduce the need for additional rescue medication in adults and adolescents ≥ 12 years of age.</p> <p>Limited evidence from one fair trial is available for children < 12 years of age. The trial reported no difference in measures of symptoms, but fewer exacerbations, less rescue medicine use, greater quality of life, and fewer emergency visits and hospitalizations for subjects treated with omalizumab.</p>
	<p>High (≥ 12 years)</p> <p>Insufficient (< 12 years)</p>	<p>Combination Products: Budesonide/Formoterol (BUD/FM) compared with Fluticasone/Salmeterol (FP/SM): Results from large trials up to six months in duration comparing equipotent steroid components support no significant difference in efficacy between combination treatment with BUD/FM and combination treatment with FP/SM when each is administered via a single inhaler. The results of our meta-analysis show no difference in exacerbations between those treated with BUD/FM and those treated with FP/SM (SMD = -0.0286, 95% CI: -0.0872, 0.0299; <i>P</i> = 0.3378, 4 studies).</p> <p>None of the trials included children < 12 years of age.</p>
	<p>Moderate (≥ 12 years)</p>	<p>Combination Products: BUD/FM for maintenance and relief compared with ICS/LABA combination (BUD/FM or FP/SM) for maintenance with Short-Acting Beta-Agonist (SABA) for relief: Of note, BUD/FM is not approved for use as a relief medication in the US, but has been approved for maintenance and reliever therapy in Canada. Meta-analysis of results from large trials (10,547 subjects) up to twelve months in duration including children and adults found statistically significantly lower exacerbation rates (SMD = (SMD = -0.1216, 95% CI: -0.1595, -0.0837; 5 comparisons) for those treated with BUD/FM for maintenance and relief than for those treated with ICS/LABA (BUD/FM or FP/SM) for maintenance with SABA for relief. There</p>

Table 57. Summary of the evidence by key question for controller medications for the treatment of persistent asthma in adolescents/adults ≥ 12 years of age and children < 12 years of age

Key Question	Strength of evidence	Conclusions
		were no differences in symptom-free days, symptom scores, nocturnal awakenings, rescue-free days, or rescue medicine use.
		The one trial that included children found similar results. It enrolled children down to 4 years of age.
	Moderate (< 12 years)	It is difficult to determine the applicability of the results of these trials given the heterogeneity of study designs and dose comparisons. In addition, several of the trials significantly reduced the total ICS doses for many subjects upon randomization; some studies reduced the starting doses to levels that could be considered inadequate compared to the subjects' previous dose requirements for control.
	High (≥ 12 years)	ICSs compared with Leukotriene Modifiers: Efficacy studies up to 56 weeks in duration provide consistent evidence favoring ICSs over LTRAs for the treatment of asthma as monotherapy for both children and adults. Those treated with LTRAs had a significantly higher occurrence of exacerbations than those treated with ICSs (SMD = 0.216, 95% CI: 0.127, 0.305, 12 studies). In addition, our meta-analyses found statistically significant differences in favor of ICSs over LTRAs for measures of symptoms, rescue medicine use, and quality of life.
	High (< 12 years)	
	High (≥ 12 years)	ICSs compared with LABAs for monotherapy: LABAs are not recommended nor approved for use as monotherapy for persistent asthma because they may increase the risk of asthma-related deaths.
	High (< 12 years)	Efficacy studies up to 12 months in duration provide consistent evidence favoring ICSs over LABAs for the treatment of asthma as monotherapy for children and adults. Those treated with LABAs had a significantly higher occurrence of exacerbations than those treated with ICSs (SMD = 0.221, 95% CI: 0.025, 0.417; <i>P</i> = 0.027, 6 studies).
	Insufficient (≥ 12 years)	Leukotriene Modifiers compared with LABAs for monotherapy: LABAs are not recommended nor approved for use as monotherapy for persistent asthma because they may increase the risk of asthma-related deaths. Two small trials provide insufficient evidence to draw firm conclusions about the comparative efficacy of leukotriene modifiers and LABAs for use as monotherapy for persistent asthma.
	Insufficient (< 12 years)	
		ICS+LABA compared with ICS (same dose) as first line therapy:

Table 57. Summary of the evidence by key question for controller medications for the treatment of persistent asthma in adolescents/adults \geq 12 years of age and children $<$ 12 years of age

Key Question	Strength of evidence	Conclusions
	Moderate (\geq 12 years)	Meta-analyses of results from large trials up to twelve months in duration found mixed results and do not provide sufficient evidence to support the use of combination therapy rather than ICS alone as first line therapy. Meta-analyses found statistically significantly greater improvements in symptoms and rescue medicine use, but no difference in exacerbations for adolescents and adults treated with ICS+LABA than for those treated with ICS alone for initial therapy. However, limited data was available for exacerbations and further research may change our confidence in the estimate of effect for this outcome. Of note, ICS+LABA combination products are only indicated for patients not adequately controlled on other asthma-controller medications (e.g., low- to medium-dose inhaled corticosteroids) or whose disease severity clearly warrants initiation of treatment with two maintenance therapies.
	Insufficient ($<$ 12 years)	We found no studies for this comparison that enrolled children $<$ 12 years of age.
	High (\geq 12 years)	ICS+LABA compared with ICS (increased dose) (addition of LABA to ICS compared with increasing the ICS dose): Results from large trials up to twelve months in duration support greater efficacy with the addition of a LABA to an ICS than with a higher dose ICS for adults and adolescents with persistent asthma. Our meta-analysis shows statistically significantly greater improvement in symptom-free days, symptom scores, rescue-free days, and rescue medicine use for subjects treated with ICS+LABA. Despite a trend toward fewer subjects with exacerbations in the ICS+LABA group, the difference was not statistically significant in our analysis
	Low ($<$ 12 years)	Just one trial exclusively enrolled children $<$ 12 (four included some subjects $<$ 12) and all results are not necessarily generalizable to pediatric populations.
	High (\geq 12 years)	ICS+LABA compared with ICS (same dose) (addition of LABA to ICS compared with continuing same dose ICS): Results from large trials up to one year in duration support greater efficacy with the addition of a LABA to an ICS over continuing the current dose of ICS alone for patients with poorly controlled persistent asthma.

Table 57. Summary of the evidence by key question for controller medications for the treatment of persistent asthma in adolescents/adults \geq 12 years of age and children $<$ 12 years of age

Key Question	Strength of evidence	Conclusions
	High ($<$ 12 years)	Five trials included pediatric populations $<$ 12 years of age.
	Low (\geq 12 years)	ICS+LTRA compared with ICS (same dose): The addition of LTRAs to ICSs compared to continuing the same dose of ICSs resulted in improvement in rescue medicine use and a non-statistically significant trend toward fewer exacerbations requiring systemic steroids. There were no statistically significant differences in other health outcomes.
	Insufficient ($<$ 12 years)	None of the included trials enrolled children $<$ 12 years of age.
	Moderate (\geq 12 years)	ICS+LTRA compared with ICS (increased dose): There is no apparent difference in health outcomes between those treated with ICSs plus LTRAs compared to those treated with increasing the dose of ICSs. There were some conflicting results and further research may alter the results.
	Low ($<$ 12 years)	The only included trial enrolling children $<$ 12 years of age was a 12-week Indian trial that reported fewer exacerbations in those treated with ICS+LTRA compared to increasing the dose of BUD.
	High (\geq 12 years)	Combination products (ICS/LABA) compared with LTRAs: Overall, our meta-analysis and results from four RCTs find the combination of fluticasone plus salmeterol to be more efficacious than montelukast for the treatment of persistent asthma.
	Moderate ($<$ 12 years)	One of the trials enrolled children ages 6-14 and another included about 15% of subjects $<$ 12 years of age.
	High (\geq 12 years)	ICS+LABA compared with ICS+LTRA (addition of LABA compared with LTRA to ongoing ICS therapy): Overall, results from a good quality systematic review with meta-analysis and seven RCTs provide strong evidence that the addition of a LABA to ICS therapy is more efficacious than the addition of an LTRA to ICS therapy for adolescents and adults with persistent asthma.
	Insufficient ($<$ 12 years)	We found no trials in children $<$ 12 years of age and none contributed data to the meta-analysis.

Table 57. Summary of the evidence by key question for controller medications for the treatment of persistent asthma in adolescents/adults \geq 12 years of age and children $<$ 12 years of age

Key Question	Strength of evidence	Conclusions
	Moderate (\geq 12 years)	LTRA+LABA compared with ICS+LABA: Results from one 32 week cross-over trial, which was terminated early, reported that subjects treated with LTRA+LABA had significantly shorter time to treatment failure than those treated with ICS+LABA ($P = 0.0008$). Indirect evidence from other comparisons supports our confidence that the ICS+LABA combination is more efficacious than the LTRA+LABA combination.
	Insufficient ($<$ 12 years)	We found no studies for this comparison that enrolled children $<$ 12 years of age.
Key Question 2.		Inhaled Corticosteroids (ICSs):
What is the comparative tolerability and frequency of adverse events for controller medications used to treat outpatients with persistent asthma?	Moderate (\geq 12 years)	The overall incidence of adverse events, withdrawals due to adverse events, and specific adverse events (other than reduction in growth velocity) are similar for equipotent doses of ICSs.
	Moderate ($<$ 12 years)	Three fair head-to-head trials provide evidence that short-term growth velocity is reduced less with fluticasone than with beclomethasone or budesonide. In addition, two meta-analyses report a reduction in growth velocity for beclomethasone or fluticasone compared to placebo. The best longer-term evidence (avg 4.3 years) is from the CAMP study, which found a 1.1cm difference in mean increase in height ($P = 0.005$) between BUD- and placebo-treated patients. The differences in growth occurred primarily during the first year of treatment, suggesting that the small decrease in growth velocity with ICSs occurs early in treatment and is not progressive.
	Insufficient	Evidence is insufficient to determine if long-term treatment with ICSs leads to a reduction in final adult height.
	Moderate (\geq 12 years)	Leukotriene Modifiers: There is insufficient head-to-head data (one trial) to determine differences in tolerability or overall adverse events between any of the leukotriene modifiers using direct evidence. Indirect evidence from placebo-controlled trials and large safety databases suggests that zileuton has an increased risk of liver toxicity compared with either montelukast or zafirlukast.
	Moderate ($<$ 12 years)	
	Moderate (\geq 12 years)	Long-Acting Beta-2 Agonists (LABAs): Limited direct evidence from head-to-head trials and indirect evidence from systematic reviews provides no evidence of a difference in tolerability or adverse events between formoterol and salmeterol.
	Moderate	

Table 57. Summary of the evidence by key question for controller medications for the treatment of persistent asthma in adolescents/adults \geq 12 years of age and children $<$ 12 years of age

Key Question	Strength of evidence	Conclusions
	(< 12 years)	
	High (all ages)	Anti-IgE Therapy (Omalizumab): Omalizumab is the only available anti-IgE drug approved for the treatment of asthma; therefore, there are no studies of intra-class comparisons. Omalizumab-treated patients have an increased incidence of injection site reactions and anaphylaxis compared to placebo-treated patients. Omalizumab has a boxed (or “black box”) warning for anaphylaxis.
	Low (all ages)	Omalizumab also has a warning for a potential increased risk of malignancy, based on short term data from studies less than one year in duration.
	High (\geq 12 years)	Combination Products: Budesonide/Formoterol (BUD/FM) compared with Fluticasone/Salmeterol (FP/SM): Data from four large head-to-head trials (5,818 subjects) provides no evidence of a difference in tolerability or overall adverse events between BUD/FM and FP/SM in adults and adolescents.
	Insufficient (< 12 years)	There is insufficient evidence to draw conclusions in children \leq 12.
	Moderate (\geq 12 years)	ICSs compared with Leukotriene Modifiers: Data from one good quality systematic review and numerous head-to-head RCTs provides no evidence of a difference in tolerability or overall adverse events (risk of experiencing any adverse effects: RR 0.99, 95% CI: 0.93, 1.04, 15 trials) between ICSs and leukotriene modifiers. Trials were generally not designed to compare tolerability and adverse events. Specific adverse events reported with ICSs, such as cataracts and decreased growth velocity, were not found among patients taking leukotriene modifiers. One 56-week RCT found that the mean growth rate of subjects treated with beclomethasone was 0.81 cm less than that of subjects treated with montelukast.
	Moderate (< 12 years)	
	High (all ages)	ICSs compared with LABAs for monotherapy: LABAs are not recommended nor approved for use as monotherapy for persistent asthma because they may increase the risk of asthma-related deaths. Overall evidence indicates that ICSs are safer than LABAs for use as monotherapy.
	High	Leukotriene Modifiers compared with LABAs for monotherapy:

Table 57. Summary of the evidence by key question for controller medications for the treatment of persistent asthma in adolescents/adults \geq 12 years of age and children $<$ 12 years of age

Key Question	Strength of evidence	Conclusions
	(all ages)	LABAs are not recommended nor approved for use as monotherapy for persistent asthma because they may increase the risk of asthma-related deaths. Indirect evidence indicates that leukotriene modifiers are safer than LABAs for use as monotherapy.
	Moderate (\geq 12 years)	ICS+LABA compared with ICS (same dose) as first line therapy: Results from a good quality systematic review with meta-analysis and five RCTs found no difference in overall adverse events or withdrawals due to adverse events between subjects treated with ICSs plus LABAs and subjects treated with ICSs alone as first line therapy. Trials were 12-24 weeks in duration and were generally not designed to compare tolerability and adverse events. Indirect evidence from a recent systematic review that included a post-hoc analysis of data from SMART suggests that the potential increased risk of asthma-related death for those taking LABAs may be confined to patients not taking ICSs at baseline. Of note, ICS+LABA combination products are only indicated for patients not adequately controlled on other asthma-controller medications (e.g., low- to medium-dose inhaled corticosteroids) or whose disease severity clearly warrants initiation of treatment with two maintenance therapies.
	Insufficient ($<$ 12 years)	We found no studies for this comparison that enrolled children $<$ 12 years of age. Thus, there is insufficient evidence to draw conclusions in children $<$ 12 years of age.
	Moderate (\geq 12 years)	ICS+LABA compared with ICS (increased dose) (addition of LABA to ICS compared with increasing the ICS dose): Results from a good quality systematic review with meta-analysis and numerous RCTs found no difference in overall adverse events or withdrawals between subjects treated with ICSs plus LABAs and subjects treated with an increased dose of ICSs. Those treated with ICSs plus LABAs had an increased rate of tremor (N = 10, RR 2.96, 95% CI: 1.60, 5.45). Indirect evidence from a recent systematic review that included a post-hoc analysis of data from SMART suggests that the potential increased risk of asthma-related death for those taking LABAs may be confined to patients not taking ICSs at baseline.
		Just one of the RCTs enrolled an exclusively pediatric population $<$ 12 years of age (four included

Table 57. Summary of the evidence by key question for controller medications for the treatment of persistent asthma in adolescents/adults \geq 12 years of age and children $<$ 12 years of age

Key Question	Strength of evidence	Conclusions
	Low ($<$ 12 years)	some subjects $<$ 12) and results are not necessarily applicable to pediatric populations.
	Moderate (\geq 12 years)	<p>ICS+LABA compared with ICS (same dose) (addition of LABA to ICS compared with continuing same dose ICS): Results from a good quality systematic review with meta-analysis and numerous RCTs found no difference in overall adverse events or withdrawals between subjects treated with ICSs plus LABAs and subjects treated with the same dose of ICSs. Although not statistically significantly different, the upper limits of the confidence intervals for tachycardia or palpitations (N = 5, RR 2.13, 95% CI: 0.77, 5.88) and tremor (N = 7, RR 2.48, 95% CI: 0.78, 7.89) were relatively high, suggesting that these may be more frequent in patients treated with ICSs plus LABAs. Indirect evidence from a recent systematic review that included a post-hoc analysis of data from SMART suggests that the potential increased risk of asthma-related death for those taking LABAs may be confined to patients not taking ICSs at baseline.</p> <p>Five studies (21%) included pediatric populations under 12 years of age</p>
	Low ($<$ 12 years)	
	Moderate (\geq 12 years)	<p>ICS+LTRA compared with ICS (same dose): Evidence from one good quality systematic review with meta-analysis (including 27 trials) found that the addition of LTRAs to ICSs compared to continuing the same dose of ICSs resulted in no significant differences in overall adverse events or withdrawals due to adverse events. Trials were generally not designed to compare tolerability and adverse events and many used higher than licensed doses of LTRAs.</p>
	Low ($<$ 12 years)	Evidence in children $<$ 12 years of age is limited. Just two of the 27 trials in the systematic review enrolled children.
	Moderate (\geq 12 years)	<p>ICS+LTRA compared with ICS (increased dose): Evidence from one good quality systematic review with meta-analysis (including 27 trials) found that the addition of LTRAs to ICSs compared to increasing the dose of ICSs resulted in no significant differences in overall adverse events or withdrawals due to adverse events. Trials were generally not designed to compare tolerability and adverse events and many used higher than licensed doses of LTRAs.</p>

Table 57. Summary of the evidence by key question for controller medications for the treatment of persistent asthma in adolescents/adults ≥ 12 years of age and children < 12 years of age

Key Question	Strength of evidence	Conclusions
	Low (< 12 years)	Evidence in children < 12 years of age is limited. Just two of the 27 trials in the systematic review enrolled children.
	Low (≥ 12 years)	Combination products (ICS/LABA) compared with LTRAs: ICS/LABA combinations and leukotriene modifiers have similar rates of overall adverse events and withdrawals due to adverse events based on limited direct evidence from three short-term trials.
	Very Low (< 12 years)	One of the three trials enrolled subjects at least six years of age (about 15% were <12 years old)
	Moderate (≥12 years)	ICS+LABA compared with ICS+LTRA (addition of LABA compared with LTRA to ongoing ICS therapy): Results from a good quality systematic review with meta-analysis and six RCTs provide moderate evidence that there is no difference in overall adverse events or withdrawals due to adverse events between ICS+LABA and ICS+LTRA. Trials were generally not designed to compare tolerability and adverse events.
	Insufficient (<12 years)	We found no RCTs enrolling children <12 years of age; the systematic review included just one trial in children (that did not contribute data to the meta-analysis). Thus, there is insufficient evidence to draw conclusions in children < 12 years of age.
Key Question 3. Are there subgroups of these patients based on demographics (age, racial groups, gender), asthma severity, comorbidities (drug-disease interactions, including obesity), other medications (drug-drug interactions), smoking status, genetics, or pregnancy for which asthma controller medications differ in efficacy, effectiveness, or frequency of adverse events?	Insufficient	Age: Differences in the efficacy, tolerability, or adverse events between children <12 years of age and adolescents or adults ≥12 are described in the body of the report (Key Questions 1 and 2) and summaries above. Children ≤ 4 years of age We found no head-to-head studies comparing the efficacy or safety of our included drugs in this age group with older children, adolescents, or adults.
	Low	Racial groups: A large randomized trial (26,355 subjects) comparing salmeterol with placebo (SMART) was discontinued early due to findings in African Americans, safety concerns, and difficulties in enrollment. The trial reported an increased risk of asthma-related deaths (13 compared with 3; RR

Table 57. Summary of the evidence by key question for controller medications for the treatment of persistent asthma in adolescents/adults ≥ 12 years of age and children < 12 years of age

Key Question	Strength of evidence	Conclusions
		4.37; 95% CI: 1.25 to 15.34). The increased risk was thought to be largely attributable to the African-American subpopulation. Although the study was not designed to assess subgroups, there were approximately four-fold relative increases in respiratory-related deaths or life-threatening experiences (20 compared with 5; RR 4.10; 95% CI: 1.54 to 10.90) and combined asthma-related deaths or life-threatening experiences (19 compared with 4; RR 4.92; 95% CI: 1.68 to 14.45) in African-Americans treated with salmeterol compared to those treated with placebo.
	Insufficient	Gender: We did not find any study reporting a difference between the included medications.
	Insufficient	Comorbidities: We did not find any studies meeting our inclusion/exclusion criteria that directly compared the efficacy, effectiveness, or tolerability of our included drugs in populations with specific comorbidities.
	Insufficient	Other medications (drug-drug interactions): We did not find any studies meeting our inclusion/exclusion criteria that examined the impact of other medications on the comparative efficacy, tolerability, or adverse events of our included medications.
	Low	Smoking status: One study comparing ML and BDP in smokers and non-smokers provides some information that there may be differential responses to treatment between smokers and non-smokers.
	Insufficient	Pregnancy: We did not find any studies that directly examined the comparative efficacy, tolerability, or adverse events of our included medications. Budesonide is the only ICS labeled pregnancy category B; the other ICSs are category C.
	Insufficient	Genetics: To date, there is not sufficient evidence to determine whether genetic polymorphisms result in clinically important differences in responses to asthma medications. Multiple studies have investigated the impact of polymorphisms (e.g. the Beta-2 adrenoceptor gene, ADRB2) on response to

Table 57. Summary of the evidence by key question for controller medications for the treatment of persistent asthma in adolescents/adults ≥ 12 years of age and children < 12 years of age

Key Question	Strength of evidence	Conclusions
		various asthma treatments, but none have demonstrated clinical validity or clinical utility of testing for polymorphisms.

Abbreviations: CI = confidence interval; FP = Fluticasone Propionate; ICS= Inhaled Corticosteroids; LABAs = Long-Acting Beta-2 Agonists; LM= Leukotriene Modifiers; LTRAs = Leukotriene receptor antagonists; RCT= randomized controlled trial; RR = relative risk; SABA = Short-Acting Beta-Agonist; SMD = standard mean difference

Strength of Evidence ratings:

High = High confidence in the estimate of effect and that the evidence reflects the true effect. Further research is unlikely to change our confidence.

Moderate = Moderate confidence that the evidence reflects the true effect. Further research may change our confidence in the estimate and may change the estimate.

Low = Low confidence that the evidence reflects the true effect. Further research is likely to change our confidence in the estimate and is likely to change the estimate.

Insufficient = evidence is unavailable or does not permit estimation of an effect.

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Appendix A. Search Strategies

#3 Search "Asthma"[Majr]	65353
#4 Search "Asthma"[Majr] Limits: Publication Date from 1990, Humans, English	30878
#12 Search "inhaled corticosteroids" OR "Beclomethasone"[Mesh] OR qvar OR vanceril OR "Budesonide"[Mesh] OR pulmicort OR "flunisolide "[Substance Name] OR aerobid OR aerospan OR bronalide OR "fluticasone "[Substance Name] OR flovent OR "Triamcinolone"[Mesh] OR azmacort OR "mometasone furoate "[Substance Name] OR asmanex	14453
#13 Search #4 AND #12	3191
#14 Search ("Randomized Controlled Trials"[MeSH] OR "Randomized Controlled Trial"[Publication Type]) OR "Single-Blind Method"[MeSH] OR "Double-Blind Method"[MeSH] OR "Random Allocation"[MeSH]	342286
#15 Search #13 AND #14	1352
#16 Search ("Case-Control Studies"[MeSH] OR "Cohort Studies"[MeSH] OR "Cross-Sectional Studies"[MeSH] OR "Follow-Up Studies"[MeSH] OR "Longitudinal Studies"[MeSH] OR "Retrospective Studies"[MeSH] OR observational studies	959680
#17 Search #13 AND #16	581
#23 Search ("Adrenergic beta-Agonists"[Mesh] AND "long acting") OR "formoterol "[Substance Name] OR foradil OR oxis OR performomist OR "salmeterol "[Substance Name] OR serevent	2104
#24 Search #4 AND #23	1018
#25 Search #24 AND #14	546
#26 Search #24 AND #16	104
#34 Search "Leukotriene Antagonists"[Mesh] OR "montelukast "[Substance Name] OR singulair OR "zafirlukast "[Substance Name] OR accolate OR "zileuton "[Substance Name] OR zyflo OR "pranlukast "[Substance Name] OR onon	2574
#35 Search #4 AND #34	954
#36 Search #14 AND #35	323
#37 Search #16 AND #35	91
#39 Search Anti-IgE OR "omalizumab "[Substance Name] OR xolair	2448
#40 Search #4 AND #39	245
#41 Search #40 AND #14	51
#42 Search #40 AND #16	8
#45 Search "fluticasone-salmeterol combination "[Substance Name] OR "fluticasone propionate - salmeterol combination "[Substance Name] OR advair OR budesonide-formoterol OR "symbicort "[Substance Name]	3140

#46 Search #4 AND #45	1017
#47 Search #46 AND #14	544
#48 Search #46 AND #16	163
#49 Search #15 OR #17 OR #25 OR #26 OR #36 OR #37 OR #41 OR #42 OR #47 OR #48	2305

COCHRANE = 46 = 34 NEW

EMBASE =

1. Inhaled Corticosteroids = 445 = 103 NEW
2. LABAs = 232 = 29 NEW
3. LTRAs = 134 = 14 NEW
4. Anti-IgE = 0
5. Combination Studies = 5 = 0 NEW

IPA =

1. Inhaled Corticosteroids = 40 = 32 NEW
2. LABAs = 34 = 31 NEW
3. LTRAs = 1 = 0 NEW
4. Anti-IgE = 8 = 8 NEW
5. Combination Studies = 22 = 15 NEW

NEW TOTAL DATABASE = 2571

#1 Search "Asthma"[Majr]	67440
#2 Search "Asthma"[Majr] Limits: added to PubMed in the last 1 year, Humans, English	1705
#3 Search "inhaled corticosteroids" OR "Beclomethasone"[Mesh] OR qvar OR vanceril OR "Budesonide"[Mesh] OR pulmicort OR "flunisolide "[Substance Name] OR aerobid OR aerospan OR bronalide OR "fluticasone "[Substance Name] OR flovent OR "Triamcinolone"[Mesh] OR azmacort OR "mometasone furoate "[Substance Name] OR asmanex	15093
#4 Search #2 AND #3	187
#5 Search ("Randomized Controlled Trials"[MeSH] OR "Randomized Controlled Trial"[Publication Type]) OR "Single-Blind Method"[MeSH] OR "Double-Blind Method"[MeSH] OR "Random Allocation"[MeSH]	315353
#6 Search #4 AND #5	55
#7 Search ("Case-Control Studies"[MeSH] OR "Cohort Studies"[MeSH] OR "Cross-Sectional Studies"[MeSH] OR "Follow-Up Studies"[MeSH] OR "Longitudinal	1017347

Studies"[MeSH] OR "Retrospective Studies"[MeSH] OR observational studies	
#8 Search #4 AND #7	31
#9 Search ("Adrenergic beta-Agonists"[Mesh] AND "long acting") OR "formoterol "[Substance Name] OR foradil OR oxis OR perforomist OR "salmeterol "[Substance Name] OR serevent	2263
#10 Search #2 AND #9	60
#11 Search #10 AND #5	21
#12 Search #10 AND #7	6
#13 Search "Leukotriene Antagonists"[Mesh] OR "montelukast "[Substance Name] OR singular OR "zafirlukast "[Substance Name] OR accolate OR "zileuton "[Substance Name] OR zyflo OR "pranlukast "[Substance Name] OR onon	2702
#14 Search #2 AND #13	52
#15 Search #14 AND #5	23
#16 Search #14 AND #7	10
#17 Search Anti-IgE OR "omalizumab "[Substance Name] OR xolair	2545
#18 Search #2 AND #17	37
#19 Search #18 AND #5	2
#20 Search #18 AND #7	2
#21 Search "fluticasone-salmeterol combination "[Substance Name] OR "fluticasone propionate - salmeterol combination "[Substance Name] OR advair OR budesonide-formoterol OR "symbicort "[Substance Name]	198
#22 Search #2 AND #21	16
#23 Search #22 AND #5	10
#24 Search #22 AND #7	0
#25 Search #6 OR #8 OR #11 OR #12 OR #15 OR #16 OR #19 OR #20 OR #23 OR #24	101

PUBMED = 86 new

COCHRANE = 3 = 3 new (protocols)

EMBASE = 33 = 16 new

IPA = 8 = 7 new

NEW TOTAL DATABASE = 112

Systematic Reviews

#1 Search (Anti-IgE OR "omalizumab "[Substance Name] OR xolair) AND systematic[sb]	27
#2 Search "Asthma"[Majr]	67544
#3 Search "Asthma"[Majr] Limits: Humans, English	45554
#4 Search #1 AND #3	19

- [#5](#) Search ("Leukotriene Antagonists"[Mesh] OR "montelukast "[Substance Name] OR singular OR "zafirlukast "[Substance Name] OR accolate OR "zileuton "[Substance Name] OR zyflo OR "pranlukast "[Substance Name] OR onon) AND systematic[sb] [81](#)
- [#6](#) Search #5 AND #3 [55](#)
- [#7](#) Search (("Adrenergic beta-Agonists"[Mesh] AND "long acting") OR "formoterol "[Substance Name] OR foradil OR oxis OR performist OR "salmeterol "[Substance Name] OR serevent) AND systematic[sb] [89](#)
- [#8](#) Search #3 AND #7 [52](#)
- [#9](#) Search systematic[sb] AND ("inhaled corticosteroids" OR "Beclomethasone"[Mesh] OR qvar OR vanceril OR "Budesonide"[Mesh] OR pulmicort OR "flunisolide "[Substance Name] OR aerobid OR aerospan OR bronalide OR "fluticasone "[Substance Name] OR flovent OR "Triamcinolone"[Mesh] OR azmacort OR "mometasone furoate "[Substance Name] OR asmanex) [357](#)
- [#13](#) Search #9 AND #3 [177](#)
- [#14](#) Search "fluticasone-salmeterol combination "[Substance Name] OR "fluticasone propionate - salmeterol combination "[Substance Name] OR advair OR budesonide-formoterol OR "symbicort "[Substance Name] AND systematic [sb] [12](#)

212 citations

1. Inhaled Corticosteroids = 177 = 87 new
2. LABAs = 52 = 23 new
3. LTRAs = 55 = 33 new
4. Anti-IgE = 27= 10
5. Combination Studies =12 = 9 NEW

131 new citations

Appendix B. Glossary

Following is a listing of terms commonly used in reports produced by the Drug Effectiveness Review Project *as they apply to these reports*. For that reason, some definitions may vary slightly from other published definitions.

Adherence: Following the course of treatment proscribed by a study protocol.

Adverse effect: An *adverse event* for which the causal relation between the drug/intervention and the event is at least a reasonable possibility.

Adverse event: An adverse outcome that occurs during or after the use of a drug or other intervention but is not necessarily caused by it.

Active-control trial: A trial comparing a drug in a particular class or group to another drug outside of that class or group.

Allocation concealment: The process by which the person determining randomization is blinded to a study participant's group allocation.

Before-after study: A type non-randomized study where data are collected before and after patients receive an intervention. Before-after studies can have a single arm or can include a control group.

Bias: A systematic error or deviation in results or inferences from the truth. Several types of bias can appear in published trials, including selection bias, performance bias, detection bias and reporting bias.

Blinding: The process of preventing those involved in a trial from knowing to which comparison group a particular participant belongs. Trials are frequently referred to as "double-blind" without further describing if this refers to patients, caregivers, investigators or other study staff.

Case series: A study reporting observations on a series of patients, all receiving the same intervention with no control group.

Case study: A study reporting observations on a single patient.

Case-control study: A study that compares people with a specific disease or outcome of interest (cases) to people from the same population without that disease or outcome (controls).

Clinically significant: A result that is large enough to affect a patient's disease state in a manner that is noticeable to a patient and/or caregiver.

Cohort study: An observational study in which a defined group of people (the cohort) is followed over time and compared to a group of people who were exposed or not exposed to a particular intervention or other factor of interest. A prospective cohort study assembles participants and follows them into the future. A retrospective cohort study identifies subjects from past records and follows them from the time of those records to the present.

Confidence interval: The range of values calculated from the data such that there is a level of confidence, or certainty, that it contains the true value. The 95% confidence interval is generally used in DERP reports.

Confounder: A factor that is associated with both an intervention and an outcome of interest.

Controlled clinical trial: A clinical trial that includes a control group but no or inadequate methods of randomization.

Convenience sample: A group of individuals being studied because they are conveniently accessible in some way. Convenience samples may or may not be representative of a population that would normally be receiving an intervention.

Cross-over trial: A type of clinical trial comparing two or more interventions in which the participants, upon completion of the course of one treatment, are switched to another.

Direct analysis: The practice of using data from head-to-head trials to draw conclusions about the comparative effectiveness of drugs within a class or group. Results of direct analysis are the preferred source of data in DERP reports.

Dose-response relationship: The relationship between the quantity of treatment given and its effect on outcome. In meta-analysis, dose-response relationships can be investigated using meta-regression.

Double-blind: The process of preventing those involved in a trial from knowing to which comparison group a particular participant belongs. While double-blind is a frequently used term in trials, its meaning can vary to include blinding of patients, caregivers, investigators and/or other study staff.

Double-dummy: The use of two placebos in a trial that match the active interventions when they vary in appearance or method of administrations (for example, an oral agent compared to an injectable agent).

Effectiveness: The extent to which a specific intervention, when used under ordinary circumstances, does what it is intended to do.

Effectiveness outcomes: Those outcomes that are generally important to patients and caregivers, such as quality of life, hospitalizations and ability to work. Data on

effectiveness outcomes usually comes from longer-term studies of a “real-world” population.

Efficacy: The extent to which an intervention produces a beneficial result under ideal conditions in a selected and controlled population.

Estimate of effect: The observed relationship between an intervention and an outcome. Estimate of effect can be expressed in a number of ways, including number needed to treat, odds ratio, risk difference and risk ratio.

Equivalence trial: A trial designed to determine whether the response to two or more treatments differs by an amount that is clinically unimportant. This is usually demonstrated by showing that the true treatment difference is likely to lie between a lower and an upper equivalence level of clinically acceptable differences.

External validity: The extent to which reported results are generalizable to a relevant population.

Fixed-effect model: A model that calculates a pooled effect estimate using the assumption that all observed variation between studies is caused by the play of chance. Studies are assumed to be measuring the same overall effect. An alternative model is the random-effects model.

Forest plot: A graphical representation of the individual results of each study included in a meta-analysis together with the combined meta-analysis result. The plot also allows readers to see the heterogeneity among the results of the studies. The results of individual studies are shown as squares centered on each study’s point estimate. A horizontal line runs through each square to show each study’s confidence interval - usually, but not always, a 95% confidence interval. The overall estimate from the meta-analysis and its confidence interval are shown at the bottom, represented as a diamond. The centre of the diamond represents the pooled point estimate, and its horizontal tips represent the confidence interval.

Funnel plot: A graphical display of some measure of study precision plotted against effect size that can be used to investigate whether there is a link between study size and treatment effect.

Generalizability: see *External Validity*

Hazard ratio: The increased risk with which one group is likely to experience an outcome of interest. It is similar to a risk ratio. For example, if the hazard ratio for death for a treatment is 0.5, then we can say that treated patients are likely to die at half the rate of untreated patients.

Head-to-head trial: A trial that directly compares one drug in a particular class or group to another in the same class or group.

Heterogeneity: The variation in, or diversity of, participants, interventions, and measurement of outcomes across a set of studies.

Indirect analysis: The practice of using data from trials comparing one drug in a particular class or group to another drug outside of that class or group or to placebo and attempting to draw conclusions about the comparative effectiveness of drugs within a class or group based on that data. For example, using direct comparisons between drugs A and B and between drugs B and C to make indirect comparisons between drugs A and C.

Intention to treat (ITT): The use of data from a randomized controlled trial in which data from all randomized patients are accounted for in the final results. Trials often report results as being based on ITT despite the fact that some patients are excluded from the analysis.

Internal validity: The extent to which the design and conduct of a study are likely to have prevented bias. Generally, the higher the internal validity, the better the quality of the study publication.

Inter-rater reliability: The degree of stability exhibited when a measurement is repeated under identical conditions by different raters.

Intermediate outcome: An outcome not of direct practical importance but believed to reflect outcomes that are important. For example, blood pressure is not directly important to patients but it is often used as an outcome in clinical trials because it is a risk factor for stroke and heart attacks.

Logistic regression: A form of regression analysis that models an individual's odds of disease or some other outcome as a function of a risk factor or intervention.

Mean difference: A method used to combine measures on continuous scales (such as weight), where the mean, standard deviation and sample size in each group are known.

Meta-analysis: The use of statistical techniques in a systematic review to integrate the results of included studies. Although they are sometimes used interchangeably, meta-analyses are not synonymous with systematic reviews. However, systematic reviews often include meta-analyses.

Meta-regression: A technique used to explore the relationship between study characteristics (e.g. concealment of allocation, baseline risk, timing of the intervention) and study results (the magnitude of effect observed in each study) in a systematic review.

Multivariate analysis: Measuring the impact of more than one variable at a time while analyzing a set of data.

N of 1 trial: A randomized trial in an individual to determine the optimum treatment for that individual.

Non-inferiority trial: A trial designed to determine whether the effect of a new treatment is not worse than a standard treatment by more than a pre-specified amount. A one-sided version of an equivalence trial.

