Drug Class Review

Controller Medications for Asthma

Final Update 1 Report

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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.

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The medical literature relating to this topic is scanned periodically. (See http://www.ohsu.edu/xd/research/centers-institutes/evidence-based-policy-center/derp/documents/methods.cfm for description of scanning process). Prior versions of this report can be accessed at the DERP website.

STRUCTURED ABSTRACT

Purpose

To compare the efficacy and safety of inhaled corticosteroids (ICSs), long-acting beta-2 agonists (LABAs), leukotriene modifiers (LMs), anti-IgE therapy, combination products, and tiotropium for people with persistent asthma.

Data Sources

To identify published studies, we searched MEDLINE, The Cochrane Library, Embase, International Pharmaceutical Abstracts, and reference lists of included studies through September 2010. We also requested dossiers of information from pharmaceutical manufacturers.

Review Methods

Study selection, data abstraction, validity assessment, grading the strength of the evidence, and data synthesis were all carried out according to standard Drug Effectiveness Review Project methods.

Results

Efficacy studies provide moderate strength of evidence (SOE) that equipotent doses of ICSs administered through comparable delivery devices do not differ in their ability to control asthma symptoms, prevent exacerbations, reduce the need for additional rescue medication, or in their overall incidence of adverse events or withdrawals due to adverse events. Evidence does not support a difference between montelukast and zafirlukast in their ability to decrease rescue medicine use or improve quality of life (low SOE for ≥12 years of age, insufficient <12), between formoterol and salmeterol in their ability to control symptoms, prevent exacerbations, improve quality of life, or cause harms among patients not controlled on ICSs alone (moderate SOE), or between budesonide/formoterol and fluticasone/salmeterol for efficacy or harms when each combination is administered via a single inhaler (moderate SOE for ≥12, insufficient <12). Meta-analyses and efficacy studies provide consistent evidence favoring omalizumab over placebo for most included outcomes. Omalizumab-treated patients have an increased incidence of injection site reactions and anaphylaxis compared to placebo-treated patients.

We found consistent evidence of greater benefit for subjects treated with ICS monotherapy compared with those treated with LM monotherapy (high SOE). Direct evidence suggests no difference in tolerability or overall adverse events between ICSs and LMs (moderate SOE). Specific adverse events reported with ICSs, such as cataracts and decreased growth velocity, were not found among patients taking LMs. The best longer-term evidence on growth (avg 4.3 years) for ICSs compared with placebo found that very small differences (1.1 cm) occurred primarily during the first year of treatment, suggesting that the effect on growth velocity occurs early in treatment and is not progressive. Evidence is insufficient to determine if long-term treatment with ICSs leads to a reduction in final adult height. Overall evidence indicates that ICSs and leukotriene receptor antagonists (LTRAs) are safer than LABAs for use as monotherapy (high SOE). Indirect evidence 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 did not find sufficient evidence to support the routine use of combination therapy rather than an ICS alone as first line therapy (moderate SOE for ≥12, insufficient <12). Results from large trials support greater efficacy with the addition of a LABA to an ICS than with a higher dose ICS (high SOE for ≥12, low <12) and greater efficacy with the addition of a LABA to an ICS over continuing the current dose of ICS alone for poorly controlled persistent asthma (high SOE). The addition of LMs to ICSs compared to continuing the same dose of ICSs resulted in improvement in rescue medicine use and no statistically significant differences in other health outcomes (low SOE for ≥12, insufficient <12). There is no apparent difference in symptoms, exacerbations, rescue medicine use, overall adverse events, or withdrawals due to adverse events between those treated with ICSs plus LTRAs compared to those treated with increasing the dose of ICSs (moderate SOE for ≥12, low <12). Results provide strong evidence that the addition of a LABA to ICS therapy (ICS+LABA) is more efficacious than the addition of an LTRA to ICS therapy (ICS+LTRA) (high SOE for ≥12, low <12). We found no difference in overall adverse events or withdrawals due to adverse events between ICS+LABA and ICS+LTRA (moderate SOE for ≥12, insufficient <12).

Conclusion

Overall findings do not suggest that one medication within any of the classes evaluated is significantly more effective or harmful than the other medications within the same class, with the exception of zileuton being more harmful than the other LMs. Our results support the general clinical practice of starting initial treatment for persistent asthma with an ICS. For people with poorly controlled persistent asthma taking an ICS, our findings suggest that the addition of a LABA is most likely to provide the greatest benefit as the next step in treatment.

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Published in two separate documents: Original Report Evidence Tables and Update Report Evidence Tables. References throughout this report identify the respective documents as Evidence Tables A or B.

Suggested citation

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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 asthma[1]

	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 7 ICSs currently available include: beclomethasone dipropionate, budesonide, ciclesonide, 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. Although it is not approved for the treatment of asthma and thus is not included in Table 2, tiotropium (Spiriva®) was included in this report to determine if there is any published evidence for its use in people with asthma. Dulera (mometasone/formoterol), now approved for treatment of asthma in people ≥12 years, is not included in this report because it was approved after our cutoff date for the inclusion of new medications.

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 and Canada
Inhaled corticosteroids	Beclomethasone dipropionate	QVAR®	Ivax	HFA	40 mcg/puff 50 mcg/puff[a] 80 mcg/puff 100 mcg/puff[a]	Asthma (age ≥ 5)
		Vanceril®[b]	Schering	MDI	42 mcg/puff 84 mcg/puff	Asthma (age ≥ 5)
	Budesonide	Pulmicort Flexhaler®[c]	AstraZeneca	DPI	90 mcg/dose 180 mcg/dose	Asthma (age ≥ 6)
		Pulmicort Turbuhaler®[a]	AstraZeneca	DPI	100 mcg/dose 200 mcg/dose 400 mcg/dose	
		Pulmicort Respules®[c]	AstraZeneca	Inhalation suspension	0.25 mg/2ml 0.5 mg/2ml 1 mg/2ml	Asthma (age 1-8)
		Pulmicort Nebuamp®[a]	AstraZeneca (Canada)	Inhalation suspension	0.125 mg/ml 0.25 mg/ml 0.5 mg/ml	Asthma (age ≥ 3 months)
	Ciclesonide	Alvesco®[d]	Sunovion (US) Nycomed Canada Inc (Canada)	HFA-MDI	80 mcg/puff 160 mcg/puff 100 mcg/dose[a] 200 mcg/dose[a]	Asthma (age ≥ 12)
	Flunisolide	AeroBid®[c] AeroBid-M®[c]	Forest	MDI MDI-menthol	250 mcg/puff	Asthma (age ≥ 6)
		AeroSpan®[e]	Acton	HFA	80 mcg/puff	
		Bronalide®[b]	Boehringer Ingleheim (Canada)	MDI	250 mcg/puff	Asthma (age ≥ 4)
	Fluticasone propionate	Flovent® HFA	GlaxoSmithKline	HFA	44 mcg/puff 50 mcg/puff[a] 110 mcg/puff 125 mcg/puff[a] 220 mcg/puff 250 mcg/puff[a]	Asthma (age ≥ 4)
		Flovent Rotadisk®[b]	GlaxoSmithKline	DPI	50 mcg/dose 100 mcg/dose 250 mcg/dose	Asthma (age ≥ 12)
		Flovent Diskus®	GlaxoSmithKline	DPI	50 mcg/dose	Asthma (age ≥ 4 yrs)

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 and Canada
					100 mcg/dose 250 mcg/dose 500 mcg/dose[a]	
	Mometasone furoate	Asmanex Twisthaler®[c]	Schering	DPI	110 mcg/dose 220 mcg/dose	Asthma (age ≥ 4)
	Triamcinolone acetonide	Azmacort®[b]	Abbot	MDI – with spacer mouthpiece	75 mcg/dose	Asthma (age ≥ 6)
Leukotriene modifiers Leukotriene receptor antagonists	Montelukast	Singulair®	Merck	Tablets Chewable tablets Granules	10 mg 4 mg, 5 mg 4 mg/packet	Asthma (age ≥ 1)
	Zafirlukast	Accolate®	AstraZeneca	Tablets	10 mg[c] 20 mg	Asthma (age ≥ 5 yrs in US); (age ≥ 12 yrs in Canada)
5-lipoxygenase Inhibitor	Zileuton	Zyflo®[c] Zyflo CR®[c]	Critical Therapeutics	Tablets Extended release tablets	600 mg 600 mg	Asthma (age ≥ 12 yrs)
Long-Acting Beta-2 Agonists	Arformoterol	Brovana®[c]	Sunovion	Inhalation solution	15 mcg/2ml	Not approved for asthma (COPD only)
	Formoterol fumarate/ Eformoterol	Foradil Aerolizer®[c]	Schering	DPI	12 mcg/capsule	Asthma (age ≥ 5 yrs)
		Foradil®[a]	Novartis Pharmaceuticals Canada Inc.	DPI	12 mcg/capsule	Asthma (age ≥ 6 yrs)
		Oxeze Turbuhaler®[a]	AstraZeneca (Canada)	DPI	6 mcg/capsule 12 mcg/capsule	Asthma (age ≥ 6 yrs)
		Oxis Turbohaler®[f]	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®[a]	GlaxoSmithKline	DPI	50 mcg/blister	Asthma (age ≥ 4 yrs)
Anti-IgE medications	Omalizumab	Xolair®	Genentech (US) Novartis Pharmaceuticals Inc (Canada)	Powder for subcutaneous injection	202.5 mg (delivers 150 mg/1.2ml)	Asthma (age ≥ 12 yrs)

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 and Canada
Combination products[g]	Fluticasone propionate/ Salmeterol xinafoate	Advair Diskus®	GlaxoSmith Kline	DPI	100mcg/50mcg 250mcg/50mcg 500mcg/50mcg	Asthma (age ≥ 4 yrs)
		Advair HFA®[c]	GlaxoSmith Kline	HFA	45mcg/21mcg 115mcg/21mcg 230mcg/21mcg	Asthma (age ≥ 12 yrs)
		Advair®[a]	GlaxoSmith Kline	HFA	50 mcg/25 mcg 125mcg/25mcg 250mcg/25mcg	Asthma (age ≥ 12 yrs)
	Budesonide/ Formoterol	Symbicort®[c]	AstraZeneca	HFA	80mcg/4.5mcg 160mcg/4.5mcg	Asthma (age ≥ 12 yrs)
		Symbicort Turbuhaler®[a]	AstraZeneca (Canada)	DPI	100mcg/6mcg 200mcg/6mcg	Asthma (age ≥ 12 yrs)
		Symbicort Forte Turbuhaler®[a]	AstraZeneca (Canada)	DPI	400mcg/12/cg	Asthma (age ≥ 12 yrs)

Abbreviations: DPI = dry powder inhaler; HFA = hydrofluoroalkane propellant; MDI = metered dose inhaler.
Note: Unless otherwise noted, the products are available in both the US and Canada
[a] This product is available in Canada only.
[b] This product has been discontinued by the manufacturer.
[c] This product is available in the US only.
[d] The FDA approved dosing regimen for ciclesonide is twice daily.
[e] This product is not yet available.
[f] This product is not available in the US or Canada.
[g] Dulera® (Zenhale® in Canada) (mometasone furoate/formoterol fumarate), now approved for treatment of asthma in people >12 years, is not included in this report because it was approved after our cutoff date for the inclusion of new medication.
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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 corticosteroids[1, 11]

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	
Ciclesonide[a]			80-160 mcg			>160-320 mcg			>320 mcg/d
80mcg/puff			2 puffs/d			2-4 puffs/d			4-16 puffs/d
160mcg/puff			NA			2 puffs/d			2-8 puffs/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

Table 3. Estimated comparative daily dosages for inhaled corticosteroids[1, 11]

	Low daily dose			Medium daily dose			High Daily Dose		
Drug	**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**
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
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.[12] and Agertoft & Pedersen;[13] CFC = Contains chlorofluorocarbons; substances known to destroy ozone in the upper atmosphere.

[a] FDA approved labeling for ciclesonide: Initial treatment for patients on prior therapy with bronchodilators alone: 80 mcg twice daily (for a total of 160mcg/day, considered low dose; maximum dose 320 mcg/day). Initial treatment for patients with prior therapy with inhaled corticosteroids: 80 mcg twice daily (maximum dose: 640 mcg/day). For patients with prior therapy with oral corticosteroids: 320 mcg twice daily (maximum dose: 640 mcg/day). Canadian labeling: Initial: 400 mcg once daily; maintenance: 100-800 mcg/day (1-2 puffs once or twice daily)

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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. Terms commonly used, such as statistical terms, are provided in Appendix A and are defined as they apply to reports produced by the Drug Effectiveness Review Project. Topic-specific abbreviations used in this report are presented in Appendix B.

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), other medications (drug-drug interactions), 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, ciclesonide, flunisolide, fluticasone propionate, triamcinolone, mometasone), Long-Acting Beta-2 Agonists (formoterol, arformoterol, salmeterol), leukotriene modifiers (montelukast, zafirlukast, zileuton), anti-IgE therapy (omalizumab), combination products (fluticasone propionate/salmeterol xinafoate, budesonide/formoterol), or tiotropium. 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). Further details related to inclusion criteria are provided below in the Methods section under Study Selection. Boxed warnings associated with these products are provided in Appendix C. Dosing equivalency of the agents was based on the 2007 NAEPP Expert Panel publication.[1] A comparison of labeled and delivered doses for inhalers is provided in Appendix D.

Table 4. Outcome measures and study eligibility criteria

Outcome	Outcome measures	Study eligibility criteria
Efficacy / Effectiveness	• Asthma control - 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	• Randomized controlled clinical trials of at least 6 weeks duration and n ≥ 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	• Overall adverse events reported • Withdrawals due to adverse events • Serious adverse events • Specific adverse events including: - *Growth* - *Bone mineral density* - *Osteoporosis/fractures* - *Ocular toxicity* - *Suppression of HPA axis* - *Anaphylaxis* - *Death*	• Randomized controlled clinical trials of at least 6 weeks duration and n ≥ 40 • Observational studies of at least 6 months duration and n ≥ 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®, the Cochrane Central Register of Controlled Trials®, and the International Pharmaceutical Abstracts (through September 2010), using terms for included drugs, indications, and study designs (see Appendix E 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 and unpublished data 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 classification[1] (see Table 1)
Interventions/Treatments
Inhaled corticosteroids: • Beclomethasone • Budesonide • Ciclesonide • Flunisolide • Fluticasone propionate • 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 Long-Acting Anticholinergics • Tiotropium
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

Table 5. Study inclusion criteria

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 ≥ 40) and observational studies of at least 6 months duration (N ≥ 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 of interest (those listed in Table 5) with another treatment of interest. 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. We did not include studies that compare step-down therapy for people with stable asthma, different doses of the same medication, or different delivery devices with the same medication unless there was another eligible comparator arm. We did not include studies evaluating adjustable dosing strategies.

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. A second reviewer read each abstracted article and evaluated the accuracy and completeness of the data abstraction. We abstracted the following data from included trials: study design, population characteristics (including age, sex, asthma severity, smoking status), inclusion and exclusion criteria, interventions (drugs, dose, delivery device, duration), comparisons, numbers 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 (see www.ohsu.edu/drugeffectiveness). 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.[14, 15]

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.

Systematic reviews which fulfilled inclusion criteria were rated for quality using predefined criteria (www.ohsu.edu/drugeffectiveness): 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,[16] 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.

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.[17] Forest plots are presented to graphically summarize the study results and the pooled results.[18] 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.[19, 20] 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 Comprehensive Meta Analysis V2.exe.

Grading the Strength of Evidence

We graded strength of evidence using a modified GRADE approach that included assessment of the following domains: design, quality, consistency, directness, and magnitude of effect of the set of studies relevant to the question. We also considered other domains that may be relevant for some scenarios, such as equipotency (for inhaled corticosteroids), a dose-response association, strength of association (magnitude of effect), and publication bias.

Table 6 describes the grades of evidence that can be assigned. Grades reflect the strength of the body of evidence to answer key questions on the comparative effectiveness, efficacy, and harms of the drugs included in this review. Grades do not refer to the general efficacy or effectiveness of pharmaceuticals. Two reviewers assessed each domain for each comparison and differences were resolved by consensus.

We graded the strength of evidence for the outcomes deemed to be of greatest importance to decision makers and those most commonly reported in the literature. These included improvement in symptoms, exacerbations, rescue medication use, growth, overall adverse events, and asthma-related death. Because of time and resource constraints we did not grade the strength of evidence for every possible outcome reported everywhere in the included literature.

Table 6. Definitions of the grades of overall strength of evidence[21]

Grade	Definition
High	High confidence that the evidence reflects the true effect. Further research is very unlikely to change our confidence in the estimate of effect.
Moderate	Moderate confidence that the evidence reflects the true effect. Further research may change our confidence in the estimate of the effect 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 of the effect and is likely to change the estimate.
Insufficient	Evidence either is unavailable or does not permit estimation of an effect.

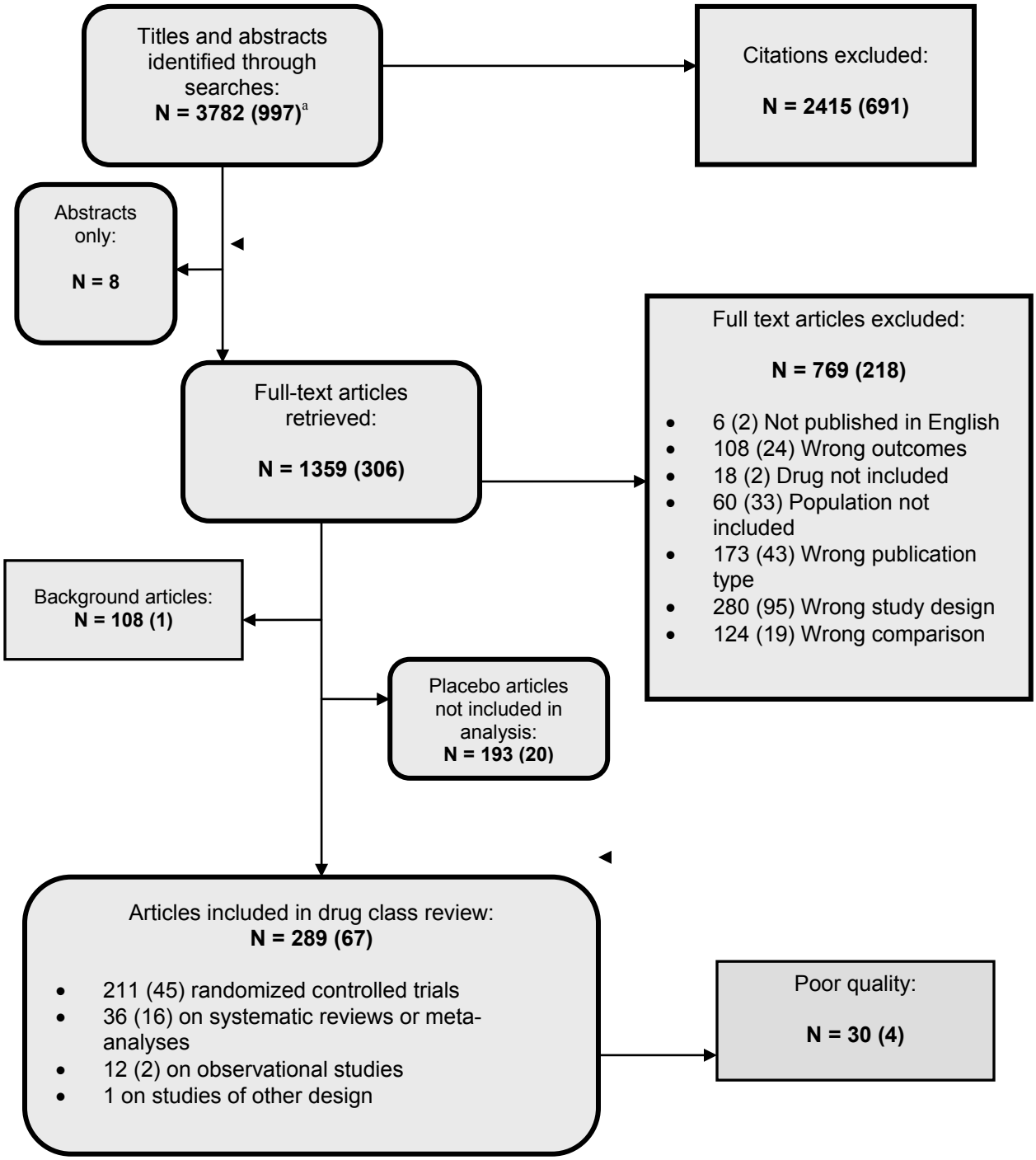
RESULTS

Overview

We identified 3,745 citations from database searches and reviewing reference lists, with 960 new citations for Update 1. We identified 32 additional references (9 in the original report, 23 for Update 1) from dossiers submitted by pharmaceutical companies and 5 from public comments. The total number of citations in our database was 3,782. In total we included 289 articles: 36 systematic reviews with meta-analyses, 211 articles for randomized controlled trials 12 articles for observational studies, and one study of other design. Thirty of the included studies were rated poor quality.(Appendix F) We retrieved 108 articles for background information.

Reasons for exclusions were based on eligibility or quality criteria (Figure 1). Studies excluded from the update report at the full text level are listed in Appendix G. A complete list of the placebo-controlled trials that were not included in the report will be provided upon request. Requests should be directed to the Center for Evidence-based Policy at Oregon Health & Science University (www.ohsu.edu/drugeffectiveness).

Figure 1. Results of Literature Search



[a] Numbers in parentheses are new for Update 1.

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 3 systematic reviews with meta-analyses[22-24] and 48 head-to-head RCTs (47 publications)[25-71] (Table 7). Seven of the head-to-head RCTs included children < 12 (Table 8).[31, 34, 44, 46, 62, 68, 69] 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 (Appendix H, Table H-1). 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 5 comparisons (3 systematic reviews and 7 RCTs): beclomethasone compared with budesonide, beclomethasone compared with fluticasone, budesonide compared with ciclesonide, budesonide compared with fluticasone, and ciclesonide compared with fluticasone. We conducted meta-analyses for comparisons within this section when sufficient data were available and a recent meta-analysis was not already published. There were often too few trials comparing equipotent ICS doses reporting similar outcomes measures to allow quantitative synthesis.

Detailed Assessment

Description of Studies

Of the included studies (Table 7), one systematic review with meta-analysis and two RCTs compared beclomethasone with budesonide; two systematic reviews with meta-analyses and eleven RCTs compared beclomethasone with fluticasone; two RCTs compared beclomethasone with mometasone; two RCTs compared beclomethasone with triamcinolone; five RCTs compared budesonide with ciclesonide; one RCT compared budesonide with flunisolide; one meta-analysis and eight RCTs compared budesonide with fluticasone; two RCTs compared budesonide with mometasone; one RCT compared budesonide with triamcinolone; eight RCTs compared ciclesonide with fluticasone; one RCT compared flunisolide with fluticasone; three RCTs compared fluticasone with mometasone; three RCTs compared fluticasone with triamcinolone.

Based on National Asthma Education and Prevention Program equipotent dose estimates (Table 3), 36 head-to-head RCTs (75%) included equipotent comparisons for some arms (seven of these had multiple arms, with both equipotent and non-equipotent comparisons)[36, 38, 39, 43, 48, 52, 59] and 12 RCTs (25%) compared only non-equipotent doses.[43, 45, 46, 49, 51, 54, 55, 58, 60, 66] Of the 36 head-to-head trials that compared equivalent doses, 10 compared high dose to high dose, 16 compared medium dose to medium dose, 10 compared low dose to low dose. The most commonly used delivery devices were MDIs and DPIs; 19 studies (40%) compared MDI to

MDI; 12 studies (25%) compared DPI to DPI; 15 studies (31%) compared MDI to DPI; one study (2%) compared both MDI to MDI and MDI to DPI;[36] one study (2%) compared both DPI to DPI and MDI to DPI.[27]

Study Populations

The 48 head-to-head RCTs included a total of 19,071 patients. Most studies were conducted in adult populations. Seven studies[31, 34, 44, 46, 62, 68, 69] were conducted primarily in pediatric populations. Ten studies (21%) were conducted in the United States, 15 (31%) in Europe, one in Canada, one in Japan, and 19 (40%) were other multinational combinations often including Europe, Canada, or the US. Asthma severity ranged from mild persistent to severe persistent: nine studies (19%) were conducted in patients with mild to moderate persistent asthma, nine (19%) in patients with mild to severe persistent asthma, 11 (23%) in patients with moderate persistent asthma, eight (17%) in patients with moderate to severe persistent asthma, and five (10%) in patients with severe persistent asthma. Six studies did not report the severity or it was unable to be determined.

Smoking status was not reported for 15 studies (31%), including six studies in pediatric populations. Among the others, 16 studies (33%) excluded individuals with a recent or current history of smoking and 17 (35%) allowed participants to smoke. Among the studies that allowed and reported smoking status, 2% 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 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 48 head-to-head trials, 40 (83%) were funded by pharmaceutical companies; 4 trials (8%) did not report the source of funding but at least one author had a primary affiliation with a pharmaceutical company, and 4 studies (8%) did not report funding sources.

Head-to-head comparisons

1. Beclomethasone compared with budesonide

One good systematic review[22] and two fair head-to-head RCTs[27, 28] comparing beclomethasone (BDP) to budesonide (BUD) met our inclusion criteria.

The systematic review[22] 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[27, 28] 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).[27] 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)[28] 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 ciclesonide

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

3. 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.

4. Beclomethasone compared with fluticasone

Two systematic reviews and 11 head-to-head RCTs comparing fluticasone (FP) to BDP met our inclusion criteria. One systematic review[23] 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.

The other systematic review[24]compared either CFC or HFA-propelled FP with HFA-propelled extrafine BDP. The review included nine studies (1265 participants) and found no statistically significant difference between treatments for symptom scores and quality of life.

Eleven trials, one good-rated[33] and ten fair-rated[27, 29-32, 34-37, 56] 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.[33] 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 ten fair-rated RCTs that compared BDP to FP,[27, 29-32, 34-37, 56] just two included children and adolescents <12 years of age. One was conducted exclusively in a population of children and adolescents aged 4-11[31] and one included children, adolescents, and young adults aged 4-19.[34] 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 two trials[35, 56] assessed asthma symptoms and rescue medicine use.

The majority of trials reported no difference between BPD- 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,[37] nighttime symptoms,[36] rescue medicine use—increase in percent of rescue free days[34] or mean change in rescue puffs per day,[37] or exacerbations.[32] One study found BDP-treated patients to have lower daytime symptom scores.[36]

5. Beclomethasone compared with mometasone

Two fair-quality RCTs[38, 39] 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),[38] 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.

6. Beclomethasone compared with triamcinolone

We found two fair-quality multicenter RCTs comparing BDP to triamcinolone (TAA).[40, 41] 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.[41] They reported conflicting results for improvement of symptoms: one reported greater improvement with BDP than TAA[41] and one reported no difference.[40]

7. Budesonide compared with ciclesonide

Five fair-quality multicenter RCTs meeting our inclusion criteria compared BUD with ciclesonide.[58-62] All five were 12 weeks in duration. One was conducted in children age 6-11[62] and one in adolescents 12-17 years old.[61] One was conducted using subjects with mild to moderate persistent asthma, two with mild to severe, one with moderate to severe, and one with severe persistent asthma. Two trials only compared nonequivalent doses with ciclesonide given at a higher relative dose than BUD.[58, 60] The three studies comparing equivalent doses were non-inferiority trials. All studies used dry powder formulations of BUD and HFA-MDI for ciclesonide. All five trials evaluated outcomes for asthma symptoms and rescue medicine use and all but one[59] reported exacerbations. All five trials were funded by pharmaceutical companies.

Overall, the evidence from the three studies comparing equivalent doses (low versus low or medium versus medium doses of ICSs) was consistent, finding ciclesonide to be non-inferior to BUD. All three studies reported similar improvement in symptoms, [59, 61, 62] rescue medication use,[59, 61, 62] and quality of life [61, 62] for subjects treated with ciclesonide and those treated with BUD.

8. 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.[42] They reported no statistically significant differences between BUD and flunisolide in change from baseline in asthma symptoms, nocturnal awakenings, or rescue medicine use.

9. Budesonide compared with fluticasone

One previously described systematic review and eight head-to-head RCTs comparing FP to BUD met our inclusion criteria. The systematic review[23] included studies comparing FP with BDP or BUD. Of the 71 studies included in this review, 37 compared FP to BUD. 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 the effectiveness of BUD and FP cannot be clearly ascertained from this systematic review[23] because the comparator group contains both BUD and BDP.

Eight fair-rated head-to-head RCTs meeting our inclusion criteria compared budesonide to fluticasone.[25-27, 43-47] Trial duration ranged from six to 24 weeks. Two were conducted in children and adolescents;[44, 46] five were conducted in patients with moderate and/or severe persistent asthma, one was conducted in patients with mild persistent asthma,[26] one in mild to moderate persistent asthma,[46] and the severity was not reported in one trial.[25] Three trials compared nonequivalent doses with FP given at a higher relative dose than BUD.[43, 45, 46] All but one study[43] used dry powder formulations of both medications. All eight 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[27, 44, 47] that compared equipotent doses and one[46] that compared medium- with low-doses of BUD and FP found no difference for symptoms, exacerbations, or rescue medicine use. In addition, one trial[43] 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. Two open-label trials from the 1990s compared FP Diskhaler with BUD reservoir powder device and reported some differences in certain secondary outcomes favoring FP, but no statistically significant differences for most outcomes.[25, 26] Specifically, one reported a higher percentage of subjects treated with FP rating their asthma control "excellent"[25] and one reported greater improvement in rescue-free days and nights.[26] The remaining trial[45] 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.

10. Budesonide compared with mometasone

One fair-rated 12-week RCT[48] and one fair-rated 8-week trial[49] 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.[48] 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.[49] 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.

11. Budesonide compared with triamcinolone

One fair-rated 52-week RCT[50] 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.

12. Ciclesonide compared with flunisolide

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

13. Ciclesonide compared with fluticasone

Eight fair-quality RCTs meeting our inclusion criteria compared ciclesonide with fluticasone.[63-70] Six were 12 weeks in duration, one was 24 weeks,[70] and one was 6 months.[63] Two enrolled children.[68, 69] Three were conducted in subjects with mild to severe persistent asthma; two in subjects with moderate persistent asthma;[64, 65] and one each in mild to moderate[70] and moderate to severe persistent asthma.[63] One trial did not report sufficient information to determine the severity of persistent asthma.[66] All but one trial compared equipotent doses of ICSs.[66] Five of the trials comparing equipotent doses compared low dose ciclesonide with low dose fluticasone; one compared medium doses[64] and one compared high doses.[63] All but one trial used HFA-MDI for delivery of both medications.[64] All eight RCTs were funded by pharmaceutical companies producing ciclesonide.

Overall, the evidence from these studies supports the conclusion that there is no difference in the outcomes of interest between equipotent doses of ciclesonide and FP. All seven trials comparing equipotent doses reported non-inferiority of ciclesonide compared to FP or no statistically significant difference for the outcomes of interest with one exception. All of the trials used some measure to assess symptoms and rescue medication use; all but one assessed exacerbations; and four assessed quality of life. The one exception was reported in a 12 week trial of 474 subjects, finding greater improvement in quality of life with ciclesonide than with FP (mean change from baseline in AQLQ: 0.29 vs. 0.11, $P = 0.005$ for one-sided superiority).[64] The same trial reported non-inferiority or no statistically significant difference between medications for symptoms.

We conducted meta-analyses of these studies for exacerbations, symptoms, and rescue medication use and found no statistically significant differences between ciclesonide and FP (Appendix I). There was no statistically significant difference between ciclesonide and FP for exacerbations requiring treatment with oral steroids (OR 0.97, 95% CI: 0.50 to 1.88), improvement in symptom scores (SMD 0.016, 95% CI: -0.05 to 0.08), or change in rescue medication use (SMD 0.03, 95% CI: -0.03 to 0.09). There was no significant statistical heterogeneity for any of these analyses ($I^2 = 0$ for all).

14. Ciclesonide compared with mometasone

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

15. Ciclesonide compared with triamcinolone

We did not identify any good or fair quality systematic reviews or head-to-head trials that compared ciclesonide with triamcinolone.

16. Flunisolide compared with fluticasone

We found two RCTs reported in one publication[51] 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).

17. 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.

18. 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.

19. Fluticasone compared with mometasone

Three fair-rated trials comparing FP with mometasone met our inclusion/exclusion criteria.[52, 57, 71] 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.[52] 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 ($P < 0.05$).

Another study was a multinational trial (N=203) that compared high dose mometasone (800 mcg/day) with high dose fluticasone (1000 mcg/day) for 12 weeks.[57] The investigators found no statistically significant differences at endpoint with respect to rescue medication use, symptoms, and exacerbations. The third study did not compare equipotent doses; it compared medium dose mometasone with high dose fluticasone.[71]

20. Fluticasone compared with triamcinolone

Three fair-rated trials comparing FP to TAA met our inclusion/exclusion criteria.[53-55] The only one of the three trials comparing equipotent doses[53] found greater improvements in subjects treated with FP. The other two trials comparing non-equipotent doses[54, 55] reported greater improvements for FP-treated subjects for some outcomes and no difference for the others.

The trial comparing equipotent doses[53] 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[54, 55] 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 awakenings[55] for those treated with FP, but the other reported no difference.[54] One reported significantly better improvements in quality of life for FP-treated patients compared to TAA-treated patients.[55]

Table 7. Characteristics 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	Quality Rating
Beclomethasone compared with budesonide					
Adams et al. 2000[22]	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	Good
Molimard et al. 2005[27]	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)	Fair
Worth et al. 2001[28]	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)	Fair
Beclomethasone compared with ciclesonide					
No systematic reviews or head-to-head trials found					
Beclomethasone compared with flunisolide					
No systematic reviews or head-to-head trials found					
Beclomethasone compared with Fluticasone					
Adams et al. 2007[23]	Systematic review with meta-analysis 71 trials (14,602 participants), 59 parallel, 14 cross-over (four had	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)	For some of the included studies	Good

Table 7. Characteristics 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	Quality Rating
	a washout) Majority of studies (47) were between 6 weeks and 5 months; 14 were ≤4 weeks		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		
Lasserson et al. 2010[24]	Systematic review with meta-analysis 9 trials (1265 participants) 3 to 12 weeks	Multinational (most in Europe) Severity ranged from mild to severe persistent	FP compared with extrafine HFA BDP	Yes	Good
Barnes et al. 1993[29]	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)	Fair
Boe et al. 1994[30]	RCT, DB 134 12 weeks	Norway Age ≥ 18, poorly controlled, 34% smokers Multicenter	FP DPI (1600) compared with BDP DPI (2000)	Yes (high)	Fair
de Benedictis et al. 2001[31]	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) compared with BDP DPI (400)	Yes (medium)	Fair
Fabbri et al. 1993[32]	RCT, DB 274 12 months (daily symptom outcomes collected for initial 12	Multinational (10 European) Age 12-80, moderate to severe, not controlled on ICS, 11% smokers Multicenter (25)	FP MDI (1500) compared with BDP MDI (1500)	Yes (high)	Fair

Table 7. Characteristics 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	Quality Rating
	weeks)				
Fairfax et al. 2001[33]	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)	Good
Gustafsson et al. 1993[34]	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)	Fair
Lorentzen et al. 1996[35]	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)	Fair
Lundback et al. 1993[36]	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	Fair
Molimard et al. 2005[27]	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)	Fair
Ohbayashi et al. 2008[56]	RCT, double cross-over every 3 months	Japan	FP DPI (NR) compared with	Yes	Fair

Table 7. Characteristics 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	Quality Rating
	50 10 months	Age, mild to moderate persistent, controlled on FP	BDP MDI (NR)		
Raphael et al. 1999[37]	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)	Fair
Beclomethasone compared with mometasone					
Bernstein et al. 1999[38]	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)	Fair
Nathan et al. 2001[39]	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	Fair
Beclomethasone compared with triamcinolone					
Berkowitz et al. 1998[40]	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)	Fair

Table 7. Characteristics 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	Quality Rating
Bronsky et al. 1998[41]	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)	Fair
Budesonide compared with ciclesonide					
Boulet et al. 2006[58]	RCT, DB, DD 359 12 weeks	Multinational - Canada and Europe Age 12-75, mild to moderate, on ICS, heavy smokers or ex-smokers excluded (>10 cigarettes/day) Multicenter	CIC HFA-MDI (320) vs. BUD DPI (320)	No (medium vs. low)	Fair
Hansel et al. 2006[59]	RCT 554 12 weeks	Multinational - Europe Age 12-75, mild to severe, on ICS, 9% smokers Multicenter	CIC HFA-MDI (80) vs. CIC HFA-MDI (320) vs. BUD DPI (400)	Yes for CIC 80 vs. BUD 400 No for CIC 320 vs. BUD (low vs. medium vs. low)	Fair
Ukena et al. 2007[60]	RCT, DB, DD 399 12 weeks	Germany Age 12-75, mild to severe, smokers excluded Multicenter	CIC HFA-MDI (320) vs. BUD DPI (400)	No (medium vs. low)	Fair
Vermeulen et al. 2007[61]	RCT, DB, DD 403 12 weeks	Multinational - Hungary, Poland, Serbia/Montenegro, South Africa, Spain Age 12-17, severe, not controlled on ICS, excluded smokers Multicenter	CIC HFA-MDI (320) vs. BUD DPI (800)	Yes (medium)	Fair
von Berg et al.	RCT, DB, DD	Multinational - Australia, Germany,	CIC HFA-MDI (160)	Yes (low)	Fair

Table 7. Characteristics 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	Quality Rating
2007[62]	621 12 weeks	Hungary, Poland, Portugal, Serbia and Montenegro, South Africa and Spain Age 6-11, moderate to severe, smoking status NR Multicenter	vs. BUD DPI (400)		
Budesonide compared with flunisolide					
Newhouse et al. 2000[42]	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)	Fair
Budesonide compared with fluticasone					
Adams et al. 2007[23]	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	Good
Ayres et al. 1995[43]	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)	Fair
Connolly et al 1995[26]	RCT 189	UK Age 18-70, mild, mixed population of	FP DPI (200) BUD DPI (400)	Yes (low)	Fair

Table 7. Characteristics 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	Quality Rating
	8 weeks	subjects previously on ICS and not on ICS, smoking status NR			
Ferguson et al. 1999[44]	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)	Fair
Heinig et al. 1999[45]	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)	Fair
Hoekx et al, 1996[46]	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)	Fair
Langdon et al 1994[25]	RCT 281 8 weeks	UK Age 18-70, severity NR, mixed population of subjects previously on ICS and not on ICS, smoking status NR	FP DPI (400) BUD DPI (800)	Yes (medium)	Fair
Molimard et al. 2005[27]	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)	Fair

Table 7. Characteristics 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	Quality Rating
Ringdal et al. 1996[47]	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)	Fair
Budesonide compared with mometasone					
Bousquet et al. 2000[48]	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 M 400 vs. BUD, both medium)	Fair
Corren et al. 2003[49]	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)	Fair
Budesonide compared with triamcinolone					
Weiss et al. 2004[50]	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	Fair

Table 7. Characteristics 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	Quality Rating
Ciclesonide compared with flunisolide					
No systematic reviews or head-to-head trials found					
Ciclesonide compared with fluticasone					
Bateman 2008[63]	RCT 528 6 months	Multinational - Europe, North America, South Africa Age 12-75, moderate to severe, on ICS, 33% ex-smokers or current smokders Multicenter	CIC HFA-MDI (640) vs. FP HFA-MDI (660)	Yes (high)	Fair
Boulet 2007[64]	RCT 474 12 weeks	Multinational - Austria, Canada, Germany, Hungary, South Africa, Spain Age 12-75, moderate, 30% ex-smokers or current smokders Multicenter	CIC HFA-MDI (320) vs. FP DPI (400)	Yes (medium)	Fair
Buhl 2006[65]	RCT 529 12 weeks	Multinational - Germany, Austria, The Netherlands, Spainn, Hungary, Poland, South Africa Age 12-75, moderate, on ICS, smoking status NR Multicenter	CIC HFA-MDI (160) vs. FP HFA-MDI (176)	Yes (low)	Fair
Dahl 2010[70]	RCT, DB, DD 480 24 weeks	Multinational – Austria, Canada, Germany, Poland, and South Africa Age 12-75, on ICS, mild to moderate, excluded current and ex-smokers with ≥ 10 pack-year history, 22-31% current or ex-smokers enrolled Multicenter	CIC HFA-MDI (80) vs. FP HFA-MDI (200)	Yes (low)	Fair
Knox 2007[66]	RCT	United Kingdom, Belgium	CIC HFA-MDI (160)	No (low vs.	Fair

Table 7. Characteristics 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	Quality Rating
			vs.	medium)	
	111	Age 17-75, on ICS, severity NR, 2-3% smokers	FP HFA-MDI (500)		
	12 weeks	Multicenter			
Magnussen 2007[67]	RCT	Multinational - Germany, Poland, Czech Republic, France, Italy, The Netherlands,	CIC HFA-MDI (80) vs.	Yes (low)	Fair
	808	Slovakia, Spain	CIC HFA-MDI (160) vs.		
	12 weeks	Age >12, mild to severe, 21-24% ex- and current smokers	FP HFA-MDI (176)		
		Multicenter			
Pedersen 2009[68]	RCT	Multinational - Brazil, Germany, Hungary, Poland, Portugal, South Africa	CIC HFA-MDI (80) vs.	Yes (low)	Fair
	744	Age 6-11, mild to severe, smoking status	CIC HFA-MDI (160) vs.		
	12 weeks	NR	FP HFA-MDI (176)		
		Multicenter			
Pedersen 2006[69]	RCT	Multinational - 8 countries	CIC HFA-MDI (160) vs.	Yes (low)	Fair
	556	Age 6-15, mild to severe, excluded current smokers	FP HFA-MDI (176)		
	12 weeks	Multicenter			
Ciclesonide compared with mometasone					
No systematic reviews or head-to-head trials found					
Ciclesonide compared with triamcinolone					
No systematic reviews or head-to-head trials found					
Flunisolide compared with fluticasone					
Volmer et al. 1999[51]	Two RCTs (one DB, one open), results reported within a cost-effectiveness analysis	Germany Age 18-70, moderate, ICS naïve, 26% and	FP MDI (500) vs. Flunisolide MDI (1000)	No (high vs. medium)	Fair

Table 7. Characteristics 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	Quality Rating
	publication 321 and 332 8 weeks and 6 weeks	19% smokers Multicenter			
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					
Harnest et al. 2008[57]	RCT 203 12 weeks	Multinational Age ≥18, moderate to severe, on ICS, smoking status NR Multicenter	MF DPI (800) vs. FP DPI (1000)	Yes (high)	Fair
O'Connor et al. 2001[52]	RCT, DB 733 12 weeks	Multinational (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)	Fair
Wardlaw et al. 2004[71]	RCT 167 8 weeks	Multinational Age ≥12, moderate, on ICS, smoking status NR Multicenter	MF DPI (400) vs. FP MDI (500)	No	Fair
Fluticasone compared with triamcinolone					
Baraniuk et al. 1999[53]	RCT, DB, triple- dummy 680	US Age ≥12, not controlled on ICS, excluded smokers	FP MDI (196) + Salmeterol (84) vs. FP MDI (440) vs.	Yes (medium for both ICS-only arms)	Fair

Table 7. Characteristics 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	Quality Rating
	12 weeks	Multicenter, Pulmonary/allergy medicine clinics (50)	TAA MDI (1200)		
Condemi et al. 1997[54]	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)	Fair
Gross et al. 1998[55]	RCT, DB, DD 304 24 weeks	US Age ≥12, 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)	Fair

Abbreviations: AQLQ = Asthma Quality of Life Questionnaire; BDP = beclomethasone dipropionate; BUD = Budesonide; CI =confidence interval; CIC = ciclesonide; 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.

Table 8. Characteristics of head-to-head studies comparing inhaled corticosteroids that included children

Study	Study Design N Duration	Study Population	Comparison (total daily dose)	Equivalent dosing	Quality Rating
Beclomethasone compared with budesonide					
Adams, N et al. 2002[22]	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 vs. BUD all studies assessed equal nominal daily doses of BDP and BUD	Yes	Good
Beclomethasone compared with fluticasone					
Adams, et al. 2007[23]	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	Good
Lasserson et al. 2010[24]	Systematic review with meta-analysis 9 trials (1265 participants) 3 to 12 weeks	Multinational (most in Europe) Severity ranged from mild to severe persistent 2/9 trials in children	FP compared with extrafine HFA BDP	Yes	Good
De Benedicts et al. 2001[31]	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)	Fair
Gustafsson et al. 1993[34]	RCT, DB 398	Multinational (11 worldwide) Age 4-19, mild to moderate, not	FP MDI (200) vs. BDP MDI (400)	Yes (medium)	Fair

Table 8. Characteristics of head-to-head studies comparing inhaled corticosteroids that included children

Study	Study Design N Duration	Study Population	Comparison (total daily dose)	Equivalent dosing	Quality Rating
	6 weeks	controlled on current meds, smoking status NR Multicenter (32)			
Budesonide compared with Ciclesonide					
von Berg et al. 2007[62]	RCT, DB, DD 621 12 weeks	Multinational - Australia, Germany, Hungary, Poland, Portugal, Serbia and Montenegro, South Africa and Spain Age 6-11, moderate to severe, smoking status NR Multicenter	CIC HFA-MDI (160) vs. BUD DPI (400)	Yes (low)	Fair
Budesonide compared with Fluticasone					
Adams et al. 2007[23]	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	Good
Ferguson et al. 1999[44]	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)	Fair
Hoekx et al. 1996[46]	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)	Fair

Table 8. Characteristics of head-to-head studies comparing inhaled corticosteroids that included children

Study	Study Design N Duration	Study Population	Comparison (total daily dose)	Equivalent dosing	Quality Rating
Ciclesonide compared with Fluticasone					
Pedersen 2009[68]	RCT 744 12 weeks	Multinational - Brazil, Germany, Hungary, Poland, Portugal, South Africa Age 6-11, mild to severe, smoking status NR Multicenter	CIC HFA-MDI (80) vs. CIC HFA-MDI (160) vs. FP HFA-MDI (176)	Yes (low)	Fair
Pedersen 2006[69]	RCT 556 12 weeks	Multinational - 8 countries Age 6-15, mild to severe, excluded current smokers Multicenter	CIC HFA-MDI (160) vs. FP HFA-MDI (176)	Yes (low)	Fair

Abbreviations: AQLQ = Asthma Quality of Life Questionnaire; BDP = beclomethasone dipropionate; BUD = Budesonide; CI = confidence interval; CIC = ciclesonide; 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.

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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 9).[72] 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 (Appendix H, Table H-2).

Detailed Assessment

Head-to-head comparisons

1. Montelukast compared with Zafirlukast

One fair-rated 12-week[72] 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 9. Characteristics 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)	Quality rating
Montelukast (ML) compared with zafirlukast				
Riccioni et al.[72]	RCT 40 12 weeks	Italy Age ≥12, mild, smoking status NR Respiratory Pathophysiology Center	ML (10) compared with ZAF (40)	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.

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

Summary of findings

We found three fair RCTs[73-76] that included head-to-head comparisons of one LABA with another LABA meeting our inclusion/exclusion criteria. Two compared eformoterol with salmeterol[73, 74] and one compared formoterol with salmeterol.[75, 76] 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.[77] (Table 10)

Overall, results from three efficacy studies provide moderate evidence (Appendix H, Table H-3) 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 (Evidence Tables A).

Detailed Assessment

Description of Studies

Of the 3 trials, two compared eformoterol (eFM) with salmeterol (SM) and one compared formoterol (FM) with SM (Table 10). 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).[74]

Study Populations
The three head-to-head RCTs included a total of 1107 subjects. Two were conducted primarily in adult populations.[73, 75, 76] One study[74] was conducted in a pediatric and adolescent population (age 6-17) (Table 10). Two trials (66%) were conducted in the UK and Republic of Ireland[73, 74] and one was conducted in France, Italy, Spain, Sweden, Switzerland and the UK.[75, 76] Asthma severity ranged from mild to severe persistent: one study (33%) was conducted in patients with mild to moderate persistent asthma,[73] one (33%) in patients with moderate persistent,[74] and one (33%) in patients with moderate to severe persistent.[75, 76] All three trials enrolled subjects that were not adequately controlled on ICSs. Smoking status was not reported for the pediatric/adolescent trial.[74] 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.[73, 74] 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.[73] The other was a 12-week trial that enrolled 156 children and adolescents between six and 17 years of age with moderate persistent asthma.[74]

Both trials assessed asthma symptoms, nocturnal awakenings, and exacerbations. One trial also reported hospital admission or visits to A&E[73] while the other study also reported rescue medication use, quality of life, missed work, missed school, and compliance as well.[74] The trials found no difference between those treated with eFM and those treated with SM for all outcomes except for rescue medicine use: one trial[74] found a greater decrease in rescue medicine use in those treated with eFM than in those treated with SM (Evidence Tables A).

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.[75, 76] 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.

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 10. Characteristics 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)	Quality rating
Eformoterol compared with Salmeterol				
Campbell et al. 1999[73]	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)	Fair
Everden et al. 2004[74]	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) vs. SM DPI (100)	Fair
Formoterol compared with Salmeterol				
Vervloet et al. 1998[75] *AND* Rutten-van Molken et al. 1998[76]	RCT, open 482 6 months	France, Italy, Spain, Sweden, Switzerland & UK Age ≥ 18, moderate-severe, not controlled on ICS, 14-16% current smokers Outpatient centres	FM DPI (24) vs. SM DPI (100)	Fair

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.

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 eight RCTs (13 publications)[78-91] and two systematic reviews with meta-analyses[92, 93] that met our eligibility criteria. Only two of the RCTs[83, 84, 90] enrolled children (6-12 years old). Five of the other RCTs included adolescents and adults ≥ 12 years of age, and one included only adults 20-75 years old.[91] (Table 11)

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 in patients already on ICSs with or without other controller medications (high strength of evidence, Appendix H, Table H-4). 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. Most trials were 28-32 weeks in duration with the exception being one 52 week trial.[90] In addition, two trials conducted optional double-blind extensions providing data for up to 52 weeks. Our meta-analyses (Appendix I) and previously published systematic reviews with meta-analyses showed omalizumab to be statistically significantly superior to placebo for several outcome measures.

Detailed Assessment

Description of Studies

Six of the RCTs were 28 weeks in duration, with the others being 32 and 52 weeks in duration[81, 90] (Table 11). Four trials had 16 weeks of stable ICS dose followed by a 12-16 week phase of ICS tapering. One trial used only a 16 week stable ICS phase without subsequent tapering,[91] and another, longer trial included 24 weeks of stable ICS dose followed by 28 weeks of tapering.[90] In all included RCTs, subjects continued ICS treatment throughout the study duration. In three trials, all patients were also taking either a LABA or other standard maintenance therapy at constant doses throughout the study,[82, 90, 91] In all eight RCTs and one systematic review,[92] 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.[93]

Study Populations

The eight RCTs included a total of 3,480 patients. Five trials were conducted in adolescent and adult populations (ranging from 12 to 75 years of age) and one was conducted only in adults age 20 to 75.[91] Only two studies were conducted in pediatric populations (6-12 years of age).[83, 90] In addition, all patients had moderate to severe asthma with concurrent allergies and/or rhinitis. One trial was conducted in the US, one in the US and UK, and one in Japan; the remaining five trials were multinational.

Current smoking status was not reported in either of the two studies that enrolled children (age 6-12).[83, 90] One study explicitly excluded smokers[82] and one included both current and ex-smokers;[91] 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. Two efficacy studies that met our eligibility criteria were not included in our analysis because they were rated poor quality (Appendix F).

Sponsorship
Of the 8 included RCTs, 7 (88%) 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.[82]

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 (Evidence Tables A and B). One RCT conducted in children reported nocturnal awakenings.[83] One study reported no deaths in either the omalizumab or placebo groups,[90] but no other studies reported mortality or adherence. We conducted meta-analyes on these outcomes when sufficient data was reported by multiple studies (Appendix I).

The five trials in adolescent and adult populations reported statistically significant differences favoring omalizumab in overall symptom scores. The study including only adult subjects also showed an improvement in asthma symptom score in the omalizumab group, but the difference was not statistically significant.[91] One of the pediatric studies reported "little change" in scores and "minimal difference" between omalizumab and placebo (data NR).[83] The other also noted no statistically significant difference between groups with respect to mean change from baseline in nocturnal symptom scores at 24 weeks (–0.63 [0.72] vs –0.50 [0.71], $P = 0.114$.[90] Two trials reported the proportion of "low symptom days."[78, 85, 89] Both studies used the term "asthma-free days" but defined the concept to allow for some daily symptoms and daily use of rescue-medication.

Seven studies assessed the number of exacerbations per patient. The results of our meta-analysis show fewer exacerbations per patient with omalizumab compared to placebo (WMD = -0.18, 95% CI: -0.24, -0.11, I^2 7.5). In addition, six studies reported the percentage of patients with one or more exacerbations. Our meta-analysis results show significantly fewer omalizumab-treated subjects with one or more exacerbations compared to placebo-treated subjects (OR = 0.51, 95% CI: 0.40, 0.67, I^2 25.8). There was no significant heterogeneity between studies. Finally, three studies reported the rate of clinically significant asthma exacerbations.[82, 90, 91]

All RCTs assessing rescue medication use (seven trials) reported a greater decrease in use of rescue medication for omalizumab. Differences were statistically significant in five of the seven studies. The difference was not significant in two studies,[82, 91] and the *P* value was not reported in one.[88] We were not able to conduct meta-analyses for rescue medicine use outcomes because too few studies reported sufficient data.

Six of the 8 RCTs that met our eligibility criteria utilized the AQLQ and demonstrated significantly higher scores in omalizumab-treated patients. Results of our meta-analyses show greater improvement 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 = 0.26, 95% CI: 0.18, 0.35, I^2 0).

Two systematic reviews with meta-analyses reported results consistent with our findings. One good quality systematic review included 14 RCTs (3143 subjects) comparing omalizumab and placebo in children and adults with chronic asthma.[93] This review included 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). Another fair quality systematic review conducted a meta-analysis of asthma-related quality of life from five RCTs.[92] We included these trials in our analysis; in addition, we included the INNOVATE trial.[82] Results from this meta-analysis are consistent with our findings.

Table 11. Characteristics of head-to-head studies comparing omalizumab with placebo in children and adults

Study	Study design N Duration	Country Population Setting	Dose	Quality rating
Niebauer et al. 2006[92]	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 ICS use in all trials	0.016 mg/kg per IU/mL of IgE every 2 or 4 weeks	Fair
Walker et al. 2006[93]	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)	Good
Busse, et al. 2001[78] Finn et al. 2003[79] Lanier et al. 2005[80] + Unpublished data from FDA[89]	RCT DB 525 28 weeks (16 weeks followed by 12 weeks tapering ICS dose) Optional 24 week DB extension (N = 460)	US and UK 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 Multicenter (5)	0.016 mg/kg per IU/mL of IgE every 4 weeks (150 mg or 300 mg every 4 wks or 225 mg, 300 mg, or 375 mg every 2 wks)	Fair
Holgate et al. 2004[81] + Unpublished data from FDA[89]	RCT DB 246 32 weeks (16 week treatment phase, 16 week steroid 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; allergic response (> 1 positive SPT) to aeroallergen(s) Multicenter	0.016 mg/kg per IU/mL of IgE every 4 weeks	Good
Humbert et al. 2005[82]	RCT DB 482	Multinational Age 12-75, positive SPT to ≥ 1 perennial aeroallergen, severe	0.016 mg/kg per IU/mL of IgE	Fair

Table 11. Characteristics of head-to-head studies comparing omalizumab with placebo in children and adults

Study	Study design N Duration	Country Population Setting	Dose	Quality rating
INNOVATE	28 weeks	persistent asthma requiring regular treatment with >1000 mcg BDP or equivalent LABA, continued high dose ICS + LABA throughout study Multicenter (hospital clinics)		
Lanier et al 2009[90]	RCT DB (2:1) 627 52 weeks (24 week fixed steroid phase, 28 week adjustable steroid phase)	Multinational Age 6-12 with uncontrolled moderate to severe IgE-mediated asthma despite treatment with medium- or high-dose ICSs with or without other controller medications Multicenter	75-375 mg SC every 2 or 4 weeks	Fair
Milgrom et al. 2001[83] Lemanske et al. 2002[84] + Unpublished data from FDA[89]	RCT DB 334 28 weeks (16 week stable steroid phase,12 week steroid reduction phase)	United States 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 per IU/mL of IgE every 2 or 4 weeks	Fair
Ohta et al. 2009[91]	RCT DB 315 28 weeks (16 week treatment phase, 12 week follow up phase)	Japan Age 20-75, uncontrolled moderate to severe asthma despite high-dose ICSs (≥ 800 mcg/day BDP or equivalent) + ≥ 1 other standard therapy (LABA, LRTA, theophylline, etc), positive SPT or *in vitro* reactivity to ≥ 1 perennial aeroallergen, serum total IgE 30-700 IU/mL Multicenter (73)	≥ 0.016 mg/kg per IU/mL of IgE every 2 or 4 weeks	Fair
Solèr et al. 2001[85] Buhl et al. 2002[86] Buhl et al. 2002[87] + Unpublished	RCT DB 546 28 weeks (16 week stable ICS phase, 8 week reduction phase,4 week	Multinational Age 12-75, Moderate-severe allergic asthma Multicenter	≥ 0.016 mg/kg per IU/mL of IgE	Good

Table 11. Characteristics of head-to-head studies comparing omalizumab with placebo in children and adults

Study	Study design N Duration	Country Population Setting	Dose	Quality rating
data from FDA[89]	stable phase) 24 week DB extension (N = 483)			
Vignola et al. 2004[88] 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 per IU/mL of IgE every 4 weeks	Fair

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.