Non-randomized study: Any study estimating the effectiveness of an intervention (harm or benefit) that does not use randomization to allocate patients to comparison groups. There are many possible types of non-randomized studies, including cohort studies, case-control studies, and before -after studies.

Null hypothesis: The statistical hypothesis that one variable (e.g. which treatment a study participant was allocated to receive) has no association with another variable or set of variables.

Number needed to treat (NNT): An estimate of how many people need to receive a treatment before one person would experience a beneficial outcome.

Observational study: A type of non-randomized study in which the investigators do not seek to intervene, and simply observe the course of events.

Odds ratio (OR): The ratio of the odds of an event in one group to the odds of an event in another group. An odds ratio of 1.0 indicates no difference between comparison groups. For undesirable outcomes an OR that is < 1.0 indicates that the intervention was effective in reducing the risk of that outcome.

One-tailed test : A hypothesis test in which the values for which we can reject the null hypothesis are located entirely in one tail of the probability distribution. For example, testing whether one treatment is better than another (rather than testing whether one treatment is either better or worse than another).

Open-label trial: A clinical trial in which the investigator and participant are aware which intervention is being used for which participant (i.e. not blinded). Random allocation may or may not be used in open-label trials.

Per protocol: The subset of participants from a randomized controlled trial who complied with the protocol sufficiently to ensure that their data would be likely to exhibit the effect of treatment. Per protocol analyses are sometimes misidentified in published trials as ITT.

Point estimate: The results (e.g. mean, weighted mean difference, odds ratio, risk ratio or risk difference) obtained in a sample (a study or a meta-analysis) which are used as the best estimate of what is true for the relevant population from which the sample is taken.

Pooling: The practice of combining data from several studies to draw conclusions regarding treatment effects.

Power: The probability that a trial will detect statistically significant differences among intervention effects. Studies with small sample sizes can frequently be underpowered to detect difference.

Precision: The likelihood of random errors in the results of a study, meta-analysis or measurement. The greater the precision, the less random error. Confidence intervals around the estimate of effect from each study are one way of expressing precision, with a narrower confidence interval meaning more precision.

Prospective study: A study in which people are identified according to current risk status or exposure, and followed forwards through time to observe outcome.

Publication bias: A bias caused by only a subset of all the relevant data being available. The publication of research can depend on the nature and direction of the study results. Studies in which an intervention is not found to be effective are sometimes not published. Because of this, systematic reviews that fail to include unpublished studies may overestimate the true effect of an intervention. In addition, a published report might present a biased set of results (e.g. only outcomes or sub-groups where a statistically significant difference was found).

P-value: The probability (ranging from zero to one) that the results observed in a study could have occurred by chance if in reality the null hypothesis was true. A *P* value of ≤ 0.05 is often used as a threshold to indicate statistical significance.

Random-effects model: A statistical model in which both within-study sampling error (variance) and between-studies variation are included in the assessment of the uncertainty (confidence interval) of the results of a meta-analysis. When there is heterogeneity among the results of the included studies beyond chance, random-effects models will give wider confidence intervals than fixed-effect models.

Randomization: The process by which study participants are allocated to treatment groups in a trial. Adequate (i.e. unbiased) methods of randomization include computer generated schedules and random numbers tables.

Randomized controlled trial (RCT): A trial in which two or more interventions are compared through random allocation of participants.

Regression analysis: A statistical modelling technique used to estimate or predict the influence of one or more independent variables on a dependent variable, e.g. the effect of age, sex, and confounding disease on the effectiveness of an intervention.

Relative risk (RR): The ratio of risks in two groups; same as a risk ratio.

Retrospective study: A study in which the outcomes have occurred prior to study entry.

Risk difference: The difference in size of risk between two groups.

Risk ratio (RR): The ratio of risks in two groups. In intervention studies, it is the ratio of the risk in the intervention group to the risk in the control group. A risk ratio of one indicates no difference between comparison groups. For undesirable outcomes, a risk ratio that is <1 indicates that the intervention was effective in reducing the risk of that outcome.

Sensitivity analysis: An analysis used to determine how sensitive the results of a study or systematic review are to changes in how it was done. Sensitivity analyses are used to assess how robust the results are to uncertain decisions or assumptions about the data and the methods that were used.

Standard deviation (SD): A measure of the spread or dispersion of a set of observations, calculated as the average difference from the mean value in the sample.

Standard error (SE): A measure of the variation in the sample statistic over all possible samples of the same size. The standard error decreases as the sample size increases.

Statistically significant (SS): A result that is unlikely to have happened by chance.

Subgroup analysis: An analysis in which an intervention is evaluated in a defined subset of the participants in a trial, such as by sex or in age categories.

Superiority trial: A trial designed to test if one intervention is superior to another.

Systematic review: A review of a clearly formulated question that uses systematic and explicit methods to identify, select, and critically appraise relevant research, and to collect and analyze data from the studies that are included in the review.

Tolerability: Unpleasant adverse effects of drugs that are usually transient and not clinically significant, although they can affect a person's quality of life and willingness to continue a treatment.

Type I error: A conclusion that there is evidence that a treatment works, when it actually does not work (false-positive).

Type II error: A conclusion that there is no evidence that a treatment works, when it actually does work (false-negative).

Validity: The degree to which a result (of a measurement or study) is likely to be true and free of bias (systematic errors).

Appendix C. Quality assessment methods for drug class reviews for the Drug Effectiveness Review Project

Study quality is objectively assessed using predetermined criteria for internal validity, based on the combination of the US Preventive Services Task Force and the NNS Center for Reviews and Dissemination criteria.

Regardless of design, all studies that are included are assessed for quality and assigned a rating of “good,” “fair,” or “poor.” Studies with fatal flaws are rated poor quality. A fatal flaw is failure to meet combinations of criteria which may be related in indicating the presence of bias. An example would be inadequate procedure for randomization or allocation concealment combined with important differences in prognostic factors at baseline. Studies that meet all criteria are rated good quality, and the remainder is rated fair quality. As the fair-quality category is broad, studies with this rating vary in their strengths and weaknesses: The results of some fair-quality studies are likely to be valid, while others are only probably valid. A poor-quality trial is not valid; the results are at least as likely to reflect flaws in the study design as a true difference between the compared drugs.

Systematic Reviews

1. Does the review report a clear review question and inclusion/exclusion criteria that relate to the primary studies? A good-quality review should focus on a well-defined question or set of questions, which ideally are reflected in the inclusion/exclusion criteria, which guide the decision of whether to include or exclude specific primary studies. The criteria should relate to the four components of study design, indications (patient populations), interventions (drugs), and outcomes of interest. In addition, details should be reported relating to the process of decision-making, such as how many reviewers were involved, whether the studies were examined independently, and how disagreements between reviewers were resolved.

2. Is there evidence of a substantial effort to search for all relevant research? If details of electronic database searches and other identification strategies are given, the answer to this question usually is yes. Ideally, details of the search terms, date, and language restrictions should be presented. In addition, descriptions of hand searching, attempts to identify unpublished material, and any contact with authors, industry, and research institutes should be provided. The appropriateness of the database(s) searched by the authors should also be considered. For example, if only MEDLINE was searched for a review looking at health education, then it is unlikely that all relevant studies were located.

3. Is the validity of included studies adequately assessed? A systematic assessment of the quality of primary studies should include an explanation of the criteria used (for example, how randomization was done, whether outcome assessment was blinded, whether analysis was on an intention-to-treat basis). Authors may use a published checklist or scale or one that they have designed specifically for

their review. Again, the process relating to the assessment should be explained (how many reviewers were involved, whether the assessment was independent, and how discrepancies between reviewers were resolved).

4. Is sufficient detail of the individual studies presented?

The review should demonstrate that the studies included are suitable to answer the question posed and that a judgment on the appropriateness of the authors' conclusions can be made. If a paper includes a table giving information on the design and results of the individual studies, or includes a narrative description of the studies within the text, this criterion is usually fulfilled. If relevant, the tables or text should include information on study design, sample size in each study group, patient characteristics, description of interventions, settings, outcome measures, follow-up, drop-out rate (withdrawals), effectiveness results, and adverse events.

5. Are the primary studies summarized appropriately?

The authors should attempt to synthesize the results from individual studies. In all cases, there should be a narrative summary of results, which may or may not be accompanied by a quantitative summary (meta-analysis).

For reviews that use a meta-analysis, heterogeneity between studies should be assessed using statistical techniques. If heterogeneity is present, the possible reasons (including chance) should be investigated. In addition, the individual evaluations should be weighted in some way (for example, according to sample size or inverse of the variance) so that studies that are considered to provide the most reliable data have greater impact on the summary statistic.

Controlled Trials

Assessment of Internal Validity

1. Was the assignment to the treatment groups really random?

Adequate approaches to sequence generation:

Computer-generated random numbers

Random numbers tables

Inferior approaches to sequence generation:

Use of alternation, case record numbers, birth dates or week days

Not reported

2. Was the treatment allocation concealed?

Adequate approaches to concealment of randomization:

Centralized or pharmacy-controlled randomization

Serially-numbered identical containers

On-site computer based system with a randomization sequence that is not readable until allocation

Inferior approaches to concealment of randomization:

Use of alternation, case record numbers, birth dates or week days

Open random numbers lists

Serially numbered envelopes (even sealed opaque envelopes can be subject to manipulation)

Not reported

3. Were the groups similar at baseline in terms of prognostic factors?
4. Were the eligibility criteria specified?
5. Were outcome assessors blinded to the treatment allocation?
6. Was the care provider blinded?
7. Was the patient kept unaware of the treatment received?
8. Did the article include an intention-to-treat analysis, or provide the data needed to calculate it (i.e., number assigned to each group, number of subjects who finished in each group, and their results)?
9. Did the study maintain comparable groups?
10. Did the article report attrition, crossovers, adherence, and contamination?
11. Is there important differential loss to follow-up or overall high loss to follow-up? (giving numbers for each group)?

Assessment of External Validity (Generalizability)

1. How similar is the population to the population to whom the intervention would be applied?
2. How many patients were recruited?
3. What were the exclusion criteria for recruitment? (Give numbers excluded at each step).
4. What was the funding source and role of funder in the study?
5. Did the control group receive the standard of care?
6. What was the length of follow-up? (Give numbers at each stage of attrition.)

Non-randomized Studies

Assessment of internal validity

1. Was the selection of patients for inclusion non-biased? In other words, was any group of patients systematically excluded?
2. Is there important differential loss to follow-up or overall high loss to follow-up? (Give numbers in each group.)
3. Were the events investigated specified and defined?
4. Was there a clear description of the techniques used to identify the events?
5. Was there non-biased and accurate ascertainment of events (independent ascertainers and validation of ascertainment technique)?
6. Were potential confounding variables and risk factors identified and examined using acceptable statistical techniques?
7. Did the duration of follow-up correlate with reasonable timing for investigated events? (Does it meet the stated threshold?)

Assessment of External Validity

1. Was the description of the population adequate?
2. How similar is the population to the population to whom the intervention would be applied?
3. How many patients were recruited?
4. What were the exclusion criteria for recruitment? (Give numbers excluded at each step.)
5. What was the funding source and role of funder in the study?

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Appendix D. Characteristics of excluded studies for poor quality

The full-text of the following studies were considered for analysis, but were deemed to have fatal flaws in internal validity.

Study	Design	Sample size	Intervention	Reason for exclusion
Abuekteish et al. 1995 ²³²	Observational	140	BUD vs. BDP	No comparison group, cross-sectional analysis of 140 asthmatics with ICS treatment over 5 years.; no description of analysis; no adjustment for duration and dose of ICS;
Acun et al. 2005 ²³³	RCT	100	BUD vs. FP	Insufficient reporting to allow for appraisal of methods and analysis; Results not reported.
Agertoft et al. 1994 ²³⁴	Observational	278	BUD vs. control	Attrition NR, but high in other corresponding publication; high potential selection bias
Agertoft et al. 2000 ²³⁵	Observational	338	BUD vs. control	High attrition and differential attrition; high potential for selection bias (mainly due to attrition); 97/270 in the BUD group had not yet attained adult height and were thus not analyzed.
Allen et al. 1994 ²³⁶	Meta-analysis	810	BUD	Lack of an appropriately described comprehensive, systematic literature search...
Anthracopoulos et al. 2007 ²³⁷	Observational	641	BUD vs. FP	High potential for selection bias and confounding, very high attrition (low participation rate), unclear how patients were identified/selected/recruited, unclear if appropriate dosage comparison, open-label, unclear which confounders were adjusted for in the analyses (and no mention of parental height), analysis excluded children that required more than 36 months of ICS and those that entered puberty.
Aubier et al. 1999 ²³⁸	RCT	503	FP/SM vs. FP + SM vs. FP	Poor reporting of methods and results of meaningful outcome
Bakhireva et al. 2007 ²²⁴	Observational	96	LTRAs vs. SABAs and control	Small sample size (inadequate to detect differences in adverse events of interest).
Barnes et al. 2007 ²³⁹	RCT	75	MOM vs. BUD	Baseline differences, lack of reporting of randomization, blinding, equal assessment of both groups,
Bleecker et al. 2006 ²²⁸	Pooled analysis	183	FP/SM	Potential selection bias (from two different RCTs, just 183 (43%) of subjects had available genotype information; not clear how these were chosen; potential confounding, analyses don't adjust for baseline SABA use or

Study	Design	Sample size	Intervention	Reason for exclusion
				symptom scores which were slightly worse in the B16 Gly/Gly group; sample size--studies not powered to detect differences among genotypes
Davis et al. ²⁴⁰	Meta-analysis	NR	Omalizumab	Methods not reported
Ferguson et al. 2007 ²⁴¹	RCT		BUD vs. FP	Attrition high (> 40%), potential selection bias, less than 60% of subjects completed the 1 year study; did not account for greater # of steroid courses in BUD group (15 vs. 6); post-randomization exclusions
Kallen et al. ²⁴²	Observational	2014	Bud	Poor measurement and uncontrolled confounders
Karaman et al. 2007 ²⁴³	RCT	67	BUD vs. BUD+MOM vs. BUD+FM	High attrition, masking not reported at any level, type or withdrawal/exclusion not reported and dropout rate significant, no ITT analysis, no explanation of why many randomized subjects not included in the analyses, no mention of statistical power
Lipworth et al. 1999 ²⁴⁴	Meta-analysis	NR	ICS	Search terms not specified; meta-analysis methods not adequately reported; not independently reviewed; no report of publication bias, heterogeneity, or clear eligibility criteria; unclear how meta-analysis was carried out other than multiple regression.
Nong et al. 2001 ²⁴⁵	RCT	77	BDP vs. FP	High potential for bias; Completer's analysis; 22% post-randomization exclusions; incomplete inclusion/exclusion criteria; not sure it was actually randomized;
Ohaju-Obodo et al. 2005 ²⁴⁶	RCT	109	BUD vs. BDP	High potential for selection and measurement bias; no blinding, analysis not described, unable to determine attrition, did not report randomization/allocation concealment methods
Palmer et al. 2006 ²³⁰	Observational	546	SM	No baseline data given for comparison of groups so unable to adequately assess potential for selection bias
Pauwels et al. 1998 ²⁴⁷	RCT	340	FP vs. BDP	Poor reporting, confounding
Peng et al. 2004 ²⁴⁸	RCT	49	BUD vs. BUD+ZAF	High potential for selection bias and measurement bias
Riccioni et al. 2002 ²⁴⁹	RCT	45	BUD vs. MOM	Open-label, no ITT analysis, no reporting of majority of criteria for critical appraisal
Scott et al. 1999 ²⁵⁰	Pooled data	670	BUD	Pooled data analysis without a systematic literature search
Wardlaw et al. 2004 ²⁵¹	RCT	167	MOM vs. FP	No blinding, randomisation method nr, no withdrawal information reported

Study	Design	Sample size	Intervention	Reason for exclusion
Weiss et al. 2005 ²⁵²	RCT	945	BUD vs. TRA	High potential for selection and measurement bias; all groups unblinded, not ITT analysis, ICS dosing was left to the discretion of the physician (starting dose and subsequent adjustments) making us unable to determine if the comparison is appropriate (nothing reported on actual dosing received).
Yurdakul et al. 2002 ²⁵³	RCT	64	BUD+FM vs. BUD+ZAF	Not truly randomized---thus not really an RCT, allocation, blinding, etc. Nothing about withdrawals. Unable to determine if ITT analysis or what was done.

Appendix E. Placebo-controlled trials (not included)

1. Clinical trial of low-dose theophylline and montelukast in patients with poorly controlled asthma. *Am J Respir Crit Care Med* 2007;175(3):235-42.
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Appendix F. Summary table of adverse events and tolerability from head-to-head RCTs comparing ICSs

Study	Study design N Duration	Country Population Setting	Comparison (total daily dose in mcg)	Equivalent dosing	Results	Quality rating
<i>Beclomethasone compared with budesonide</i>						
Molimard et al. 2005 ²²	RCT, open-label 460 12 weeks	France Age 18-60, moderate to severe persistent, not controlled on ICS, smoking status NR Multicenter, subspecialty clinics	BDP MDI (800) vs. BUD DPI (1600) vs. FP DPI (1000)	Yes (all high)	Overall AEs(%): 38 vs 35 vs 37, <i>P</i> = 0.791 between all Withdrawals due to AEs (#): 1 vs 1 vs 2 Dysphonia (%): 13 vs 16 vs 20 Respiratory infection (%): 19 vs 14 vs 16 Central and peripheral nervous system disorders (%): 18 vs 19 vs 20	<i>Fair</i>
Tattersfield et al. 2001 ¹⁹⁵	RCT, open-label 377 24 months	Multinational (France, New Zealand, Spain, UK) Age 20-60, mild, no ICS for previous 3 months Multicenter (19)	BUD DPI (adjustable dosing; range 133-1729) vs. BDP MDI with spacer (176-1906) vs. non-steriod treatment "placebo"	Yes (range low to high for both)	Overall AEs(%): NR Withdrawals due to AEs (%): 4.6 vs 2.7 vs 6.4 Oral candidiasis- thrush (%): 3 vs 2 vs 0 Dysphonia (%): 2 vs 1 vs 1 Upper respiratory tract infection (%): 20 vs 23 vs 12 Back pain (%): 7 vs 8 vs 2 Fractures (%): 1.1 vs 0 vs 0 Reduction in bone mineral density (%): did not differ among treatment groups over the 2 years No difference in BMD/fractures between BDP, BUD, and placebo over 2 years	<i>Fair</i>
Worth et al. 2001 ²³	RCT, open-label 209 8 weeks	Germany, France, Netherlands Age 18-75, moderate to severe, on ICS, smoking status NR Multicenter	BDP MDI (800) vs. BUD DPI (1600)	Yes (high)	Overall AEs (%): 24.3 vs. 26.5 Withdrawals due to AEs(%): 3 vs. 5 Dysphonia (%): 5.4 vs. 4.08 fungal infection (%): 2.7 vs. 4.08	<i>Fair</i>

Study	Study design N Duration	Country Population Setting (39)	Comparison (total daily dose in mcg)	Equivalent dosing	Results	Quality rating
<i>Beclomethasone compared with flunisolide</i>						
No systematic reviews or head-to-head trials found						
<i>Beclomethasone compared with fluticasone</i>						
Barnes et al. 1993 ²⁴	RCT, DB 154 6 weeks	Multinational (7 countries worldwide) Age ≥ 18, severe, 20% smokers Multicenter (18 outpatient clinics)	FP MDI (1000) vs. BDP MDI (2000)	Yes (high)	Overall AEs: 52% vs. 51%, $P > 0.15$ Withdrawals due to AEs(%): 2.4% vs. 4.2% Oral candidiasis- thrush (%): 6% vs. 4% Cough (%): 2% vs. 3% Sore throat (%): 5% vs. 6% Headache (%): 4% vs. 1% Upper respiratory tract infection (%): 6% vs. 3% Rhinitis (%): 7% vs. 3% Additional adverse events and comments: no significant differences ($P > 0.15$) between treatments in the incidence or nature of AEs	Fair
Boe et al. 1994 ²⁵	RCT, DB 134 12 weeks	Norway Age ≥ 18, poorly controlled, 34% smokers Multicenter	FP DPI (1600) vs. BDP DPI (2000)	Yes (high)	Overall AEs: NR Withdrawals due to AEs (%): 8 vs. 2 Oral candidiasis- thrush (%): 31 vs. 30 Sore throat (%): 28 vs. 14 Upper respiratory tract infection (%): 27 vs. 38 Respiratory infection (%): 14 vs. 10 Hoarseness (%): 14 vs. 5 GI disorders(%): 13 vs. 19 Musculoskeletal disorders(%): 13 vs. 25	Fair
de Benedictis	RCT, DB	Multinational (7 countries:	FP DPI (400) vs.	Yes (medium)	Overall AEs(%): 80 vs. 80.9	Fair

Study	Study design N Duration	Country Population Setting	Comparison (total daily dose in mcg)	Equivalent dosing	Results	Quality rating
et al. 2001 ²⁶	343 52 weeks	Holland, Hungary, Italy, Poland, Argentina, Chile, South Africa) Age 4-11, prepubertal, severity and smoking status NR Multicenter (32)	BDP DPI (400)		Withdrawals due to AEs: NR Growth: Adjusted mean growth velocity greater in FP treated subjects (4.76 cm/year (0.28)) than BDP treated subjects (4.06 cm/year (0.29) (Difference 0.70 (95% CI: 0.13, 1.26 cm, $P < 0.02$)) Cough (%): 5.3 vs. 8.1 Upper respiratory tract infection (%): 13.5 vs. 14.5 Rhinitis (%): 25.3 vs. 11.6 Bronchitis (%): 14.1 vs. 11.6 Ear, nose, and throat infection (%): 14.1 vs. 9.2 Pharyngitis/throat infection(%): 12.4 vs. 14.5 Viral infection(%): 11.8 vs. 7.5 Viral respiratory infection(%): 9.4 vs. 10.4	
Fabrizi et al. 1993 ²⁷	RCT, DB 274 12 months (daily symptom outcomes collected for initial 12 weeks)	Multinational (10 European) Age 12-80, moderate to severe, not controlled on ICS, 11% smokers Multicentre (25)	FP MDI (1500) vs. BDP MDI (1500)	Yes (high)	Overall AEs(%): 70% vs. 73% of pts Withdrawals due to AEs (%): 8 vs. 8 Deaths (#): 2 deaths, not asthma related vs. 1 death, not asthma related Oral candidiasis- thrush (%): 4 vs. 7 Sore throat (%): 5 vs. 2 Headache (%): 4 vs. 5 Upper respiratory tract infection (%): 6 vs. 5 Respiratory infection (%): 15 vs. 11 Hoarseness (%): 6 vs. 3 influenza (%):	<i>Fair</i>

Study	Study design N Duration	Country Population Setting	Comparison (total daily dose in mcg)	Equivalent dosing	Results	Quality rating
Fairfax et al. 2001 ²⁸	RCT, DB, DD 172 6 weeks	UK and Ireland Age 18-65, mild to severe, symptomatic on ICS, 24% current smokers Multicenter (30 general practice sites)	BDP MDI (extrafine HFA, 400) vs. FP MDI (CFC, 400)	Yes (medium)	4 vs. 5 Overall AEs(%): 41 vs. 37 Withdrawals due to AEs: NR Deaths: 0 vs. 0	Fair
Lorentzen et al. 1996 ³⁰	RCT, DB 213 12 months	Multinational (7, Europe) Age 18-77, severe, well controlled on high dose ICS, 19% smokers Multicenter (20 outpatient clinics)	FP MDI (1000) vs. BDP MDI (2000)	Yes (high)	Overall AEs(%): 72 vs. 72 Withdrawals due to AEs (%): 13 vs. 9 Oral candidiasis- thrush (%): 4 vs. 4 Cough (%): 7 vs. 2 Sore throat (%): 4 vs. 7 Headache (%): < 1 vs. 7, <i>P</i> = 0.03 Respiratory infection (%): 6 vs. 9 Rhinitis (%): 10 vs. 1 Hoarseness (%): 6 vs. 7 influenza (%): 5 vs. 13	Fair
Lundback et al. 1993 ³¹	RCT, DB 585 6 weeks (N = 48989 continued an additional 46 weeks)	Multinational (10) Age 15-90, moderate, not controlled on ICS, smoking status NR Multicenter (47)	FP MDI (500) vs. FP DPI (500) vs. BDP MDI (1000)	No, only for FP MDI vs. BDP MDI (high); FP DPI 500 is medium	Overall AEs: NR Withdrawals due to AEs (%): 3.6 vs 4.0 vs 2.6 Oral candidiasis- thrush (%): 2 vs 2 vs 4 Sore throat (%): 5 vs 2 vs 1 Headache (%): 5 vs 7 vs 7 Upper respiratory tract infection (%): 6 vs 9 vs 7 Rhinitis (%): 2 vs 5 vs 2	Fair

Study	Study design N Duration	Country Population Setting	Comparison (total daily dose in mcg)	Equivalent dosing	Results	Quality rating
Malo et al. 1999 ¹⁹³	RCT, DB, crossover 69 16 weeks	Canada Age ≥18, severity NR, excluded current or former smokers multicenter	FP MDI (400- 1000) vs. BDP MDI (800- 2000)	No (medium – high vs. medium - really high)	Hoarseness (%): 2 vs 2 vs < 1 Overall AEs: NR Withdrawals due to AEs: NR Skin bruising: was not significantly different in terms of the number of subjects affected; its severity and frequency, as well as the number of bruises on direct examination were significantly greater in subjects taking BDP (mean 1.64 lesions on BDP and 1.24 lesions on FP)	<i>Fair</i>
Medici et al. 2000 ¹⁹⁴	RCT, DB 69 12 months	Switzerland Age 20-55, mild to moderate, on ICS for 6 months, 5-23% current smokers Multicenter (7 outpatient sites)	FP MDI (400) vs. FP MDI (750) vs. BDP MDI (800) vs. BDP MDI (1500)	Yes (medium vs high vs medium vs high)	Overall AEs: NR Adverse events caused withdrawal (%): 0 vs 0 vs 0 vs 7.7 Hoarseness/dysphonia (#): 1 vs 1 vs 1 vs 0 Oral candidiasis: 0 for all Allergic skin reactions: 0 for all Rash/skin eruptions: 0 for all Reduction in bone mineral density (%): No difference in BMD between BDP- and FP-treated patients over 1 year	<i>Fair</i>
Molimard, M et al. 2005 ²²	RCT, open- label 460 12 weeks	France Age 18-60, moderate to severe persistent, not controlled on ICS, smoking status NR Multicenter, subspecialty clinics (69 pulmonologists)	BDP MDI (800) vs. BUD DPI (1600) vs. FP DPI (1000)	Yes (all high)	Overall AEs(%): 38 vs 35 vs 37, <i>P</i> = 0.791 between all Withdrawals due to AEs (#): 1 vs 1 vs 2 Dysphonia (%): 13 vs 16 vs 20 Respiratory infection (%): 19 vs 14 vs 16 Central and peripheral nervous system disorders (%): 18 vs 19 vs 20	<i>Fair</i>
Raphael et al. 1999 ³²	RCT, DB, DD 399 12 weeks	US Age ≥ 12 years, mild to severe, not controlled on ICS, smokers excluded	FP MDI (164) vs FP MDI (440) vs BDP MDI (336) vs BDP MDI	Yes (low, medium, low, medium)	FP all vs. BDP all reported for those with two percentages Overall AEs (%): 9 vs. 15, <i>P</i> = 0.664 Withdrawals due to AEs (%): 3 vs 3 vs 4 vs 2	<i>Fair</i>

Study	Study design N Duration	Country Population Setting	Comparison (total daily dose in mcg) (672)	Equivalent dosing	Results	Quality rating
		Multicenter, specialty asthma and primary care centers (23)			Oral candidiasis- thrush (%): 1 vs. 4, <i>P</i> = 0.472 Dysphonia (%): 3 vs. 7, <i>P</i> = 0.577 Sore throat (%): 1 vs. 3, <i>P</i> = 0.797 Headache (%): 1 vs. 3, <i>P</i> = 0.721	
Beclomethasone compared with mometasone						
Bernstein et al. 1999 ³³	RCT, DB, DD 365 12 weeks	US Age ≥12, mild to moderate, on ICS, smokers excluded Multicenter (20)	Mometasone DPI (200) vs Mometasone DPI (400) vs Mometasone DPI (800) vs BDP MDI (336) vs placebo	No; only for MOM 400 vs. BDP 336 (both medium)	Overall AEs(%): 18 vs 26 vs 28 vs 21 vs 22 Withdrawals due to AEs (%): 5 vs 3 vs 4 vs 8 vs 11 Oral candidiasis- thrush (%): 4 vs 6 vs 15 vs 3 vs 1 Dysphonia (%): 1 vs 1 vs 3 vs 1 vs 1 Cough (%): 1 vs 0 vs 0 vs 0 vs 3 Headache (%): 3 vs 4 vs 4 vs 4 vs 5	<i>Fair</i>
Nathan et al. 2001 ³⁴	RCT, DB, DD 227 12 weeks	US Age ≥12, moderate, on ICS, smokers excluded Multicenter (15)	Placebo vs Mometasone DPI (200) vs Mometasone DPI (400) vs BDP MDI (336)	No; only for MF 200 vs. BDP (both low), MF 400 is medium	Overall AEs: NR Withdrawals due to AEs(%): 8.8 vs 1.8 vs 3.6 vs 1.8 Oral candidiasis- thrush (%): 0 vs 4 vs 11 vs 5 Dysphonia (%): 0 vs 4 vs 4 vs 2 Headache (%): 2 vs 5 vs 2 vs 4 Hoarseness (%): 2 vs 7 vs 2 vs 0	<i>Fair</i>
Beclomethasone compared with triamcinolone						
Berkowitz et al. 1998 ³⁵	RCT, DB, DD 339 8weeks	US Age 18-65, mild to moderate, on ICS, smokers excluded	BDP MDI (336) vs TAA MDI (800) vs placebo	Yes (medium)	Overall AEs(%): 50 vs 57.4 vs 55.5 Withdrawals due to AEs (%): 9.8 vs 8.3 vs 16.3 Oral candidiasis/thrush (%): 1.8 vs 0 vs 0	<i>Fair</i>

Study	Study design N Duration	Country Population Setting	Comparison (total daily dose in mcg)	Equivalent dosing	Results	Quality rating
		Multicenter (17), asthma/allergy centers			Dysphonia (%): 1.8 vs 1.9 vs 0 Cough (%): 3.6 vs 2.8 vs 2.7 Dry throat (%): 0 vs 0.9 vs 0 Death (%): 0 vs 0 vs 0 Pharyngitis (%): 2.7 vs 0.9 vs 2.7	
Bronsky et al. 1998 ³⁶	RCT, DB, DD 329 8 weeks	US Age 18-65, mild to severe, on ICS, smokers excluded Multicenter	BDP MDI (336) vs TAA MDI (800) vs placebo	Yes (medium)	Overall AEs(%): 48.2 vs 50.9 vs 59.8, <i>P</i> = 0.786 BDP vs. TAA Withdrawals due to AEs(%): 2.7 vs 8.4 vs 17.9 Oral candidiasis- thrush (%): 0.0 vs 0.9 vs 0.0 Dysphonia (%): 0.9 vs 1.9 vs 0.0 Cough: 0.9 vs 0.9 vs 1.8 Upper respiratory tract infection (%): 2.7 vs 10.4 vs NR, <i>P</i> = 0.027 Death (%): 0.0 vs 0.0 vs 0.0	Fair
Budesonide compared with flunisolide						
Newhouse et al. 2000 ³⁷	RCT 179 6 weeks	Canada Age 18-75, moderate, on ICS, 5% current smokers Multicenter (17)	Flunisolide MDI + AeroChamber (1500) vs. BUD DPI (1200)	Yes (medium)	Overall AEs(%): 48 vs. 54.4 Withdrawals due to AEs: NR Headache (%): 6.7 vs. 3.8 flu syndrome (%): 4.0 vs. 6.3 Paresthesia (%): 2.7 vs. 0.0 Migraine (%): 2.7 vs. 0.0 Emesis (%): 2.7 vs. 0.0 Insomnia (%): 1.3 vs. 2.5 Back pain (%): 1.3 vs. 2.5	Fair
Budesonide compared with fluticasone						
Ayres et al. 1995 ³⁸	RCT, DB, DD 671 6 weeks	Multinational (13 countries worldwide) Age 18-70, severe, on ICS, smokers	FP MDI (1000) vs FP MDI (2000) vs BUD MDI	No (high vs high vs medium)	Overall AEs: NR Withdrawals due to AEs: NR Overall adverse events (%): 61 vs 49 vs 51	Fair

Study	Study design N Duration	Country Population Setting	Comparison (total daily dose in mcg)	Equivalent dosing	Results	Quality rating
		excluded Multicenter (66)	(1600)		Oral candidiasis- thrush (%): 3 vs 4 vs 5 Cough (%): 3 vs 6 vs 5 Sore throat (%): 4 vs 4 vs 2 Headache (%): 5 vs 7 vs 6 Upper respiratory tract infection (%): 11 vs 10 vs 6 Respiratory infection (%): 4 vs 1 vs 2 Rhinitis (%): 4 vs 1 vs 3 Hoarseness (%): 6 vs 3 vs 3	
Ferguson et al. 1999 ³⁹	RCT, DB, DD 333 20 weeks	Multinational (6 countries worldwide) Ages 4-12, moderate to severe, on ICS, smoking status NR Multicenter	FP DPI (400) vs. BUD DPI (800)	Yes (medium)	Overall AEs(%): NR Withdrawals due to AEs(%): NR Oral candidiasis- thrush (%): 0 vs. 0 Upper respiratory tract infection (%): 28 vs. 32 Growth: linear growth velocity was statistically greater for FP compared to BUD (adjusted mean increase in height: 2.51 cm vs. 1.89; difference was 6.2 mm (95% CI: 2.9-9.6, <i>P</i> = .0003)	<i>Fair</i>
Heinig et al. 1999 ⁴⁰	RCT, DB, DD 395 24 weeks	Multinational (Belgium, Canada, Denmark, Netherlands) Age 18-75, severe, not controlled on ICS, 15% current smokers Multicenter (47)	FP DPI (2000) vs. BUD DPI (2000)	No (both are high doses, but relative potency of fluticasone is greater at the given doses)	Overall AEs(%): 78 vs. 77 Withdrawals due to AEs: NR	<i>Fair</i>
Hoekx et al. 1996 ⁴¹	RCT, DB, DD 229 8 weeks	Multinational (4: Netherlands, Sweden, Denmark, Finland)	FP DPI (400) vs. BUD DPI (400)	No (medium vs. low)	Overall AEs(%): 63 vs. 69 Withdrawals due to AEs (%): 2 (1.7%) vs. 3 (2.7%) Oral candidiasis- thrush (%): 3 vs. < 1	<i>Fair</i>

Study	Study design N Duration	Country Population Setting	Comparison (total daily dose in mcg)	Equivalent dosing	Results	Quality rating
		Children up to 13, mild to moderate, on ICS, smoking status NR Multicenter (22)			Cough (%): 6 vs. 4 Sore throat (%): 4 vs. 5 Headache (%): 3 vs. 7 Upper respiratory tract infection (%): 12 vs. 15 Rhinitis (%): 11 vs. 12 Hoarseness (%): 0 vs. 4 allergic skin reaction (%): < 1 vs. 5	
Kannisto et al. 2000 ¹⁹²	RCT 75 6 months for lab outcomes, 12 months for growth outcome	Finland Age 5-15, severity NR, new onset of asthma tertiary center, University clinic	BUD DPI (800 for 2 months, then 400) vs. FP DPI (500 for 2 months, then 200) vs. Cromone (non-ICS control)	Yes Steroid dosing range: medium, low vs. medium, low	Overall AEs: NR Withdrawals due to AEs (%): NR Growth: Greater growth velocity in FP than in BUD group [FP treated children had less growth reduction than BUD treated children (height SD score: 0.03 vs. 0.23; $P < 0.05$)	Fair
Molimard et al. 2005 ²²	RCT, open-label 460 12 weeks	France Age 18-60, moderate to severe persistent, not controlled on ICS, smoking status NR Multicenter, subspecialty clinics (69 pulmonologists)	BDP MDI (800) vs BUD DPI (1600) vs FP DPI (1000)	Yes (all high)	Overall AEs(%): 38 vs 35 vs 37, $P = 0.791$ between all Withdrawals due to AEs (#): 1 vs 1 vs 2 Dysphonia (%): 13 vs 16 vs 20 Respiratory infection (%): 19 vs 14 vs 16 Central and peripheral nervous system disorders (%): 18 vs 19 vs 20	Fair
Ringdal et al. 1996 ⁴²	RCT, DB, DD 518 12 weeks	Multinational Age 18-75, moderate to severe, not controlled on ICS, 19%	FP DPI (800) vs. BUD DPI (1600)	Yes (high)	Overall AEs(%): 61.7 vs. 61.5 Withdrawals due to AEs (%): 3.9 vs. 5.0 Sore throat (%): 5.9 vs. 4.2	Fair