E. Combination Products

1. ICS+LABA compared with ICS+LABA

Summary of findings

We found 1 good quality systematic review[94] and four randomized controlled trials[95-101] that compared the combination of an ICS plus a LABA with another ICS/LABA combination for controller therapy. (Table 12) The review and all four trials compared fixed (non-adjustable) doses of the combination of budesonide and formoterol (BUD/FM) to fixed (non-adjustable) doses of the combination of fluticasone and salmeterol (FP/SM).

Overall, results from large trials up to six months in duration 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. (Appendix H, Table H-5) The results of our meta-analysis show no statistically significant difference between those treated with BUD/FM and those treated with FP/SM for exacerbations requiring oral steroids (OR =1.16, 95% CI:0.95, 1.4; *P* = 0.15, 3 studies) or exacerbations requiring emergency visits or hospital admissions (SMD = 0.74, 95% CI: 0.53, 1.04; *P* = 0.083, 3 studies). (Appendix I)

Detailed Assessment

Description of Studies

Systematic review

We found 1 systematic review of good quality that compared the combination of an ICS plus a LABA with another ICS/LABA combination for controller therapy.[94] The review included only randomized, controlled, parallel-design trials and required that only single inhaler devices were used to administer study drugs. Studies lasting fewer than 12 weeks or administering "adjustable maintenance dosing" or "single inhaler therapy" rather than fixed doses were excluded. The review included five studies, all of which compared BUD/FM with FP/SM and included a total of 5,537 adult and adolescent subjects. Three of the five are included in the RCT section of this report;[95, 97, 98] one was excluded from this report due to the study design, with a second randomization at one month (only allowing a valid comparison of FP/SM with BUD/FM for one month; our duration criteria was at least 6 weeks).[102] The fifth was a study whose results were not published. Doses of BUD and FM in the included trials ranged from 400-800mcg/day and 12-24mcg/day, respectively. All of the studies administered 500mcg and 100mcg of FP and SM per day. Included studies ranged from 12 weeks to 30 weeks and took place in the United States and Europe.

All included studies enrolled adolescents and adults, and neither restricted asthma severity or current treatment, although participants had to have a history of chronic asthma, treated with moderate to high maintenance doses of ICS prior to entry. All trials required patients to be stable for one month before the run-in period and to continue to demonstrate the need for frequent reliever use during the run-in. Demographics of the included studies indicated that treatment and comparison groups were well-balanced. All included studies were funded by pharmaceutical manufacturers.

Four of the trials measured symptom scores, rescue medication use and exacerbations.[95, 97, 98, 102] Two trials used a double-blind, double-dummy design; [97, 98] the other two were open-

label. There were no statistically significant differences between FP/SM and BUD/FM in mean change in daytime symptom scores (three studies; treatment difference = -0.02; 95% CI -0.6 to 0.03; N = 3,464) or percent of symptom-free days (two studies; treatment difference = 1.25; 95% CI -1.18 to 3.67; N = 3,027). Exacerbations were reported as participants experiencing an exacerbation requiring oral steroid treatment and as participants experiencing exacerbations resulting in hospital admission. For exacerbations requiring oral steroid treatment, there was no statistically significant difference between FP/SM and BUD/FM (four studies; OR = 0.89; 95% CI 0.74 to 1.07; N=4,515). Similarly, no statistically significant difference was found between FP/SM and BUD/FM groups for exacerbations resulting in hospital admissions (four studies; OR = 1.29; 95% CI 0.68 to 2.47; N = 4,053). In addition, a composite measure was created in order to measure exacerbations resulting in a hospital admission or an emergency department visit. This comparison also failed to yield a statistically significant difference between treatments (four studies; OR 1.3; 95% CI 0.94, 1.8; N = 4,861). There was also no significant difference between FP/SM and BUF/FM in rescue medication use (three studies; treatment difference = -0.06 puffs/day; 95% CI -0.13 to 0.02; N = 3,469).

Randomized controlled trials

Of the four RCTs we included (seven articles) **(**Table 12), 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.[101] Study duration ranged from 12 weeks[101] to seven months.[95] All four trials administered BUD and FM via DPI; three did so in a single DPI; one trial administered BUD+FM in separate inhalers.[101]

Within-trial equipotency of daily ICS dose varied. All four trials administered the same total daily dose of FP/SM (500/100), which is considered a medium daily dose of ICS when delivered via DPI and a high daily dose when delivered via pMDI (Table 3). In two trials, 500mcg of FP was compared with an equipotent daily dose of BUD.[95-97] In one of these, there was a third arm that contained an adjustable-dose BUD/FM arm, although this is not a comparison of interest for the current report. Of the non-equipotent dosage studies, one study compared low (but adjustable) and medium (but fixed) daily doses of BUD with a high dose of FP,[98-100] and another compared a high daily dose of BUD with a medium dose of FP.[101]

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.[98, 99] 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 and the systematic review reported asthma symptoms and exacerbations (Evidence Tables A and B). Symptoms reported by at least two of the trials were weeks with "well-controlled" asthma,[95-97] symptom-free days,[97-100], nocturnal awakenings / symptom-free nights,[95-101], and asthma symptoms scores – as either total[98-100] or daytime[95-97] scores. In addition, one trial reported nights with a symptom score <2, [101] and another reported ACQ and AQLQ(S) scores.[98-100]

All four trials reported either number or rate of exacerbations; one measured the number of exacerbations requiring hospitalization or emergency treatment,[96]and two measured the number or rate of exacerbations classified as moderate and/or severe.[97-100]

All but one trial[101] reported use of rescue medication. Number of missed days of work and AQLQ(S) score were reported by one study,[98-100] Finally, one study reported rates of non-emergency health care services utilization, including general practitioner (GP) home visits, GP clinic visits and GP telephone contacts.[101]

For most of these outcomes, there were no statistically significant differences between the BUD/FM and FP/SM groups. The systematic review and 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.[101] 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)[98, 99] It reported no difference in symptoms, nocturnal awakenings, exacerbations, asthma-related quality of life or missed work, but found mixed results for rescue medicine use and hospitalizations or emergency visits. Specifically, the authors 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, $P = 0.013$) . The total number of hospitalizations or emergency visits was not analyzed for statistical significance, but there were fewer such events in the BUD/FM arm compared with the FP/SM arm (72 and 106, respectively). A post-hoc analysis of the original study that was limited to participants ages 16 and above yielded similar results. Of note, the total daily dose of BUD delivered by DPI in this study is considered medium and the total daily dose of FP delivered by pMDI is considered high.

There were additional numerical trends for some outcomes that favored one intervention over the other but for which statistical tests were not performed. One study [95] reported numerically fewer hospitalizations/ER visits in patients treated with BUD/FM; another [101] reported the same number of ER contacts in both arms but more inpatient days and outpatient hospital visits in the BUD/FM arm than in the FP/SM arm. It is unclear in the latter study how many hospital visits contributed to the total number of inpatient days. Median percentage of patients with symptom-free days was slightly higher in the FP/SM arm than in the BUD/FM arm (between-group difference = 3%) in another study.[97] In the aforementioned 6-month trial, [98, 99] fewer severe exacerbations were reported in the BUD/FM arm, compared with the FP/SM arm (173 and 208, respectively), but this difference was not reported to be statistically significant.

We conducted meta-analyses for exacerbations requiring oral steroid treatment for ≥ 3 days and for exacerbations requiring emergency department visits and/or hospital admissions (Appendix I). The results of our meta-analyses show no statistically significant difference between those treated with BUD/FM and those treated with FP/SM in exacerbations requiring oral steroids or exacerbations requiring emergency visits or hospital admissions.

Table 12. Characteristics of head-to-head studies comparing ICS+LABA with ICS+LABA

Study	Study design N Duration	Country Population Setting	Comparison (total daily ex-mouthpiece dose in mcg)	Equipotent steroid component	Quality rating
Budesonide/formoterol (BUD/FM) compared with fluticasone/salmeterol (FP/SM)					
Lasserson et al. 2008[94]	SR 5,537 > 12 weeks	Multinational Any age; chronic asthma diagnosis, unrestricted by severity, previous or current treatment Multicenter	BUD/FM (320-640/9-18) DPI, pMDI vs. FP/SM (500/100) DPI	Variable	Good
Aalbers et al. 2004[95] AND Aalbers et al. 2010[96a]	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) AD DPI vs. BUD/FM (640/18) DPI vs. FP/SM (500/100) DPI	Yes, for the non-adjustable arms	Fair
Dahl et al. 2006[97] EXCEL trial	RCT 1397 24 weeks	Multinational Age ≥ 18 years with asthma for a minimum of 6 months, not controlled on 1000-2000 BDP or equivalent, moderate to severe, excluded smokers with ≥ 10 pack-year history Multicenter	BUD/FM (640/18) DPI vs. FP/SM (500/100) DPI	Yes	Good
Kuna et al. 2007[98] AND Price et al. 2007[99] AND Kuna 2010[100b]	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 (mean BUD/FM dose including rescue use 483/13.6) vs. BUD/FM (640/18) DPI vs. FP/SM (500/100) pMDI	No (low compared with medium compared with high)	Good

Table 12. Characteristics of head-to-head studies comparing ICS+LABA with ICS+LABA

Study	Study design N Duration	Country Population Setting	Comparison (total daily ex-mouthpiece dose in mcg)	Equipotent steroid component	Quality rating
Ringdal et al. 2002[101] EDICT trial	RCT 428 12 weeks	Multinational (11 European countries) 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	BUD (1280) DPI + FM (24) DPI vs. FP/SM (500/100) DPI	No (high BUD compared with medium FP)	Good

Abbreviations: AD= adjustable dosing; BUD+FM= budesonide and formoterol in seperate inhalers; BUD/FM= budesonide and formoterol in one inhaler; DPI= dry powder inhaler; FP = fluticasone propionate; FP+SM= fluticasone and salmeterol in separate inhalers; FP/SM= fluticasone and salmeterol in one inhaler; ICS = inhaled corticosteroid; LABA = long-acting beta-2 agonist; NS= not statistically significant; pMDI= pressurized metered dose inhaler; SR = systematic review; RCT= randomized controlled trial.

[a] Post-hoc analysis of ages ≥ 16 (N = 644) from the full study population.

[b] Post-hoc analysis of ages ≥ 16 (N = 2854) from the full study population.

2. ICS/LABA for both maintenance and as-needed relief (ICS/LABA MART) 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 13).[98-100, 103-106] All 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. BUD/FM is not approved for use as a relief medication in the United States, but it has been approved for maintenance and reliever therapy in Canada when administered via a DPI. Delivery of BUD/FM via pMDI is not indicated for MART. Two trials compared BUD/FM for maintenance and relief to BUD/FM for maintenance with a SABA for relief;[98-100, 103, 105] 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.[98, 100, 104, 106] Several of the trials included in this section significantly reduced the total ICS doses for many of the subjects upon randomization (some studies averaged a 75% dose reduction).

Overall, results from large trials up to twelve months in duration found statistically significantly lower odds of exacerbations requiring medical intervention for those treated with BUD/FM for maintenance and relief than for those treated with ICS/LABA for maintenance and a SABA for relief (moderate strength of evidence, Appendix H, Table H-6). Our meta-analysis showed an odds ratio of 0.746 (95% CI: 0.656, 0.848; 5 comparisons) favoring MART. A separate meta-analysis of exacerbations resulting in emergency department visits or hospital admissions revealed similar findings; the odds ratio for MART was 0.733 (95% CI: 0.597, 0.900; 4 comparisons). MART was also associated with fewer nocturnal awakenings, compared with ICS/LABA + SABA (SMD = -0.076; 95% CI = -0.124, -0.027; 4 comparisons). I^2 values for each of those meta-analyses were < 25%, indicating low heterogeneity, and sensitivity analysis results did not change our conclusions in either case. (Appendix I)

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-analyses found no statistically significant differences in symptom-free days (SMD = 0.023, 95% CI: -0.019, 0.065; 4 comparisons), symptom scores (SMD = -0.018, 95% CI: -0.066, 0.031; 5 comparisons), rescue-free days (SMD = -0.040, 95% CI: -0.088, 0.009; 4 comparisons), or rescue medicine puffs per day (SMD = -0.058, 95% CI: -0.137, 0.020; 5 comparisons). Sensitivity analyses for each of these comparisons did not reveal anything that would change our conclusions. (Appendix I) It is difficult to determine the applicability of the results of these trials given the heterogeneity of study designs and dose comparisons.

Detailed Assessment

Description of Studies

Of the four RCTs we included **(**Table 13), two compared BUD/FM MART to BUD/FM for maintenance and SABA for relief,[98-100, 103, 105] and three compared BUD/FM MART 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[98, 100, 104] to 12 months.[103, 105, 106]

Total daily maintenance ICS components of the BUD/FM MART groups varied. One study compared low starting and mean ex-mouthpiece doses of BUD (in the MART arm) with low fixed-dose BUD (fixed-dose BUD/FM arm),[103, 105] one compared low mean daily dose of BUD (MART arm) with medium and high doses of non-adjustable combinations,[98-100] one compared medium dose with medium dose,[106] and one compared medium dose BUD (MART arm) with high fixed-dose FP (FP/SM + SABA arm).[104] In two studies, the mean total daily dose of ICS administered ex-mouthpiece in the BUD/FM MART group was less than the total daily dose in the ICS/LABA with a SABA for relief group.[98-100, 104] Several of the trials significantly reduced the total ICS doses for many of the subjects upon randomization. Some studies reduced the starting ICS 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.[98-100]

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,[105] and one publication further described the subset of children four to 11 years of age from that study.[103] Another publication examined only the subset of participants ages 16 and older.[100]

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 asthma[103-105] and two did not report asthma severity classification.[98-100, 106] Two trials did not report smoking rates and two allowed some smokers.[98-100, 104] 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 MART compared with ICS/LABA for maintenance and SABA for relief

The results of the four RCTs contributing five comparisons (one study compared BUD/FM MART 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 MART, but no differences in symptoms.

We conducted meta-analyses for seven outcomes that were reported with sufficient data in multiple trials (Appendix I). These included symptom-free days, symptom scores, nocturnal awakenings, exacerbations requiring medical intervention, exacerbations resulting in emergency visit or hospital admission, rescue-free days, and rescue medicine use (puffs/day).

Our meta-analysis for exacerbations requiring medical intervention shows an odds ratio of 0.75 (95% CI: 0.66, 0.85; 5 comparisons) favoring MART. A separate meta-analysis of exacerbations resulting in emergency department visits or hospital admissions revealed similar findings; the odds ratio for MART was 0.73 (95% CI: 0.60, 0.90; 4 comparisons). MART was also associated with fewer nocturnal awakenings, compared with ICS/LABA + SABA (SMD = -0.08; 95% CI = -0.12, -0.03; 4 comparisons). I^2 values for each of these analyses was < 25%.

We found no statistically significant differences in symptom-free days (SMD = 0.02, 95% CI:-0.02, 0.06, 3 studies contributing 4 comparisons), symptom scores (SMD = -0.02, 95%

CI: -0.07, 0.03, $P = 0.48$; 4 studies contributing 5 comparisons), rescue-free days (SMD = -0.04, 95% CI: -0.09, 0.01, 3 studies contributing 4 comparisons), or rescue medicine puffs per day (SMD = -0.06, 95% CI: -0.14, 0.02, $P = 0.14$; 4 studies contributing 5 comparisons). The I^2 value for rescue medication use was 76.6, indicating high statistical heterogeneity.

Of note, the comparisons that administered scheduled maintenance ICS doses that were lower in the BUD/FM MART group all found statistically significantly lower exacerbation rates for those treated with BUD/FM MART.[98-100, 104] In addition, the BUD/FM MART 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.[98-100, 104, 106] Thus, it does not appear that delivering a higher total ICS dose explains the better exacerbations outcomes in the BUD/FM MART group.

2. BUD/FM MART compared with BUD/FM for maintenance and SABA for relief

We found one good-[98-100] and one fair-quality [103, 105] RCT for this comparison. Both trials reported asthma symptoms, nocturnal awakenings, exacerbations, and rescue medicine use (Table 13). One trial also reported missed work, hospitalizations, and emergency visits[98-100] (Evidence Tables A and B). The results are mixed but show a trend favoring the BUD/FM MART for several outcomes. Both reported statistically significant differences in exacerbations favoring BUD/FM MART, but reported no difference in symptoms. One trial reported fewer nocturnal awakenings in both children and adults treated with BUD/FM MART.[103, 105] The single study reporting hospitalizations and emergency visits found no difference between groups in the full population analysis[98, 99] but a small but significant decrease in hospitalizations / emergency visits favoring BUD/FM MART among those age 16 and older.[100] The trial reporting missed work found a numerical difference favoring BUD/FM MART, but the statistical significance was not reported.[98-100]

None of the trials reported any outcomes favoring the BUD/FM for maintenance and SABA for relief.

3. BUD/FM MART compared with FP/SM for maintenance and SABA for relief

We found two good-[98-100, 104] and one fair-quality RCTs[106] comparing these treatments. All three trials reported asthma symptoms, exacerbations, and rescue medicine use (Evidence Tables A and B). Two trials reported nocturnal awakenings and hospitalizations or emergency visits.[98-100, 104] One trial also reported missed work[98-100] and two reported quality of life.[98-100, 106]

The results are mixed but show a trend favoring BUD/FM MART 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 MART. Outcomes related to rescue medications use were mixed. One trial reported no difference in rescue medicine use or rescue-free days;[104] 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%, $P < 0.05$);[98-100] one reported less rescue medicine use for those treated with BUD/FM MART (0.58 puffs/day compared with 0.93, $P < 0.001$).[106] The trials reporting quality of life, and hospitalizations or emergency visits found no difference between treatment groups. The single trial reporting missed work found the lowest mean number of sick days in the FP/SM arm (2.36 per 6 months), the highest in the BUD/FM fixed-dose arm (3.11 per 6 months), and 2.48 days per 6 months in the MART arm, but the statistical significance was not reported.[98-100]

Of note, the fair-quality trial[106] 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 MART 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 MART group.

Table 13. Characteristics of head-to-head studies comparing BUD/FM for maintenance and relief (MART) with ICS/LABA for maintenance and Short-Acting Beta-Agonist (SABA) for relief

Study	Study design N Duration	Country Population Setting	Comparison (total daily ex-mouthpiece dose in mcg)	Equipotent[a]	Quality rating
BUD/FM MART 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[103b]	RCT, DB 341 12 months	Multinational (12) Age 4-11, mild-moderate persistent asthma ≥ 6 months, not controlled on ICS, smoking status NR Multicenter (41)	BUD/FM MART (80/4.5 + as needed) DPI; overall mean daily dose including rescue use 126/7.1 vs. BUD/FM (80/4.5) DPI + terbutaline 0.4mg as needed vs. BUD (80) DPI + terbutaline 0.4mg as needed	Yes	Fair
Bousquet et al. 2007[104]	RCT 2309 6 months	Multinational (17) Age ≥ 12, uncontrolled on ICS or ICS+LABA, moderate persistent asthma, excluded smokers with ≥ 10 pack-year history, 4-5% were current smokers Multicenter (184 centers)	BUD/FM MART (640/18 + as-needed) DPI (overall mean daily BUD dose including rescue use 792) vs. FP/SM (1000/100 + terbutaline 0.4mg as needed) DPI	No (medium BUD vs. high FP)	Fair
O'Byrne et al. 2005[105] AND Bisgaard et al. 2006[103]	RCT 2760 1 year	Multinational (22) Age 4-80, uncontrolled on ICS, moderate persistent asthma, smoking status NR Multicenter (246)	Adults: BUD/FM MART (160/9 + as-needed) DPI; overall mean daily dose approx. 250 – estimated from graph) vs. BUD/FM (160/9) DPI + terbutaline 0.4mg as needed) vs. BUD (640) DPI med + terbutaline 0.4mg as needed; Children: BUD/FM MART (80/4.5 + as needed) DPI; overall mean daily dose including rescue use 126/7.1 vs. BUD/FM (80/4.5) DPI + terbutaline 0.4mg as needed vs. BUD (80) DPI + terbutaline 0.4mg as needed	Yes (for the 2 arms of interest in this comparison)	Fair

Table 13. Characteristics of head-to-head studies comparing BUD/FM for maintenance and relief (MART) with ICS/LABA for maintenance and Short-Acting Beta-Agonist (SABA) for relief

Study	Study design N Duration	Country Population Setting	Comparison (total daily ex-mouthpiece dose in mcg)	Equipotent[a]	Quality rating
Kuna et al. 2007[98] AND Price et al. 2007[99] AND Kuna 2010[100]	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	BUD/FM MART (320/9 + as-needed use) DPI (mean BUD/FM dose including rescue use 483/13.6) vs. BUD/FM (640/18) med DPI + terbutaline 0.4mg as needed vs. FP/SM (500/100) high pMDI + terbutaline 0.4mg as needed	No (low mean AD dose BUD compared with medium fixed dose BUD compared with high fixed dose FP)	Good
Vogelmeier, et al.[106]	RCT 2135 12 months	Multinational (16) Age ≥12, not controlled, taking ICS at entry,smoking status NR Multicenter (246)	BUD/FM MART (640/18 + as-needed) DPI med (overall mean daily BUD dose including rescue use ~ 650) vs. FP/SM (500/100 + as-needed SABA) DPI med + salbutamol as needed DPI or pMDI	Yes	Good

Abbreviations: BUD = budesonide; BUD/FM budesonide and formoterol administered in a single inhaler; DB = double-blind; DPI = dry powder inhaler; FD= fixed dose; FM = formoterol; FP = fluticasone propionate; FP/SM = fluticasone and salmeterol administered in a single inhaler; ICS = inhaled corticosteroids; LABAs = long-acting beta-2 agonists; MART = maintenance and reliever therapy; OL = open-label; pMDI= pressurized metered dose inhaler; RCT= randomized controlled trial; SABA = short-acting beta agonist; SM = salmeterol

[a] Equipotency in BUD/FM + as-needed arms was determined by overall mean daily dose of ICS

[b] This publication describes the pediatric subset of the population in the O'Byrne et al. 2005 trial below.[105] Thus it is not a separate trial and is not included in meta-analyses, to avoid double counting subjects

F. Long-Acting Anticholinergics

1. Tiotropium

Summary of findings
Tiotropium is not approved for the treatment of asthma. It is approved for the treatment of chronic obstructive pulmonary disease (COPD). We found no studies of tiotropium meeting our inclusion criteria.

II. Inter-class comparisons (between classes)

A. Monotherapy

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

Summary of findings
We found three systematic reviews with meta-analyses[107-109] and 22 RCTs[110-134] (Tables 14 and 15). Fourteen of the RCTs were in adolescents and adults ≥12 years of age and 8 (9 articles) were in children < 12.[124-130, 132, 133]

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 for rescue medicine use, symptoms, exacerbations, and quality of life (high strength of evidence, Appendix H, Table H-7, meta-analysis results in Appendix I).

Detailed Assessment

Description of Studies
Of the 22 RCTs (Tables 14 and 15), 6 RCTs compared montelukast with beclomethasone; 9 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. Three trials included extension phases ranging 36-48 weeks in duration.[112, 130, 134]

Study Populations
The 22 RCTs included a total of 9,873 patients. Most studies were conducted in adult populations. Eight studies (9 articles)[124-130, 132, 133] were conducted primarily in pediatric populations. Fourteen studies (45%) were conducted in the United States, two (9%) in Europe, and six (27%) were other multinational combinations often including Europe, Canada, or the US. Asthma severity ranged from mild persistent to severe persistent: six studies (27%) were conducted in patients with mild persistent asthma, 11 (50%) in patients with mild to moderate persistent asthma, 3 (14%) in patients with mild to severe persistent asthma, and two (9%) did not report the severity or it was unable to be determined.

Methodologic Quality
The 22 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 22 RCTs, 17 (77%) were funded by pharmaceutical companies; only three studies (14%) were funded primarily by sources other than pharmaceutical companies; 2 studies (9%) 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 I). Those treated with ICSs had a greater increase in the proportion of days free from rescue medication (SMD -0.25, 95% CI: -0.31, -0.19, 12 studies), greater reduction in rescue medicine use per day (SMD -0.23, 95% CI: -0.29, -0.17, 13 studies), greater increase in percent of symptom free days (SMD -0.21, 95% CI: -0.28, -0.15, 13 studies), greater improvement in symptom score (SMD -0.28, 95% CI: -0.34, -0.22, 10 studies), less frequent exacerbations (SMD -0.17, 95% CI: -0.22, -0.12, 13 studies), and a greater increase in quality of life (AQLQ scores; SMD -0.19, 95% CI: -0.27, -0.12, 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 I).

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, greater reduction in rescue medicine use per day, greater increase in the proportion of symptom free days, greater improvement in symptom score, fewer exacerbations, and greater improvement in quality of life than those treated with montelukast (Appendix I).

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, greater increase of the proportion of symptom free days, greater change in symptom score, and fewer exacerbations than those treated with zafirlukast (Appendix I).

A previously published good quality systematic review included18 RCTs (N = 3,757), 13 of which compared ICS therapy to ML therapy in children and adolescents 18 years and younger diagnosed with asthma at least 6 months prior to enrollment.[109] Six of the included trials also met our inclusion criteria[125, 126, 129-132]; seven did not. Duration of studies varied but ranged from 4-12 weeks, 24-28 weeks, and 48-56 weeks, with one study being 112 weeks long. While most of the studies included patients age 6-18, one study included children younger than 6 (2-8 years) for which a nebulizer was used for ICS administration. Intervention drugs included oral montelukast (4 to 10 mg) compared to either inhaled BDP 200-400 mcg/day (0.5 mg nebulized), FP 200 mcg/day, BUD 200-800 mcg/day or TAA 400 mcg/day.

Seven trials (N = 2,429) contributed to the primary outcome, with ICS-treated patients showing a significantly lower risk of developing an exacerbation requiring systemic corticosteroids (RR 0.83, 95% CI: 0.72 – 0.96; NNT 24). However, no statistically significant difference was noted between groups with respect to withdrawals due to exacerbations (N = 680, RR 0.73, 95% CI: 0.36 – 1.48) and hospitalizations due to exacerbations (N = 533, RR 0.33, 95% CI: 0.03 – 3.15). Additional data were pooled based on secondary outcomes of interest and found ICS significantly improved mean change from baseline of symptom score (N = 575, SMD 0.18, 95% CI 0.01 – 0.34]), rescue inhaler use (puffs/24 hours: N = 1823, SMD 0.34 puffs/day, 95% CI 0.16 – 0.53]), and rescue-free days (N = 1904, SMD 0.16, 95% CI 0.07 – 0.25).

Another good quality systematic review with meta-analysis compared licensed doses of LTRAs with ICSs.[107] 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.[110-115, 118, 120-123] 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).

A third and final fair-rated meta-analysis compared LTRAs to ICSs.[108] 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 9 fair quality RCTs (10 articles) that compared ML with FP[114-117, 125-130, 133] 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 -0.25, 95% CI: -0.34, -0.16, 7 studies), greater reduction in rescue medicine use per day (SMD -0.25, 95% CI: -0.33, -0.16, 5 studies), greater increase in the proportion of symptom-free days (SMD -0.24, 95% CI: -0.32, -0.16, 6 studies), greater improvement in symptom score (SMD -0.24, 95% CI: -0.33, -0.14, 4 studies), fewer exacerbations (SMD -0.17, 95% CI: -0.26, -0.09, 6 studies), and greater improvement in quality of life (AQLQ scores: SMD -0.15, 95% CI: -0.25, -0.06, 4 studies) than those treated with ML (Appendix I).

Details of the characteristics of the 9 individual RCTs[114-117, 125-130, 133] are summarized in Tables 14 and 15.

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

Six fair quality RCTs[110-113, 118, 124, 134] meeting our inclusion criteria compared montelukast with beclomethasone (Tables 14 and 15). 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 using sufficient data from multiple trials shows that compared to ML-treated patients, those treated with BDP had fewer exacerbations (SMD -0.15, 95% CI: -0.30, -0.002), and trends toward a greater proportion of rescue free days (SMD -0.08, 95% CI: -0.19, -0.04) and a greater proportion of symptom-free days (SMD -0.11, 95% CI: -0.25, 0.02), neither of which reached statistical significance (Appendix I).

Details of the individual RCTs are summarized in Tables 14 and 15. The only trial enrolling children < 12 years of age 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.[124] 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[119, 131, 132] that met our inclusion criteria (Tables 14 and 15). Too few studies reported sufficient data for meta-analysis of our included outcomes. Of the three RCTs, one enrolled adult populations, one[131] enrolled children and adolescents ages 6-18, and one[132] 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[119, 131] 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.[119, 132] The single trial reporting quality of life found no difference between the treatments for overall quality of life measures.[132]

5. Fluticasone (FP) compared with Zafirlukast

We found four fair quality RCTs comparing FP with zafirlukast[120-123] 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 -0.30, 95% CI: -0.40, -0.20, 4 studies), greater increase of the proportion of symptom free days (SMD -0.29, 95% CI: -0.39, -

0.19, 4 studies), greater improvement in symptom score (SMD -0.31, 95% CI: -0.41, -0.21, 4 studies), and fewer exacerbations (SMD 0.21, 95% CI: -0.31, -0.11, 4 studies) than those treated with zafirlukast (Appendix I).

Table 14. Characteristics of head-to-head studies comparing ICSs with LTRAs in children and adults

Study	Study design N Duration	Country Study population Setting	Comparison (total daily dose)	Quality rating
Inhaled corticosteroids (ICSs) compared with Leukotriene receptor antagonists (LTRAs)				
Castro-Rodriguez et al. 2010[109]	Systematic review with meta-analysis 18 RCTs (3,757 subjects total); 13 studies compared ICSs with ML ≥ 4 weeks treatment with ICS or ML	Children < 18 yrs, diagnosed > 6 months before study entry	ICS vs. ML and/or vs. ICS + ML	Good
Ducharme et al. 2004[107]	Systematic review with meta-analysis 27 studies (91,00 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)	Good
Halpern et al. 2003[108]	Meta-analysis 6 studies (5278 subjects)	United States 5 retrospective cohort, 1 prospective trial	ICS vs. LTRA	Fair
Fluticasone (FP) compared with Montelukast (ML)				
Busse et al. 2001[114]	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) vs. ML (10 mg) Low dose ICS	Fair
Garcia et al. 2005[125] MOSAIC Study	RCT 994 52 weeks	Multinational (24 including Asia, Africa, North and South America) Children age 6 – 14, mild persistent asthma, smoking status NR Multicenter (104) Primary care	FP (200 mcg) via MDI vs. ML (5 mg) Medium to Low (12-14 years of age) dose ICS	Fair

Table 14. Characteristics of head-to-head studies comparing ICSs with LTRAs in children and adults

Study	Study design N Duration	Country Study population Setting	Comparison (total daily dose)	Quality rating
Meltzer et al. 2002[115]	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) vs. ML (10 mg) Low dose ICS	Fair
Ostrom et al. 2005[126]	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) vs. ML (5 mg) Low dose ICS	Fair
Peters et al. 2007[127]	RCT 500 16 weeks	United States Age 6 and older, mild to moderate asthma, smoking status NR Multicenter	FP (200 mcg) vs. FP (200 mcg)/ SM (100 mcg) vs. ML (5 – 10mg) Low dose ICS	Fair
Sorkness et al. 2007[128, 133] 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) vs. FP (100 mcg)/ SM (50 mcg) plus SM (50 mg) vs. ML (5 mg) Low dose ICS	Fair
Szefler et al. 2005[129]	RCT 144 16 weeks	United States Children age 6-17, mild to moderate persistent asthma, smoking status NR University Clinics	FP (200 mcg) vs. ML (5 – 10mg) Low dose ICS	Fair

Table 14. Characteristics of head-to-head studies comparing ICSs with LTRAs in children and adults

Study	Study design N Duration	Country Study population Setting	Comparison (total daily dose)	Quality rating
Zeiger et al. 2005[116, 117] MIAMI Trial	RCT 400 12 weeks 36 week open label extension	United States Age 15 – 85, mild persistent asthma, smoking status NR Multicenter (39)	ML (10mg) vs. FP (176 mcg) Low dose ICS	Fair
Zeiger et al. 2006[130] CARE Network Trial	RCT 144 (127 in analysis) 16 weeks (8 weeks, crossover, 8 weeks); additionally, only included data from the last 4 weeks of each treatment period	United States Children age 6-17, mild to moderate persistent asthma, smoking status NR Multicenter	FP (200 mcg) vs. ML (5 – 10mg) Low dose ICS	Fair
Beclomethasone (BDP) compared with Montelukast (ML)				
Baumgartner et al. 2003[110]	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) vs. ML (10mg) vs. placebo Medium Dose ICS	Fair
Becker et al. 2006[124]	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) vs. BDP (400 mcg) vs. placebo High dose ICS	Fair
Israel et al. 2002[111]	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	ML (10 mg) vs. BDP (400 mcg) vs. placebo	Fair

Table 14. Characteristics of head-to-head studies comparing ICSs with LTRAs in children and adults

Study	Study design N Duration	Country Study population Setting	Comparison (total daily dose)	Quality rating
		Multicenter (64)	Medium dose ICS	
Laviolette et al. 1999[118]	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	Fair
Lu et al. 2009[134]	RCT, three-part 2x2 crossover study 406 (126 in extension) 12 weeks 48 week open label extension study[a]	United States Adults age 15-65, ≥ 1 year clinical history of mild to severe persistent asthma Multicenter (42 total, 30 extension)	ML 10mg daily vs. Loratadine 10mg daily vs. ML 10mg + loratadine 10mg daily vs. BDP 400 mcg Medium dose ICS	Fair
Malmstrom et al. 1999[112, 113]	RCT 895 (436 in extension) 12 weeks plus a 3 week placebo washout period where patients were switched from treatment to placebo 37 week double-blind extension phase	Multinational (19 in Europe, Africa, Australia, Central and South America) Age 15 and older, mild to severe persistent asthma, excluded current on former smokers Multicenter (36), clinical centers	ML 10mg vs. BDP 400 mcg vs. placebo (extension: ML vs. BDP in pre-assigned groups) Medium dose ICS	Fair
Budesonide (BUD) vs. Montelukast (ML)				
Stelmach et al. 2005[131]	RCT	Poland	BUD (400 mcg) vs.	Fair

Table 14. Characteristics of head-to-head studies comparing ICSs with LTRAs in children and adults

Study	Study design N Duration	Country Study population Setting	Comparison (total daily dose)	Quality rating
	51 24 weeks	Children age 6-18, newly diagnosed asthma with sensitivity to house dust mites, smoking status NR University clinics	BUD (800 mcg) vs. ML (5 – 10 mg) Low to Medium Dose ICS	
Szefler et al. 2007[132]	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	Fair
Yurdakul et al. 2003[119]	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	Fair
Fluticasone (FP) compared with Zafirlukast (ZAF)				
Bleecker et al. 2000[120]	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) vs. ZAF (40mg) Low dose ICS	Fair
Brabson et al. 2002[121]	RCT 440 6 weeks	United States Age 12 and older, mild to moderate persistent asthma, smoking status NR Multicenter (44)	FP (176 mcg) vs. ZAF (40mg) Low dose ICS	Fair
Busse et al. 2001[122]	RCT 338 12 weeks	United States Age 15 and older, mild to severe persistent asthma, excluded current smokers within the past year and those	FP (176 mcg) vs. ZAF (40mg) vs.	Fair

Table 14. Characteristics of head-to-head studies comparing ICSs with LTRAs in children and adults

Study	Study design N Duration	Country Study population Setting	Comparison (total daily dose)	Quality rating
		with ≥ 10 pack-year history	placebo	
		Multicenter 50% primary care	Low dose ICS	
Kim et al. 2000[123]	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. ZAF (40mg) Low dose ICS	Fair

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.

[a] Extension study: ML 10mg + loratadine 10mg daily vs. BDP 400 mcg

Table 15. Characteristics of head to head studies comparing ICSs with LTRAs in children < 12

Study	Study design N Duration	Country Study population Setting	Comparison (total daily dose)	Quality rating
Inhaled corticosteroids (ICSs) compared with Montelukast (ML)				
Castro-Rodriguez et al. 2010[109]	Systematic review with meta-analysis 18 RCTs (3,757 subjects total); 13 studies compared ICSs with ML ≥ 4 weeks treatment with	Children < 18 yrs, diagnosed > 6 months before study entry	ICS vs. ML and/or vs. ICS + ML	Good

Table 15. Characteristics of head to head studies comparing ICSs with LTRAs in children < 12

Study	Study design N Duration	Country Study population Setting	Comparison (total daily dose)	Quality rating
	ICS or ML			
Fluticasone (FP) compared with Montelukast (ML)				
Garcia et al. 2005[125] MOSAIC Study	RCT 994 52 weeks	Multinational (24 including Asia, Africa, North and South America) Children age 6-14, mild persistent asthma, smoking status NR Multicenter (104) Primary care	FP (200 mcg) via MDI vs. ML (5mg) Medium to Low (12-14 years of age) dose ICS	Fair
Ostrom et al. 2005[126]	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) vs. ML (5mg) Low dose ICS	Fair
Peters et al. 2007[127]	RCT 500 16 weeks	United States Age ≥ 6, mild to moderate asthma, smoking status NR Multicenter	FP (200 mcg) vs. FP (200mcg)/ SM (100 mcg) vs. ML (5 – 10mg) Low dose ICS	Fair
Sorkness et al. 2007[128, 133] 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) vs. FP (100 mcg)/SM (50 mcg) plus SM (50mg) vs. ML (5 mg) Low dose ICS	Fair
Szefler et al. 2005[129]	RCT 144	United States Children age 6-17, mild to moderate persistent asthma, smoking status NR	FP (200 mcg) vs. ML (5 – 10 mg)	Fair

Table 15. Characteristics of head to head studies comparing ICSs with LTRAs in children < 12

Study	Study design N Duration	Country Study population Setting	Comparison (total daily dose)	Quality rating
	16 weeks	University Clinics	Low dose ICS	
Zeiger et al. 2006[130] CARE Network Trial	RCT 144 (127 in analysis) 16 weeks (8 weeks, crossover, 8 weeks); additionally, only included data from the last 4 weeks of each treatment period	United States Children age 6-17, mild to moderate persistent asthma, smoking status NR Multicenter	FP (200 mcg) vs. ML (5 – 10mg) Low dose ICS	Fair
Beclomethasone (BDP) compared with Montelukast (ML)				
Becker et al. 2006[124]	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) vs. BDP (400 mcg) vs. placebo High dose ICS	Fair
Budesonide (BUD) compared with Montelukast (ML)				
Szefler et al. 2007[132]	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	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.

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

Summary of findings

We found 13 fair or good quality RCTs[135-150] that included head-to-head comparisons of one ICS with one LABA meeting our inclusion/exclusion criteria. Nine of these were multi-arm trials that compared an ICS/LABA combination product with the individual ICS and LABA components.[135-144, 150] (Table 16)

Overall, efficacy studies provide consistent evidence favoring ICSs over LABAs for the treatment of asthma as monotherapy for children and adults (high strength of evidence, Appendix H, Table H-8). Those treated with LABAs had significantly higher odds of experiencing an exacerbation (as defined by each study) than those treated with ICSs (OR = 2.845; 95% CI = 1.644, 4.863; 6 studies). Although our meta-analyses found no statistically significant differences 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]

Detailed Assessment

Description of Studies

Of the 13 trials, 7 (54%) compared fluticasone with salmeterol, three (23%) compared beclomethasone with salmeterol, one (8%) compared triamcinolone with salmeterol, and two (15%) compared budesonide with formoterol (Table 16). Study duration ranged from 12 weeks to 12 months. LABAs were compared with low-dose ICSs in seven trials (54%) and with medium-dose ICSs in six (46%). The most commonly used delivery devices were MDIs and DPIs; 6 studies (50%) compared DPI to DPI; 5 studies (42%) compared MDI to MDI, and two studies (17%) compared pMDI to DPI.

Study Populations

The 13 head-to-head RCTs included a total of 4196 subjects. Most were conducted primarily in adult populations. Two studies[148, 149] were conducted in pediatric and adolescent populations. Nine trials (69%) 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: three studies (23%) were conducted in patients with mild to moderate persistent asthma, one (8%) in patients with moderate to severe persistent, and the severity was not reported in nine (69%) trials.

Smoking status was not reported for the two pediatric/adolescent trials and one of the adolescent/adult trials.[136] Among the others, 9 (90%) excluded current smokers or those with a recent history of smoking and 1 (10%) allowed smokers and reported that 12-17% in each group were smokers.

Sponsorship

Of the 13 head-to-head trials, 12 (92%) were funded by pharmaceutical companies; only one study (8%) was funded primarily by a source other than a pharmaceutical company.

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 similar trials (Appendix I). 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 = 0.05; 95% CI = -0.10, 0.21; 7 studies), change in symptom scores (SMD = 0.14; 95% CI = -0.05, 0.34; 6 studies), percentage improvement in rescue-free days (SMD = -0.14; 95% CI = -0.35, 0.07; *P* = 0.186; 5 studies), and change in rescue medicine use (as number of puffs per day) (SMD = 0.14; 95% CI = -0.11, 0.40; 7 studies). We found that those treated with LABAs had a significantly higher odds of experiencing an exacerbation than those treated with ICSs (OR = 2.8; 95% CI = 1.7, 4.9; 6 studies). The measure of statistical heterogeneity was high in the analysis of rescue puffs per day (I^2 78.4). For all analyses except percentage of rescue free days, sensitivity analyses indicate no difference in overall meta-analysis conclusions with single studies removed. For the percent rescue free days analysis, removal of Lundback et al caused the difference between ICS and LABA to reach statistical significance (favoring LABA) (point estimate = -0251; 95% CI: -0.390, -0.113; P < 0.001).

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

Seven fair-quality RCTs compared FP with SM for monotherapy.[135, 137-141, 143, 144, 150] None included children ≤ 12 years of age. All seven also included comparisons with an FP/SM combination product. Study duration was 12-weeks for six trialsand 12 months for one.[137] Four compared SM with low-dose FP and three compared SM with medium-dose FP. Six of the seven were conducted in the United States; one was conducted in Sweden.[137]

The majority of trials assessed asthma symptoms, nocturnal awakenings, exacerbations, and rescue medicine use. Two trials[140, 143] 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 (Evidence Tables A and B).

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

Three fair-quality RCTs compared BDP with SM.[147-149] One[147] enrolled adolescents and adults ≥ 12 years of age; the other two studies enrolled children and adolescents aged 6-14[148] or 6-16.[149] 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[147, 149] and nocturnal awakenings;[147, 148] one reported missed school.[148] 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),[147] all three trials reported no differences or better outcomes for those treated with BDP than for those treated with SM (Evidence Tables A).

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

One good-rated 16-week multicenter RCT[145, 146] (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 (Evidence Tables A).

5. Budesonide (BUD) compared with Formoterol (FM)
Two fair-rated 12-week multicenter RCTs[136, 142] compared BUD with FM in 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 (Evidence Tables A). Whether these trends were statistically significantly different was not reported (the studies focused on comparing BUD/FM with the other treatments).

Table 16. Characteristics of head-to-head studies comparing ICSs with LABAs

Study	Study design N Duration	Country Population Setting	Comparison (total daily dose in mcg)	Quality Rating
Fluticasone (FP) compared with Salmeterol (SM)				
Kavuru et al. 2000[135] AND Nathan et al. 2003[144]	RCT, DB 356 12 weeks	US Age ≥12yr, asthma ≥ 6 months, 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)	Fair
Lundback et al. 2006[137]	RCT, DB 282 12 months	Sweden Age 18 to 70, mild or moderate persistent, uncontrolled on current medication,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) vs. FP DPI (500) vs. SM DPI (100)	Fair
Murray et al. 2004[138]	RCT, DB 267 12 weeks	US Age ≥12yr, asthma ≥6 months, not controlled severity NR, smokers excluded Multicenter (33 sites)	SM DPI (100) vs. FP DPI (200) vs. FP/SM DPI (200/100)	Fair
Nathan et al. 2006[139] AND Edin et al. 2009[140]	RCT, DB 365 12 weeks	US Age ≥12yr, asthma ≥6 months, not controlled on ICS, severity NR, smokers excluded Multicenter (45)	FP/SM MDI (440/84) vs. FP MDI (440) vs. SM MDI (84) vs. Placebo	Fair
Nelson et al. 2003[141]	RCT, DB 283 12 weeks	US Age ≥12, persistent asthma not controlled, severity NR, smokers excluded Multicenter (33)	FP/SM MDI (176/84) vs. FP MDI (176) vs. SM MDI (84)	Fair

Table 16. Characteristics of head-to-head studies comparing ICSs with LABAs

Study	Study design N Duration	Country Population Setting	Comparison (total daily dose in mcg)	Quality Rating
Shapiro et al. 2000[143]	RCT, DB	US	Placebo vs.	Fair
AND	349	Age ≥12, asthma ≥6 months, previously treated with low to medium ICS, severity NR, smokers excluded	FP/SM DPI (500/100) vs.	
Nathan et al. 2003[144]	12 weeks		SM DPI (100) vs.	
		Multicenter (42)	FP DPI (500)	
Pearlman et al. 2004[150]	RCT, DB	US	FP/SM MDI (176/84) vs.	Fair
AND	360	Age ≥12yr, asthma ≥ 6 months, 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	FP MDI (176) vs.	
Edin et al. 2009[140]	12 weeks		SM MDI (84) vs.	
			Placebo	
		Multicenter (36)		
Beclomethasone (BDP) compared with Salmeterol (SM)				
Nathan et al. 1999[147]	RCT, DB	US	SM MDI (84) vs.	Fair
	386	Age ≥12yr, on SABAs, not on inhaled or oral corticosteroids, severity NR, smokers excluded	BDP MDI (336) vs.	
	26 weeks		placebo	
		Multicenter (25)		
Simons et al. 1997[148]	RCT, DB	Canada	BDP DPI (400) vs.	Fair
	241	Age 6-14, clinically stable asthma, not currently on ICS, severity NR, smoking status NR	SM DPI (100) vs.	
	52 weeks		placebo	
		Multicenter		
Verberne et al. 1997[149]	RCT, DB	Netherlands	SM DPI (100) vs.	Fair
	67	Age 6-16, on ICS ≥3 months, mild to moderate persistent asthma, smoking status NR	BDP DPI (400)	
	54 weeks			
		Multicenter (18)		
Triamcinolone (TAA) compared with Salmeterol (SM)				
Lazarus et al. 2001[145]	RCT, triple-blind	North America	TAA MDI (800) vs.	Good
AND	164	Age 12-65, persistent asthma, well controlled on TAA,	SM MDI (84)	

Table 16. Characteristics of head-to-head studies comparing ICSs with LABAs

Study	Study design N Duration	Country Population Setting	Comparison (total daily dose in mcg)	Quality Rating
		severity NR, smokers excluded	vs.	
Deykin et al. 2005[146]	16 weeks		placebo	
SOCS Trial		Multicenter (6)		
Budesonide (BUD) compared with Formoterol (FM)				
Noonan et al. 2006[142]	RCT; DB	US	BUD/FM pMDI (640/18) vs.	Fair
	596	Age ≥12, moderate to severe persistent asthma not controlled, on moderate to high dose ICS for ≥4	BUD pMDI (640) vs.	
	12 weeks	weeks, smokers excluded	FM DPI (18) vs.	
		Multicenter (84)	BUD pMDI (640) + FM DPI (18) vs. placebo	
Corren et al. 2007[136]	RCT, DB	US	BUD/FM pMDI (320/18) vs.	Fair
	480	Age ≥12, mild to moderate persistent asthma, treated with low to medium dose ICS for ≥4 weeks, smoking	BUD pMDI (320) vs.	
	12 weeks	status NR	FM DPI (18) vs.	
		Multicenter (56)	placebo	

Abbreviations: 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; RCT= randomized controlled trial; SM = Salmeterol; SR=systematic review; TAA = Triamcinolone Acetonide

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

Summary of findings

We found 2 fair quality RCTs[151, 152] that included head-to-head comparisons of one leukotriene modifier with one LABA meeting our inclusion/exclusion criteria. One trial compared montelukast with salmeterol[151] and one compared montelukast with eformoterol.[152] (Table 17)

Overall, the 2 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 (Appendix H, Table H-9). Of note, LABAs are neither recommended nor approved for use as monotherapy for persistent asthma.[1]

Detailed Assessment

Description of Studies

We found two fair quality RCTs[151, 152] that included head-to-head comparisons of one leukotriene modifier with one LABA meeting our inclusion/exclusion criteria (Table 17). One 8-week trial compared montelukast with salmeterol[151] and one 18-week trial compared montelukast with eformoterol.[152]

Study Populations

The two RCTs included a total of 249 subjects. All were conducted primarily in adult populations. One was conducted in the United States[151] and one was conducted in Australia.[152] One trial included patients with moderate to severe asthma,[152] and asthma severity was not reported in the second trial.[151] 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,[151] and one trial was funded by a combination of industry and federal government sources.[152]

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.[151] 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 = 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).[152] 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 17. Characteristics of head-to-head studies comparing leukotriene modifiers with LABAs for monotherapy

Study	Study design N Duration	Country Study population Setting	Comparison (total daily dose)	Quality rating
Montelukast compared with Salmeterol				
Edelman et al.[151]	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)	Fair
Montelukast compared with Eformoterol				
Jenkins et al. 2005[152]	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 + placebo	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.

B. Combination therapy

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

Summary of findings

We found one good systematic review that was recently updated[153] and 9 fair RCTs,[138, 141, 154-160] 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 18). Seven 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 same dose ICS alone for initial therapy (Appendix H, Table H-10). Results were consistent for estimates in differences in symptoms between our meta-analysis and a previously published meta-analysis.[153] However, limited data were available for exacerbations and further research may change our confidence in the estimate of effect for this outcome. The updated systematic review included studies with children, but we found no studies for this comparison that met our inclusion criteria and 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., inhaled corticosteroids) or whose disease severity clearly warrants initiation of treatment with both an inhaled corticosteroid and LABA.

Detailed Assessment

Description of Studies

The systematic review[153] included 24 studies from 19 publications and 4 unpublished sources. Eight of those trials met our inclusion criteria,[138, 141, 154-157, 159, 160]. Fourteen did not meet our inclusion criteria and 1 study [161] was included but rated poor. We included 1 trial[158] that was not in the systematic review (it was published after the review).

We identified two other systematic reviews[162, 163] that included studies of ICS+LABA compared with same dose ICS. One review focused on FP+SM compared with FP[163]. This review included 30 studies of adults and adolescents (N = 10,873) and 3 studies in children (N = 1,173). The other review focused on BUD+FM compared with BUD[162]. It included 21 studies of adults (N = 8,028) and children (N = 2,788). These reviews combined studies of steroid naïve patients with studies of patients who had previously used steroids and therefore are not included in our assessment of ICS + LABA compared with same dose ICS alone as first line therapy.

Of the 9 RCTs we included (Table 18), 7 compared fluticasone + salmeterol with fluticasone alone[138, 141, 154, 155, 158-160] and two compared budesonide + formoterol with budesonide alone.[156, 157]

Study duration was 12 weeks for 6 trials, 24 weeks for 2 trials,[155, 158] and one year for one trial.[157] Eight trials used low doses of ICSs and 1 trial used medium doses.[154] In 7 studies, all medications were delivered via DPIs; 2 used MDIs.[141, 160] Seven studies tested the combination of a LABA and an ICS administered in a single inhaler and two used separate inhalers.[156, 157]

Study Populations

The 9 head-to-head RCTs included a total of 3,932 subjects. All studies were conducted in adolescent and/or adult populations. None included children < 12 years of age. Three trials were multinational,[154, 157, 160] 4 were conducted in North America,[138, 141, 158, 159] one in Denmark,[155] and one in Russia.[156] 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: 3 studies were conducted in patients with mild asthma,[157, 158, 160] one in patients with mild to moderate asthma,[156] and one in patients with moderate asthma.[154] Severity classification was not reported in 4 studies.[138, 141, 155, 159]

Three trials (33%) excluded current smokers or those with a recent history of smoking,[138, 141, 159] 5 (56%) allowed some smokers, and one (11%) did not report any information about smoking status.[157] Among those that allowed some smokers, 4[154, 156, 158, 160] only allowed those with less than a 10 pack-year smoking history and 2[155, 158] reported that 9-46% of subjects in each group were current smokers.

Sponsorship

Of the 9 head-to-head trials, all (100%) were funded by pharmaceutical companies.

Head-to-head comparisons

1. ICS+LABA compared with ICS

The results of the 9 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 I). 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 = 0.24 , 95% CI: 0.14, 0.33; 6 studies), symptom scores (SMD = 0.28, 95% CI: 0.15, 0.41; 4 studies), percentage of rescue medicine-free days (SMD 0.32, 95% CI 0.20, 0.43; 4 studies), and rescue medicine use (puffs per day) (SMD 0.25, 95% CI 0.12, 0.38; 7 studies) (Appendix I)

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

Seven fair-quality RCTs[138, 141, 154, 155, 158-160] (2896 subjects) compared FP+SM with FP alone (Table 18). All 7 compared the combination of FP and SM administered in a single inhaler with FP alone. Six of the studies used low dose FP; one used medium dose FP.[154] Five were 12-week trials and 2 were 24-week trials.[155, 158] All were conducted in populations of ≥ 12 or 18 years of age.

All 7 trials reported outcome measures for symptoms and rescue medicine use, two trials reported nocturnal awakenings,[138, 141] and 3 reported exacerbations.[155, 158, 160] Six 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.[141] All 7 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).[141] The trials reporting

nocturnal awakenings and exacerbations found no difference between groups (Evidence Tables A and B).

3. Budesonide (BUD)+Formoterol (FM) compared with Budesonide (BUD)
Two fair-quality RCTs (1,036 subjects) compared BUD+FM with BUD alone.[156, 157] Both compared BUD+FM administered in separate inhalers with low-dose BUD alone. One was a 12-week Russian trial that enrolled 338 adults.[156] The other was a 1-year multinational trial that enrolled 1970 adolescents and adults ≥ 12 years of age.[157] 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 18. Characteristics of head-to-head studies comparing ICS+LABA with ICS alone as first line therapy in children and adults

Study	Study Design N Duration	Country Population Setting	Comparison (total daily dose in mcg)	Quality Rating
ICS + LABA compared with ICS alone (same dose) as *first line therapy*				
Ni Chroinin et al. 2009[153]	Systematic review with meta-analysis 24 studies comparing ICS + LABA with similar dose ICS, 4 studies comparing ICS + LABA with higher dose ICS Range: 4 to 52 weeks	Multinational Age > 2 yr; persistent asthma and steroid-naïve (no inhaled steroid within one month of enrollment)	ICS + LABA vs. ICS alone (same dose) ICS + LABA vs. ICS alone (higher dose)	Good
Fluticasone + salmeterol compared with fluticasone				
Boonsawat,et al 2008[160]	RCT, DB 464 12 weeks	Multinational Ages 12-79, ≥6 month history of mild asthma receiving SABA only, allowed smokers if <10 pack-year history, smoking status NR Multicenter (69)	FP/SM MDI (100/50) vs FP MDI (100, low) vs Placebo	Fair
Kerwin et al. 2008[159]	RCT, DB 844 12 weeks	US and Canada Age ≥12, uncontrolled on SABAs alone, excluded smokers within the past year or history of > 10 pack-years Multicenter (121)	FP/SM (250/50) vs FP (250, low) vs FP/SM (200/100) vs Placebo	Fair
Murray et al. 2004[138]	RCT, DB 267 12 weeks	US Age ≥12yr, 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)	Fair
Nelson et al. 2003[141]	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)	Fair
Renzi et al. 2010[158]	RCT, DB 526 24 weeks	Canada Age ≥12 with a history of mild asthma treated with SABAs only, allowed smokers if < 10 pack-year history Multicenter (60)	FP/SM DPI (200/100) vs. FP DPI (200, low) FP/SM N = 253 FP N = 253	Fair

Table 18. Characteristics of head-to-head studies comparing ICS+LABA with ICS alone as first line therapy in children and adults

Study	Study Design N Duration	Country Population Setting	Comparison (total daily dose in mcg)	Quality Rating
Rojas et al. 2007[154]	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	Fair
Strand et al. 2004[155]	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) Multicenter (44 general practices and 1 hospital)	FP/SM DPI (200/100) vs. FP DPI (200, low) Steroid dose range: low	Fair
Budesonide + formoterol compared with budesonide				
Chuchalin et al. 2002[156] And Chuchalin et al. 2002[164]	RCT, DB, DD 338 12 weeks	Russia adults ≥18, mild to moderate persistent asthma, allowed smokers if < 10 pack-year history pulmonology center	FM DPI (24) + BUD DPI (400) vs. BUD DPI (400, low) vs. “investigator’s choice of non-corticosteroid treatment”	Fair
O’Byrne et al. 2001[157] OPTIMA trial	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) Group B (N = 1272 ICS-treated, were taking ICS for ≥ 3 months): 4 treatment arms All delivery devices were DPIs	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.

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 4 systematic reviews with meta-analysis[165-168] and 33 RCTs (37 publications)[53, 103, 105, 127, 157, 169-200] 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. Twenty-one of the 33 (64%) administered the ICS and LABA in a single inhaler and twelve (36%) administered the ICS and LABA in separate inhalers. Seven trials[103, 105, 127, 185, 195, 197, 200] included children, and two enrolled an exclusively pediatric population under 12 years of age.[103, 195] (Table 19)

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, Appendix H, Table H-11). Our meta-analysis shows statistically significantly greater improvement in percent symptom-free days (SMD = -0.20, 95% CI: -0.25, -0.14; 15 studies), symptom scores (SMD = -0.22, 95% CI: -0.34, -0.11; 10 studies), percent rescue-free days (SMD = -0.24, 95% CI: -0.31, -0.16; 11 studies), and rescue medicine use (SMD = -0.22, 95% CI: -0.28, -0.16; 16 studies) 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 (OR = 0.89, 95% CI: 0.78, 1.01; 22 studies). Just one trial exclusively enrolled children under 12 (four included some subjects < 12) and results are not necessarily generalizable to pediatric populations.

Detailed Assessment

Description of Studies

Four large systematic reviews with meta-analyses[165-168] compared the addition of any LABA to any ICS (ICS+LABA) with increasing the ICS dose. The largest review by Ducharme et al.[167] was an update to Greenstone, 2005.[201] It included 48 trials (47 publications) (6 of them in pediatric populations). Twenty-three of those trials met our inclusion/exclusion criteria. One of the reviews included studies only in children aged 2 to 18 years.[166]

Of the 33 RCTs we included (Table 19), 14 (42%) compared fluticasone + salmeterol with fluticasone; 7 (21%) compared budesonide + formoterol with budesonide, six (18%) compared beclomethasone + salmeterol with beclomethasone, 3 (9%) compared beclomethasone + formoterol with beclomethasone, two (6%) compared fluticasone + salmeterol with budesonide, one (3%) compared budesonide + formoterol with fluticasone, and one (3%) compared fluticasone + salmeterol with triamcinolone (the total number of comparisons, 34, 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).[53]

Study duration ranged from 8 weeks to 12 months. The most commonly used delivery devices were DPIs: 22 studies (67%) delivered all medicines via DPIs, 8 studies (24%) delivered all via MDIs, and 3 studies (9%) used MDIs for the ICSs in both groups and DPIs for the LABAs.[181, 189, 199] Twenty-one of the 33 (67%) administered the ICS and LABA in a single inhaler and twelve (36%) administered the ICS and LABA in separate inhalers.

Study Populations

The 33 head-to-head RCTs included a total of 18,153 subjects (Table 19). Most were conducted primarily in adult populations. Eight studies (24%) included pediatric populations under 12 years of age.[103, 105, 127, 185, 195, 197, 200] Seventeen trials (52%) were multinational, 8 (24%) were conducted in the United States, 3 in the Netherlands, 2 in Germany, and one each in Greece, Australia, and the United Kingdom.

Asthma severity ranged from mild to severe persistent: 3 studies (9%) were conducted in patients with mild persistent asthma, 8 (24%) in patients with mild to moderate persistent asthma, 4 (12%) in patients with moderate persistent asthma, 6 (18%) in patients with moderate to severe persistent, and the severity was not reported in 12 (36%) trials. Smoking status was not reported for 14 trials (42%). Eleven (33%) excluded current smokers or those with greater than a 10 pack-year history. Eight (24%) 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/SM[169] and one trial enrolled patients that were uncontrolled on previous therapy (80% had been on ICS).[192] 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.[127, 171, 174, 185]

Sponsorship

Of the 33 head-to-head trials, 30 (91%) were funded by pharmaceutical companies; one trial (3%) did not report the source of funding but at least one author had a primary affiliation with a pharmaceutical company. Two studies (6%) were funded primarily by a source other than a pharmaceutical company.

Head-to-head comparisons

Using data from the 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 I). These included percent symptom-free days, symptom scores, exacerbations, percent 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 = -0.20. 95% CI: -0.25, -0.14, 14 studies contributing 15 comparisons), greater improvement in symptom scores (SMD = -0.22, 95% CI: -0.34, -0.11, 9 studies contributing 10 comparisons), greater improvement in the percentage of rescue-free days (SMD = -0.24, 95% CI: -0.31, -0.16, 10 studies contributing 11 comparisons), and greater reduction in rescue medicine use (SMD = -0.22, 95% CI: -0.28, -0.16, 15 studies contributing 16 comparisons) than those treated with a higher dose ICS alone. However, there was no statistically significant difference in the odds of experiencing an exacerbation, but the pooled odds ratio favored those treated with ICS+LABA (OR = 0.89, 95% CI: 0.78, 1.01, 22 studies). For all of the meta-analyses except the analysis for exacerbations, sensitivity analyses indicate no significant difference in overall meta-analysis conclusions with any single study removed. With the exception of the analysis for symptom score, there was no significant heterogeneity between studies for these outcomes (Appendix I). The statistical heterogeneity for the symptom score analysis was substantial ($I^2 = 70.5$, $P < 0.001$) with the inclusion of the FP arm of the Baraniuk et al, 1999 study, but was no longer significant ($I^2 = 40.8$, $P = 0.095$) when this was removed from the analysis. Additional sensitivity analyses

removing studies enrolling subjects that were well controlled on current therapy[169, 171, 174, 185] found no difference in overall meta-analysis conclusions.

One good systematic review[167] compared the addition of any LABA to any ICS (ICS+LABA) with increasing the ICS dose (Table 19). The review included 48 trials (6 of them in pediatric populations) that included a total of 15,155 subjects. Trial duration ranged from 4 to 54 weeks. The systematic review reported a significant difference between groups for the primary outcome, the rate of patients with exacerbations requiring systemic corticosteroids (RR 0.88, 95% CI: 0.78, 0.98, N = 25). They reported no significant difference in exacerbations requiring hospitalization. Results from meta-analyses for some measures of symptoms (change in daytime symptom score, overall 24-hour symptom score, change in percent symptom free days, and % nighttime awakenings) were statistically significant with a trend toward favoring ICS + LABA therapy. Analyses of rescue medicine use (change in daytime rescue inhalations, change in nighttime inhalations, change in rescue inhalations over 24 hours, and change in mean percent of rescue free days) also showed a statistically significant trend toward improvement with ICS + LABA therapy. However, there was no significant group difference in percent symptom-free days at endpoint or percent overall rescue free days.

Another good systematic review with meta-analysis[165] 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) (full details available in Evidence Tables A and B).

One recent good quality systematic review with meta-analyses compared the addition of any LABA to any ICS (ICS+LABA) with increasing the ICS dose in children aged 2 to 18 years.[166]. The review included six studies for this comparison and the mean age of participants across the studies was 10 years. A meta-analysis of the primary outcome (exacerbations requiring oral steroids) included only 2 studies and found no statistically significant difference between the ICS + LABA or higher dose ICS groups (RR = 1.5, 95% CI 0.65 to 3.48). The review did not report results for outcomes such as daytime rescue inhalations, nighttime awakenings, and daytime or nighttime symptoms because of insufficient data. (Evidence Tables B)

A fair quality systematic review by Jaeschke et al.[168] included 31 studies with 14,409 patients that compared ICS + LABA to higher dose ICS. The review analyzed studies of SM and FM separately. The meta-analysis results for both medications for asthma related hospitalizations were not statistically significant [(FM + ICS v ICS): OR = 0.68, 95% CI 0.38, 1.24 (N = 6); (SM + ICs v ICS): OR = 1.12, 95% CI 0.54 to 2.35 (N = 13)]. The results of analyses for total mortality were also not statistically significant for either group [(FM + ICS v ICS): OR = 0.71, 95% CI 0.13 to 3.91 (N= 2); (SM + ICs v ICS): OR = 3.12, 95% CI 0.30 to 25.49 (N = 2)]. The authors noted that asthma-related mortality could not be assessed because of low frequency of events.

An additional systematic review by Rodrigo et al.[202] analyzed 57 studies with 34,747 patients; 32 of these studies compared LABA + ICS to a higher dose of ICS. This review combined studies of ICS + LABA compared with same dose ICS and ICS + LABA compared with a higher dose ICS in the analyses, therefore it is not considered in our assessment of ICS + LABA compared with higher dose ICS. The results of the combined analysis for exacerbations requiring systemic steroids showed a statistically significant result in favor of LABA + ICS (RR = 0.73, 95% CI 0.67 to 0.79, N = 30).

2. Fluticasone (FP) + Salmeterol (SM) compared with Fluticasone (FP)
Fourteen fair-quality RCTs (7,091 subjects) compared FP+SM with a higher dose of FP[53, 127, 169-176, 195-197, 200] (Table 19). Eleven administered FP+SM in a single inhaler device[127, 169-171, 173-175, 195-197, 200] and 3 tested the combination delivered by separate inhalers. Three studies[127] included children ≤ 12 years of age. Study duration was 8 weeks for 1 trial, 12 weeks for 6 trials, 16 weeks for 2 trials, 24 weeks for 4 trials, and 52 weeks for 1 trial.

The majority of trials assessed asthma symptoms and rescue medicine use. Eight trials also reported exacerbations and two reported quality of life. For these outcomes, most of the trials either reported no difference or outcomes favoring FP+SM combination therapy over the increased dose of FP. One trial, comparing FP twice daily with FP/SM once daily, reported a statistically significant difference in favor of FP alone for mean daily asthma symptom score.[196] For subjects treated with FP+SM compared to those treated with FP alone, 7 trials reported fewer symptoms or better improvement in symptoms,[169, 170, 172, 173, 175, 176, 200] 9 trials reported a greater decrease or less frequent use of rescue medicine,[53, 169-173, 176, 195, 200] one trial reported a trend toward fewer exacerbations,[170] and one trial reported greater improvement in nocturnal awakenings.[172] The two trials reporting quality of life found no statistically significant difference in overall quality of life measures[127, 175] (Evidence Tables A and B).

Meta-analyses of 8 trials show no statistically significant difference in exacerbations, but the pooled odds ratio favors those treated with FP+SM (OR = 0.86, 95% CI: 0.67, 1.1; 8 studies). Sensitivity analyses indicate that the removal of any one study does not change the overall conclusion. There was no significant heterogeneity between studies ($I^2 = 0$). Additional 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.

3. Budesonide (BUD) + Formoterol (FM) compared with Budesonide (BUD)
Seven fair quality RCTs (6,460 patients) compared BUD+FM with a higher dose of BUD[103, 105, 157, 177-180, 198] (Table 19). Five administered BUD+FM in a single inhaler device[103, 105, 177, 178] and two tested the combination delivered by separate inhalers. Two of the trials[103, 105] included children ≤ 12 years of age. One enrolled children with mild to moderate persistent asthma between the ages of four and 11.[103] The other enrolled subjects with moderate persistent asthma between the ages of 4 and 80.[105] Study duration was 12 months for 6 trials and 12 weeks for one trial.[178]

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, 5 of 6 trials reported fewer symptoms or better improvement in symptoms,[103, 105, 178-180, 198] 1 trial (of five reporting) found greater reduction in nocturnal awakenings,[178] and 4 trials reported a greater decrease or less frequent use of rescue medicine.[105, 178-180, 198] Four trials found no difference in exacerbations.[103, 105, 177, 178] One study found that the number of asthma exacerbations per patient-treatment year was significantly lower with BUD+FM (0.185) compared with a higher dose of BUD alone (0.315) ($P = 0.049$).[198]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[179, 180].

Meta-analyses of 7 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 = -0.19, 95% CI: -0.27, -0.11, 6 studies), greater improvement in symptom scores (SMD = -0.18, 95% CI: -0.28, -0.07; 2 studies), greater improvement in the percentage of rescue-free days (SMD = -0.21, 95% CI: -0.36, -0.05, 3 studies), and greater reduction in rescue medicine use (SMD = -0.16, 95% CI: -0.26, -0.06 , 5 studies) than those treated with a higher dose BUD alone. There was no statistically significant difference in exacerbations (OR = 0.98, 95% CI: 0.72, 1.34, 5 studies).

4. Beclomethasone (BDP) + Salmeterol (SM) compared with Beclomethasone (BDP)
Six fair quality RCTs (2,574 subjects) compared BDP+SM with a higher dose of BDP[181-187] (Table 19). All six administered BDP+SM in separate inhalers. One trial[185] 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,[186] 21-24 weeks for four,[181-184, 187] and one year for one.[185]

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 improvment for those treated with BDP alone. For symptoms, three trials reported no difference[181, 182, 185, 186] and three found results favoring BDP+SM.[183, 184, 187] For nocturnal awakenings, one trial reported no difference[184] and three found results favoring BDP+SM.[181-183, 187] For exacerbations, five trials reported no difference[181-184, 186, 187] and one reported a trend toward fewer exacerbations requiring steroids for those treated with BDP alone.[185] All but one trial[181, 182] 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[181, 182, 186].

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 = 0.18, 95% CI: 0.05, 0.31; 4 studies) and trended toward greater improvement in the percentage of symptom-free days (SMD = 0.14, 95% CI: -0.01, 0.28; 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 = -0.019, 95% CI: -0.095, 0.058; 5 studies contributing 6 comparisons).

5. Beclomethasone (BDP) + Formoterol (FM) compared with Beclomethasone (BDP)
Three fair RCTs (982 subjects) meeting our inclusion/exclusion criteria compared BDP+FM with a higher dose of BDP alone.[188, 189, 199] All 3 enrolled adults ≥18 that were not controlled on ICSs. Two compared BDP+FM in a single inhaler device[188] and one tested the combination delivered by separate inhalers.[189] Two studies[188, 189] reported statistically significantly better symptom and rescue medicine use outcomes for subjects treated with BDP+FM than those treated with FM alone (Evidence Tables A and B). Huchon et al.[199] reported that a reduction in rescue medication use was statistically significant from baseline for the BDP+FM group and did not change for the BDP alone group, but did not report whether the difference between the groups was significant. Two studies found a trend toward fewer exacerbations in those treated with BDP+FM.[189, 199]

6. Fluticasone (FP) + Salmeterol (SM) compared with Budesonide (BUD)
One good 12-week RCT (N = 349)[192] and one fair 24-week RCT (N = 353)[190, 191] 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.

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.[193] 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.

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.[53] 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 19. Characteristics of head-to-head studies comparing ICS+LABA (in one or separate inhalers) with higher dose ICS

Study	Study Design N Duration	Country Population Setting	Comparison (total daily dose in mcg)	Quality Rating
Fluticasone + salmeterol compared with fluticasone				
Baraniuk et al. 1999[53]	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)	Fair
Bateman et al. 2006[169]	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	Fair
Bergmann et al. 2004[170]	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)	Fair
Busse et al. 2003[171]	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)	Fair
Chuchalin,et al 2008[196]	RCT, DD 2258 1 year	Ages 12-79, ≥6 month history of mild asthma receiving SABA only, allowed smokers if <10 pack-year history,	FP/SM DPI (100/50) vs FP DPI (200) vs Placebo	Fair
Condemi et al. 1999[172]	RCT, DB, DD 437	US age ≥12, uncontrolled on ICS, severity NR, smokers excluded	FP MDI (196) +SM MDI (84) compared with FP MDI (440)	Fair

Table 19. Characteristics of head-to-head studies comparing ICS+LABA (in one or separate inhalers) with higher dose ICS

Study	Study Design N Duration	Country Population Setting	Comparison (total daily dose in mcg)	Quality Rating
	24 weeks	Multicenter (36)		
de Blic et al. 2009[195]	RCT, DB, DD 321 12 weeks	12 European Countries Children, aged 4–11 yrs, with a clinical history of asthma for at least 6 months and uncontrolled on ICS Multicenter	FP (100) + SM (200) Vs. FP (400) All delivery devices - DPI	Fair
Gappa et al. 2009[200]	RCT, DB, DD 281 8 weeks	Germany Age 4-16; symptomatic persistent mild to moderate seasonal or perennial asthma and currently using low-dose ICS Multicenter	FP/SM DPI (100/ 200) Vs. FP (400) All delivery devices - DPI	Fair
Ind et al. 2003[173]	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)	Fair
Jarjour et al. 2006[174]	RCT, DB 88 24 weeks Note: the subjects in this study were a subset of the subjects in Busse et al. 2003[171] and thus were not included in meta-analyses to avoid	Multinational (US, Canada, UK) Age≥18, well controlled during final run-in on FP (500), excluded smokers with > 10 pack-year history Multicenter	FP/SM DPI (200/100) compared with FP DPI (500)	Fair

Table 19. Characteristics of head-to-head studies comparing ICS+LABA (in one or separate inhalers) with higher dose ICS

Study	Study Design N Duration	Country Population Setting	Comparison (total daily dose in mcg)	Quality Rating
	double-counting.			
Lemanske et al. 2010[197]	RCT 182 48 wks (3 cross-over periods of 16 wks each)	USA Age 6-17 years, mild-to-moderate asthma uncontrolled on low-dose ICS Childhood Asthma Research and Education Network Centers	FP DPI (500) FP/SM DPI (200/100) FP (200) DPI + ML (5-10mg)	Fair
Peters et al. 2007[127]	RCT, DB 500 16 weeks	US Age ≥6, controlled on FP (200), severity NR, 10-18% were former smokers Multicenter	FP/SM (100/50) QID vs. FP (200) vs. ML (5-10mg) All delivery devices=DPIs	Fair
Schermer et al. 2007[175]	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) All delivery devices - DPI	Fair
van Noord et al. 1999[176]	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 FP (200) + SM (100) vs FP (400) FP (500) + SM (100) vs FP (1000) All delivery devices - DPI	Fair

Table 19. Characteristics of head-to-head studies comparing ICS+LABA (in one or separate inhalers) with higher dose ICS

Study	Study Design N Duration	Country Population Setting	Comparison (total daily dose in mcg)	Quality Rating
Budesonide + formoterol compared with budesonide				
Bisgaard et al. 2006[103]	RCT, DB 341 12 months	Multinational (12) Age 4-11, mild-moderate persistent asthma, not controlled on ICS, smoking status NR Multicenter (41)	SMART [BUD/FM (80/4.5) +BUD/FM as needed] vs BUD/FM (80/4.5) compared with BUD (320) All given via DPI,	Fair
Kips et al. 2000[177]	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)[a] compared with BUD DPI (800)	Fair
Lalloo et al. 2003[178]	RCT, DB 467 12 weeks	Multinational (Czech Republic, Hungary, Norway, Poland, South Africa, United Kingdom) Age ≥ 18, mild to moderate, uncontrolled on ICS, smokers excluded Multicenter (51) University Hospitals	BUD/FM DPI (160/9) compared with BUD DPI (400)	Fair
O'Byrne et al. 2001[157] OPTIMA trial	RCT, DB 1970 (698 in Group A, 1272 Group B) 1 year	Multinational (Eastern Europe, Canada, Spain) Age ≥ 12, uncontrolled, mild persistent asthma (Group A ICS naïve, Group B on ICS), smoking status NR multicenter (198)	**Group A** (used no ICS for ≥ 3 months): Placebo compared with BUD (200) compared with BUD+FM (200+9) **Group B** (taking ICS for ≥ 3 months): BUD (200) vs. BUD(200) +FM (9) vs. BUD (400) vs.	Fair

Table 19. Characteristics of head-to-head studies comparing ICS+LABA (in one or separate inhalers) with higher dose ICS

Study	Study Design N Duration	Country Population Setting	Comparison (total daily dose in mcg)	Quality Rating
			FM + BUD (9/400) All delivery devices=DPIs	
O'Byrne et al. 2005[105]	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 (640) Drug 1: 909 Drug 2: 925 Drug 3: 926 All delivery devices=DPIs	Fair
Peters et al. 2008[198]	RCT 708 52 weeks	USA ≥ 12 years with a documented clinical diagnosis of moderate to severe asthma Multicenter	BUD (640) + FM (18) BID (160/4.5 x 4 inhalations) vs. BUD (320) + FM (9) BID (160/4.5 x 2 inhalations) vs. BUD (640) BID All delivery devices - pMDI	Fair
Pauwels, et al. 1997[179] AND Juniper, et al. 1999[180] FACET (Formoteral And Corticosteroids Establishing Therapy) International study group	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, smoking status NR Multicenter (71)	BUD (200) compared with BUD (200)+ FM (24) compared with BUD (800) compared with BUD (800)+ FM (24) All delivery devices - DPI	Fair

Table 19. Characteristics of head-to-head studies comparing ICS+LABA (in one or separate inhalers) with higher dose ICS

Study	Study Design N Duration	Country Population Setting	Comparison (total daily dose in mcg)	Quality Rating
O'Byrne et al. 2008[194]				
Beclomethasone + salmeterol compared with beclomethasone				
Greening et al. 1994[181] AND Hyland, 1995[182]	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)	Fair
Kelsen et al. 1999[183]	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)	Fair
Murray et al. 1999[184]	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)	Fair
Verberne et al. 1998[185]	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	Fair
Vermetten et al. 1999[186]	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	Fair

Table 19. Characteristics of head-to-head studies comparing ICS+LABA (in one or separate inhalers) with higher dose ICS

Study	Study Design N Duration	Country Population Setting	Comparison (total daily dose in mcg)	Quality Rating
Woolcock et al. 1996[187]	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	Fair
Beclomethasone + formoterol compared with beclomethasone				
Bouros et al. 1999[188]	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)	Fair
Huchon et al. 2009[199]	RCT 645 24 weeks	Russia, France, Poland, Romania, Hungary, Belgium Men and non-pregnant women (18-70 years), moderate to severe persistent asthma Multicenter	BDP/FM pMDI (400/24 Vs. BDP pMDI (1000) + FM DPI (24) Vs. BDP pMDI (1000)	Good
Mitchell et al. 2003[189]	RCT, DB, DD 203 12 weeks	Australia Age ≥ 18, moderate to severe, uncontrolled on ICS, 8-10% smokers in each group Multicenter (16), outpatients	BDP MDI (1000) + FM DPI (24) compared with BDP MDI (2000)	Fair
Fluticasone + salmeterol compared with budesonide				
Jenkins et al. 2000[190] AND Juniper et al. 2002[191]	RCT, DB, DD 353 (subanalysis 113 for AQLQ) 24 weeks	Multinational (Australia, Finland, Sweden) Age ≥12, moderate to severe persistent asthma, uncontrolled on ICS, excluded smokers with > 10 pack-year smoking history Multicenter (44)	FP/SM DPI (500/100) compared with BUD DPI (1600)	Fair
Johansson et al. 2001[192]	RCT, DB, DD	Multinational (6: Canada, Greece, Israel, Italy, S Africa, and	FP/SM DPI (200/100)	Good

Table 19. Characteristics of head-to-head studies comparing ICS+LABA (in one or separate inhalers) with higher dose ICS

Study	Study Design N Duration	Country Population Setting	Comparison (total daily dose in mcg)	Quality Rating
		Sweden)	compared with	
	349		BUD DPI (800)	
		Age ≥ 12, mild to moderate persistent asthma, uncontrolled on previous therapy (~80% ICS), excluded smokers or those with > 10 pack-year smoking history		
	12 weeks			
		Multicenter		
Budesonide + formoterol compared with fluticasone				
Bateman et al. 2003[193]	RCT, DB, DD	Multinational (6: Germany, Greece, Israel, Netherlands, Portugal, S. Africa)	BUD/FM DPI (320/9) compared with	Fair
	344		FP DPI (500)	
		Age ≥ 18; moderate persistent asthma, previous use of constant dose of ICS > 30 days, 5-7% smokers in each group		
	12 weeks			
		Multicenter (37)		
Fluticasone + salmeterol compared with triamcinolone				
Baraniuk et al. 1999[53]	RCT, DB, triple-dummy	US	FP MDI (196) + SM (84) vs.	Fair
This study is also listed above under FP+SM compared with FP section	680	Age ≥ 12, uncontrolled with low-dose ICS, severity NR, smokers excluded	FP MDI (440) vs.	
	12 weeks		TAA MDI (1200)	
		Pulmonary/allergy medicine clinics (50)		

Abbreviations: AQLQ = Asthma Quality of Life Questionnaire; BDP = beclomethasone dipropionate; BID – twice per day; BUD = Budesonide; CI = confidence interval; FP = Fluticasone Propionate; ICS = Inhaled Corticosteroids; LABAs = Long-Acting Beta-2 Agonists; MA=meta-analysis; OCS = oral corticosteroids; QID = once per day; 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.

[a] The dose of BUD/FM (200mcg BUD/6mcg FM) used in this study is only available Canada.

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

Summary of findings

We found 3 systematic reviews with meta-analyses[166, 168, 203] and 32 RCTs (37 publications)[135-137, 139, 140, 142-144, 157, 173, 179, 180, 185, 198, 199, 204-225] that included head-to-head comparisons of an ICS+LABA and the same dose ICS meeting our inclusion/exclusion criteria (Table 20). These trials compared the addition of a LABA to an ICS with continuing the same dose of the ICS. Eighteen of the 32 (56%) administered the ICS and LABA in a single inhaler, 10 (31%) administered them in separate inhalers, and 4 studies (13%) 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, Appendix H, Table H-12). Our meta-analysis shows statistically significantly greater improvement in rescue medication-free days (SMD 0.31 , 95% CI: 0.25, 0.37), rescue medicine use (SMD -0.29, 95% CI: -0.36, -0.23), symptom free days (SMD 0.27, 95% CI: 0.22, 0.32), symptom scores (SMD -0.27, 95% CI: -0.33, -0.21), and quality of life (AQLQ scores; SMD 0.26, 95% CI: 0.14, 0.37). Results were generally consistent with a previously published meta-analysis[203] which also reported fewer exacerbations in those treated with the addition of a LABA to ICS (RRR 23% with LABA) (N = 6808, RR = 0.77, 95% CI 0.68 to 0.87).

Detailed Assessment

Description of Studies

Of the included studies (Table 20), the 3 systematic reviews with meta-analyses[166, 168, 203] 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 largest review[203] included 77 trials (16,623 adults and 4,625 children). Seventeen of these were unpublished.

Of the 32 RCTs that met our inclusion/exclusion criteria, 16 (50%) compared budesonide + formoterol with budesonide (one used eformoterol), 9 (28%) compared fluticasone + salmeterol with fluticasone, 3 (9%) compared an ICS (not specified) + salmeterol with an ICS, 2 (6%) compared an ICS (not specified) + formoterol with an ICS, 1 (3%) compared beclomethasone + salmeterol with beclomethasone, and 1 (3%) compared beclomethasone + formoterol with beclomethasone. We also found one study of ICS+LABA compared with the same dose of ICS, however the patient population included both steroid naïve and current ICS users, therefore this study is not included in the analyses for this section.[150]

Study duration ranged from 12 weeks to 12 months. The most commonly used delivery devices were DPIs: 18 studies (56%) delivered all study medicines via DPIs, 7 studies (22%) delivered all via MDIs, and 7 studies (22%) used both MDIs and DPIs. Eighteen of the 32 (56%) administered the ICS and LABA in a single inhaler, 10 (31%) administered them in separate inhalers, and 4 studies (13%) administered them both as a single inhaler and in separate inhalers to different study groups.

Study Populations

The 32 head-to-head RCTs included a total of 14,737 subjects (Table 20). Most were conducted primarily in adult populations. Nine studies (28%) included pediatric populations under 12 years of age.[185, 212, 214, 215, 218-222] The majority of trials were multinational (17 trials, 53%); 10 (31%) were conducted in the United States, 2 (6%) 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.[135, 137, 213] 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.[213] Another enrolled subjects that were well controlled on current therapy (either ICS or ICS+SM).[135] The last one enrolled subjects uncontrolled on current medication, but only 68% were on ICSs.[137]

Sponsorship

Of the 32 head-to-head trials, 29 (91%) were funded by pharmaceutical companies; only two studies (6%) were funded primarily by sources other than pharmaceutical companies; one study (3%) 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 I). Those treated with ICS+LABA had a greater increase in the proportion of days free from rescue medication (SMD 0.31 , 95% CI: 0.25, 0.37, 20 comparisons), greater reduction in rescue medicine use per day (SMD -0.29, 95% CI: -0.36, -0.23, 21 comparisons), greater increase in percentage of symptom free days (SMD 0.27, 95% CI: 0.22, 0.32, 25 comparisons), greater improvement in symptom score (SMD -0.27, 95% CI: -0.33, -0.21, 17 comparisons), and a greater increase in quality of life (AQLQ scores; SMD 0.26, 95% CI: 0.14, 0.37, 7 comparisons) than those treated with ICS alone.

One previously published good systematic review[203] compared the addition of any LABA to any ICS (ICS+LABA) with continuing the same dose of ICS. The review included 77 trials (N = 21,248 with 16,623 adults and 4,625 children) that contributed information. Trial duration ranged from 4 to 54 weeks. Most studies (N = 43) were 12 to 16 weeks. Twenty-seven 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 23% (RR 0.77, 95% CI: 0.68 to 0.87) 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.

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

Two good[207, 217] and 14 fair RCTs[136, 142, 157, 179, 198, 206, 210-213, 215, 219, 221, 222] (9,298 subjects total) compared the addition of FM to BUD with continuing the same dose of BUD (Table 20). One of these trials reported using eformoterol (eFM).[213] Eight trials administered BUD+FM in a single inhaler device,[136, 198, 206, 211, 215, 219, 221, 222] three tested the combination delivered by separate inhalers,[157, 179, 213] and five administered them both as a single inhaler and in separate inhalers to different study groups.[142, 207, 210, 212, 217]

Five trials included children ≤ 12 years of age.[212, 215, 219, 221, 222] Study duration was 12 weeks for 11 trials, 26 weeks for 1 trial,[222]32 weeks for one trial,[213] and one year for three trials.[157, 179, 198]

The majority of trials assessed asthma symptoms, nocturnal awakenings, exacerbations, and rescue medicine use. Six trials also assessed quality of life and one assessed missed work or school. For these outcomes, all 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, 10 trials (71%) reported fewer symptoms or better improvement in symptoms,[135, 137, 139, 142-144, 157, 173, 179, 180, 185, 198, 204-211, 213, 214, 216-218] six trials (of seven reporting the outcome) reported fewer exacerbations or a lower risk exacerbations,[136, 157, 179, 206, 213, 215] and 10 trials (71%) reported a greater decrease or less frequent use of rescue medicine.[135, 137, 139, 143, 144, 157, 173, 179, 180, 185, 204-211, 213-218, 221] For three of the eleven trials reporting nocturnal awakenings, results favored the BUD+FM group.[206, 207, 211] The other eight reported no difference.[136, 142, 157, 210, 212, 215, 217, 219] Three[212, 213, 219] of the four trials reporting quality of life found no statistically significant difference in overall quality of life measures and one[211] reported greater improvement in those treated with BUD+FM. The single trial reporting missed work or school found no significant difference between groups.[213]

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

Nine fair quality RCTs (3,029 subjects) compared the addition of SM to FP with continuing the same dose of FP[135, 137, 139, 143, 173, 204, 209, 220, 223] (Table 20). All 9 administered FP+SM in a single inhaler device.[135, 137, 139, 143, 173, 204, 209, 220, 223] None tested the combination delivered by separate inhalers. One trial included children ≤ 12 years of age.[220] Study duration was 12 weeks for 5 trials,[135, 139, 143, 204, 220] 24 weeks for one trial,[173] and 12 months for 3 trials.[137, 209, 223]

The majority of trials assessed asthma symptoms, exacerbations, and rescue medicine use. Three trials also reported nocturnal awakenings and one reported quality of life. For these outcomes, all 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,[135, 143, 173, 204, 209] three trials (of five reporting) reported fewer patients having exacerbations or withdrawn due to exacerbations,[135, 137, 143] and 6 trials (86%) reported a greater decrease or less frequent use of rescue medicine.[135, 139, 143, 173, 204, 209] Two of the three trials reporting nocturnal awakenings found no difference between groups,[135, 139] one reported a higher percentage of awakening-free nights for the FP+SM group.[143] 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 = NR).[143]

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)[205, 208, 214] (Table 20). All three administered ICS+SM by separate inhalers. One trial included children, enrolling 210 subjects between the ages of 4 and 16.[214] Study duration was 12 weeks for two trials[205, 214] and 14 weeks for one.[208]

All three trials reported symptoms and rescue medicine use, one reported exacerbations,[205] and one reported quality of life measures.[208] 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)[205] 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, $P = 0.19$).[205] 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, $P = 0.47$).[208]

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)[216, 218] (Table 20). 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.[216] The other was a 12-week trial that enrolled 302 children (ages 6-11) not adequately controlled on ICSs.[218] 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.[216] The 12-week trial in children found no statistically significant difference in symptoms, rescue medicine use, or quality of life.[218]

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.[185] The trial reported no statistically significant difference in symptoms, exacerbations, or rescue medicine use.

7. Beclomethasone (BDP) + Formoterol(FM) compared with Beclomethasone (BDP)

One 24-week fair quality RCT meeting our inclusion criteria compared BDP+FM in separate inhalers with same dose of BDP alone in 645 patients with moderate to severe asthma uncontrolled by regular treatment. The results did not provide between group differences for this comparison. Analyses were focused on the comparison of BDP+FM in a single inhaler with BDP+FM in separate inhalers and with a higher dose of BDP alone.

Table 20. Characteristics of head-to-head studies comparing ICS+LABA compared with same dose ICS

Study	Study Design N Duration	Country Population Setting	Comparison (total daily dose in mcg)	Quality Rating
Budesonide + formoterol compared with budesonide				
Berger et al. 2010[222]	RCT 187 26 weeks	USA Ages 6-11 with a documented diagnosis of mild to moderate asthma >=6 months Setting	Budesonide (640) + Formoterol (18) vs. Budesonide (800)	Fair
Buhl et al. 2003[206]	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) vs. BUD/FM (320/9 divided into two doses) vs. BUD (400)[a] All given by DPI	Fair
Corren et al. 2007[136] Murphy et al., 2008[225]	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	Fair
Eid et al. 2010[221]	RCT, DB 522 12 weeks	USA 6 to 15 years; with a documented mild to moderate asthma diagnosis for 6 months Multicenter (95)	Budesonide (160) + Fomoterol (9) vs. Budesonide (160) + Fomoterol (18) vs. Budesonide (160)	Fair
Jenkins et al. 2006[207]	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)[a] All given by MDI	Good

Table 20. Characteristics of head-to-head studies comparing ICS+LABA compared with same dose ICS

Study	Study Design N Duration	Country Population Setting	Comparison (total daily dose in mcg)	Quality Rating
Kuna et al. 2006[210]	RCT, DB, DD 617 12 weeks	Multinational (8) Age ≥18, mild or moderate persistent, uncontrolled on ICS Multicenter (61)	BUD/FM (160/9 give once daily) vs. BUD+FM (160/9 divided twice daily) vs. BUD (200)[a] All given by DPI	Fair
Morice et al. 2007[211]	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)	Fair
Morice et al. 2008[219]	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)	Fair
Noonan et al. 2006[142] Chervinsky et al, 2008 [224]	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	Fair
O'Byrne et al. 2001[157] OPTIMA trial	RCT, DB 1970 (698 in Group A, 1272 Group B) 1 year	Multinational (Eastern Europe, Canada, Spain) Age ≥ 12, Group B was not controlled with ICS Multicenter (198)	**Group A** (used no ICS for ≥ 3 months): Placebo vs. BUD (200 mcg/d) vs. FM + BUD (9/200 mcg/d) **Group B** (taking ICS for ≥ 3 months): BUD (200) vs.	Fair

Table 20. Characteristics of head-to-head studies comparing ICS+LABA compared with same dose ICS

Study	Study Design N Duration	Country Population Setting	Comparison (total daily dose in mcg)	Quality Rating
			BUD (200)+ FM (9) vs. BUD (400) vs. BUD (400)+ FM (9) All delivery devices=DPIs	
Morice et al. 2008[219]	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)	Fair
Noonan et al. 2006[142] Chervinsky et al, 2008 [224]	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	Fair
O'Byrne et al. 2001[157] OPTIMA trial	RCT, DB 1970 (698 in Group A, 1272 Group B) 1 year	Multinational (Eastern Europe, Canada, Spain) Age ≥ 12, Group B was not controlled with ICS Multicenter (198)	**Group A** (used no ICS for ≥ 3 months): Placebo vs. BUD (200 mcg/d) vs. FM + BUD (9/200 mcg/d) **Group B** (taking ICS for ≥ 3 months): BUD (200) vs. BUD (200)+ FM (9) vs. BUD (400) vs. BUD (400)+ FM (9) All delivery devices=DPIs	Fair

Table 20. Characteristics of head-to-head studies comparing ICS+LABA compared with same dose ICS

Study	Study Design N Duration	Country Population Setting	Comparison (total daily dose in mcg)	Quality Rating
Price et al. 2002[213] FLOW research group	RCT, DB 663 (505 for second randomization) 32 weeks (Part I = 4 weeks, Part II = well controlled subjects were re-randomized for 28 more weeks)	UK and Ireland 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 Multicenter (152 general practices)	BUD DPI (800) + eFM DPI (18) vs. BUD DPI (800) + placebo	Fair
Tal et al. 2002[215]	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	Fair
Zetterstrom et al. 2001[217]	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)[a] All given by DPI	Good
Fluticasone + salmeterol compared with fluticasone				
Bailey et al., 2008[223]	RCT, DB 475 52 weeks	USA African Americans aged 12 – 65 years with persistent asthma and symptomatic while being treated with ICS at a low and consistent dose Multicenter (59)	FP/SM DPI (200/100) vs. FP DPI (200)	Fair
Bateman et al. 2001[204]	RCT, DB, DD	Multinational (10)	FP/SM MDI (200/100) vs.	Fair

Table 20. Characteristics of head-to-head studies comparing ICS+LABA compared with same dose ICS

Study	Study Design N Duration	Country Population Setting	Comparison (total daily dose in mcg)	Quality Rating
	497 12 weeks	Age≥12, mild-moderate persistent asthma, not controlled on ICS Multicenter (69)	FP/SM DPI (200/100) vs. FP MDI (200)	
Ind et al. 2003[173]	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)	Fair
Kavuru et al. 2000[135]	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 Multicenter	Placebo vs. FP/SM DPI (200/100) vs. SM DPI (100) vs. FP DPI (200)	Fair
Koopmans et al. 2006[209]	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	Fair
Lundback et al. 2006[137]	RCT, DB 282 12 months	Sweden Age ≥18, mild or moderate persistent, uncontrolled on current medication (68% were on ICS) Patients recruited from ~4000 individuals with asthma who had particpated in large epidemiologic studies	FP/SM DPI (500/100) vs. FP DPI (500) vs. SM DPI (100)	Fair

Table 20. Characteristics of head-to-head studies comparing ICS+LABA compared with same dose ICS

Study	Study Design N Duration	Country Population Setting	Comparison (total daily dose in mcg)	Quality Rating
Malone et al, 2005[220]	RCT, DB, DD 203 12 weeks	US and Canada Children aged 4 – 11 years with persistent asthma who used ICS for at least 1 month prior to visit 1 Multicenter	FP/SM HFA (200/100) vs. FP HFA (200)	Fair
Nathan et al. 2006[139] Edin et al. 2009[140b]	RCT, DB 365 12 weeks	US Age ≥12yr, not controlled on ICS, severity NR Multicenter (45)	FP/SM MDI (440/84) vs. FP MDI (440) vs. SM MDI (84) vs. placebo	Fair
Shapiro et al. 2000[143] AND Nathan et al. 2003[144]	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)	Fair
ICS + salmeterol compared with ICS				
Boyd et al. 1995[205]	RCT, DB 119 12 weeks	UK Age ≥18, uncontrolled on ICS (≥ 1,500 mcg of BDP or equivalent), under consideration for maintenance oral corticosteroid therapy Multicenter (15 out-patient departments)	ICS + SM DPI (200) vs. ICS + placebo Subjects continued their current ICS and were randomized to SM compared with placebo	Fair
Kemp et al. 1998[208]	RCT, DB 506	US Age ≥12yr, used a SABA on a daily basis, symptomatic despite using fixed and	ICS + SM MDI (84) vs. ICS + placebo	Fair

Table 20. Characteristics of head-to-head studies comparing ICS+LABA compared with same dose ICS

Study	Study Design N Duration	Country Population Setting	Comparison (total daily dose in mcg)	Quality Rating
	14 weeks	approved dose of ICS Multicenter (44)	Subjects continued their current ICS and were randomized to SM compared with placebo	
Russell et al. 1995[214]	RCT, DB 210 12 weeks	UK Age 4-16, uncontrolled on high-dose ICS (≥ 400 BDP daily or equivalent), moderate to severe persistent asthma Multicenter (78 hospitals)	ICS + SM DPI (100) vs. ICS + placebo DPI Subjects continued their current ICS and were randomized to SM compared with placebo	Fair
ICS + formoterol compared with ICS				
van der Molen et al. 1997[216]	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) vs. ICS + placebo DPI ICS + FM N = 125 ICS + placebo N = 114 Subjects continued their current ICS and were randomized to FM compared with placebo	Fair
Zimmerman et al. 2004[218]	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	Fair

Table 20. Characteristics of head-to-head studies comparing ICS+LABA compared with same dose ICS

Study	Study Design N Duration	Country Population Setting	Comparison (total daily dose in mcg)	Quality Rating
Beclomethasone + salmeterol compared with beclomethasone				
Verberne et al. 1998[185]	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	Fair
Beclomethasone + formoterol compared with beclomethasone				
Huchon, et al., 2009[199]	RCT, DB, DD 645 24 weeks	Multinational Patients aged 18 – 70 years with moderate to severe persistent asthma uncontrolled by regular treatment with ICS.	BDP/FM pMDI (400/24) vs. BDP pMDI (1000) + FM DPI(24) vs. BDP pMDI (1000)	Fair

Abbreviations: BDP = beclomethasone dipropionate; BUD = Budesonide; 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; OCS= oral corticosteroids; pMDI= pressurized metered dose inhaler; RCT= randomized controlled trial; SM = Salmeterol; SR=systematic review;

[a] 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.

[b] Edin et al., 2009 is related to two other publications trials (Pearlman, 2004[150] and Nathan, 2006[139]).

4. ICS+LTRA compared with ICS

Summary of findings

We found two systematic reviews with meta-analyses[226, 227] and five RCTs[118, 197, 228-231] meeting our inclusion/exclusion criteria (Table 21). Most studies were conducted in adolescent and adult populations; one study enrolled a pediatric population ages six to 14[231] and one enrolled children and adolescents (6 to 17 years of age).[197]

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. (Appendix H, Table H-13) There is no apparent difference in symptoms, exacerbations, or rescue medicine use 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 (Evidence Tables A and B).

Detailed Assessment

Description of Studies

We found two systematic reviews with meta-analyses[226, 227] and five RCTs[118, 197, 228-231] meeting our inclusion/exclusion criteria (Table 21). Three compared budesonide plus montelukast with budesonide alone. Two studies[118, 230] compared the combination of an ICS plus LTRA with the same dose ICS and three studies[197, 228, 229, 231] compared the combination with an increased dose of ICS.

Study Populations

The five RCTs included a total of 2,423 patients. Most studies were conducted in adolescent and adult populations; one study enrolled a pediatric population ages six to 14[231] and one enrolled children and adolescents (6 to 17 years of age).[197] One was conducted in the United States, one in Europe, one in India, and two were other multinational combinations. Asthma severity ranged from mild persistent to severe persistent. Two 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 five 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

Of the two systematic reviews meeting our inclusion criteria, one[227] identified just three studies comparing ICS+LTRA with ICS that used constant doses of ICS. It did not find three others that we identified.[197, 228, 229, 231] Thus, we do not discuss this review further in this section and we do not include it in our overall assessment of the evidence or our strength of evidence grades as it is missing about half of trials relevant to this section.

One good systematic review with meta-analysis[226] 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.[118, 228-230] 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 RCT[230] comparing the combination of BUD+ML with the same dose of BUD (Table 21). 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.[230] 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:[118] 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[228, 229, 231] comparing the combination of BUD+ML with an increased dose of BUD (Table 21). 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.[228, 229] 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 trial[231] (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.

5. Fluticasone (FP)+Montelukast (ML) compared with Fluticasone (FP) increased dose
We found one fair RCT[197] (N = 182) comparing the combination of FP+ML with an increased dose of FP in children and adolescents (6 to 17 years of age). The trial used a triple cross-over design. Subjects with uncontrolled asthma while receiving FP (100 twice daily) were randomized to FP (250 twice daily), FP (100 twice daily) plus salmeterol, or FP (100 twice daily) plus montelukast. The primary outcome was a composite of exacerbations, number of asthma control days, and FEV1. One hospitalization for asthma-related symptoms occurred in each of

the three treatment groups. A total of 120 prednisone bursts were prescribed for exacerbations (47 during treatment with FP compared with 43 during treatment with FP+ML, *P* = NR).

Table 21. Characteristics of head-to-head studies comparing ICS + LTRA with ICS

Study	Study design N Duration	Country Study population Setting	Comparison (total daily dose)	Quality rating
ICS + LTRA compared with ICS same dose				
Ducharm et al. 2004[226]	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.	Good
Budesonide + montelukast compared with budesonide same dose				
Vaquerizo et al. 2003[230] CASIOPEA	RCT 639 16 weeks	Spain Age 18 – 70 Hospital centers	BUD (400 – 1600) + placebo vs. BUD (400 – 1600) + ML (10) Low to High dose ICS	Fair
Beclomethasone + montelukast compared with beclomethasone same dose				
Laviolette et al. 1999[118]	RCT 642 16 weeks	Multinational Age ≥ 15 Multicenter	BDP (400) + ML (10) vs. BDP (400) vs. ML (10) vs. placebo Low dose ICS	Fair
ICS + LTRA compared with ICS increased dose				
Ducharm et al. 2004[226]	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.	Good
Budesonide (BUD)+Montelukast (ML) compared with Budesonide (BUD) increased dose				
Jat et al. 2006[231]	RCT 71 12 weeks	India Age 6-14 Pediatric Asthma Clinic	BUD (400) vs. BUD (200) + ML (5) Low dose ICS	Fair
Price et al. 2003[228, 229]	RCT 889	Multinational	ML (10) + BUD (800) vs.	Fair

Table 21. Characteristics of head-to-head studies comparing ICS + LTRA with ICS

Study	Study design N Duration	Country Study population Setting	Comparison (total daily dose)	Quality rating
COMPACT	16 weeks	Age 15 – 75 Multicenter	BUD (1600) Medium to High dose ICS	
Fluticasone (FP)+Montelukast (ML) compared with Fluticasone (FP) increased dose				
Lemanske et al. 2010[197] BADGER	RCT 182 48 wks (3 cross-over periods of 16 wks each)	United States Age 6-17 Multicenter	FP (500) vs. FP/SM (200/100) vs. FP (200) + ML (5-10) High vs. low vs. low dose ICS	Fair

Abbreviations: AQLQ = Asthma Quality of Life Questionaire; 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.

5. Combination products compared with Leukotriene Modifiers

Summary of findings

We found 5 RCTs [127, 128, 232-234] meeting our inclusion/exclusion criteria for this comparison (Table 22). All 5 compared low dose fluticasone plus salmeterol with montelukast. Two of the RCTs were in adolescents and adults, one enrolled subjects over the age of six[127] (~15% of subjects < 12 years of age), and 2 enrolled children ages 6-14.[128, 234]

Overall, our meta-analysis and results from 5 RCTs found the combination of fluticasone plus salmeterol to be more efficacious than montelukast for the treatment of persistent asthma (Appendix I and Appendix H, Table H-14).

Detailed Assessment

Description of Studies

We found 5 RCTs [127, 128, 232-234] meeting our inclusion/exclusion criteria (Table 22). Of the included studies, all compared montelukast with low dose fluticasone plus salmeterol.

Study Populations

The 5 RCTs included a total of 2,188 patients. Two studies were conducted in adult populations; three studies[127, 128, 234] included children < 12 years of age. Four studies were conducted in the United States and one study was conducted at sites in both Latin America and Turkey.[234] Asthma severity ranged from mild persistent to severe persistent: 2 studies enrolled subjects with mild to moderate persistent asthma; three studies enrolled subjects with any severity of persistent asthma.

Methodologic Quality

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

Sponsorship

Of the 5 RCTs, 3 (60%) were funded by pharmaceutical companies; only one (20%) was funded primarily by sources other than pharmaceutical companies, and one (20%) did not report the source of funding but a significant portion of the study design was dictated by a pharmaceutical company and several authors reported a primary affiliation with the company.[234]

Head-to-head comparisons

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

The 5 included studies are described below. We conducted meta-analyses for outcomes that were reported with sufficient data in multiple trials (Appendix I). 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 -0.25, 95% CI: -0.35, -0.15), greater improvement in the percentage of rescue medicine-free days (SMD -0.27, 95% CI: -0.37, -0.17), and fewer exacerbations (SMD 0.26, 95% CI: 0.16, 0.35). (Appendix I)

The 5 studies included one good quality RCT[232] and 4 fair quality RCTs (Table 22).[127, 128, 233, 234] 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.[232] 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 = 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.[233] 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 above[232] 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 22).

A third fair-rated RCTs showed 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.[127] 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.[128] 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 = NR).

A final RCT showing mixed results, known as the Pediatric Asthma Control Evaluation (PEACE) study, enrolled children age 6 to 14 with mild to moderate persistent asthma in outpatient centers at 4 sites in Turkey and 23 in Latin America.[234] Using a double-blind, double-dummy design, 281 children treated with FP/SM 100mcg/50mcg twice daily were compared to 267 patients treated with ML 5mg daily. While the results showed significant improvement in

the percentage of symptom free days (OR 1.74, 95% CI 1.07 – 2.82), asthma controlled weeks (16.7% more in FP/SM group, 95% CI 8.3 – 16.7), they found no difference between groups in the percentage of nights without awakenings due to nocturnal symptoms (OR 2.33, 95% CI 0.73 – 7.47). The mean exacerbation rate and time was significantly reduced with FP/SM therapy (0.12 vs. 0.3, OR 0.4, 95% CI 0.29 – 0.57) and the number of patients exacerbation free at 84 days was 89.6% in FP/SM patients compared with 74.8% in the ML group (95% CI 8 – 22). In addition, the percentage of rescue free days increased significantly with FP/SM treatment (OR 3.24, 95% CI 2.09– 5.02). Quality of life measures, however, demonstrated mixed results. While *PACQLQ* scores were higher in the FP/SM group (mean treatment difference 0.54, 95% CI 0.06 – 1.02), no difference was noted between groups with respect to *PAQLQ* score (mean treatment difference 0.09, 95% CI -0.12 – 0.30). Finally, while 7.5% of FP/SM treated patients required some form of unscheduled health care contact during the study period, substantially more patients on ML therapy required medical attention (*P* = NR). Adherence was similar between groups (87% compared with 84%; *P* = NR).

Table 22. Characteristics of head-to-head studies comparing ICS+LABA with leukotriene modifiers

Study	Study design N Duration	Country Study population Setting	Comparison (total daily dose)	Quality rating
Montelukast (ML) compared with Fluticasone (FP) plus Salmeterol (SM)				
Pearlman et al. 2002[232]	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	Good
Calhoun et al. 2001[233]	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	Fair
Maspero et al. 2008[234] Pediatric Asthma Control Evaluation (PEACE) study	RCT DB, double dummy 548 14 weeks (2 week run-in period, 12 week treatment period)	Latin America & Turkey Children 6-14, mild to moderate persistent asthma Multicenter (23 Latin America, 4 Turkey) Outpatient setting	FP (200 mcg)/SM (100 mcg) vs. ML (5mg) Low dose ICS	Fair
Peters et al. 2007[127]	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	Fair

Table 22. Characteristics of head-to-head studies comparing ICS+LABA with leukotriene modifiers

Study	Study design N Duration	Country Study population Setting	Comparison (total daily dose)	Quality rating
Montelukast (ML) compared with Fluticasone (FP) plus Salmeterol (SM)				
Sorkness et al. 2007[128] 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) vs. FP/SM (100 mcg/50 mcg) once in the morning + SM (50 mcg) in the evening vs. ML (5 mg) Low dose ICS	Fair

Abbreviations: AQLQ = Asthma Quality of Life Questionaire; 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.

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-analysis[235] and eight RCTs[197, 236-242] 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 23). Seven of the RCTs were in adolescents and adults ≥ 12 years of age and one enrolled children and adolescents 6 to 17 years of age.[197]

Overall, results from a good quality systematic review with meta-analysis and eight RCTs provide high strength of evidence (Appendix H, Table H-15) 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 (Evidence Tables A and B). We found just one RCT that included children < 12 years of age.[197]

Detailed Assessment

Description of Studies

We found one systematic review with meta-analysis[235] and eight RCTs.[197, 236-242] Of the included studies (Table 23), seven RCTs compared montelukast plus fluticasone with salmeterol plus fluticasone, one RCT[242] compared montelukast plus budesonide with formoterol plus budesonide. All but two of the included RCTs[197, 240] were included in the systematic review and meta-analysis.[235]

Study Populations

All but one of the included RCTs were conducted in adult populations.[197] Four studies (50%) were conducted in the United States, two (25%) in Europe, and two (25%) were other multinational combinations often including Europe, Canada, or the US. Asthma severity ranged from mild persistent to severe persistent: two studies (25%) were conducted in patients with mild to moderate persistent asthma, two (25%) in patients with mild to severe persistent asthma, one (12%) in patients with moderate persistent asthma, and two (25%) 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 eight 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

Six of the included RCTs(75%) were funded by pharmaceutical companies; one trial[197] was funded by grants from the National Heart, Lung and Blood Institute, National Institute of Allergy and Infectious Diseases, and National Center for Research Resources; and one trial 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.[235] 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.[235] 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.[236-239, 241, 242] 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.[235] 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; I2 = 61%; $P < 0.05$).

The eight RCTs meeting the inclusion/exclusion criteria for our review are summarized in Table 23. Six of the eight trials were included in the systematic review with meta-analysis[235] described above. One of those not included was a fair-rated RCT,[240] the SOLTA study. It compared low dose FP (200 mcg/day) plus SM (100 mcg/day) (N = 33) 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 = NS), but there was a difference in rescue use at night favoring FP/SM (median rescue free nights at endpoint: 93% compared with 82%; $P = 0.01$).

The other trial (BADGER) not included in the systematic review described above enrolled 182 children and adolescents (6 to 17 years of age).[197] The trial used a triple cross-over

design. Subjects with uncontrolled asthma while receiving FP (100 twice daily) were randomized to FP (250 twice daily), FP (100 twice daily) plus salmeterol, or FP (100 twice daily) plus montelukast for 16 weeks of each treatment (total of 48 week treatment phase). The primary outcome was a composite of exacerbations, number of asthma control days, and FEV1. The response to LABA step-up therapy was most likely to be the best response compared with LTRA step-up (relative probability, 1.6; 95% CI: 1.1 to 2.3). One hospitalization for asthma-related symptoms occurred in each of the three treatment groups. A total of 120 prednisone bursts were prescribed for exacerbations (30 during treatment with FP+SM compared with 43 during treatment with FP+ML, *P* = NR).

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 (Evidence Tables A and B).

Table 23. Characteristics of head-to-head studies comparing ICS+LABA with ICS+leukotriene modifiers

Study	Study design N Duration	Study population	Comparison (total daily dose)	Quality rating
LTRA plus ICS compared with LABA plus ICS				
Ducharme et al. 2006[235]	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)	Good
Montelukast plus fluticasone compared with salmeterol plus fluticasone				
Bjermer et al.[236] IMPACT	RCT 1490 48 weeks	Multinational (37 countries - eastern Europe) Age 15 – 72, mild to severe persistent asthma currently uncontrolled on low dose ICS, smoking status NR Multicenter (148)	ML (10mg) plus FP (200 mcg) vs. SM (100 mcg) plus FP (200 mcg) Same Low dose ICS	Good
Fish et al. 2001[237]	RCT 948 12 weeks	United States and Puerto Rico Age 15 and older, moderate to severe persistent asthma despite low to high dose ICS, smoking status NR Multicenter (71)	SM (100 mcg) plus baseline ICS vs. ML plus baseline ICS (10mg) Same Low to High dose ICS	Fair
Ilowite et al. 2004[238]	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	Fair
Lemanske et al. 2010[197] BADGER	RCT 182 48 wks (3 cross-over periods of 16 wks each)	United States Age 6-17 Multicenter	FP (500 mcg) vs. FP/SM (200 mcg/100 mcg) vs. FP (200 mcg) + ML (5-10 mg) High vs. low vs. low dose ICS	Fair

Table 23. Characteristics of head-to-head studies comparing ICS+LABA with ICS+leukotriene modifiers

Study	Study design N Duration	Study population	Comparison (total daily dose)	Quality rating
Nelson et al. 2000[239]	RCT 447 12 weeks	United States Age 15 and older, moderate to severe persistent asthma uncontrolled don 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	Fair
Pavord et al. 2007[240] SOLTA Study Group	RCT 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	Fair
Ringdal et al. 2003[241]	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.	Fair
Montelukast plus budesonide compared with formoterol plus budesonide				
Ceylan et al. 2004[242]	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	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; 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.

7. LTRA+LABA compared with ICS+LABA

Summary of findings

We found one fair quality RCT comparing LTRA plus LABA with ICS plus LABA (Appendix H, Table H-16 and Table 24).[243] 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.[243] 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 24. Characteristics of head-to-head studies comparing ICS+LABA with LTRA+LABA

Study	Study design N Duration	Country Study population Setting	Comparison (total daily dose)	Quality rating
Montelukast plus salmeterol compared with beclomethasone plus salmeterol				
Deykin et al. 2007[243]	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 Low dose ICS	Fair

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.

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,[22, 23, 244-248] 50 RCTs[27-33, 35-50, 52-55, 58-70, 249-258] and 12 observational studies[259-269] reporting the tolerability or frequency of adverse events for inhaled corticosteroids meeting our inclusion/exclusion criteria (Table 7 and Evidence Tables A and B). 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 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 that examined the efficacy of one ICS relative to another (described in Key Question 1) also reported tolerability and adverse events. Six head-to-head RCTs that did not report efficacy met our inclusion/exclusion criteria for tolerability or adverse events.[249-252, 257, 258] Seven of the head-to-head RCTs included children < 12.[31, 44, 46, 62, 68, 69, 249] 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; some studies were post hoc analyses or retrospective reviews of databases.

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

Of the 47 head-to-head studies reviewed for this section, most reported frequency of adverse events without tests of statistical significance (Appendix I). The vast majority of studies reported similar results for equipotent ICS doses. Only five studies reported a difference of greater than 5% in overall adverse events for equipotent doses.[37, 40, 42, 61, 68] 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.[55] Four studies reported a difference of greater than 5% in withdrawals due to AEs for equipotent doses.[30, 41, 68, 251]

Most head-to-head trials reported specific adverse events (Appendix J). 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 three trials reported a statistically significant difference between equipotent doses of different ICSs.[35, 41, 64] One reported a greater incidence of headache in those treated with BDP than those treated with FP (7% compared with < 1%, $P = 0.03$);[35] one reported a greater incidence of upper respiratory tract infection with TAA than with BDP (10.4% compared with 2.7%, $P = 0.027$);[41] one reported a greater incidence of oral candidiasis with FP than with ciclesonide (3.8% vs. 0%, $P = 0.002$);[64] and one reported that a greater proportion of patients experienced local oropharyngeal adverse effects (candidiasis and dysphonia) with FP than with ciclesonide ($p = 0.0023$).[63] Meta-analysis of trials reporting "oral candidiasis-thrush" that compared equipotent doses of ciclesonide with FP revealed lower odds of oral candidiasis-thrush for those treated with ciclesonide (OR 0.33, 95% CI 0.17, 0.64, Appendix I).