Study	Study design N Duration	Country Population Setting	Comparison (total daily dose in mcg)	Equivalent dosing	Results	Quality rating
		smokers Multicenter			Upper respiratory tract infection (%): 21.5 vs. 24.9 Rhinitis (%): 11.3 vs. 8.0	
Budesonide compared with mometasone						
Bousquet et al. 2000 ⁴³	RCT, single- blind 730 12 weeks	Multinational (17) Age ≥ 12, moderate, on ICS, smokers excluded Multicenter (57)	Mometasone DPI (200) vs Mometasone DPI (400) vs Mometasone DPI (800) vs Budesonide DPI (800)	No (only for MF 400 vs. BUD, both medium)	Overall AEs: NR Withdrawals due to AEs (%): 3 vs < 1 vs 2 vs 4 vs 2 Dysphonia (%): 4.3 vs 2.8 vs 4.8 vs 2.2 The most common treatment- related adverse events were headache (4-8%), pharyngitis (4- 5%), and dysphonia (2-5%). Oral candidiasis was uncommon in this study, reported by only 16 patients overall, and had a similar incidence among the treatment groups (N = 4, 6, 4, and 3)	Fair
Corren et al. 2003 ⁴⁴	RCT, DB, DD 262 8 weeks	US Age ≥12, moderate, on ICS, smokers excluded Multicenter (17)	Mometasone DPI (400) vs BUD DPI (320) vs placebo	No (medium vs. low)	Overall AEs(%): 8 vs 9 vs 8 Withdrawals due to AEs: NR Most frequently reported treatment-related AEs were headache and pharyngitis (both 4% or less: data by treatment arm NR). There was only one report of oral candidiasis in one MF-treated patient.	Fair
Budesonide compared with triamcinolone						
Weiss et al. 2004 ⁴⁵	RCT 945 52 weeks	US Age ≥18, mild to severe, smoking status NR Multicenter, patients from 25 managed care plans	BUD DPI (mean dose at start and end: 941.9 and 956.8 mcg/d) vs. TAA pMDI (1028.2/1042 .9 mcg/d)	Yes, on average both are medium	Overall AEs (%): 85 vs. 86 Withdrawals due to AEs (%): 3.0 vs. 2.5 The most frequently reported AEs were respiratory tract infection, sinusitis, bronchitis, and accident/injury.	Fair
Flunisolide compared with fluticasone						

Study	Study design N Duration	Country Population Setting	Comparison (total daily dose in mcg)	Equivalent dosing	Results	Quality rating
No systematic reviews or head-to-head trials found for KQ2						
Flunisolide compared with mometasone						
No systematic reviews or head-to-head trials found						
Flunisolide compared with triamcinolone						
No systematic reviews or head-to-head trials found						
Fluticasone compared with mometasone						
O'Connor et al. 2001 ⁴⁷	RCT, DB 733 12 weeks	Multi-national (20) Age ≥12, moderate, on ICS, excluded smokers Multicenter, University hospitals	MF DPI (200) vs MF DPI (400) vs MF DPI (800) vs FP DPI (500)	No (only for medium doses of each: MF 400 vs. FP 500)	Overall AEs (%): 20 vs 26 vs 30 vs 29 Withdrawals due to AEs (%): 5 vs 3 vs 5 vs 4 Oral candidiasis- thrush (%): 1 vs 7 vs 10 vs 10	<i>Fair</i>
Fluticasone compared with triamcinolone						
Baraniuk et al. 1999 ⁴⁸	RCT, DB, triple- dummy 680 12 weeks	US Age ≥12, not controlled on ICS, excluded smokers Multicenter, Pulmonary/alle rgy medicine clinics (50)	FP MDI (196) + Salmeterol (84) vs FP MDI (440) vs TAA MDI (1200)	Yes (medium for both ICS- only arms)	Overall AEs(%): Drug-related: 14 vs 13 vs 8 Withdrawals due to AEs (%): 4 vs 1 vs 2 Oral candidiasis- thrush (%): 2 vs 2 vs 1 Dysphonia (%): 3 vs 4 vs < 1 Sore throat (%): 3 vs < 1 vs 2	<i>Fair</i>
Condemni et al. 1997 ⁴⁹	RCT, DB, DD 291 24 weeks	US Age ≥12, persistent asthma, on ICS, excluded smokers Multicenter (24 outpatient centers)	FP DPI (500) vs TAA MDI (800) vs placebo	No (medium vs low)	Overall AEs(%): 15 vs 8 vs 13, <i>P</i> = 0.174 Withdrawals due to AEs: 4 vs 5 vs 8 Oral candidiasis- thrush (%): 8 vs 3 vs 1 Sore throat (%): 3 vs 1 vs 0 Headache (%): 1 vs 0 vs 2 Hoarseness (%): 3 vs 0 vs 0 Candidiasis, unspecified site (%): 2 vs 0 vs 0	<i>Fair</i>
Gross et	RCT, DB,	US	FP DPI (500)	No (medium	Overall AEs (%):	<i>Fair</i>

Study	Study design N Duration	Country Population Setting	Comparison (total daily dose in mcg)	Equivalent dosing	Results	Quality rating
al. 1998 ⁵⁰	DD 304 24 weeks	Age ≥12, mild to moderate, on ICS, excluded smokers Multicenter (24 respiratory care or allergy University Clinics)	vs TAA MDI (800) vs placebo	vs low)	20 vs 5 vs 5, $P < 0.001$ FP vs TAA Withdrawals due to AEs (%): 9 vs 7 vs 9 Oral candidiasis- thrush (%): 5 vs 0 vs 0 Sore throat (%): 3 vs 2 vs 2 Headache (%): 1 vs 1 vs 2 Hoarseness (%): 3 vs 0 vs 0 Migraine(%): 2 vs 0 vs 0	

Note: "No difference" in the above results section indicates that there was no statistically significant difference between active treatments with ICSs.

Appendix G. Meta-analyses

Omalizumab Meta-Analysis Results

All studies compare Omalizumab compared with Placebo.

Summary of outcomes evaluated:

1. Proportion of low symptom days
2. Number of exacerbations per patient
3. Percentage of patients with one or more exacerbation
4. Change in AQLQ score
5. Proportion of Patients with Significant QOL scores

Results

Proportion of Low Symptom Days

Studies included:

Busse et al 2001; Finn et al 2003; Lanier et al 2005 (single study population)

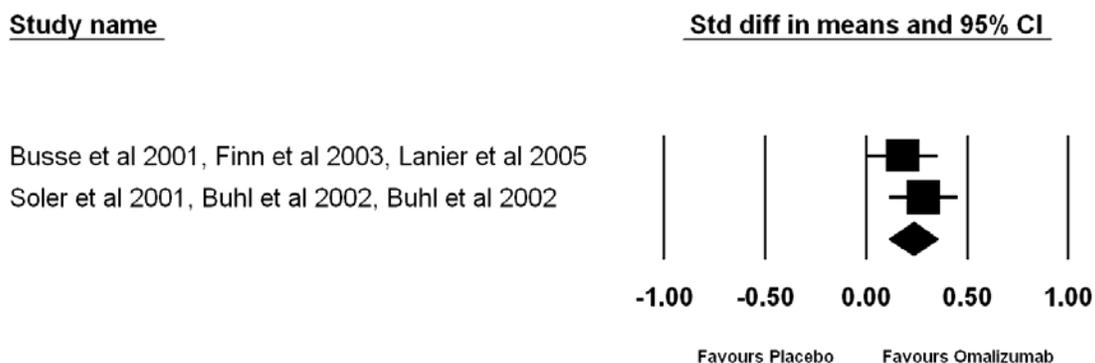
Soler et al 2001; Buhl et al 2002; Buhl et al., 2002 (single study population)

Studies that reported outcome, but are not included: NA

Summary of overall results:

Study Name	Statistics for each study						
	Std. Diff in Means	Std. Error	Variance	Lower Limit	Upper Limit	Z-value	P value
Busse et al. 2001; Finn et al. 2003; Lanier et al. 2005	.180	.087	.008	.008	.351	2.055	.040
Soler et al. 2001; Buhl et al. 2002; Buhl et al. 2002	.283	.086	.007	.115	.452	3.292	.001
Random effects model	.232	.061	.004	.112	.353	3.788	< .001

Overall results of the meta-analysis are highlighted in gray.



Sensitivity analysis results:

Because there are only two studies in the current comparison, the overall Z-scores and P values of the individual studies represent the overall estimate of the meta-analysis results with the other study removed.

Results for Heterogeneity among studies:

Value of Q Statistic	d.f. for test of Q	P value	I-squared
0.7106	1	0.3992	0

Number of Exacerbations per Patient

Studies included:

- Busse et al. 2001; Finn et al 2003; Lanier et al. 2005 (single study population)
- Humbert et al. 2005
- Soler et al. 2001; Buhl et al 2002; Buhl et al. 2002 (single study population)
- Vignola et al. 2004
- Milgrom et al. 2001

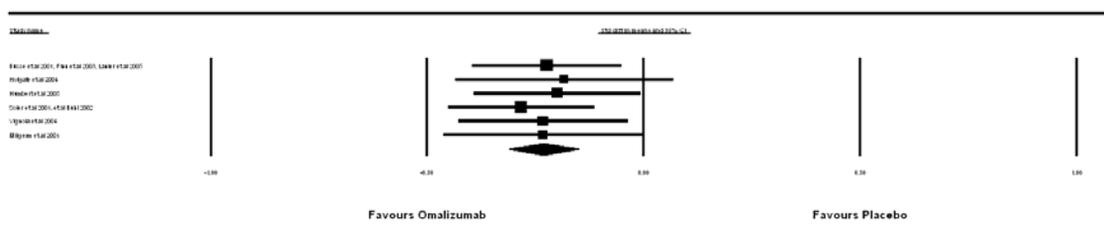
Studies that reported outcome, but are not included: NA

Summary of overall results:

Study name	Statistics for each study						
	Std. diff in Means	Std. error	Variance	Lower limit	Upper limit	Z-value	P value
Busse et al. 2001; Finn et al. 2003; Lanier et al. 2005	-.224	.088	.008	-.395	-.052	-2.554	.011
Holgate et al. 2004	-.183	.128	.016	-.434	.067	-1.434	.152
Humbert et al. 2005	-.199	.098	.010	-.391	-.007	-2.035	.042
Soler et al.	-.283	.086	.007	-.452	-.115	-3.292	.001

Study name	Statistics for each study						
	Std. diff in Means	Std. error	Variance	Lower limit	Upper limit	Z-value	P value
2001; Buhl et al. 2002; Buhl et al. 2002							
Vignola et al. 2004	-0.232	.100	.010	-.428	-.037	-2.328	.020
Milgrom et al. 2001	-0.233	.117	.014	-.462	-.003	-1.988	.047
Random effects model	-0.231	.041	.002	-.311	-.151	-5.684	< .001

Overall results of the meta-analysis are highlighted in gray.



Sensitivity analysis results:

Study Name	Statistics with study removed	
	Z-score	P value
Busse et al. 2001; Finn et al. 2003; Lanier et al 2005	-5.079	< .001
Holgate et al. 2004	-5.514	< .001
Humbert et al. 2005	-5.319	< .001
Soler et al. 2001; Buhl et al. 2002; Buhl et al. 2002	-4.684	< .001
Vignola et al. 2004	-5.185	< .001
Milgrom et al. 2001	-5.325	< .001
Overall Model	-5.684	< .001

Results for Heterogeneity among studies:

Value of Q Statistic	d.f. for test of Q	P value	I-squared
0.619	5	.9871	0

Percentage of Patients with 1 or more Exacerbations

Studies included:

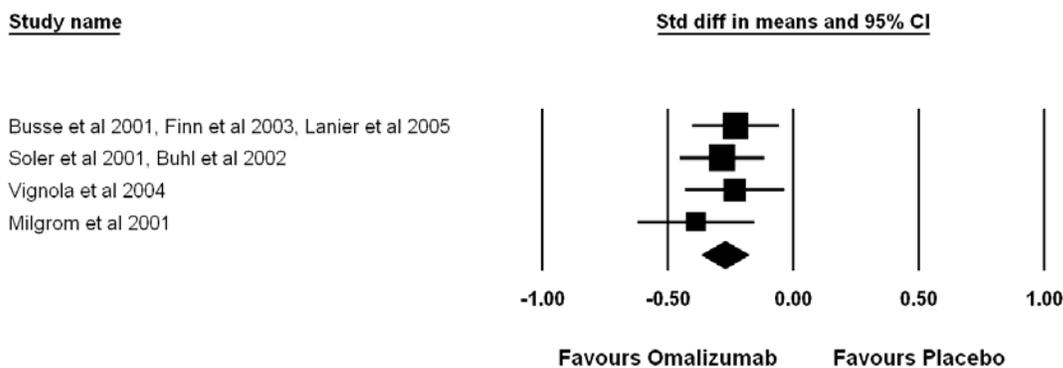
- Busse et al 2001; Finn et al 2003; Lanier et al 2005 (single study population)
- Soler et al 2001; Buhl et al 2002; Buhl et al., 2002 (single study population)
- Vignola et al 2004
- Milgrom et al 2001

Studies that reported outcome, but are not included: NA

Summary of overall results:

Study Name	Statistics for each study						
	Std. Diff in Means	Std. Error	Variance	Lower Limit	Upper Limit	Z-value	P value
Busse et al. 2001; Finn et al. 2003; Lanier et al. 2005	-0.229	.088	.008	-.401	-.057	-2.613	.009
Soler et al. 2001; Buhl et al. 2002; Buhl et al. 2002	-.283	.086	.007	-.452	-.115	-3.292	.001
Vignola et al. 2004	-.232	.100	.010	-.428	-.037	-2.328	.020
Milgrom et al. 2001	-.387	.118	.014	-.618	-.157	-3.293	.001
Random effects model	-.273	.048	.002	-.366	-.179	-5.705	< .001

Overall results of the meta-analysis are highlighted in gray.



Sensitivity analysis results:

Study Name	Statistics with study removed	
	Z-score	P value
Busse et al. 2001; Finn et al. 2003; Lanier et al. 2005	-5.106	< .001
Soler et al. 2001; Buhl et al. 2002; Buhl et al. 2002	-4.662	< .001
Vignola et al. 2004	-5.229	< .001
Milgrom et al. 2001	-4.780	< .001
Overall Model	-5.705	< .001

Results for Heterogeneity among studies:

Value of Q Statistic	d.f. for test of Q	P value	I-squared
1.381	3	.710	0

Change in AQLQ Score

Studies included:

Busse et al. 2001; Finn et al. 2003; Lanier et al. 2005 (single study population)

Holgate et al. 2004

Humbert et al. 2005

Soler et al. 2001; Buhl et al. 2002; Buhl et al., 2002 (single study population)

Vignola et al. 2004

Milgrom et al. 2001

Studies that reported outcome, but are not included: NA

Summary of overall results:

Study Name	Statistics for each study						Z-value	P value
	Std. Diff in Means	Std. Error	Variance	Lower Limit	Upper Limit			
Busse et al 2001; Finn et al. 2003; Lanier et al. 2005	.226	.088	.008	.54	.397	2.577	.010	
Holgate et al. 2004	.331	.128	.016	.079	.583	2.579	.010	
Humbert et al. 2005	.324	.098	.010	.131	.517	3.293	.001	
Soler et al. 2001; Buhl et al. 2002; Buhl et al., 2002	.283	.086	.007	.115	.452	3.292	.001	
Vignola et al 2004	.330	.100	.010	.133	.526	3.293	.001	
Milgrom et al 2001	.387	.118	.014	.157	.618	3.293	.001	
Random effects model	.303	.041	.002	.223	.383	7.426	< .001	

Overall results of the meta-analysis are highlighted in gray.



Sensitivity analysis results:

Study Name	Statistics with study removed	
	Z-score	P value
Busse et al. 2001; Finn et al. 2003; Lanier et al. 2005	7.035	< .001
Holgate et al 2004	6.968	< .001
Humbert et al 2005	6.660	< .001
Soler et al. 2001; Buhl et al. 2002; Buhl et al., 2002	6.661	< .001
Vignola et al. 2004	6.662	< .001
Milgrom et al. 2001	6.700	< .001
Overall Model	7.426	< .001

Results for Heterogeneity among studies:

Value of Q Statistic	d.f. for test of Q	P value	I-squared
1.510	5	.2191	0

Proportion of Patients with Significant QOL Scores

Studies included:

- Busse et al. 2001; Finn et al. 2003; Lanier et al. 2005 (single study population)
- Holgate et al. 2004
- Humbert et al. 2005
- Soler et al. 2001; Buhl et al. 2002; Buhl et al. 2002 (single study population)
- Vignola et al. 2004
- Milgrom et al. 2001

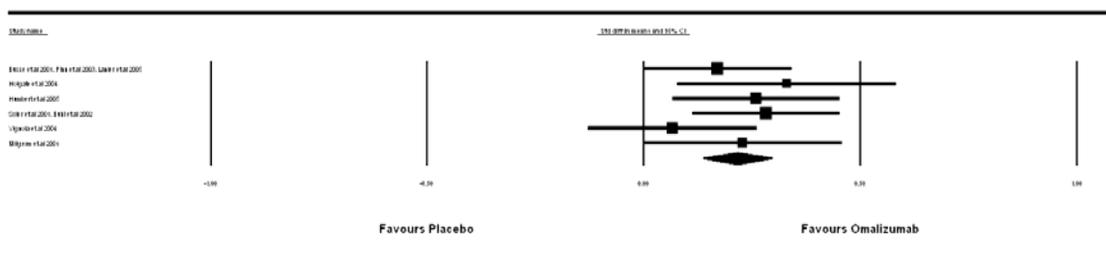
Studies that reported outcome, but are not included: NA

Summary of overall results:

Study Name	Statistics for each study						
	Std. Diff in Means	Std. Error	Variance	Lower Limit	Upper Limit	Z-value	P value
Busse et al. 2001; Finn et al. 2003; Lanier et al. 2005	0.25	0.02	0.0004	0.21	0.29	12.5	< .001
Holgate et al 2004	0.30	0.02	0.0004	0.26	0.34	15.0	< .001
Humbert et al 2005	0.35	0.02	0.0004	0.31	0.39	17.5	< .001
Soler et al. 2001; Buhl et al. 2002; Buhl et al., 2002	0.30	0.02	0.0004	0.26	0.34	15.0	< .001
Vignola et al. 2004	0.35	0.02	0.0004	0.31	0.39	17.5	< .001
Milgrom et al. 2001	0.40	0.02	0.0004	0.36	0.44	20.0	< .001
Overall Model	0.426	0.02	0.0004	0.38	0.47	21.2	< .001

Busse et al. 2001; Finn et al. 2003; Lanier et al. 2005	.172	.087	.008	.000	.343	1.961	.050
Holgate et al. 2004	.331	.128	.016	.079	.583	2.579	.010
Humbert et al. 2005	.260	.098	.010	.068	.453	2.654	.008
Soler et al. 2001; Buhl et al. 2002; Buhl et al. 2002	.283	.086	.007	.115	.452	3.292	.001
Vignola et al. 2004	.067	.099	.010	-.128	.262	.675	.500
Milgrom et al. 2001	.230	.117	.014	.459	-0.00	-1.961	.050
Random effects model	.217	.041	.002	.138	.297	5.343	< .001

Overall results of the meta-analysis are highlighted in gray.



Sensitivity analysis results:

Study Name	Statistics with study removed	
	Z-score	P value
Busse et al. 2001; Finn et al. 2003; Lanier et al. 2005	5.005	< .001
Holgate et al. 2004	4.772	< .001
Humbert et al. 2005	4.662	< .001
Soler et al 2001; Buhl et al. 2002; Buhl et al. 2002	4.297	< .001
Vignola et al. 2004	5.552	< .001
Milgrom et al. 2001	4.896	< .001
Overall Model	5.343	< .001

Results for Heterogeneity among studies (with Milgrom et al included):

Value of Q Statistic	d.f. for test of Q	P value	I-squared
4.130	5	.5309	0

ICS+LABA VS. ICS+LABA (Combination products) Meta-Analysis Results

Study compares fixed Dose Combo of BUD/FM compared with Fixed Dose Combo FP/SM

Outcome evaluated: Exacerbations

Studies included:

Aalbers et al. 2004, Dahl et al. 2006, Kuna et al. 2007 and Price et al. 2007, Ringdal et al. 2002

Studies that reported outcome, but are not included: NA

Summary of overall results:

Study name	Statistics for each study						
	Std diff in means	Variance	Standard error	Lower limit	Upper limit	Z-Value	P Value
Aalbers et al. 2004	-0.0590	0.0091	0.0955	-0.2462	0.1282	-0.6177	0.5368
Dahl et al. 2006	0.0304	0.0029	0.0536	-0.0747	0.1355	0.5667	0.5709
Kuna et al. 2007 and Price et al. 2007	-0.0697	0.0018	0.0424	-0.1528	0.0133	-1.6450	0.1000
Ringdal et al. 2002	0.0245	0.0093	0.0967	-0.1650	0.2140	0.2535	0.7999
Random effects model	-0.0286	0.0009	0.0299	-0.0872	0.0299	-0.9585	0.3378



Sensitivity analysis results:

Study name	Statistics with study removed						
	Point	Standard error	Variance	Lower limit	Upper limit	Z-Value	P Value
Aalbers et al. 2004	-0.0215	0.0362	0.0013	-0.0925	0.0495	-0.5941	0.5525
Dahl et al. 2006	-0.0552	0.0360	0.0013	-0.1256	0.0153	-1.5340	0.1250
Kuna et al. 2007 AND Price et al. 2007 A	0.0119	0.0421	0.0018	-0.0706	0.0944	0.2829	0.7773
Ringdal et al. 2002	-0.0332	0.0339	0.0011	-0.0996	0.0332	-0.9787	0.3277
Overall model	-0.0286	0.0299	0.0009	-0.0872	0.0299	-0.9585	0.3378

Results for Heterogeneity among studies:

value of Q statistic	d.f. for test of Q	P value	I-squared
2.554	3	0.466	0

BUD/FM (MART) compared with ICS+LABA (fixed dose) Meta-Analysis Results

All studies compare BUD/FM MART vs. BUD/FM except Kuna et al 2007 and price et al 2007, which in addition, compares BUD/FM MART vs. FP/SM. denoted with *

Summary of outcomes evaluated

1. Exacerbations
2. Rescue medication use (puffs/day)
3. Rescue medication use (% rescue-free days)
4. Symptoms (% symptom-free days)
5. Symptoms (score)
6. Nocturnal Awakenings

Exacerbations

Studies included:

Bosquet et al 2007

O'Byrne et al 2005

Kuna et al 2007 and Price et al 2007

Vogelmeier et al 2005

Studies that reported outcome, but are not included: NA

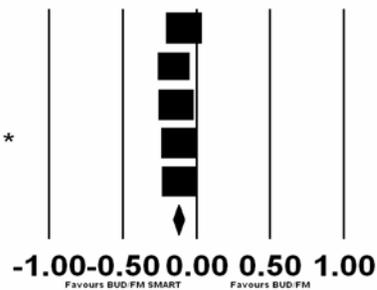
Summary of overall results:

Study name	Std diff in means	Standard error	Statistics for each study				Z-Value	p-Value
			Variance	Lower limit	Upper limit			
Bosquet et al 2007	-0.0860	0.0416	0.0017	-0.1676	-0.0043	-2.0644	0.0390	
O'Byrne et al 2005	-0.1539	0.0468	0.0022	-0.2456	-0.0623	-3.2910	0.0010	
Kuna et al 2007 and Price et al 2007	-0.1396	0.0424	0.0018	-0.2227	-0.0564	-3.2909	0.0010	
Kuna et al 2007 and Price et al 2007*	-0.1200	0.0426	0.0018	-0.2035	-0.0366	-2.8205	0.0048	
Vogelmeier et al 2005	-0.1154	0.0432	0.0019	-0.2002	-0.0307	-2.6697	0.0076	
Random effects model	-0.1216	0.0193	0.0004	-0.1595	-0.0837	-6.2923	0.0000	

Study name

Std diff in means and 95% CI

Bosquet et al 2007
 O'Byrne et al 2005
 Kuna et al 2007 AND Price et al
 Kuna et al 2007 AND Price et al *
 Vogelmeier et al 2005



BUD/FM SMART vs. FP/SM

Sensitivity analysis results:

Study name	Statistics with study removed	
	Z-Value	p-Value
Bosquet et al 2007	-6.0222	0.0000
O'Byrne et al 2005	-5.4165	0.0000
Kuna et al 2007 and Price et al	-5.3842	0.0000
Kuna et al 2007 and Price et al *	-5.6250	0.0000
Vogelmeier et al 2005	-5.7002	0.0000
Overall model	-6.2923	0.0000

Results for Heterogeneity among studies:

value of Q statistic	d.f. for test of Q	P-value	I-squared
1.411	4	0.842	0.000

Rescue medication use (puffs/day)

Studies included:

Bosquet et al 2007

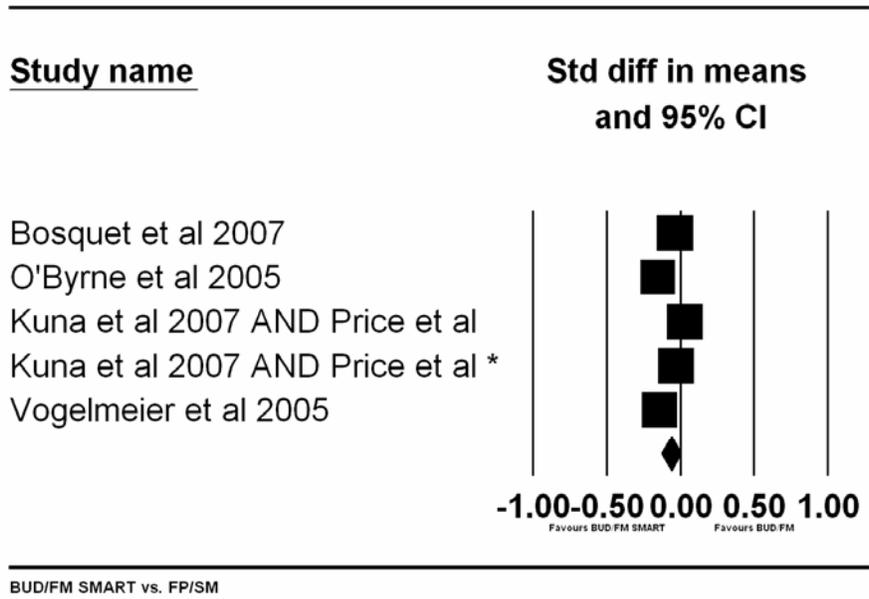
O'Byrne et al 2005

Kuna et al 2007 and Price et al 2007

Studies that reported outcome, but are not included: NA

Summary of overall results:

Study name	Std diff in means	Standard error	Statistics for each study				
			Variance	Lower limit	Upper limit	Z-Value p-Value	
Bosquet et al 2007	-0.0381	0.0416	0.0017	-0.1197	0.0435	-0.9155	0.3599
O'Byrne et al 2005	-0.1539	0.0468	0.0022	-0.2456	-0.0623	-3.2910	0.0010
Kuna et al 2007 and Price et al	0.0300	0.0424	0.0018	-0.0530	0.1130	0.7080	0.4790
Kuna et al 2007 and Price et al *	-0.0301	0.0425	0.0018	-0.1135	0.0532	-0.7080	0.4790
Vogelmeier et al 2005	-0.1424	0.0433	0.0019	-0.2271	-0.0576	-3.2909	0.0010
Random effects model	-0.0656	0.0348	0.0012	-0.1337	0.0026	-1.8861	0.0593



Sensitivity analysis results:

Study name	Statistics with study removed	
	Z-Value	p-Value
Bosquet et al 2007	-1.6389	0.1012
O'Byrne et al 2005	-1.2647	0.2060
Kuna et al 2007 and Price et al	-2.7190	0.0065
Kuna et al 2007 and Price et al *	-1.7111	0.0871
Vogelmeier et al 2005	-1.2536	0.2100
Overall model	-1.8861	0.0593

Results for Heterogeneity among studies:

value of Q statistic	d.f. for test of Q	P-value	I-squared
12.9203	4.0000	0.0117	69.0410

Rescue medication use (% rescue-free days)

Studies included:

Bosquet et al 2007

O'Byrne et al 2005

Kuna et al 2007 and Price et al 2007

Studies that reported outcome, but are not included: NA

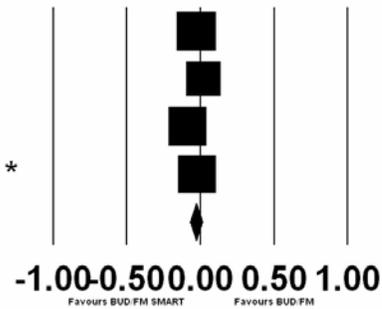
Summary of overall results:

Study name	Std diff in means	Standard error	Statistics for each study				
			Variance	Lower limit	Upper limit	Z-Value p-Value	
Bosquet et al 2007	-0.0243	0.0416	0.0017	-0.1058	0.0573	-0.5829	0.5600
O'Byrne et al 2005	0.0245	0.0467	0.0022	-0.0670	0.1160	0.5245	0.6000
Kuna et al 2007 and Price et al	-0.0831	0.0424	0.0018	-0.1661	0.0000	-1.9602	0.0500
Kuna et al 2007 and Price et al *	-0.0184	0.0425	0.0018	-0.1017	0.0650	-0.4317	0.6660
Random effects model	-0.0276	0.0216	0.0005	-0.0700	0.0148	-1.2751	0.2023

Study name

Std diff in means and 95% CI

Bosquet et al 2007
 O'Byrne et al 2005
 Kuna et al 2007 AND Price et al
 Kuna et al 2007 AND Price et al *



BUD/FM SMART vs. FP/SM

Sensitivity analysis results:

Study name	Statistics with study removed	
	Z-Value	p-Value
Bosquet et al 2007	-0.8971	0.3697
O'Byrne et al 2005	-1.7144	0.0865
Kuna et al 2007 and Price et al	-0.3243	0.7457
Kuna et al 2007 and Price et al *	-0.9790	0.3276
Overall model	-1.2751	0.2023

Results for Heterogeneity among studies:

value of Q statistic	d.f. for test of Q	P-value	I-squared
3.0108	3.0000	0.3900	0.3583

Symptoms (% symptom-free days)

Studies included:

Bosquet et al 2007

O'Byrne et al 2005

Kuna et al 2007 and Price et al 2007

Studies that reported outcome, but are not included: NA

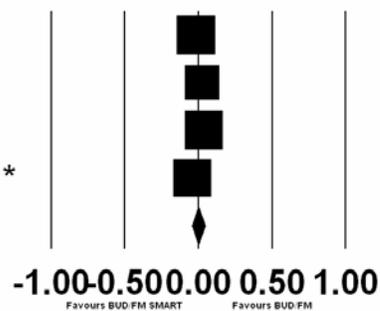
Summary of overall results:

Study name	Std diff in means	Standard error	Statistics for each study				
			Variance	Lower limit	Upper limit	Z-Value p-Value	
Bosquet et al 2007	-0.0144	0.0416	0.0017	-0.0959	0.0672	-0.3452	0.7300
O'Byrne et al 2005	0.0301	0.0467	0.0022	-0.0615	0.1216	0.6434	0.5199
Kuna et al 2007 and Price et al	0.0384	0.0424	0.0018	-0.0446	0.1214	0.9060	0.3649
Kuna et al 2007 and Price et al *	-0.0384	0.0425	0.0018	-0.1217	0.0450	-0.9022	0.3669
Random effects model	0.0026	0.0216	0.0005	-0.0397	0.0449	0.1221	0.9028

Study name

Std diff in means and 95% CI

Bosquet et al 2007
 O'Byrne et al 2005
 Kuna et al 2007 AND Price et al
 Kuna et al 2007 AND Price et al *



BUD/FM SMART vs. FP/SM

Sensitivity analysis results:

Study name	Statistics with study removed	
	Z-Value	p-Value
Bosquet et al 2007	0.3522	0.7247
O'Byrne et al 2005	-0.1976	0.8433
Kuna et al 2007 and Price et al	-0.3947	0.6931
Kuna et al 2007 and Price et al *	0.6733	0.5008
Overall model	0.1221	0.9028

Results for Heterogeneity among studies:

value of Q statistic	d.f. for test of Q	P-value	I-squared
2.153	3.0000	0.5413	0

Symptoms (score)

Studies included:

Bosquet at al 2007

O'Byrne et al 2005

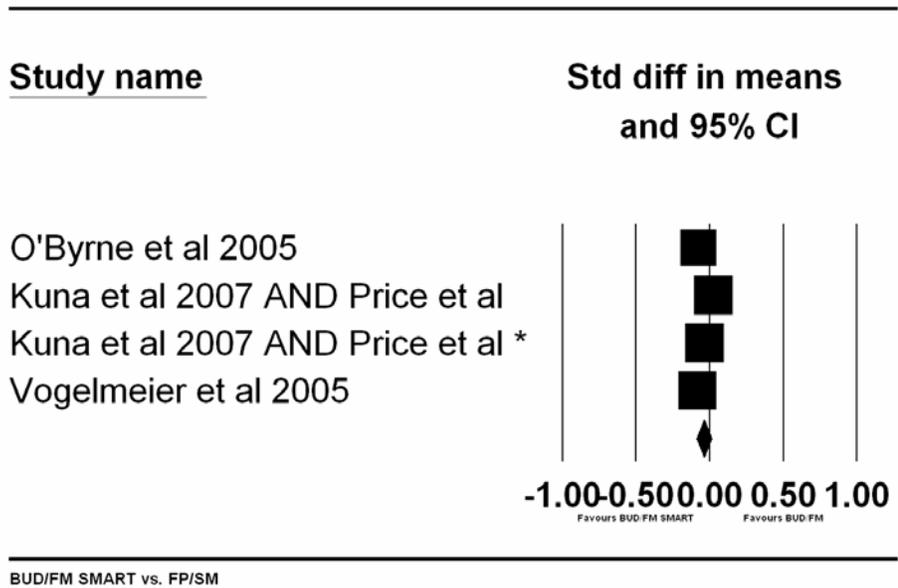
Kuna et al 2007 and Price at al 2007

Vogelmeier et al 2005

Studies that reported outcome, but are not included: NA

Summary of overall results:

Study name	Std diff in means	Standard error	Statistics for each study				Z-Value	p-Value
			Variance	Lower limit	Upper limit			
O'Byrne et al 2005	-0.0726	0.0467	0.0022	-0.1642	0.0189	-1.5550	0.1199	
Kuna et al 2007 and Price et al	0.0300	0.0424	0.0018	-0.0530	0.1130	0.7080	0.4790	
Kuna et al 2007 and Price et al *	-0.0301	0.0425	0.0018	-0.1135	0.0532	-0.7080	0.4790	
Vogelmeier et al 2005	-0.0786	0.0432	0.0019	-0.1633	0.0061	-1.8186	0.0690	
Random effects model	-0.0363	0.0253	0.0006	-0.0859	0.0133	-1.4347	0.1514	



Sensitivity analysis results:

Study name	Statistics with study removed	
	Z-Value	p-Value
O'Byrne et al 2005	-0.8226	0.4108
Kuna et al 2007 AND Price et al	-2.3398	0.0193
Kuna et al 2007 AND Price et al *	-1.0861	0.2774
Vogelmeier et al 2005	-0.7450	0.4563
Overall model	-1.4347	0.1514

Results for Heterogeneity among studies:

value of Q statistic	d.f. for test of Q	P-value	I-squared
4.0332	3.0000	0.2579	25.6166

Nocturnal Awakenings

Studies included:

Bosquet et al 2007

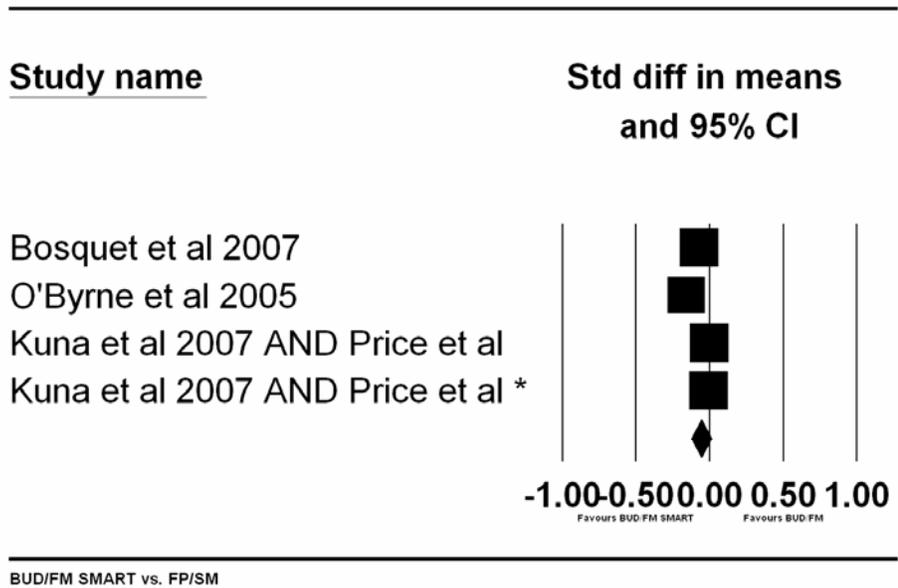
O'Byrne et al 2005

Kuna et al 2007 and Price et al 2007

Studies that reported outcome, but are not included: NA

Summary of overall results:

Study name	Std diff in means	Standard error	Statistics for each study				
			Variance	Lower limit	Upper limit	Z-Value p-Value	
Bosquet et al 2007	-0.0665	0.0416	0.0017	-0.1481	0.0151	-1.5984	0.1100
O'Byrne et al 2005	-0.1539	0.0468	0.0022	-0.2456	-0.0623	-3.2910	0.0010
Kuna et al 2007 and Price et al	0.0026	0.0424	0.0018	-0.0804	0.0856	0.0615	0.9510
Kuna et al 2007 and Price et al *	-0.0026	0.0425	0.0018	-0.0860	0.0807	-0.0615	0.9510
Random effects model	-0.0533	0.0351	0.0012	-0.1220	0.0154	-1.5207	0.1283



Sensitivity analysis results:

Study name	Statistics with study removed	
	Z-Value	p-Value
Bosquet et al 2007	-0.9989	0.3179
O'Byrne et al 2005	-0.9345	0.3501
Kuna et al 2007 and Price et al	-1.7016	0.0888
Kuna et al 2007 and Price et al *	-1.6062	0.1082
Overall model	-1.5207	0.1283

Results for Heterogeneity among studies:

Value of Q statistic	d.f. for test of Q	P-value	I-squared
7.8783	3.0000	0.0486	61.9207

Inter-class comparisons (Between classes) Leukotriene Receptor Antagonist Meta-Analysis Results

LTRA compared with ICS Results

Summary of Outcome Measures Analyzed:

1. Rescue medication use (percent improved rescue free days)
2. Rescue medication use (decrease in puffs)
3. Symptom control (percent improved symptom free days)
4. Symptom control (change in score)
5. Percent Exacerbations
6. Change in AQLQ Scores

Results

Rescue Medication Use (percent rescue free days)

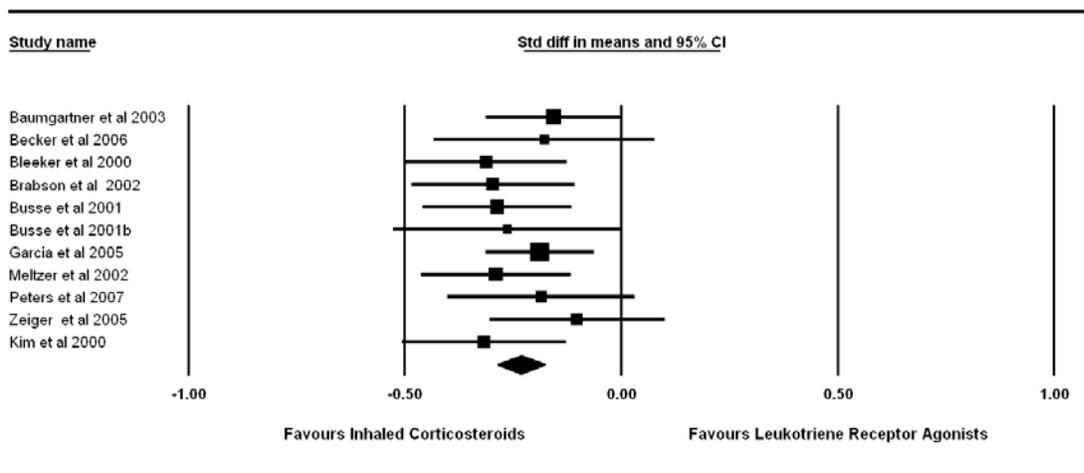
Studies that reported outcome, but are not included:

<i>Study</i>	<i>Reason</i>
Ducharme et al 2004	Review paper
Halpern et al. 2003	Review paper
Malmstrom et al. 1999	P values reported are for placebo comparisons

Summary of overall results:

<i>Study Name</i>	<i>Statistics for each study</i>						
	<i>Std. Diff in Means</i>	<i>Std. Error</i>	<i>Variance</i>	<i>Lower Limit</i>	<i>Upper Limit</i>	<i>Z-value</i>	<i>P value</i>
Baumgartner et al. 2003	-.157	.080	.006	-.314	-.000	-1.961	.05
Becker et al. 2006	.178	.130	.017	-.076	.432	1.374	.170
Bleeker et al. 2000	-.312	.095	.009	-.498	-.126	-3.292	.001
Brabson et al. 2002	-.296	.096	.009	-.484	-.109	-3.092	.002
Busse et al. 2001a	-.287	.087	.008	-.457	-.116	-3.292	.001
Busse et al. 2001b	-.263	.134	.018	-.526	-.000	-1.962	.050
Garcia et al. 2005	-.189	.064	.004	-.313	-.064	-2.968	.003
Meltzer et al. 2002	-.290	.088	.008	-.462	-.117	-3.292	.001
Peters et al. 2007	.186	.110	.012	-.029	.400	1.697	.090
Zeiger et al. 2005	-.102	.103	.011	-.303	.099	-.995	.320
Kim et al. 2000	-.317	.096	.009	-.506	-.128	-3.292	.001
Random effects model	-.232	.028	.001	-.286	-.177	-8.310	< .001

Overall results of the meta-analysis are highlighted in gray.



Sensitivity analysis results:

Study Name	Statistics with study removed	
	Z-value	P value
Baumgartner et al. 2003	-8.137	< .001
Becker et al. 2006	-8.207	< .001
Bleeker et al. 2000	-7.681	< .001
Brabson et al. 2002	-7.746	< .001
Busse et al. 2001a	-7.659	< .001
Busse et al. 2001b	-8.079	< .001
Garcia et al. 2005	-7.798	< .001
Meltzer et al. 2002	-7.662	< .001
Peters et al. 2007	-8.147	< .001
Zeiger et al. 2005	-8.354	< .001
Kim et al. 2000	-7.686	< .001
Overall Model	-8.310	< .001

Results for Heterogeneity among studies:

Value of Q Statistic	d.f. for test of Q	P value	I-squared
6.120	10	.8051	0

Rescue Medication Use (puffs per day)

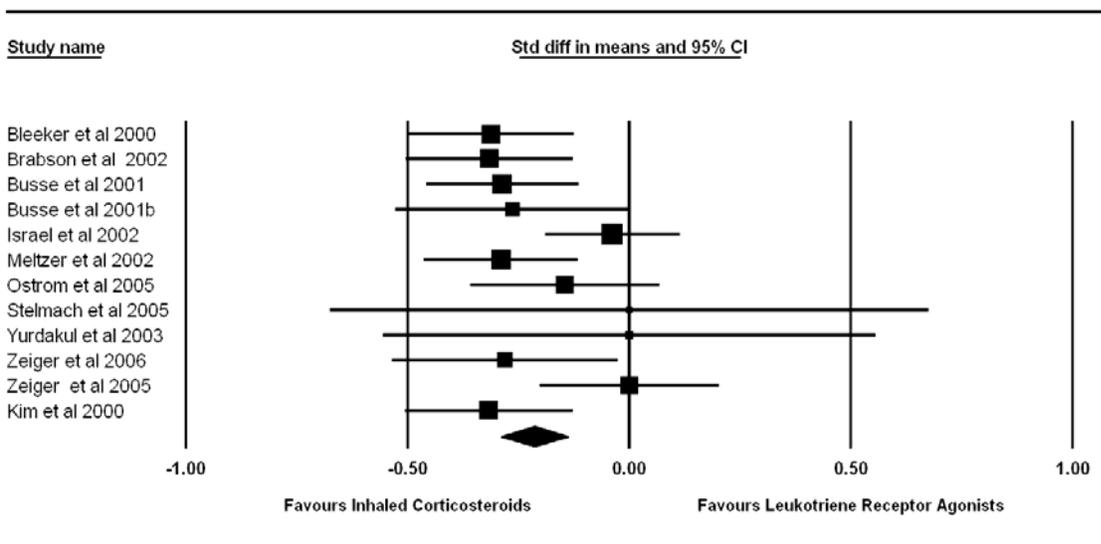
Studies that reported outcome, but are not included:

Study	Reason
Ducharme et al 2004	Review paper
Halpern et al 2003	Review paper
Malmstrom et al 1999	p-values reported are for placebo comparisons

Summary of overall results:

Study Name	Statistics for each study						
	Std. Diff in Means	Std. Error	Variance	Lower Limit	Upper Limit	Z-value	p-value
Bleeker et al 2000	-.312	.095	.009	-.498	-.126	-3.292	.001
Brabson et al 2002	-.316	.096	.009	-.504	-.128	-3.292	.001
Busse et al 2001a	-.287	.087	.008	-.457	-.116	-3.292	.001
Busse et al 2001b	-.263	.134	.018	-.526	.000	-1.962	.050
Israel et al 2002	-.038	.077	.006	-.190	.113	-.495	.621
Meltzer et al 2002	-.290	.088	.008	-.462	-.117	-3.292	.001
Ostrom et al 2005	-.145	.108	.012	-.358	.067	-1.342	.180
Stelmach et al 2005	.000	.344	.118	-.673	.673	.000	1.000
Yurdakul et al 2003	.000	.283	.080	-.554	.554	.000	1.000
Zeiger et al 2006	-.281	.130	.017	-.535	-.027	-2.166	.030
Zeiger et al 2005	.000	.103	.011	-.201	.201	.000	1.000
Kim et al 2000	-.317	.096	.009	-.498	-.128	-3.292	.001
Random effects model	-.214	.038	.001	-.289	-.139	-5.590	<.001

Overall results of the meta-analysis are highlighted in gray.



The results of this meta-analysis show a significant reduction in rescue med puffs with ICS over LTRA.

Sensitivity analysis results:

<i>Study Name</i>	<i>Statistics with study removed</i>	
	<i>Z-value</i>	<i>p-value</i>
Bleeker et al 2000	-4.945	<.001
Brabson et al 2002	-4.957	<.001
Busse et al 2001a	-4.869	<.001
Busse et al 2001b	-5.101	<.001
Israel et al 2002	-7.385	<.001
Meltzer et al 2002	-4.877	<.001
Ostrom et al 2005	-5.296	<.001
Stelmach et al 2005	-5.497	<.001
Yurdakul et al 2003	-5.542	<.001
Zeiger et al 2006	-5.078	<.001
Zeiger et al 2005	-6.780	<.001
Kim et al 2000	-4.961	<.001
Overall Model	-5.590	<.001

Sensitivity analyses indicate no difference in overall meta-analysis conclusions with single studies removed.

Results for Heterogeneity among studies:

<i>Value of Q Statistic</i>	<i>d.f. for test of Q</i>	<i>P-value</i>	<i>I-squared</i>
10.104	11	.5211	0

Percent Improved Symptom Control (symptom free days)

Studies that reported outcome, but are not included:

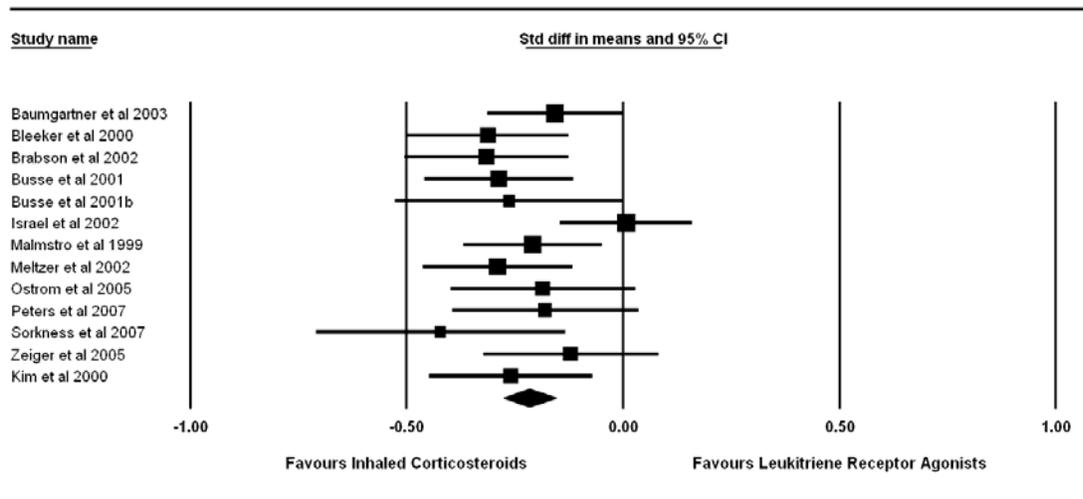
<i>Study</i>	<i>Reason</i>
Ducharme et al. 2004	Review paper
Halpern et al. 2003	Review paper
Zeiger et al. 2006	Measured different outcomes

Summary of overall results:

<i>Study Name</i>	<i>Statistics for each study</i>						
	<i>Std. Diff in Means</i>	<i>Std. Error</i>	<i>Variance</i>	<i>Lower Limit</i>	<i>Upper Limit</i>	<i>Z-value</i>	<i>P value</i>
Baumgartner et al. 2003	-.157	.080	.006	-.314	-.000	-1.961	.050
Bleeker et al. 2000	-.312	.095	.009	-.498	-.126	-3.292	.001
Brabson et al. 2002	-.316	.096	.009	-.504	-.128	-3.292	.001
Busse et al. 2001a	-.287	.087	.008	-.457	-.116	-3.292	.001
Busse et al. 2001b	-.263	.134	.018	-.526	-.000	-1.962	.050
Israel et al. 2002	.007	.077	.006	-.144	.158	.089	.929

Malmstro et al. 1999	-.209	.081	.007	-.369	-.050	-2.577	.010
Meltzer et al. 2002	-.290	.088	.008	-.462	-.117	-3.292	.001
Ostrom et al. 2005	-.186	.108	.012	-.398	.027	-1.713	.087
Peters et al. 2007	-.180	.109	.012	-.395	.034	-1.646	.100
Sorkness et al. 2007	-.422	.146	.021	-.708	-.135	-2.882	.004
Zeiger et al. 2005	-.121	.103	.011	-.322	.081	-1.176	.240
Kim et al. 2000	-.216	.096	.009	-.448	-.071	-2.698	.007
Random effects model	-.216	.031	.001	-.276	-.157	-7.081	< .001

Overall results of the meta-analysis are highlighted in gray.



Sensitivity analysis results:

Study Name	Statistics with study removed	
	Z-value	P value
Baumgartner et al. 2003	-6.726	< .001
Bleeker et al. 2000	-6.511	< .001
Brabson et al. 2002	-6.525	< .001
Busse et al. 2001a	-6.422	< .001
Busse et al. 2001b	-6.636	< .001
Israel et al. 2002	-8.589	< .001
Malmstro et al. 1999	-6.455	< .001
Meltzer et al. 2002	-6.432	< .001
Ostrom et al. 2005	-6.668	< .001
Peters et al. 2007	-6.668	< .001
Sorkness et al. 2007	-6.905	< .001
Zeiger et al. 2005	-6.963	< .001
Kim et al. 2000	-6.470	
Overall Model	-7.081	< .001

Results for Heterogeneity among studies:

Value of Q Statistic	d.f. for test of Q	P value	I-squared
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11.485

12

.4879

0

Percent Improved Symptom Control (symptom score)

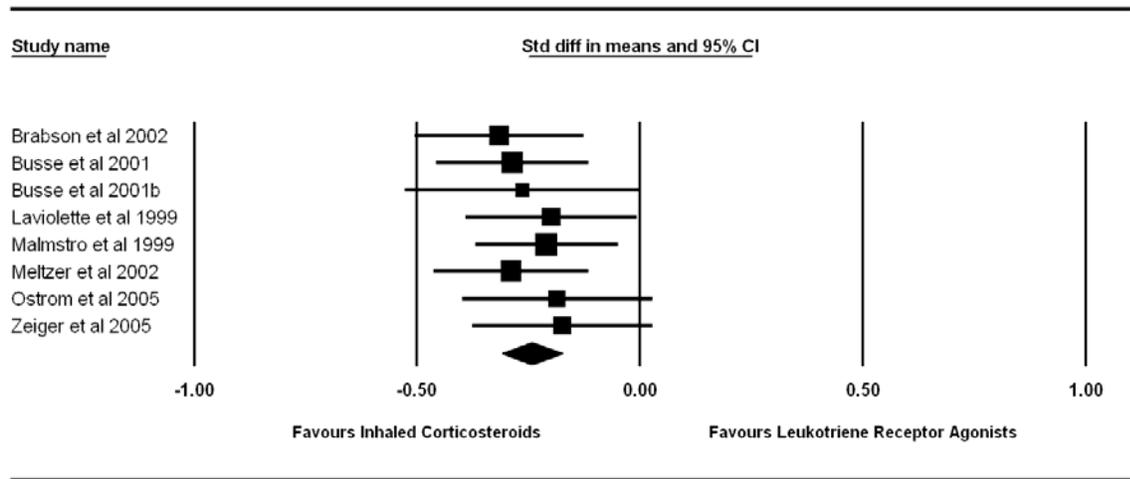
Studies that reported outcome, but are not included:

<i>Study</i>	<i>Reason</i>
Ducharme et al 2004	Review paper
Halpern et al 2003	Review paper
Stelmack et al 2005	Different measure
Yurdulak et al 2003	P-value only reported as NS, no measures of variation reported

Summary of overall results:

<i>Study Name</i>	<i>Statistics for each study</i>						
	<i>Std. Diff in Means</i>	<i>Std. Error</i>	<i>Variance</i>	<i>Lower Limit</i>	<i>Upper Limit</i>	<i>Z-value</i>	<i>p-value</i>
Brabson et al 2002	-.316	.096	.009	-.504	-.128	-3.292	.001
Busse et al 2001a	-.287	.087	.008	-.457	-.116	-3.292	.001
Busse et al 2001b	-.263	.134	.018	-.526	-.000	-1.962	.050
Laviolette et al 1999	-.200	.098	.010	-.391	-.008	-2.045	.041
Malmstro et al 1999	-.209	.081	.007	-.369	-.050	-2.577	.010
Meltzer et al 2002	-.290	.088	.008	-.462	-.117	-3.292	.001
Ostrom et al 2005	-.186	.108	.012	-.398	.027	-1.713	.087
Zeiger et al 2005	-.174	.103	.011	-.376	.0027	-1.698	.090
Random effects model	-.243	.034	.001	-.310	-.176	-7.125	<.001

Overall results of the meta-analysis are highlighted in gray.



Sensitivity analysis results:

Study Name	Statistics with study removed	
	Z-value	p-value
Brabson et al 2002	-6.371	<.001
Busse et al 2001a	-6.343	<.001
Busse et al 2001b	-6.852	<.001
Laviolette et al 1999	-6.842	<.001
Malmstro et al 1999	-6.659	<.001
Meltzer et al 2002	-6.346	<.001
Ostrom et al 2005	-6.939	<.001
Zeiger et al 2005	-6.956	<.001
Overall Model	-7.125	<.001

Results for Heterogeneity among studies:

Value of Q Statistic	d.f. for test of Q	P-value	I-squared
2.228	7	.9462	0

Percent Exacerbations

Studies that reported outcome, but are not included:

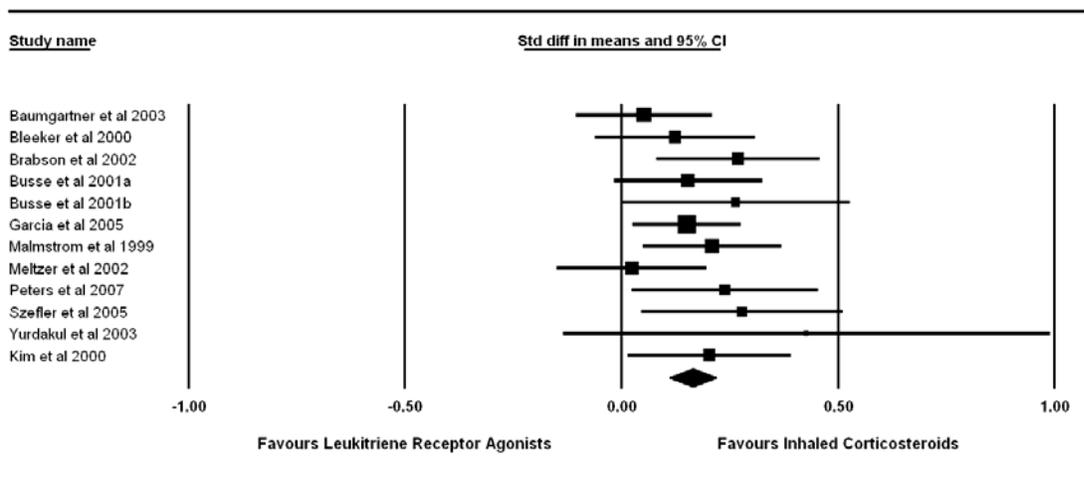
Study	Reason
Ducharme et al. 2004	Review paper
Halpern et al. 2003	Review paper

Summary of overall results:

Study Name	Statistics for each study						
	Std. Diff in Means	Std. Error	Variance	Lower Limit	Upper Limit	Z-value	P value
Baumgartner et	.052	.080	.006	-.105	.208	.650	.516

al. 2003							
Bleeker et al. 2000	.123	.094	.009	-.061	.308	1.308	.191
Brabson et al. 2002	.269	.096	.009	.081	.457	2.809	.005
Busse et al. 2001a	.153	.087	.008	-.017	.323	1.763	.078
Busse et al. 2001b	.263	.134	.018	.000	.526	1.962	.050
Garcia et al. 2005	.150	.064	.004	.026	.275	2.366	.018
Malmstrom et al. 1999	.209	.081	.007	.050	.369	2.577	.010
Meltzer et al. 2002	.023	.088	.008	-.148	.195	.268	.789
Peters et al. 2007	.238	.110	.012	.023	.453	2.172	.030
Szeffler et al. 2005	.278	.118	.014	.046	.510	2.348	.019
Yurdakul et al. 2003	.427	.286	.082	-.134	.987	1.492	.136
Kim et al. 2000	.202	.096	.009	.014	.390	2.110	.035
Random effects model	.216	.045	.002	.127	.305	4.761	< .001

Overall results of the meta-analysis are highlighted in gray.



Sensitivity analysis results:

Study Name	Statistics with study removed	
	Z-value	P value
Baumgartner et al. 2003	6.226	< .001
Bleeker et al. 2000	5.953	< .001
Brabson et al. 2002	5.511	< .001
Busse et al. 2001a	5.819	< .001
Busse et al. 2001b	5.803	< .001
Garcia et al. 2005	5.604	< .001
Malmstrom et al. 1999	5.537	< .001
Meltzer et al. 2002	6.303	< .001
Peters et al. 2007	5.720	< .001
Szeffler et al. 2005	5.693	< .001
Yurdakul et al. 2003	5.965	< .001

Kim et al. 2000	5.716	< .001
Random effects model	6.079	< .001

Results for Heterogeneity among studies:

<i>Value of Q Statistic</i>	<i>d.f. for test of Q</i>	<i>P value</i>	<i>I-squared</i>
9.244	11	.5994	0

Change in AQLQ Score

Studies included:

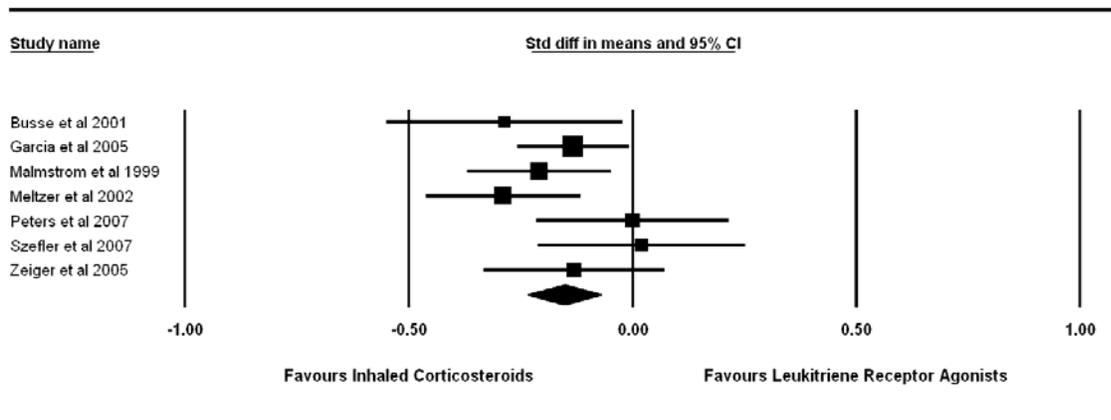
Studies that reported outcome, but are not included:

<i>Study</i>	<i>Reason</i>
Busse et al 2001a	P value reported, but no raw data

Summary of overall results:

<i>Study Name</i>	<i>Statistics for each study</i>						
	<i>Std. Diff in Means</i>	<i>Std. Error</i>	<i>Variance</i>	<i>Lower Limit</i>	<i>Upper Limit</i>	<i>Z-value</i>	<i>P value</i>
Busse et al. 2001	-0.287	.134	.018	-0.550	-0.023	-2.135	.033
Garcia et al. 2005	-.133	.064	.004	-.258	-.009	-2.097	.036
Malmstrom et al. 1999	-.209	.081	.007	-.369	-.050	-2.577	.010
Meltzer et al. 2002	-.290	.088	.008	-.462	-.117	-3.292	.001
Peters et al. 2007	.000	.109	.012	-.214	.214	.000	1.00
Szefler et al. 2007	.020	.118	.014	-.211	.251	.169	.866
Zeiger et al. 2005	-.132	.103	.011	-.333	.070	-1.282	.200
Random effects model	-.153	.042	.002	-.234	-.072	-3.688	< .001

Overall results of the meta-analysis are highlighted in gray.



Sensitivity analysis results:

Study Name	Statistics with study removed	
	Z-value	P value
Busse et al. 2001	-3.215	.001
Garcia et al. 2005	-2.958	.003
Malmstrom et al. 1999	-2.853	.004
Meltzer et al. 2002	-3.280	.001
Peters et al. 2007	-4.261	< .001
Szeffler et al. 2007	-4.361	< .001
Zeiger et al. 2005	-3.186	.001
Overall Model	-3.688	< .001

Results for Heterogeneity among studies:

Value of Q Statistic	d.f. for test of Q	P value	I-squared
6.291	6	.3914	4.626

ML compared with ICS Results

Summary of Outcome Measures Analyzed:

1. Rescue medication use (percent improved)
2. Rescue medication use (puffs)
3. Symptom control (percent improved)
4. Symptom score
5. Percent Exacerbations
6. Change in AQLQ Scores

Results

Rescue Medication Use (percent improved symptom free days)

Studies that reported outcome, but are not included:

Study	Reason
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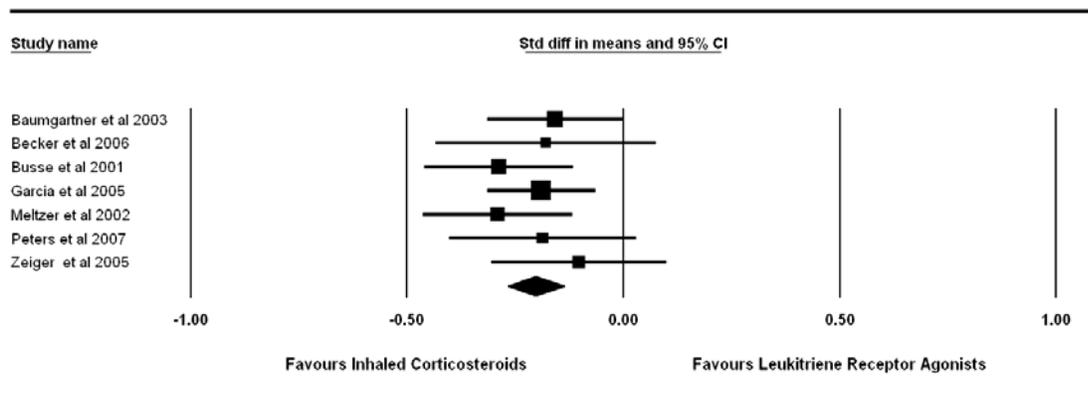
Yurdakul et al 2003

P value nonsignificant, no variance reported

Summary of overall results:

Study Name	Std. Diff in Means	Std. Error	Statistics for each study				
			Variance	Lower Limit	Upper Limit	Z-value	P value
Baumgartner et al. 2003	-.157	.080	.006	-.314	-.000	-1.961	.050
Becker et al. 2006	-.178	.130	.017	-.432	.076	-1.374	.170
Busse et al. 2001	-.287	.087	.008	-.457	-.116	-3.292	.001
Garcia et al. 2005	-.189	.064	.004	-.313	-.064	-2.968	.003
Meltzer et al. 2002	-.290	.088	.008	-.462	-.117	-3.292	.001
Peters et al. 2007	-.186	.110	.012	-.400	.029	-1.697	.090
Zeiger et al. 2005	-.102	.103	.011	-.303	.099	-.995	.320
Random effects model	-.202	.033	.001	-.267	-.137	-6.065	< .001

Overall results of the meta-analysis are highlighted in gray.



Sensitivity analysis results:

Study Name	Statistics with study removed	
	Z-value	P value
Baumgartner et al. 2003	-5.773	< .001
Becker et al. 2006	-5.911	< .001
Busse et al. 2001	-5.202	< .001
Garcia et al. 2005	-5.295	< .001
Meltzer et al. 2002	-5.207	< .001
Peters et al. 2007	-5.825	< .001
Zeiger et al. 2005	-6.070	< .001
Overall Model	6.065	< .001

Results for Heterogeneity among studies:

Value of Q Statistic	d.f. for test of Q	P value	I-squared
3.303	6	.7700	0

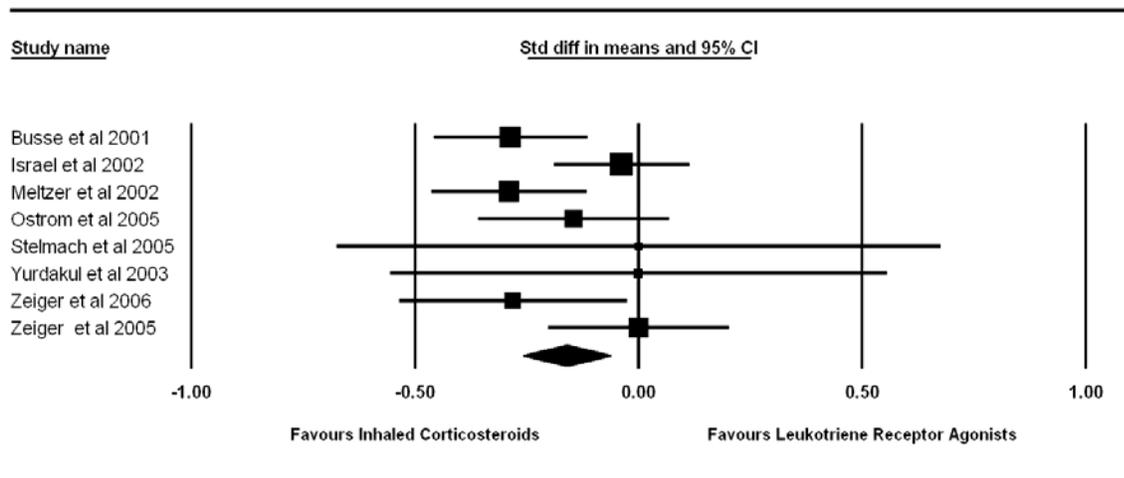
Rescue Medication Use (puffs per day)

Studies that reported outcome, but are not included:

Summary of overall results:

Study Name	Statistics for each study						
	Std. Diff in Means	Std. Error	Variance	Lower Limit	Upper Limit	Z-value	p-value
Busse et al 2001a	-.287	.087	.008	-.457	-.116	-3.292	.001
Israel et al 2002	-.038	.077	.006	-.190	.113	-.495	.621
Meltzer et al 2002	-.290	.088	.008	-.462	-.117	-3.292	.001
Ostrom et al 2005	-.145	.108	.012	-.358	.067	-1.342	.180
Stelmach et al 2005	.000	.344	.118	-.673	.673	.000	1.000
Yurdakul et al 2003	.000	.283	.080	-.554	.554	.000	1.000
Zeiger et al 2006	-.281	.130	.017	-.535	-.027	-2.166	.030
Zeiger et al 2005	.000	.103	.011	-.201	.201	.000	1.000
Random effects model	-.160	.050	.002	-.258	-.063	-3.212	.001

Overall results of the meta-analysis are highlighted in gray.



Sensitivity analysis results:

Study Name	Statistics with study removed	
	Z-value	p-value
Busse et al 2001a	-2.551	.011
Israel et al 2002	-3.879	<.001
Meltzer et al 2002	-2.564	.010
Ostrom et al 2005	-2.744	.006
Stelmach et al 2005	-3.098	.002

Yurdakul et al 2003	-3.125	.002
Zeiger et al 2006	-2.670	.008
Zeiger et al 2005	-3.811	<.001
Overall Model	-3.212	.001

Results for Heterogeneity among studies:

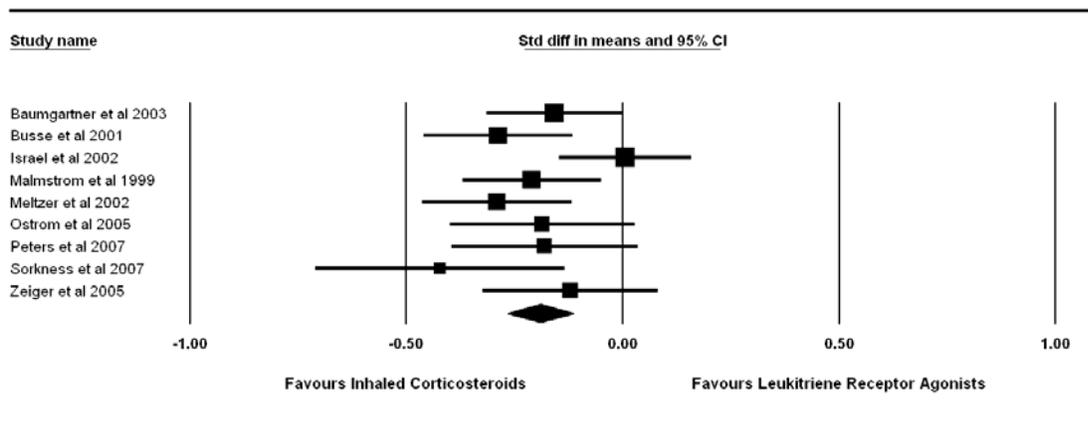
<i>Value of Q Statistic</i>	<i>d.f. for test of Q</i>	<i>P-value</i>	<i>I-squared</i>
6.204	7	.5161	0

Percent Improved Symptom Control (symptom free days)

Summary of overall results:

Study Name	Statistics for each study						
	Std. Diff in Means	Std. Error	Variance	Lower Limit	Upper Limit	Z-value	P value
Baumgartner et al. 2003	-.157	.080	.006	-.314	-.000	-1.961	.050
Busse et al. 2001a	-.287	.087	.008	-.457	-.116	-3.292	.001
Israel et al. 2002	.007	.077	.006	-.144	.158	.089	.929
Malmstro et al. 1999	-.209	.081	.007	-.369	-.050	-2.577	.010
Meltzer et al. 2002	-.290	.088	.008	-.462	-.117	-3.292	.001
Ostrom et al. 2005	-.186	.108	.012	-.398	.027	-1.713	.087
Peters et al. 2007	-.180	.109	.012	-.395	.034	-1.646	.100
Sorkness et al. 2007	-.422	.146	.021	-.708	-.135	-2.882	.004
Zeiger et al. 2005	-.121	.103	.011	-.322	.081	-1.176	.240
Random effects model	-.189	.039	.002	-.265	-.113	-4.887	< .001

Overall results of the meta-analysis are highlighted in gray.