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.[244, 245] One included 14 studies (2,302 subjects) of patients with asthma or COPD (both RCTs and prospective cohort studies) assessing BMD.[244] The other included six studies of asthmatic subjects with median duration of ICS use of at least three years.[245] Pooled results from both meta-anlyses 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.[244]

Our review includes nine studies: three of the trials[251, 252, 259] in the systematic reviews, as well as six additional studies.[253, 255, 256, 260-262, 269] 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,[255, 256] three fair-rated RCTs,[251-253] and five observational studies.[259-262, 269]

All nine studies assessed BMD, facture risk, or both (Table 25). In total, four studies evaluated the risk of fracture[252, 260, 261, 269] and seven measured BMD as an intermediate outcome.[251-253, 255, 256, 259, 262, 269] Two studies compared one ICS to another,[251, 252] three compared one ICS to placebo,[253, 255, 256, 262] and four studies compared one ICS or any ICS to a population

that did not use an ICS.[259-261, 269] Most studies evaluated the risk of bone weakening over two to six years.

Two of the trials were head-to-head RCTs comparing one ICS with another ICS in adult subjects.[251, 252] One 24-month open-label trial measuring BMD and vertebral fractures randomized 374 adult patients with asthma to beclomethasone, budesonide, or placebo.[252] 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.[251] At one year, no significant differences in bone mass or metabolism were noted between the two treatment groups.

Seven studies (three 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;[253, 255, 256, 259-262, 269] three of these studies measured bone fractures.[260, 261, 269] The studies conducted in pediatric populations reported no difference in BMD between ICS- and placebo-treated subjects and no difference in risk of osteoporosis or time to first fracture between ICS-treated subjects and those not treated with ICS.[255, 256, 262, 269] Of the remaining studies, one reported a dose-related decline in BMD with ICS-treated subjects,[259] one reported a dose-related increase in the risk of vertebral and nonvertebral fractures with ICS,[261] and two reported no difference in nonvertebral fracture[260] or BMD[253] between ICS-treated subjects and controls (Table 25).

Table 25. Summary of studies on bone density or fractures

Author Year	N	Design	Population	Results	Quality rating
Adult populations					
Israel et al. 2001[259]	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[260]	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[253]	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[251]	69	RCT	Asthma (adult)	No difference in BMD between BDP- and FP-treated patients over 1 year	Fair
Tattersfield et al. 2001[252]	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[261]	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[255, 256]	1041	RCT	Asthma (pediatric)	No difference in bone density between BUD- and placebo-treated patients	Good

Table 25. Summary of studies on bone density or fractures

Author Year	N	Design	Population	Results	Quality rating
Agertoft & Pedersen, 1998[262]	157	Cross-sectional	Asthma (pediatric)	No difference between BUD and placebo (3-6 years use) in BMD	Fair
Kelly, 2008[269]	877	Cohort study (CAMP subjects)	Asthma (pediatric)	ICS use was not related to time to first fracture or to risk for osteopenia	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

Four head-to-head RCTs comparing fluticasone to beclomethasone, [31], fluticasone to budesonide,[44, 249], or ciclesonide to budesonide[62] 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.[31] 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.[249] 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.[44] 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, $P = 0.0003$). The forth RCT compared growth in 621 children (age 6-11) treated with either a low dose of ciclesonide (160 mcg/day) or a low dose of budesonide (400 mgc/day) over 12 weeks. Ciclesonide-treated subjects had a greater mean body height increase (1.18cm vs. 0.70cm, $P = 0.0025$).

Four additional studies provide general evidence of growth retardation for ICSs (Table 26). These included two meta-analyses[246, 247] and three RCTs.[124, 254-256] 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.[246] 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.[247]

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.[255, 256] 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 result 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.[254, 270] 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).[124]

Table 26. 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[31]	343	RCT	Pre-pubertal children with asthma	1 year	Greater growth velocity in FP than in BDP group	Fair
Ferguson et al, 1999[44]	333	RCT	Children with asthma	20 weeks	Greater growth velocity in FP than in BUD group	Fair
Kannisto et al. 2000[249]	75	RCT	Children with asthma	1 year	Greater growth velocity in FP than in BUD group	Fair
von Berg et al. 2007[62]	621	RCT	Children with asthma	12 weeks	Greater increase in growth in CIC than in BUD group	Fair
General evidence from ICS-treated subjects compared with non-ICS treated controls						
Sharek et al. 1999[246]	273	Meta-analysis	Children with asthma	More than 3 months	Reduction in growth for BDP compared to placebo	Good
Sharek et al. 2000[247]	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[255, 256]	1041	RCT	Children with asthma	4.3 years	Reduction in growth (1.1 cm) for BUD-treated children	Good
Allen et al. 1998[254]	268	RCT	Children with asthma	1 year	No differences in height and growth velocity between FP and placebo	Fair
Becker et al. 2006[124]	360	RCT	Children with asthma	56 weeks	Reduction in growth for BDP-treated children	Fair

Abbreviations: BDP = beclomethasone dipropionate; BUD = Budesonide; CIC = Ciclesonide; 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.[271-273] 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 27).

No study compared the risk of developing PSC between one ICS and another. One head-to-head RCT evaluated the effect of ciclesonide and beclomethasone on eye lens opacity.[257] One placebo-controlled trial[255, 256] and five observational studies[263-267] evaluated the risk of developing cataracts between ICS- and non-ICS-treated patients. One RCT[255, 256] and one observational study[263] compared budesonide to placebo; the other studies all compared nonspecific ICS use to no ICS use. Two studies were conducted in pediatric populations,[255, 256, 263] one in a mixed population of children and adults,[266] and four evaluated adult populations (≥ 40 years).[257, 264, 265, 267]

The single head-to-head RCT[257] evaluating eye lens opacity found ciclesonide to be non-inferior to beclomethasone (both delivered at high doses). Both treatments were found to have minimal impact on lenticular opacities development and/or progression. Both trials conducted in children reported no significant differences in the development of PSC between budesonide-treated patients and placebo or matched controls.[255, 256, 263] 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.[255, 256] 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.[266]

Consistent evidence from two case-control studies[265, 267] and one cross-sectional study[264] 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/day[267] and one study reported a higher relative risk for budesonide or beclomethasone doses greater than 1,000 mcg/day.[265]

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.[264]

Table 27. Summary of studies on posterior subcapsular cataracts

Author Year	N	Design	Population	Results	Quality rating
Chylack et al. 2008[257]	1,568	RCT	Adults (age ≥ 18)	Mean changes in nuclear opalescence and cortical and posterior subcapsular opacification were small and similar between groups	Fair
Childhood Asthma Management Program Research Group, 2000[255, 256]	1041	RCT	Children	No significant differences in PSC between BUD-, nedocromil-, or placebo-treated children	Good
Agertoft et al., 1998[263]	268	Prospective cohort	Children (age 5-16)	No significant differences in PSC between BUD-treated children and matched controls	Fair
Cumming et al. 1997[264]	3654	Cross-sectional	Adults (age 49-97)	Increased risk of nuclear and PSC among ICS users	NA
Garbe et al. 1998[265]	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[266]	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[267]	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 older[265] and one cross-sectional population-based study of 3,654 Australians 49 to 97 years of age[268] 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).[265] 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).[268] Both studies adjusted for age, sex, oral steroid use, history of diabetes, and history of hypertension (Table 28).

Table 28. Summary of studies on ocular hypertension or open-angle glaucoma

Author Year	N	Design	Population	Results	Quality rating
Garbe et al. 1997[265]	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[268]	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.[252, 260, 261] Two of these studies, one RCT (N = 374)[252] and one case-control study (N = 18,942)[260] 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.[261] Of four studies reporting BMD in adult subjects, three RCTs reported no difference between ICS-treated subjects and controls[251-253] and one small prospective cohort study (N = 109) reported a small dose-related decline in BMD in premenopausal women treated with ICSs.[259] 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; and one cohort study reported no relationship between ICS use and to time to first fracture or risk for osteopenia. 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 moderate strength of evidence that short-term (20 weeks to 1 year) growth velocity is reduced less with fluticasone than with beclomethasone[31] or budesonide.[44, 249] A forth head-to-head trial found that ciclesonide-treated subjects had a greater mean body height increase than budesonide-treated subjects over 12 weeks.[62] In addition, two meta-analyses report a reduction in growth velocity for beclomethasone or fluticasone compared to placebo.[246, 247] 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.[255, 256] 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.[271-273] Evidence from intermediate outcomes can not be extrapolated reliably to form conclusions about the comparative frequency of acute adrenal crisis for ICSs.

Cataracts
The single head-to-head RCT[257] evaluating eye lens opacity found ciclesonide to be non-inferior to beclomethasone (both delivered at high doses), with both treatments having minimal impact on the development and/or progression of lenticular opacities. No study compared the risk of developing PSC, per se, between one ICS and another. In adults, general evidence of an association between ICS use and PSC is moderate. 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 low.

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.[72] 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]

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 increase the risk of asthma-related death.[274-278] Subgroup analysis from one study[274] has suggested this risk may be significantly higher in African Americans (see Key Question 3). These concerns have resulted in an FDA boxed 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] LABAs are contraindicated for use as monotherapy in patients with persistent asthma.[275-278]

In February 2010, the FDA announced it was requiring manufacturers to revise their drug labels.[279] The new recommendations in the updated labels state the following:[279]

- Use of a LABA alone without use of a long-term asthma control medication, such as an inhaled corticosteroid, is contraindicated (absolutely advised against) in the treatment of asthma.
- LABAs should not be used in patients whose asthma is adequately controlled on low or medium dose inhaled corticosteroids.
- LABAs should only be used as additional therapy for patients with asthma who are currently taking but are not adequately controlled on a long-term asthma control medication, such as an inhaled corticosteroid.
- Once asthma control is achieved and maintained, patients should be assessed at regular intervals and step down therapy should begin (e.g., discontinue LABA), if possible without loss of asthma control, and the patient should continue to be treated with a long-term asthma control medication, such as an inhaled corticosteroid.
- Pediatric and adolescent patients who require the addition of a LABA to an inhaled corticosteroid should use a combination product containing both an inhaled corticosteroid and a LABA, to ensure adherence with both medications.

The FDA believes that when LABAs are used according to the recommendations outlined above and in the approved drug labels, the benefits of LABAs in improving asthma symptoms outweigh their risks of increasing severe asthma exacerbations and deaths from asthma.[279]

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. (Appendix K) We rated three studies[73, 75-77] as fair quality for assessment of adverse events. The fourth[74] 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 two systematic reviews with meta-analyses that directly compared subjects treated with formoterol and subjects treated with salmeterol[280, 281] and five systematic reviews with meta-analysis of placebo-controlled studies of LABAs that provided some indirect evidence regarding the relative harms associated with LABAs as well as more robust evidence of their harms (as a class) when compared with placebo.[282-286]

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, regardless of whether or not corticosteroids are used concurrently.

Detailed Assessment

Direct Evidence

Of the four included head to head trials, two were conducted only in adults,[76, 77] one enrolled adults and adolescents[73] and one enrolled only children and adolescents between 5-18 years old.[74] All four trials compared FM (12 mcg twice daily) with SM (50 mcg twice daily) (Appendix K). Only one[73] 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.[77]

One open-label RCT conducted in the United States[77] 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[73, 287] 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 trial[75] 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 adolescents[74] randomized subject (N = 156) to FM or SM and also found similar rates of study withdrawals and withdrawals due to adverse events.

Two systematic reviews compared SM and FM directly. The first review[281] compared the risk of adverse events in patients with chronic asthma who received formoterol *and corticosteroid* versus salmeterol *and corticosteroid* for chronic asthma. One trial compared formoterol and beclomethasone to salmeterol and fluticasone, and the other 7 trials compared formoterol and budesonide to salmeterol and fluticasone. They found no significant differences in any serious adverse events, including all-cause mortality (OR 1.03, 95%: CI 0.06 to 16.44), all-cause non-fatal serious adverse events (OR 1.14, 95% CI: 0.82 to 1.59), and asthma-related serious adverse events (OR 0.69, 95% CI: 0.37 to 1.26). The study using beclomethasone instead of budesonide was relatively small (N=228 participants) and showed no deaths or hospital admissions.

The second systematic review[280] compared the risk of adverse events in patients with chronic asthma who received formoterol versus salmeterol, without the addition of inhaled corticosteroids (ICS). They found no statistically significant differences in any serious adverse events, including all-cause mortality (one total death in the salmeterol group, not attributable to asthma), all-cause serious adverse events in adults (OR 0.77, 95% CI: 0.46 to 1.28) all-cause serious events in children (OR 0.95, 95% CI: 0.06 to 15.33), and asthma-related serious adverse events in adults (OR 0.86, 95% CI: 0.29 to 2.57) or children (no events in either group).

Indirect evidence

Among the 5 systematic reviews with meta-analysis of placebo-controlled studies of LABAs we included for this section, the most recent was published in 2009 (Appendix K).[286] This review[286] aimed to assess the risk of serious adverse events in patients with chronic asthma who received regular salmeterol versus placebo or short-acting beta$_2$-agonists. They found 26 trials comparing salmeterol to placebo, and eight trials comparing salmeterol to salbutamol (albuterol). For salmeterol versus placebo, the meta-analysis found significant increases in non-fatal serious adverse events in adults (OR 1.14; 95% CI: 1.01 to 1.28) but not children (OR 1.3; 95% CI: 0.82 to 2.05), and asthma-related mortality in adults (OR 3.49, 95% CI: 1.31 to 9.31). They found no statistically significant difference in all-cause mortality in adults (OR 1.33, 95% CI: 0.85 to 2.08) or in children (no deaths in either group), and no statistically significant difference in asthma-related non-fatal serious events (OR 1.43; 95% CI: 0.75 to 2.71). They found a borderline statistically significant increase in asthma-related non-fatal events in children (OR 1.72, 95% CI: 1.0 to 2.98) with salmeterol. Meta-analysis of trials comparing salmeterol to salbutamol (a SABA) showed no statistically significant differences in all-cause mortality or non-fatal serious adverse events.

Another systematic review published in 2007[283] 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.[274] 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 5 systematic reviews included in this section (Appendix K), one[282] 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.[282, 283] Twelve of 14 (86%) published studies included in the 2006 meta-analysis[282] were also included in the 2007 meta-analysis.[283] The 2007 analysis included studies of shorter duration, which partially accounted for the greater number of included studies.

An older systematic review[284] 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),[274] 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.[274] 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.[274]

Finally, another systematic review with meta-analysis[285] 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 dues to adverse effects. They did find an increased risk for tremor associated with LABA (RR 5.05; 95% CI: 1.33 to 19.17).

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 omilizumab. 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 seven fair to good quality RCTs[78, 80-83, 85, 86, 88, 91] and one systematic review with meta-analysis[93] 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 seven included RCTs, only one[83] focused on children (6-12 years old); one RCT focused only on adults 20-75 years of age and all others included adolescents and adults ≥12 years. The systematic review included six of the seven RCTs. These studies are described in detail in the

Key Question 1 section of this report and the detailed results are provided in the Evidence Tables.

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.[93] 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.[83] Wide variance in the occurrence of injection site reactions 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 applied 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.In the pediatric study, 1.8% of omalizumab- and 1.8% of placebo-treated patients withdrew because of pain or fear of injection.[83]

E. Combination Products ICS+LABA compared with ICS+LABA

1. ICS+LABA compared with ICS+LABA

Summary of findings

We found two good-quality systematic reviews [94, 281] (Table 29) and four head-to-head RCTs comparing fixed-dose budesonide/formoterol (BUD/FM) with fixed-dose fluticasone/salmeterol (FP/SM)[95-101] for maintenance therapy.

Overall, data from the two systematic reviews and the four large head-to-head trials (5,818 subjects) provide 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.(Appendix H, Table H-17)

Detailed Assessment

Description of Studies

Systematic review

We found 2 systematic reviews of good quality that compared the fixed-dose combination of an ICS plus a LABA with another ICS/LABA combination for controller therapy.[94, 281] One review included only randomized, controlled, parallel-design trials and required that only single inhaler devices were used to administer study drugs;[94] the other allowed administration by either single or multiple inhalers. Studies lasting fewer than 12 weeks or administering "adjustable maintenance dosing" or "single inhaler therapy" rather than fixed doses were excluded from both reviews.

One review has been described in detail in Key Question 1 (section IE) [94]. The other included eight studies, seven of which compared BUD/FM with FP/SM. The eighth compared

FP/SM with beclomethasone/FM, a comparison not relevant to this section of the report. Among the seven relevant studies in the 2010 review,[281] four were also included in the earlier review and in the RCT section of this report.[95, 97, 98]. An additional trial is also included in our RCT section but not the earlier review due to its delivery of study medications via separate inhalers[101], and results of one unpublished trial and one trial we deemed poor quality[102] were included in the earlier review but not in our report. Results from a second unpublished trial were not reported in either the earlier review, nor are they reported in our RCT section.

Doses of BUD and FM in the included trials ranged from 400-800 (320-640 ex-mouthpiece) mcg/day and 12-24 (9-18 ex-mouthpiece) mcg/day, respectively. All of the published studies administered 500mcg and 100mcg of FP and SM per day; the two unpublished studies administered 12mcg of FM daily and either 200 or 500mcg of FP daily. Included studies ranged from 12 weeks to 30 weeks and took place in the United States and Europe. The total number of participants in the seven relevant trials was 5,935. All included studies enrolled adolescents and adults (no studies in children were identified), and neither restricted asthma severity or current treatment. All included studies were funded by pharmaceutical manufacturers.

Randomized controlled trials

The studies that examined the efficacy of one fixed-dose combination treatment relative to another (described in Key Question 1) also reported tolerability and adverse events. All trials included adolescents and adults; Study duration ranged from 12 weeks to seven months. 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 in trials (Evidence Tables A and B). 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 (Evidence Tables A and B). Frequency of adverse events was similar between those treated with BUD/FM and those treated with FP/SM.

Table 29. Tolerability and frequency of adverse events results from systematic reviews comparing ICS+LABA with ICS+LABA

Study Design Comparison	Overall AEs	Withdrawals due to AEs	Specific AEs [odds ratio (CI)]
Cates et al. 2010[281] SR BUD/FM or BUD+FM compared with FP/SM	All-cause non-fatal SAE PETO OR = 1.14 (0.82, 1.59) Asthma-related non-fatal SAEs: Peto OR = 0.69 (0.37, 1.26)	NR	All-cause mortality: Peto OR = 1.03; 0.06-16.44
Lasserson et al. 2008[94] SR BUD/FM compared with FP/SM	Overall AEs: OR = 0.92 (0.76, 1.12) Asthma-related serious adverse event: OR = 0.53 (0.35, 1.33)	OR = 1.06 (0.68, 1.67)	Headache: 0.92 (0.70, 1.22) Candidiasis: 0.36 (0.25, 1.47) Dysphonia: 0.55 (0.41, 1.15) Upper respiratory tract infection: 0.91 (0.68, 1.23) Throat irritation: 0.61 (0.43, 1.22) Cough: 0.85 (0.49, 1.56) Tremor OR: 1.87 (0.96, 50)

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 head-to-head RCTs[98, 100, 103-106] 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. (Trial characteristics summarized in KQ 1 IE).

No studies reported statistical significance of differences between 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. Most of the trials reported a numerical trend favoring BUD/FM MART when considering withdrawals due to adverse events. The reported frequencies of specific adverse events do not suggest a difference between treatments. Because of heterogeneity of the reported safety data, we did not perform meta-analyses for tolerability or adverse events.

Detailed Assessment

Description of Studies

All four trials (five relevant comparisons) compared the combination of budesonide (BUD) plus formoterol (FM) *in a single DPI* for maintenance *and* as-needed relief with a fixed dose ICS/LABA combination plus a Short-Acting Beta-Agonist (SABA) for as-needed relief. Summary data for these trials can be found in Key Question 1 IE**.**

Head-to-head comparisons

1. Budesonide/formoterol for maintenance and relief (BUD/FM MART) compared with Inhaled corticosteroid/Long-Acting Beta Agonist (ICS/LABA) for maintenance and Short-Acting Beta-Agonist (SABA) for relief

The results of the four RCTs contributing five comparisons (one study compared BUD/FM MART with BUD/FM for maintenance and SABA for relief and with FP/SM for maintenance and SABA for relief) are described below under the appropriate drug comparisons. Overall, no studies reported statistical significance of differences between treatments. However, the reported frequencies of adverse events suggest either no difference or a trend toward favoring BUD/FM MART.

Most of the trials reported a numerical trend favoring BUD/FM MART when considering withdrawals due to adverse events. The few trials reporting occurrences of specific adverse events found no difference between treatments.

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

Neither trial comparing BUD/FM MART to BUD/FM for maintenance with a SABA for relief[98, 100, 103, 105] found a difference in adverse events between treatments. The percentage of patients experiencing at least one serious adverse event ranged from 3% to 7% among adults.
A subset analysis of the pediatric population of a larger study[103] found a trend favoring BUD/FM MART (2% of patients had a serious adverse event compared with 14%).

Rate of withdrawal due to adverse events was numerically higher in the BUD/FM+SABA arms of both trials. The magnitude differed between them, possibly due to inconsistency in the definition of an event. In one trial, 1.0% of patients in the BUD/FM MART arm and 1.2% in the BUD/FM+SABA arm withdrew due to adverse events.[98] In the other, 2.0% (BUD/FM MART) and 4.4% (BUD/FM+SABA) of patients withdrew due to adverse events.

Specific adverse events were reported in only one of the two trials.[103, 105] The most frequently reported events (those occurring in at least 5% of patients) were respiratory infection, pharyngitis, rhinitis, bronchitis, sinusitis and headache. There were no major qualitative differences between treatments for occurrence of those events, nor were there major qualitative differences in reports of tremor, palpitation, tachycardia, candidiasis or dysphonia, reports of which were rare. In the subset of children within that trial, there was a trend favoring BUD/FM MART for occurrences of serious adverse events, fractures, and pneumonia.

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

Three trials compared BUD/FM MART to FP/SM for maintenance with a SABA for relief.[98, 100, 104, 106] The percentage of patients experiencing at least one serious adverse event ranged from 3% to 8.2% among adults and adolescents. None of the three included children.

Rate of withdrawal due to adverse events was numerically higher in the FP/SM+SABA arms of two of the three trials.[104, 106] One percent and 1.2% of participants receiving BUD/FM

for maintenance and relief withdrew due to adverse events, compared with 1.7% and 2.0% of patients receiving FP/SM+SABA. One trial[104] reported withdrawals due to "class effect," a composite measure that included dysphonia, oral candidiasis, oral fungal infection, tremor, tachycardia, palpitations and headache. Fewer patients in the BUD/FM for maintenance and relief arm withdrew due to class effects compared with those receiving FP/SM+SABA, although the rate was <1% in each. In one trial,[106]27 (2.5%) and 28 (2.6%) patients in the BUD/FM MART and FP/SM+SABA arms, respectively, discontinued the study drug but remained in the trial.

In the third trial, the difference in withdrawals due to adverse event was 0.1% in favor of FP/SM+SABA. Deaths were reported in all three trials, though occurrence was rare. A total of 2 patients treated with BUD/FM MART and three patients receiving FP/SM+SABA treatment died during the trials. In the BUD/FM arms, one death was from severe typhoid fever and the other was due to respiratory failure. One of the patients receiving FP/SM died from cardiac failure; causes of the other two deaths were not specified.

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[107, 109] and 15 RCTs[110, 112-117, 119-127, 132] (Evidence Tables A and B). These were described in the Key Question 1 section of this report.

Overall, data from two good quality systematic reviews and numerous fair-rated head-to-head RCTs provides no evidence of a difference in tolerability or overall adverse events between ICSs and leukotriene modifiers. Of note, trials were generally not designed to compare tolerability and adverse events. Indirect evidence suggests that ICSs may increase the risk of cataracts and may decrease short term growth velocity and bone mineral density, none of which have been identified with LMs.

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 difficult 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-analysis[107] 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 (Evidence Table A). 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 – 1.6), which appeared to be due to poor asthma control (N = 17 trials, RR 2.6, 95% CI: 2.0 – 3.4) rather than due to adverse effects (N = 14 trials, RR 1.2, 95% CI: 0.9 – 1.6).

A second systematic review with meta-analysis[109] included 18 studies (N = 3,757) enrolling children and adolescents less than 18 years of age, 13 of which compared ICS therapy to that of ML. Six of the included trials also met our inclusion criteria[125, 126, 129-132]; seven did not. Duration of studies varied but ranged from 4-12 weeks, 24-28 weeks, and 48-56 weeks, with one study being 112 weeks long. While most of the studies included patients age 6-18, one study included children younger than 6 (2-8 years) for which a nebulizer was used for ICS administration. Intervention drugs included oral montelukast (4 to 10 mg) compared to either inhaled BDP 200-400 mcg/day (0.5 mg nebulized), FP 200 mcg/day, BUD 200-800 mcg/day or TAA 400 mcg/day.

Data related to adverse effects was available in five of the 18 trials. Overall, the meta-analysis reported no statistically significant difference between ICS- and ML-treated patients with respect to incidence of adverse effects (N = 1,767, RR 0.98, 95% CI 0.86 – 1.11, P = 0.73).

Overall tolerability and adverse events from individual head-to-head trials are summarized in Evidence Tables A and B. 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.[124] 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.

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 from 13 head-to-head trials (4,003 subjects) provides no evidence of a difference in overall adverse events between ICSs and LABAs in adults and adolescents.

Direct Evidence

We found 13 fair or good quality RCTs[135-139, 141-143, 145, 147-150] 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 (Evidence Tables A and B). 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).

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[151, 152] 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 (Evidence Tables A).

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).

B. Combination therapy

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

Summary of findings

We found one good systematic review[153] and 8 fair RCTs[138, 141, 154-156, 158-160] 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. Seven 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 8 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 12-52 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 both an inhaled corticosteroid and a LABA.

Detailed Assessment

Direct evidence

We found one good systematic review that was recently updated[153] and 8 fair RCTs[138, 141, 154-160]. Seven 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 1.02, 95% CI: 0.96, 1.09, 14 trials), withdrawals due to adverse events (RR 1.07, 95% CI: 0.67, 1.71, 11 trials), overall withdrawals (RR 0.95; 95% CI: 0.82, 1.11, 17 trials), or in any of the specific adverse events (including headache, oral candidiasis, or tremor).[153] 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 (Evidence Tables A and B). 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.[274, 282, 283] 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).

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 4 systematic reviews with meta-analysis[165-168] and 33 RCTs (37 publications)[53, 103, 105, 127, 157, 169-200] that included head-to-head comparisons between an ICS+LABA with a higher dose ICS meeting our inclusion/exclusion criteria. Seven trials[103, 105, 127, 185, 195, 197, 200] included children, and 2 enrolled an exclusively pediatric population under 12 years of age.[103, 195]

Overall, results from a good quality systematic review with meta-analysis[167] 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 4 systematic reviews with meta-analysis[165-168] and 33 RCTs[53, 103, 105, 127, 157, 169-200] 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. Twenty-one of the 33 (64%) administered the ICS and LABA in a single inhaler and twelve (36%) administered the ICS and LABA in separate inhalers. Although 6 trials[103, 105, 127, 185, 197, 200] included children, just one enrolled an exclusively pediatric population under 12 years of age.[103] The trials are described in the Key Question 1 section of the report.

The largest systematic review reported no difference in overall withdrawals (all reasons) (N = 39, RR 0.92, 95% CI: 0.84 to 1.00), overall side events (N = 30, RR 0..99, 95% CI: 0.95 to 1.03), or specific side effects, with the exception of an increase rate of tremor in the LABA group (N = 11, RR 1.84, 95% CI: 1.20 to 2.82), however this result became insignificant when a single study using a higher dose of LABA was removed from the analysis. The rate of withdrawals due to poor asthma control favored the combination of LABA and ICS (N = 29, RR 0.71, 95% CI: 0.56 to 0.91). The overall adverse events, withdrawals due to adverse events, and specific adverse events for the included RCTs appear consistent with these findings (Evidence Tables A and B).

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.[274, 282, 283] 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 3 systematic reviews with meta-analyses[166, 168, 203] and 32 RCTs (37 publications)[135-137, 139, 140, 142-144, 157, 173, 179, 180, 185, 198, 199, 204-219, 221-225, 288] that included head-to-head comparisons between an ICS+LABA with the same dose ICS meeting our inclusion/exclusion criteria (Table 20). Nine studies (28%) included pediatric populations under 12 years of age.[185, 212, 214, 215, 218, 219, 221, 222, 288]

Overall, results from a large good quality systematic review with meta-analysis and numerous RCTs[203] 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 = 12, RR 2.11, 95% CI: 0.83, 5.37) and tremor (N = 16, RR 1.74, 95% CI: 0.72, 4.20) 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 3 systematic reviews with meta-analyses[166, 168, 203]and and 33 RCTs (38 publications)[135-137, 139, 140, 142-144, 157, 173, 179, 180, 185, 198, 199, 204-225, 288] that included head-to-head comparisons between an ICS+LABA with the same dose ICS meeting our inclusion criteria (Table 20 and Evidence Tables A and B).

Eighteen of the 33 (54%) administered the ICS and LABA in a single inhaler, 10 administered them in separate inhalers, and 4 studies administered them both as a single inhaler and in separate inhalers to different study groups. Eight studies (24%) included pediatric populations under 12 years of age.[185, 212, 214, 215, 218-220, 288] With the exception of Li et al, these trials are described in greater detail in the Key Question 1 section of the report. Li et al only reports harms and did not report efficacy and effectiveness outcomes for Key Question 1.

The largest systematic review reported no difference between treatments in the risk of overall adverse effects (N = 41, RR 1.00, 95% CI: 0.97 to 1.04), withdrawals due to adverse effects (N = 52, RR 1.04, 95% CI: 0.86 to 1.26), or in any of the reported specific side effects including headache (N = 37, RR .99, 95% CI: 0.87 to 1.13), hoarseness (N = 6 comparisons, RR 0.1.17, 95% CI: 0.44 to 3.1), oral thrush (N = 9, RR 1.65, 95% CI: 0.71 to 3.86), tachycardia or palpitations (N = 12, RR 2.11, 95% CI: 0.83 to 5.37), cardiovascular adverse effects such as chest pain (N = 4, RR 0.90, 95% CI: 0.32 to 2.54), or tremor (N = 16, RR 1.74, 95% CI: 0.72 to 4.20). 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 A and B).

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.[274, 282, 283] 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-analysis[226] and two RCTs[228-230] 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-analysis[226] and two RCTs[228-230] meeting our inclusion/exclusion criteria (Evidence Tables A). 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 (Evidence Tables A).

One fair 16 week trial[230] (N = 639) reported similar rates of overall adverse events (41% compared with 44%; *P* = NR) and withdrawals due to adverse events (2% compared with 3%; *P* = 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).

One fair 16 week trial[228, 229] (N = 889) reported similar rates of overall adverse events (37.1% compared with 41.3%; *P* = 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.

5. Combination products compared with Leukotriene Modifiers

Summary of findings

We found 4 RCTs[127, 232-234] meeting our inclusion/exclusion criteria for this comparison. All three compared low dose fluticasone plus salmeterol with montelukast. Two of the RCTs were in adolescents and adults age 15 and older, one enrolled subjects over the age of six[127] (~15% of subjects were < 12 years of age), and one enrolled only children ages 6 to 14.[234]

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 4 short-term trials.

Detailed Assessment

Direct Evidence

We found 4 RCTs[127, 232-234] comparing low dose fluticasone plus salmeterol with montelukast. Two of the RCTs were in adolescents and adults, one enrolled subjects over the age of six[127] (~15% of subjects were < 12 years of age) and one enrolled only children age 6-14 years.[234]

The trials are described in more detail in the Key Question 1 section of the report. The four trials reporting withdrawals due to adverse events reported similar rates for those treated with ML and those treated with FP/SM. The 3 trials reporting overall adverse events also reported similar rates between groups (Evidence Tables A and B). One trial reported a greater incidence of upper respiratory tract infections for those treated with FP/SM than those treated with ML.[127]

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-analysis[235] and six RCTs[236-241] 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-analysis[235] and six RCTs.[236-241] All six of the RCTs were in adolescents and adults ≥ 12 years of age. Of the included studies (Evidence Tables A), 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 (Evidence Tables A).

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. 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]

A pooled analysis of 5 placebo-controlled trials of omalizumab aimed to evaluate the effectiveness of omalizumab among adolescents (n=146) with moderate to severe allergic asthma (a subset of the subjects enrolled in the 5 trials).[289] In this population, omalizumab improved asthma symptom scores and resulted in fewer exacerbations, school days missed, and unscheduled office visits (Evidence Tables B).

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 30).

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.[283] 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 Reseach Trial (SMART),[274] 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.[274]

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.[290]

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.[243] 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.[259] 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).[291] 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.[292] 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, 293, 294] 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 two observational studies 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.[295] 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.[296] Studies were eligible for inclusion in this analysis if the included women were exposed to any therapeutic doseage 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.

One observational study reported no significant differences between ICS- and non-ICS-treated mothers.[297] 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. A second observational study [298] aimed to investigate the association between doses of ICSs during the first trimester of pregnancy and the risk of congenital malformations among women with asthma. The study found that women using low to moderate doses of ICSs (>0 to 1000 µg/d equivalent BDP) were not at increased risk of having a baby with a malformation than women who did not use ICSs during the first trimester. Women using high doses of ICSs (>1000 µg/d) were more likely to have a baby with a malformation than women who used low to moderate doses (adjusted RR, 1.63; 95% CI, 1.02 to 2.60). However, these results should be interpreted with caution as confounding by severity of asthma cannot be ruled out as the cause of these findings.

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, 129, 299-303] 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 adrenorecptor gene (ADRB2) on response to beta-agonist therapy, but none have demonstrated clinical validity or clinical utility of testing for ADRB2 polymorphisms.[1, 299, 300, 303, 304] The only prospective RCT (N=544) to evaluate therapy with a LABA alone and in combination with an ICS found no evidence of a pharmacogenetic effect of β-receptor variation on salmeterol response.[304] It reported no difference over 16 weeks in response to salmeterol for various ADRB2 genotype (Arg/Arg vs. Gly/Gly vs. Arg/Gly).

Table 30. Summary of studies evaluating subgroups of patients for whom 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[283]	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.)	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[243]	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	No difference in proportion of Caucasian subjects with preferential[a] protection against treatment failure while using ICS + LABA (relative to an LTRA/LABA) as vs. that in the African-American subjects (*P* = 1.0)	Fair
Nelson et al. 2006[274] SMART	DB Randomized Observational study 26,355 28 weeks	US Age ≥ 12, asthma severity=NR; smoking status=NR Multicenter	SM (84 mcg/d) vs. placebo	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)	Fair
Smoking status					
Lazarus et al. 2007[292] SMOG study	RCT, DB, DD crossover 83 24 weeks (16 weeks with 8 week washout between)	US Age 18-50 Multicenter	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
Pregnancy					
Blais et al. 2009[298]	Cohort 13,280 pregnancies	Pregnant women with asthma Canada	no ICS use (8, 734 pregnancies)	Adjusted RRs, all malformations: G1: 1.08 (0.94-1.24) G2: Reference	Fair

Table 30. Summary of studies evaluating subgroups of patients for whom 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
			vs. >0-1000 µg/d (4,392 pregnancies) vs. >1,000 µg/d (154 pregnancies)	G3: 1.66 (1.02-2.68) Adjusted RRs, major malformations: G1: 1.06 (0.89-1.26) G2: Reference G3: 1.67 (0.91-3.06)	
Norjavaara & Gerhardsson de Verdier, 2003[297]	Database review 293,948	Pregnant asthmatic women (Swedish)	BUD vs. control (no BUD exposure during pregnancy)	No difference in gestational age, 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 ($P < 0.05$)	Fair
Rahimi et al. 2006[296]	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); $P = 0.9932$	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.

[a] 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

Strength of Evidence (SOE)

The main results of this review are summarized in Table 31. Summaries of the strength of evidence (SOE) for each comparison are presented in Appendix H. Efficacy studies provide moderate strength of evidence (SOE) that equipotent doses of ICSs administered through comparable delivery devices do not differ in their ability to control asthma symptoms, prevent exacerbations, reduce the need for additional rescue medication, or in the overall incidence of

adverse events or withdrawals due to adverse events. Evidence does not support a difference between montelukast and zafirlukast in their ability to decrease rescue medicine use or improve quality of life (low SOE for ≥12 years of age, insufficient <12), or between formoterol and salmeterol in their ability to control symptoms, prevent exacerbations, improve quality of life, or cause harms among patients not controlled on ICSs alone (moderate SOE). Evidence does not support a difference between budesonide/formoterol and fluticasone/salmeterol for efficacy or harms when each combination is administered via a single inhaler (moderate SOE for ≥12, insufficient <12).

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. Omalizumab-treated patients have an increased incidence of injection site reactions and anaphylaxis compared to placebo-treated patients.

Efficacy studies up to 56 weeks in duration provide consistent evidence of greater benefit for subjects treated with ICS monotherapy compared with those treated with LM monotherapy (high SOE). Direct evidence suggests no difference in tolerability or overall adverse events between ICSs and LMs (moderate SOE). Specific adverse events reported with ICSs, such as cataracts and decreased growth velocity, were not found among patients taking LMs. The best longer-term evidence on growth (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. Evidence is insufficient to determine if long-term treatment with ICSs leads to a reduction in final adult height. Overall evidence indicates that ICSs and leukotriene receptor antagonists (LTRAs) are safer than LABAs for use as monotherapy (high SOE). 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 suggests that the potential increased risk of asthma-related death for those taking LABAs may be confined to patients not taking ICSs at baseline.

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 routine use of combination therapy rather than an ICS alone as first line therapy (moderate SOE for ≥12, insufficient <12). Of note, FDA approved prescribing information and guidelines from the NAEPP suggest that combination therapy should only be used for patients not adequately controlled on a long-term asthma controller medication, such as an ICS, or whose disease severity clearly warrants initiation of treatment with both an inhaled corticosteroid and a LABA. 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 (high SOE for ≥12, low <12). 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 poorly controlled persistent asthma (high SOE). The addition of LMs to ICSs compared to continuing the same dose of ICSs resulted in improvement in rescue medicine use and no statistically significant differences in other health outcomes (low SOE for ≥12, insufficient <12). There is no apparent difference in symptoms, exacerbations, rescue medicine use, overall adverse events, or withdrawals due to adverse events between those treated with ICSs plus LTRAs compared to those treated with increasing the dose of ICSs (moderate SOE for ≥12, low <12). Results provide strong evidence that the addition of a LABA to ICS therapy (ICS+LABA) is more efficacious than the addition of an LTRAs to ICS therapy (ICS+LTRA) (high SOE for ≥12, low <12). We found no difference in overall adverse events or

withdrawals due to adverse events between ICS+LABA and ICS+ LTRAs (moderate SOE for ≥12, insufficient <12).

Limitations of this Report

As with other types of research, the limitations of this systematic review are important to recognize. These can be divided into 2 groups, those relating to applicability of the results (addressed below) and those relating to methodology within the scope of this review.

Methodological limitations of the review within the defined scope included the exclusion of studies published in languages other than English and lack of a specific search for unpublished studies. In addition, the data from RCTs included in this report have limited utility for assessing real-world adherence to medications. This is largely because they enrolled selected populations, often requiring a high degree of adherence to be included in the trial. For example, many of the trials had a run-in period during which adherence was assessed and then only included subjects that met a threshold for good adherence (e.g., adherence to 80% of recommended doses).

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.

Applicability

The applicability of the results are limited by the scope of the Key Questions and inclusion criteria and by the applicability of the studies included. Most studies included narrowly defined populations of patients who met strict criteria for case definition, had few comorbidities, and used few or no concomitant medications. Minorities, older patients, and the most seriously ill patients were often underrepresented.

Studies Currently Being Conducted

We identified no trials in progress that would meet inclusion criteria for this review that would potentially change conclusions.

Table 31. 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 1. What is the comparative efficacy and effectiveness of controller medications used to treat outpatients with persistent asthma?

Strength of evidence	Conclusions
	Inhaled Corticosteroids (ICSs) compared with ICSs:
Moderate (≥ 12 years)	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 years)	In children, the body of evidence supports the above conclusion, but data was only available for five comparisons (three systematic reviews and seven RCTs): beclomethasone compared with budesonide, beclomethasone compared with fluticasone, budesonide compared with ciclesonide, budesonide compared with fluticasone, and ciclesonide compared with fluticasone.
	Leukotriene Modifiers (LMs) compared with LMs:
Low (≥ 12 years)	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 years)	We found no head to head trials in children < 12 years of age.
	Long-Acting Beta-2 Agonists (LABAs) compared with LABAs:
Moderate (≥ 12 years)	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 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 missed school, but found a greater decrease in rescue medicine use in subjects treated with eformoterol compared to those treated with salmeterol.
	Anti-IgE Therapy (Omalizumab):
High (≥ 12 years)	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.

Key Question 1. What is the comparative efficacy and effectiveness of controller medications used to treat outpatients with persistent asthma?	
Strength of evidence	**Conclusions**
Moderate (< 12 years)	Limited evidence from two fair trials are available for children < 12 years of age. Both trials reported fewer exacerbations. Both reported no statistically significant difference in measures of symptoms. There were mixed results for other outcomes with one reporting less rescue medicine use, greater quality of life, and fewer emergency visits and hospitalizations for subjects treated with omalizumab and the other reporting no statistically significant difference for rescue medicine use or quality of life.
	Combination Products: Budesonide/Formoterol (BUD/FM) compared with Fluticasone/Salmeterol (FP/SM):
Moderate (≥ 12 years)	Results from large trials up to seven 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-analyses show no difference between those treated with BUD/FM and those treated with FP/SM in either exacerbations requiring oral steroids or exacerbations requiring emergency visit or hospital admission.
Insufficient (< 12 years)	None of the trials included children < 12 years of age.
	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:
Moderate (≥ 12 years)	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 when administered via a DPI. Meta-analyses of results from large trials (10,547 subjects) up to twelve months in duration including children and adults revealed that MART was associated with significantly lower odds of exacerbations requiring medical interventions (OR = 0.75; 95% CI: 0.66, 0.85) and of exacerbations resulting in emergency department visits or hospital admissions (OR = 0.73; 95% CI: 0.60, 0.90). MART was also associated with fewer nocturnal awakenings, compared with ICS/LABA + SABA, but no statistically significant difference in symptoms or rescue medicine use.
Moderate (< 12 years)	The one trial that included children found similar results. It enrolled children down to 4 years of age. 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.
	ICSs compared with Leukotriene Modifiers:
High (≥ 12 years)	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 = -0.17, 95% CI: -0.22, -0.12). 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)	

Key Question 1. What is the comparative efficacy and effectiveness of controller medications used to treat outpatients with persistent asthma?	
Strength of evidence	**Conclusions**
	ICSs compared with LABAs for monotherapy:
High (≥ 12 years)	LABAs are not recommended nor approved for use as monotherapy for persistent asthma because they may increase the risk of asthma-related deaths. 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 = 0.456; 95% CI = 0.225, 0.688; *P* < 0.001; 2 studies).
High (< 12 years)	
	Leukotriene Modifiers compared with LABAs for monotherapy:
Insufficient (≥ 12 years)	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:
Moderate (≥ 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 same-dose ICS alone for initial therapy. However, limited data were 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., 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.
	ICS+LABA compared with ICS (increased dose) (addition of LABA to ICS compared with increasing the ICS dose):
High (≥ 12 years)	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 results are not necessarily generalizable to pediatric populations.
	ICS+LABA compared with ICS (same dose) (addition of LABA to ICS compared with continuing same dose ICS):
High (≥ 12 years)	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.

Key Question 1. What is the comparative efficacy and effectiveness of controller medications used to treat outpatients with persistent asthma?	
Strength of evidence	**Conclusions**
High (< 12 years)	Nine trials included pediatric populations < 12 years of age.
	ICS+LTRA compared with ICS (same dose):
Low (≥ 12 years)	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.
	ICS+LTRA compared with ICS (increased dose):
Moderate (≥ 12 years)	There is no apparent difference in symptoms, exacerbations, or rescue medicine use 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)	Two trials enrolled children < 12 years of age. One 12-week trial conduced in India reported fewer exacerbations in those treated with ICS+LTRA compared to increasing the dose of BUD. The other reported no difference between groups for hospitalizations due to asthma and similar numbers of oral steroid courses (43 vs. 47, *P* = NR)
	Combination products (ICS/LABA) compared with LTRAs:
High (≥ 12 years)	Overall, our meta-analysis and results from 5 RCTs find the combination of fluticasone plus salmeterol to be more efficacious than montelukast for the treatment of persistent asthma.
Moderate (< 12 years)	Two of the trials enrolled children ages 6-14 and another included about 15% of subjects < 12 years of age.
	ICS+LABA compared with ICS+LTRA (addition of LABA compared with LTRA to ongoing ICS therapy):
High (≥ 12 years)	Overall, results from a good quality systematic review with meta-analysis and eight 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.
Low (< 12 years)	We found one trial including children < 12 years of age. It enrolled 182 subjects 6 to 17 years of age and reported results consistent with those from trials in adolescents and adults (i.e., the addition of a LABA to ICS therapy was more efficacious).
	LTRA+LABA compared with ICS+LABA:
Moderate (≥ 12 years)	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 1. What is the comparative efficacy and effectiveness of controller medications used to treat outpatients with persistent asthma?	
Strength of evidence	**Conclusions**
	Long-acting anticholinergics:
Insufficient (all ages)	Tiotropium is not approved for the treatment of asthma. It is approved for the treatment of chronic obstructive pulmonary disease (COPD). We found no studies of tiotropium meeting our inclusion criteria for any key question.

Key Question 2. What is the comparative tolerability and frequency of adverse events for controller medications used to treat outpatients with persistent asthma?	
Strength of evidence	**Conclusions**
	Inhaled Corticosteroids (ICSs):
Moderate (≥ 12 years)	The overall incidence of adverse events, withdrawals due to adverse events, and specific adverse events (other than reduction in growth velocity and oral candidiasis) are similar for equipotent doses of ICSs.
Moderate (< 12 years)	Three fair head-to-head trials provide evidence that short-term (20 weeks to 1 year) growth velocity is reduced less with fluticasone than with beclomethasone or budesonide. A forth head-to-head trial found that ciclesonide-treated subjects had a greater mean body height increase than budesonide-treated subjects over 12 weeks. 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.
Moderate	Meta-analysis of trials reporting “oral candidiasis-thrush” that compared equipotent doses of ciclesonide with FP revealed lower odds of oral candidiasis-thrush for those treated with ciclesonide (OR 0.33, 95% CI 0.17, 0.64).
Insufficient	Evidence is insufficient to determine if long-term treatment with ICSs leads to a reduction in final adult height.
	Leukotriene Modifiers:
Moderate (≥ 12 years) **Moderate** (< 12 years)	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.
	Long-Acting Beta-2 Agonists (LABAs):
Moderate (≥ 12 years) **Moderate** (< 12 years)	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.
	Anti-IgE Therapy (Omalizumab):
High (all ages)	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 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.

Key Question 2. What is the comparative tolerability and frequency of adverse events for controller medications used to treat outpatients with persistent asthma?	
Strength of evidence	**Conclusions**
	Combination Products: Budesonide/Formoterol (BUD/FM) compared with Fluticasone/Salmeterol (FP/SM):
Moderate (≥ 12 years)	Data from four large head-to-head trials (5,818 subjects) provide 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 ≤ 12.
	Combination Products: BUD/FM for maintenance and relief compared with ICS/LABA combination 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 when administered via a DPI.
Low (all ages)	No studies reported statistical significance of differences between 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. The reported frequencies of adverse events do not suggest a difference between treatments.
	ICSs compared with Leukotriene Modifiers:
Moderate (≥ 12 years)	Data from two good quality systematic reviews 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.
Moderate (< 12 years)	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.
	ICSs compared with LABAs for monotherapy:
High (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. Overall evidence indicates that ICSs are safer than LABAs for use as monotherapy.
	Leukotriene Modifiers compared with LABAs for monotherapy:
High (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.
	ICS+LABA compared with ICS (same dose) as first line therapy:
Moderate (≥ 12 years)	Results from a good quality systematic review with meta-analysis and 8 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 12-52 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.

Key Question 2. What is the comparative tolerability and frequency of adverse events for controller medications used to treat outpatients with persistent asthma?	
Strength of evidence	**Conclusions**
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.
	ICS+LABA compared with ICS (increased dose) **(addition of LABA to ICS compared with increasing the ICS dose):**
Moderate (≥ 12 years)	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 = 11, RR 1.84, 95% CI: 1.20 to 2.82). 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.
Low (< 12 years)	Two of the RCTs enrolled an exclusively pediatric population < 12 years of age (7 included some subjects < 12) and results are not necessarily applicable to pediatric populations.
	ICS+LABA compared with ICS (same dose) **(addition of LABA to ICS compared with continuing same dose ICS):**
Moderate (≥ 12 years)	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 = 12, RR 2.11, 95% CI: 0.83 to 5.37) and tremor (N = 16, RR 1.74, 95% CI: 0.72 to 4.20) 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.
Low (< 12 years)	Nine studies (27%) included pediatric populations under 12 years of age
	ICS+LTRA compared with ICS (same dose):
Moderate (≥ 12 years)	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.
Low (< 12 years)	Evidence in children < 12 years of age is limited. Just two of the 27 trials in the systematic review enrolled children.
	ICS+LTRA compared with ICS (increased dose):
Moderate (≥ 12 years)	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.
Low (< 12 years)	Evidence in children < 12 years of age is limited. Just two of the 27 trials in the systematic review enrolled children.

Key Question 2. What is the comparative tolerability and frequency of adverse events for controller medications used to treat outpatients with persistent asthma?	
Strength of evidence	**Conclusions**
	Combination products (ICS/LABA) compared with LTRAs:
Low (≥ 12 years)	ICS/LABA combinations and leukotriene modifiers have similar rates of overall adverse events and withdrawals due to adverse events based on direct evidence from 4 short-term trials.
Low (< 12 years)	One of the 4 trials enrolled subjects at least six years of age (about 15% were <12 years old) and one enrolled only children ages 6 to 14
	ICS+LABA compared with ICS+LTRA (addition of LABA compared with LTRA to ongoing ICS therapy):
Moderate (≥12 years)	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?	
Strength of evidence	**Conclusions**
	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
Insufficient	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.
	Racial groups:
Low	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 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.
	Gender:
Insufficient	We did not find any study reporting a difference between the included medications.
	Comorbidities:
Insufficient	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.
	Other medications (drug-drug interactions):
Insufficient	We did not find any studies meeting our inclusion/exclusion criteria that examined the

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?	
Strength of evidence	**Conclusions**
	impact of other medications on the comparative efficacy, tolerability, or adverse events of our included medications.
	Smoking status:
Low	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.
	Pregnancy:
Insufficient	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.
	Genetics:
Insufficient	To date, there is not sufficient evidence to determine whether genetic polymorphisms in general result in clinically important differences in responses to asthma medications. Multiple studies have investigated the impact of polymorphisms on response to various asthma treatments, but none have demonstrated clinical validity or clinical utility of testing for polymorphisms.
Low	One RCT provides low strength of evidence of no difference in response to salmeterol (with or without ICSs) for people with various ADRB2 (Beta-2 adrenorecptor gene) genotypes (Arg/Arg vs. Gly/Gly vs. Arg/Gly)

CONCLUSIONS

Overall findings do not suggest that one medication within any of the classes evaluated is significantly more effective or harmful than the other medications within the same class, with the exception of zileuton being more harmful than the other LMs. Our results support the general clinical practice of starting initial treatment for persistent asthma with an ICS. For people with poorly controlled persistent asthma taking an ICS, our findings suggest that the addition of a LABA is most likely to provide the greatest benefit as the next step in treatment.

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Appendix A. 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 interval 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 combing 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 B. Abbreviations

Abbreviaton	Term
ACTH	adrenocorticotropin hormone
AD	adjustable dosing
AQLQ	Asthma Quality of Life Questionnaire
ARF	Arformoterol
BDP	beclomethasone dipropionate
BMD	bone mineral density
BUD	budesonide
CFC	chlorofluorocarbon
CI	confidence interval
CIC	ciclesonide
COPD	chronic obstructive pulmonary disease
DPI	dry powder inhaler
ED	emergency department
FD	fixed dosing
FEV1	forced expired volume in one second
FLUN	flunisolide
FP	fluticasone propionate
FM	formoterol
FVC	forced vital capacity
GINA	Global Initiative for Asthma
HFA	hydrofluoroalkane
HPA	hypothalamo-pituitary-adrenal
HR	hazard ratio
ICS	inhaled corticosteroid
IS	inhalation suspension
ITT	intent to treat
LABA	long-acting beta-agonist
LM	leukotriene modifiers
LOCF	last observation carried forward
LTRA	leukotriene receptor antagonist
LTSI	leukotriene synthesis inhibitor
MART	maintenance and reliever therapy
MDI	metered dose inhaler
MOM	mometasone
ML	montelukast
NAEPP	National Asthma Education and Prevention Program
NHLBI	National Heart, Lung and Blood Institute
NA	not applicable
NR	not reported
NS	not statistically significant

Abbreviaton	Term
OCS	oral corticosteroids
OM	omalizumab
OR	odds ratio
PEF	peak expiratory flow
pMDI	pressurized metered dose inhaler
QOL	quality of life
RR	relative risk
SF-36	Medical Outcomes Study Short Form-36
SGRQ	St. George Respiratory Questionnaire
SM	salmeterol
SMART	Symbicort® maintenance and reliever therapy
SMD	standard mean difference (standard difference in means)
TAA	triamcinolone acetonide
WMD	weighted mean difference

Appendix C. Boxed warnings

Trade name	Active ingredient(s)	Boxed warnings
Qvar®	Beclomethasone	No Box
Vanceril®	Beclomethasone	No Box
Pulmicort Turbuhaler®	Budesonide	No Box
Pulmicort Flexhaler®	Budesonide	No Box
Pulmicort Respules®	Budesonide	No Box
Pulmicort Nebuamp®	Budesonide	No Box
AeroBid®	Flunisolide	No Box
AeroBid-M®	Flunisolide	No Box
AeroSpan®	Flunisolide	No Box
Bronalide®	Flunisolide	No Box
Flovent®	Fluticasone	No Box
Flovent Rotadisk®	Fluticasone	No Box
Flovent Diskus®	Fluticasone	No Box
Flovent HFA®	Fluticasone	No Box
Azmacort®	Triamcinolone	No Box
Asmanex Twisthaler®	Mometasone	No Box
Alvesco®	Ciclesonide	No Box
Foradil®	Formoterol	Long-acting beta2-adrenergic agonists (LABA), such as formoterol the active ingredient in FORADIL, increase the risk of asthma-related death. Data from a large placebo-controlled US study that compared the safety of another LABA (salmeterol) or placebo added to usual asthma therapy showed an increase in asthma-related deaths in patients receiving salmeterol. This finding with salmeterol is considered a class effect of LABA, including formoterol. Currently available data are inadequate to determine whether concurrent use of inhaled corticosteroids or other long-term asthma control drugs mitigates the increased risk of asthma-related death from LABA. Because of this risk, use of FORADIL for the treatment of asthma without a concomitant long-term asthma control medication, such as an inhaled corticosteroid, is contraindicated. Use FORADIL only as additional therapy for patients with asthma who are currently taking but are inadequately controlled on a long-term asthma control medication, such as an inhaled corticosteroid. Once asthma control is achieved and maintained, assess the patient at regular intervals and step down therapy (e.g. discontinue FORADIL) if possible without loss of asthma control, and maintain the patient on a long-term asthma control medication, such as an inhaled corticosteroid. Do not use FORADIL for patients whose asthma is adequately controlled on low or medium dose inhaled corticosteroids.

Trade name	Active ingredient(s)	Boxed warnings
Certihaler®	Formoterol	Long-acting beta2-adrenergic agonists (LABA), such as formoterol the active ingredient in CERTIHALER, increase the risk of asthma-related death. Data from a large placebo-controlled US study that compared the safety of another LABA (salmeterol) or placebo added to usual asthma therapy showed an increase in asthma-related deaths in patients receiving salmeterol. This finding with salmeterol is considered a class effect of LABA, including formoterol. Currently available data are inadequate to determine whether concurrent use of inhaled corticosteroids or other long-term asthma control drugs mitigates the increased risk of asthma-related death from LABA. Because of this risk, use of CERTIHALER for the treatment of asthma without a concomitant long-term asthma control medication, such as an inhaled corticosteroid, is contraindicated. Use CERTIHALER only as additional therapy for patients with asthma who are currently taking but are inadequately controlled on a long-term asthma control medication, such as an inhaled corticosteroid. Once asthma control is achieved and maintained, assess the patient at regular intervals and step down therapy (e.g. discontinue CERTIHALER) if possible without loss of asthma control, and maintain the patient on a long-term asthma control medication, such as an inhaled corticosteroid. Do not use CERTIHALER for patients whose asthma is adequately controlled on low or medium dose inhaled corticosteroids.
Foradil Aerolizer®	Formoterol	Long-acting beta2-adrenergic agonists (LABA), such as formoterol the active ingredient in FORADIL AEROLIZER, increase the risk of asthma-related death. Data from a large placebo-controlled US study that compared the safety of another LABA (salmeterol) or placebo added to usual asthma therapy showed an increase in asthma-related deaths in patients receiving salmeterol. This finding with salmeterol is considered a class effect of LABA, including formoterol. Currently available data are inadequate to determine whether concurrent use of inhaled corticosteroids or other long-term asthma control drugs mitigates the increased risk of asthma-related death from LABA. Because of this risk, use of FORADIL AEROLIZER for the treatment of asthma without a concomitant long-term asthma control medication, such as an inhaled corticosteroid, is contraindicated. Use FORADIL AEROLIZER only as additional therapy for patients with asthma who are currently taking but are inadequately controlled on a long-term asthma control medication, such as an inhaled corticosteroid. Once asthma control is achieved and maintained, assess the patient at regular intervals and step down therapy (e.g. discontinue FORADIL AEROLIZER) if possible without loss of asthma control, and maintain the patient on a long-term asthma control medication, such as an inhaled corticosteroid. Do not use FORADIL AEROLIZER for patients whose asthma is adequately controlled on low or medium dose inhaled corticosteroids.
Oxis®	Eformoterol	No Box (not available in the US or Canada)
Perforomist®	Formoterol	Long-acting beta2-adrenergic agonists (LABA) increase the risk of asthma-related death. Data from a large placebo-controlled US study that compared the safety of another long-acting beta2-adrenergic agonist (salmeterol) or placebo added to usual asthma therapy showed an increase in asthma-related deaths in patients receiving salmeterol. This finding with salmeterol is considered a class effect of LABA, including formoterol, the active ingredient in PERFOROMIST Inhalation Solution. The safety and efficacy of PERFOROMIST in patients with asthma have not been established. All LABA, including PERFOROMIST, are contraindicated in patients with asthma without use of a long-term asthma control medication.

Trade name	Active ingredient(s)	Boxed warnings
Oxeze Turbuhaler®	Formoterol	Data from a large placebo-controlled US study (Salmeterol Multi-center Asthma Research Trial) comparing the safety of the long-acting beta2-adrenergic agonist salmeterol to that of a placebo added to the original asthma therapy showed an increase in asthma-related deaths in patients receiving salmeterol. Although the trial results were specific to salmeterol, one of the conclusions derived from this study is that long-acting beta2-adrenergic agonists may increase the risk of asthma exacerbation and possibly asthma-related death. Although available data for formoterol fumarate dihydrate do not suggest increased risk, it cannot be excluded that the findings with salmeterol may apply to all longacting beta2-adrenergic agonists including formoterol fumarate dihydrate, the active ingredient in OXEZE TURBUHALER. When treating asthma patients, OXEZE TURBUHALER should be used only as additional therapy for patients whose conditions are not adequately controlled using low-to-medium dose inhaled corticosteroids or whose disease severity clearly warrants the initiation of treatment with two maintenance therapies, i.e. OXEZE TURBUHALER in addition to an inhaled corticosteroid. (Canadian labeling)
Brovana®	Arformoterol	Long-acting beta2 –adrenergic agonists (LABA) increase the risk of asthma-related death. Data from a large placebo-controlled US study that compared the safety of another long-acting beta2 –adrenergic agonist (salmeterol) or placebo added to usual asthma therapy showed an increase in asthma-related deaths in patients receiving salmeterol. This finding with salmeterol is considered a class effect of LABA, including arformoterol, the active ingredient in BROVANA . The safety and efficacy of BROVANA in patients with asthma have not been established. All LABA, including BROVANA, are contraindicated in patients with asthma without the use of a long-term asthma control medications
Serevent®	Salmeterol	Long-acting beta2-agonists (LABAs), such as salmeterol, the active ingredient in SEREVENT, increase the risk of asthma-related death. Currently available data are inadequate to determine whether concurrent use of inhaled corticosteroids or other long-term asthma control drugs mitigates the increased risk of asthma-related death from LABA. Because of this risk, use of SEREVENT for the treatment of asthma without concomitant use of a long-term asthma control medication, such as an inhaled corticosteroid, is contraindicated. Use SEREVENT only as additional therapy for patients with asthma who are currently taking but are inadequately controlled on a long-term asthma control medication, such as an inhaled corticosteroid. Once asthma control is achieved and maintained, assess the patient at regular intervals and step down therapy (e.g., discontinue SEREVENT) if possible without loss of asthma control and maintain the patient on a long-term asthma control medication, such as an inhaled corticosteroid. Do not use SEREVENT for patients whose asthma is adequately controlled on low- or medium-dose inhaled corticosteroids.
Serevent Diskhaler®	Salmeterol	Long-acting beta2-agonists (LABAs), such as salmeterol, the active ingredient in SEREVENT DISKHALER, increase the risk of asthma-related death. Currently available data are inadequate to determine whether concurrent use of inhaled corticosteroids or other long-term asthma control drugs mitigates the increased risk of asthma-related death from LABA. Because of this risk, use of SEREVENT DISKHALER for the treatment of asthma without concomitant use of a long-term asthma control medication, such as an inhaled corticosteroid, is contraindicated. Use SEREVENT DISKHALER only as additional therapy for patients with asthma who are currently taking but are inadequately controlled on a long-term asthma control medication, such as an inhaled corticosteroid. Once asthma control is achieved and maintained, assess the patient at regular intervals and step down therapy (e.g., discontinue SEREVENT DISKHALER) if possible without loss of asthma control and maintain the patient on a long-term asthma control medication, such as an inhaled corticosteroid. Do not use SEREVENT DISKHALER for patients whose asthma is adequately controlled on low- or medium-dose inhaled corticosteroids.

Trade name	Active ingredient(s)	Boxed warnings
Serevent Diskus®	Salmeterol	Long-acting beta2-agonists (LABAs), such as salmeterol, the active ingredient in SEREVENT DISKUS, increase the risk of asthma-related death. Currently available data are inadequate to determine whether concurrent use of inhaled corticosteroids or other long-term asthma control drugs mitigates the increased risk of asthma-related death from LABA. Because of this risk, use of SEREVENT DISKUS for the treatment of asthma without concomitant use of a long-term asthma control medication, such as an inhaled corticosteroid, is contraindicated. Use SEREVENT DISKUS only as additional therapy for patients with asthma who are currently taking but are inadequately controlled on a long-term asthma control medication, such as an inhaled corticosteroid. Once asthma control is achieved and maintained, assess the patient at regular intervals and step down therapy (e.g., discontinue SEREVENT DISKUS) if possible without loss of asthma control and maintain the patient on a long-term asthma control medication, such as an inhaled corticosteroid. Do not use SEREVENT DISKUS for patients whose asthma is adequately controlled on low- or medium-dose inhaled corticosteroids.
Singulair®	Montelukast	No Box
Accolate®	Zafirlukast	No Box
Zyflo®	Zileuton	No Box
ZyfloCR®	Zileuton	No Box
Xolair®	Omalizumab	Anaphylaxis has been reported to occur after administration of Xolair in premarketing clinical trials and in postmarketing spontaneous reports. Signs and symptoms in these reported cases have included bronchospasm, hypotension, syncope, urticaria, and/or angioedema of the throat or tongue. Some of these events have been life-threatening. In premarketing clinical trials the frequency of anaphylaxis attributed to Xolair use was estimated to be 0.1%. In postmarketing spontaneous reports, the frequency of anaphylaxis attributed to Xolair use was estimated to be at least 0.2% of patients based on an estimated exposure of about 57,300 patients from June 2003 through December 2006. Anaphylaxis has occurred as early as after the first dose of Xolair, but also has occurred beyond one year after beginning regularly scheduled treatment. Administer Xolair only in a healthcare setting by healthcare providers prepared to manage anaphylaxis that can be life-threatening. Observe patients closely for an appropriate period of time after administration of Xolair, taking into account the time to onset of anaphylaxis seen in premarketing clinical trials and postmarketing spontaneous reports [see Adverse Reactions (6)]. Inform patients of the signs and symptoms of anaphylaxis, and instruct them to seek immediate medical care should signs or symptoms occur. Discontinue Xolair in patients who experience a severe hypersensitivity reaction [see Contraindications (4)].

Trade name	Active ingredient(s)	Boxed warnings
Advair®	Fluticasone propionate/Salmeterol xinafoate	Long-acting beta2-agonists (LABAs), such as salmeterol, one of the active ingredients in ADVAIR, increase the risk of asthma-related death. Currently available data are inadequate to determine whether concurrent use of inhaled corticosteroids or other long-term asthma control drugs mitigates the increased risk of asthma-related death from LABAs. Available data from controlled clinical trials suggest that LABAs increase the risk of asthma-related hospitalization in pediatric and adolescent patients. Therefore, when treating patients with asthma, physicians should only prescribe ADVAIR for patients not adequately controlled on a long-term asthma-control medication, such as an inhaled corticosteroid, or whose disease severity clearly warrants initiation of treatment with both an inhaled corticosteroid and a LABA. Once asthma control is achieved and maintained, assess the patient at regular intervals and step down therapy (e.g., discontinue ADVAIR) if possible without loss of asthma control and maintain the patient on a long-term asthma control medication, such as an inhaled corticosteroid. Do not use ADVAIR for patients whose asthma is adequately controlled on low- or medium-dose inhaled corticosteroids.
Advair Diskus®	Fluticasone propionate/Salmeterol xinafoate	Long-acting beta2-agonists (LABAs), such as salmeterol, one of the active ingredients in ADVAIR DISKUS, increase the risk of asthma-related death. Currently available data are inadequate to determine whether concurrent use of inhaled corticosteroids or other long-term asthma control drugs mitigates the increased risk of asthma-related death from LABAs. Available data from controlled clinical trials suggest that LABAs increase the risk of asthma-related hospitalization in pediatric and adolescent patients. Therefore, when treating patients with asthma, physicians should only prescribe ADVAIR DISKUS for patients not adequately controlled on a long-term asthma-control medication, such as an inhaled corticosteroid, or whose disease severity clearly warrants initiation of treatment with both an inhaled corticosteroid and a LABA. Once asthma control is achieved and maintained, assess the patient at regular intervals and step down therapy (e.g., discontinue ADVAIR DISKUS) if possible without loss of asthma control and maintain the patient on a long-term asthma control medication, such as an inhaled corticosteroid. Do not use ADVAIR DISKUS for patients whose asthma is adequately controlled on low- or medium-dose inhaled corticosteroids.
Advair HFA®	Fluticasone propionate/Salmeterol xinafoate	Long-acting beta2-agonists (LABAs), such as salmeterol, one of the active ingredients in ADVAIR HFA, increase the risk of asthma-related death. Currently available data are inadequate to determine whether concurrent use of inhaled corticosteroids or other long-term asthma control drugs mitigates the increased risk of asthma-related death from LABAs. Available data from controlled clinical trials suggest that LABAs increase the risk of asthma-related hospitalization in pediatric and adolescent patients. Therefore, when treating patients with asthma, physicians should only prescribe ADVAIR HFA for patients not adequately controlled on a long-term asthma-control medication, such as an inhaled corticosteroid, or whose disease severity clearly warrants initiation of treatment with both an inhaled corticosteroid and a LABA. Once asthma control is achieved and maintained, assess the patient at regular intervals and step down therapy (e.g., discontinue ADVAIR HFA) if possible without loss of asthma control and maintain the patient on a long-term asthma control medication, such as an inhaled corticosteroid. Do not use ADVAIR HFA for patients whose asthma is adequately controlled on low- or medium-dose inhaled corticosteroids.

Trade name	Active ingredient(s)	Boxed warnings
Symbicort®	Budesonide/formoterol	Long-acting beta2-adrenergic agonists, such as formoterol, one of the active ingredients in SYMBICORT, increase the risk of asthma-related death. Currently available data are inadequate to determine whether concurrent use of inhaled corticosteroids or other long-term asthma control drugs mitigates the increased risk of asthma-related death from LABA. Available data from controlled clinical trials suggest that LABA increase the risk of asthma-related hospitalization in pediatric and adolescent patients. Therefore, when treating patients with asthma, SYMBICORT should only be used for patients not adequately controlled on a long-term asthma-control medication, such as an inhaled corticosteroid or whose disease severity clearly warrants initiation of treatment with both an inhaled corticosteroid and LABA. Once asthma control is achieved and maintained, assess the patient at regular intervals and step down therapy (e.g. discontinue SYMBICORT) if possible without loss of asthma control, and maintain the patient on a long-term asthma control medication, such as an inhaled corticosteroid. Do not use SYMBICORT for patients whose asthma is adequately controlled on low or medium dose inhaled corticosteroids.
Symbicort Turbuhaler®	Budesonide/formoterol	Long-acting beta2-adrenergic agonists, such as formoterol, one of the active ingredients in SYMBICORT TURBUHALER, increase the risk of asthma-related death. Currently available data are inadequate to determine whether concurrent use of inhaled corticosteroids or other long-term asthma control drugs mitigates the increased risk of asthma-related death from LABA. Available data from controlled clinical trials suggest that LABA increase the risk of asthma-related hospitalization in pediatric and adolescent patients. Therefore, when treating patients with asthma, SYMBICORT TURBUHALER should only be used for patients not adequately controlled on a long-term asthma-control medication, such as an inhaled corticosteroid or whose disease severity clearly warrants initiation of treatment with both an inhaled corticosteroid and LABA. Once asthma control is achieved and maintained, assess the patient at regular intervals and step down therapy (e.g. discontinue SYMBICORT TURBUHALER) if possible without loss of asthma control, and maintain the patient on a long-term asthma control medication, such as an inhaled corticosteroid. Do not use SYMBICORT TURBUHALER for patients whose asthma is adequately controlled on low or medium dose inhaled corticosteroids.
Spiriva®	Tiotropium	No Box

Appendix D. Labeled and delivered doses

Examples of variation in labeled and delivered doses of inhaled asthma controller medications

Brand Name/Product (Generic Name)	Labeled Dose (mcg)	"Ex-Valve" Dose (mcg)	"Ex-Actuator Dose" (Delivered Dose, mcg)
Advair Diskus® DPI (fluticasone/salmeterol)	100/50 250/50 500/50	100/50 250/50 500/50	93/45 233/45 465/45
Alvesco® (ciclesonide)	80 160	100 200	80 160
Flovent Diskus® (fluticasone)	50 100 250	50 100 250	46 94 229
Flovent® HFA (fluticasone)	44 110 220	50 125 250	44 110 220
Foradil Aerolizer® DPI (formoterol)	12	12	10
Pulmicort Flexhaler® (budesonide)	180 90	180 90	160 80
QVAR® HFA (beclomethasone)	40 80	50 100	40 80
Serevent Diskus® (salmeterol)	50	50	47
Serevent® Inhalation Aerosol (salmeterol)	21	25	21
Symbicort Turbuhaler® (budesonide/formoterol) **Available in Canada**	100/6 200/6	100/6 200/6	80/4.5 160/4.5
Symbicort® (budesonide/formoterol)	80/4.5 160/4.5	91/5.1 181/5.1	80/4.5 160/4.5

Appendix E. Search strategies

Original Report

#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 perforomist 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 Studies"[MeSH] OR "Retrospective Studies"[MeSH] OR observational studies	1017347
#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 singulair 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 singulair 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 perforomist OR "salmeterol "[Substance	89

	Name] OR serevent) AND systematic[sb]	
#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

Search Strategies: Asthma Medication Update 1
19 March 2010

Search	Most Recent Queries	Result
#1	Search "Asthma"[Majr]	73021
#2	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	18315
#3	Search ("Adrenergic beta-Agonists"[Mesh] AND "long acting") OR "formoterol "[Substance Name] OR foradil OR oxis OR perforomist OR "salmeterol "[Substance Name] OR serevent	3100
#4	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	3349
#5	Search Anti-IgE OR "omalizumab "[Substance Name] OR xolair	2926
#6	Search "fluticasone, salmeterol drug combination "[Substance Name] OR "fluticasone propionate - salmeterol combination "[Substance Name] OR advair OR budesonide-formoterol OR "symbicort "[Substance Name]	317
#7	Search "tiotropium "[Substance Name] OR Spiriva	514
#8	Search "ciclesonide "[Substance Name] OR Alvesco	204
#9	Search ("Randomized Controlled Trial"[Publication Type] OR "Randomized Controlled Trials as Topic"[MeSH]) OR "Single-Blind Method"[MeSH] OR "Double-Blind Method"[MeSH] OR "Random Allocation"[MeSH]	413141
#10	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	1181884
#11	Search #1 AND #2	5414
#12	Search #1 AND #3	1604
#13	Search #1 AND #4	1406
#14	Search #1 AND #5	508
#15	Search #1 AND #6	189
#16	Search #1 AND #7	27
#17	Search #1 AND #8	102
#18	Search #11 AND #9	1924
#19	Search #11 AND #10	896
#20	Search #12 AND #9	752
#21	Search #12 AND #10	186
#22	Search #13 AND #9	419

#23 Search #13 AND #10	160
#24 Search #14 AND #9	80
#25 Search #14 AND #10	20
#26 Search #15 AND #9	112
#27 Search #15 AND #10	21
#28 Search #16 AND #9	7
#29 Search #16 AND #10	2
#30 Search #17 AND #9	54
#31 Search #17 AND #10	7
#32 Search #18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25 OR #26 OR #27	3234
#33 Search (#32) AND "2008/01/01"[Entrez Date] : "3000"[Entrez Date]	387
#34 Search #28 OR #29 OR #30 OR #31	67
#35 Search #34 OR #33	443
#36 Search #35 Limits: Animals	8
#37 Search #35 NOT #36	435
#38 Search #37 Limits: English Sort by: PublicationDate	406

PubMed: 406
Cochrane Database: 202 (418-216 duplicates)
IPA: 131 (220-89 duplicates)
EMBASE: 153 (372-219 duplicates)

27 September 2010

Search	Most Recent Queries	Result
#1	Search "Asthma"[Majr]	74620
#2	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	18893
#3	Search ("Adrenergic beta-Agonists"[Mesh] AND "long acting") OR "formoterol "[Substance Name] OR foradil OR oxis OR perforomist OR "salmeterol "[Substance Name] OR serevent	3272
#4	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	3477
#5	Search Anti-IgE OR "omalizumab "[Substance Name] OR xolair	3017
#6	Search "fluticasone, salmeterol drug combination "[Substance Name] OR	348

	"fluticasone propionate - salmeterol combination "[Substance Name] OR advair OR budesonide-formoterol OR "symbicort "[Substance Name]	
#7	Search "tiotropium "[Substance Name] OR Spiriva	586
#8	Search "ciclesonide "[Substance Name] OR Alvesco	218
#9	Search ("Randomized Controlled Trial"[Publication Type] OR "Randomized Controlled Trials as Topic"[MeSH]) OR "Single-Blind Method"[MeSH] OR "Double-Blind Method"[MeSH] OR "Random Allocation"[MeSH]	427780
#10	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	1227204
#11	Search #1 AND (#2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8)	7722
#12	Search #11 AND #9	2605
#13	Search #11 AND #10	1109
#14	Search #12 OR #13	3392
#15	Search ((#14) AND "2010/01/01"[Entrez Date] : "3000"[Entrez Date]) AND "0"[Entrez Date] : "3000"[Entrez Date]	89
#16	Search #15 Limits: Animals	4
#17	Search #15 NOT #16	85
#18	Search #17 Limits: English	85

PubMed: 85 (85 before duplicates removed)
Cochrane Database: 42 (61 before duplicates removed)
IPA: 16 (36 before duplicates removed)
EMBASE: 63 (125 before duplicates removed)

Appendix F. Studies of 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[1]	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[2]	RCT	100	BUD vs. FP	Insufficient reporting to allow for appraisal of methods and analysis; Results not reported.
Adachi et al., 2007[3]	RCT	319	CIC vs. BUD	Comparisons were between medium dose CIC, high dose CIC, and low dose BUD; no information on randomization scheme; no blinding (BUD group used a spacer whereas CIC groups did not); some baseline differences between groups; no information on attrition/dropouts for those who were randomized; no information on whether intention to treat or per protocol analysis used.
Agertoft et al. 1994[4]	Observational	278	BUD vs. control	Attrition NR, but high in other corresponding publication; high potential selection bias
Agertoft et al.2000[5]	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[6]	Meta-analysis	810	BUD	Lack of an appropriately described comprehensive, systematic literature search...
Anthracopoulos et al. 2007[7]	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

Study	Design	Sample size	Intervention	Reason for exclusion
				36 months of ICS and those that entered puberty.
Aubier et al. 1999[8]	RCT	503	FP/SM vs. FP + SM vs. FP	Poor reporting of methods and results of meaningful outcome
Bakhireva et al. 2007[9]	Observational	96	LTRAs vs. SABAs and control	Small sample size (inadequate to detect differences in adverse events of interest).
Barnes et al. 2007[10]	RCT	75	MOM vs. BUD	Baseline differences, lack of reporting of randomization, blinding, equal assessment of both groups,
Bleecker et al. 2006[11]	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 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.[12]	Meta-analysis	NR	Omalizumab	Methods not reported
Ferguson et al. 2007[13]	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.[14]	Observational	2014	BBUD	Poor measurement and uncontrolled confounders
Karaman et al. 2007[15]	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[16]	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[17]	RCT	77	BDP vs. FP	High potential for bias;

Study	Design	Sample size	Intervention	Reason for exclusion
				Completer's analysis; 22% post-randomization exclusions; incomplete inclusion/exclusion criteria; not sure it was actually randomized;
Ohaju-Obodo et al. 2005[18]	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[19]	Observational	546	SM	No baseline data given for comparison of groups so unable to adequately assess potential for selection bias
Pauwels et al. 1998[20]	RCT	340	FP vs. BDP	Poor reporting, confounding
Perng et al. 2004[21]	RCT	49	BUD vs. BUD+ ZAF	High potential for selection bias and measurement bias
Riccioni et al. 2002[22]	RCT	45	BUD vs. MOM	Open-label, no ITT analysis, no reporting of majority of criteria for critical appraisal
Scott et al. 1999[23]	Pooled data	670	BUD	Pooled data analysis without a systematic literature search
Wardlaw et al. 2004[24]	RCT	167	MOM vs. FP	No blinding, randomisation method nr, no withdrawal information reported
Weiss et al. 2005[25]	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[26]	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.

References for Appendix F

1. Abuekteish F, Kirkpatrick JN, Russell G. Posterior subcapsular cataract and inhaled corticosteroid therapy. *Thorax.* Jun 1995;50(6):674-676.

2. Acun C, Tomac N, Ermis B, Onk G. Effects of inhaled corticosteroids on growth in asthmatic children: a comparison of fluticasone propionate with budesonide. *Allergy Asthma Proc.* May-Jun 2005;26(3):204-206.

3. Adachi M, Ishihara K, Inoue H, et al. Efficacy and safety of inhaled ciclesonide compared with chlorofluorocarbon beclomethasone dipropionate in adults with moderate to severe persistent asthma. *Respirology.* Jul 2007;12(4):573-580.

4. Agertoft L, Pedersen S. Effects of long-term treatment with an inhaled corticosteroid on growth and pulmonary function in asthmatic children. *Respir Med.* May 1994;88(5):373-381.

5. Agertoft L, Pedersen S. Effect of long-term treatment with inhaled budesonide on adult height in children with asthma. *N Engl J Med.* Oct 12 2000;343(15):1064-1069.

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7. Anthracopoulos MB, Papadimitriou A, Panagiotakos DB, et al. Growth deceleration of children on inhaled corticosteroids is compensated for after the first 12 months of treatment. *Pediatr Pulmonol.* May 2007;42(5):465-470.

8. Aubier M, Pieters WR, Schlosser NJ, Steinmetz KO. Salmeterol/fluticasone propionate (50/500 microg) in combination in a Diskus inhaler (Seretide) is effective and safe in the treatment of steroid-dependent asthma. *Respir Med.* Dec 1999;93(12):876-884.

9. Bakhireva LN, Jones KL, Schatz M, et al. Safety of leukotriene receptor antagonists in pregnancy. *J Allergy Clin Immunol.* Mar 2007;119(3):618-625.

10. Barnes N, Laviolette M, Allen D, et al. Effects of montelukast compared to double dose budesonide on airway inflammation and asthma control. *Respir Med.* Aug 2007;101(8):1652-1658.

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16. Lipworth BJ. Systemic adverse effects of inhaled corticosteroid therapy: A systematic review and meta-analysis. *Arch Intern Med.* May 10 1999;159(9):941-955.

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Appendix G. Excluded studies at full-text level

The following full-text publications were considered for inclusion for the update report but failed to meet the criteria for this report. In addition to the references listed below there were 45 studies excluded because they were not published in English (2) or they were not an eligible study design (43). A list of studies excluded from the original report is available as an appendix to that report.

Exclude Reasons
2 = Ineligible outcome(s)
3 = Ineligible drug
4 = Ineligible population
6 = Ineligible design (e.g., small sample size, insufficient study duration)
7 = Ineligible comparison

Excluded Publication	Reason
Aballea S, Cure S, Vogelmeier C, Wiren A. A retrospective database study comparing treatment outcomes and cost associated with choice of fixed-dose inhaled corticosteroid/long-acting beta-agonists for asthma maintenance treatment in Germany. Int J Clin Pract 2008;62(12):1870-9.	6
Agertoft L, Pedersen S. Short-term lower-leg growth rate and urine cortisol excretion in children treated with ciclesonide. J Allergy Clin Immunol 2005;115(5):940-5.	6
Anonymous, Feb. Ciclesonide (<it>Alvesco</it>) - A new inhaled corticosteroid for asthma. In: Medical Letter on Drugs and Therapeutics (USA); 2008. p. 75-76.	
Anonymous, Jun. Budenosia/formoterol (<it>Symbicort</it>) for asthma. In: Medical Letter on Drugs and Therapeutics (USA); 2008. p. 9-1.	
Anonymous. Long-Acting Beta-2 Agonists in Asthma. Medical Letter on Drugs and Therapeutics (USA) 2009;51:1.	6
Antoniu SA, Monica Pop C. Ciclesonide therapy in asthma: a potential effect on small airway inflammation? Expert Opin Pharmacother 2009;10(5):917-9.	2
Antoniu SA. Effects of montelukast-desloratadine combination on early and late asthma responses. Expert Opinion on Pharmacotherapy 2009;10(15):2577-2579.	2
Appleton SL, Ruffin RE, Wilson DH, Taylor AW, Adams RJ. Cardiovascular disease risk associated with asthma and respiratory morbidity might be mediated by short-acting beta2-agonists. J Allergy Clin Immunol 2009;123(1):124-130 e1.	6
Apter AJ. Advances in adult asthma diagnosis and treatment and health outcomes, education, delivery, and quality in 2008. Journal of Allergy and Clinical Immunology 2009;123:35.	6
Apter AJ. Advances in the care of adults with asthma and allergy in 2007. Journal of Allergy and Clinical Immunology 2008;121(4):839-844.	6
Backman RBCSRK. Fluticasone propionate via Diskus inhaler at half the microgram dose of budesonide via Turbuhaler inhaler. Clinical Drug Investigation 2001;21(11):735-743.	6
Baptist AP, Reddy RC. Inhaled corticosteroids for asthma: are they all the same? Journal of Clinical Pharmacy and Therapeutics (England) 2009;34:1.	6
Basu K, Palmer CN, Tavendale R, Lipworth BJ, Mukhopadhyay S. Adrenergic beta<INF>2</INF>-receptor genotype predisposes to exacerbations in steroid-treated asthmatic patients taking frequent albuterol or salmeterol. Journal of Allergy and Clinical Immunology 2009;124:1188.	6
Bateman ED, Bousquet J, Busse WW, Clark TJ, Gul N, Gibbs M, et al. Stability of asthma control with regular treatment: an analysis of the Gaining Optimal Asthma controL (GOAL) study. Allergy 2008;63(7):932-8.	6
Berger WE, Bleecker ER, O'Dowd L, Miller CJ, Mezzanotte W. Efficacy and safety of budesonide/formoterol pressurized metered-dose inhaler: Randomized controlled trial comparing once- and twice-daily dosing in patients with asthma. Allergy and Asthma Proceedings 2010;31(1):49-59.	4
Bisgaard H, Skoner D, Boza ML, Tozzi CA, Newcomb K, Reiss TF, et al. Safety and tolerability of montelukast in placebo-controlled pediatric studies and their open-label extensions. Pediatric Pulmonology 2009;44(6):568-579.	6
Blais L, Beauchesne MF, Forget A. Acute care among asthma patients using budesonide/formoterol or fluticasone propionate/salmeterol. Respir Med 2009;103(2):237-43.	6
Boulet LP, Franssen E. Influence of obesity on response to fluticasone with or without salmeterol in moderate asthma. Respir Med 2007;101(11):2240-7.	4
Boulet LP, Turcotte H, Prince P, Lemiere C, Olivenstein R, Laprise C, et al. Benefits of low-dose	2

inhaled fluticasone on airway response and inflammation in mild asthma. Respir Med 2009;103(10):1554-63.	
Breekveldt-Postma NS, Koerselman J, Erkens JA, Herings RM, Grp CS, et al., et al. Treatment with inhaled corticosteroids in asthma is too often discontinued. In: Pharmacoepidemiology and Drug Safety (England); 2008. p. 411-422.	
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Appendix H. Strength of evidence

Table H-1. Strength of evidence for the comparative efficacy of inhaled corticosteroids

No. of Studies (# of subjects)	Design	Quality	Consistency	Directness	Result (for equipotent doses)	Other modifying factors[a]	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 Ciclesonide							
We did not identify any good or fair quality systematic reviews or head-to-head trials							
Beclomethasone compared with Flunisolide							
We did not identify any good or fair quality systematic reviews or head-to-head trials							
Beclomethasone compared with Fluticasone							
2 SRs (15,867) 11 RCTs (3,273)	2 SRs w/ MA 11 RCTs	Good Good (1), Fair (10)	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 for all outcomes	None	Moderate
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 Ciclesonide							
5 (2336)	RCTs	Fair	Consistent	Direct	No difference for equipotent comparisons	No long-term data (all were 12-weeks); 3 of the 5 RCTs compared equipotent doses	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) 8 RCTs (3076)	1 SR w/ MA 8 RCTs	Good Fair	Consistent	SR not direct (compared FP compared with combined effect of BDP/BUD) RCTs were direct	No difference for all outcomes for equipotent comparisons	5 of the 8 RCTs compared equipotent doses and consistently found no difference for most outcomes	High
Budesonide compared with Mometasone							
2 (992)	RCTs	Fair	Some	Direct	No difference for	Only 1 RCT	Low

Table H-1. Strength of evidence for the comparative efficacy of inhaled corticosteroids

No. of Studies (# of subjects)	Design	Quality	Consistency	Directness	Result (for equipotent doses)	Other modifying factors[a]	Overall strength of the evidence
			inconsistency		symptoms, MOM > BUD for rescue use	included an equipotent comparison	
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
Ciclesonide compared with Flunisolide							
We did not identify any good or fair quality systematic reviews or head-to-head trials							
Ciclesonide compared with Fluticasone							
8 (4230)	RCTs	Fair	Consistent	Direct	No difference for equipotent comparisons	7 of 8 RCTs compared equipotent doses	High
Ciclesonide compared with Mometasone							
We did not identify any good or fair quality systematic reviews or head-to-head trials							
Ciclesonide compared with Triamcinolone							
We did not identify any good or fair quality systematic reviews or head-to-head trials							
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							
3 (1103)	RCTs	Fair	Consistent	Direct	No difference for most outcomes for equipotent comparisons	No long-term data (12-week trials)	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

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

Table H-2. Strength of evidence for the comparative efficacy of leukotriene modifiers (LMs)

Number of studies (# of subjects)	Design	Quality	Consistency	Directness	Result and magnitude of effect	Other modifying factors[a]	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.
[a] Imprecise or sparse data; a strong or very strong association; high risk of reporting bias; dose response gradient; effect of plausible residual confounding.

Table H-3. Strength of evidence for the comparative efficacy of LABAs

Number of studies (# of subjects)	Design	Quality	Consistency	Directness	Result and magnitude of effect	Other modifying factors[a]	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.
[a]Imprecise or sparse data; a strong or very strong association; high risk of reporting bias; dose response gradient; effect of plausible residual confounding.

Table H-4. Strength of evidence for the comparative efficacy of omalizumab and placebo

Omalizumab compared with placebo							
No. of studies (# of subjects)	**Design**	**Quality**	**Consistency**	**Directness**	**Results and magnitude of effect[a]**	**Other modifying factors[a]**	**Overall strength of evidence**
Overall total: Omalizumab compared with placebo							
2 SRs (5,199) 8 RCTs (3480)	2 SR w/ MA 6 RCTs	Good (1), Fair (1) Good (2), Fair (6)	Consistent	Direct	OM > placebo Change in # of exacerbations per patient: WMD = -0.18, 95% CI: -0.24, -0.11 Percentage/number of patients with ≥ 1 exacerbation: OR = 0.51, 95% CI: 0.40, 0.67 Increase in AQLQ scores: SMD = 0.26, 95% CI: 0.18, 0.35	None	High

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.
[a] Selected results from our meta-analyses of included RCTs; the complete meta-analyses is in Appendix I.

Table H-5. Strength of evidence for the comparative efficacy of BUD/FM and 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							
1 (5,537) 4 (5,818)	SR RCTs	Good Good (3); Fair (1)	Consistent when both BUD/FM and FP/SM delivered via a single inhaler	Direct	No difference	None	Moderate
BUD/FM compared with FP/SM							
1 (5,537) 3 (5,390)	SR RCTs	Good Good (2); Fair (1)	Consistent	Direct	No difference; Exacerbations requiring oral steroids: OR (95% CI) = 1.16 (0.95, 1.4) Exacerbations requiring emergency visit or hospital admission: OR (95% CI) = 0.74 (0.53, 1.04)	lack of precision, wide confidence intervals; not all studies compared equipotent steroid doses	Moderate
BUD+FM compared with FP/SM							
1 (428)	RCT	Good	NA	Direct	FP/SM > BUD/FM (despite BUD administered at higher dose equipotency than FP)	Compared non-equipotent steroid components	Low

Abbreviations: BUD = budesonide; FM = formoterol; FP = fluticasone propionate; ICS= inhaled corticosteroids; OR = odds ratio; RCT=randomized controlled trial; SM = salmeterol; SMD = standard mean difference; SR = systematic review

Table H-6. Strength of evidence for for the comparative efficacy of BUD/FM for maintenance and as-needed relief (BUD/FM MART) and ICS/LABA with a Short-Acting Beta-Agonist (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[a] (10,547)	RCTs	Good (2); Fair (2)	Consistent for symptoms and exacerbations Some inconsistency for other outcomes	Direct	BUD/FM MART associated with lower odds of exacerbations and fewer nocturnal awakenings: Exacerbations requiring medical intervention: OR (95% CI) = 0.75 (0.66, 0.85) Exacerbations requiring emergency visit or hospital admission: OR (95% CI) = 0.73 (0.60, 0.90) Nocturnal awakenings: OR (95% CI) = -0.076 (-0.124, -0.027) No difference in symptom-free days, symptom scores, 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 MART 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 MART and no difference in symptom measures		Moderate
BUD/FM MART 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 MART 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; MART = maintenance and reliever therapy; SABA = Short-Acting Beta-Agonist; SMD = standard mean difference.

[a]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).

Table H-7. Strength of evidence for the comparative efficacy of ICSs and 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							
22 (9,873)	RCTs	Fair	Consistent	Direct	ICS > LTRA; ICSs had less rescue medicine use (% rescue free days: SMD -0.25; rescue medicine use per day: SMD -0.23), fewer symptoms (% symptom free days: SMD -0.21; lower symptom score: SMD -0.28), less frequent exacerbations (SMD -0.17), and increase in quality of life (AQLQ scores: SMD -0.19). All were statistically significant favoring ICSs (Appendix I).	None	High
FP compared with ML							
9 (3,864)	RCTs	Fair	Consistent	Direct	FP > ML; had less rescue medicine use (% rescue medicine free days: SMD -0.25), less symptoms (% symptom-free days: SMD -0.24; lower symptom score: SMD -0.24), fewer exacerbations (SMD -0.17), and greater improvement in quality of life (AQLQ scores: SMD -0.15). All were statistically significant favoring FP.	None	High
BDP compared with ML							
6 (3,823)	RCTs	Fair	Consistent	Direct	BDP > ML; had fewer exacerbations (SMD -0.15, 95% CI: -0.30, -0.00), and a trend toward less rescue medication use (mean change puffs per day: SMD -0.08, 95% CI: -0.19, 0.04) and fewer symptoms (% symptom-free days: SMD -0.11, 95% CI: -0.25, 0.02)	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 ZAF							
4 (1,666)	RCTs	Fair	Consistent	Direct	FP > ZAF; less rescue medicine use (rescue medicine free days: SMD -0.30, 95% CI: -0.40, -0.20); fewer symptoms (% symptom free days: SMD -0.29, 95% CI: -0.39, -0.19; greater improvement in	None	High

Table H-7. Strength of evidence for the comparative efficacy of ICSs and LTRAs

Number of studies (# of subjects)	Design	Quality	Consistency	Directness	Results (magnitude of effect)	Other modifying factors	Overall strength of evidence
					symptom score: SMD -0.31, 95% CI: -0.41, -0.21), and fewer exacerbations (SMD -0.21, 95% CI: -0.31, -0.11)		

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.

Table H-8. Strength of evidence for the comparative efficacy of ICSs and LABAs for monotherapy

Number of studies (# of subjects)	Design	Quality	Consistency	Directness	Results, magnitude of effect	Other modifying factors[a]	Overall strength of evidence
ICS compared with LABA for monotherapy							
13 (4196)	RCTs	Good (1) Fair (12)	Some inconsistency	Direct	LABAs had a significantly higher odds of exacerbations than ICSs (OR = 2.845; 95% CI = 1.664, 4.863; *P* < 0.001; 6 studies)); no statistically significant difference found in meta-analyses of other outcomes[b]	None	High
FP compared with SM							
7 (2262)	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 outcomes for those treated with BDP than with SM	None	High
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,	None	Moderate

Number of studies (# of subjects)	Design	Quality	Consistency	Directness	Results, magnitude of effect	Other modifying factors[a]	Overall strength of evidence
					rescue use, or QOL		
BUD compared with FM							
2 (1076)	RCTs (12 weeks)	Fair	NA	Direct	Trend toward fewer symptoms, nocturnal awakenings, and exacerbations; 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.

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

[b] The selected results are from our meta-analyses of included RCTs; the complete meta-analyses are in Appendix I.

Table H-9. Strength of evidence for the comparative efficacy of leukotriene modifiers and LABAs for monotherapy

Number of studies (# of subjects)	Design	Quality	Consistency	Directness	Results, magnitude of effect	Other modifying factors[a]	Overall strength of evidence
Montelukast compared with Salmeterol							
1 (191)	RCT (8 weeks)	Fair	NA	Direct	Zero compared with one death in one study (*P* = NR)	None	Insufficient
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	Insufficient

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

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

Table H-10. Strength of evidence for the comparative efficacy of ICS + LABA and same dose 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 (8050[a]) 9 RCTs (3,932)	1 SR w/ MA 9 RCTs	Good Fair	Some inconsistency	Direct	No difference in number of patients with exacerbations requiring systemic steroids (RR 1.04, 95% CI: 0.73, 1.47) or with exacerbations requiring hospital admissions (RR 0.38, 95% CI 0.09 to 1.65)[b] Greater improvement in the % of symptom-free days (SMD = 0.24 , 95% CI: 0.14, 0.33; 6 studies), symptom scores (SMD = 0.28, 95% CI: 0.15, 0.41; 4 studies), % rescue medicine-free days (SMD 0.32, 95% CI 0.20, 0.43; 4 studies), and rescue medicine use (puffs per day) (SMD 0.25, 95% CI 0.12, 0.38; 7 studies) for those treated with ICS+LABA[c]	None	Moderate
Fluticasone + salmeterol compared with fluticasone							
7 (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.

[a]This is the total number of patients for both comparisons (ICS + LABA v ICS (same dose) and ICS + LABA v ICS (higher dose)) studied in the systematic review.[153]

[b]This result is from a previously published systematic review with meta-analysis.[153]

[c] Our meta-analysis results and forest plots are in Appendix I.

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

Table H-11. Strength of evidence for the comparative efficacy of ICS + LABA compared with higher dose ICS

Number of studies (Number of subjects[a])	Study design (Number using 1 inhaler for ICS+ LABA[b])	Quality	Consistency	Directness	Result, magnitude of effect[c]	Other modifying factors	Overall strength of evidence
Overall total: ICS + LABA compared with higher dose of ICS RCTs							
33[d] (18,153)	33 RCTs	Good (2) Fair (31)	Some inconsistency	Direct	ICS+LABA had greater improvement in the percentage of symptom-free days (SMD = -0.20, 95% CI: -0.25, -0.14), symptom scores (SMD = -0.22, 95% CI: -0.34, -0.11), % rescue-free days (SMD = -0.24, 95% CI: -0.31, -0.16), and rescue medicine use (SMD = -0.22, 95% CI: -0.28, -0.16) No statistically significant difference in the percentage of subjects with exacerbations, but trend favors those treated with ICS+LABA (OR = 0.89, 95% CI: 0.78, 1.01)	None	High
FP+SM compared with FP							
14 (7,091)	RCTs (11)	Fair	Some inconsistency	Direct	no statistically significant difference in the number of people with exacerbations, but the pooled odds ratio favors FP+SM (OR = 0.86, 95% CI: 0.67, 1.10, 8 studies) 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		High
BUD+FM compared with BUD							
7 (6,460)	RCTs (5)	Fair	Some inconsistency	Direct	Meta-analyses show 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	None	High

Table H-11. Strength of evidence for the comparative efficacy of ICS + LABA compared with higher dose ICS

Number of studies (Number of subjects[a])	Study design (Number using 1 inhaler for ICS+ LABA[b])	Quality	Consistency	Directness	Result, magnitude of effect[c]	Other modifying factors	Overall strength of evidence
					(SMD = 0.18, 95% CI: 0.05, 0.31; 3 studies) and trend toward greater improvement in the percentage of symptom-free days with BDP+SM No difference in exacerbations (OR = 0.84, 95% CI: 0.65, 1.10)		
BDP+FM compared with BDP							
3 (982)	RCT (2)	Fair	Consistent	Direct	Better symptom and rescue medicine use outcomes for BDP+FM in all trials; results showed 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 statistically significant 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 medicine use for FP+SM	None	Moderate

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.

[a] 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.

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

[c] This includes the selected results of meta-analyses presented; see Appendix I and text for complete results.

[d] 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.

[e] These results are from a previously published meta-analysis.[165]

[f] These are selected results from a previously published meta-analysis;Ducharme, 2010[167], which is an update to Greenstone, 2005[201].

[g] This is the total number of patients for both comparisons included in the review. The review looked at two groups of studies, ICS + LABA v same dose ICS and ICS + LABA v higher dose ICS.

Table H-12. Strength of evidence for the comparative efficacy of addition of LABA to ICS compared with continuing same dose ICS

Number of studies (Number of subjects[a])	Study design (Number using single combo inhaler[b])	Quality	Consistency	Directness	Result (magnitude of effect)	Other modifying factors	Overall strength of evidence
ICS + LABA compared with same dose of ICS							
32 (14,737)	RCTs	Good (2), Fair (31)	Consistent	Direct	ICS+LABA > ICS for symptom free days (SMD 0.27, 95% CI: 0.22, 0.32), symptom scores (SMD -0.27, 95% CI: -0.33, -0.21), rescue medicine use (SMD -0.29, 95% CI: -0.36, -0.23), and quality of life (AQLQ scores; SMD 0.26, 95% CI: 0.14, 0.37)[c]	None	High
BUD+FM (or eFM) compared with BUD							
16 (9,456)	RCTs (13)[e]	Good (2) Fair (14)	Consistent	Direct	BUD+FM > BUD	None	High
FP+SM compared with FP							
9 (3029)	RCTs (9)	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
BDP+FM compared with BDP							
1 (645)	RCT (0)	Fair	NA	Direct	Rescue medication use was significantly reduced from baseline in the BDP+FM group (mean difference: -0.36 95% CI -0.52 to -0.19) and unchanged in the BDP along group. No between group difference was reported.	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.

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

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

[c] See Appendix I for complete results of meta-analyses.
[d] Results from previously published meta-analysis.
[e] Five trials had an arm with BUD+FM in single inhaler and an arm with them in separate inhalers.

Table H-13. Strength of evidence for the comparative efficacy of ICS + LTRA and ICS

Number of studies (Number 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 the equivalence	Moderate
BUD + ML compared with BUD increased dose							
2 (960)	RCTs (12-16	Fair	Some inconsistency	Direct	No difference for most outcomes (one trial);	None	Low

Table H-13. Strength of evidence for the comparative efficacy of ICS + LTRA and ICS

Number of studies (Number of subjects)	Design	Quality	Consistency	Directness	Result, magnitude of effect	Other modifying factors*	Overall strength of evidence
	weeks)				One trial reported fewer exacerbations with increased dose BUD		
Fluticasone (FP)+Montelukast (ML) compared with Fluticasone (FP) increased dose							
1 (182)	RCT (48 weeks, triple cross-over)	Fair	Not applicable	Direct	No difference in hospitalizations due to asthma symptoms; 43 (FP+ML) vs. 47 (FP) oral steroid courses	Primary outcome was a composite outcome including FEV1	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.

Table H-14. Strength of evidence for the comparative efficacy of LABA + ICS and LTRA

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							
5 (2,188)	RCTs (12 to 48 weeks)	Good (1) Fair (4)	Consistent	Direct	FP+SM > ML Greater improvement in symptom-free days (SMD -0.25, 95% CI: -0.35, -0.15) and percentage of rescue medicine-free days (SMD -0.27, 95% CI: -0.37, -0.17) Fewer exacerbations (SMD 0.26, 95% CI: 0.16, 0.35)	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.

Table H-15. Strength of evidence for the comparative efficacy of LTRA + ICS and LABA + 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
8 (5,459)	8 RCTs	Good (1); Fair (7)			Exacerbations requiring systemic steroids (RR 0.83; 95% CI: 0.71, 0.97)[a]		
ML + FP compared with SM + FP							
7 (5,411)	RCTs	Good (1) Fair (6)	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.

Table H-16. Strength of evidence for the comparative efficacy of ICS + LABA and 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 H-17. Strength of evidence for tolerability and frequency of adverse events 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							
2 (5,935)[a] 4 (5,818)	SRs RCTs	Good (2) Good (3); Fair (1)	Consistent when both BUD/FM and FP/SM delivered via a single inhaler	Direct	No difference[b]: All-cause non-fatal SAEs: OR (95%CI) = 1.14 (0.82, 1.59); Asthma-related non-fatal SAEs: OR 0.69 (0.37, 1.26)	imprecise results and not all studies compared equipotent steroid doses	Moderate
BUD/FM compared with FP/SM							
2 (5,935)[a] 3 (5,390)	SRs[c] RCTs	Good (2) Good (2); Fair (1)	Consistent	Direct		imprecise results and not all studies compared equipotent steroid doses	Moderate
BUD+FM compared with FP/SM							
1 (428)	RCT	Good	NA	Direct		Compared non-equipotent steroid	Low

Table H-17. Strength of evidence for tolerability and frequency of adverse events 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
						components, only study that administered BUD+FM in separate inhalers	

BUD = budesonide; FM = formoterol; FP = fluticasone propionate; OR = odds ratio; RCT = randomized controlled trial; SAE = serious adverse event; SM = salmeterol; SR = systematic review
[a] This number is from the larger SR[281] that includes the same studies as the other SR[94] plus three others
[b] These results are from the larger SR[281]
[c] One of the SRs[281] includes trials of BUD/FM and BUD+FM

Appendix I. Meta-analyses

Ciclesonide Meta-Analysis Results

Ciclesonide compared with fluticasone

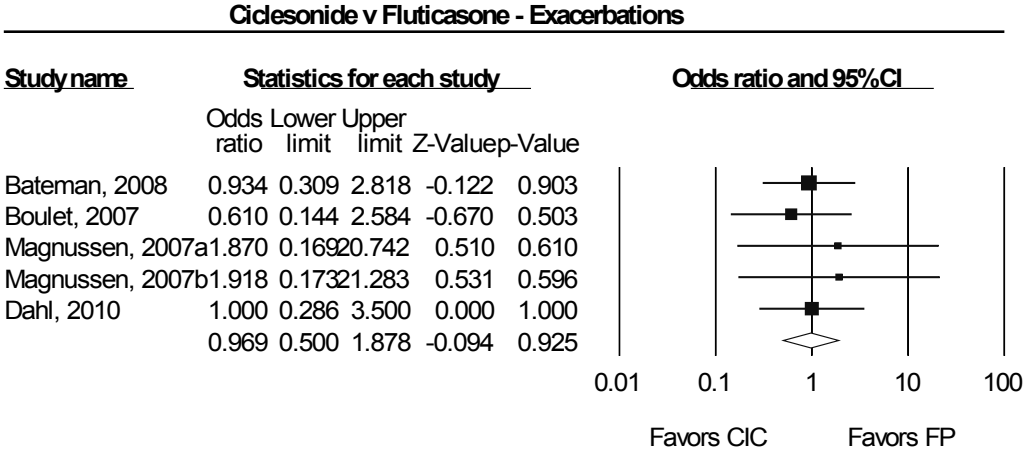
Summary of outcomes evaluated:

1. **Exacerbations**
2. **Rescue medication use (puffs per day)**
3. **Change in symptom score**
4. **Oral Candidiasis (Thrush)**

Results

Exacerbations (studies using the same definition of exacerbation)

Studies included:
Bateman et al. 2008
Boulet et al. 2007
Magnussen et al. 2007a
Magnussen et al. 2007b
Dahl et al. 2010



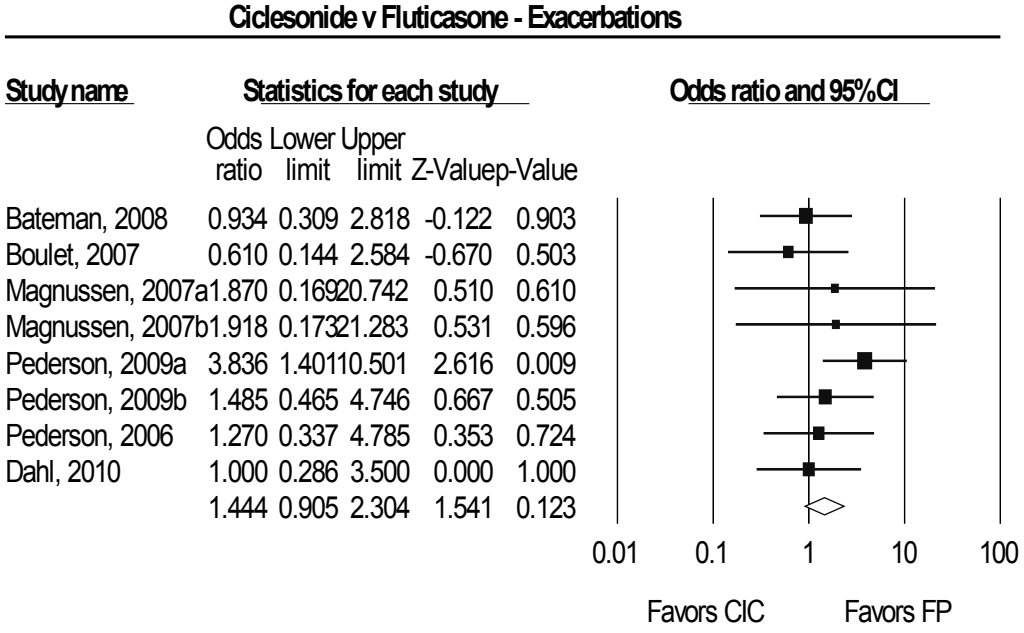
Results for Heterogeneity among studies:

Q-value	d.f. (Q)	*P* value	I-squared
0.99658	4	0.910314	0

Only includes studies in which exacerbations were defined as worsening asthma that required treatment with oral steroids. Includes all doses (Magnussen (a) is CIC 80 mcg v FP 88 mcg Bateman and Boulet are CIC 320 mcg v FP 330 or 200 mcg; Magnussen (b) is CIC 160 mcg once/day v FP 88 mcg bid; Dahl is CIC 80 mcg once/day v 100mcg FP bid).

Exacerbations (All studies, regardless of definition)

Studies included:
Bateman et al. 2008
Boulet et al. 2007
Magnussen et al. 2007a
Magnussen et al. 2007b
Pederson et al. 2009a
Pederson et al. 2009b
Pederson et al. 2006
Dahl et al. 2010



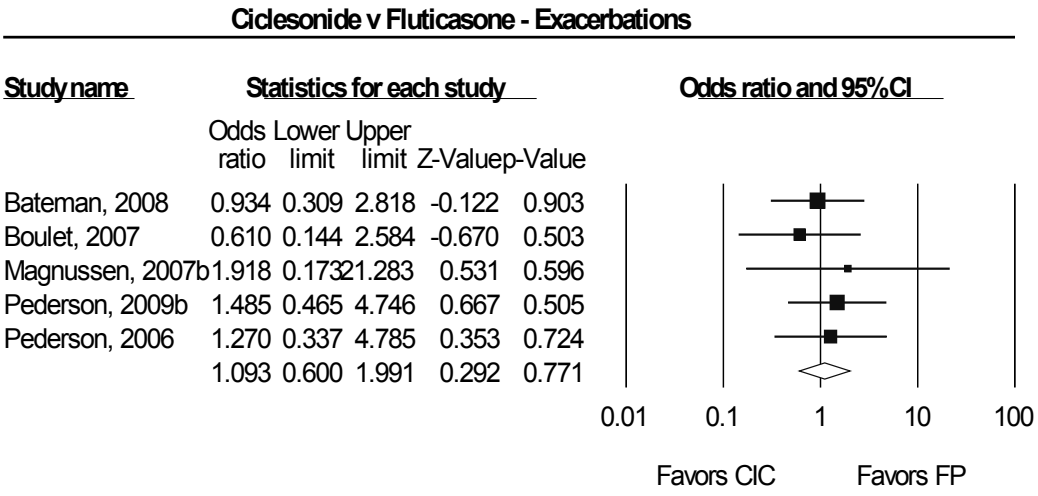
Results for Heterogeneity among studies:

Q-value	d.f. (Q)	*P* value	I-squared
6.047684	7	0.534193	0

Exacerbations (excluding studies using low-dose CIC)

Studies included:
Bateman et al. 2008
Boulet et al. 2007
Magnussen et al. 2007b
Pederson et al. 2009b
Pederson et al. 2006

Excluded studies (low-dose CIC):
Magnussen et al. 2007a
Pederson et al. 2009a
Dahl et al. 2010



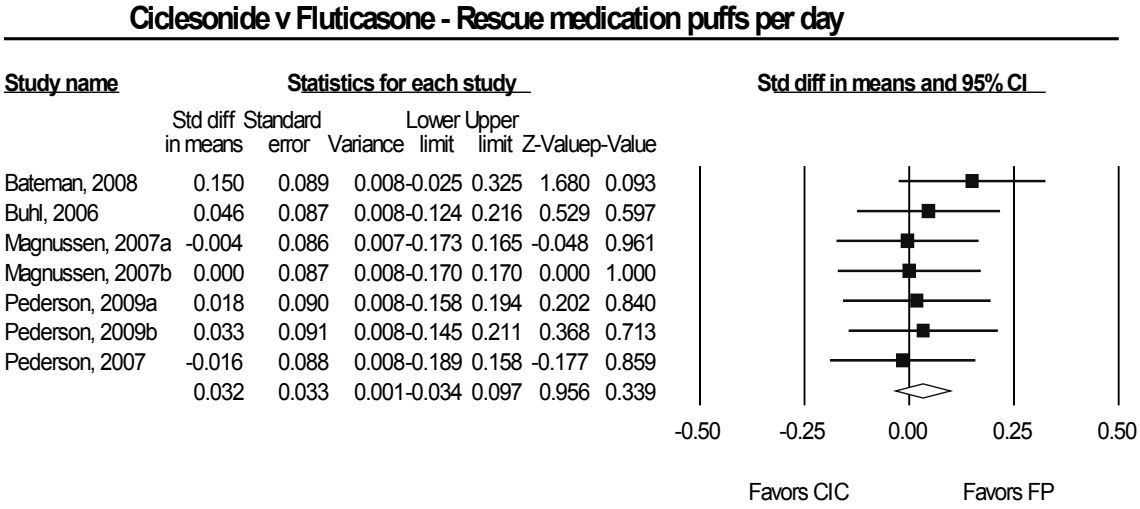
Results for Heterogeneity among studies:

Q-value	d.f. (Q)	*P* value	I-squared
1.230898	4	0.872986	0

Rescue medication use (puffs per day)

Studies included:
Bateman et al. 2008
Buhl et al. 2006
Magnussen et al. 2007a
Magnussen et al. 2007b
Pederson et al. 2009a
Pederson et al. 2009b
Pederson et al. 2007

Note: Data from included studies are reported as median number of puffs per day. The overall effect measure should be interpreted cautiously.