Sensitivity analysis results:

Study Name	Statistics with study removed	
	Z-value	P value
Baumgartner et al. 2003	-4.377	< .001
Busse et al. 2001	-4.243	< .001
Israel et al. 2002	-6.525	< .001
Malmstro et al. 1999	-4.204	< .001
Meltzer et al. 2002	-4.253	< .001
Ostrom et al. 2005	-4.413	< .001
Peters et al. 2007	-4.430	< .001
Sorkness et al. 2007	-4.723	< .001
Zeiger et al 2005	-4.627	< .001
Overall Model	-4.887	< .001

Results for Heterogeneity among studies:

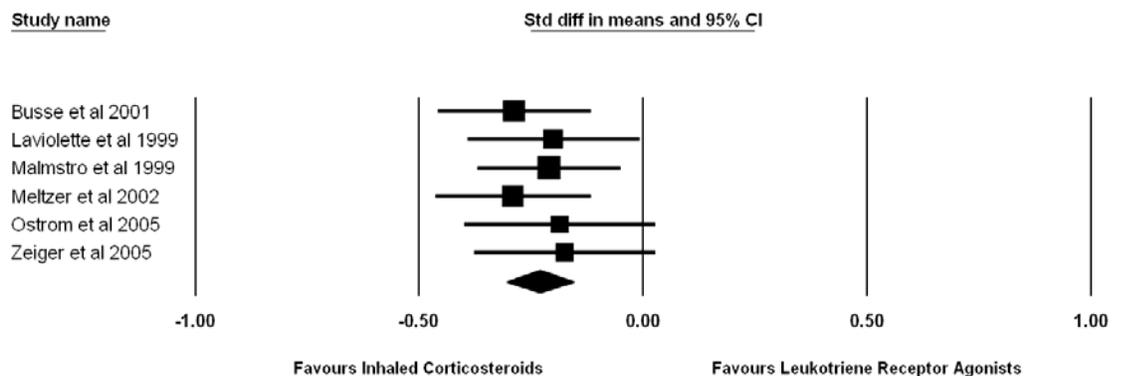
Value of Q Statistic	d.f. for test of Q	P value	I-squared
7.791	8	.4541	0

Percent Improved Symptom Control (symptom score)

Summary of overall results:

Study Name	Statistics for each study						
	Std. Diff in Means	Std. Error	Variance	Lower Limit	Upper Limit	Z-value	p-value
Busse et al 2001a	-0.287	.087	.008	-0.457	-0.116	-3.292	.001
Lavolette et al 1999	-0.200	.098	.010	-0.391	-0.008	-2.045	.041
Malmstro et al 1999	-0.209	.081	.007	-0.369	-0.050	-2.577	.010
Meltzer et al 2002	-0.290	.088	.008	-0.462	-0.117	-3.292	.001
Ostrom et al 2005	-0.186	.108	.012	-0.398	.027	-1.713	.087
Zeiger et al 2005	-0.174	.103	.011	-0.376	.0027	-1.698	.090
Random effects model	-0.230	.038	.001	-0.304	-0.156	-6.067	<.001

Overall results of the meta-analysis are highlighted in gray.



Sensitivity analysis results:

Study Name	Statistics with study removed	
	Z-value	p-value
Busse et al 2001a	-5.147	<.001
Laviolette et al 1999	-5.721	
Malmstro et al 1999	-5.499	<.001
Meltzer et al 2002	-5.151	<.001
Ostrom et al 2005	-5.836	<.001
Zeiger et al 2005	-5.853	<.001
Overall Model	-6.067	<.001

Results for Heterogeneity among studies:

Value of Q Statistic	d.f. for test of Q	P-value	I-squared
1.506	5	.9124	0

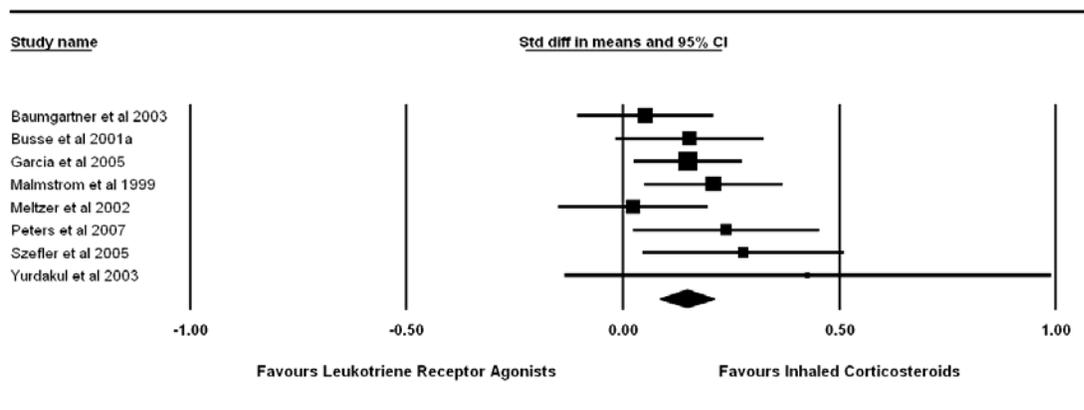
Percent Exacerbations

Summary of overall results:

Study Name	Statistics for each study						
	Std. Diff in Means	Std. Error	Variance	Lower Limit	Upper Limit	Z-value	P value
Baumgartner et al. 2003	.052	.080	.006	-.105	.208	.650	.516
Busse et al. 2001a	.153	.087	.008	-.017	.323	1.763	.078
Garcia et al. 2005	.150	.064	.004	.026	.275	2.366	.018
Malmstrom et al. 1999	.209	.081	.007	.050	.369	2.577	.010
Meltzer et al. 2002	.023	.088	.008	-.148	.195	.268	.789
Peters et al. 2007	.238	.110	.012	.023	.453	2.172	.030
Szeffler et al. 2005	.278	.118	.014	.046	.510	2.348	.019

Yurdakul et al. 2003	.427	.286	.082	-.134	.987	1.492	.136
Random effects model	.216	.045	.002	.127	.305	4.761	< .001

Overall results of the meta-analysis are highlighted in gray.



Sensitivity analysis results:

Study Name	Statistics with study removed	
	Z-value	P value
Baumgartner et al 2003	4.764	< .001
Busse et al. 2001a	3.962	< .001
Garcia et al. 2005	3.727	< .001
Malmstrom et al. 1999	3.861	< .001
Meltzer et al. 2002	4.864	< .001
Peters et al. 2007	4.124	< .001
Szeffler et al. 2005	4.150	< .001
Yurdakul et al. 2003	4.490	< .001
Random effects model	4.628	< .001

Results for Heterogeneity among studies:

Value of Q Statistic	d.f. for test of Q	P value	I-squared
6.876	7	.4419	0

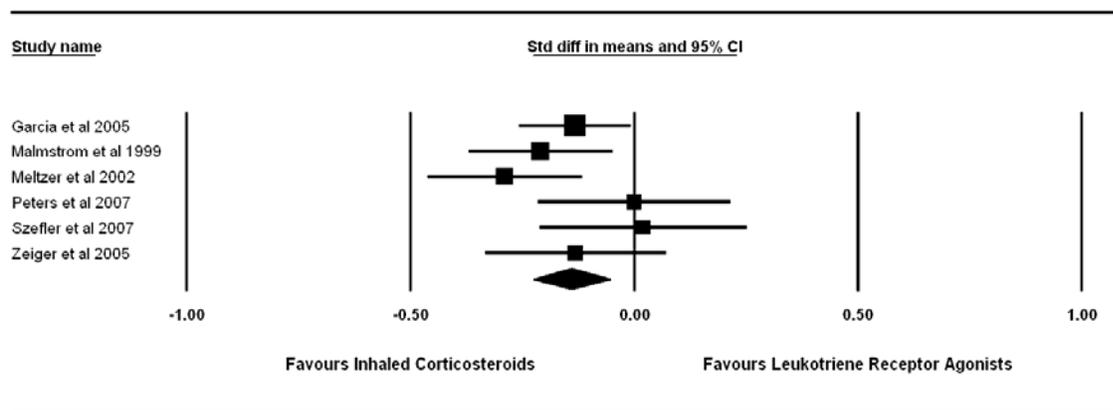
Change in AQLQ Score

Summary of overall results:

Study Name	Statistics for each study						
	Std. Diff in Means	Std. Error	Variance	Lower Limit	Upper Limit	Z-value	P value
Garcia et al. 2005	-.133	.064	.004	-.258	-.009	-2.097	.036
Malmstrom et al. 1999	-.209	.081	.007	-.369	-.050	-2.577	.010
Meltzer et al. 2002	-.290	.088	.008	-.462	-.117	-3.292	.001
Peters et al. 2007	.000	.109	.012	-.214	.214	.000	1.00
Szeffler et al.	.020	.118	.014	-.211	.251	.169	.866

2007							
Zeiger et al. 2005	-.132	.103	.011	-.333	.070	-1.282	.200
Random effects model	-.141	.044	.002	-.227	-.055	-3.215	.001

Overall results of the meta-analysis are highlighted in gray.



Sensitivity analysis results:

Study Name	Statistics with study removed	
	Z-value	P value
Garcia et al. 2005	-2.377	.017
Malmstrom et al. 1999	-2.353	.019
Meltzer et al. 2002	-2.973	.003
Peters et al. 2007	-3.693	.001
Szeffler et al. 2007	-3.806	< .001
Zeiger et al. 2005	-2.649	.008
Overall Model	-3.215	< .001

Results for Heterogeneity among studies:

Value of Q Statistic	d.f. for test of Q	P value	I-squared
5.268	5	.3841	5.093

Zaf compared with ICS Results

Summary of Outcome Measures Analyzed:

1. Rescue medication use (percent improved)
2. Symptom control (percent improved)
3. Symptom control (score)
4. Percent Exacerbations

Results

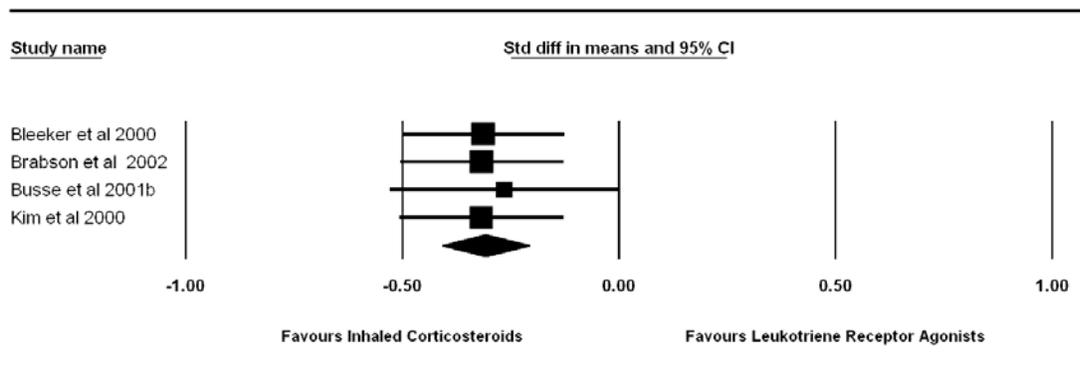
Rescue Medication Use (percent improved)

***Note – results are identical for both percent improved and puffs outcomes, so the results are only presented once.**

Summary of overall results:

Study Name	Statistics for each study						
	Std. Diff in Means	Std. Error	Variance	Lower Limit	Upper Limit	Z-value	P value
Bleecker et al. 2000	-.312	.095	.009	-.498	-.126	-3.292	.001
Brabson et al. 2002	-.316	.096	.009	-.504	-.128	-3.292	.001
Busse et al. 2001	-.263	.134	.018	-.526	.000	-1.962	.050
Kim et al. 2000	-.317	.096	.009	-.506	-.128	-3.292	.001
Random effects model	-.307	.051	.003	-.408	-.207	-6.020	<.001

Overall results of the meta-analysis are highlighted in gray.



Sensitivity analysis results:

Study Name	Statistics with study removed	
	Z-value	P value
Bleecker et al. 2000	-5.040	< .001
Brabson et al. 2002	-5.041	< .001
Busse et al. 2001	-5.702	< .001
Kim et al. 2000	-5.041	< .001
Overall Model	-6.020	< .001

Results for Heterogeneity among studies:

Value of Q Statistic	d.f. for test of Q	P value	I-squared
.128	3	.9983	0

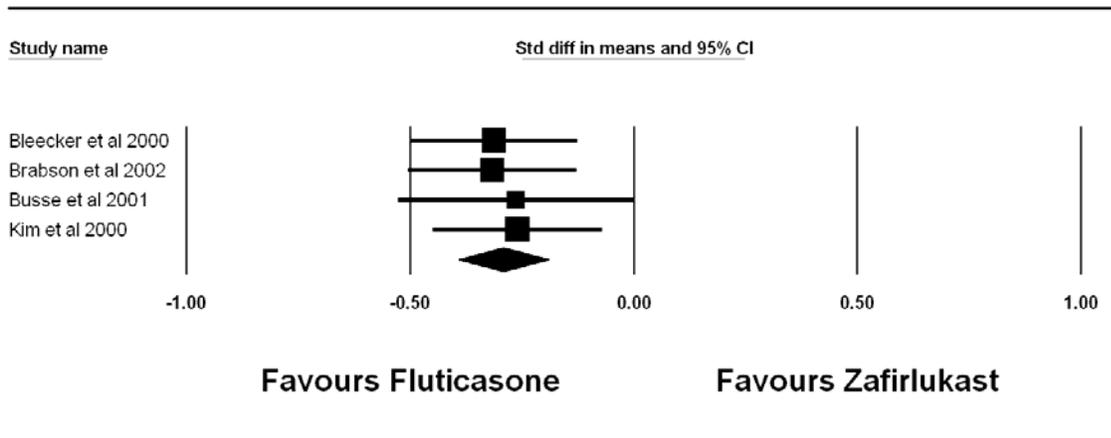
Symptom Control (percent improved symptom free days)

Studies that reported outcome, but are not included: NA

Summary of overall results:

Study Name	Statistics for each study						
	Std. Diff in Means	Std. Error	Variance	Lower Limit	Upper Limit	Z-value	P value
Bleecker et al. 2000	-.312	.095	.009	-.498	-.126	-3.292	.001
Brabson et al. 2002	-.316	.096	.009	-.504	-.128	-3.292	.001
Busse et al. 2001	-.263	.134	.018	-.526	.000	-1.962	.050
Kim et al. 2000	-.259	.096	.009	-.448	-.071	-3.698	.007
Random effects model	-.291	.051	.003	-.391	-.191	-5.705	< .001

Overall results of the meta-analysis are highlighted in gray.



Sensitivity analysis results:

Study Name	Statistics with study removed	
	Z-value	P value
Bleecker et al. 2000	-4.666	< .001
Brabson et al. 2002	-4.669	< .001
Busse et al. 2001	-5.361	< .001
Kim et al. 2000	-5.041	< .001
Overall Model	-5.705	< .001

Results for Heterogeneity among studies:

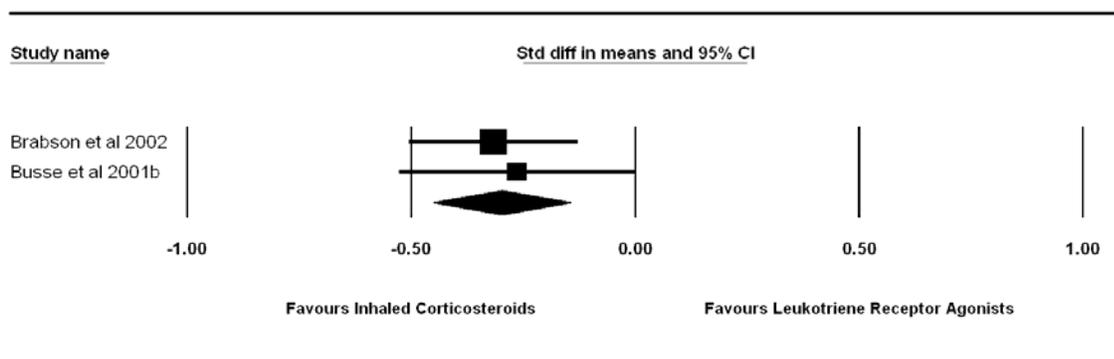
Value of Q Statistic	d.f. for test of Q	P value	I-squared
.268	3	.9659	0

Symptom Control (change in score)

Summary of overall results:

Study Name	Statistics for each study						
	Std. Diff in Means	Std. Error	Variance	Lower Limit	Upper Limit	Z-value	P value
Brabson et al. 2002	-.316	.096	.009	-.504	-.128	-3.292	.001
Busse et al. 2001	-.263	.134	.018	-.526	.000	-1.962	.050
Random effects model	-.298	.078	.006	-.451	-.145	-3.820	< .001

Overall results of the meta-analysis are highlighted in gray.



Sensitivity analysis results:

Study Name	Statistics with study removed	
	Z-value	P value
Brabson et al. 2002	-1.962	.050
Busse et al. 2001	-3.292	.001
Overall Model	-3.820	< .001

Results for Heterogeneity among studies:

Value of Q Statistic	d.f. for test of Q	P value	I-squared
.102	1	.7494	0

Percent Exacerbations

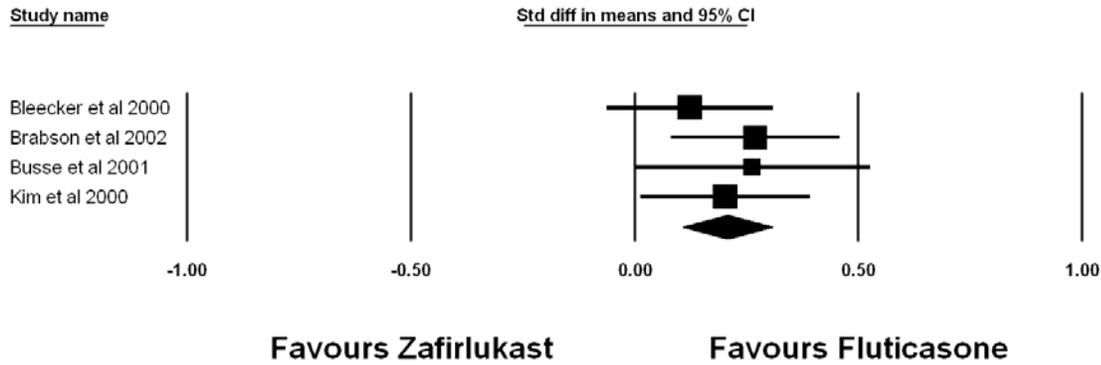
Studies that reported outcome, but are not included: NA

Summary of overall results:

Study Name	Statistics for each study						
	Std. Diff in Means	Std. Error	Variance	Lower Limit	Upper Limit	Z-value	P value
Bleecker et al. 2000	.123	.094	.009	-.061	.308	1.308	.191
Brabson et al.	.269	.096	.009	.081	.457	2.809	.005

2002							
Busse et al. 2001	.262	.134	.018	-.001	.525	1.954	.051
Kim et al. 2000	.202	.096	.009	.014	.390	2.110	.035
Random effects model	.207	.051	.003	.107	.307	4.061	< .001

Overall results of the meta-analysis are highlighted in gray.



Sensitivity analysis results:

Study Name	Statistics with study removed	
	Z-value	P value
Bleecker et al. 2000	3.985	< .001
Brabson et al. 2002	3.032	.002
Busse et al. 2001	3.588	< .001
Kim et al. 2000	3.470	.001
Overall Model	4.061	< .001

Results for Heterogeneity among studies:

Value of Q Statistic	d.f. for test of Q	P value	I-squared
1.378	3	.7107	0

ML compared with BDP Results

Summary of Outcome Measures Analyzed:

1. Rescue medication use (percent improved)
2. Symptom control (percent improved)

Results

Rescue Medication Use (percent improved)

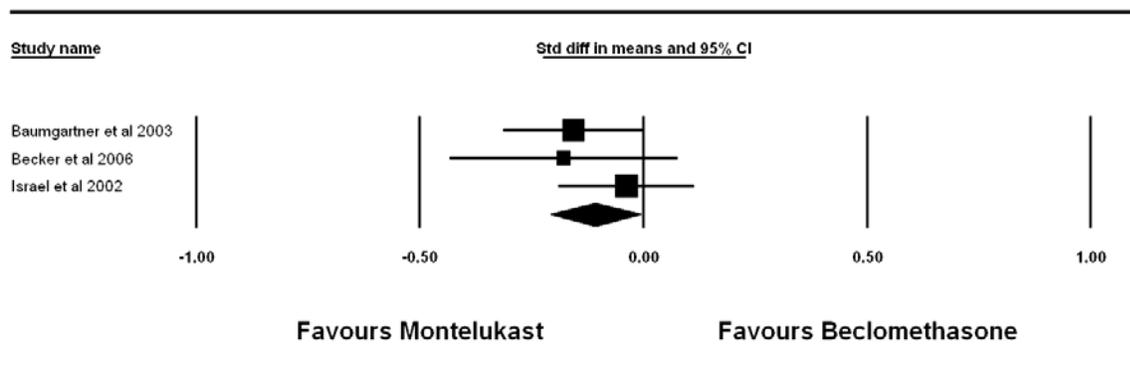
Studies that reported outcome, but are not included:

Study	Reason
Malmstrom et al. 1999	P vales reported for comparisons to placebo only

Summary of overall results:

Study Name	Statistics for each study						
	Std. Diff in Means	Std. Error	Variance	Lower Limit	Upper Limit	Z-value	P value
Baumgartner et al. 2003	-.157	.080	.006	-.314	-.000	-1.961	.050
Becker et al. 2006	-.178	.130	.017	-.432	.076	-1.374	.170
Israel et al. 2002	-.038	.077	.006	-.190	.113	-.495	.621
Random effects model	-.108	.051	.003	-.208	-.008	-2.120	.034

Overall results of the meta-analysis are highlighted in gray.



Sensitivity analysis results:

Study Name	Statistics with study removed	
	Z-value	P value
Baumgartner et al. 2003	-1.128	.259
Becker et al. 2006	-1.614	.107
Israel et al. 2002	-2.390	.017
Overall Model	-2.120	.034

Results for Heterogeneity among studies:

Value of Q Statistic	d.f. for test of Q	P value	I-squared
1.482	2	.4766	0

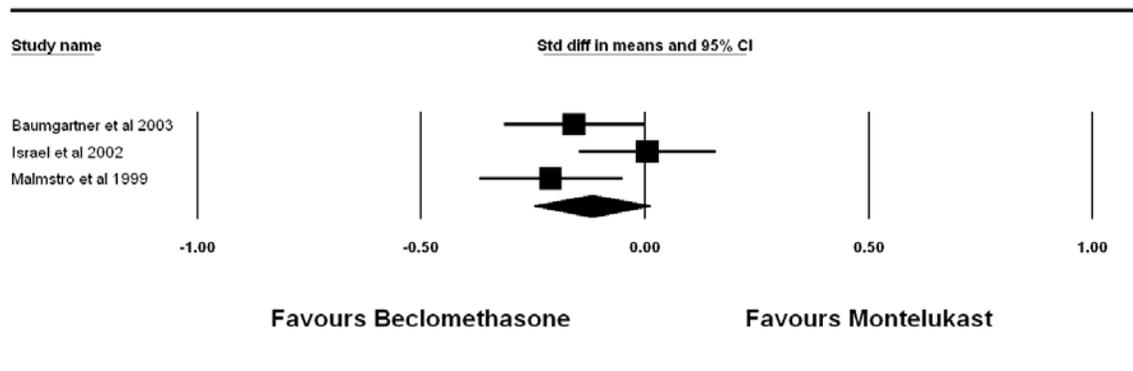
Symptom Control

Studies that reported outcome, but are not included: NA

Summary of overall results:

Study Name	Statistics for each study						
	Std. Diff in Means	Std. Error	Variance	Lower Limit	Upper Limit	Z-value	P value
Baumgartner et al. 2003	-.157	.080	.006	-.314	-.000	-1.961	.050
Israel et al. 2002	.007	.077	.006	-.144	.158	.089	.929
Malmstrom et al. 1999	-.209	.081	.007	-.369	-.050	-2.577	.010
Random effects model	-.118	.066	.004	-.247	-.011	-1.791	.073

Overall results of the meta-analysis are highlighted in gray.



Sensitivity analysis results:

Study Name	Statistics with study removed	
	Z-value	P value
Baumgartner et al. 2003	-.923	.356
Israel et al. 2002	-3.205	.001
Malmstrom et al. 1999	-.900	.358
Overall Model	-1.791	.073

Results for Heterogeneity among studies:

Value of Q Statistic	d.f. for test of Q	P value	I-squared
1.978	2	.3719	0

Montelukast compared with Fluticasone Results

Summary of Outcome Measures Analyzed:

1. Rescue medication use (percent improved rescue free days)
2. Rescue medication use (decrease in puffs)
3. Symptom control (percent improved symptom free days)
4. Symptom control (change in score)
5. Percent Exacerbations
6. Change in AQLQ Scores

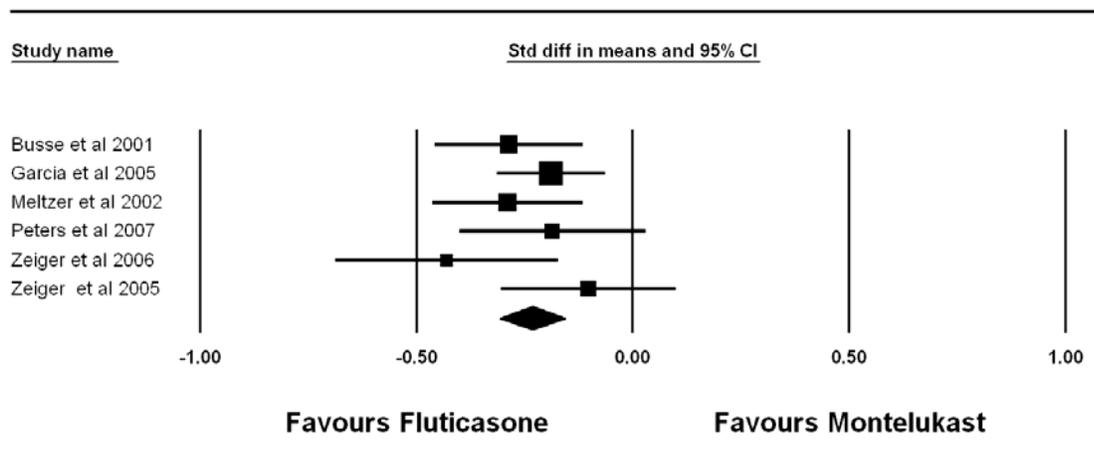
Results

Rescue Medication Use (percent rescue free days)

Summary of overall results:

Study Name	Statistics for each study						
	Std. Diff in Means	Std. Error	Variance	Lower Limit	Upper Limit	Z-value	P value
Busse et al. 2001	-0.287	.087	.008	-0.457	-.116	-3.292	.001
Garcia et al. 2005	-.189	.064	.004	-.313	-.064	-2.968	.003
Meltzer et al. 2002	-.290	.088	.008	-.462	-.117	-3.292	.001
Peters et al. 2007	-.186	.110	.012	-.400	.029	-1.697	.090
Zeiger et al. 2006	-.430	.131	.017	-.686	-.174	-3.294	.001
Zeiger et al. 2006	-.102	.103	.011	-.303	.099	-.995	.320
Random effects model	-.232	.038	.001	-.307	-.157	-6.064	< .001

Overall results of the meta-analysis are highlighted in gray.



Sensitivity analysis results:

Study Name	Statistics with study removed	
	Z-value	P value
Busse et al. 2001	-4.852	< .001
Garcia et al. 2005	-5.162	< .001
Meltzer et al. 2002	-4.876	< .001
Peters et al. 2007	-5.319	< .001
Zeiger et al. 2006	-5.613	< .001
Zeiger et al. 2006	-6.377	< .001
Overall Model	-6.064	< .001

Results for Heterogeneity among studies:

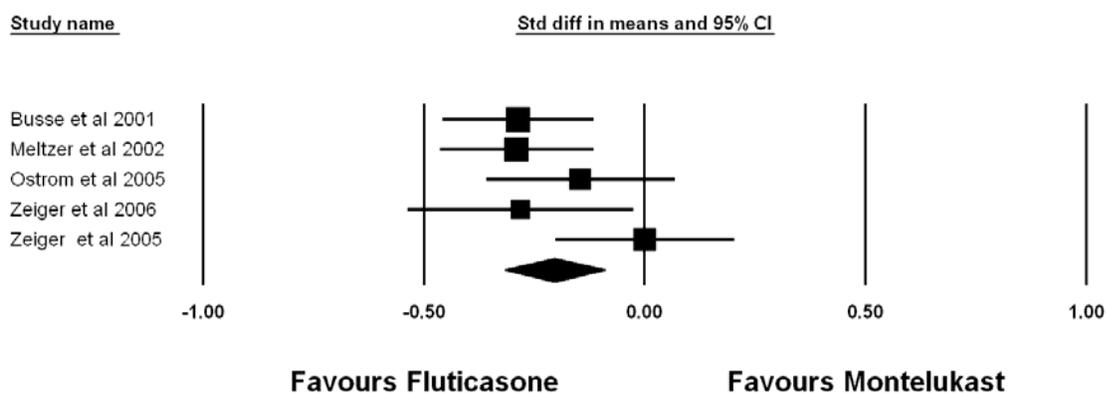
Value of Q Statistic	d.f. for test of Q	P value	I-squared
5.065	5	.4080	1.293

Rescue Medication Use (puffs per day)

Summary of overall results:

Study Name	Statistics for each study						
	Std. Diff in Means	Std. Error	Variance	Lower Limit	Upper Limit	Z-value	p-value
Busse et al 2001	-.287	.087	.008	-.457	-.116	-3.292	.001
Meltzer et al 2002	-.290	.088	.008	-.462	-.117	-3.292	.001
Ostrom et al 2005	-.145	.108	.012	-.358	.067	-1.342	.180
Zeiger et al 2006	-.281	.130	.017	-.535	-.027	-2.166	.030
Zeiger et al 2005	.000	.103	.011	-.201	.201	.000	1.000
Random effects model	-.204	.057	.003	-.317	-.091	-3.552	<.001

Overall results of the meta-analysis are highlighted in gray.



Sensitivity analysis results:

Study Name	Statistics with study removed	
	Z-value	p-value
Busse et al 2001	-2.523	.012
Meltzer et al 2002	-2.535	.011
Ostrom et al 2005	-3.054	.002
Zeiger et al 2006	-2.772	.006
Zeiger et al 2005	-5.178	<.001
Overall Model	-3.552	<.001

Results for Heterogeneity among studies:

Value of Q Statistic	d.f. for test of Q	P-value	I-squared
3.958	4	.4117	0

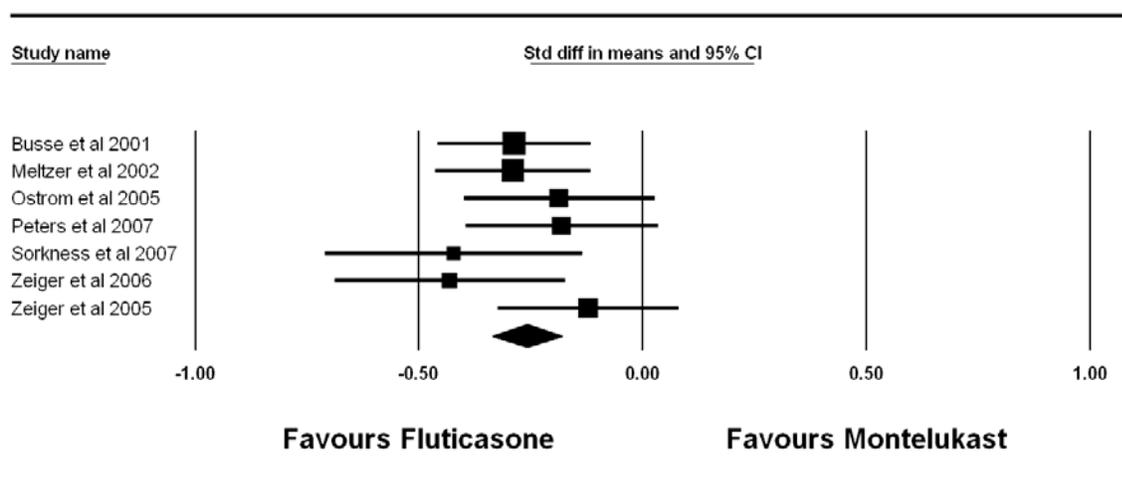
Percent Improved Symptom Control (symptom free days)

Summary of overall results:

Study Name	Statistics for each study						
	Std. Diff in Means	Std. Error	Variance	Lower Limit	Upper Limit	Z-value	P value
Busse et al. 2001a	-0.287	.087	.008	-0.457	-0.116	-3.292	.001
Meltzer et al. 2002	-0.290	.088	.008	-0.462	-0.117	-3.292	.001
Ostrom et al. 2005	-0.186	.108	.012	-0.398	0.027	-1.713	.087
Peters et al. 2007	-0.180	.109	.012	-0.395	0.034	-1.646	.100
Sorkness et al. 2007	-0.422	.146	.021	-0.708	-0.135	-2.882	.004
Zeiger et al. 2006	-0.430	.131	.017	-0.686	-0.174	-3.294	.001
Zeiger et al. 2005	-0.121	.103	.011	-0.322	0.081	-1.176	.240

Random effects model	-.258	.040	.002	-.336	-.180	-6.473	< .001
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Overall results of the meta-analysis are highlighted in gray.



Sensitivity analysis results:

Study Name	Statistics with study removed	
	Z-value	P value
Busse et al. 2001a	-5.172	< .001
Meltzer et al. 2002	-5.183	< .001
Ostrom et al. 2005	-6.000	< .001
Peters et al. 2007	-6.061	< .001
Sorkness et al. 2007	-5.911	< .001
Zeiger et al. 2006	-5.741	< .001
Zeiger et al. 2005	-6.528	< .001
Overall Model	-6.473	< .001

Results for Heterogeneity among studies:

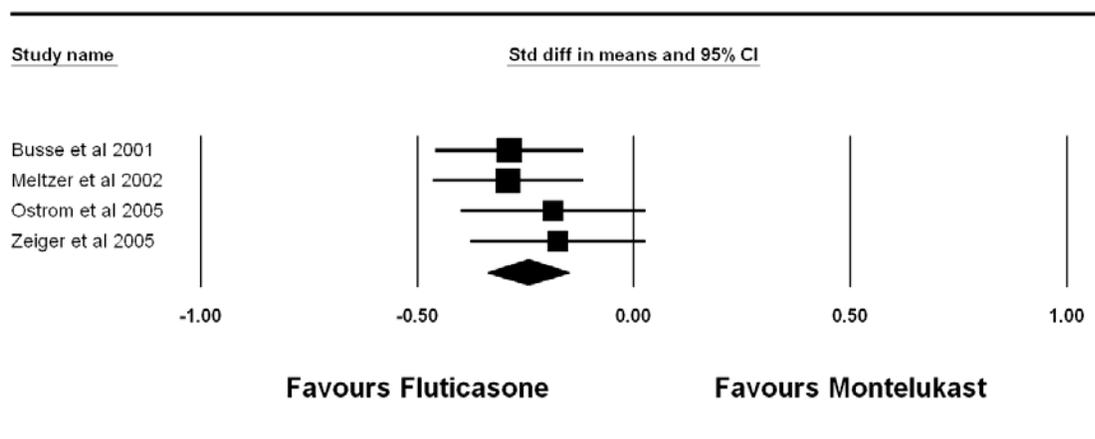
Value of Q Statistic	d.f. for test of Q	P value	I-squared
5.964	6	.4272	0

Percent Improved Symptom Control (symptom score)

Summary of overall results:

Study Name	Statistics for each study						
	Std. Diff in Means	Std. Error	Variance	Lower Limit	Upper Limit	Z-value	P value
Busse et al. 2001	-0.287	.087	.008	-0.457	-0.116	-3.292	.001
Meltzer et al. 2002	-0.290	.088	.008	-0.462	-0.117	-3.292	.001
Ostrom et al. 2005	-0.186	.108	.012	-0.398	.027	-1.713	.087
Zeiger et al. 2005	-0.174	.103	.011	-0.376	.0027	-1.698	.090
Random effects model	-0.244	.048	.002	-0.337	-0.151	-5.121	<.001

Overall results of the meta-analysis are highlighted in gray.