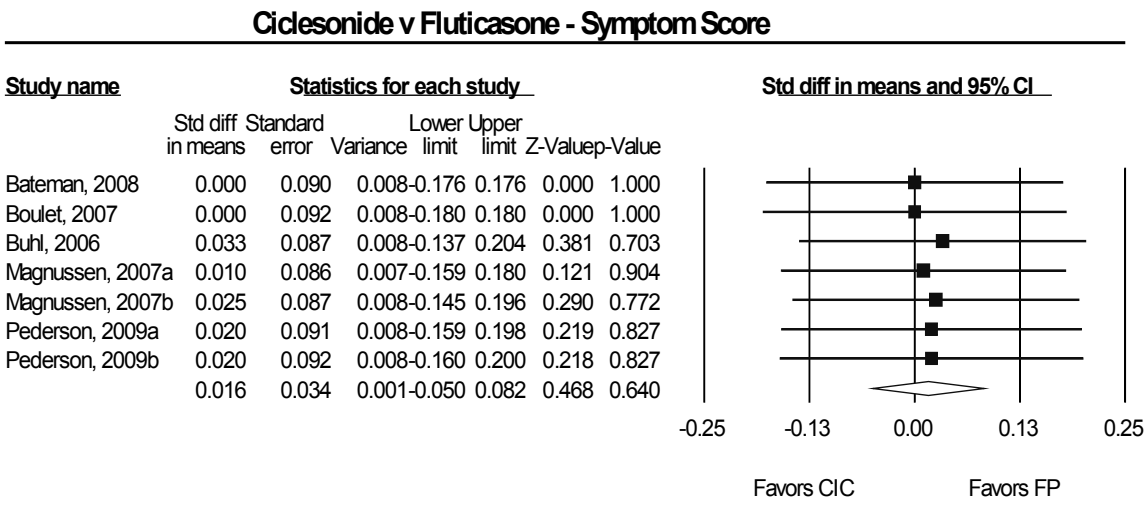
Results for Heterogeneity among studies:

Q-value	d.f. (Q)	*P* value	I-squared
2.39888006	6	0.879609	0

Symptom score

Studies included:
Bateman et al. 2008
Boulet et al. 2007
Buhl et al. 2006
Magnussen et al. 2007a
Magnussen et al. 2007b
Pederson et al. 2009a
Pederson et al. 2009b

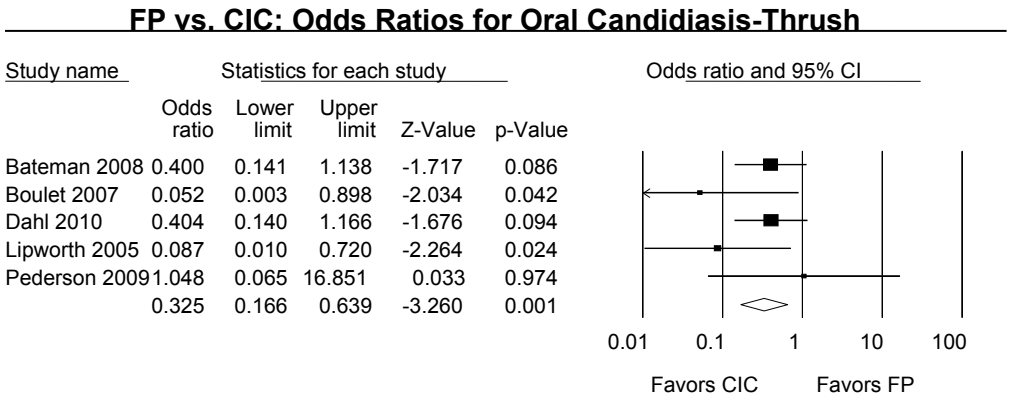
Note: Data from included studies are reported as median changes in asthma symptom score. The overall effect measure should be interpreted cautiously.



Results for Heterogeneity among studies:

Q-value	d.f. (Q)	*P* value	I-squared
0.11983843	6	0.999966	0

Oral Candidiasis (Thrush) – Odds Ratio – New Analysis



Heterogeneity

Q-value	df (Q)	P-value	I-squared
4.082539064	4	0.394950636	2.021758103

Sensitivity analyses indicate no difference in overall meta-analysis conclusions with single studies removed.

Omalizumab Meta-Analysis Results

All studies compare Omalizumab with Placebo.

Summary of outcomes evaluated:

1. **Number of exacerbations per patient**
2. **Percentage of patients with one or more exacerbation**
3. **Change in AQLQ score**

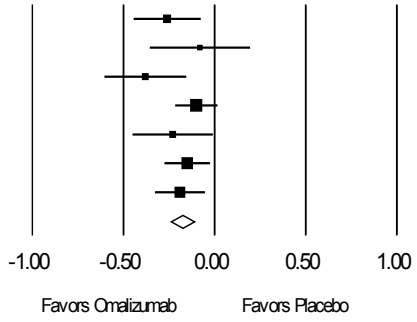
Results

Number of Exacerbations per Patient: Updated Analysis

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
Lanier et al. 2009

Omalizumab v Placebo: Number of Exacerbations per Patient

Study name	Difference in means	Standard error	Variance	Lower limit	Upper limit	Z-Value	p-Value
Busse, 2001	-0.260	0.094	0.009	-0.445	-0.075	-2.759	0.006
Holgate, 2004	-0.080	0.141	0.020	-0.356	0.196	-0.569	0.569
Soler, 2001	-0.380	0.115	0.013	-0.605	-0.155	-3.309	0.001
Milgrom, 2001	-0.100	0.059	0.004	-0.216	0.016	-1.685	0.092
Humbert, 2005	-0.230	0.113	0.013	-0.451	-0.009	-2.040	0.041
Vignola, 2004	-0.150	0.064	0.004	-0.276	-0.024	-2.336	0.020
Lanier, 2009	-0.190	0.070	0.005	-0.328	-0.052	-2.707	0.007
	-0.178	0.033	0.001	-0.241	-0.114	-5.450	0.000



Results for Heterogeneity among studies:

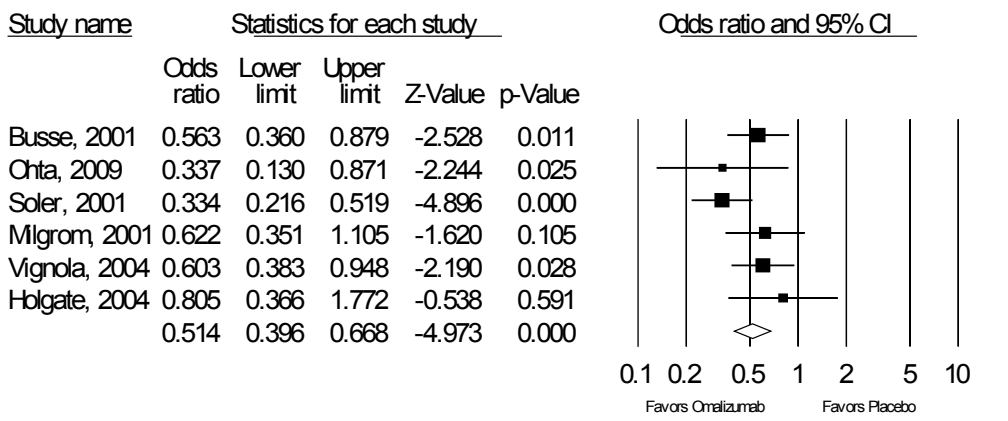
Value of Q-statistic	d.f. (Q)	*P* value	I-squared
6.487	6	0.371	7.506

Odds Ratio for 1 or more Exacerbations per patient

Studies included:
Busse et al 2001; Finn et al 2003; Lanier et al 2005 (single study population)
Ohta et al. 2009
Soler et al 2001; Buhl et al 2002; Buhl et al., 2002 (single study population)
Milgrom et al 2001
Vignola et al 2004
Holgate, 2004

Studies that reported outcome, but are not included: NA

Omalizumab v Placebo: Proportion of Patients with One or More Exacerbation



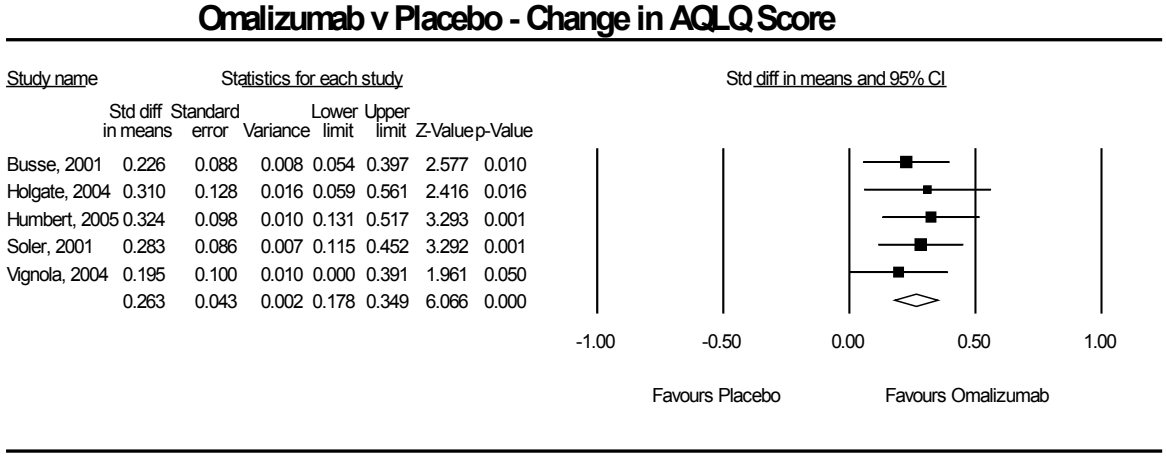
Results for Heterogeneity among studies:

Value of Q-statistic	d.f. (Q)	*P* value	I-squared
6.743	5	0.240	25.847

Change in AQLQ Score: Updated Analysis

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

Studies that reported outcome, but are not included: NA



Results for Heterogeneity among studies:

Value of Q-statistic	d.f. (Q)	*P* value	I-squared
1.212	4	0.876	0.000

ICS+LABA VS. ICS+LABA (Combination products) Meta-Analysis Results

Summary of Outcomes Evaluated:

1. **Exacerbations requiring oral steroids**
2. **Exacerbations requiring emergency visit/hospital admission**

Study compares fixed Dose Combo of BUD/FM with Fixed Dose Combo FP/SM
Data were gathered from the individual articles when possible; when exacerbation data were not reported in the articles, available data were gathered by contacting the authors or from a published systematic review (Lasserson, 2008).

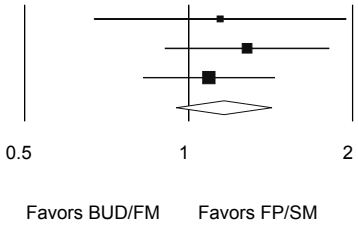
Exacerbations requiring oral steroids

Studies included:
Aalbers et al. 2004 ; Aalbers et al. 2010
Dahl et al. 2006
Kuna et al. 2007 and Price et al. 2007

Studies that reported outcome, but are not included:
Ringdal et al. 2002: Administered BUD and FM in separate inhalers; daily BUD dose was twice the BUD dose in included studies.

Budesonide+Formoterol vs. Fluticasone+Salmeterol - Exacerbations (requiring oral steroids)

Study name	Odds ratio	Lower limit	Upper limit	p-Value
Aalbers et al 2004; Aalbers et al 2010	1.142	0.669	1.950	0.626
Dahl et al 2006	1.280	0.903	1.815	0.165
Kuna et al 2007; Price et al 2007; Kuna 2010	1.090	0.824	1.441	0.547
	1.158	0.946	1.417	0.155



Heterogeneity			
Q-value	df (Q)	P-value	I-squared
0.501296225	2	0.778296196	0

Sensitivity analyses indicate no difference in overall meta-analysis conclusions with single studies removed.

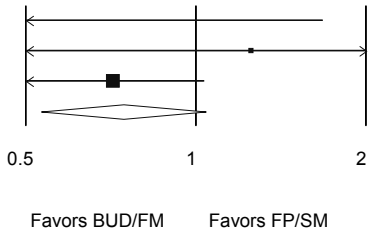
Exacerbations requiring emergency visit/hospital admission

Studies included:
Aalbers et al. 2004; Aalbers et al. 2010
Dahl et al. 2006
Kuna et al. 2007 and Price et al. 2007

Studies that reported outcome, but are not included:
Ringdal et al. 2002 :
Administered BUD and FM in separate inhalers; daily BUD dose was twice the BUD dose in included studies

Budesonide+Formoterol vs. Fluticasone+Salmeterol - Exacerbations (requiring ER/hospital admission)

Study name	Odds ratio	Lower limit	Upper limit	p-Value
Aalbers et al 2004; Aalbers et al 2010	0.429	0.109	1.680	0.224
Dahl et al 2006	1.252	0.491	3.191	0.638
Kuna et al 2007; Price et al 2007; Kuna 2010	0.713	0.491	1.035	0.075
	0.743	0.531	1.040	0.083



Heterogeneity

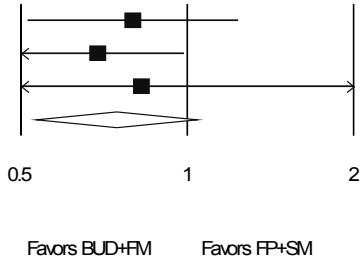
Q-value	df (Q)	P-value	I-squared
1.864494918	2	0.393667963	0

Sensitivity analyses indicate no difference in overall meta-analysis conclusions with single studies removed with the exception of removing Dahl et al, 2006. The overall result became significant in favor of BUD + FM when Dahl et al, 2006 [OR 0.688 (9% CI 0.480 to 0.986)] was removed.

Sensitivity Analyses – Exacerbations (requiring ER/hospital admission – BUD+FM vs. FP+SM

BUD+FM vs. FP+SM - Exacerbations (requiring ER/hospital admission) Sensitivity Analysis

Study name	Point	Lower limit	Upper limit	Z-Value	p-Value
Aalbers et al 2004; Aalbers et al 2010	0.797	0.514	1.236	-1.014	0.311
Dahl et al 2006	0.688	0.480	0.986	-2.036	0.042
Kuna et al 2007; Price et al 2007; Kuna 2010	0.826	0.297	2.299	-0.366	0.714
	0.743	0.531	1.040	-1.732	0.083



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. **Severe exacerbations requiring medical intervention**
2. **Severe exacerbations requiring emergency visit or hospital admission**
3. **Rescue medication use (puffs/day)**
4. **Rescue medication use (% rescue-free days)**
5. **Symptoms (% symptom-free days)**
6. **Symptoms (score)**
7. **Nocturnal Awakenings**

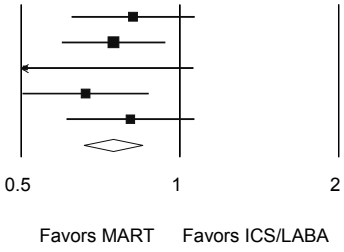
Severe exacerbations requiring medical intervention

Studies included:
Vogelmeier et al. 2005
O'Byrne et al. 2005
Bousquet et al. 2007
Kuna et al. 2007; Price et al. 2007 ; Kuna 2010 vs FP/SM
Kuna et al. 2007; Price et al. 2007 ; Kuna 2010 vs BUD/FM

Studies that reported outcome, but are not included:
Bisgaard et al. 2006:
Post-hoc subset analysis of O'Byrne et al. 2005 ; inclusion would result in double-counting data

Severe Exacerbations (requiring medical intervention) - BUD/FM MART vs. ICS/LABA

Study name	Odds ratio	Lower limit	Upper limit	p-Value
Bousquet 2007	0.815	0.622	1.067	0.136
Vogelmeier, 2005	0.749	0.596	0.939	0.012
O'Byrne 2005	0.509	0.244	1.062	0.072
Kuna 2007; Price 2007; Kuna 2010 vs FP/SM	0.662	0.502	0.873	0.003
Kuna 2007; Price 2007; Kuna 2010 vs BUD/FM	0.806	0.609	1.067	0.131
	0.746	0.656	0.848	0.000



Heterogeneity			
Q-value	df (Q)	P-value	I-squared
2.453449782	4	0.652990274	0

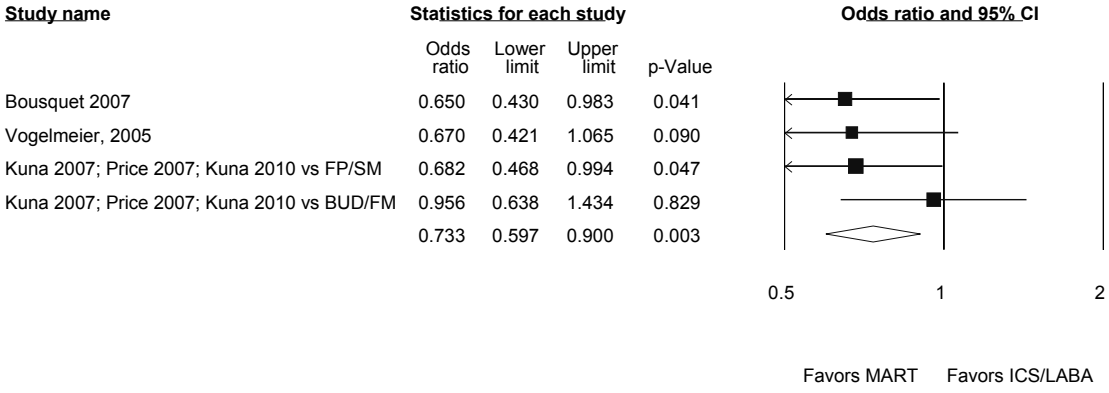
Sensitivity analyses indicate no difference in overall meta-analysis conclusions with single studies removed.

Severe exacerbations requiring emergency visit or hospital admission

Studies included:
Vogelmeier et al. 2005
Bousquet et al. 2007
Kuna et al. 2007; Price et al. 2007 ; Kuna 2010 vs FP/SM
Kuna et al. 2007; Price et al. 2007 ; Kuna 2010 vs BUD/FM

Studies that reported outcome, but are not included: NA

Severe Exacerbations (requiring emergency department visits or hospital admission) - BUD/FM MART vs. ICS/LABA



Heterogeneity			
Q-value	df (Q)	P-value	I-squared
2.264524	3	0.519351	0

Sensitivity analyses indicate no difference in overall meta-analysis conclusions with single studies removed.

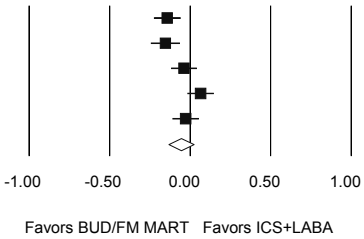
Rescue medication use (puffs/day) – Updated Analysis

Studies included:
Vogelmeier et al. 2005
O'Byrne et al. 2005
Bousquet et al. 2007
Kuna et al. 2007; Price et al. 2007 ; Kuna 2010 vs FP/SM
Kuna et al. 2007; Price et al. 2007 ; Kuna 2010 vs BUD/FM

Studies that reported outcome, but are not included:
Bisgaard et al. 2006:
Post-hoc subset analysis of O'Byrne et al. 2005 ; inclusion would result in double-counting data

Rescue medication use (puffs/day) - BUD/FM MART vs. ICS/LABA

Study name	Std diff in means	Standard error	Variance	Lower limit	Upper limit	Z-Value	p-Value
Vogelmeier, 2005	-0.142	0.043	0.002	-0.227	-0.058	-3.291	0.001
O'Byrne, 2005	-0.154	0.047	0.002	-0.246	-0.062	-3.291	0.001
Bousquet, 2007	-0.038	0.042	0.002	-0.120	0.044	-0.915	0.360
Kuna 2007; Price 2007; Kuna 2010 vs FP/SM	0.065	0.042	0.002	-0.018	0.148	1.525	0.127
Kuna 2007; Price 2007; Kuna 2010 vs BUD/FM	-0.028	0.043	0.002	-0.111	0.056	-0.654	0.513
	-0.058	0.040	0.002	-0.137	0.020	-1.461	0.144



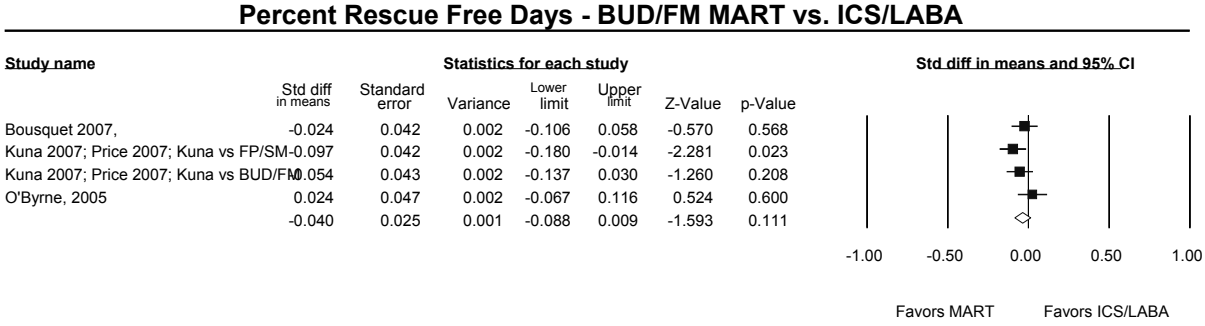
Heterogeneity			
Q-value	df (Q)	P-value	I-squared
17.090854	4	1.86E-03	76.5956697

Sensitivity analyses indicate no difference in overall meta-analysis conclusions with single studies removed.

Rescue medication use (% rescue-free days): Updated Analysis

Studies included:
O'Byrne et al. 2005
Bousquet et al. 2007
Kuna et al. 2007; Price et al. 2007 ; Kuna 2010 vs FP/SM
Kuna et al. 2007; Price et al. 2007 ; Kuna 2010 vs BUD/FM

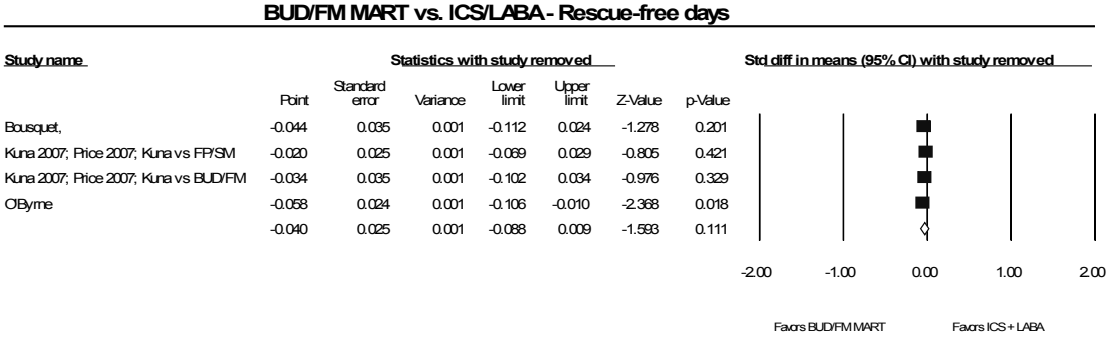
Studies that reported outcome, but are not included:
Bisgaard et al. 2006:
Post-hoc subset analysis of O'Byrne et al. 2005; inclusion would result in double-counting data



Heterogeneity			
Q-value	df (Q)	P-value	I-squared
3.945357456	3	0.26742531	23.96126248

Sensitivity analyses indicate no difference in overall meta-analysis conclusions with single studies removed with the exception of removing O'Byrne. The overall result becomes significant in favor of BUD/FM MART (SMD -0.058 (95% CI -0.106 to -010).

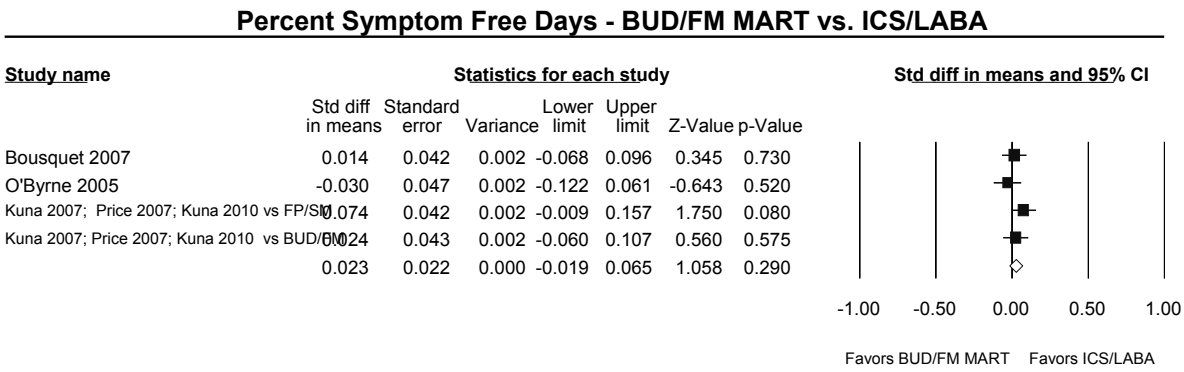
Sensitivity Analysis - % Rescue-free days BUD/FM MART vs. ICS/LABA MART



Symptoms (% symptom-free days): Updated Analysis

Studies included:
O'Byrne et al. 2005
Bousquet et al. 2007
Kuna et al. 2007; Price et al. 2007 ; Kuna 2010 vs FP/SM
Kuna et al. 2007; Price et al. 2007 ; Kuna 2010 vs BUD/FM

Studies that reported outcome, but are not included:
Bisgaard et al. 2006:
Post-hoc subset analysis of O'Byrne et al. 2005; inclusion would result in double-counting data



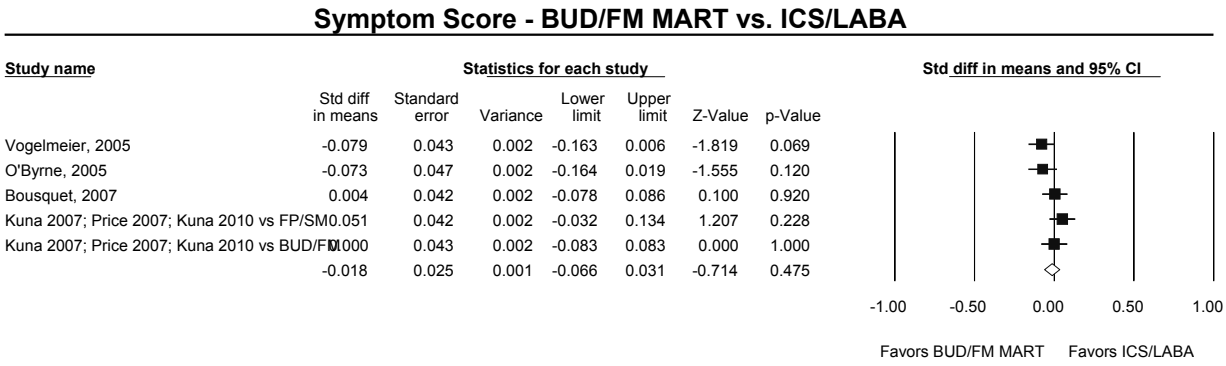
Heterogeneity			
Q-value	df (Q)	P-value	I-squared
2.790543715	3	0.42505896	0

Sensitivity analyses indicate no difference in overall meta-analysis conclusions with single studies removed.

Symptoms (score) – Updated Analysis

Studies included:
Vogelmeier et al. 2005
O'Byrne et al. 2005
Bousquet et al. 2007
Kuna et al. 2007; Price et al. 2007 ; Kuna 2010 vs FP/SM
Kuna et al. 2007; Price et al. 2007 ; Kuna 2010 vs BUD/FM

Studies that reported outcome, but are not included:
Bisgaard et al. 2006:
Post-hoc subset analysis of O'Byrne et al. 2005; inclusion would result in double-counting data



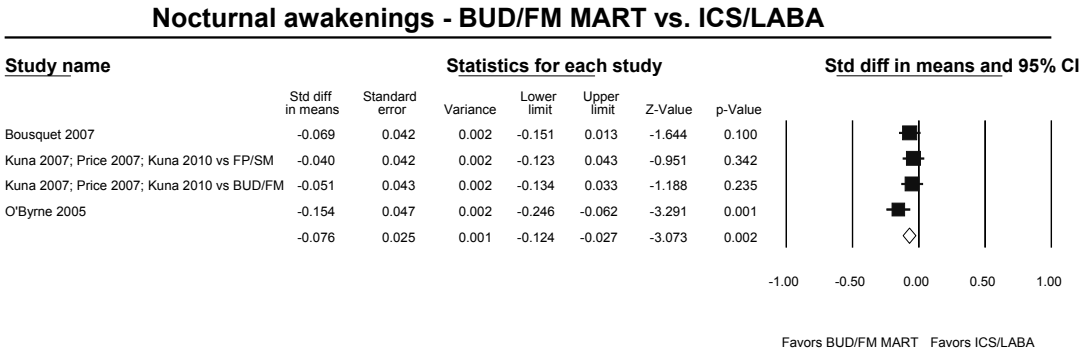
Heterogeneity			
Q-value	df (Q)	P-value	I-squared
6.453186856	4	0.16776399	38.01512199

Sensitivity analyses indicate no difference in overall meta-analysis conclusions with single studies removed.

Nocturnal Awakenings: Updated Analysis

Studies included:
Bosquet at al 2007
O'Byrne et al 2005
Kuna et al 2007; Price at al 2007; Kuna 2010

Studies that reported outcome, but are not included: NA



Heterogeneity			
Q-value	df (Q)	P-value	I-squared
3.872799	3	0.275531	22.53664

Sensitivity analyses indicate no difference in overall meta-analysis conclusions with single studies removed.

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

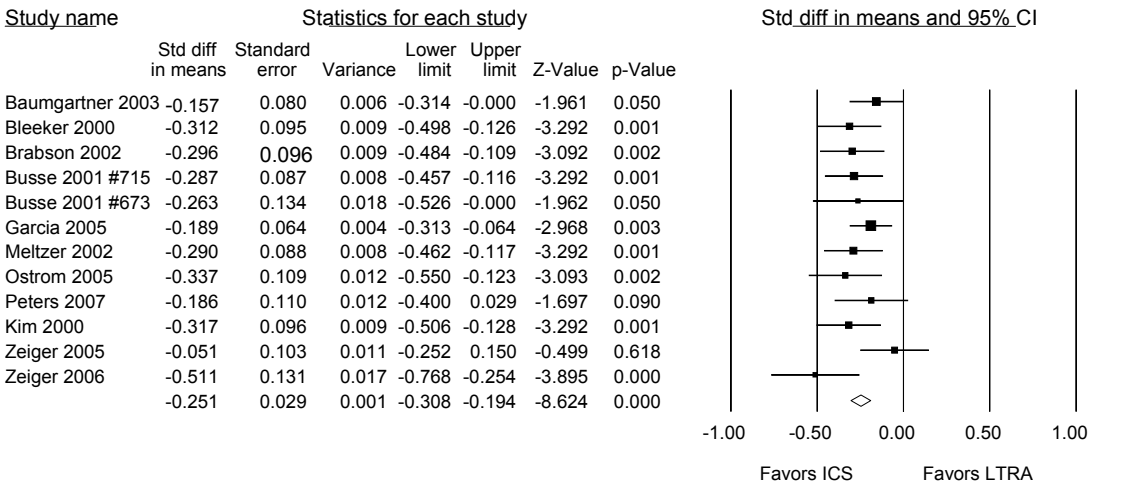
Rescue Medication Use (percent rescue free days): Updated Analysis

Included studies:
Baumgartner et al. 2003
Bleeker et al. 2000
Brabson et al. 2002
Busse et al. 2001a
Busse et al. 2001b
Garcia et al. 2005
Meltzer et al. 2002
Ostrom 2005
Kim et al. 2000
Peters et al. 2007
Zeiger et al. 2005
Zeiger et al. 2006

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

ICS v LTRA: Rescue Medication Use (Percent Rescue Free Days)



Sensitivity analyses indicate no difference in overall meta-analysis conclusions with single studies removed.

Results for Heterogeneity among studies:

Q-value	*d.f. (Q)*	*P value*	*I-squared*
12.509	11	0.327	12.062

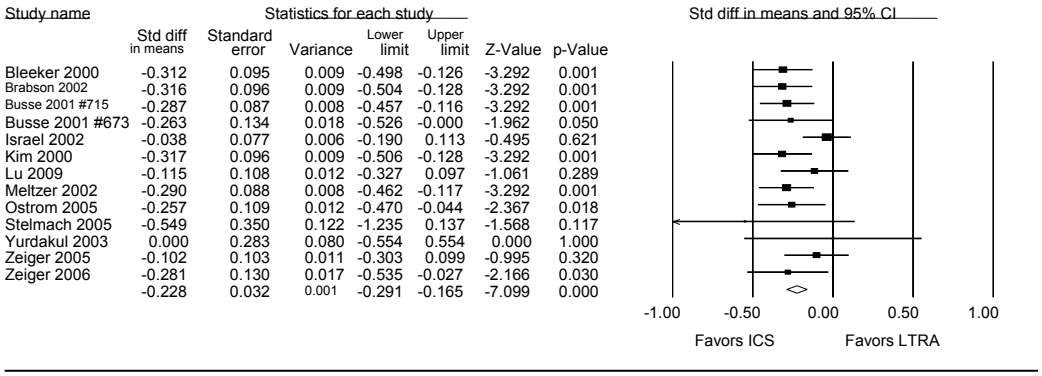
Rescue Medication Use (puffs per day): Updated Analysis

Included studies:
Bleeker et al. 2000
Brabson et al. 2002
Busse et al. 2001a
Busse et al. 2001b
Israel et al. 2002
Kim et al. 2000
Lu et al. 2009
Meltzer et al. 2002
Ostrom et al. 2005
Stelmach et al. 2005
Yurdukal et al. 2003
Zeiger et al. 2005
Zeiger et al. 2006

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

ICS v LTRA: Rescue Medication Use (Mean Change in Puffs per Day)



The results of this meta-analysis show a significant reduction in the use of rescue medication (measured in puffs per day) with ICS over LTRA.

Sensitivity analyses indicate no difference in overall meta-analysis conclusions with single studies removed.

Results for Heterogeneity among studies:

Q-value	*d.f. (Q)*	*P-value*	*I-squared*
13.862	12	0.310	13.433

Percent Improved Symptom Control (symptom free days): Updated Analysis

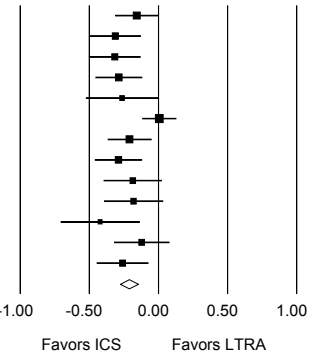
Included studies:
Baumgartner et al. 2003
Bleeker et al. 2000
Brabson et al. 2002
Busse et al. 2001a
Busse et al. 2001b
Israel et al. 2002
Kim et al. 2000
Malmstrom et al. 1999
Meltzer et al. 2002
Ostrom et al. 2005
Peters et al. 2007
Sorkness et al. 2007
Yurdukal et al. 2003
Zeiger et al. 2005

Studies that reported outcome, but are not included:

Study	*Reason*
Ducharme et al. 2004	Review paper
Halpern et al. 2003	Review paper
Zeiger et al. 2006	Measured different outcomes

ICS v LTRA: Symptom Control (Percent Symptom Free Days)

Study name	Std diff in means	Standard error	Variance	Lower limit	Upper limit	Z-Value	p-Value
Baumgartner 2003	0.157	0.080	0.006	-0.314	-0.000	-1.961	0.050
Bleeker 2000	-0.312	0.095	0.009	-0.498	-0.126	-3.292	0.001
Brabson 2002	-0.316	0.096	0.009	-0.504	-0.128	-3.292	0.001
Busse 2001 #715	-0.287	0.087	0.008	-0.457	-0.116	-3.292	0.001
Busse 2001 #673	-0.263	0.134	0.018	-0.526	-0.000	-1.962	0.050
Israel 2002	0.006	0.063	0.004	-0.119	0.130	0.089	0.929
Malmstrom 1999	-0.209	0.081	0.007	-0.369	-0.050	-2.577	0.010
Meltzer 2002	-0.290	0.088	0.008	-0.462	-0.117	-3.292	0.001
Ostrom 2005	-0.186	0.108	0.012	-0.398	0.027	-1.713	0.087
Peters 2007	-0.180	0.109	0.012	-0.395	0.034	-1.646	0.100
Sorkness 2007	-0.422	0.146	0.021	-0.708	-0.135	-2.882	0.004
Zeiger 2005	-0.121	0.103	0.011	-0.322	0.081	-1.176	0.240
Kim 2000	-0.259	0.096	0.009	-0.448	-0.071	-2.698	0.007
	-0.214	0.033	0.001	-0.279	-0.149	-6.421	0.000



Sensitivity analyses indicate no difference in overall meta-analysis conclusions with single studies removed.

Results for Heterogeneity among studies:

Q-value	*d.f. (Q)*	*P value*	*I-squared*
19.244	12	0.083	37.644

Percent Improved Symptom Control (symptom score)

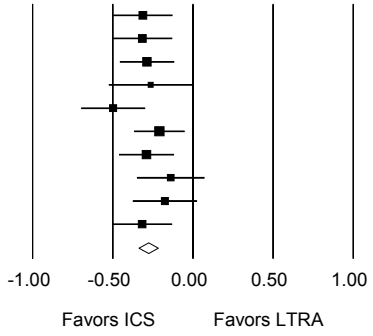
Included studies:
Bleeker et al. 2000
Brabson et al. 2002
Busse et al. 2001a
Busse et al. 2001b
Laviolette et al. 1999
Malmstrom et al. 1999
Meltzer et al. 2002
Ostrom et al. 2005
Zeiger et al. 2005
Kim et al. 2000

Studies that reported outcome, but are not included:

Study	*Reason*
Ducharme et al 2004	Review paper
Halpern et al 2003	Review paper
Stelmack et al 2005	Composite measure that includes more than just symptom score
Yurdulak et al 2003	P-value only reported as NS, no measures of variation reported

ICS v LTRA: Symptom Control (Change in Symptom Score)

Study name	Std diff in means	Standard error	Variance	Lower limit	Upper limit	Z-Value	p-Value
Bleeker 2000	-0.312	0.095	0.009	-0.498	-0.126	-3.292	0.001
Brabson 2002	-0.316	0.096	0.009	-0.504	-0.128	-3.292	0.001
Busse 2001 #715	-0.287	0.087	0.008	-0.457	-0.116	-3.292	0.001
Busse 2001 #673	-0.263	0.134	0.018	-0.526	-0.000	-1.962	0.050
Laviolette 1999	-0.498	0.102	0.010	-0.699	-0.297	-4.860	0.000
Malmstrom 1999	-0.209	0.081	0.007	-0.369	-0.050	-2.577	0.010
Meltzer 2002	-0.290	0.088	0.008	-0.462	-0.117	-3.292	0.001
Ostrom 2005	-0.138	0.108	0.012	-0.350	0.074	-1.277	0.202
Zeiger 2005	-0.174	0.103	0.011	-0.376	0.027	-1.697	0.090
Kim 2000	-0.317	0.096	0.009	-0.506	-0.128	-3.292	0.001
	-0.281	0.031	0.001	-0.340	-0.221	-9.183	0.000



Sensitivity analyses indicate no difference in overall meta-analysis conclusions with single studies removed.

Results for Heterogeneity among studies:

Q-value	*d.f. (Q)*	*P-value*	*I-squared*
8.483	9	0.486	0.000

Percent Exacerbations: Updated Analysis

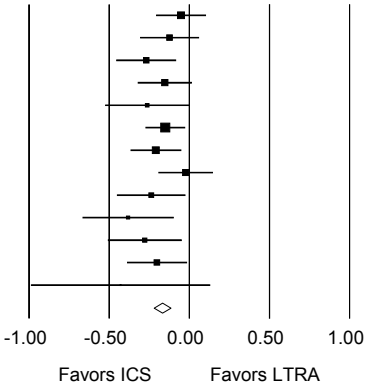
Included studies:
Baumgartner et al. 2003
Bleeker et al. 2000
Brabson et al. 2002
Busse et al. 2001a
Busse et al. 2001b
Garcia et al. 2005
Malmstrom et al. 1999
Meltzer et al. 2002
Peters et al. 2007
Sorkness et al. 2007
Szefler et al. 2005
Kim et al. 2000
Yurdukal et al. 2003

Studies that reported outcome, but are not included:

Study	*Reason*
Ducharme et al. 2004	Review paper
Halpern et al. 2003	Review paper

ICS v LTRA: Percent Exacerbations

Study name	Std diff in means	Standard error	Variance	Lower limit	Upper limit	Z-Value	p-Value
Baumgartner 2003	-0.052	0.080	0.006	-0.208	0.105	-0.650	0.516
Bleeker 2000	-0.123	0.094	0.009	-0.308	0.061	-1.308	0.191
Brabson 2002	-0.269	0.096	0.009	-0.457	-0.081	-2.809	0.005
Busse 2001 #715	-0.153	0.087	0.008	-0.323	0.017	-1.763	0.078
Busse 2001 #673	-0.263	0.134	0.018	-0.526	-0.000	-1.962	0.050
Garcia 2005	-0.150	0.064	0.004	-0.275	-0.026	-2.366	0.018
Malmstrom 1999	-0.209	0.081	0.007	-0.369	-0.050	-2.577	0.010
Meltzer 2002	-0.023	0.088	0.008	-0.195	0.148	-0.268	0.789
Peters 2007	-0.238	0.110	0.012	-0.453	-0.023	-2.172	0.030
Sorkness 2007	-0.382	0.146	0.021	-0.668	-0.096	-2.616	0.009
Szefler 2005	-0.278	0.118	0.014	-0.510	-0.046	-2.348	0.019
Kim 2000	-0.202	0.096	0.009	-0.390	-0.014	-2.110	0.035
Yurdakul 2003	-0.429	0.286	0.082	-0.990	0.132	-1.499	0.134
	-0.171	0.027	0.001	-0.223	-0.119	-6.454	0.000



Sensitivity analyses indicate no difference in overall meta-analysis conclusions with single studies removed.

Results for Heterogeneity among studies:

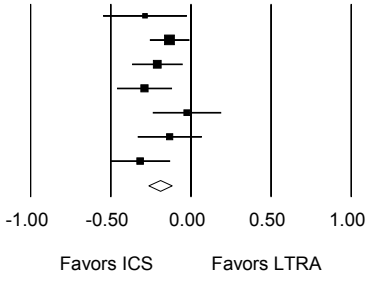
Q-value	*d.f. (Q)*	*P value*	*I-squared*
11.410	12	0.494	0.000

Change in AQLQ Score: Updated Analysis

Studies included:
Busse et al. 2001a
Garcia et al. 2005
Malmstrom et al. 1999
Meltzer et al. 2002
Peters et al. 2007
Zeiger et al. 2005
Kim et al. 2000

ICS v LTRA: Change in AQLQ Score

Study name	Std diff in means	Standard error	Variance	Lower limit	Upper limit	Z-Value	p-Value
Busse 2001 #673	-0.287	0.134	0.018	-0.550	-0.023	-2.135	0.033
Garcia 2005	-0.133	0.064	0.004	-0.258	-0.009	-2.097	0.036
Malmstrom 1999	-0.209	0.081	0.007	-0.369	-0.050	-2.577	0.010
Meltzer 2002	-0.290	0.088	0.008	-0.462	-0.117	-3.292	0.001
Peters 2007	-0.025	0.109	0.012	-0.239	0.189	-0.228	0.820
Zeiger 2005	-0.132	0.103	0.011	-0.333	0.070	-1.282	0.200
Kim 2000	-0.317	0.096	0.009	-0.506	-0.128	-3.292	0.001
	-0.193	0.037	0.001	-0.266	-0.121	-5.201	0.000



Sensitivity analyses indicate no difference in overall meta-analysis conclusions with single studies removed.

Results for Heterogeneity among studies:

Q-value	*d.f. (Q)*	*P value*	*I-squared*
7.001	6	0.321	14.301

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

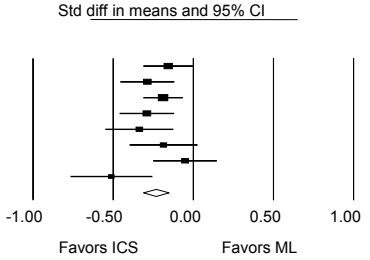
Rescue Medication Use (percent improved symptom free days): Updated Analysis

Studies that reported outcome, but are not included:

Study	*Reason*
Yurdukal et al 2003	*P* value nonsignificant, no variance reported
Becker et al. 2006	Outcome is reported as a median
Malmstrom et al. 1999	P-Value for comparison of interest not reported

ICS v ML: Rescue Medication Use (Percent Rescue Free Days)

Study name	Std diff in means	Standard error	Variance	Lower limit	Upper limit	Z-Value	p-Value
Baumgartner 2003	-0.157	0.080	0.006	-0.314	-0.000	-1.961	0.050
Busse 2001 #715	-0.287	0.087	0.008	-0.457	-0.116	-3.292	0.001
Garcia 2005	-0.189	0.064	0.004	-0.313	-0.064	-2.968	0.003
Meltzer 2002	-0.290	0.088	0.008	-0.462	-0.117	-3.292	0.001
Ostrom 2005	-0.337	0.109	0.012	-0.550	-0.123	-3.093	0.002
Peters 2007	-0.186	0.110	0.012	-0.400	0.029	-1.697	0.090
Zeiger 2005	-0.051	0.103	0.011	-0.252	0.150	-0.499	0.618
Zeiger 2006	-0.511	0.131	0.017	-0.768	-0.254	-3.895	0.000
	-0.235	0.041	0.002	-0.315	-0.155	-5.758	0.000



Sensitivity analyses indicate no difference in overall meta-analysis conclusions with single studies removed.

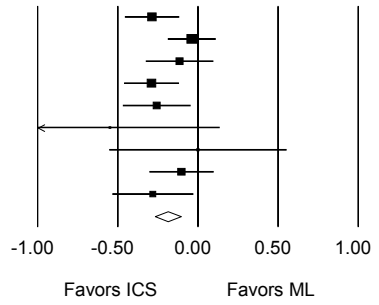
Results for Heterogeneity among studies:

Q-value	*d.f. (Q)*	*P value*	*I-squared*
10.884	7	0.144	35.686

Rescue Medication Use (puffs per day): Updated Analysis

ICS v ML: Rescue Medication Use (Mean Change in Puffs per Day)

Study name	Std diff in means	Standard error	Variance	Lower limit	Upper limit	Z-Value	p-Value
Busse 2001 #715	-0.287	0.087	0.008	-0.457	-0.116	-3.292	0.001
Israel 2002	-0.038	0.077	0.006	-0.190	0.113	-0.495	0.621
Lu 2009	-0.115	0.108	0.012	-0.327	0.097	-1.061	0.289
Meltzer 2002	-0.290	0.088	0.008	-0.462	-0.117	-3.292	0.001
Ostrom 2005	-0.257	0.109	0.012	-0.470	-0.044	-2.367	0.018
Stelmach 2005	-0.549	0.350	0.122	-1.235	0.137	-1.568	0.117
Yurdakul 2003	0.000	0.283	0.080	-0.554	0.554	0.000	1.000
Zeiger 2005	-0.102	0.103	0.011	-0.303	0.099	-0.995	0.320
Zeiger 2006	-0.281	0.130	0.017	-0.535	-0.027	-2.166	0.030
	-0.189	0.042	0.002	-0.271	-0.108	-4.557	0.000

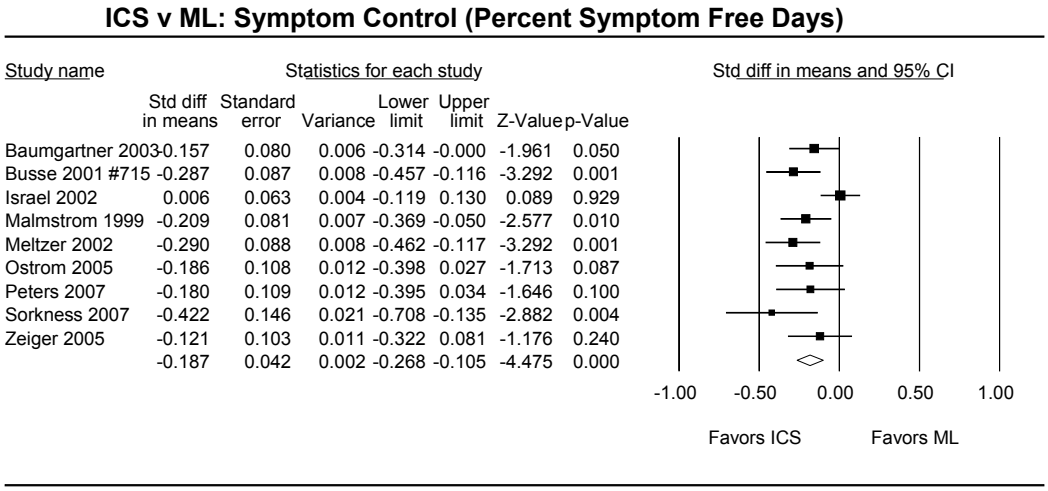


Sensitivity analyses indicate no difference in overall meta-analysis conclusions with single studies removed.

Results for Heterogeneity among studies:

Q-value	*d.f. (Q)*	*P-value*	*I-squared*
9.962	8	0.268	19.699

Percent Improved Symptom Control (symptom free days): Updated Analysis

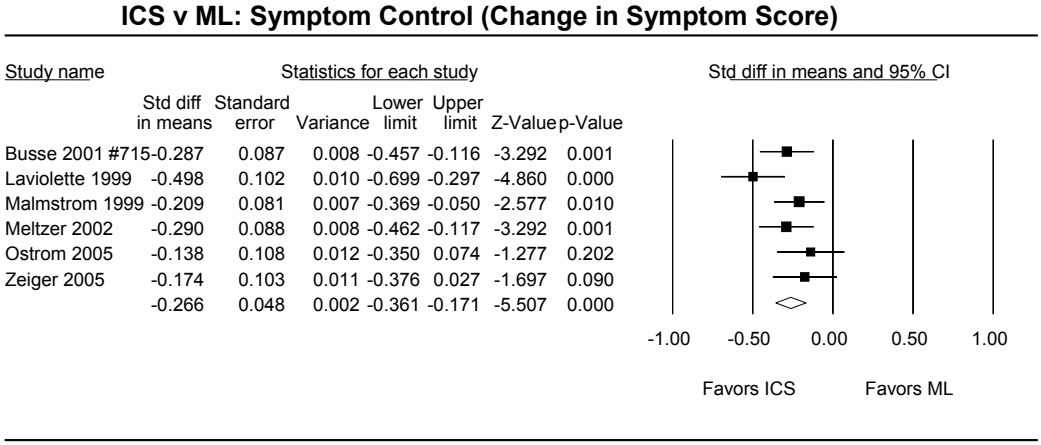


Sensitivity analyses indicate no difference in overall meta-analysis conclusions with single studies removed.

Results for Heterogeneity among studies:

Q-value	*d.f. (Q)*	*P value*	*I-squared*
14.794	8	0.063	45.923

Percent Improved Symptom Control (symptom score): Updated Analysis



Sensitivity analyses indicate no difference in overall meta-analysis conclusions with single studies removed.

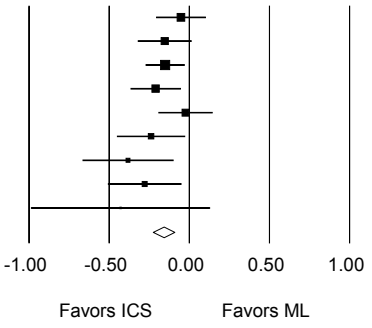
Results for Heterogeneity among studies:

Q-value	*d.f. (Q)*	*P-value*	*I-squared*
7.924	5	0.160	36.899

Percent Exacerbations: Updated Analysis

ICS v ML: Percent Exacerbations

Study name	Std diff in means	Standard error	Variance	Lower limit	Upper limit	Z-Value	p-Value
Baumgartner 2003	-0.052	0.080	0.006	-0.208	0.105	-0.650	0.516
Busse 2001 #715	-0.153	0.087	0.008	-0.323	0.017	-1.763	0.078
Garcia 2005	-0.150	0.064	0.004	-0.275	-0.026	-2.366	0.018
Malmstrom 1999	-0.209	0.081	0.007	-0.369	-0.050	-2.577	0.010
Meltzer 2002	-0.023	0.088	0.008	-0.195	0.148	-0.268	0.789
Peters 2007	-0.238	0.110	0.012	-0.453	-0.023	-2.172	0.030
Sorkness 2007	-0.382	0.146	0.021	-0.668	-0.096	-2.616	0.009
Szefler 2005	-0.278	0.118	0.014	-0.510	-0.046	-2.348	0.019
Yurdakul 2003	-0.429	0.286	0.082	-0.990	0.132	-1.499	0.134
	-0.162	0.034	0.001	-0.229	-0.094	-4.687	0.000

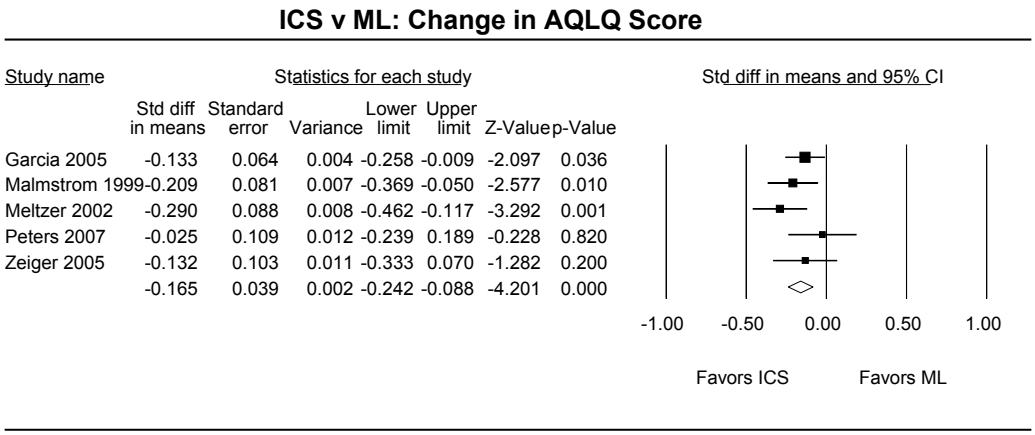


Sensitivity analyses indicate no difference in overall meta-analysis conclusions with single studies removed.

Results for Heterogeneity among studies:

Q-value	*d.f. (Q)*	*P value*	*I-squared*
9.354	8	0.313	14.473

Change in AQLQ Score: Updated Analysis



Sensitivity analyses indicate no difference in overall meta-analysis conclusions with single studies removed.

Results for Heterogeneity among studies:

Q-value	*d.f. (Q)*	*P value*	*I-squared*
4.306	4	0.366	7.112

Zaf compared with ICS Results

Summary of Outcome Measures Analyzed:

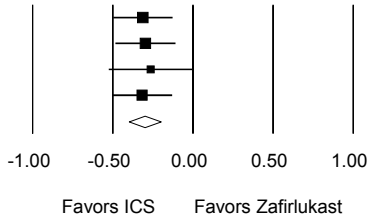
1. **Rescue medication use (percent improved)**
2. **Rescue medication use (puffs per day)**
3. **Symptom control (percent improved)**
4. **Symptom control (score)**
5. **Percent Exacerbations**

Results

Rescue Medication Use (percent improved): Updated Analysis

ICS v Zafirlukast: Rescue Medication Use (Percent Rescue Free Days)

Study name	Std diff in means	Standard error	Variance	Lower limit	Upper limit	Z-Value	p-Value
Bleeker 2000	-0.312	0.095	0.009	-0.498	-0.126	-3.292	0.001
Brabson 2002	-0.296	0.096	0.009	-0.484	-0.109	-3.092	0.002
Busse 2001 #673	-0.263	0.134	0.018	-0.526	-0.000	-1.962	0.050
Kim 2000	-0.317	0.096	0.009	-0.506	-0.128	-3.292	0.001
	-0.302	0.051	0.003	-0.402	-0.202	-5.913	0.000



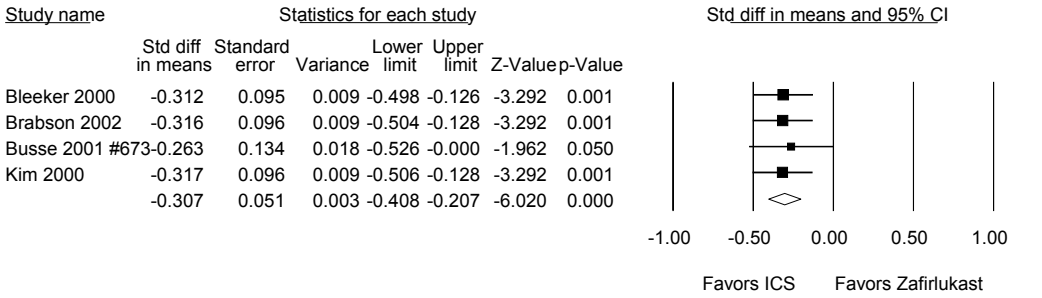
Sensitivity analyses indicate no difference in overall meta-analysis conclusions with single studies removed.

Results for Heterogeneity among studies:

Q-value	*d.f. (Q)*	*P value*	*I-squared*
0.122	3	0.989	0.000

Rescue Medication Use (change in puffs per day): New Analysis

ICS v Zafirlukast: Rescue Medication Use (Mean Change in Puffs per Day)



Sensitivity analyses indicate no difference in overall meta-analysis conclusions with single studies removed.

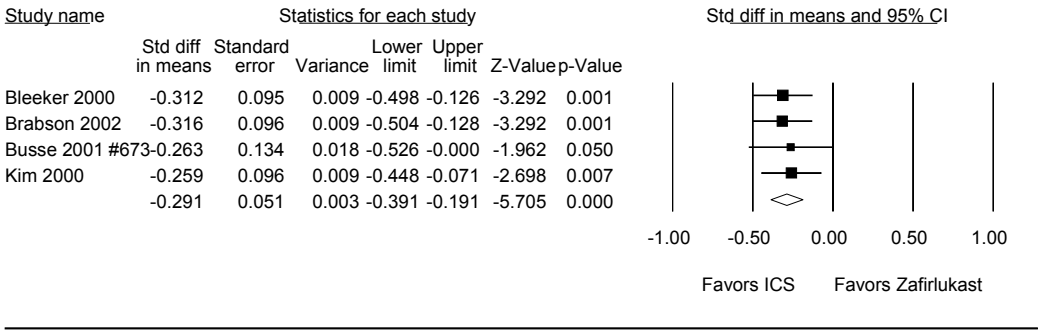
Results for Heterogeneity among studies:

Q-value	*d.f. (Q)*	*P value*	*I-squared*
0.128	3	0.622	0.000

Symptom Control (percent improved symptom free days): Updated Analysis

Studies that reported outcome, but are not included: NA

ICS v Zafirlukast: Symptom Control (Percent Symptom Free Days)

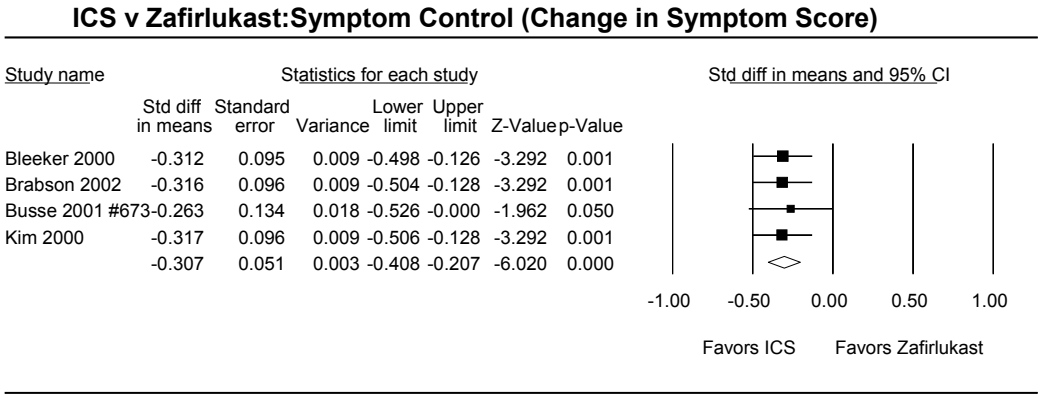


Sensitivity analyses indicate no difference in overall meta-analysis conclusions with single studies removed.