Sensitivity analysis results:

Study Name	Statistics with study removed	
	Z-value	P value
Busse et al. 2001	-3.967	< .001
Meltzer et al. 2002	-3.972	< .001
Ostrom et al. 2005	-4.864	< .001
Zeiger et al. 2005	-4.892	< .001
Overall Model	-5.121	< .001

Results for Heterogeneity among studies:

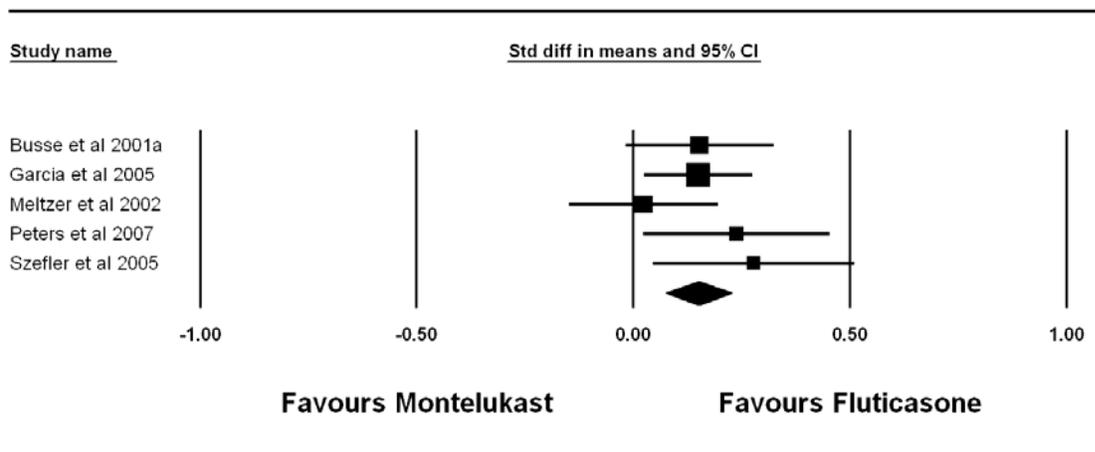
Value of Q Statistic	d.f. for test of Q	P value	I-squared
1.259	3	.7389	0

Percent Exacerbations

Summary of overall results:

Study Name	Statistics for each study						
	Std. Diff in Means	Std. Error	Variance	Lower Limit	Upper Limit	Z-value	P value
Busse et al. 2001a	.153	.087	.008	-.017	.323	1.763	.078
Garcia et al. 2005	.150	.064	.004	.026	.275	2.366	.018
Meltzer et al. 2002	.023	.088	.008	-.148	.195	.268	.789
Peters et al. 2007	.238	.110	.012	.023	.453	2.172	.030
Szeffler et al. 2005	.278	.118	.014	.046	.510	2.348	.019
Random effects model	.151	.039	.002	.075	.227	3.886	< .001

Overall results of the meta-analysis are highlighted in gray.



Sensitivity analysis results:

Study Name	Statistics with study removed	
	Z-value	P value
Busse et al. 2001a	3.000	.003
Garcia et al. 2005	2.764	.006
Meltzer et al. 2002	4.202	< .001
Peters et al. 2007	3.220	.001
Szeffler et al. 2005	3.299	.001
Random effects model	3.886	< .001

Results for Heterogeneity among studies:

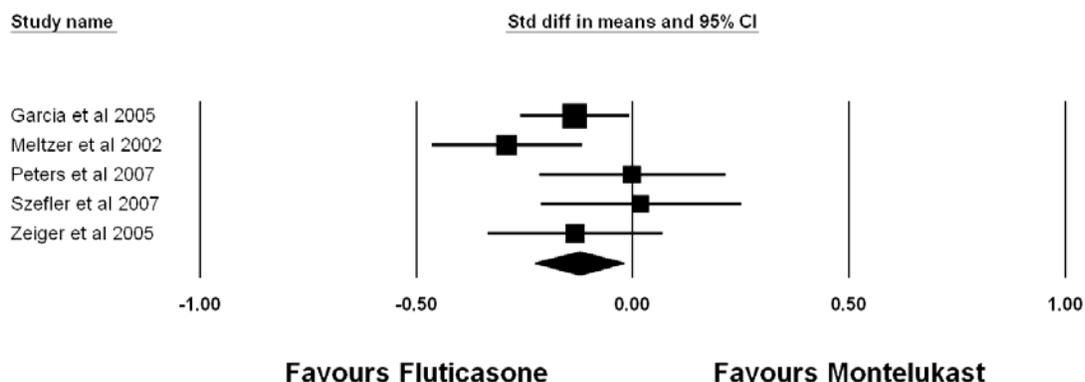
Value of Q Statistic	d.f. for test of Q	P value	I-squared
3.906	4	.4189	0

Change in AQLQ Score

Summary of overall results:

Study Name	Std. Diff in Means	Std. Error	Statistics for each study				
			Variance	Lower Limit	Upper Limit	Z-value	P value
Garcia et al. 2005	-.133	.064	.004	-.258	-.009	-2.097	.036
Meltzer et al. 2002	-.290	.088	.008	-.462	-.117	-3.292	.001
Peters et al. 2007	.000	.109	.012	-.214	.214	.000	1.00
Szeffler et al. 2007	.020	.118	.014	-.211	.251	.169	.866
Zeiger et al. 2005	-.132	.103	.011	-.333	.070	-1.282	.200
Random effects model	-.123	.052	.003	-.225	-.021	-2.353	.019

Overall results of the meta-analysis are highlighted in gray.



Sensitivity analysis results:

Study Name	Statistics with study removed	
	Z-value	P value
Garcia et al. 2005	-1.496	.135
Meltzer et al. 2002	-1.974	.048
Peters et al. 2007	-2.620	.009
Szeffler et al. 2007	-2.737	.006
Zeiger et al. 2005	-1.755	.079
Overall Model	-2.353	.019

Results for Heterogeneity among studies:

Value of Q Statistic	d.f. for test of Q	P value	I-squared
4.182	4	.3819	4.343

ML compared with BDP Results

Summary of Outcome Measures Analyzed:

- 7. Rescue medication use (percent improved)
- 8. Symptom control (percent improved)

Results

Rescue Medication Use (percent improved)

Studies that reported outcome, but are not included:

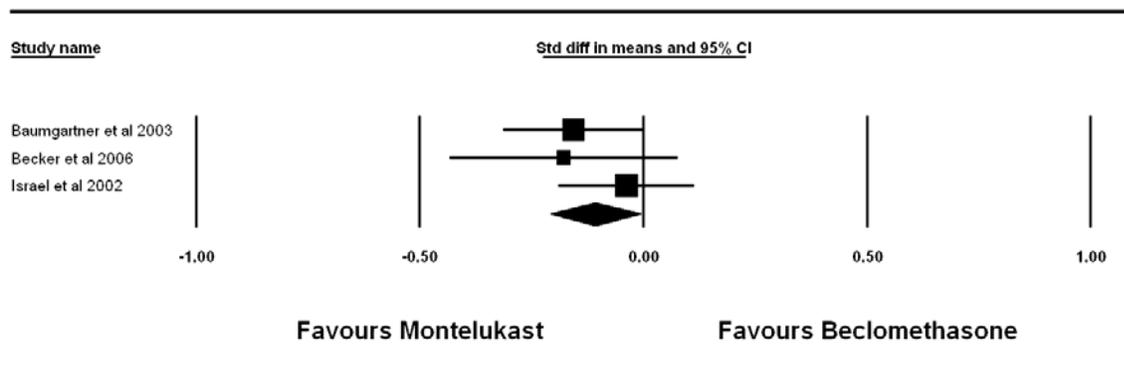
Study	Reason
Malmstrom et al. 1999	P values reported for comparisons to placebo only

Summary of overall results:

Study Name	Statistics for each study						
	Std. Diff in Means	Std. Error	Variance	Lower Limit	Upper Limit	Z-value	P value
Baumgartner et	-.157	.080	.006	-.314	-.000	-1.961	.050

al. 2003							
Becker et al. 2006	-.178	.130	.017	-.432	.076	-1.374	.170
Israel et al. 2002	-.038	.077	.006	-.190	.113	-.495	.621
Random effects model	-.108	.051	.003	-.208	-.008	-2.120	.034

Overall results of the meta-analysis are highlighted in gray.



Sensitivity analysis results:

Study Name	Statistics with study removed	
	Z-value	P value
Baumgartner et al. 2003	-1.128	.259
Becker et al. 2006	-1.614	.107
Israel et al. 2002	-2.390	.017
Overall Model	-2.120	.034

Results for Heterogeneity among studies:

Value of Q Statistic	d.f. for test of Q	P value	I-squared
1.482	2	.4766	0

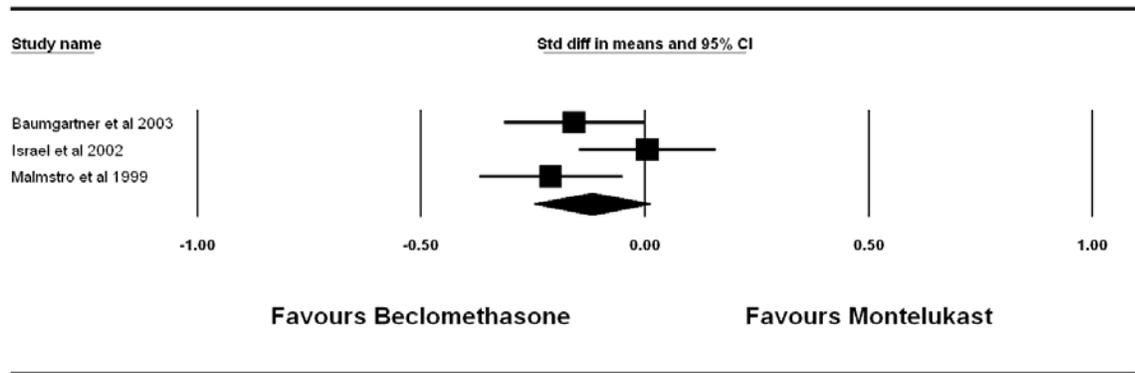
Symptom Control

Studies that reported outcome, but are not included: NA

Summary of overall results:

Study Name	Statistics for each study						
	Std. Diff in Means	Std. Error	Variance	Lower Limit	Upper Limit	Z-value	P value
Baumgartner et al. 2003	-.157	.080	.006	-.314	-.000	-1.961	.050
Israel et al. 2002	.007	.077	.006	-.144	.158	.089	.929
Malmstrom et al. 1999	-.209	.081	.007	-.369	-.050	-2.577	.010
Random effects model	-.118	.066	.004	-.247	-.011	-1.791	.073

Overall results of the meta-analysis are highlighted in gray.



Sensitivity analysis results:

Study Name	Statistics with study removed	
	Z-value	P value
Baumgartner et al. 2003	-.923	.356
Israel et al. 2002	-3.205	.001
Malmstrom et al. 1999	-.900	.358
Overall Model	-1.791	.073

Results for Heterogeneity among studies:

Value of Q Statistic	d.f. for test of Q	P value	I-squared
1.978	2	.3719	0

Zaf compared with ICS Results

Summary of Outcome Measures Analyzed:

- 9. Rescue medication use (percent improved)
- 10. Symptom control (percent improved)
- 11. Symptom control (score)
- 12. Percent Exacerbations

Results

Rescue Medication Use (percent improved)

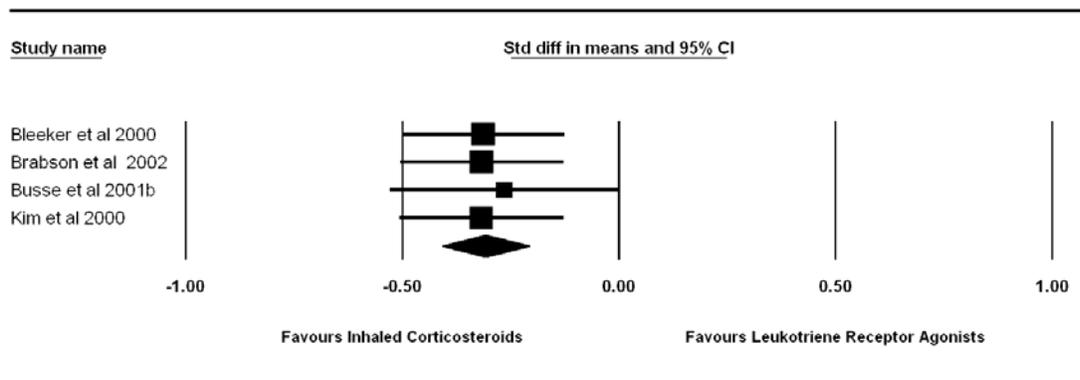
***Note – results are identical for both percent improved and puffs outcomes, so the results are only presented once.**

Summary of overall results:

Study Name	Statistics for each study						
	Std. Diff in Means	Std. Error	Variance	Lower Limit	Upper Limit	Z-value	P value

Bleecker et al. 2000	-.312	.095	.009	-.498	-.126	-3.292	.001
Brabson et al. 2002	-.316	.096	.009	-.504	-.128	-3.292	.001
Busse et al. 2001	-.263	.134	.018	-.526	.000	-1.962	.050
Kim et al. 2000	-.317	.096	.009	-.506	-.128	-3.292	.001
Random effects model	-.307	.051	.003	-.408	-.207	-6.020	< .001

Overall results of the meta-analysis are highlighted in gray.



Sensitivity analysis results:

Study Name	Statistics with study removed	
	Z-value	P value
Bleecker et al. 2000	-5.040	< .001
Brabson et al. 2002	-5.041	< .001
Busse et al. 2001	-5.702	< .001
Kim et al. 2000	-5.041	< .001
Overall Model	-6.020	< .001

Results for Heterogeneity among studies:

Value of Q Statistic	d.f. for test of Q	P value	I-squared
.128	3	.9983	0

Symptom Control (percent improved symptom free days)

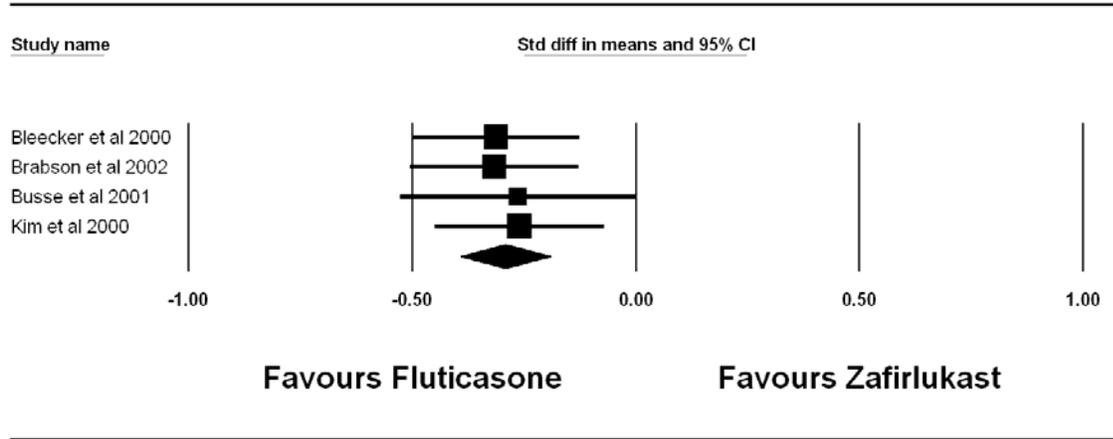
Studies that reported outcome, but are not included: NA

Summary of overall results:

Study Name	Statistics for each study						
	Std. Diff in Means	Std. Error	Variance	Lower Limit	Upper Limit	Z-value	P value
Bleecker et al. 2000	-.312	.095	.009	-.498	-.126	-3.292	.001
Brabson et al. 2002	-.316	.096	.009	-.504	-.128	-3.292	.001
Busse et al. 2001	-.263	.134	.018	-.526	.000	-1.962	.050

Kim et al. 2000	- .259	.096	.009	-.448	-.071	-3.698	.007
Random effects model	- .291	.051	.003	-.391	-.191	-5.705	< .001

Overall results of the meta-analysis are highlighted in gray.



Sensitivity analysis results:

Study Name	Statistics with study removed	
	Z-value	P value
Bleecker et al. 2000	-4.666	< .001
Brabson et al. 2002	-4.669	< .001
Busse et al. 2001	-5.361	< .001
Kim et al. 2000	-5.041	< .001
Overall Model	-5.705	< .001

Results for Heterogeneity among studies:

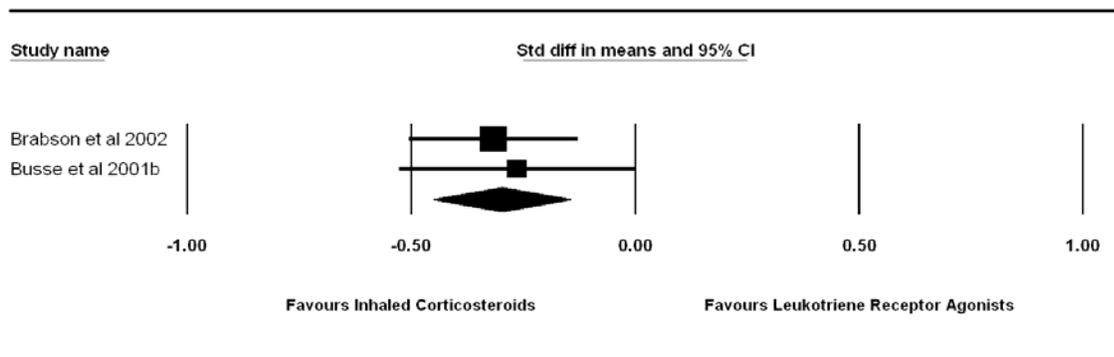
Value of Q Statistic	d.f. for test of Q	P value	I-squared
.268	3	.9659	0

Symptom Control (change in score)

Summary of overall results:

Study Name	Statistics for each study						
	Std. Diff in Means	Std. Error	Variance	Lower Limit	Upper Limit	Z-value	P value
Brabson et al. 2002	-.316	.096	.009	-.504	-.128	-3.292	.001
Busse et al. 2001	-.263	.134	.018	-.526	.000	-1.962	.050
Random effects model	- .298	.078	.006	-.451	-.145	-3.820	< .001

Overall results of the meta-analysis are highlighted in gray.



Sensitivity analysis results:

Study Name	Statistics with study removed	
	Z-value	P value
Brabson et al. 2002	-1.962	.050
Busse et al. 2001	-3.292	.001
Overall Model	-3.820	< .001

Results for Heterogeneity among studies:

Value of Q Statistic	d.f. for test of Q	P value	I-squared
.102	1	.7494	0

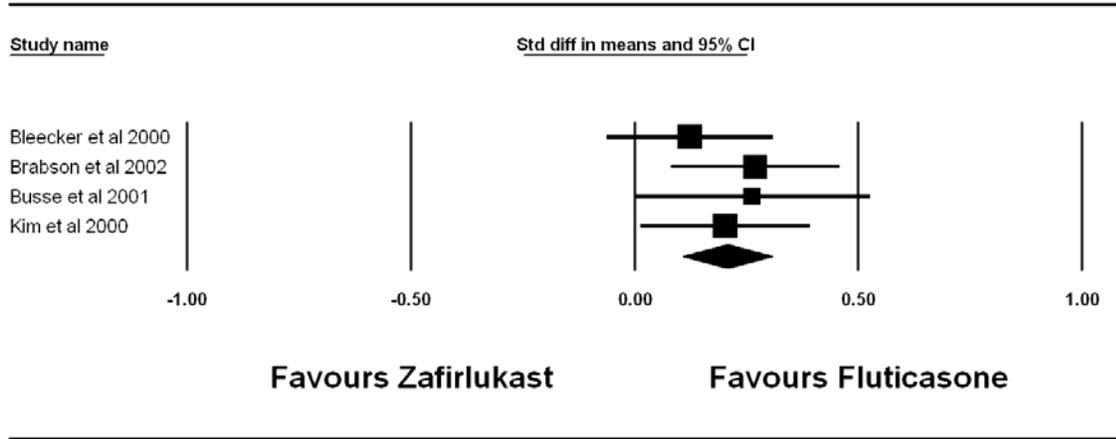
Percent Exacerbations

Studies that reported outcome, but are not included: NA

Summary of overall results:

Study Name	Statistics for each study						
	Std. Diff in Means	Std. Error	Variance	Lower Limit	Upper Limit	Z-value	P value
Bleecker et al. 2000	.123	.094	.009	-.061	.308	1.308	.191
Brabson et al. 2002	.269	.096	.009	.081	.457	2.809	.005
Busse et al. 2001	.262	.134	.018	-.001	.525	1.954	.051
Kim et al. 2000	.202	.096	.009	.014	.390	2.110	.035
Random effects model	.207	.051	.003	.107	.307	4.061	< .001

Overall results of the meta-analysis are highlighted in gray.



Sensitivity analysis results:

Study Name	Statistics with study removed	
	Z-value	P value
Bleecker et al. 2000	3.985	< .001
Brabson et al. 2002	3.032	.002
Busse et al. 2001	3.588	< .001
Kim et al. 2000	3.470	.001
Overall Model	4.061	< .001

Results for Heterogeneity among studies:

Value of Q Statistic	d.f. for test of Q	P value	I-squared
1.378	3	.7107	0

ICS compared with LABA Monotherapy

Summary of Outcome Measures Analyzed:

- 1) Rescue medication free days (percent improved)
- 2) Rescue medication reduction in puffs
- 3) Symptom control (symptom free days) (percent improved)
- 4) Change in symptom scores
- 5) Percent Exacerbations

Results

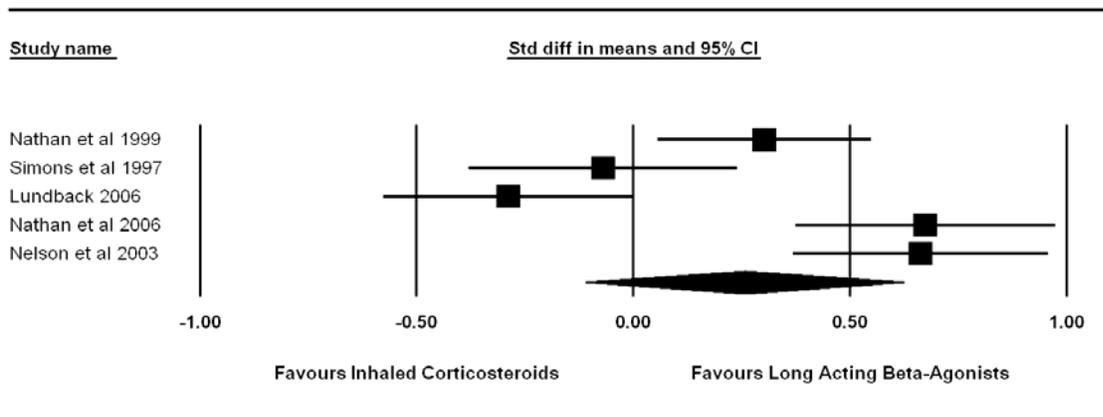
Rescue Medication Use (percent improved, rescue med free days)

Studies that reported outcome, but are not included: NA

Summary of overall results:

Study Name	Statistics for each study						
	Std. Diff in Means	Std. Error	Variance	Lower Limit	Upper Limit	Z-value	P value
Nathan et al. 1999	.303	.125	.016	.057	.548	2.411	.016
Simons et al. 1997	-.07	.158	.025	-.379	.239	-.442	.658
Lundback et al. 2006	-.289	.147	.022	-.577	-.000	-1.963	.050
Nathan et al. 2006	.674	.152	.023	.375	.973	4.422	.000
Nelson et al. 2003	.663	.150	.022	.369	.957	4.422	.000
Random effects model	.257	.187	.035	-.110	.624	1.370	.171

Overall results of the meta-analysis are highlighted in gray.



Sensitivity analysis results:

Study Name	Statistics with study removed	
	Z-value	P value
Nathan et al. 1999	.975	.330
Simons et al. 1997	1.545	.122
Lundback et al. 2006	2.353	.019
Nathan et al. 2006	.753	.452
Nelson et al. 2003	.758	.448
Overall Model	1.370	.171

Results for Heterogeneity among studies:

Value of Q Statistic	d.f. for test of Q	P value	I-squared
4.223	4	.3767	5.284

Rescue Medication Use (percent improved, puffs per day)

Note: Nathan et al. 2006 and Shapiro et al. 2000 do not report the comparison as significant, but using their raw values, they are.

Studies that reported outcome, but are not included:

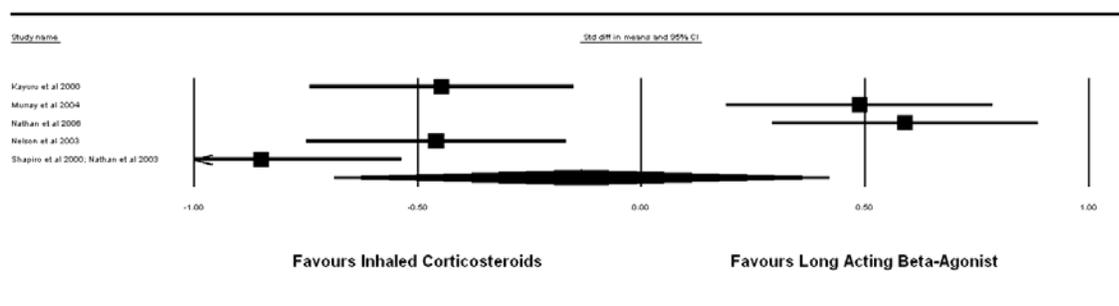
Study	Reason
Noonan et al. 2006	P values not reported, no measure of variation reported
Verberne et al. 1997	P value reported as NS, no measure of variation reported

Summary of overall results:

Study Name	Statistics for each study						
	Std. Diff in Means	Std. Error	Variance	Lower Limit	Upper Limit	Z-value	P value
Kayuru et al.	-.446	.150	.023	-.740	-.152	-2.972	.003

2000							
Murray et al. 2004	.489	.152	.023	.191	.786	3.221	.001
Nathan et al. 2006	.590	.151	.023	.293	.887	3.896	< .001
Nelson et al. 2003	-.457	.148	.022	-.747	-.168	-3.094	.002
Shapiro et al. 2000; Nathan et al. 2003	-.849	.159	.025	-1.161	-.537	-5.331	< .001
Random effects model	-.134	.282	.080	-.687	.419	-.476	.634

Overall results of the meta-analysis are highlighted in gray.



Sensitivity analysis results:

Study Name	Statistics with study removed	
	Z-value	P value
Kayuru et al. 2000	-.161	.872
Murray et al. 2004	-.949	.343
Nathan et al. 2006	-1.121	.262
Nelson et al. 2003	-.152	.879
Shapiro et al. 2000; Nathan et al. 2003	.150	.880
Overall Model	-.476	.634

Results for Heterogeneity among studies:

Value of Q Statistic	d.f. for test of Q	P value	I-squared
4.077	4	.3957	1.880

Symptom control (percent improved, symptom free days)

Studies that reported outcome, but are not included:

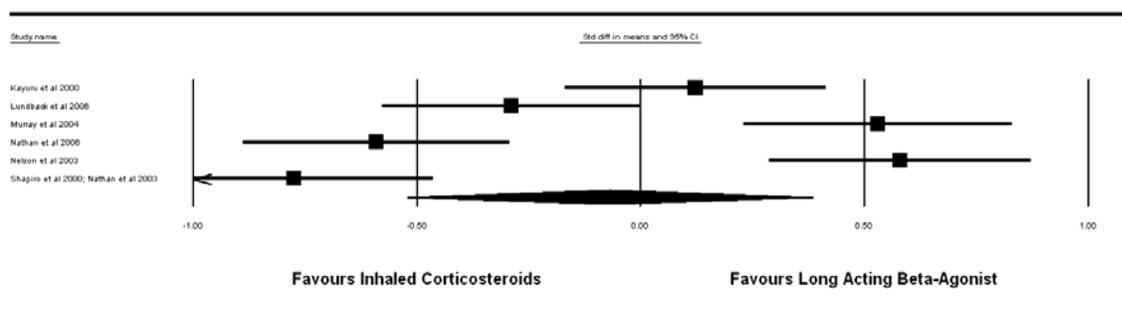
Study	Reason
Noonan et al. 2006	P values not reported, no measure of variation reported

Summary of overall results:

Study Name	Statistics for each study						
	Std. Diff in Means	Std. Error	Variance	Lower Limit	Upper Limit	Z-value	P value
Kayuru et al. 2000	.122	.148	.022	-.168	.413	.825	.409
Lundback et al.	-.289	.147	.022	-.577	-.000	-1.963	.050

2006							
Murray et al. 2004	.530	.152	.023	.232	.828	3.486	< .001
Nathan et al. 2006	-.590	.151	.023	-.887	-.293	-3.896	< .001
Nelson et al. 2003	.580	.149	.022	.288	.872	3.896	< .001
Shapiro et al. 2000; Nathan et al. 2003	-.774	.158	.025	-1.084	-.464	-4.897	< .001
Random effects model	-.069	.231	.053	-.521	.383	-.300	.765

Overall results of the meta-analysis are highlighted in gray.



Sensitivity analysis results:

Study Name	Statistics with study removed	
	Z-value	P value
Kayuru et al. 2000	-.385	.700
Lundback et al. 2006	-.091	.928
Murray et al. 2004	-.775	.438
Nathan et al. 2006	.140	.889
Nelson et al. 2003	-.850	.395
Shapiro et al. 2000; Nathan et al. 2003	.312	.755
Overall Model	-.300	.765

Results for Heterogeneity among studies:

Value of Q Statistic	d.f. for test of Q	P value	I-squared
5.108	5	.4028	2.122

Symptom control (change in symptom score, percentage improvement)

Studies that reported outcome, but are not included:

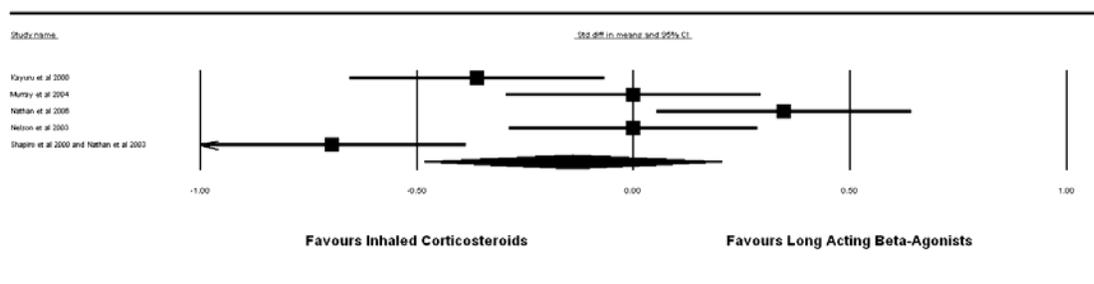
Study	Reason
Noonan et al. 2006	P values not reported, no measure of variation reported

Summary of overall results:

Study Name	Statistics for each study						
	Std. Diff in Means	Std. Error	Variance	Lower Limit	Upper Limit	Z-value	P value

Kayuru et al. 2000	-.361	.149	.022	-.653	-.068	-2.412	.016
Murray et al. 2004	.000	.149	.022	-.293	.293	.000	1.00
Nathan et al. 2006	.348	.149	.022	.055	.641	2.330	.020
Nelson et al. 2003	.000	.146	.021	-.286	.286	.000	1.00
Shapiro et al. 2000; Nathan et al. 2003	-.695	.157	.025	-1.033	-.387	-4.423	< .001
Random effects model	-.140	.175	.031	-.482	.203	-.798	.425

Overall results of the meta-analysis are highlighted in gray.



Sensitivity analysis results:

Study Name	Statistics with study removed	
	Z-value	P value
Kayuru et al. 2000	-.397	.691
Murray et al. 2004	-.788	.430
Nathan et al. 2006	-1.589	.112
Nelson et al. 2003	-.789	.432
Shapiro et al. 2000; Nathan et al. 2003	-.022	.983
Overall Model	-.798	.425

Results for Heterogeneity among studies:

Value of Q Statistic	d.f. for test of Q	P value	I-squared
4.124	4	.3895	3.018

Exacerbations (percentage)

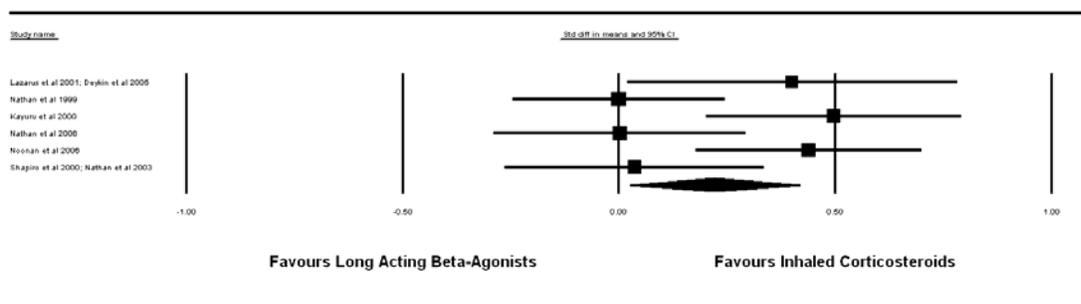
Studies that reported outcome, but are not included: NA

Summary of overall results:

Study Name	Statistics for each study						
	Std. Diff in Means	Std. Error	Variance	Lower Limit	Upper Limit	Z-value	P value
Lazarus et al.	.400	.194	.038	.019	.781	2.059	.040

2001; Deykin et al. 2005							
Nathan et al. 1999	.000	.125	.016	-.245	.245	.000	1.000
Kayuru et al. 2000	.496	.151	.023	.201	.791	3.295	.001
Nathan et al. 2006	.002	.148	.022	-.289	.292	.013	.990
Noonan et al. 2006	.438	.133	.018	.178	.699	3.294	.001
Shapiro et al. 2000; Nathan et al. 2003	.036	.153	.023	-.263	.335	.234	.815
Random effects model	.221	.100	.010	.025	.417	2.211	.027

Overall results of the meta-analysis are highlighted in gray.



Sensitivity analysis results:

Study Name	Statistics with study removed	
	Z-value	P value
Lazarus et al. 2001; Deykin et al. 2005	1.729	.084
Nathan et al. 1999	2.509	.012
Kayuru et al. 2000	1.631	.103
Nathan et al. 2006	2.383	.017
Noonan et al. 2006	1.607	.108
Shapiro et al. 2000; Nathan et al. 2003	2.252	.024
Overall Model	2.211	.027

Results for Heterogeneity among studies:

Value of Q Statistic	d.f. for test of Q	P value	I-squared
4.835	5	.4363	0

LABA + ICS compared with ICS (same dose, first line therapy)

Summary of Outcome Measures Analyzed:

1) Rescue medication reduction in puffs

- 2) Rescue medicine free days (percent improved)
- 3) Symptom Control (percent improved symptom free days)
- 4) Symptom Control (percent improved symptom score)

Results

Rescue Medication Use (percent improved, reduction in puffs)

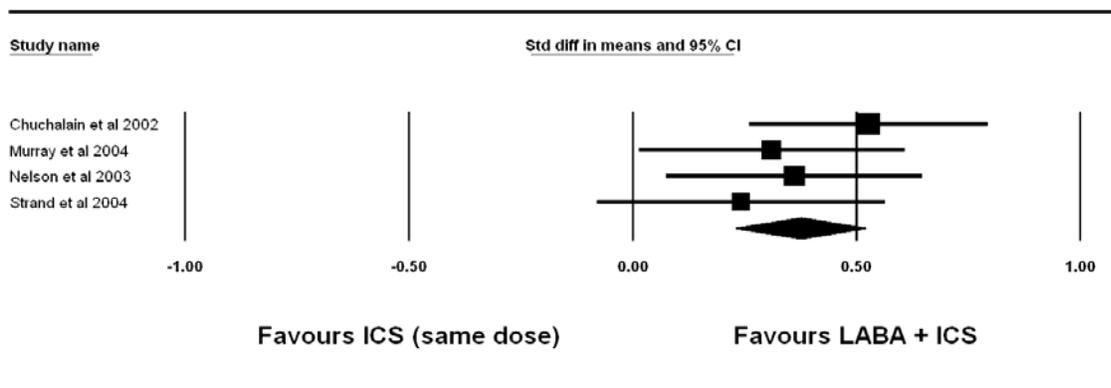
Studies that reported outcome, but are not included:

Study	Reason
Chroinin al 2004	Review paper

Summary of overall results:

Study Name	Statistics for each study						
	Std. Diff in Means	Std. Error	Variance	Lower Limit	Upper Limit	Z-value	P value
Chuchalain et al. 2002	.528	.136	.018	.262	.794	3.895	< .001
Murray et al. 2004	.311	.151	.023	.015	.607	2.057	.040
Nelson et al. 2003	.362	.146	.021	.077	.647	2.487	.013
Strand et al. 2004	.164	.242	.027	-.079	.564	1.478	.139
Random effects model	.074	.375	.005	.230	.520	5.065	< .001

Overall results of the meta-analysis are highlighted in gray.