Results for Heterogeneity among studies:

Q-value	*d.f. (Q)*	*P value*	*I-squared*
.268	3	.966	0.000

Symptom Control (change in score): Updated Analysis



Sensitivity analyses indicate no difference in overall meta-analysis conclusions with single studies removed.

Results for Heterogeneity among studies:

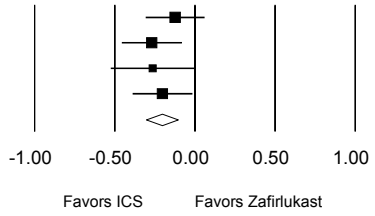
Q-value	*d.f. (Q)*	*P value*	*I-squared*
0.128	3	0.988	0.000

Percent Exacerbations: Updated Analysis

Studies that reported outcome, but are not included: NA

ICS v Zafirlukast: Percent Exacerbations

Study name	Std diff in means	Standard error	Variance	Lower limit	Upper limit	Z-Value	p-Value
Bleeker 2000	-0.123	0.094	0.009	-0.308	0.061	-1.308	0.191
Brabson 2002	-0.269	0.096	0.009	-0.457	-0.081	-2.809	0.005
Busse 2001 #673	-0.263	0.134	0.018	-0.526	-0.000	-1.962	0.050
Kim 2000	-0.202	0.096	0.009	-0.390	-0.014	-2.110	0.035
	-0.207	0.051	0.003	-0.307	-0.107	-4.064	0.000



Sensitivity analyses indicate no difference in overall meta-analysis conclusions with single studies removed.

Results for Heterogeneity among studies:

Q-value	*d.f. (Q)*	*P value*	*I-squared*
1.385	3	0.709	0.000

ML compared with BDP Results

Summary of Outcome Measures Analyzed:

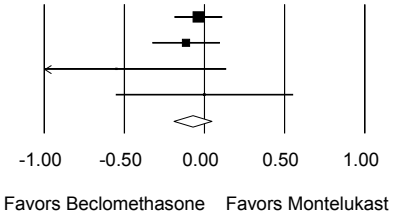
1. **Rescue medication use (change in puffs per day)**
2. **Symptom control (percent improved)**
3. **Percent Exacerbations**

Results

Rescue Medication Use (puffs per day): Updated Analysis

Montelukast v Beclomethasone: Rescue Medication Use (Mean Change in Puffs per Day)

Study name	Std diff in means	Standard error	Variance	Lower limit	Upper limit	Z-Value	p-Value
Israel 2002	-0.038	0.077	0.006	-0.190	0.113	-0.495	0.621
Lu 2009	-0.115	0.108	0.012	-0.327	0.097	-1.061	0.289
Stelmach 2005	-0.549	0.350	0.122	-1.235	0.137	-1.568	0.117
Yurdakul 2003	0.000	0.283	0.080	-0.554	0.554	0.000	1.000
	-0.076	0.060	0.004	-0.194	0.043	-1.251	0.211



Sensitivity analyses indicate no difference in overall meta-analysis conclusions with single studies removed.

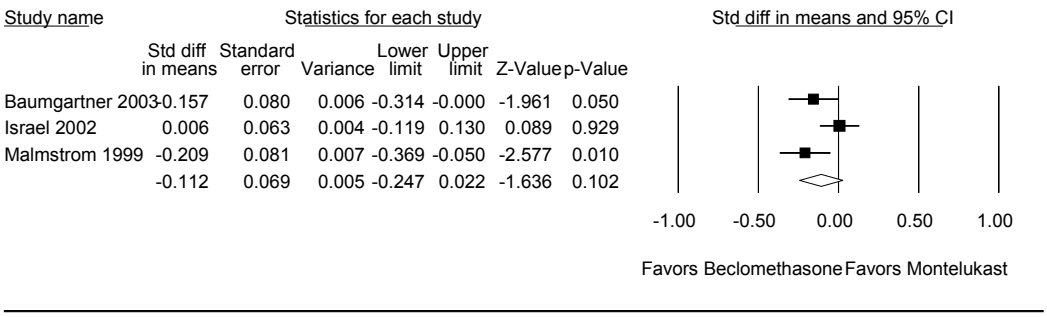
Results for Heterogeneity among studies:

Q-value	*d.f. (Q)*	*P value*	*I-squared*
2.266	3	0.519	0.000

Symptom Control (Percent Improvement in Symptom Free Days)

Studies that reported outcome, but are not included: NA

Montelukast v Beclomethasone: Symptom Control (Percent Symptom Free Days)



Sensitivity analysis results:

	Statistics with study removed	
Study Name	*Z-value*	*P value*
Baumgartner 2004	-0.8930	0.3718
Israel 2002	-3.2051	0.0014
Malmstrom 1999	-0.8439	0.3987
Overall Model	-1.6356	0.1019

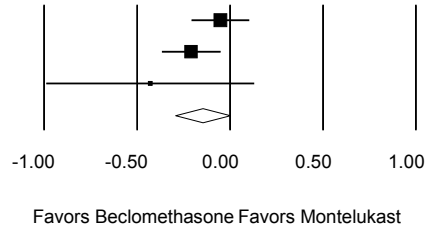
Results for Heterogeneity among studies:

Q-value	*d.f. (Q)*	*P value*	*I-squared*
5.090	2	0.078	60.707

Percent Exacerbations

Montelukast v Beclomethasone: Percent Exacerbations

Study name	Std diff in means	Standard error	Variance	Lower limit	Upper limit	Z-Value	p-Value
Baumgartner 2003	-0.052	0.080	0.006	-0.208	0.105	-0.650	0.516
Malmstrom 1999	-0.209	0.081	0.007	-0.369	-0.050	-2.577	0.010
Yurdakul 2003	-0.429	0.286	0.082	-0.990	0.132	-1.499	0.134
	-0.149	0.075	0.006	-0.297	-0.002	-1.984	0.047



Heterogeneity			
Q-value	df (Q)	P-value	I-squared
2.965	2	0.227	32.537

**Sensitivity analysis: Baumgartner is influential.

Study name	Statistics with study removed						
	Point	Standard error	Variance	Lower limit	Upper limit	Z-Value	p-Value
Baumgartner 2003	-0.2258	0.0782	0.0061	-0.3790	-0.0726	-2.8884	0.0039
Malmstrom 1999	-0.1403	0.1597	0.0255	-0.4533	0.1727	-0.8785	0.3797
Yurdakul 2003	-0.1299	0.0787	0.0062	-0.2843	0.0244	-1.6504	0.0989
	-0.1493	0.0753	0.0057	-0.2968	-0.0018	-1.9838	0.0473

Montelukast compared with Fluticasone Results

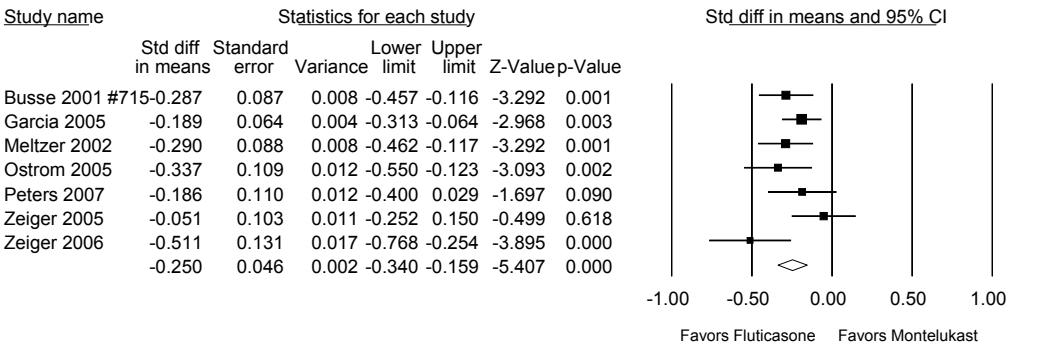
Summary of Outcome Measures Analyzed:

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 (% rescue free days): Updated Analysis

Fluticasone v Montelukast: Rescue Medication Use (Percent Rescue Free Days)



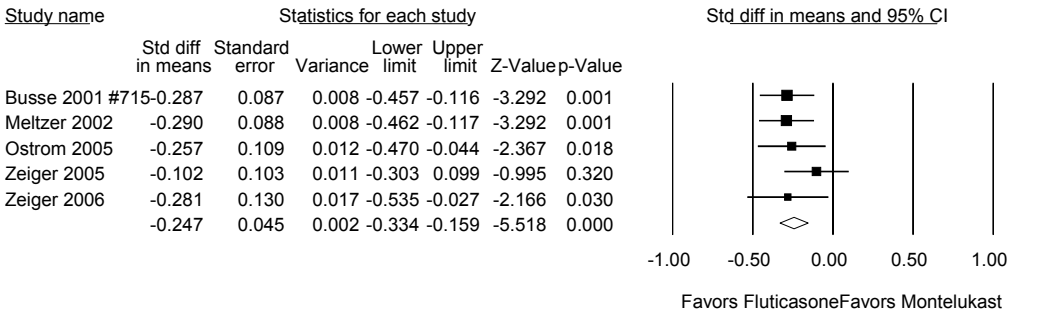
Sensitivity analyses indicate no difference in overall meta-analysis conclusions with single studies removed.

Results for Heterogeneity among studies:

Q-value	*d.f. (Q)*	*P value*	*I-squared*
9.939	6	0.127	39.633

Rescue Medication Use (puffs per day): Updated Analysis

Fluticasone v Montelukast: Rescue Medication Use (Mean Change in Puffs per Day)



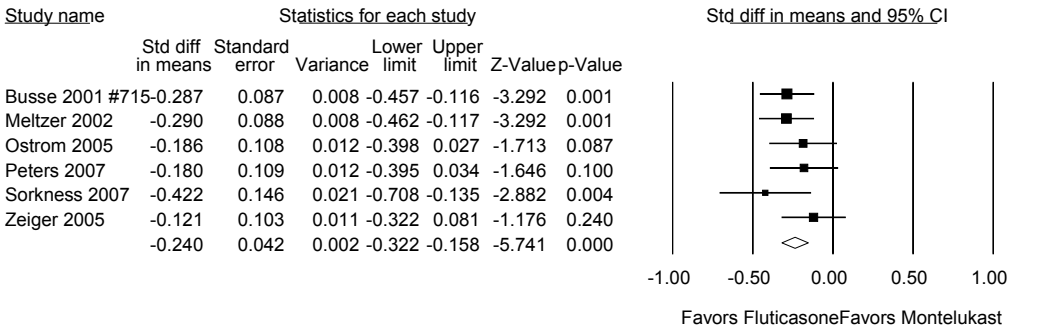
Sensitivity analyses indicate no difference in overall meta-analysis conclusions with single studies removed.

Results for Heterogeneity among studies:

Q-value	*d.f. (Q)*	*P-value*	*I-squared*
2.511	4	0.643	0.000

Percent Improved Symptom Control (symptom free days): Updated Analysis

Fluticasone v Montelukast: Symptom Control (Percent Symptom Free Days)



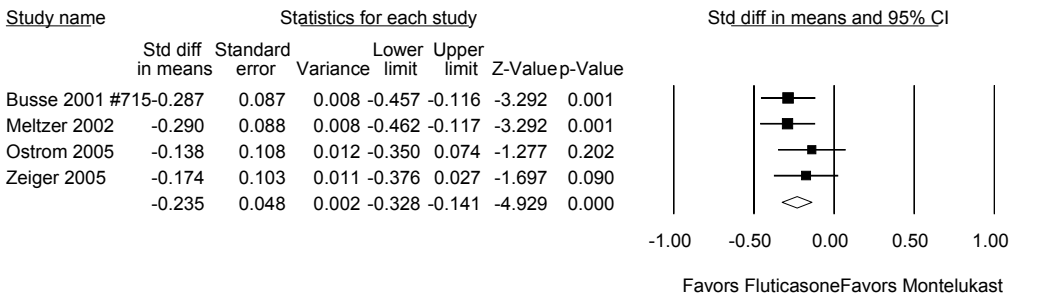
Sensitivity analyses indicate no difference in overall meta-analysis conclusions with single studies removed.

Results for Heterogeneity among studies:

Q-value	*d.f. (Q)*	*P value*	*I-squared*
4.047	5	0.543	0.000

Percent Improved Symptom Control (symptom score): Updated Analysis

Fluticasone v Montelukast: Symptom Control (Change in Symptom Score)

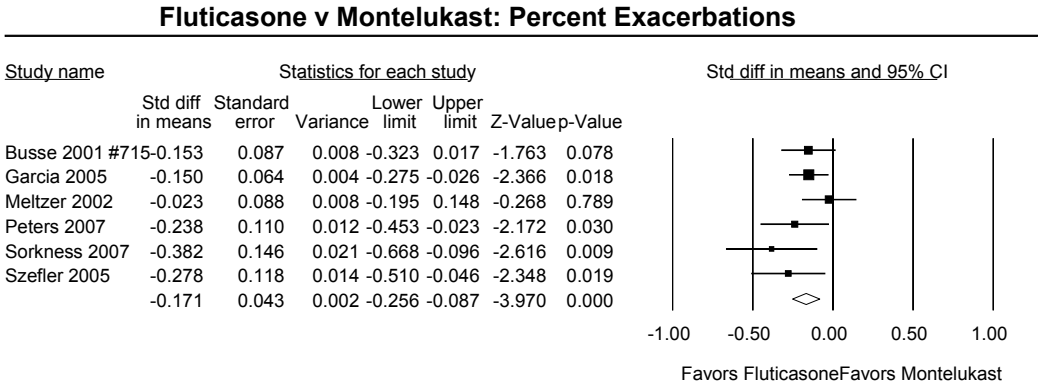


Sensitivity analyses indicate no difference in overall meta-analysis conclusions with single studies removed.

Results for Heterogeneity among studies:

Q-value	*d.f. (Q)*	*P value*	*I-squared*
1.885	3	0.597	0.000

Percent Exacerbations: Updated Analysis

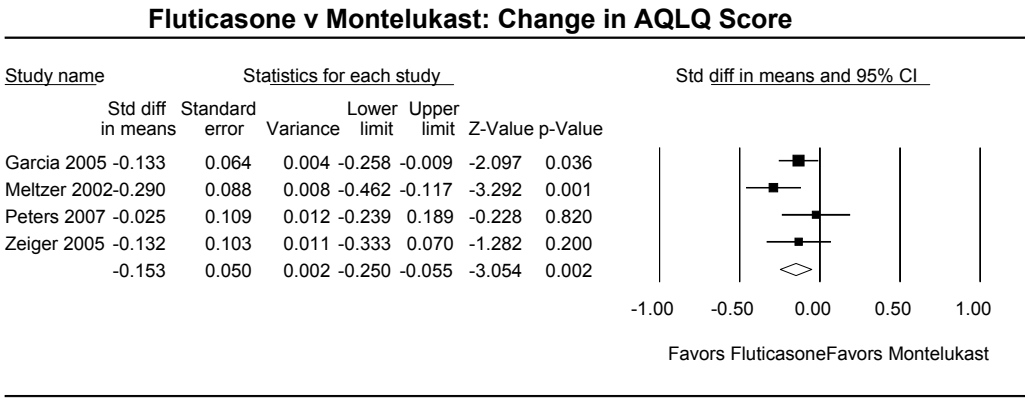


Sensitivity analyses indicate no difference in overall meta-analysis conclusions with single studies removed.

Results for Heterogeneity among studies:

Q-value	*d.f. (Q)*	*P value*	*I-squared*
6.250	5	0.283	19.996

Change in AQLQ Score: Updated Analysis



Sensitivity analyses indicate no difference in overall meta-analysis conclusions with single studies removed.

Results for Heterogeneity among studies:

Q-value	*d.f. (Q)*	*P value*	*I-squared*
3.928	3	0.269	23.623

ICS compared with LABA Monotherapy

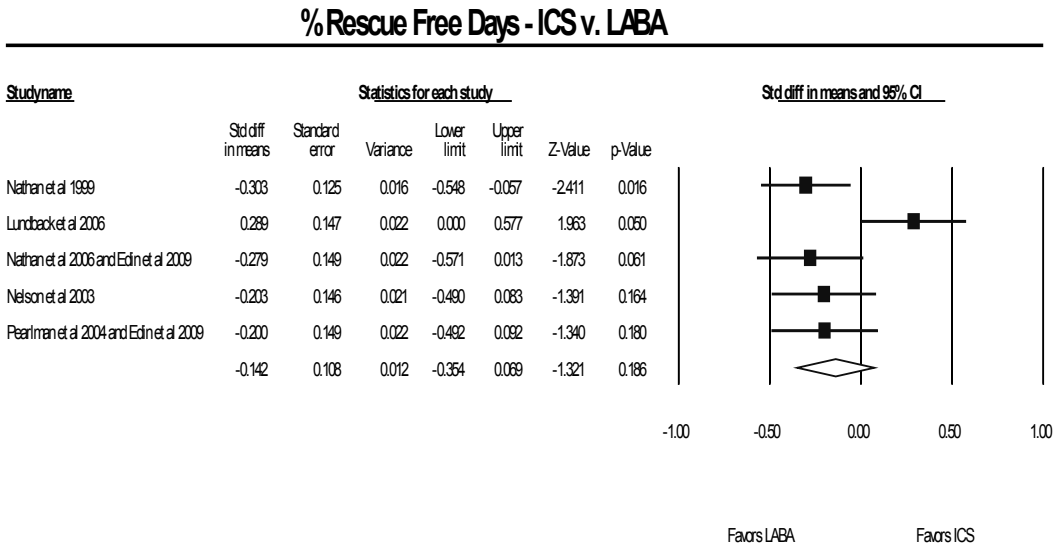
Summary of Outcome Measures Analyzed:

1) **% Rescue medication free days**
2) **Rescue medication reduction in puffs**
3) **% Symptom free days**
4) **Change in symptom scores**
5) **Percent Exacerbations**

Results

% Rescue Medication Free Days – Updated Analysis

Studies not included because of lack of appropriate data: Lazarus et al, 2001 and Deykin et al 2005; Simons et al 1997; Kavuru et al 2000 and Nathan et al 2003; Murray et al 2004; Noonan et al 2006; Shapiro et al 2000 and Nathan et al 2003; Corren et al 2007; Verberne et al 1997.

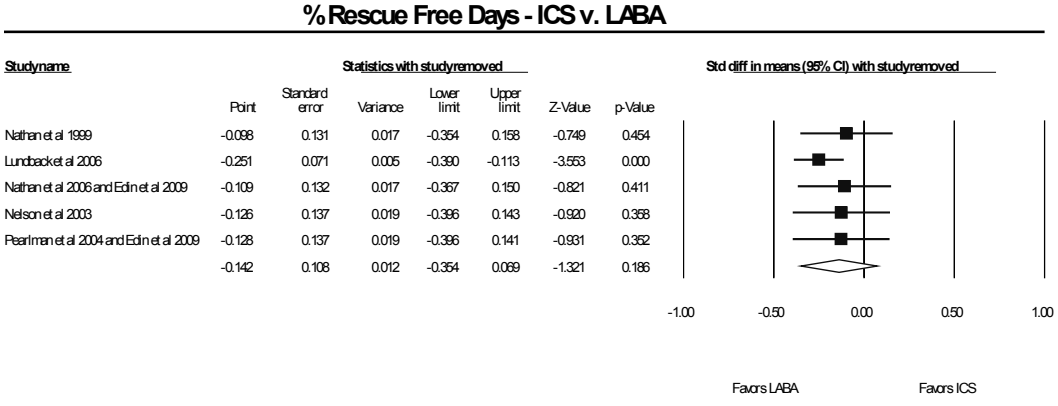


Heterogeneity

Q-value	df (Q)	P-value	I-squared
11.36999371	4	2.27E-02	64.81968151

Sensitivity analyses indicate no difference in overall meta-analysis conclusions with single studies removed with the exception of removing Lundback et al. The overall result becomes significant in favor of LABA (SMD -0.25 (95% CI -0.39, -0.11).

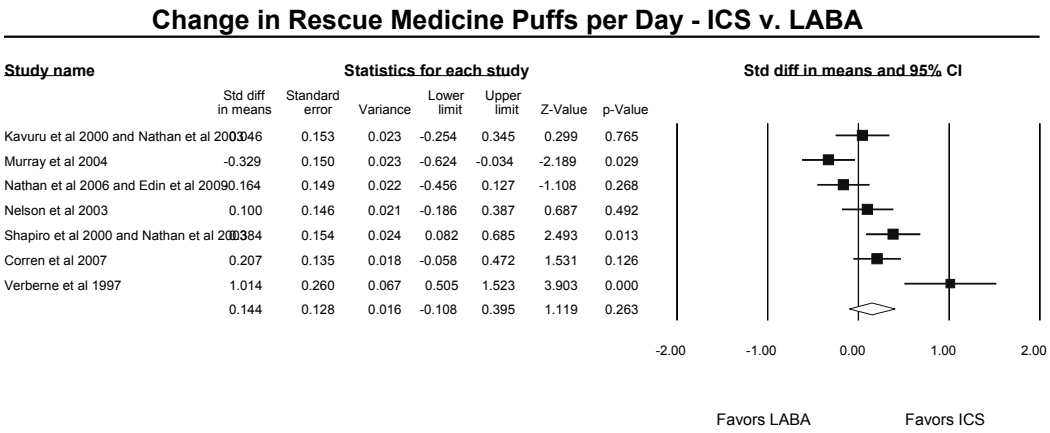
Sensitivity Analyses - % Rescue Free Days – ICS v. LABA



Rescue Medication Use (puffs per day) – Updated Analysis

Included Studies:
Kavuru et al 2000 and Nathan et al 2003
Murray et al 2004
Nathan et al 2006 and Edin et al 2009
Nelson et al 2003
Shapiro et al 2000 and Nathan et al 2003
Corren et al 2007
Verberne et al 1997

Studies not included because of lack of applicable data:
Lazarus et al 2001 and Deykin et al, 2005
Nathan et al, 1999
Simons et al, 1997
Lundback et al, 2006
Noonan et al, 2006
Verberne et al, 1997
Pearlman et al, 2004 and Edin et al, 2009



Heterogeneity

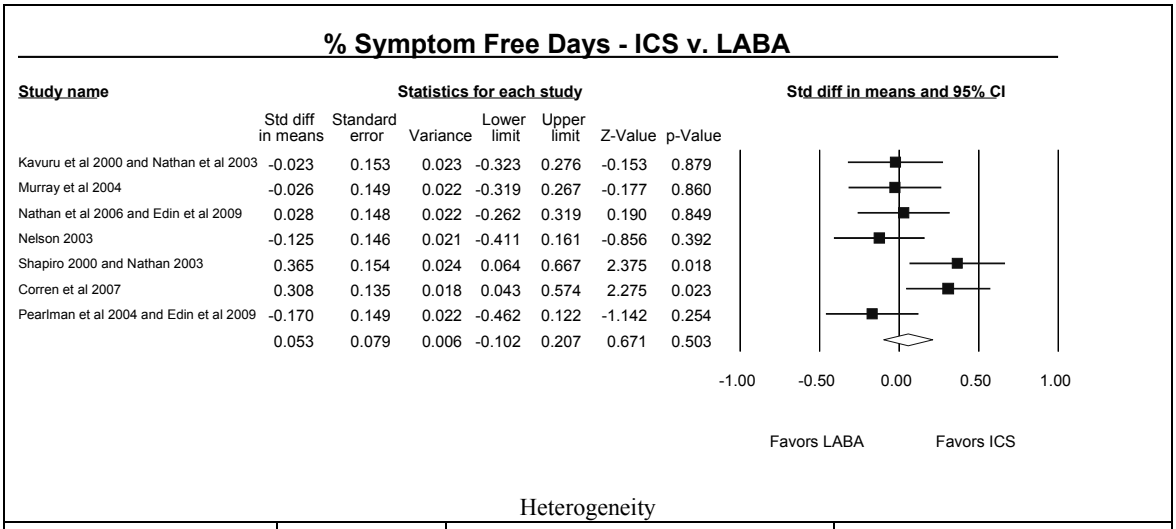
Q-value	df (Q)	P-value	I-squared
27.82665345	6	1.01E-04	78.43793896

Sensitivity analyses indicate no difference in overall meta-analysis conclusions with single studies removed.

% Symptom free days – Updated Analysis

Included Studies:
Kavuru et al 2000 and Nathan et al 2003
Murray et al 2004
Nathan et al 2006 and Edin et al 2009
Nelson et al 2003
Shapiro et al 2000 and Nathan et al 2003
Corren et al 2007
Pearlman et al 2004 and Edin et al 2009

Studies not included:
Lazarus et al 2001; Deykin 2005Nathan et al 1999Simons et al 1997Lundback 2006Noonan 2006Verberne et al 1997



Heterogeneity

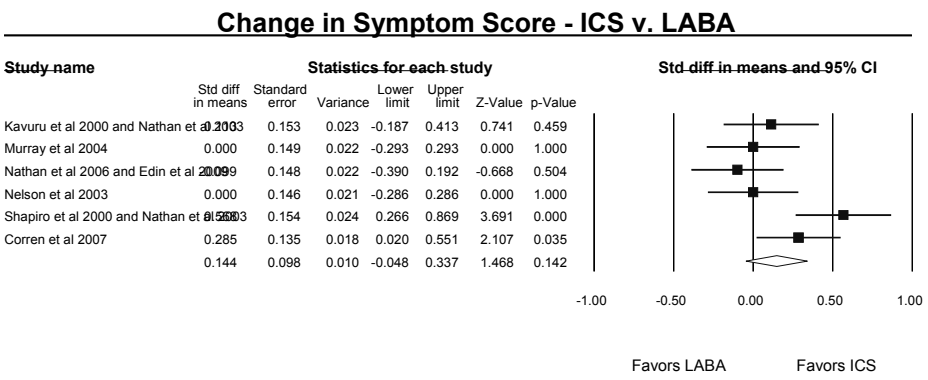
Q-value	df (Q)	P-value	I-squared
11.95317722	6	0.063021552	49.80414084

Sensitivity analyses indicate no difference in overall meta-analysis conclusions with single studies removed.

Symptom control (symptom score) – Update Analysis

Included studies:
Kavuru et al 2000 and Nathan et al 2003
Murray et al 2004
Nathan et al 2006 and Edin et al 2009
Nelson et al 2003
Shapiro et al 2000 and Nathan et al 2003
Corren et al 2007

Studies not included:
Lazarus et al 2001 and Deykin et al 2005
Nathan et al 1999
Simons et al 1997
Lundback et al 2006
Noonan et al 2006
Verberne et al 1997
Pearlman et al 2004 and Edin 2009



Heterogeneity

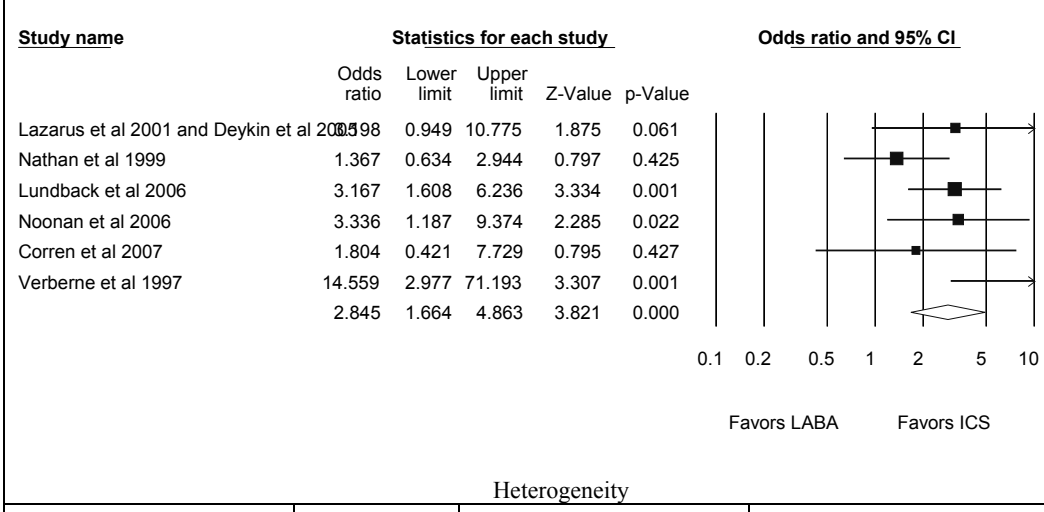
Q-value	df (Q)	P-value	I-squared
13.30378884	5	2.07E-02	62.41672158

Sensitivity analyses indicate no difference in overall meta-analysis conclusions with single studies removed.

Exacerbations (Odds Ratio): Updated Analysis

Note:
Studies included in this analysis were those that provided definitions of "exacerbation" and reported a measure of patients experiencing exacerbations. Three studies reported numbers of patients experiencing clearly defined exacerbations;{Lazarus, 2001 #694; Corren, 2007 #4799; Noonan, 2006 #38} two reported the numbers of patients receiving oral steroids for exacerbations;{Nathan, 1999 #907; Verberne, 1997 #1082} and one reported the number of patients experiencing at least two defined exacerbations.{Lundback, 2006 #168} Studies reporting only withdrawals from the trial due to exacerbations and those failing to clearly define "exacerbation" were not included in our analysis.

Studies not included:
Simons et al. 1997
Kavuru et al. 2000; Nathan et al. 2003
Murray et al. 2004
Nathan et al. 2006; Edin et al. 2009
Nelson et al. 2003
Shapiro et al. 2000; Nathan et al. 2003
Pearlman et al. 2004; Edin et al. 2009



Heterogeneity

Q-value	df (Q)	P-value	I-squared
8.095029256	5	0.151075559	38.23370068

Sensitivity analyses indicate no difference in overall meta-analysis conclusions with single studies removed.

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)**

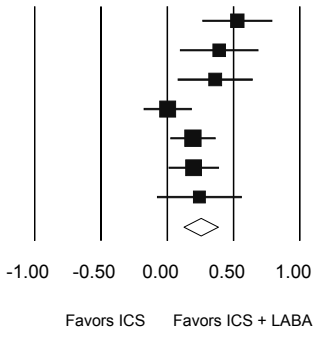
Results

Rescue Medication Use (puffs per day): Updated Analysis

Studies not included: Boonsawat et al 2008; Rojas et al 2007

ICS + LABA vs. ICS (same dose, 1st line therapy) - Rescue medicine use, puffs per day

Study name	Std diff in means	Standard error	Variance	Lower limit	Upper limit	Z-Value	p-Value
Chuchalain 2002	0.528	0.136	0.018	0.262	0.794	3.895	0.000
Murray 2004	0.391	0.152	0.023	0.094	0.689	2.580	0.010
Nelson 2003	0.362	0.146	0.021	0.077	0.647	2.487	0.013
O'Byrne 2001	0.004	0.093	0.009	-0.179	0.186	0.038	0.970
Renzi, 2010	0.194	0.088	0.008	0.021	0.367	2.198	0.028
Kerwin, 2008	0.200	0.098	0.010	0.008	0.391	2.045	0.041
Strand, 2007	0.242	0.164	0.027	-0.079	0.564	1.478	0.139
	0.251	0.066	0.004	0.121	0.381	3.790	0.000



Heterogeneity

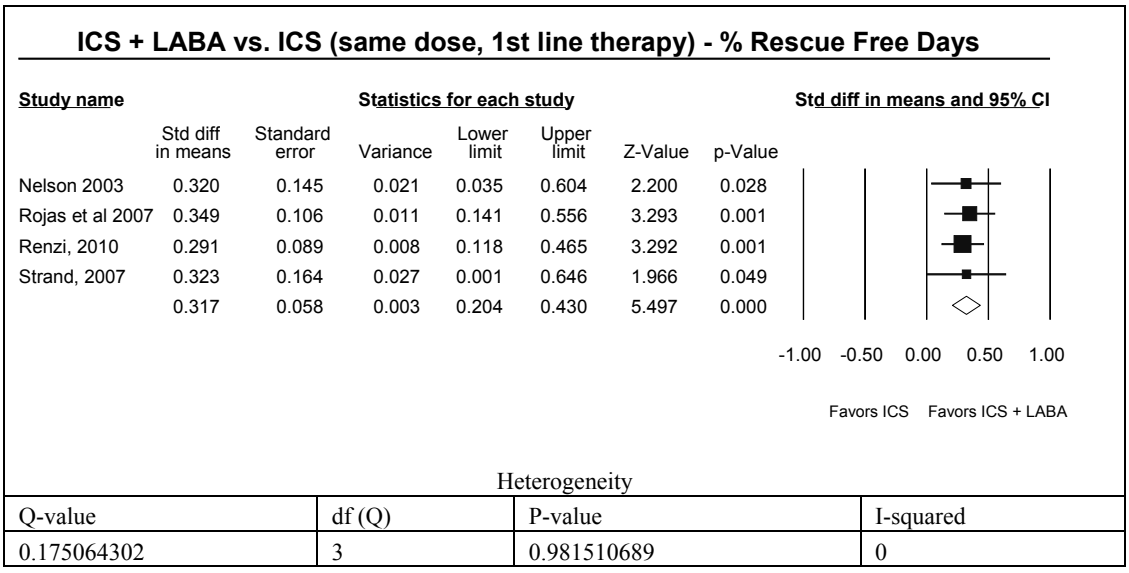
Q-value	df (Q)	P-value	I-squared
12.91750977	6	4.44E-02	53.5514189

Sensitivity analyses indicate no difference in overall meta-analysis conclusions with single studies removed.

% Rescue Medication Free Days – Updated Analysis

Included studies:
Nelson et al 2003
Rojas et al 2007
Renzi et al 2010
Strand 2007
(Note: Rojas et al reported the outcome as median % rescue free days; sensitivity analyses show that removing this study does not change the overall conclusion.)

Studies not included:
Chuchalain et al 2002
Boonsawat et al 2008
O'Byren et al 2001
Kerwin et al 2008
Murray et al 2004



Heterogeneity

Q-value	df (Q)	P-value	I-squared
0.175064302	3	0.981510689	0

Sensitivity analyses indicate no difference in overall meta-analysis conclusions with single studies removed.

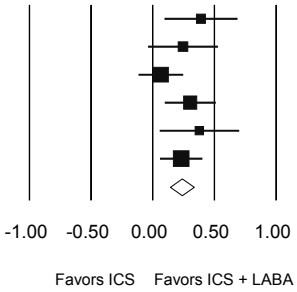
% Symptom free days: Updated Analysis

Included studies:
Murray et al. 2004
Nelson et al. 2003
O'Byrne et al. 2001
Rojas et al. 2007
Strand et al. 2007
Renzi et al. 2010

Studies not included:
Chuchalain et al 2002
Boonsawat et al 2008
Kerwin et al 2008

ICS + LABA vs. ICS (same dose, 1st line therapy) - % Symptom free days

Study name	Std diff in means	Standard error	Variance	Lower limit	Upper limit	Z-Value	p-Value
Murray 2004	0.391	0.152	0.023	0.094	0.689	2.580	0.010
Nelson 2003	0.246	0.145	0.021	-0.038	0.530	1.698	0.090
O'Byrne 2001	0.066	0.093	0.009	-0.117	0.249	0.707	0.480
Rojas et al 2007	0.305	0.106	0.011	0.097	0.512	2.880	0.004
Strand, 2007	0.378	0.165	0.027	0.055	0.701	2.294	0.022
Renzi, 2010	0.231	0.088	0.008	0.058	0.404	2.613	0.009
	0.236	0.050	0.002	0.139	0.333	4.750	0.000



Heterogeneity

Q-value	df (Q)	P-value	I-squared
5.532061896	5	0.354442985	9.617786394

Sensitivity analyses indicate no difference in overall meta-analysis conclusions with single studies removed.

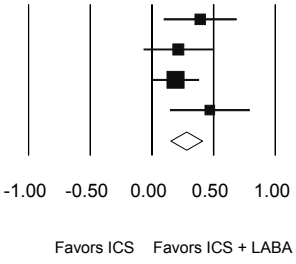
Symptom Control (symptom score): Updated Analysis

Included Studies
Murray et al 2004
Nelson et al 2003
Kerwin et al 2008
Strand et al 2007

Studies not included:
Chuchalain et al 2002
Boonsawat et al 2008
Rojas et al 2007
O'Byrne 2001
Renzi et al 2010

ICS + LABA vs. ICS (same dose, 1st line therapy) - Change in Symptom Score

	Statistics for each study							Std diff in means and 95% CI
	Std diff in means	Standard error	Variance	Lower limit	Upper limit	Z-Value	p-Value	
Murray, 2004	0.391	0.152	0.023	0.094	0.689	2.580	0.010	
Nelson, 2003	0.214	0.145	0.021	-0.069	0.498	1.482	0.138	
Kerwin, 2008	0.191	0.098	0.010	0.000	0.383	1.961	0.050	
Strand, 2007	0.469	0.166	0.027	0.144	0.794	2.832	0.005	
	0.277	0.066	0.004	0.148	0.405	4.224	0.000	



Heterogeneity

Q-value	df (Q)	P-value	I-squared
2.870736346	3	0.411987437	0

Sensitivity analyses indicate no difference in overall meta-analysis conclusions with single studies removed.

ICS compared with LABA+ICS (Higher Dose) Meta-Analysis Results

Summary of Outcome Measures Analyzed:

1) **Rescue medication use (percent rescue free days)**
2) **Rescue medication use (puffs per day)**
3) **Symptom control (percent symptom free days)**
4) **Symptom control (symptom score)**
5) **Exacerbations**

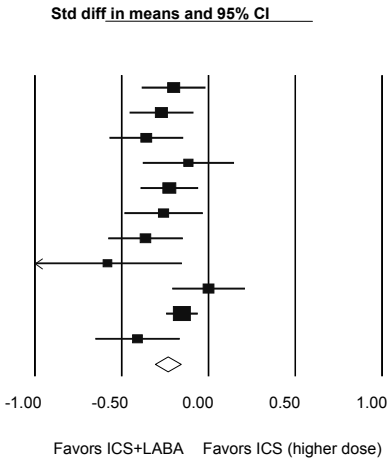
Results

% Rescue free days – Updated analysis

Studies that reported outcome but that are not included: Verberne et al, 1998 (no p-value); Jenkins et al, 2000 (data in graph only); Gappa et al, 2009 (no p-value); van Noord et al, 1999 (reported outcome as odds ratio)

ICS+LABA v ICS (higher dose) - % Rescue Free Days

Study name	Std diff in means	Lower limit	Upper limit	p-Value
Baraniuk et al 1999a	-0.201	-0.385	-0.016	0.033
Baraniuk et al 1999b	-0.271	-0.455	-0.086	0.004
Bateman et al 2003	-0.358	-0.571	-0.145	0.001
Bisgaard et al 2006	-0.115	-0.379	0.148	0.389
Busse et al 2003	-0.225	-0.392	-0.059	0.008
deBlic et al 2009	-0.259	-0.485	-0.033	0.025
Ind et al 2003	-0.362	-0.578	-0.147	0.001
Jarjour et al 2006	-0.581	-1.010	-0.153	0.008
Johansson et al 2001	0.001	-0.209	0.211	0.994
O'Byrne et al 2005	-0.153	-0.244	-0.062	0.001
Peters et al 2008	-0.409	-0.652	-0.166	0.001
	-0.235	-0.309	-0.160	0.000



Heterogeneity			
Q-value	df (Q)	P-value	I-squared
15.678	10	0.109	36.217

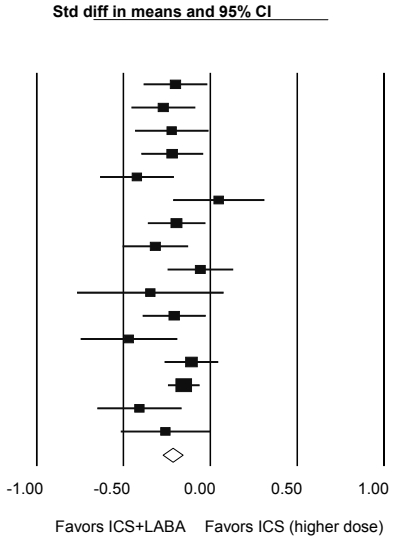
Sensitivity analyses indicate no difference in overall meta-analysis conclusions with single studies removed.

Rescue medication use (puffs per day): Updated Analysis

Studies that reported outcome but that are not included: Pauwels et al, 1997 (no p-value); Chuchalin et al 2008 (compares once daily ICS+LABA to twice daily ICS)

ICS+LABA v ICS (higher dose) - Rescue Medication Use - Puffs per day

Study name	Std diff in means	Lower limit	Upper limit	p-Value
Baraniuk et al 1999a	-0.201	-0.385	-0.016	0.033
Baraniuk et al 1999b	-0.271	-0.455	-0.086	0.004
Bateman et al 2003	-0.222	-0.434	-0.010	0.040
Bateman et al 2006	-0.220	-0.399	-0.041	0.016
Bergmann et al 2004	-0.423	-0.636	-0.210	0.000
Bisgaard et al 2006	0.048	-0.215	0.311	0.720
Busse et al 2003	-0.194	-0.361	-0.028	0.022
Condemi et al 1999	-0.317	-0.506	-0.128	0.001
Greening et al 1994	-0.058	-0.248	0.132	0.553
Jarjour et al 2006	-0.346	-0.768	0.077	0.109
Lalloo et al 2003	-0.208	-0.390	-0.026	0.025
Mitchell et al 2003	-0.469	-0.748	-0.190	0.001
O'Byrne et al 2001	-0.109	-0.265	0.047	0.170
O'Byrne et al 2005	-0.153	-0.244	-0.062	0.001
Peters et al 2008	-0.409	-0.652	-0.166	0.001
Vermetten et al 1999	-0.258	-0.516	-0.000	0.050
	-0.218	-0.275	-0.161	0.000



Heterogeneity			
Q-value	df (Q)	P-value	I-squared
21.222	15	0.130	29.317

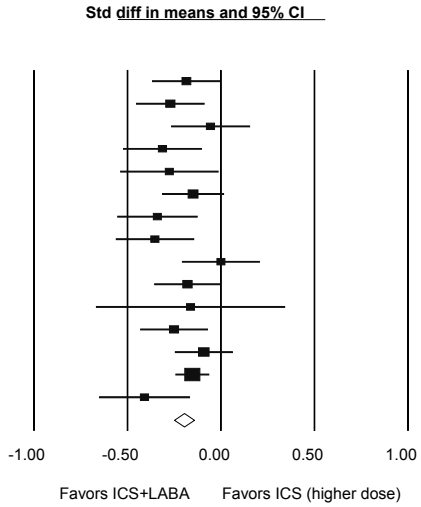
Sensitivity analyses indicate no difference in overall meta-analysis conclusions with single studies removed.

% Symptom free days: Updated Analysis

Studies that reported outcome but that are not included: Greening et al, 1994 (no p-value); Peters et al, 2007 (compares once daily ICS+LABA to twice daily ICS); Chuchalin et al, 2008 (compares once daily ICS+LABA to twice daily ICS); Gappa et al, 2009 (no p-value); Jarjour et al, 2006 (no p-value)

ICS+LABA v ICS (higher dose) - % Symptom Free Days

Study name	Statistics for each study			
	Std diff in means	Lower limit	Upper limit	p-Value
Baraniuk et al 1999a	-0.184	-0.369	-0.000	0.050
Baraniuk et al 1999b	-0.271	-0.455	-0.086	0.004
Bateman et al 2003	-0.056	-0.267	0.156	0.607
Bergmann et al 2004	-0.313	-0.525	-0.101	0.004
Bisgaard et al 2006	-0.276	-0.540	-0.012	0.041
Busse et al 2003	-0.149	-0.316	0.017	0.078
Ind et al 2003	-0.340	-0.555	-0.124	0.002
Jenkins et al 2000	-0.353	-0.564	-0.143	0.001
Johansson et al 2001	0.000	-0.210	0.210	1.000
Kelsen et al 1999	-0.179	-0.358	-0.000	0.050
Kips et al 2000	-0.162	-0.670	0.345	0.530
Lalloo et al 2003	-0.251	-0.433	-0.069	0.007
O'Byrne et al 2001	-0.091	-0.247	0.064	0.250
O'Byrne et al 2005	-0.153	-0.244	-0.062	0.001
Peters et al 2008	-0.409	-0.652	-0.166	0.001
	-0.198	-0.252	-0.144	0.000



Heterogeneity			
Q-value	df (Q)	P-value	I-squared
17.2683	14	0.2421633	18.92646

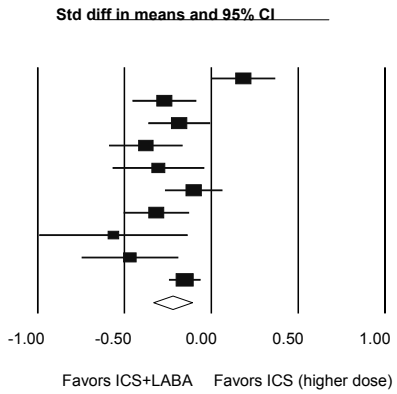
Sensitivity analyses indicate no difference in overall meta-analysis conclusions with single studies removed.

Symptom control (symptom score): Updated Analysis

Studies that reported outcome but that are not included: Lalloo et al, 2003 (no p-value); Pauwels et al 1997 (no p-value); Peters et al, 2007 (compares once daily ICS+LABA to twice daily ICS); Chuchalin et al, 2008 (compares once daily ICS+LABA to twice daily ICS)

ICS+LABA v ICS (higher dose) - Symptom Score

Study name	Std diff in means	Lower limit	Upper limit	p-Value
Baraniuk et al 1999a	0.184	0.000	0.369	0.050
Baraniuk et al 1999b	-0.271	-0.455	-0.086	0.004
Bateman et al 2006	-0.185	-0.364	-0.007	0.042
Bergmann et al 2004	-0.377	-0.590	-0.165	0.000
Bisgaard et al 2006	-0.305	-0.569	-0.040	0.024
Busse et al 2003	-0.101	-0.267	0.065	0.232
Condemi et al 1999	-0.317	-0.506	-0.128	0.001
Jarjour et al 2006	-0.564	-0.992	-0.136	0.010
Mitchell et al 2003	-0.469	-0.748	-0.190	0.001
O'Byrne et al 2005	-0.153	-0.244	-0.062	0.001
	-0.223	-0.335	-0.112	0.000



Heterogeneity with Baraniuk et al, 1999a			
Q-value	df (Q)	P-value	I-squared
30.511	9	0.000	70.502
Heterogeneity w/o Baraniuk et al, 1999a			
Q-value	df (Q)	P-value	I-squared
13.512	8	0.095	40.792

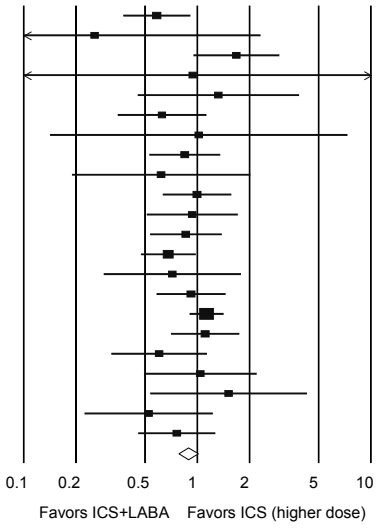
Sensitivity analyses indicate no difference in overall meta-analysis conclusions with single studies removed.

Exacerbations: Updated Analysis

Studies that reported the number of patients or the percent of patients in each group who experienced exacerbations are included.

ICS+LABA v ICS (higher dose) - Exacerbations (all)

Study name	Odds ratio	Lower limit	Upper limit	p-Value
Bateman et al 2003	0.584	0.374	0.912	0.018
Bergmann et al 2004	0.256	0.028	2.313	0.225
Bisgaard et al 2006	1.679	0.948	2.973	0.075
Bouros et al 1999	0.941	0.058	15.365	0.966
Busse et al 2003	1.324	0.453	3.865	0.608
Condemi et al 1999	0.627	0.348	1.129	0.120
deBlic et al 2009	1.020	0.142	7.338	0.984
Ind et al 2003	0.847	0.529	1.357	0.490
Jarjour et al 2006	0.619	0.189	2.024	0.428
Jenkins et al 2000	0.997	0.633	1.572	0.991
Johansson et al 2001	0.935	0.511	1.710	0.827
Kelsen et al 1999	0.859	0.534	1.383	0.533
Lalloo et al 2003	0.681	0.473	0.981	0.039
Mitchell et al 2003	0.718	0.288	1.786	0.476
Murray et al 1999	0.920	0.582	1.457	0.723
O'Byrne et al 2005	1.131	0.900	1.421	0.290
Pauwels et al 1997; O'Byrne et al 2008	1.110	0.706	1.747	0.651
Peters et al 2008	0.603	0.319	1.140	0.120
van Noord et al 1999	1.041	0.493	2.199	0.917
Verberne et al 1998	1.514	0.535	4.286	0.434
Vermetten et al 1999	0.524	0.224	1.230	0.138
Woolcock et al 1996	0.762	0.456	1.272	0.299
	0.885	0.779	1.007	0.063



Heterogeneity			
Q-value	df (Q)	P-value	I-squared
23.8841	21	0.301	11.916

Sensitivity analyses indicate no difference in overall meta-analysis conclusions with single studies removed.

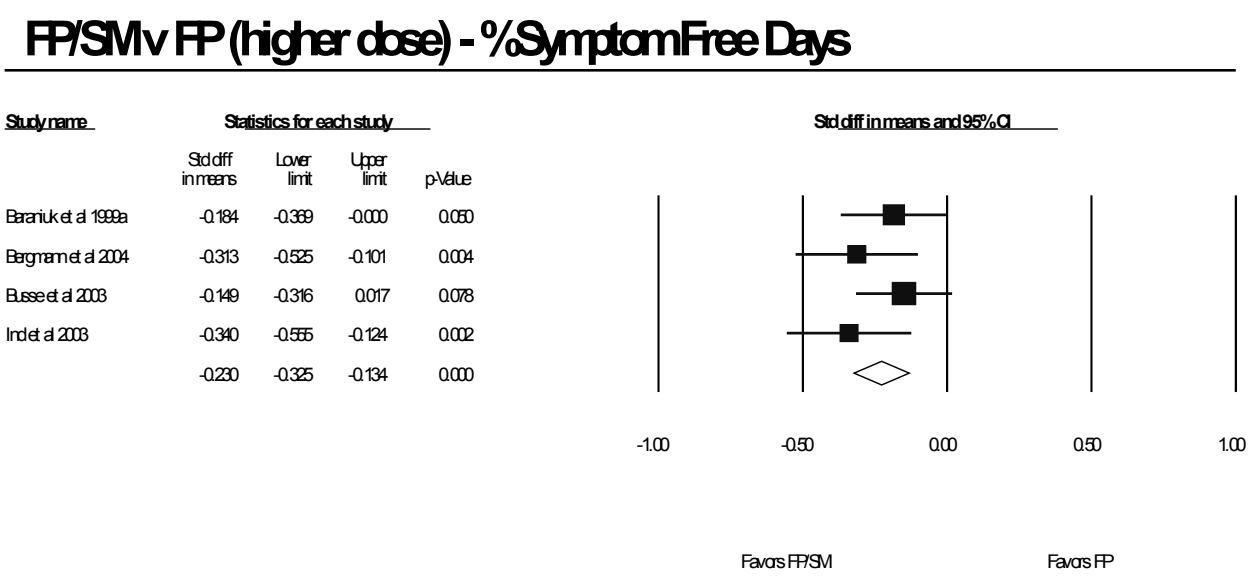
FP/SM v FP Analyses (ICS+LABA v ICS – higher dose)

1) **% Symptom Free Days**
2) **Symptom Score**
3) **% Rescue Free Days**
4) **Rescue Medication Use – Puffs per Day**
5) **Exacerbations (all)**

Results

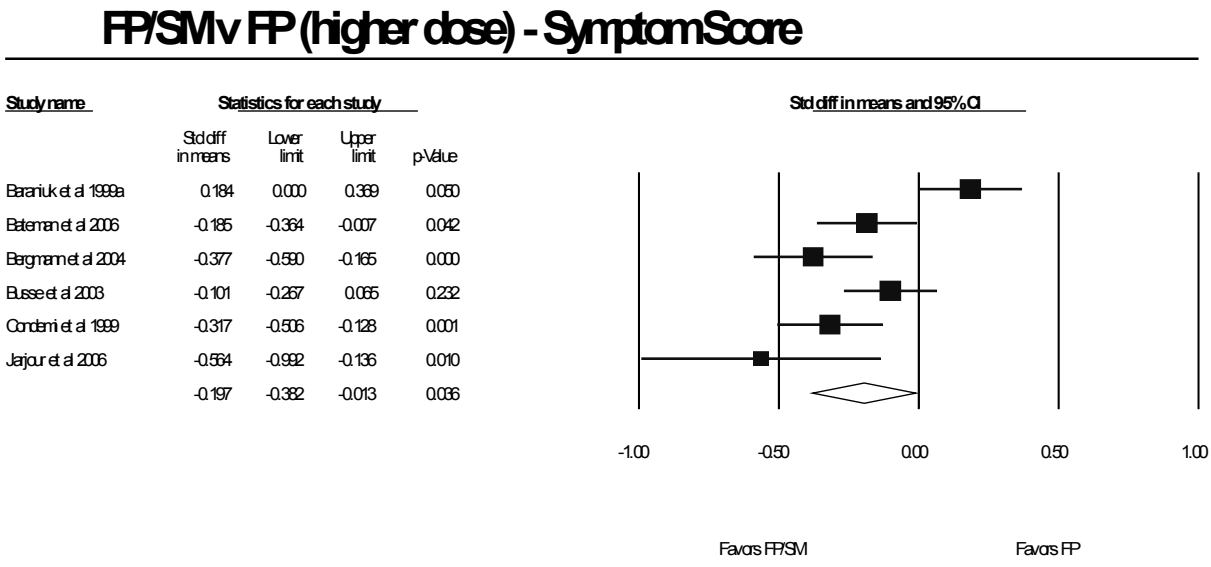
Note: For the following analyses for FP/SM v FP, see the notes above for the ICS + LABA v higher dose ICS analyses regarding studies not included.

% Symptom Free Days



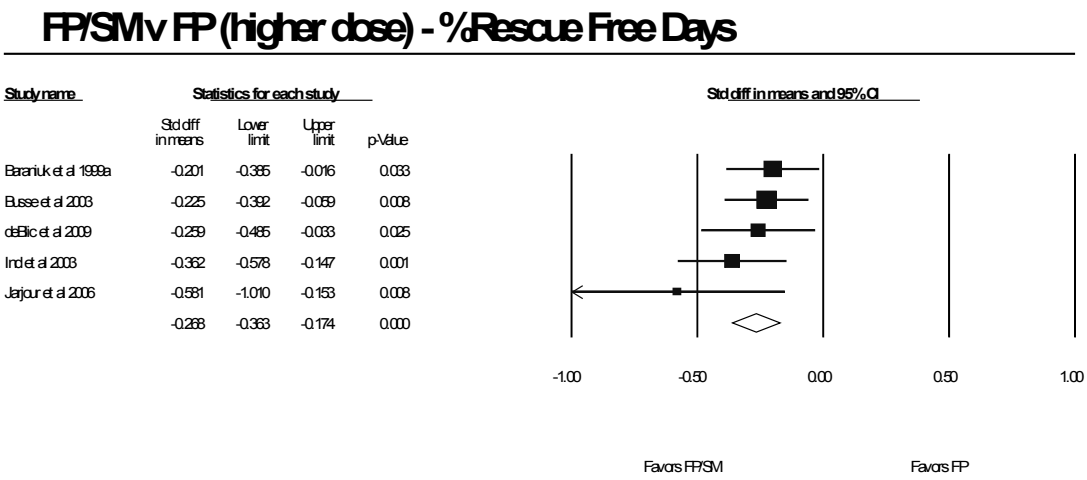
Heterogeneity			
Q-value	df (Q)	P-value	I-squared
2.725	3	0.436	0

Symptom Score



Heterogeneity			
Q-value	df (Q)	P-value	I-squared
24.07566	5	2.10E-04	79.23213

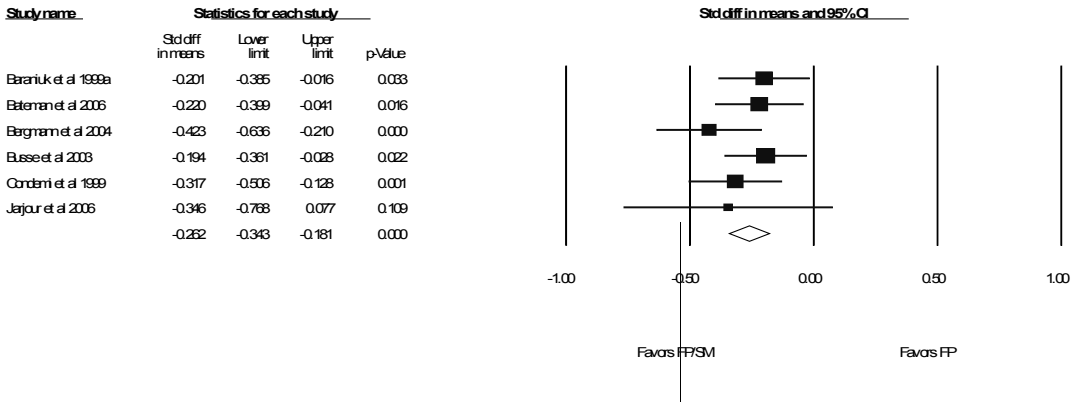
% Rescue Free Days – Updated Analysis



Heterogeneity			
Q-value	df (Q)	P-value	I-squared
3.558817	4	0.468992	0

Rescue Medication Use – Puffs per Day

FP/SMv FP (higher dose) - Rescue Medication Puffs per Day

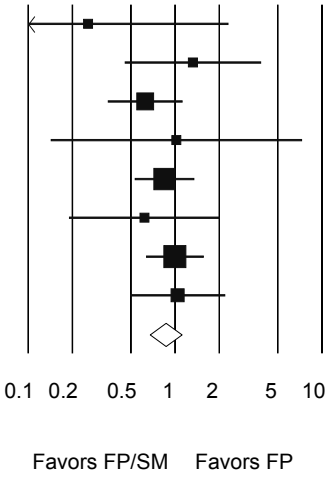


Heterogeneity			
Q-value	df (Q)	P-value	I-squared
3.938899	5	0.558246	0

Exacerbations (all) – Updated Analysis

FP/SM v FP (higher dose) - Exacerbations (all)

Study name	Odds ratio	Lower limit	Upper limit	p-Value
Bergmann et al 2004	0.256	0.028	2.313	0.225
Busse et al 2003	1.324	0.453	3.865	0.608
Condemi et al 1999	0.627	0.348	1.129	0.120
deBlic et al 2009	1.020	0.142	7.338	0.984
Ind et al 2003	0.847	0.529	1.357	0.490
Jarjour et al 2006	0.619	0.189	2.024	0.428
Jenkins et al 2000	0.997	0.633	1.572	0.991
van Noord et al 1999	1.041	0.493	2.199	0.917
	0.861	0.670	1.104	0.238



Heterogeneity

Q-value	df (Q)	P-value	I-squared
3.8808829	7	0.7933907	0

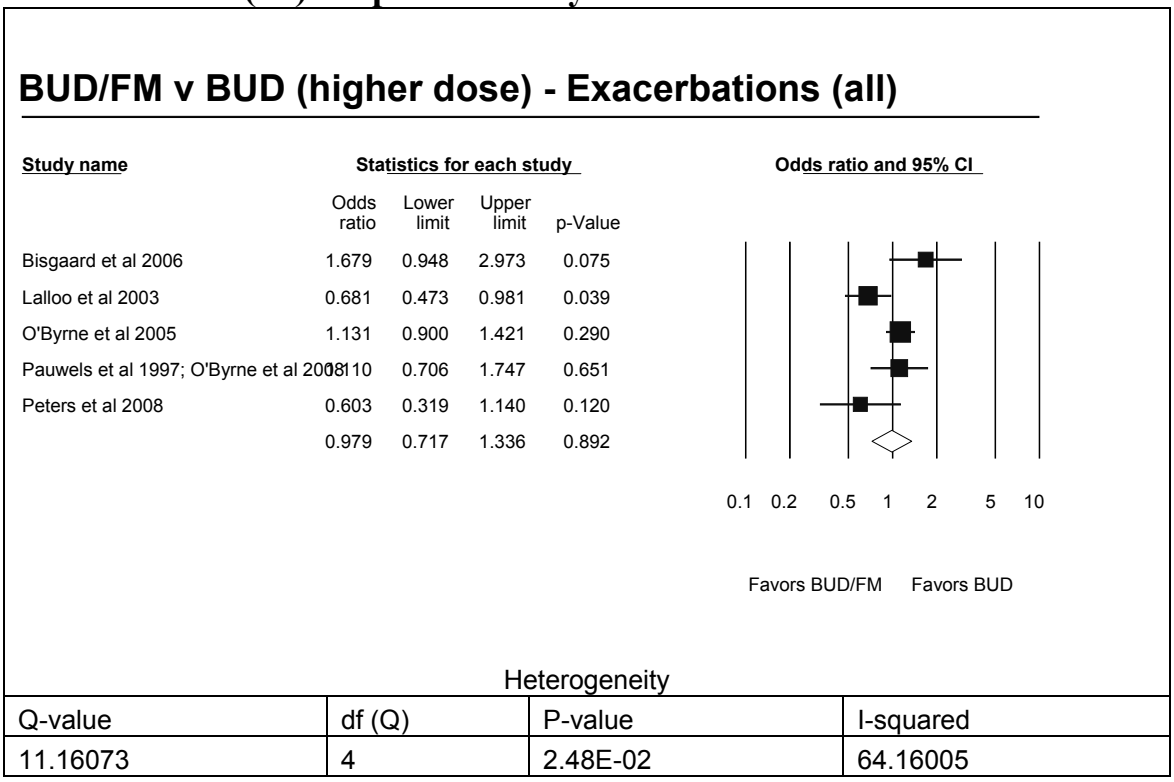
BUD/FM v BUD Analyses (ICS+LABA v ICS – higher dose)

1) **Exacerbations**
2) **% Rescue medicine free days**
3) **Rescue medicine use – puffs per day**
4) **% Symptom free days**
5) **Symptom Score**

Results

Note: For the following analyses for BUD/FM v BUD, see the notes above for the ICS + LABA v higher dose ICS analyses regarding studies not included.

Exacerbations (all) – Updated Analysis



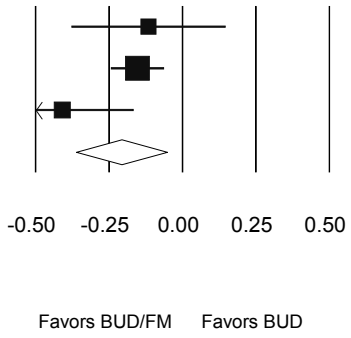
Heterogeneity

Q-value	df (Q)	P-value	I-squared
11.16073	4	2.48E-02	64.16005

% Rescue Medicine Free Days – Updated Analysis

BUD/FM v BUD (higher dose) - % Rescue medicine free days

Study name	Std diff in means	Lower limit	Upper limit	p-Value
Bisgaard et al 2006	-0.115	-0.379	0.148	0.389
O'Byrne et al 2005	-0.153	-0.244	-0.062	0.001
Peters et al 2008	-0.409	-0.652	-0.166	0.001
	-0.208	-0.363	-0.054	0.008



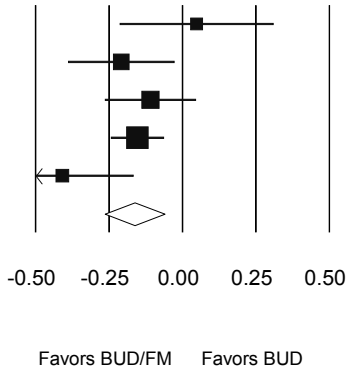
Heterogeneity

Q-value	df (Q)	P-value	I-squared
3.9591837	2	0.1381256	49.484536

Rescue Medicine Use – Puffs per day – Updated Analysis

BUD/FM v BUD (higher dose) - Rescue medicine use - Puffs per day

Study name	Std diff in means	Lower limit	Upper limit	p-Value
Bisgaard et al 2006	0.048	-0.215	0.311	0.720
Lalloo et al 2003	-0.208	-0.390	-0.026	0.025
O'Byrne et al 2001	-0.109	-0.265	0.047	0.170
O'Byrne et al 2005	-0.153	-0.244	-0.062	0.001
Peters et al 2008	-0.409	-0.652	-0.166	0.001
	-0.163	-0.265	-0.062	0.002



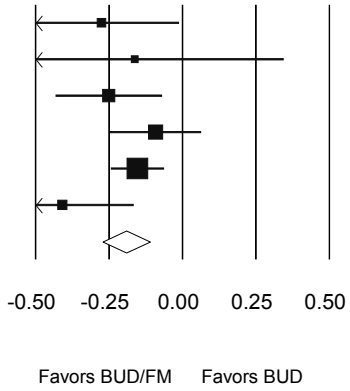
Heterogeneity

Q-value	df (Q)	P-value	I-squared
7.1278688	4	0.1292833	43.882244

% Symptom Free Days – Updated Analysis

BUD/FM v BUD (higher dose) - % Symptom free days

Study name	Std diff in means	Lower limit	Upper limit	p-Value
Bisgaard et al 2006	-0.276	-0.540	-0.012	0.041
Kips et al 2000	-0.162	-0.670	0.345	0.530
Lalloo et al 2003	-0.251	-0.433	-0.069	0.007
O'Byrne et al 2001	-0.091	-0.247	0.064	0.250
O'Byrne et al 2005	-0.153	-0.244	-0.062	0.001
Peters et al 2008	-0.409	-0.652	-0.166	0.001
	-0.192	-0.273	-0.111	0.000



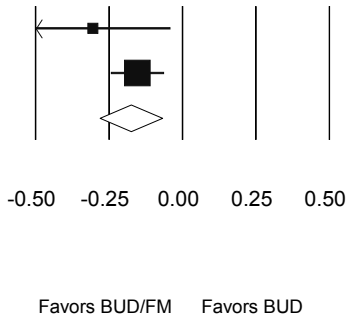
Heterogeneity

Q-value	df (Q)	P-value	I-squared
6.0596263	5	0.3004602	17.486661

Symptom Score

BUD/FM v BUD (higher dose) - Symptom Score

Study name	Std diff in means	Lower limit	Upper limit	p-Value
Bisgaard et al 2006	-0.305	-0.569	-0.040	0.024
O'Byrne et al 2005	-0.153	-0.244	-0.062	0.001
	-0.176	-0.283	-0.070	0.001



Heterogeneity

Q-value	df (Q)	P-value	I-squared
1.1283463	1	0.2881284	11.374725

BDP/SM v BDP Analyses (ICS+LABA v ICS – higher dose)

1) **Rescue medicine use – Puffs per day**
2) **% Symptom free days**
3) **Exacerbations**

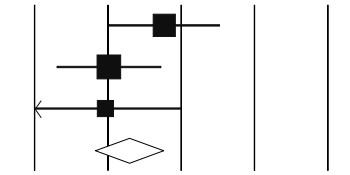
Results

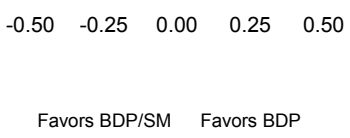
Note: For the following analyses for BDP/SM v BDP, see the notes above for the ICS + LABA v higher dose ICS analyses regarding studies not included.

Rescue medicine use – Puffs per day

BDP/SM v BDP (higher dose) - Rescue medicine use - Puffs per day

Study name	Std diff in means	Lower limit	Upper limit	p-Value
Greening et al 1994	-0.058	-0.248	0.132	0.553
Kelsen et al 1999	-0.246	-0.426	-0.067	0.007
Vermetten et al 1999	-0.258	-0.516	-0.000	0.050
	-0.178	-0.294	-0.062	0.003





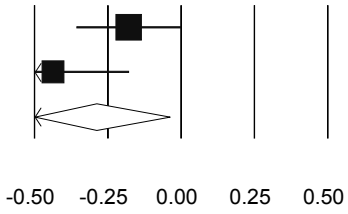
Heterogeneity

Q-value	df (Q)	P-value	I-squared
2.4764914	2	0.2898923	19.240583

% Symptom free days

BDP/SM v BDP (higher dose) - % Symptom Free Days

Study name	Std diff in means	Lower limit	Upper limit	p-Value
Kelsen et al 1999	-0.179	-0.358	-0.000	0.050
Vermetten et al 1999	-0.437	-0.697	-0.177	0.001
	-0.290	-0.540	-0.039	0.023



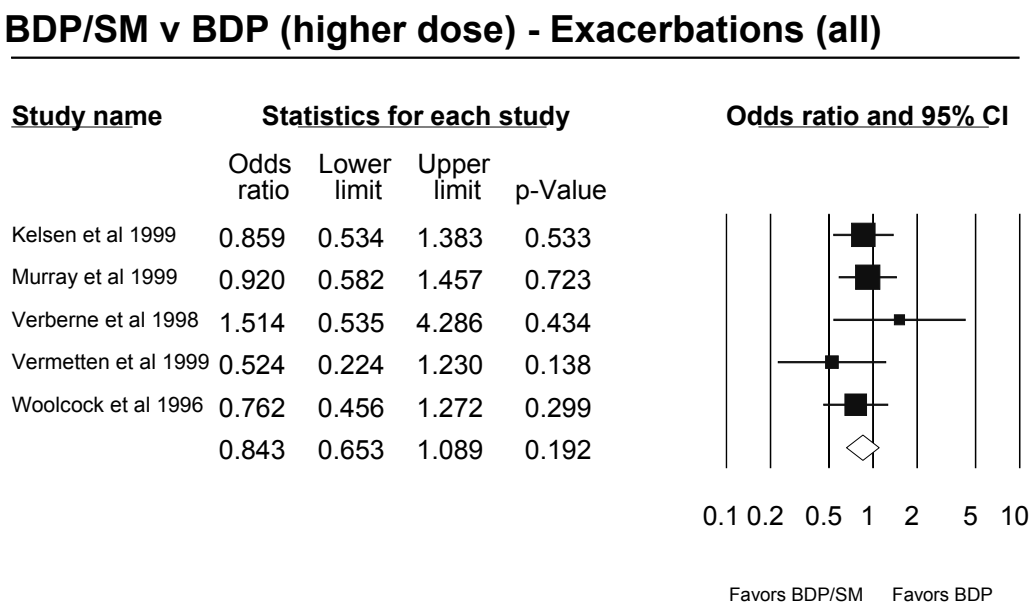
-0.50 -0.25 0.00 0.25 0.50

Favors BDP/SM Favors BDP

Heterogeneity

Q-value	df (Q)	P-value	I-squared
2.5711752	1	0.1088269	61.107279

Exacerbations (all)



Heterogeneity

Q-value	df (Q)	P-value	I-squared
2.7049752	4	0.6083443	0

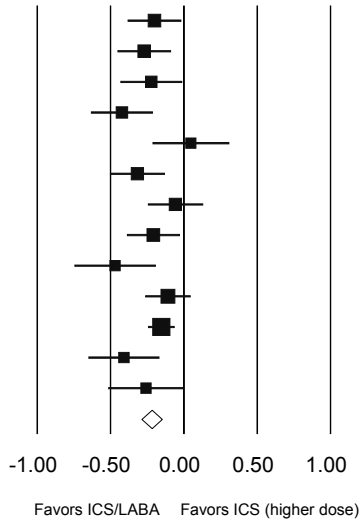
ICS compared with LABA+ICS (Higher Dose) Meta-Analysis Results – Sensitivity Analyses

1) **Rescue medicine use – Puffs per day**
2) **% Rescue free days**
3) **Symptom Score**
4) **% Symptom free days**
5) **Exacerbations**

Rescue medicine use – Puffs per day

ICS/LABA v ICS (higher dose) - Rescue medicine use - Puffs per day - Sensitivity Analyses

Study name	Std diff in means	Lower limit	Upper limit	p-Value
Baraniuk et al 1999a	-0.201	-0.385	-0.016	0.033
Baraniuk et al 1999b	-0.271	-0.455	-0.086	0.004
Bateman et al 2003	-0.222	-0.434	-0.010	0.040
Bergmann et al 2004	-0.423	-0.636	-0.210	0.000
Bisgaard et al 2006	0.048	-0.215	0.311	0.720
Condemi et al 1999	-0.317	-0.506	-0.128	0.001
Greening et al 1994	-0.058	-0.248	0.132	0.553
Lalloo et al 2003	-0.208	-0.390	-0.026	0.025
Mitchell et al 2003	-0.469	-0.748	-0.190	0.001
O'Byrne et al 2001	-0.109	-0.265	0.047	0.170
O'Byrne et al 2005	-0.153	-0.244	-0.062	0.001
Peters et al 2008	-0.409	-0.652	-0.166	0.001
Vermetten et al 1999	-0.258	-0.516	-0.000	0.050
	-0.221	-0.290	-0.151	0.000



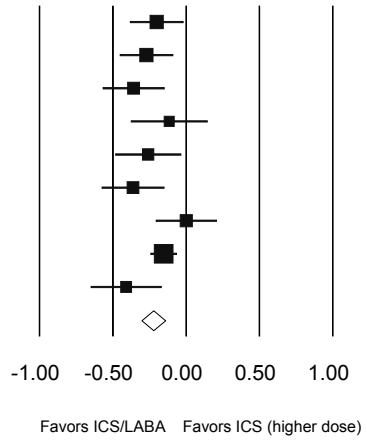
Heterogeneity

Q-value	df (Q)	P-value	I-squared
20.759591	12	5.40E-02	42.195393

% Rescue free days

ICS/LABA v ICS (higher dose) - % Rescue free days - Sensitivity Analyses

Study name	Std diff in means	Lower limit	Upper limit	p-Value
Baraniuk et al 1999a	-0.201	-0.385	-0.016	0.033
Baraniuk et al 1999b	-0.271	-0.455	-0.086	0.004
Bateman et al 2003	-0.358	-0.571	-0.145	0.001
Bisgaard et al 2006	-0.115	-0.379	0.148	0.389
deBlic et al 2009	-0.259	-0.485	-0.033	0.025
Ind et al 2003	-0.362	-0.578	-0.147	0.001
Johansson et al 2001	0.001	-0.209	0.211	0.994
O'Byrne et al 2005	-0.153	-0.244	-0.062	0.001
Peters et al 2008	-0.409	-0.652	-0.166	0.001
	-0.225	-0.306	-0.145	0.000



Heterogeneity

Q-value	df (Q)	P-value	I-squared
12.797355	8	0.1190148	37.487082

LABA + ICS compared with Continuing Same Dose ICS

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**

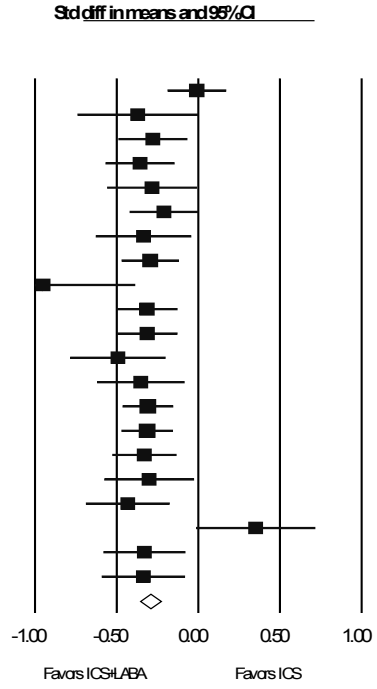
Note* - exacerbations were recorded in inconsistent measures

Results

Rescue Medication Use – Puffs per day – Updated Analysis

ICS+LABA v. Continue Same Dose ICS - Rescue Medication Use - Puffs Per Day

Study name	Std diff in means	Lower limit	Upper limit	p-Value
Bailey 2008	-0.009	-0.189	0.171	0.925
Boyd 1995	-0.371	-0.740	-0.001	0.049
BUH 2003a	-0.278	-0.490	-0.057	0.010
BUH 2003b	-0.356	-0.568	-0.144	0.001
Corren 2007; Murphy 2008	-0.283	-0.558	-0.008	0.044
Eid 2010a	-0.210	-0.420	-0.000	0.050
Kavuru 2000	-0.335	-0.628	-0.042	0.025
Kemp 1998	-0.294	-0.469	-0.119	0.001
Koopmans 2006	-0.949	-1.512	-0.387	0.001
Mahrice 2007a	-0.314	-0.501	-0.127	0.001
Mahrice 2007b	-0.312	-0.498	-0.126	0.001
Nathan 2006	-0.492	-0.784	-0.199	0.001
Noonan 2006; Chervinsky 2008a	-0.352	-0.620	-0.084	0.010
OByrne 2001a	-0.308	-0.464	-0.153	0.000
OByrne 2001b	-0.313	-0.470	-0.155	0.000
Peters 2008	-0.330	-0.527	-0.134	0.001
Russell 1995	-0.301	-0.576	-0.026	0.032
van der Molen 1997	-0.432	-0.688	-0.175	0.001
Verberne 1998	0.351	-0.014	0.717	0.059
Zetterstrom 2001a	-0.330	-0.581	-0.079	0.010
Zetterstrom 2001b	-0.336	-0.592	-0.081	0.010
	-0.294	-0.357	-0.230	0.000



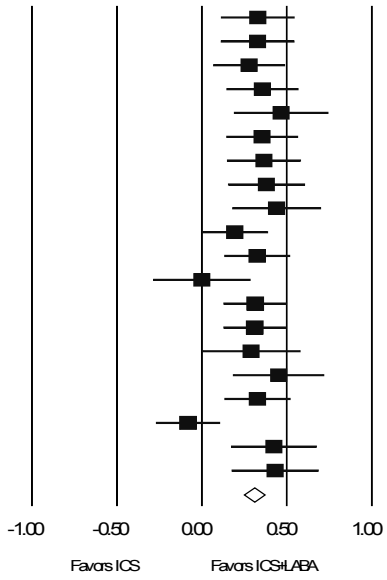
Heterogeneity			
Q-value	df (Q)	P-value	I-squared
31.58152	20	4.80E-02	36.671825

Sensitivity analyses indicate no difference in overall meta-analysis conclusions with single studies removed.

% Rescue Medication Free Days – Updated Analysis

ICS+LABA v. Continue Same Dose ICS - % Rescue Free Days

Study name	Std diff in means	Lower limit	Upper limit	p-Value
Bateman 2001a	0.329	0.112	0.546	0.003
Bateman 2001b	0.328	0.112	0.545	0.003
BUH 2003a	0.278	0.067	0.490	0.010
BUH 2003b	0.366	0.144	0.588	0.001
Corren 2007; Murphy 2008	0.467	0.189	0.744	0.001
Eid 2010a	0.365	0.144	0.586	0.001
Ind 2003	0.365	0.148	0.583	0.001
Jenkins 2006a	0.380	0.154	0.607	0.001
Jenkins 2006b	0.440	0.178	0.701	0.001
Kuna 2006a	0.194	0.000	0.389	0.050
Kuna 2006b	0.326	0.132	0.520	0.001
Lundback 2006	0.000	-0.287	0.287	1.000
Mahrice 2007a	0.314	0.127	0.501	0.001
Mahrice 2007b	0.312	0.126	0.498	0.001
Nathan 2006	0.290	0.000	0.580	0.050
Noonan 2006; Chervinsky 2008a	0.452	0.183	0.721	0.001
Peters 2008	0.327	0.132	0.522	0.001
Rohunek 2006a	-0.081	-0.270	0.107	0.398
Zetterstrom 2001a	0.424	0.172	0.676	0.001
Zetterstrom 2001b	0.431	0.175	0.688	0.001
	0.307	0.246	0.368	0.000



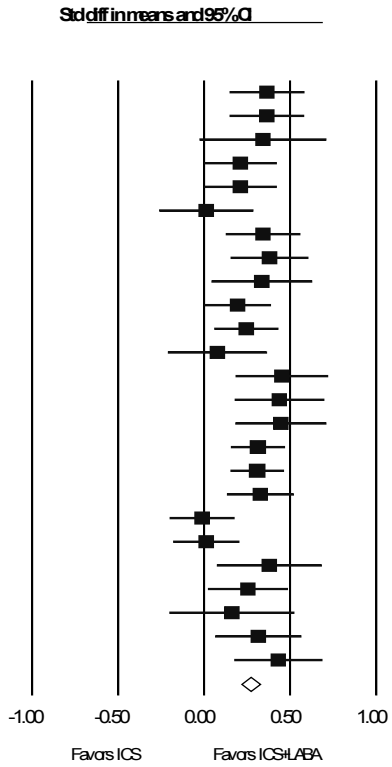
Heterogeneity			
Q-value	df (Q)	P-value	I-squared
28.37722	19	7.64E-02	33.04488

Sensitivity analyses indicate no difference in overall meta-analysis conclusions with single studies removed.

% Symptom Free Days – Updated Analysis

ICS+LABA v. Continue Same Dose ICS - % Symptom Free Days

Study name	Std diff in means	Lower limit	Upper limit	p-Value
Bateman 2001a	0.366	0.148	0.583	0.001
Bateman 2001b	0.364	0.148	0.581	0.001
Boyd 1995	0.342	-0.027	0.712	0.069
Buhl 2003a	0.211	0.000	0.422	0.050
Buhl 2003b	0.211	0.000	0.422	0.050
Corren 2007; Murphy 2008	0.012	-0.262	0.286	0.930
Ind 2003	0.343	0.125	0.560	0.002
Jenkins 2006	0.380	0.154	0.607	0.001
Kavuru 2000	0.335	0.042	0.628	0.025
Kuna 2006	0.194	0.000	0.389	0.050
Morice 2007	0.245	0.059	0.431	0.010
Nathan 2006	0.077	-0.211	0.366	0.600
Noonan 2006; Chervinsky 2008a	0.452	0.183	0.721	0.001
Noonan 2006a	0.438	0.177	0.698	0.001
Noonan 2006b	0.446	0.181	0.711	0.001
OByrne 2001b	0.313	0.155	0.470	0.000
OByrne 2001a	0.308	0.153	0.464	0.000
Peters 2008	0.327	0.132	0.522	0.001
Pohunek 2006a	-0.011	-0.201	0.178	0.906
Pohunek 2006b	0.012	-0.180	0.205	0.900
Shapiro 2000	0.379	0.074	0.684	0.015
Tal 2002	0.255	0.022	0.488	0.032
Verberne 1998	0.161	-0.202	0.524	0.384
Zetterstorm 2001a	0.315	0.064	0.566	0.014
Zetterstorm 2001b	0.431	0.175	0.688	0.001
	0.270	0.216	0.323	0.000



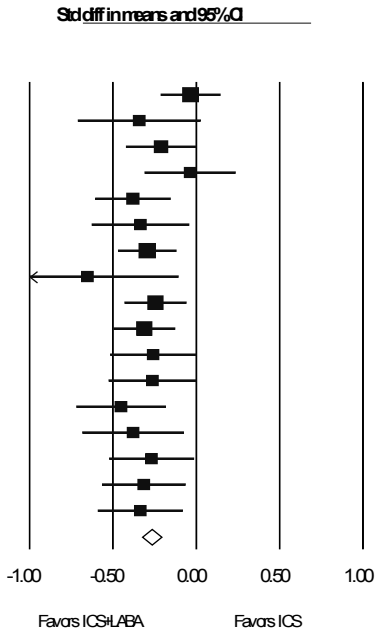
Heterogeneity			
Q-value	df (Q)	P-value	I-squared
33.2345	24	9.92E-02	27.78589

Sensitivity analyses indicate no difference in overall meta-analysis conclusions with single studies removed.

Symptom Score – Updated Analysis

ICS+LABA v. Continue Same Dose ICS - Symptom Score

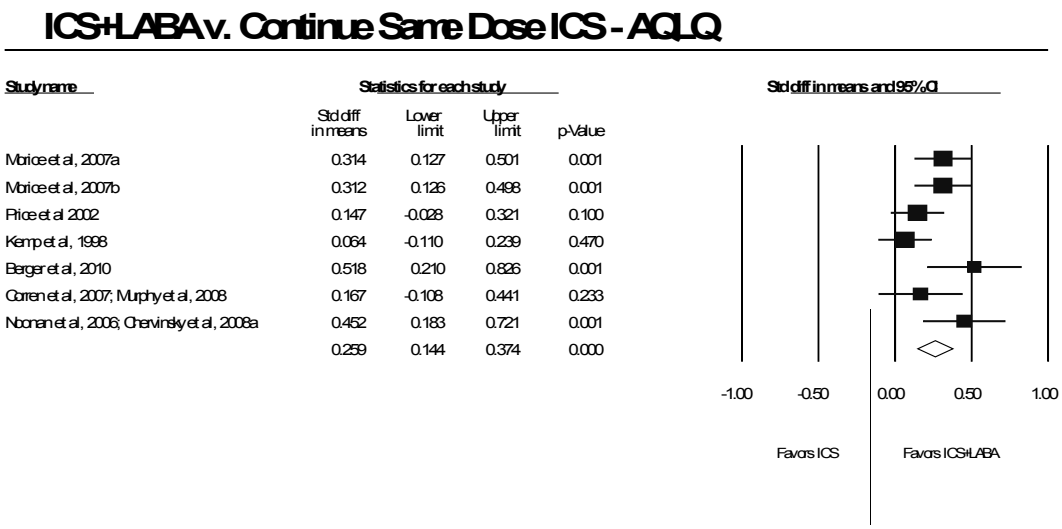
Study name	Std diff in means	Lower limit	Upper limit	p-Value
Bailey et al, 2008	-0.034	-0.214	0.145	0.708
Boyd 1995	-0.342	-0.712	0.027	0.069
Buhl 2003	-0.211	-0.422	-0.000	0.050
Corren et al, 2007; Murphy et al, 2008	-0.037	-0.311	0.237	0.793
Jenkins 2006	-0.380	-0.607	-0.154	0.001
Kavuru 2000	-0.335	-0.628	-0.042	0.025
Kemp 1998	-0.294	-0.469	-0.119	0.001
Koopmans 2006	-0.653	-1.201	-0.106	0.019
Morice 2007a	-0.245	-0.431	-0.059	0.010
Morice 2007b	-0.312	-0.498	-0.126	0.001
Noonan 2006a	-0.259	-0.517	-0.000	0.050
Noonan 2006b	-0.263	-0.527	-0.000	0.050
Noonan et al, 2006; Chervinsky et al, 2006a	-0.452	-0.721	-0.183	0.001
Shapiro 2000	-0.379	-0.684	-0.074	0.015
van der Molen 1997	-0.269	-0.524	-0.014	0.039
Zetterstorm 2001a	-0.315	-0.566	-0.064	0.014
Zetterstorm 2001b	-0.336	-0.592	-0.081	0.010
	-0.268	-0.326	-0.210	0.000



Heterogeneity			
Q-value	df (Q)	P-value	I-squared
15.78496	16	0.4680673	0

Sensitivity analyses indicate no difference in overall meta-analysis conclusions with single studies removed.

AQLQ – Updated Analysis



Heterogeneity			
Q-value	df (Q)	P-value	I-squared
11.96621	6	6.27E-02	49.85882

Sensitivity analyses indicate no difference in overall meta-analysis conclusions with single studies removed.

LTRA compared with LABA+ICS Results

Summary of Outcome Measures Analyzed:

1. **Rescue medication use (rescue free days)**
2. **Symptom control (symptom-free days)**
3. **Percent Exacerbations**

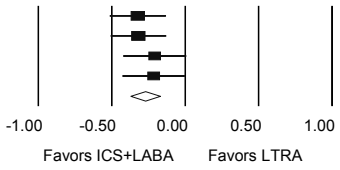
Results

Rescue Medication Use – Rescue-Free Days

Studies that reported outcome, but are not included: NA

LTRA v ICS + LABA - Rescue medication - Rescue free days

Study name	Std diff in means	Standard error	Variance	Lower limit	Upper limit	Z-Value	p-Value
Calhoun 2001	-0.322	0.098	0.010	-0.514	-0.130	-3.292	0.001
Pearlman 2002	-0.319	0.097	0.009	-0.509	-0.129	-3.292	0.001
Peters 2007	-0.207	0.110	0.012	-0.424	0.009	-1.882	0.060
Koenig 2008	-0.215	0.109	0.012	-0.429	-0.000	-1.961	0.050
	-0.272	0.052	0.003	-0.373	-0.171	-5.287	0.000

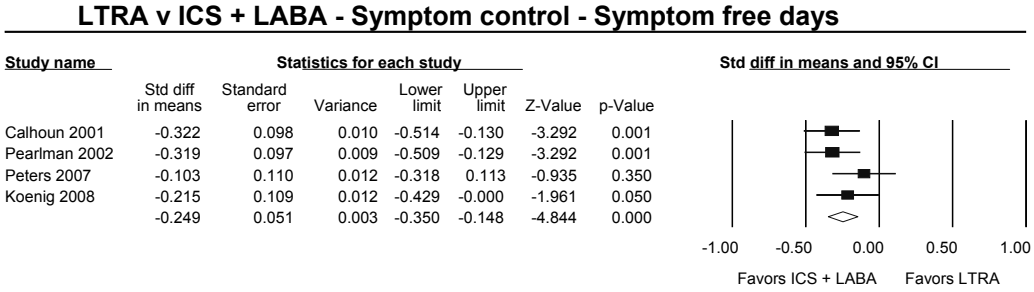


Heterogeneity

Q-value	df (Q)	P-value	I-squared
1.114178	3	0.773653	0

Symptom-Free Days

Studies that reported outcome, but are not included: NA



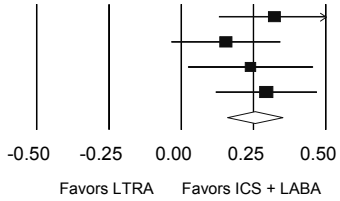
Heterogeneity			
Q-value	df (Q)	P-value	I-squared
2.942463	3	0.400582	0

Exacerbations

Studies that reported outcome, but are not included: NA

LTRA v ICS + LABA - Exacerbations

Study name	Std diff in means	Standard error	Variance	Lower limit	Upper limit	Z-Value	p-Value
Calhoun 2001	0.322	0.098	0.010	0.130	0.514	3.292	0.001
Pearlman 2002	0.155	0.096	0.009	-0.034	0.343	1.604	0.109
Peters 2007	0.240	0.110	0.012	0.023	0.456	2.172	0.030
Maspero 2008	0.294	0.089	0.008	0.119	0.469	3.292	0.001
	0.255	0.049	0.002	0.159	0.350	5.215	0.000



Heterogeneity			
Q-value	df (Q)	P-value	I-squared
1.770616	3	0.62135	0

Appendix J. Tolerability and overall adverse events of ICSs

Summary table of ICS adverse events and tolerability from head-to-head RCTs

Study	Study design N Duration	Country Population Setting	Comparison (total daily dose in mcg)	Equivalent dosing	Results	Quality rating
Beclomethasone compared with budesonide						
Molimard et al. 2005[1]	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, *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*
Tattersfield et al. 2001[2]	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	*Fair*

Study	Study design N Duration	Country Population Setting	Comparison (total daily dose in mcg)	Equivalent dosing	Results	Quality rating
Worth et al. 2001[3]	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) 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	*Fair*
Beclomethasone compared with ciclesonide						
Chylack 2008[4]	RCT 1,568	Multinational (US, Poland, South Africa) Age ≥ 18, moderate to severe, on ICS, excluded smokers Multicenter	CIC HFA-MDI (640) vs. BDP HFA-MDI (640)	Yes (high)	Overall AEs (%): incidence of treatment emergent AEs: 83.5 vs. 85.6 Withdrawals due to AEs(%): 3.7 vs. 2.8 Oral candidiasis-thrush (%): 1.4 vs. 6.3 Dysphonia (%): 2.2 vs. 1.5 Pharyngitis (%): 8.0 vs. 8.4	*Fair*
Beclomethasone compared with flunisolide						
No systematic reviews or head-to-head trials found						
Beclomethasone compared with fluticasone						
Barnes et al. 1993[5]	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	*Fair*

Study	Study design N Duration	Country Population Setting	Comparison (total daily dose in mcg)	Equivalent dosing	Results	Quality rating
					events and comments: no significant differences ($P > 0.15$) between treatments in the incidence or nature of AEs	
Boe et al. 1994[6]	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 Muscoskeletal disorders(%): 13 vs. 25	*Fair*
de Benedictis et al. 2001[7]	RCT, DB 343 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)	Overall AEs(%): 80 vs. 80.9 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.	*Fair*

Study	Study design N Duration	Country Population Setting	Comparison (total daily dose in mcg)	Equivalent dosing	Results	Quality rating
					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	
Fabbri et al. 1993[8]	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 (%): 4 vs. 5	*Fair*
Fairfax et al. 2001[9]	RCT, DB, DD 172 6 weeks	UK and Ireland Age 18-65, mild to severe, symptomatic on ICS, 24% current smokers Multicenter (30	BDP MDI (extrafine HFA, 400) vs. FP MDI (CFC, 400)	Yes (medium)	Overall AEs(%): 41 vs. 37 Withdrawals due to AEs: NR Deaths: 0 vs. 0	*Fair*

Study	Study design N Duration	Country Population Setting	Comparison (total daily dose in mcg)	Equivalent dosing	Results	Quality rating
		general practice sites)				
Lorentzen et al. 1996[10]	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, *P* = 0.03 Respiratory infection (%): 6 vs. 9 Rhinitis (%): 10 vs. 1 Hoarseness (%): 6 vs. 7 influenza (%): 5 vs. 13	*Fair*
Lundback et al. 1993[11]	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 Hoarseness (%): 2 vs 2 vs < 1	*Fair*
Malo et al. 1999[12]	RCT, DB, crossove	Canada Age ≥18, severity	FP MDI (400-1000) vs.	No (medium – high vs.	Overall AEs: NR Withdrawals due to AEs:	*Fair*

Study	Study design N Duration	Country Population Setting	Comparison (total daily dose in mcg)	Equivalent dosing	Results	Quality rating
	r 69 16 weeks	NR, excluded current or former smokers multicenter	BDP MDI (800- 2000)	medium - really high)	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)	
Medici et al. 2000[13]	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	*Fair*
Molimard, M et al. 2005[1]	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*

Study	Study design N Duration	Country Population Setting	Comparison (total daily dose in mcg)	Equivalent dosing	Results	Quality rating
Raphael et al. 1999[14]	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) vs FP MDI (440) vs BDP MDI (336) vs BDP MDI (672)	Yes (low, medium, low, medium)	FP all vs. BDP all reported for those with two percentages Overall AEs (%): 9 vs. 15, *P* = 0.664 Withdrawals due to AEs (%): 3 vs 3 vs 4 vs 2 Oral candidiasis-thrush (%): 1 vs. 4, *P* = 0.472 Dysphonia (%): 3 vs. 7, *P* = 0.577 Sore throat (%): 1 vs. 3, *P* = 0.797 Headache (%): 1 vs. 3, *P* = 0.721	*Fair*
Beclomethasone compared with mometasone						
Bernstein et al. 1999[15]	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	*Fair*
Nathan et al. 2001[16]	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	*Fair*

Study	Study design N Duration	Country Population Setting	Comparison (total daily dose in mcg)	Equivalent dosing	Results	Quality rating
					Hoarseness (%): 2 vs 7 vs 2 vs 0	
Beclomethasone compared with triamcinolone						
Berkowitz et al. 1998[17]	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)	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 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	*Fair*
Bronsky et al. 1998[18]	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, *P* = 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, *P* = 0.027 Death (%): 0.0 vs 0.0 vs 0.0	*Fair*
Budesonide compared with ciclesonide						
Boulet et al. 2006[19]	RCT, DB, DD 359	Multinational - Canada and Europe Age 12-75, mild	CIC HFA-MDI (320) vs. BUD DPI (320)	No (medium vs. low)	Overall AEs(%): 42 vs. 52 Withdrawals due to AEs(%): NR	Fair

Study	Study design N Duration	Country Population Setting	Comparison (total daily dose in mcg)	Equivalent dosing	Results	Quality rating
	12 weeks	to moderate, on ICS, heavy smokers or ex-smokers excluded (>10 cigarettes/day) Multicenter			Oral candidiasis-thrush (%): 0.0 vs 0.0 Dysphonia (%): 2 vs. 1 Cough: NR Sore throat (%): 2 vs. 1 Upper respiratory tract infection (%): 12 vs. 19	
Hansel et al. 2006[20]	RCT 554 12 weeks	Multinational - Europe Age 12-75, mild to severe, on ICS, 9% smokers Multicenter	CIC HFA-MDI (80) vs. CIC HFA-MDI (320) vs. BUD DPI (400)	Yes for CIC 80 vs. BUD 400 No for CIC 320 vs. BUD (low vs. medium vs. low)	Overall AEs(%): 36.8 vs. 40.8 vs. 33.9 Withdrawals due to AEs(%): 4.4 vs. 2.1 vs. 1.7 Oral candidiasis-thrush (%): NR Dysphonia (%): NR Increased cough (%): 0 vs. 3.1 vs. 0 Sore throat (%): NR Headache (%): 3.3 vs. 3.6 vs. 0 p=NR Upper respiratory tract infection (%): 11.5 vs. 5.1 vs. 7.9 p=NR	Fair
Ukena et al. 2007[21]	RCT, DB, DD 399 12 weeks	Germany Age 12-75, mild to severe, smokers excluded Multicenter	CIC HFA-MDI (320) vs. BUD DPI (400)	No (medium vs. low)	See Evidence Table	Fair
Vermeulen et al. 2007[22]	RCT, DB, DD 403 12 weeks	Multinational - Hungary, Poland, Serbia/Montenegro, South Africa, Spain Age 12-17, severe, not controlled on ICS, excluded smokers	CIC HFA-MDI (320) vs. BUD DPI (800)	Yes (medium)	Overall AEs(%): 26.5% of patients vs. 18.3% Withdrawals due to AEs(%): NR Oral candidiasis-thrush (%): 0 vs. 0 Dysphonia, cough, sore throat, and	Fair

Study	Study design N Duration	Country Population Setting	Comparison (total daily dose in mcg)	Equivalent dosing	Results	Quality rating
		Multicenter			headache (%): NR Upper respiratory tract infection (%): 2.2 vs. 2.3 Deaths: 0 vs. 0	
von Berg et al. 2007[23]	RCT, DB, DD 621 12 weeks	Multinational - Australia, Germany, Hungary, Poland, Portugal, Serbia and Montenegro, South Africa and Spain Age 6-11, moderate to severe, smoking status NR Multicenter	CIC HFA-MDI (160) vs. BUD DPI (400)	Yes (low)	Overall AEs(%):38% of patients (n=158 in G1, n=78 in G2) experienced an AE Withdrawals due to AEs(%): 2.9 vs. 1 Oral candidiasis/thrush and dysphonia combined (%): 0.2 vs. 1.5 Cough, sore throat, and headache: NR Upper respiratory tract infection (%): 3.6% vs. 6.3% Mean body height increase, in centimeters: 1.18 (p<.0001) vs. 0.70 (p<.0001); Increase in body height significantly greater in G1 than G2 (difference b/t groups = 0.481 cm, p = .0025, two-sided)	Fair
Budesonide compared with flunisolide						
Newhouse et al. 2000[24]	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	*Fair*

Study	Study design N Duration	Country Population Setting	Comparison (total daily dose in mcg)	Equivalent dosing	Results	Quality rating
					Back pain (%): 1.3 vs. 2.5	
Budesonide compared with fluticasone						
Ayres et al. 1995[25]	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)	Overall AEs: NR Withdrawals due to AEs: NR Overall adverse events (%): 61 vs 49 vs 51 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	*Fair*
Ferguson et al. 1999[26]	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, *P* = .0003)	*Fair*
Heinig et al. 1999[27]	RCT, DB, DD	Multinational (Belgium, Canada,	FP DPI (2000) vs.	No (both are high doses,	Overall AEs(%): 78 vs. 77	*Fair*

Study	Study design N Duration	Country Population Setting	Comparison (total daily dose in mcg)	Equivalent dosing	Results	Quality rating
	395 24 weeks	Denmark, Netherlands) Age 18-75, severe, not controlled on ICS, 15% current smokers Multicenter (47)	BUD DPI (2000)	but relative potency of fluticasone is greater at the given doses)	Withdrawals due to AEs: NR	
Hoekx et al. 1996[28]	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)	Overall AEs(%): 63 vs. 69 Withdrawals due to AEs (%): 2 (1.7%) vs. 3 (2.7%) Oral candidiasis-thrush (%): 3 vs. < 1 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	*Fair*
Kannisto et al. 2000[29]	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) At 4 months, a subgroup were switched to cromones	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[1]	RCT, open-label	France Age 18-60, moderate to	BDP MDI (800) vs BUD DPI	Yes (all high)	Overall AEs(%): 38 vs 35 vs 37, *P* = 0.791 between all	*Fair*

Study	Study design N Duration	Country Population Setting	Comparison (total daily dose in mcg)	Equivalent dosing	Results	Quality rating
	460 12 weeks	severe persistent, not controlled on ICS, smoking status NR Multicenter, subspecialty clinics (69 pulmonologists)	(1600) vs FP DPI (1000)		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	
Ringdal et al. 1996[30]	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)	Overall AEs(%): 61.7 vs. 61.5 Withdrawals due to AEs (%): 3.9 vs. 5.0 Sore throat (%): 5.9 vs. 4.2 Upper respiratory tract infection (%): 21.5 vs. 24.9 Rhinitis (%): 11.3 vs. 8.0	*Fair*
Budesonide compared with mometasone						
Bousquet et al. 2000[31]	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[32]	RCT, DB, DD	US	Mometasone DPI (400)	No (medium	Overall AEs(%): 8 vs 9 vs 8	*Fair*

Study	Study design N Duration	Country Population Setting	Comparison (total daily dose in mcg)	Equivalent dosing	Results	Quality rating
		Age ≥12,	vs	vs. low)		
	262	moderate, on ICS, smokers	BUD DPI (320)		Withdrawals due to AEs: NR	
	8 weeks	excluded	vs placebo		Most frequently reported treatment-related AEs were headache and pharyngitis (both 4% or less: data by treatment arm NR).	
		Multicenter (17)			There was only one report of oral candidiasis in one MF-reated patient.	
Budesonide compared with triamcinolone						
Weiss et al. 2004[33]	RCT	US	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	*Fair*
	945	Age ≥18, mild to severe, smoking status NR			Withdrawals due to AEs (%): 3.0 vs. 2.5	
	52 weeks	Multicenter, patients from 25 managed care plans			The most frequently reported AEs were respiratory tract infection, sinusitis, bronchitis, and accident/injury.	
Ciclesonide compared with flunisolide						
No systematic reviews or head-to-head trials found						
Ciclesonide compared with fluticasone						
Bateman 2008[34]	RCT	Multinational - Europe, North America, South Africa	CIC HFA-MDI (640) vs. FP HFA-MDI (660)	Yes (high)	Overall AEs (N): 373 vs. 401	Fair
	528				Withdrawals due to AEs (%): NR	
	6 months	Age 12-75, moderate to severe, on ICS, 33% ex-smokers or current smokders			Oral candidiasis-thrush (%): 2.0 vs. 4.8 (numbers from safety set)	
		Multicenter			Dysphonia (%): 3.1 vs. 9.2 (numbers from safety set)	
					Cough (%): NR	
					Sore throat (%):Pharyngolaryngeal pain (numbers from safety set) 4.3 vs. 4.4	
					Headache (%):2.4 vs. 4.4 (numbers from	

Study	Study design N Duration	Country Population Setting	Comparison (total daily dose in mcg)	Equivalent dosing	Results	Quality rating
					safety set) Upper respiratory tract infection (%): 8.2 vs. 7.3% (numbers from safety set) Hoarseness (%): NR Deaths: 0	
Boulet 2007[35]	RCT 474 12 weeks	Multinational - Austria, Canada, Germany, Hungary, South Africa, Spain Age 12-75, moderate, 30% ex-smokers or current smokders Multicenter	CIC HFA-MDI (320) vs. FP DPI (400)	Yes (medium)	Overall AEs(%): 36.1 vs. 39.3 Withdrawals due to AEs (%): 1.7 vs. 4.2 Oral candidiasis-thrush (%): 0 vs. 3.8; p=0.002 (1-sided) Dysphonia (N): 5 vs. 6 Cough (%): NR Sore throat (%): 3.4 vs. 1.7 Headache (%): NR Upper respiratory tract infection (%): NR Hoarseness (%): NR	Fair
Buhl 2006[36]	RCT 529 12 weeks	Multinational - Germany, Austria, The Netherlands, Spainn, Hungary, Poland, South Africa Age 12-75, moderate, on ICS, smoking status NR Multicenter	CIC HFA-MDI (160) vs. FP HFA-MDI (176)	Yes (low)	Overall AEs (%): 36 vs. 34 Withdrawals due to AEs (%): 2.26 vs. 1.14 Oral candidiasis/thrush or dysphonia: Oral candidiasis or voice alteration occurred in 3 patients treated with fluticasone proprionate but neither occurred in patients treated with ciclesonide Cough or sore throat: NR Headache (%): 3 vs. 4 Upper respiratory tract infection (%): 8 vs. 8 Deaths: 0 vs. 0	Fair

Study	Study design N Duration	Country Population Setting	Comparison (total daily dose in mcg)	Equivalent dosing	Results	Quality rating
Dahl 2010[37]	RCT, DB, DD 480 24 weeks	Multinational – Austria, Canada, Germany, Poland, and South Africa Age 12-75, on ICS, mild to moderate, excluded current and ex-smokers with ≥ 10 pack-year history, 22-31% current or ex-smokers enrolled Multicenter	CIC HFA-MDI (80) vs. FP HFA-MDI (200)	Yes (low)	Overall AEs(%): 44 vs. 43 Withdrawals due to AEs (N): 4. Vs. 8 Oral candidiasis-thrush (%): 2.1 vs. 5.0 Cough, sore throat, or headache (%): NR Upper respiratory tract infection (%): 6.7 vs. 5.0 Hoarseness (%): NR Deaths (%): 0 vs. 0	Fair
Knox 2007[38]	RCT 111 12 weeks	United Kingdom, Belgium Age 17-75, on ICS, severity NR, 2-3% smokers Multicenter	CIC HFA-MDI (160) vs. FP HFA-MDI (500)	No (low vs. medium)	Overall AEs(n): Treatment-emergent AE (TEAE) 42 vs. 49 Withdrawals due to AEs (n): 1 vs. 0 Oral candidiasis-thrush (n): 0 vs. : 1 Cough (%): NR Sore throat (%): 3.4 vs. 3.8 Headache (%): NR Upper respiratory tract infection (%): 3.4 vs. 9.4 Hoarseness (%): NR	Fair
Lipworth 2005[39]	RCT 164 12 weeks	United States Age >18, mild to moderate, smoking status NR Multicenter	Placebo vs. CIC HFA-MDI (320) vs. CIC HFA-MDI (640) vs. FP HFA-MDI (880)	Mixed (NA vs. medium vs. high vs. high)	Overall AEs(n): No. of pts/n having at least 1 tx-emergent AE: G1: 35/41 vs. G2/G3: 53/82 vs. G4: 32/41 Withdrawals due to AEs (%): G1: 7 vs. G2/G3: 1.2 vs. G4: 2.4 Oral candidiasis-thrush (%): 0 vs. 2.5% vs. 2.4% vs. 22.0% Cough, sore throat, URI, or headache (%): NR Hoarseness (n): G1: 0 vs. G2/G3: 2/82 vs. G4:	Fair

Study	Study design N Duration	Country Population Setting	Comparison (total daily dose in mcg)	Equivalent dosing	Results	Quality rating
					3/41	
Magnussen 2007[40]	RCT 808 12 weeks	Multinational - Germany, Poland, Czech Republic, France, Italy, The Netherlands, Slovakia, Spain Age >12, mild to severe, 21-24% ex- and current smokers Multicenter	CIC HFA-MDI (80) vs. CIC HFA-MDI (160) vs. FP HFA-MDI (176)	Yes (low)	Overall AEs(%): 25.2 vs. 24.4 vs. 27.4 Withdrawals due to AEs (n): 3 vs. 5 vs. 3 Oral candidiasis- thrush, cough, sore throat, headache, or hoarseness (%): NR Upper respiratory tract infection (%): Reported similar %s for the three groups (from 0.4 to 5.8%) for bronchitis, nasopharyngitis, pharyngitis, and allergic rhinitis	Fair
Pedersen 2009[41]	RCT 744 12 weeks	Multinational - Brazil, Germany, Hungary, Poland, Portugal, South Africa Age 6-11, mild to severe, smoking status NR Multicenter	CIC HFA-MDI (80) vs. CIC HFA-MDI (160) vs. FP HFA-MDI (176)	Yes (low)	Overall AEs(%): 46.4 vs. 41.7 vs. 47.6 Withdrawals due to AEs (%): 5.2% vs. 2.1 vs. 0.8 Oral candidiasis-thrush (%): 0 vs. 0.43 vs. 0.41 Cough, sore throat, headache, URI, or hoarseness (%): NR	Fair
Pedersen 2006[42]	RCT 556 12 weeks	Multinational - 8 countries Age 6-15, mild to severe, excluded current smokers Multicenter	CIC HFA-MDI (160) vs. FP HFA-MDI (176)	Yes (low)	Overall AEs (n): 277 vs. 279 Withdrawals due to AEs (n): 0 vs. 1 Oral candidiasis-thrush (%): NR Cough, sore throat, or hoarseness (%): NR Headache (%): 3.6 vs. 2.5 Upper respiratory tract infection (%): 6.9 vs. 6.5	Fair
Ciclesonide compared with mometasone						
No systematic reviews or head-to-head trials found						
Ciclesonide compared with triamcinolone						
No systematic reviews or head-to-head trials found						
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[43]	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	*Fair*
Fluticasone compared with triamcinolone						
Baraniuk et al. 1999[44]	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)	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	*Fair*
Condemi et al. 1997[45]	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, *P* = 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	*Fair*

Study	Study design N Duration	Country Population Setting	Comparison (total daily dose in mcg)	Equivalent dosing	Results	Quality rating
Gross et al. 1998[46]	*RCT, DB, DD* *304* *24 weeks*	*US* *Age ≥12, 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)*	*Overall AEs (%): 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 vs2* *Hoarseness (%): 3 vs 0 vs 0* *Migraine(%): 2 vs 0 vs 0*	*Fair*

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Appendix K. Tolerability and overall adverse events of LABAs

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)					
Cates and Lasserson 2009[1]	Systematic review with meta-analysis 4 RCTs (3 adult, 1 children) N= 1272 At least 12 weeks	Multinational Adults (age >18) and children (age 6-17), most with moderate persistent asthma	FM DPI (24) vs. SM DPI (100)	All-cause mortality: (N=4, OR not calculated, one adult non-asthma-related death in SM group, no deaths in children) All-cause SAEs in adults: (N= 3, OR 0.77; 95% CI 0.46 to 1.28, All-cause SAEs in children: (N=1, OR 0.95, 95% CI 0.06 to 15.33) Asthma-related SAEs in adults: (N=3, OR 0.86 95% CI 0.29 to 2.57), Asthma-related SAEs in children: (N=1, OR not-calculated, no asthma-related adverse events)	Good
Cates and Lasserson 2010 [2]	Systematic review with meta-analysis 8 RCTs (all adult and adolescent) N=6163 At least 12 weeks	Multinational Age >12, most with mild to moderate persistent asthma (variably defined).	SM (variable dose) and fluticasone or beclomethasone vs. FM (variable dose) and budesonide	All cause mortality: (N=7, OR 1.03, 95% CI 0.06 to 16.44) All cause SAEs: (N=7, OR 1.14, 95% CI 0.82 to 1.59) Asthma-related SAEs: (N=7, OR 0.69, 95% CI 0.37 to 1.26)	Good
Campbell et al. 1999[3]	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

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
Condemi et al. 2001[4]	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[5]	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[6] and Rutten-van Molken 1998[7]	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 *P* = 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)					

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Cates and Cates 2010 [8]	Systematic Review with meta-analysis 34 RCTs N= 62,815	Multinational Patients of any age, any asthma severity	SM vs. Placebo Or SM vs. SABA	**SM vs Placebo:** All-cause mortality in adults: (N=10 trials, OR 1.33, 95% CI: 0.85 to 2.08) All-cause mortality in children: (N=4, OR nonestimable, zero deaths reported in 793 patient-years) Non-fatal SAEs in adults: (N=13, OR 1.14, 95% CI: 1.01 to 1.28) Non-fatal SAEs in children (N=5, OR 1.3, 95% CI: 0.82 to 2.05) Asthma-related mortality in adults: (N=10, OR 3.49, 95% CI 1.31 to 9.31) Asthma-related non-fatal SAEs in adults: (N=12, OR 1.42; 95% CI 0.75 to 2.71) Asthma-related non-fatal SAEs in children: (N=5, OR 1.72, 95% CI 1.0 to 2.98) **SM vs Salbutamol** All-cause mortality in adults: (N=4, OR 1.28, 95% CI 0.79 to 2.05) All-cause mortality in children: (N=3, OR 0.04, 95% CI 0 to 2.97) All-cause non-fatal SAEs in adults and adolescents: (N=5, OR 0.96, 95% CI 0.85 to 1.1) All-cause non-fatal SAEs in children (N=3, OR 1.37, 95% CI 0.71 to 2.64) Asthma-related mortality in adults and adolescents: (N=4, OR 2.36, 95% CI 0.78 to 7.16) Asthma-related non-fatal SAEs in adults and adolescents: (N=3, OR 0.94, 95% CI 0.37 to 2.34) Asthma-related non-fatal SAEs in children: (N=3, OR 1.04, 95% CI 0.47 to 2.31)	Good

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Study	Study design N Duration	Country Study population Setting	Comparison (total daily dose)	Results	Quality rating
Ni Chroinin et al. 2004[9]	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[10]	Systematic review and meta-analysis N = 8147 26 RCTs Duration: at least 30 days (most less than 4 mo.)	Multinational RCTs conducted in adults or children aged 2 or above in whom LABA were added to ICS.	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 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	Good

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
				1.75).	
Salpeter et al. 2006[11]	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[12]	Systematic review with meta-analysis 67 RCTs (N = 42,333). Duration: at least4 wks.	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 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 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). 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). 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	Good

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Study	Study design N Duration	Country Study population Setting	Comparison (total daily dose)	Results	Quality rating
				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). Drug-related AE: more in LABA groups (OR 1.37, 95% CI: 1.01 to 1.87; seven studies, N = 2130), 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). Other AEs: NS difference for pharyngitis, cough, cramps, myalgia/ fatigue, insomnia, upper respiratory infection, musculo-skeletal pain or palpitations. 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.

References for Appendix K

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