Sensitivity analysis results:

Study Name	Statistics with study removed	
	Z-value	P value
Chuchalain et al. 2002	3.508	.001
Murray et al. 2004	4.654	< .001

Nelson et al. 2003	4.286	< .001
Strand et al. 2004	4.928	< .001
Overall Model	5.065	< .001

Results for Heterogeneity among studies:

Value of Q Statistic	d.f. for test of Q	P value	I-squared
2.117	3	.5485	0

Rescue Medication Use (percent improved, rescue free days)

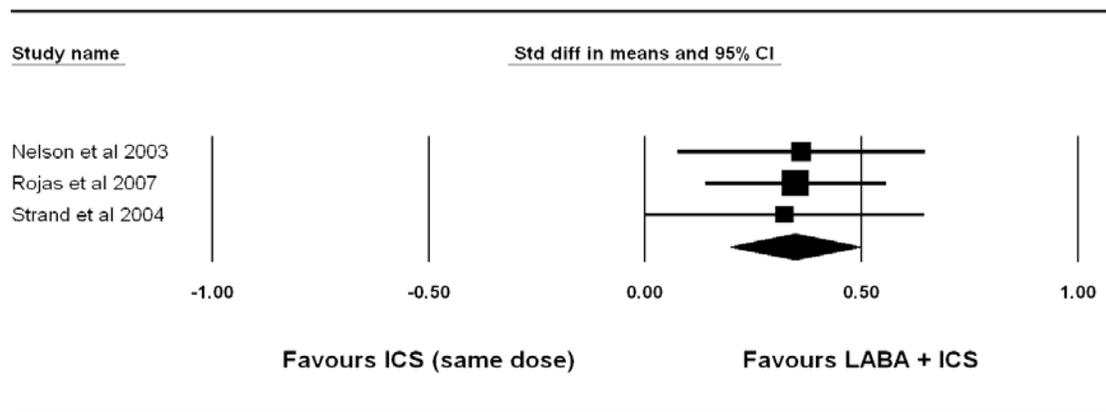
Studies that reported outcome, but are not included:

Study	Reason
Chroinin al 2004	Review paper

Summary of overall results:

Study Name	Statistics for each study						
	Std. Diff in Means	Std. Error	Variance	Lower Limit	Upper Limit	Z-value	P value
Nelson et al. 2003	.146	.362	.021	.077	.647	2.487	.013
Rojas et al. 2007	.106	.349	.011	.141	.556	3.293	.001
Strand et al. 2004	.164	.323	.027	.001	.646	1.966	.049
Random effects model	.076	.347	.006	.198	.496	4.568	<.001

Overall results of the meta-analysis are highlighted in gray.



Sensitivity analysis results:

Study Name	Statistics with study removed	
	Z-value	P value
Nelson et al. 2003	3.833	< .001
Rojas et al. 2007	3.165	.002
Strand et al. 2004	4.126	< .001
Overall Model	4.568	< .001

Results for Heterogeneity among studies:

Value of Q Statistic	d.f. for test of Q	P value	I-squared
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.031	2	.9846	0
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Symptom Control (percent improved, symptom free days)

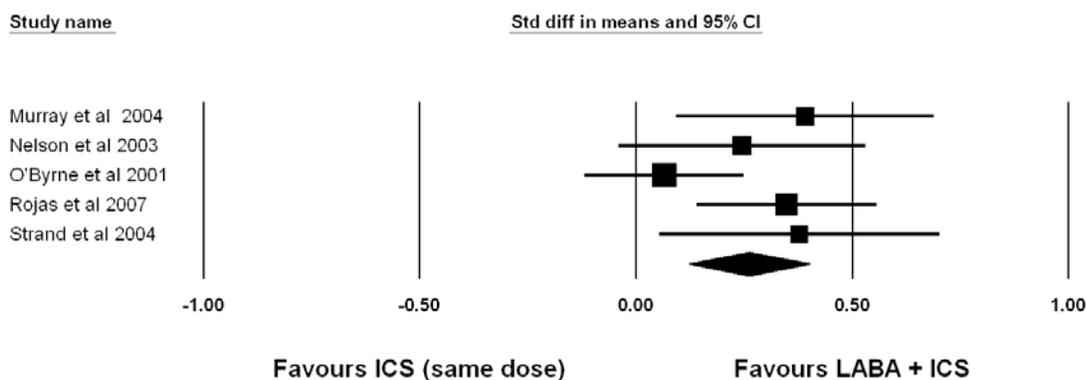
Studies that reported outcome, but are not included:

Study	Reason
Chroinin al 2004	Review paper
Chuchalain et al. 2002	Reported different outcomes for symptom control

Summary of overall results:

Study Name	Statistics for each study						
	Std. Diff in Means	Std. Error	Variance	Lower Limit	Upper Limit	Z-value	P value
Murray et al. 2004	.391	.152	.023	.094	.689	2.580	.010
Nelson et al. 2003	.246	.145	.021	-.038	.530	1.698	.090
O'Byrne et al. 2001	.066	.093	.009	-.117	.249	.707	.480
Rojas et al. 2007	.349	.106	.011	.141	.556	3.293	.001
Strand et al. 2007	.378	.165	.027	.055	.701	2.294	.022
Random effects model	.262	.071	.005	.123	.400	3.695	< .001

Overall results of the meta-analysis are highlighted in gray.



Sensitivity analysis results:

Study Name	Statistics with study removed	
	Z-value	P value
Murray et al. 2004	2.980	.003
Nelson et al. 2003	3.044	.002
O'Byrne et al. 2001	5.005	< .001
Rojas et al. 2007	2.748	.006
Strand et al. 2007	3.012	.003
Overall Model	3.695	< .001

Results for Heterogeneity among studies:

Value of Q Statistic	d.f. for test of Q	P value	I-squared
3.475	4	.4817	0

Symptom Control (symptom score improvement)

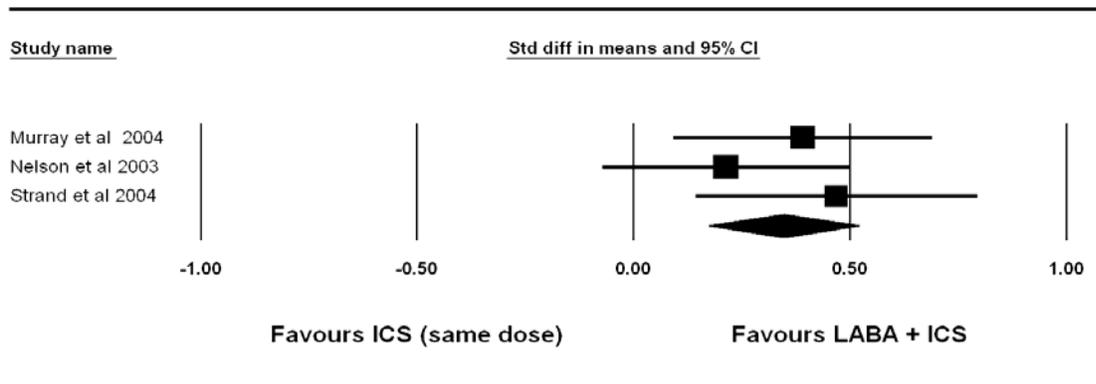
Studies that reported outcome, but are not included:

Study	Reason
Chroinin al 2004	Review paper
Chuchalain et al. 2002	Reported different outcomes for symptom control

Summary of overall results:

Study Name	Statistics for each study						
	Std. Diff in Means	Std. Error	Variance	Lower Limit	Upper Limit	Z-value	P value
Murray et al. 2004	.391	.152	.023	.094	.689	2.580	.010
Nelson et al. 2003	.214	.145	.021	-.070	.498	1.478	.139
Strand et al. 2007	.469	.166	.027	.144	.794	2.832	.005
Random effects model	.347	.089	.008	.174	.521	3.922	<.001

Overall results of the meta-analysis are highlighted in gray.



Sensitivity analysis results:

<i>Study Name</i>	<i>Statistics with study removed</i>	
	<i>Z-value</i>	<i>P value</i>
Murray et al. 2004	2.590	.010
Nelson et al. 2003	3.815	.000
Strand et al. 2007	2.850	.004
Overall Model	3.922	<.001

Results for Heterogeneity among studies:

<i>Value of Q Statistic</i>	<i>d.f. for test of Q</i>	<i>P value</i>	<i>I-squared</i>
1.475	2	.4783	0

ICS compared with LABA+ICS (Higher Dose) Results

Summary of Outcome Measures Analyzed:

- 1) Rescue medication use (percent improved rescue free days)
- 2) Rescue medication use (percent reduction in puffs)
- 3) Symptom control (percent improved symptom free days)
- 4) Symptom control (percent change in symptom score)
- 5) Percent Exacerbations

Studies that reported outcomes within this comparison, but are not included:

<i>Study</i>	<i>Reason</i>
Greenston et al. 2005	Review paper
Bouros et al. 1999	No data reported, or only reported in figures
Schermer et al. 2007	No data reported, or only reported in figures
Woolcock et al. 1996	No data reported, or only reported in figures

Results

Rescue Medication Use (Rescue Free Days)

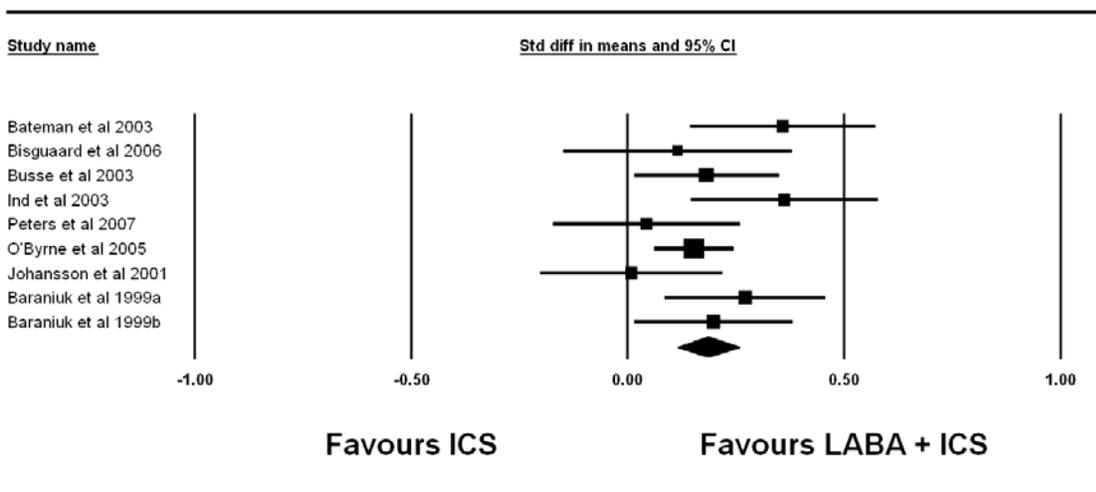
Studies that reported outcome, but are not included:

<i>Study</i>	<i>Reason</i>
Vernerne et al. 1998	<i>P</i> value not reported
Jenkins et al. 2000	Only reports rescue free nights
Kelson et al.	Only reports rescue free nights

Summary of overall results:

<i>Study Name</i>	<i>Statistics for each study</i>						
	<i>Std. Diff in Means</i>	<i>Std. Error</i>	<i>Variance</i>	<i>Lower Limit</i>	<i>Upper Limit</i>	<i>Z-value</i>	<i>p-value</i>
Bateman et al 2003	.358	.109	.012	.145	.571	3.293	.001
Bisgaard et al 2006	.115	.134	.018	-.148	.379	.861	.389
Busse et al 2003	.182	.085	.007	.016	.348	2.145	.032
Ind et al 2003	.362	.110	.012	.147	.578	3.293	.001
Peters et al 2007	.044	.109	.012	-.171	.258	.399	.690
O'Byrne et al 2005	.153	.047	.002	.062	.244	3.291	.001
Johansson et al 2001	.009	.107	.011	-.201	.219	.083	.934
Baraniuk et al 1999a	.272	.094	.009	.087	.456	2.880	.004
Baraniuk et al 1999b	.199	.093	.009	.016	.381	2.133	.033
Random effects model	.186	.036	.001	.115	.256	5.148	<.001

Overall results of the meta-analysis are highlighted in gray.



Sensitivity analysis results:

Study Name	Statistics with study removed	
	Z-value	p-value
Bateman et al 2003	4.992	<.001
Bisgaard et al 2006	4.879	<.001
Busse et al 2003	4.477	<.001
Ind et al 2003	5.023	<.001
Peters et al 2007	5.385	<.001
O'Byrne et al 2005	4.367	<.001
Johansson et al 2001	5.852	<.001
Baraniuk et al 1999a	4.497	<.001
Baraniuk et al 1999b	4.491	<.001
Overall Model	5.148	<.001

Results for Heterogeneity among studies:

Value of Q Statistic	d.f. for test of Q	P-value	I-squared
8.574	8	.3795	6.695

Rescue Medication Use (Change in puffs)

Studies that reported outcome, but are not included:

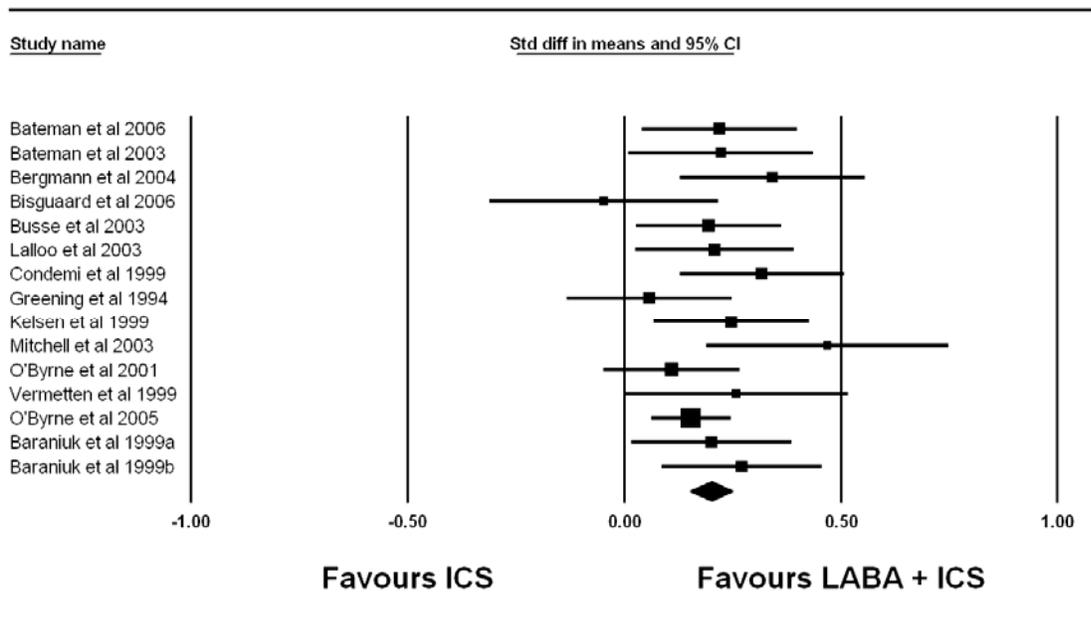
Study	Reason
Pauwels et al 1997	P-value not reported

Summary of overall results:

Study Name	Statistics for each study						
	Std. Diff in Means	Std. Error	Variance	Lower Limit	Upper Limit	Z-value	p-value
Bateman et al 2003	0.35	0.10	0.01	0.15	0.55	4.992	<.001
Bisgaard et al 2006	0.25	0.08	0.01	0.05	0.45	4.879	<.001
Busse et al 2003	0.30	0.07	0.01	0.10	0.50	4.477	<.001
Ind et al 2003	0.40	0.08	0.01	0.20	0.60	5.023	<.001
Peters et al 2007	0.20	0.06	0.01	0.00	0.40	5.385	<.001
O'Byrne et al 2005	0.35	0.08	0.01	0.15	0.55	4.367	<.001
Johansson et al 2001	0.25	0.04	0.01	0.05	0.45	5.852	<.001
Baraniuk et al 1999a	0.30	0.07	0.01	0.10	0.50	4.497	<.001
Baraniuk et al 1999b	0.35	0.08	0.01	0.15	0.55	4.491	<.001
Overall Model	0.5148	0.10	0.01	0.31	0.72	5.148	<.001

Bateman et al 2006	.220	.091	.008	-.399	-.041	-2.410	.016
Bateman et al 2003	.222	.108	.012	.010	.434	2.055	.040
Bergmann et al 2004	.342	.108	.012	.130	.554	3.158	.002
Bisgaard et al 2006	-.048	.134	.018	-.311	.215	-.359	.720
Busse et al 2003	.194	.085	.007	.028	.361	2.291	.022
Laloo et al 2003	.208	.093	.009	.026	.390	2.243	.025
Condemi et al 1999	.317	.096	.009	.128	.506	3.292	.001
Greening et al 1994	.058	.097	.009	-.132	.248	.594	.553
Kelson et al 1999	.246	.091	.008	.067	.426	2.698	.007
Mitchell et al 2003	.469	.142	.020	-.748	-.190	-3.295	.001
O'Byrne et al 2001	.109	.079	.006	-.265	.047	-1.373	.170
Vermetten et al 1999	.258	.132	.017	.000	.516	1.962	.050
O'Byrne et al 2005	.153	.047	.002	-.244	-.062	-3.291	.001
Baraniuk et al 1999a	.201	.094	.009	.016	.385	2.133	.033
Baraniuk et al 1999b	.271	.094	.009	.086	.455	2.880	.004
Random effects model	.201	.025	.001	.151	.250	8.00	<.001

Overall results of the meta-analysis are highlighted in gray.



Sensitivity analysis results:

<i>Study Name</i>	<i>Statistics with study removed</i>	
	<i>Z-value</i>	<i>p-value</i>
Bateman et al 2006	7.394	<.001
Bateman et al 2003	7.483	<.001
Bergmann et al 2004	7.752	<.001
Bisgaard et al 2006	8.758	<.001
Busse et al 2003	7.408	<.001
Lalloo et al 2003	7.424	<.001
Condemi et al 1999	7.615	<.001
Greening et al 1994	8.455	<.001
Kelson et al 1999	7.384	<.001
Mitchell et al 2003	8.141	<.001
O'Byrne et al 2001	8.028	<.001
Vermetten et al 1999	7.557	<.001
O'Byrne et al 2005	7.530	<.001
Baraniuk et al 1999a	7.447	<.001
Baraniuk et al 1999b	7.429	<.001
Overall model	8.000	<.001

Results for Heterogeneity among studies:

<i>Value of Q Statistic</i>	<i>d.f. for test of Q</i>	<i>P-value</i>	<i>I-squared</i>
14.289	14	.4284	2.025

Symptom Control (change in percentage of symptom free days)

Studies that reported outcome, but are not included:

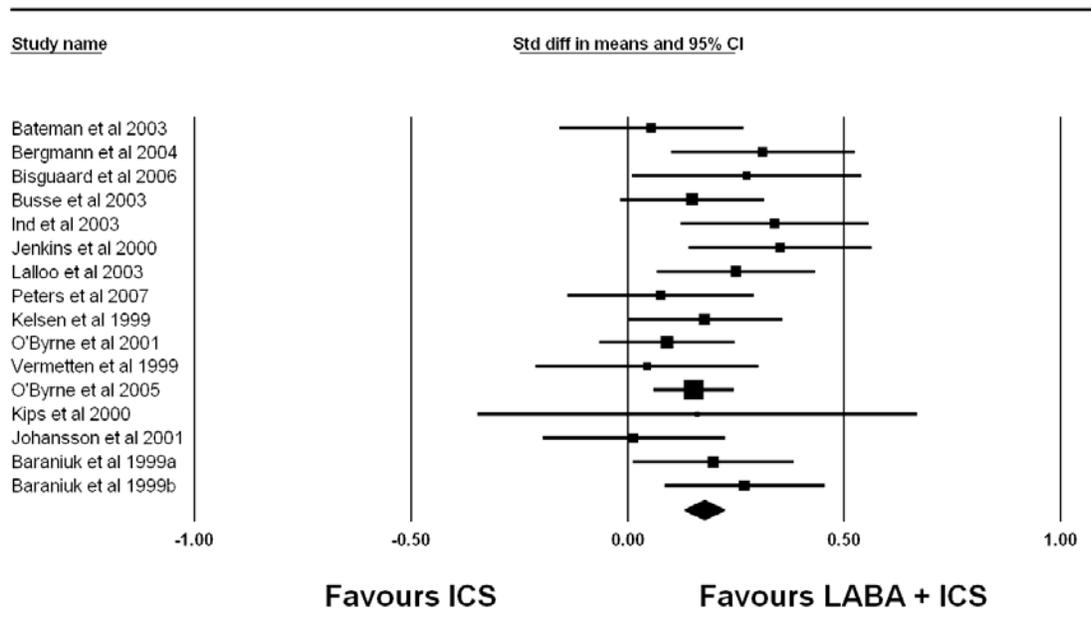
<i>Study</i>	<i>Reason</i>
Greening et al 1994	P-value reported at NS only

Summary of overall results:

<i>Study Name</i>	<i>Statistics for each study</i>						
	<i>Std. Diff in Means</i>	<i>Std. Error</i>	<i>Variance</i>	<i>Lower Limit</i>	<i>Upper Limit</i>	<i>Z-value</i>	<i>p-value</i>
Bateman et al 2003	.056	.108	.012	-.156	.267	.515	.607
Bergmann et al 2004	.313	.108	.012	.101	.525	2.896	.004
Bisgaard et al 2006	.276	.135	.018	.012	.540	2.046	.041
Busse et al 2003	.149	.085	.007	-.017	.316	1.763	.078
Ind et al 2003	.340	.110	.012	.124	.555	3.093	.002
Jenkins et al	.353	.107	.012	.143	.564	3.293	.001

2000							
Lalloo et al 2003	.251	.093	.009	.069	.433	2.698	.007
Peters et al 2007	.077	.109	.012	-.137	.292	.707	.480
Kelson et al 1999	.179	.091	.008	.000	.358	1.961	.050
O'Byrne et al 2001	.091	.079	.006	-.064	.247	1.151	.250
Vermetten et al 1999	.046	.131	.017	-.211	.303	.351	.726
O'Byrne et al 2005	.153	.047	.002	.062	.244	3.291	.001
Kips et al 2000	.162	.259	.067	-.345	.668	.625	.532
Johansson et al 2001	.015	.107	.011	-.195	.225	.140	.889
Baraniuk et al 1999a	.199	.094	.009	.014	.383	2.110	.035
Baraniuk et al 1999b	.271	.094	.009	.086	.455	2.880	.004
Random effects model	.177	.024	.001	.130	.224	7.391	<.001

Overall results of the meta-analysis are highlighted in gray.



Sensitivity analysis results:

Study Name	Statistics with study removed	
	Z-value	p-value
Bateman et al 2003	7.559	<.001
Bergmann et al 2004	7.148	<.001
Bisgaard et al 2006	6.997	<.001
Busse et al 2003	6.903	<.001

Ind et al 2003	7.111	<.001
Jenkins et al 2000	7.058	<.001
Lalloo et al 2003	6.832	<.001
Peters et al 2007	7.355	<.001
Kelson et al 1999	6.819	<.001
O'Byrne et al 2001	7.456	<.001
Vermetten et al 1999	7.449	<.001
O'Byrne et al 2005	6.561	<.001
Kips et al 2000	7.069	<.001
Johansson et al 2001	7.757	<.001
Baraniuk et al 1999a	6.799	<.001
Baraniuk et al 1999b	6.915	<.001
Random effects model	7.391	<.001

Results for Heterogeneity among studies:

<i>Value of Q Statistic</i>	<i>d.f. for test of Q</i>	<i>P-value</i>	<i>I-squared</i>
15.076	15	.4460	.502

Symptom Control (change in symptom score)

Studies that reported outcome, but are not included:

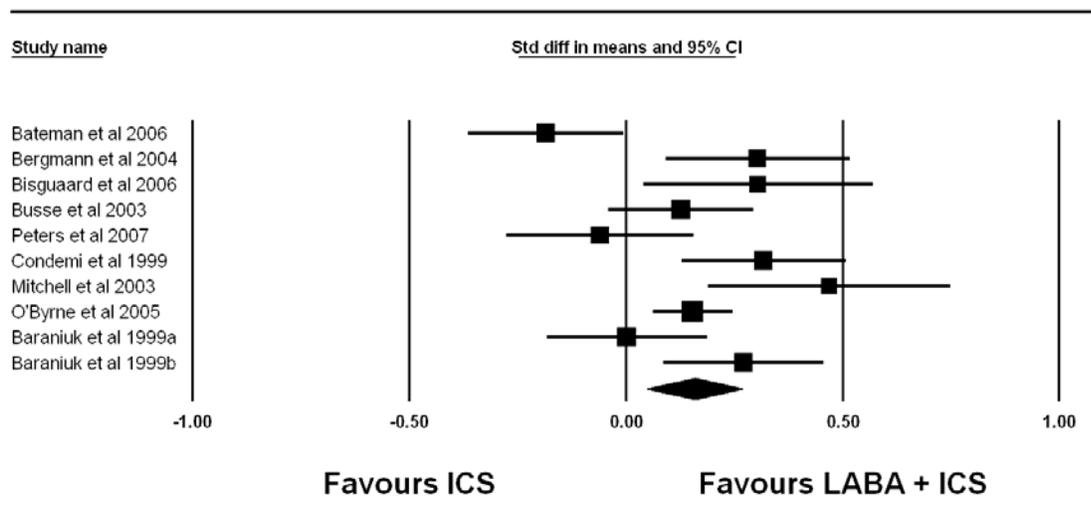
<i>Study</i>	<i>Reason</i>
Lalloo et al 2003	P-value not reported
Pauwels et al 1997	P-value not reported

Summary of overall results:

<i>Study Name</i>	<i>Statistics for each study</i>						
	<i>Std. Diff in Means</i>	<i>Std. Error</i>	<i>Variance</i>	<i>Lower Limit</i>	<i>Upper Limit</i>	<i>Z-value</i>	<i>p-value</i>
Bateman et al 2006	-.185	.091	.008	-.364	-.007	-2.035	.042
Bergmann et al 2004	.303	.108	.012	.092	.515	2.809	.005
Bisgaard et al 2006	.305	.135	.018	.040	.569	2.260	.024
Busse et al 2003	.126	.085	.007	-.040	.292	1.488	.137
Peters et al 2007	-.061	.109	.012	-.275	.154	-.554	.580
Condemi et al 1999	.317	.096	.009	.128	.506	3.292	.001
Mitchell et al 2003	.469	.142	.020	.190	.748	3.295	.001
O'Byrne et al 2005	.153	.047	.002	.062	.244	3.291	.001
Baraniuk et al 1999a	.002	.094	.009	-.182	.186	.019	.985

Baraniuk et al 1999b	.271	.094	.009	.086	.455	2.880	.004
Random effects model	.158	.056	.003	.048	.268	2.808	.005

Overall results of the meta-analysis are highlighted in gray.



Sensitivity analysis results:

Study Name	Statistics with study removed	
	Z-value	p-value
Bateman et al 2006	4.059	<.001
Bergmann et al 2004	2.388	.017
Bisgvaard et al 2006	2.448	.014
Busse et al 2003	2.563	.010
Peters et al 2007	3.088	.002
Condemi et al 1999	2.353	.019
Mitchell et al 2003	2.384	.017
O'Byrne et al 2005	2.317	.020
Baraniuk et al 1999a	2.913	.004
Baraniuk et al 1999b	2.382	.017
Overall Results	2.808	.005

Results for Heterogeneity among studies:

Value of Q Statistic	d.f. for test of Q	P-value	I-squared
10.919	9	.2813	17.577

Exacerbations

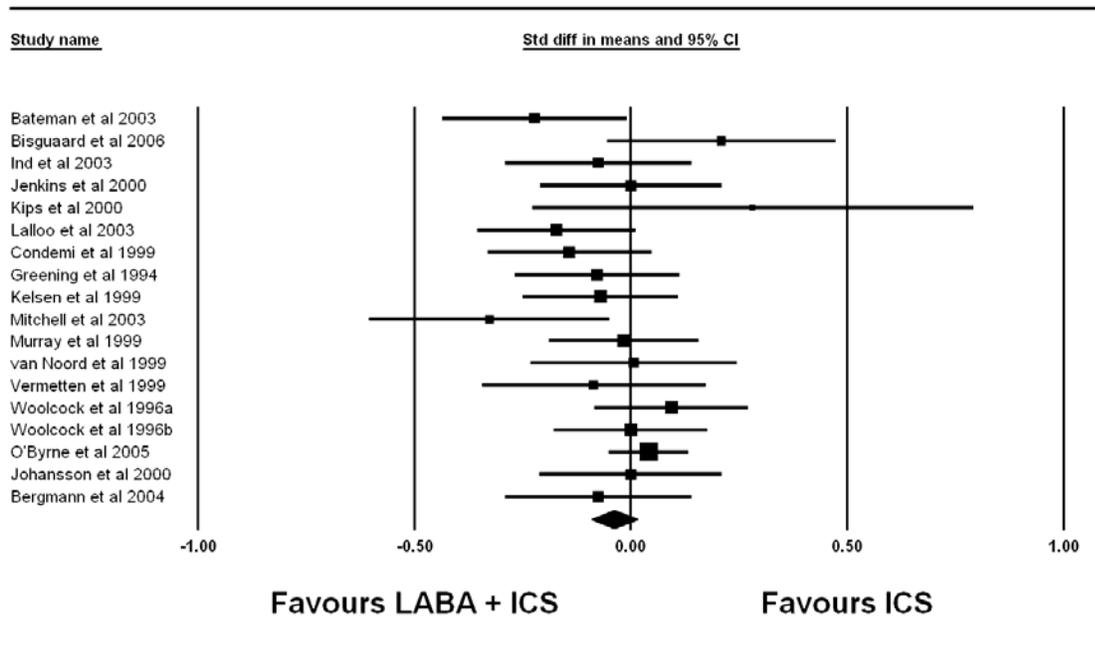
Studies that reported outcome, but are not included:

<i>Study</i>	<i>Reason</i>
O'Byrne et al 2001	Not enough info to convert from adjusted rate

Summary of overall results:

<i>Study Name</i>	<i>Statistics for each study</i>						
	<i>Std. Diff in Means</i>	<i>Std. Error</i>	<i>Variance</i>	<i>Lower Limit</i>	<i>Upper Limit</i>	<i>Z-value</i>	<i>p-value</i>
Bateman et al 2003	-.222	.108	.012	-.434	-.010	-2.055	.040
Bisgaard et al 2006	.209	.134	.018	-.054	.473	1.557	.120
Ind et al 2003	-.075	.109	.012	-.289	.139	-.689	.491
Jenkins et al 2000	.000	.106	.011	-.209	.209	.000	1.00
Kips et al 2000	.282	.260	.067	-.227	.791	1.085	.278
Laloo et al 2003	-.172	.093	.009	-.354	.010	-1.853	.064
Condemi et al 1999	-.141	.096	.009	-.329	.046	-1.477	.140
Greening et al 1994	-.078	.097	.009	-.268	.112	-.807	.420
Kelsen et al 1999	-.070	.091	.008	-.248	.109	-.768	.443
Mitchell et al 2003	-.327	.141	.020	-.604	-.050	-2.311	.021
Murray et al 1999	-.016	.088	.008	-.189	.157	-.183	.855
Van Noord et al 1999	.007	.121	.015	-.230	.244	.056	.955
Vermetten et al 1999	-.085	.131	.017	-.342	.172	-.649	.517
Woolcock et al 1996a	.094	.090	.008	-.083	.270	1.041	.298
Woolcock et al 1996b	.000	.107	.011	-.210	.210	.000	1.000
O'Byrne et al 2005	.042	.046	.002	-.049	.133	.897	.370
Johansson et al 2000	.000	.107	.011	-.210	.210	.000	1.000
Bergmann et al 2004	-.075	.109	.012	-.290	.139	-.689	.491
Random effects model	-.039	.027	.001	-.091	.013	-1.452	.147

Overall results of the meta-analysis are highlighted in gray.



Sensitivity analysis results:

<i>Study Name</i>	<i>Statistics with study removed</i>	
	<i>Z-value</i>	<i>p-value</i>
Bateman et al 2003	-1.049	.294
Bisgaard et al 2006	-1.744	.081
Ind et al 2003	-1.340	.180
Jenkins et al 2000	-1.480	.139
Kips et al 2000	-1.568	.117
Lalloo et al 2003	-1.067	.286
Condemi et al 1999	-1.166	.243
Greening et al 1994	-1.312	.190
Kelsen et al 1999	-1.319	.187
Mitchell et al 2003	-1.054	.292
Murray et al 1999	-1.449	.147
Van Noord et al 1999	-1.484	.138
Vermetten et al 1999	-1.354	.176
Woolcock et al 1996a	-1.753	.080
Woolcock et al 1996b	-1.491	.136
O'Byrne et al 2005	-1.898	.058
Johansson et al 2000	-1.480	.139
Bergmann et al 2004	-1.340	.180
Random effects model	-1.452	.147

Results for Heterogeneity among studies:

<i>Value of Q Statistic</i>	<i>d.f. for test of Q</i>	<i>P-value</i>	<i>I-squared</i>
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17.085	17	.4486	.500
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ICS compared with LABA+ICS (Higher Dose) Sensitivity Results

Summary of Outcome Measures Analyzed:

1. Rescue medication use (percent improved rescue free days)
2. Rescue medication use (percent reduction in puffs)
3. Symptom control (percent improved symptom free days)
4. Symptom control (percent change in symptom score)
5. Percent Exacerbations

Studies that reported outcomes within this comparison, but are not included:

<i>Study</i>	<i>Reason</i>
Greenston et al. 2005	Review paper
Bouros et al. 1999	No data reported, or only reported in figures
Schermer et al. 2007	No data reported, or only reported in figures
Woolcock et al. 1996	No data reported, or only reported in figures

Results

Rescue Medication Use (Rescue Free Days)

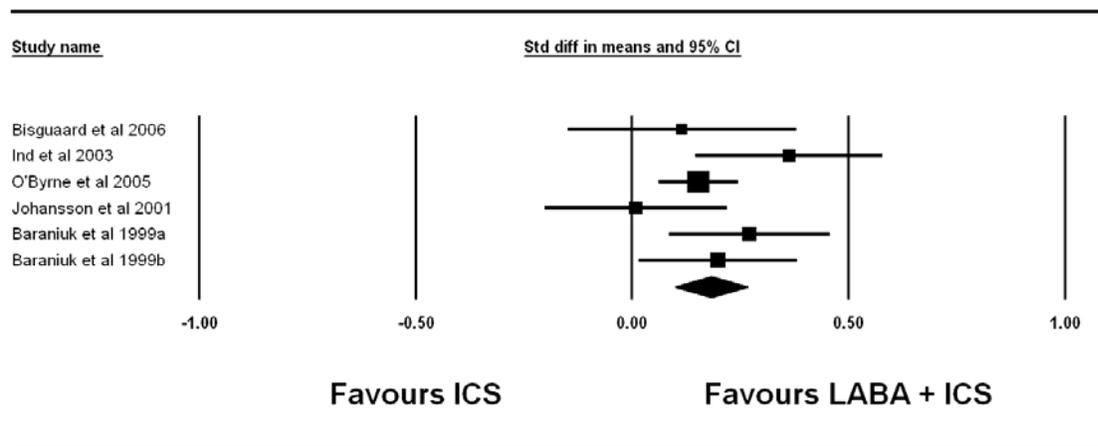
Studies that reported outcome, but are not included:

<i>Study</i>	<i>Reason</i>
Vernerne et al. 1998	<i>P</i> value not reported
Jenkins et al. 2000	Only reports rescue free nights
Kelson et al.	Only reports rescue free nights

Summary of overall results:

<i>Study Name</i>	<i>Statistics for each study</i>						
	<i>Std. Diff in Means</i>	<i>Std. Error</i>	<i>Variance</i>	<i>Lower Limit</i>	<i>Upper Limit</i>	<i>Z-value</i>	<i>P value</i>
Bisgaard et al. 2006	.115	.134	.018	-.148	.379	.861	.389
Ind et al. 2003	.362	.110	.012	.147	.578	3.293	.001
O'Byrne et al. 2005	.153	.047	.002	.062	.244	3.291	.001
Johansson et al. 2001	.009	.107	.011	-.201	.219	.083	.934
Baraniuk et al. 1999a	.272	.094	.009	.087	.456	2.880	.004
Baraniuk et al. 1999b	.199	.093	.009	.016	.381	2.133	.033
Random effects model	.182	.043	.002	.099	.266	4.287	<.001

Overall results of the meta-analysis are highlighted in gray.



Sensitivity analysis results:

Study Name	Statistics with study removed	
	Z-value	P value
Bisgaard et al. 2006	4.986	< .001
Ind et al. 2003	5.305	< .001
O'Byrne et al. 2005	4.446	< .001
Johansson et al. 2001	6.027	< .001
Baraniuk et al. 1999a	4.641	< .001
Baraniuk et al. 1999b	4.600	< .001
Overall Model	5.276	< .001

Results for Heterogeneity among studies:

Value of Q Statistic	d.f. for test of Q	P value	I-squared
5.337	5		6.310

Rescue Medication Use (Change in puffs)

Studies that reported outcome, but are not included:

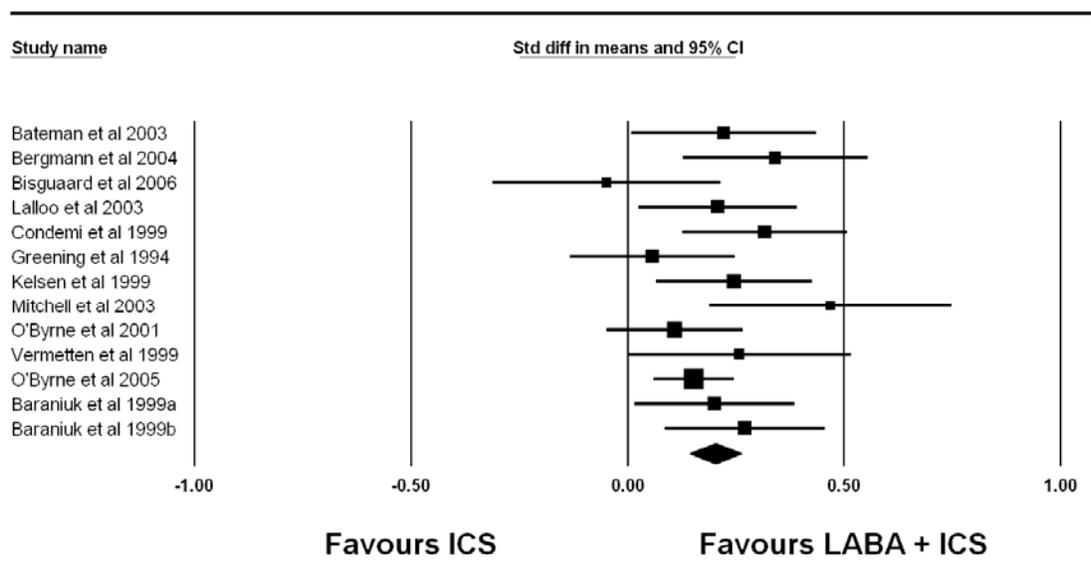
Study	Reason
Pauwels et al. 1997	P value not reported

Summary of overall results:

Study Name	Statistics for each study						
	Std. Diff in Means	Std. Error	Variance	Lower Limit	Upper Limit	Z-value	P value
Bateman et al. 2003	.222	.108	.012	.010	.434	2.055	.040
Bergmann et al. 2004	.342	.108	.012	.130	.554	3.158	.002
Bisgaard et al. 2006	-.048	.134	.018	-.311	.215	-.359	.720
Laloo et al. 2003	.208	.093	.009	.026	.390	2.243	.025
Condemi et al.	.317	.096	.009	.128	.506	3.292	.001

1999							
Greening et al. 1994	.058	.097	.009	-.132	.248	.594	.553
Kelson et al. 1999	.246	.091	.008	.067	.426	2.698	.007
Mitchell et al. 2003	.469	.142	.020	-.748	-.190	-3.295	.001
O'Byrne et al. 2001	.109	.079	.006	-.265	.047	-1.373	.170
Vermetten et al. 1999	.258	.132	.017	.000	.516	1.962	.050
O'Byrne et al. 2005	.153	.047	.002	-.244	-.062	-3.291	.001
Baraniuk et al. 1999a	.201	.094	.009	.016	.385	2.133	.033
Baraniuk et al. 1999b	.271	.094	.009	.086	.455	2.880	.004
Random effects model	.203	.030	.001	.145	.261	6.812	< .001

Overall results of the meta-analysis are highlighted in gray.



Sensitivity analysis results:

<i>Study Name</i>	<i>Statistics with study removed</i>	
	<i>Z-value</i>	<i>P value</i>
Bateman et al. 2003	6.311	< .001
Bergmann et al. 2004	6.458	< .001
Bisgaard et al. 2006	7.629	< .001
Laloo et al. 2003	6.254	< .001
Condemi et al. 1999	6.345	< .001
Greening et al. 1994	7.147	< .001
Kelson et al. 1999	6.200	< .001
Mitchell et al. 2003	7.071	< .001
O'Byrne et al. 2001	6.769	< .001
Vermetten et al. 1999	6.378	< .001
O'Byrne et al. 2005	6.316	< .001

Baraniuk et al. 1999a	6.278	< .001
Baraniuk et al. 1999b	6.226	< .001
Overall model	6.812	< .001

Results for Heterogeneity among studies:

<i>Value of Q Statistic</i>	<i>d.f. for test of Q</i>	<i>P value</i>	<i>I-squared</i>
12.621	12		4.919

LABA + ICS compared with ICS (same dose)

Summary of Outcome Measures Analyzed:

1. Rescue medication reduction in puffs
 2. Rescue medicine free days (percent improved)
 3. Symptom Control (percent improved symptom free days)
 4. Symptom Control (percent improved symptom score)
 5. Change in AQLQ score
- Note* - exacerbations were recorded in inconsistent measures

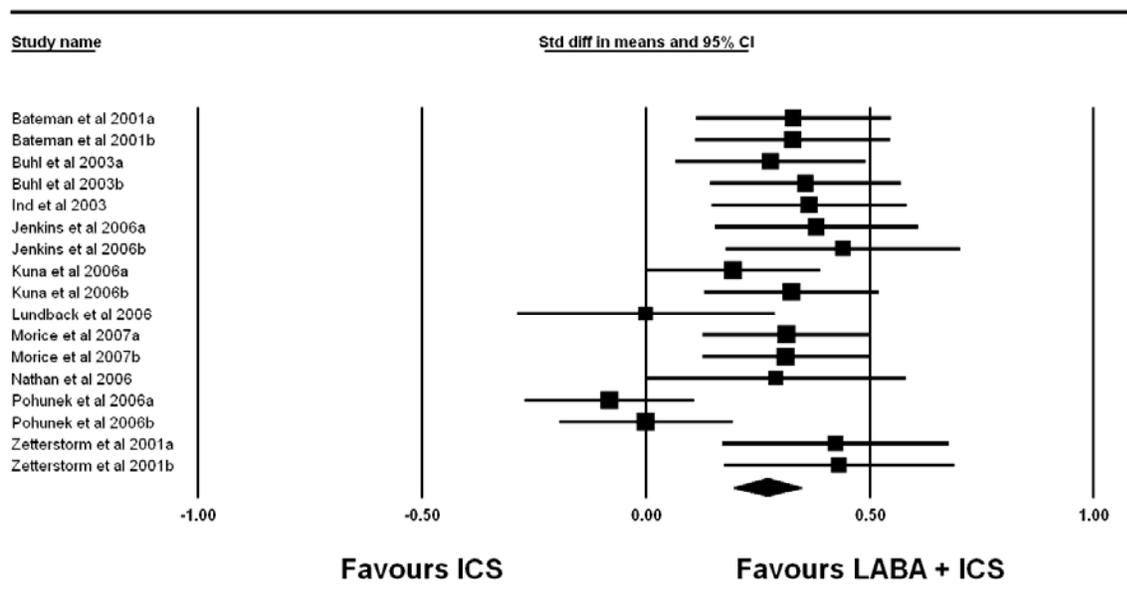
Results

Rescue Medication Use (percent improved, rescue free days)

Summary of overall results:

Study Name	Statistics for each study						
	Std. Diff in Means	Std. Error	Variance	Lower Limit	Upper Limit	Z-value	P value
Bateman et al. 2001a	.329	.111	.012	.112	.546	2.970	.003
Bateman et al. 2001b	.328	.111	.012	.112	.545	2.970	.003
Buhl et al. 2003a	.278	.108	.012	.067	.490	2.578	.010
Buhl et al. 2003b	.356	.108	.012	.144	.568	3.293	.001
Ind et al. 2003	.365	.111	.012	.148	.583	3.293	.001
Jenkins et al. 2006a	.380	.115	.013	.154	.607	3.292	.001
Jenkins et al. 2006b	.440	.133	.018	.178	.701	3.294	.001
Kuna et al. 2006a	.194	.099	.010	.000	.389	1.961	.050
Kuna et al. 2006b	.326	.099	.010	.132	.520	3.293	.001
Lundback et al. 2006	.000	.146	.021	-.287	.287	.000	1.000
Morice et al. 2007a	.314	.095	.009	.127	.501	3.292	.001
Morice et al. 2007b	.312	.095	.009	.126	.498	3.292	.001
Nathan et al. 2006	.290	.148	.022	.000	.580	1.963	.050
Pohunek et al. 2006a	-.081	.096	.009	-.270	.107	-.846	.398
Pohunek et al. 2006b	-.000	.098	.010	-.193	.193	-.001	.999
Zetterstorm et al. 2001a	.424	.129	.017	.172	.676	3.294	.001
Zetterstorm et al. 2001b	.431	.131	.017	.175	.688	3.294	.001
Random effects model	.271	.039	.002	.195	.347	6.973	< .001

Overall results of the meta-analysis are highlighted in gray.



Sensitivity analysis results:

Study Name	Statistics with study removed	
	Z-value	P value
Bateman et al. 2001a	6.500	< .001
Bateman et al. 2001b	6.499	< .001
Buhl et al. 2003a	6.534	< .001
Buhl et al. 2003b	6.484	< .001
Ind et al. 2003	6.494	< .001
Jenkins et al. 2006a	6.512	< .001
Jenkins et al. 2006b	6.587	< .001
Kuna et al. 2006a	6.689	< .001
Kuna et al. 2006b	6.453	< .001
Lundback et al. 2006	7.325	< .001
Morice et al. 2007a	6.443	< .001
Morice et al. 2007b	6.442	< .001
Nathan et al. 2006	6.639	< .001
Pohunek et al. 2006a	9.330	< .001
Pohunek et al. 2006b	7.945	< .001
Zetterstorm et al. 2001a	6.566	< .001
Zetterstorm et al. 2001b	6.576	< .001
Random effects model	6.973	<.001

Results for Heterogeneity among studies:

Value of Q Statistic	d.f. for test of Q	P value	I-squared
15.453	16	.4917	0

Rescue Medication Use (percent improved, puffs per day)
Rescue Medication Use (percent improved, puffs per day)

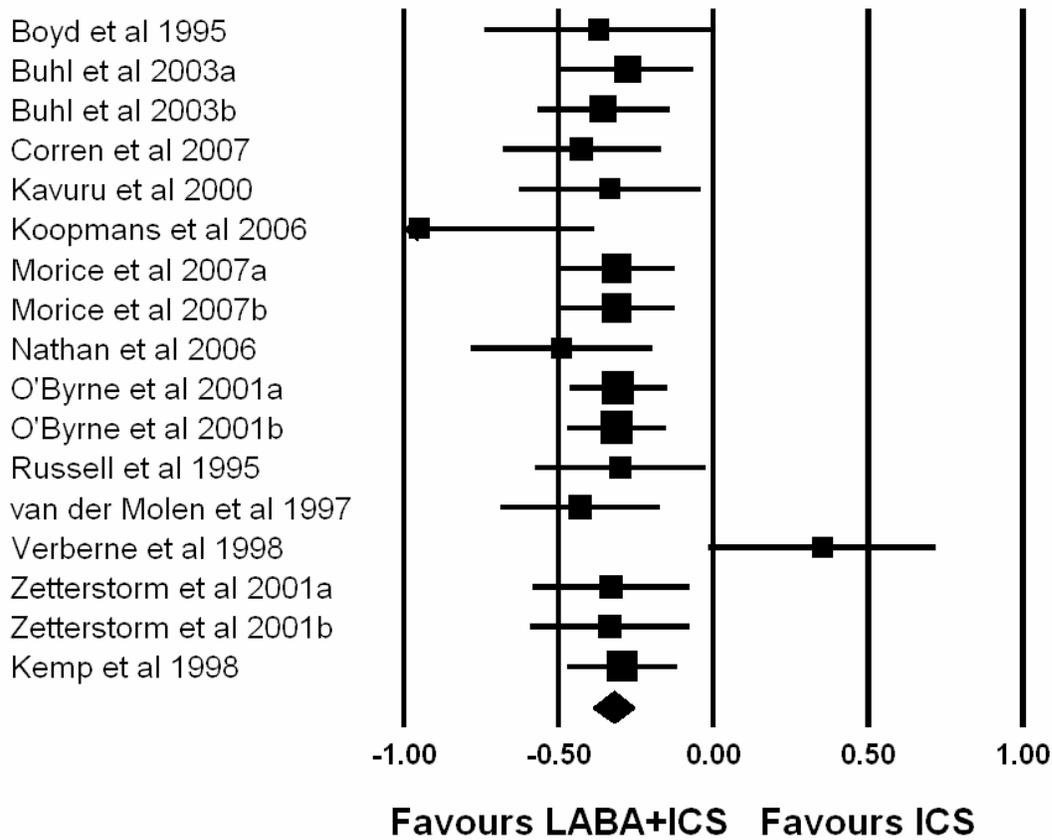
Summary of overall results:

<i>Study Name</i>	<i>Statistics for each study</i>						
	<i>Std. Diff in Means</i>	<i>Std. Error</i>	<i>Variance</i>	<i>Lower Limit</i>	<i>Upper Limit</i>	<i>Z-value</i>	<i>p-value</i>
Boyd et al 1995	-.371	.189	.036	-.740	-.001	-1.964	.050
Buhl et al 2003a	-.278	.108	.012	-.490	-.067	-2.578	.010
Buhl et al 2003b	-.356	.108	.012	-.568	-.144	-3.293	.001
Corren et al 2007	-.427	.129	.017	-.569	-.173	-3.294	.001
Kavuru et al 2000	-.335	.149	.022	-.628	-.042	-2.245	.025
Koopsmans et al 2006	-.949	.287	.082	-1.512	-.387	-3.306	.001
Morice et al 2007a	-.314	.095	.009	-.501	-.127	-3.292	.001
Morice et al 2007b	-.312	.095	.009	-.498	-.126	-3.292	.001
Nathan et al 2006	-.492	.149	.022	-.784	-.199	-3.295	.001
O'Byrne et al 2001a	-.308	.079	.006	-.464	-.153	-3.892	.000
O'Byrne et al 2001b	-.313	.080	.006	-.470	-.155	-3.892	.000
Russell et al 1995	-.301	.140	.020	-.576	-.026	-2.147	.032
Van der Molen et al 1997	-.432	.131	.017	-.688	-.175	-3.294	.001
Verberne et al 1998	.351	.189	.035	-.014	.717	1.885	.059
Zetterstorm et al 2001a	-.330	.128	.016	-.581	-.079	-2.579	.010
Zetterstorm et al 2001b	-.336	.130	.017	-.592	-.081	-2.579	.010
Kemp et al 1998	-.294	.089	.008	-.469	-.119	-3.292	.001
Random effects model	-.324	.033	.001	-.389	-.259	-9.810	<.001

Overall results of the meta-analysis are highlighted in gray.

Study name

Std diff in means and 95% CI



Sensitivity analysis results:

Study Name	Statistics with study removed	
	Z-value	p-value
Boyd et al 1995	-9.366	<.001
Buhl et al 2003a	-9.260	<.001
Buhl et al 2003b	-9.081	<.001
Corren et al 2007	-9.234	<.001
Kavuru et al 2000	-9.289	<.001
Koopmans et al 2006	-10.742	<.001
Morice et al 2007a	-9.060	<.001
Morice et al 2007b	-9.060	<.001

Nathan et al 2006	-9.429	<.001
O'Byrne et al 2001a	-8.941	<.001
O'Byrne et al 2001b	-8.935	<.001
Russell et al 1995	-9.310	<.001
Van der Molen et al 1997	-9.429	<.001
Verberne et al 1998	-11.957	<.001
Zetterstorm et al 2001a	-9.216	<.001
Zetterstorm et al 2001b	-9.218	<.001
Kemp et al 1998	-9.089	<.001
Random effects model	-9.810	<.001

Results for Heterogeneity among studies:

<i>Value of Q Statistic</i>	<i>d.f. for test of Q</i>	<i>P-value</i>	<i>I-squared</i>
21.006	16	.1783	23.830

Symptom control (percent improved, symptom free days)

Summary of overall results:

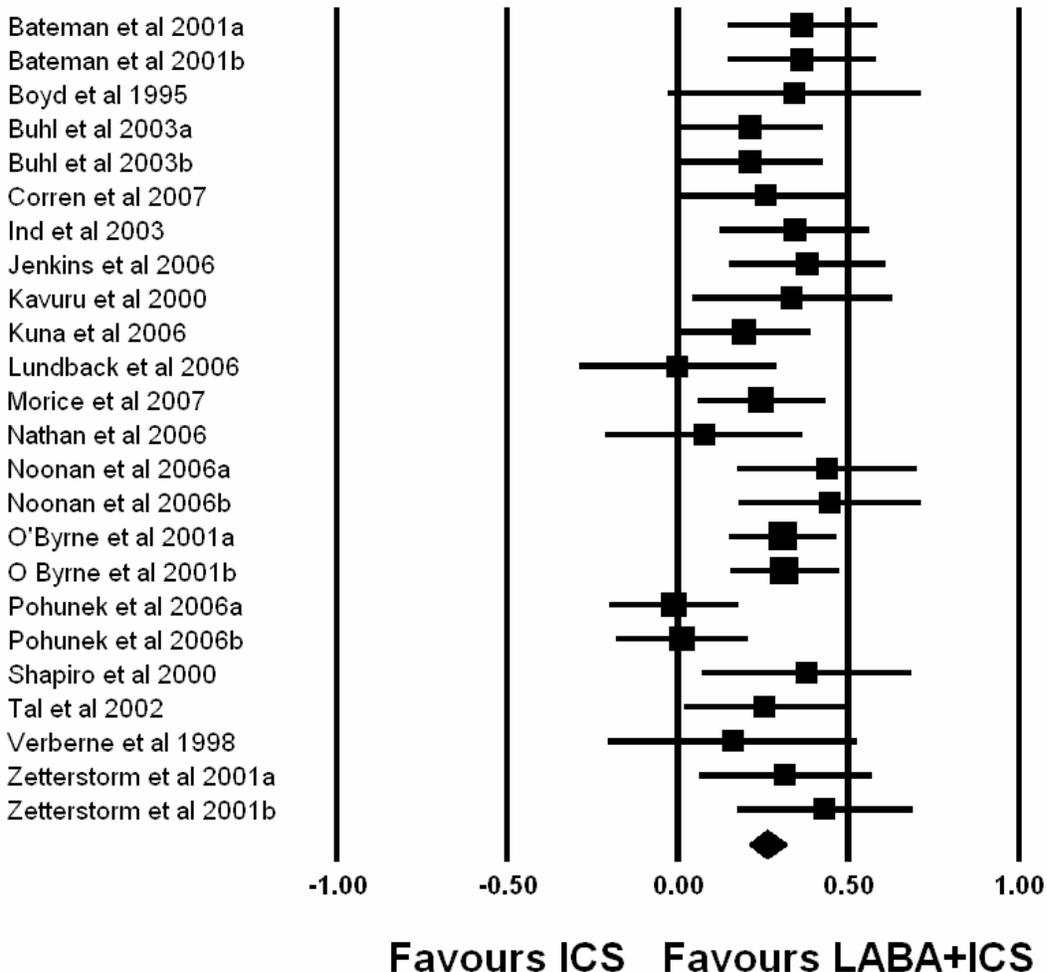
<i>Study Name</i>	<i>Statistics for each study</i>						
	<i>Std. Diff in Means</i>	<i>Std. Error</i>	<i>Variance</i>	<i>Lower Limit</i>	<i>Upper Limit</i>	<i>Z-value</i>	<i>p-value</i>
Bateman et al 2001a	.366	.111	.012	.148	.583	3.293	.001
Bateman et al 2001b	.364	.111	.012	.148	.581	3.292	.001
Boyd et al 1995	.342	.188	.036	-.027	.712	1.816	.069
Buhl et al 2003a	.211	.108	.012	.000	.422	1.961	.050
Buhl et al 2003b	.211	.108	.012	.000	.42	1.961	.050
Corren et al 2007	.257	.129	.017	.005	.509	1.997	.046
Ind et al 2003	.343	.111	.012	.125	.560	3.093	.002
Jenkins et al 2006	.380	.115	.013	.154	.607	3.293	.001
Kavuru et al 2000	.335	.149	.022	.042	.628	2.245	.025
Kuna et al 2006	.194	.099	.010	.000	.389	1.961	.050
Lundback et al 2006	.000	.146	.021	-.287	.287	-.001	.999
Morice et al 2007	.245	.095	.009	.059	.431	2.577	.010
Nathan et al 2006	.077	.147	.022	-.211	.366	.525	.600
Noonan et al 2006a	.438	.133	.018	.177	.698	3.294	.001
Noonan et al 2006b	.446	.135	.018	.181	.711	3.294	.001
O'Byrne et al 2001a	.308	.079	.006	.153	.464	3.892	.000
O'Byrne et al	.313	.080	.006	.155	.470	3.892	.000

2001b							
Pohunek et al 2006a	-.011	.097	.009	-.201	.178	-.118	.906
Pohunek et al 2006b	.012	.098	.010	-.180	.205	.126	.900
Shapiro al 2000	.379	.156	.024	.074	.684	2.436	.015
Tal et al 2002	.255	.119	.014	.022	.488	2.146	.032
Verberne et al 1998	.161	.185	.034	-.202	.524	.871	.384
Zetterstorm et al 2001a	.315	.128	.016	.064	.566	2.460	.014
Zetterstorm et al 2001b	.431	.131	.017	.175	.688	3.294	.001
Random effects model	.260	.028	.001	.206	.314	9.413	<.001

Overall results of the meta-analysis are highlighted in gray.

Study name

Std diff in means and 95% CI



Sensitivity analysis results:

Study Name	Statistics with study removed	
	Z-value	p-value
Bateman et al 2001a	8.959	<.001
Bateman et al 2001b	8.957	<.001
Boyd et al 1995	9.121	<.001
Buhl et al 2003a	9.088	<.001
Buhl et al 2003b	9.088	<.001
Corren et al 2007	9.048	

Ind et al 2003	8.939	<.001
Jenkins et al 2006	8.991	<.001
Kavuru et al 2000	9.054	<.001
Kuna et al 2006	9.129	<.001
Lundback et al 2006	9.897	<.001
Morice et al 2007	8.950	<.001
Nathan et al 2006	9.526	<.001
Noonan et al 2006a	9.124	<.001
Noonan et al 2006b	9.143	<.001
O'Byrne et al 2001a	8.761	<.001
O'Byrne et al 2001b	8.770	<.001
Pohunek et al 2006a	11.230	<.001
Pohunek et al 2006b	10.716	<.001
Shapiro al 2000	9.081	<.001
Tal et al 2002	9.022	<.001
Verberne et al 1998	9.258	<.001
Zetterstorm et al 2001a	9.000	<.001
Zetterstorm et al 2001b	9.109	<.001
Random effects model	9.413	<.001

Results for Heterogeneity among studies:

<i>Value of Q Statistic</i>	<i>d.f. for test of Q</i>	<i>P-value</i>	<i>I-squared</i>
30.943	23	.1242	25.7

Symptom control (percent improved, symptom score)

Summary of overall results:

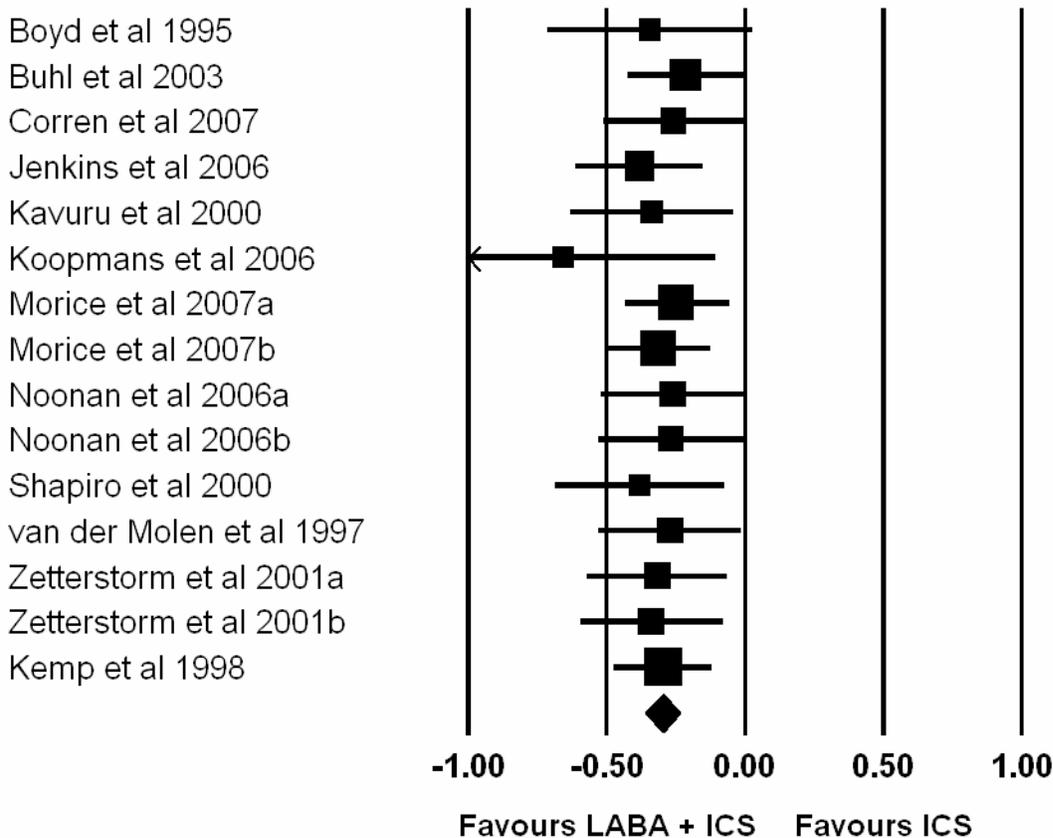
<i>Study Name</i>	<i>Statistics for each study</i>						
	<i>Std. Diff in Means</i>	<i>Std. Error</i>	<i>Variance</i>	<i>Lower Limit</i>	<i>Upper Limit</i>	<i>Z-value</i>	<i>p-value</i>
Boyd et al 1995	-.342	.188	.036	-.712	.027	-1.816	.069
Buhl et al 2003	-.211	.108	.012	-.422	-.000	-1.961	.050
Corren et al 2007	-.257	.129	.017	-.509	-.005	-1.998	.046
Jenkins et al 2006	-.380	.115	.013	-.607	-.154	-3.293	.001
Kavuru et al 2000	-.335	.149	.022	-.628	-.042	-2.245	.025
Koopmans et al 2006	-.653	.279	.078	-1.201	-.106	-2.339	.019
Morice et al 2007a	-.245	.095	.009	-.431	-.059	-2.577	.010
Morice et al 2007b	-.312	.095	.009	-.498	-.126	-3.292	.001
Noonan et al 2006a	-.259	.132	.017	-.517	-.000	-1.962	.050

Noonan et al 2006b	-.263	.134	.018	-.527	-.000	-1.962	.050
Shapiro al 2000	-.379	.156	.024	-.684	-.074	-2.436	.015
Van der Molen et al 1997	-.269	.130	.017	-.524	-.014	-2.066	.039
Zetterstorm et al 2001a	-.315	.128	.016	-.566	-.064	-2.460	.014
Zetterstorm et al 2001b	-.336	.130	.017	-.592	-0.081	-2.579	.010
Kemp et al 1998	-.294	.089	.008	-.469	-.119	-3.292	.001
Random effects model	-.298	.032	.001	-.360	-.235	-9.354	<.001

Overall results of the meta-analysis are highlighted in gray.

Study name

Std diff in means and 95% CI



Sensitivity analysis results:

<i>Study Name</i>	<i>Statistics with study removed</i>	
	<i>Z-value</i>	<i>p-value</i>
Boyd et al 1995	-9.179	<.001
Buhl et al 2003	-9.185	<.001
Corren et al 2007	-9.144	<.001
Jenkins et al 2006	-8.787	<.001
Kavuru et al 2000	-9.085	<.001
Koopmans et al 2006	-9.147	<.001
Morice et al 2007a	-9.011	<.001
Morice et al 2007b	-8.757	<.001
Noonan et al 2006a	-9.151	<.001
Noonan et al 2006b	-9.150	<.001
Shapiro al 2000	-9.048	<.001
Van der Molen et al 1997	-9.126	<.001
Zetterstorm et al 2001a	-9.026	<.001
Zetterstorm et al 2001b	-8.997	<.001
Kemp et al 1998	-8.756	<.001
Random effects model	-9.354	<.001

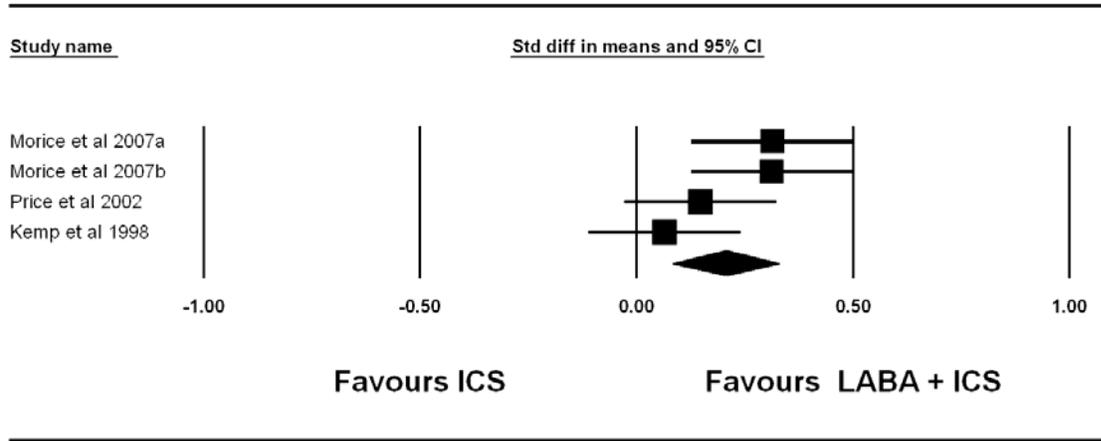
Results for Heterogeneity among studies:

<i>Value of Q Statistic</i>	<i>d.f. for test of Q</i>	<i>P-value</i>	<i>I-squared</i>
3.909	14	.9960	0

Change in AQLQ score

Summary of overall results:

<i>Study Name</i>	<i>Statistics for each study</i>						
	<i>Std. Diff in Means</i>	<i>Std. Error</i>	<i>Variance</i>	<i>Lower Limit</i>	<i>Upper Limit</i>	<i>Z-value</i>	<i>P value</i>
Morice et al. 2007a	.314	.095	.009	.127	.501	3.292	.001
Morice et al. 2007b	.312	.095	.009	.126	.498	3.292	.001
Price et al. 2002	.147	.089	.008	-.028	.321	1.646	.100
Kemp et al. 1998	.064	.089	.008	-.110	.239	.723	.470
Random effects model	.206	.062	.004	.083	.328	3.297	.001



Sensitivity analysis results:

Study Name	Statistics with study removed	
	Z-value	P value
Morice et al. 2007a	2.389	.017
Morice et al. 2007b	2.380	.017
Price et al. 2002	2.682	.007
Kemp et al. 1998	4.477	.000
Overall model	3.297	.001

Results for Heterogeneity among studies:

Value of Q Statistic	d.f. for test of Q	P value	I-squared
2.996	3	.3922	0

LTRA compared with LABA+ICS Results

Summary of Outcome Measures Analyzed:

1. Rescue medication use (puffs)
2. Rescue medication use (percent improved rescue free days)
3. Symptom control (percent improved)
4. Percent Exacerbations

Results

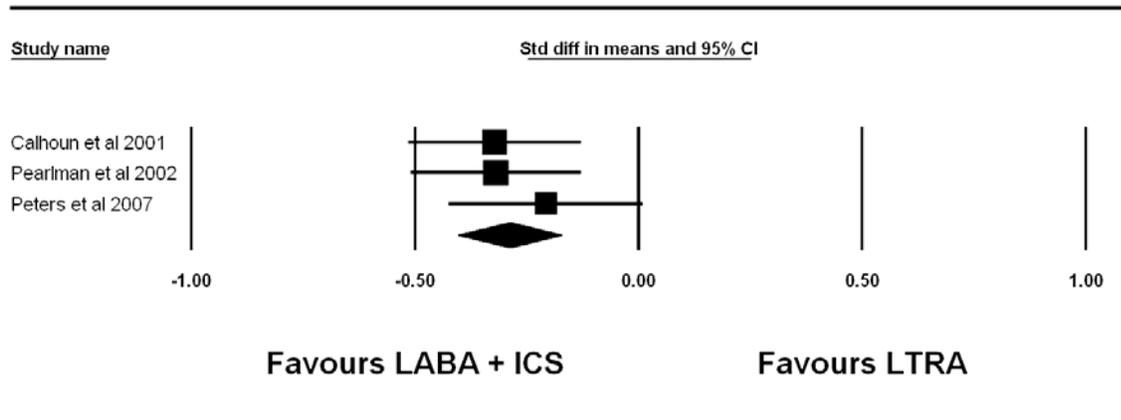
Rescue Medication Use

Studies that reported outcome, but are not included: NA

Summary of overall results:

Study Name	Statistics for each study						
	Std. Diff in Means	Std. Error	Variance	Lower Limit	Upper Limit	Z-value	P value
Calhoun et al. 2001	-0.322	.098	.010	-0.514	-0.130	-3.292	.001
Pearlman et al. 2002	-0.319	.097	.009	-0.509	-0.129	-3.292	.001
Peters et al. 2007	-0.207	.110	.012	-0.009	.424	1.882	.060
Random effects model	-0.289	.058	.003	-0.403	-0.174	-4.946	< .001

Overall results of the meta-analysis are highlighted in gray.



Sensitivity analysis results:

Study Name	Statistics with study removed	
	Z-value	P value
Calhoun et al. 2001	-3.716	< .001
Pearlman et al. 2002	-3.712	< .001
Peters et al. 2007	-4.656	< .001
Overall Model	-4.946	< .001

Results for Heterogeneity among studies:

Value of Q Statistic	d.f. for test of Q	P value	I-squared
.757	2	.6849	0

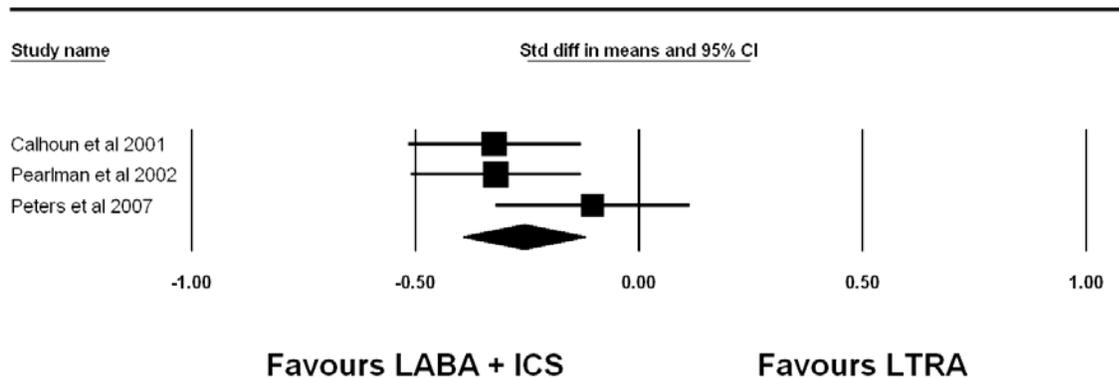
Symptom Control

Studies that reported outcome, but are not included: NA

Summary of overall results:

Study Name	Statistics for each study						
	Std. Diff in Means	Std. Error	Variance	Lower Limit	Upper Limit	Z-value	P value
Calhoun et al. 2001	-0.322	.098	.010	-0.514	-0.130	-3.292	.001
Pearlman et al. 2002	-0.319	.097	.009	-0.509	-0.129	-3.292	.001
Peters et al. 2007	-0.103	.110	.012	-0.318	.113	-0.935	.350
Random effects model	-0.256	.069	.005	-0.392	-0.120	-3.694	< .001

Overall results of the meta-analysis are highlighted in gray.



Sensitivity analysis results:

Study Name	Statistics with study removed	
	Z-value	P value
Calhoun et al. 2001	-2.015	.044
Pearlman et al. 2002	-1.993	.046
Peters et al. 2007	-4.656	< .001
Overall Model	-3.694	< .001

Sensitivity analyses indicate no difference in meta-analysis conclusions with any one study removed.

Results for Heterogeneity among studies:

Value of Q Statistic	d.f. for test of Q	P value	I-squared
2.050	2	.3588	2.445

Exacerbations

Studies that reported outcome, but are not included: NA

Summary of overall results:

