



Controller Medications for Asthma

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Based on Data collected for the DERP report of 11/2008

Produced by:

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Health Resources Commission

The State of Oregon’s Health Resources Commission is a volunteer commission appointed by the Governor. The Health Resources Commission provides a public forum for discussion and development of consensus regarding significant emerging issues related to medical technology. Created by statute in 1991, it consists of four physicians experienced in health research and the evaluation of medical technologies and clinical outcomes; one representative of hospitals; one insurance industry representative; one business representative; one representative of labor organizations; one consumer representative and two pharmacists. All Health Resources Commissioners are selected with conflict of interest guidelines in mind. Any minor conflict of interest is disclosed.

The Commission is charged with conducting medical assessment of selected technologies, including prescription drugs. The commission may use advisory committees or subcommittees, the members to be appointed by the chairperson of the commission subject to approval by a majority of the commission. The appointees have the appropriate expertise to develop a medical technology assessment. Subcommittee meetings and deliberations are public, where public testimony is encouraged. Subcommittee recommendations are presented to the Health Resources Commission in a public forum. The Commission gives strong consideration to the recommendations of the advisory subcommittee meetings and public testimony in developing its final reports.

Overview

The 2001 session of the Oregon Legislature passed Senate Bill 819, authorizing the creation of a Practitioner-managed Prescription Drug Plan (PMPDP). The statute specifically directs the Health Resources Commission (HRC) to advise the Oregon Medical Assistance (OMAP) Department of Human Services (DHS) on this Plan.

In 2007 the Oregon Health Resources Commission (HRC) appointed a pharmaceutical subcommittee to perform evidence-based reviews of pharmaceutical agents. Members of the subcommittee for this review consisted of three Physicians, a Nurse Practitioner, and two pharmacists. All meetings were held in public with appropriate notice provided. The HRC director worked with the Center for Evidence-based Policy (Center) and the

Research Triangle Institute International-University of North Carolina Evidence-based Practice Center (EPC) to develop and finalize key questions for this drug class review, specifying patient populations, medications to be studied and outcome measures for analysis, considering both effectiveness and safety. Evidence was specifically sought for subgroups of patients based on race, ethnicity and age, demographics, other medications and co-morbidities. Using standardized methods, the EPC reviewed systematic databases, the medical literature and dossiers submitted by pharmaceutical manufacturers. Inclusion and exclusion criteria were applied to titles and abstracts, and each study was assessed for quality according to predetermined criteria.

The EPC's report, *Controller Medications for Asthma*, November 2008, was circulated to subcommittee members and posted on the web. The subcommittee met to review the document and this report is the consensus result of those meetings. Time was allotted for public comment, questions and testimony.

This report does not recite or characterize all the evidence that was discussed by the EPC, the Subcommittee or the HRC. This report is not a substitute for any of the information provided during the subcommittee process, and readers are encouraged to review the source materials. This report is prepared to facilitate the HRC in providing recommendations to the Department of Human Services. The HRC, working together with the EPC, the Center for Evidence Based Policy, DMAP, and the Oregon State University College of Pharmacy, will monitor medical evidence for new developments in this drug class. Approximately twice per year new pharmaceuticals will be reviewed and if appropriate, a recommendation for inclusion in the PMPDP will be made. For pharmaceuticals on the plan, significant new evidence will be assessed and Food and Drug Administration changes in indications and safety recommendations will be evaluated. This report will be updated if indicated. Substantive changes will be brought to the attention of the Health Resources Commission, who may choose to approve the report, or reconvene a subcommittee.

The full Evidence-based Practice Center's draft report, "*Controller Medications for Asthma*" is available via the Office for Oregon Health Policy & Research, Practitioner-Managed Prescription Drug Plan website:

www.oregon.gov/DAS/OHPPR/ORRX/HRC/evidence_based_reports.shtml

Information regarding the Oregon Health Resources Commission and its subcommittee policy and process can be found on the Office for Oregon Health Policy & Research website: <http://www.oregon.gov/DAS/OHPPR/HRC/index.shtml>

You may request more information including copies of the draft report from:

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Information dossiers submitted by pharmaceutical manufacturers are available upon request from the OHSU Center for Evidence-based Policy by contacting:

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There will be a charge for copying and handling in providing documents from both the Office of Oregon Health Policy & Research and the Center for Evidence Based Policy.

Critical Policy

Senate Bill 819

– “The Department of Human Services shall adopt a Practitioner-managed Prescription Drug Plan for the Oregon Health Plan. The purpose of the plan is to ensure that enrollees of the Oregon Health Plan receive the most effective prescription drug available at the best possible price.”

Health Resources Commission

– “Clinical outcomes are the most important indicators of comparative effectiveness”

– “If evidence is insufficient to answer a question, neither a positive nor a negative association can be assumed.”

Clinical Overview

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

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 for all patients with persistent asthma current recommendations are that they should have a short-acting relief medication on hand for treatment of exacerbations and a controller medication for long-term control, this report will focus on the following currently available controller medications: inhaled corticosteroids (ICSs), Long-Acting Beta-2 Agonists (LABAs), leukotriene modifiers, anti-IgE medications, and combination products.

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

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.

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 (Table1). The main clinical difference in the two available agents is that formoterol has a quicker onset of action than salmeterol.¹

Table1: Long-term controller medication class, trade names, manufacturers, formulations, and indications1, 5-10

Generic Name	Trade Name	Dosage Form/ Device	Strength	Approved Indication	Black Box Warnings?
Inhaled Corticosteroids					
Beclomethasone dipropionate	QVAR®	HFA	40 mcg/puff 50 mcg/puff* 80 mcg/puff 100 mcg/puff*	Asthma (age ≥ 5)	No
	Vanceril®++	MDI	42 mcg/puff 84 mcg/puff	Asthma (age ≥ 5)	N/A
Budesonide	Pulmicort Flexhaler®	DPI	90 mcg/dose 180 mcg/dose	Asthma (age ≥ 6)	No
	Pulmicort Turbuhaler®*	DPI	100 mcg/dose* 200 mcg/dose* 400 mcg/dose*		N/A
	Pulmicort Respules®	Inhalation suspension	0.25 mg/2ml 0.5 mg/2ml 1 mg/2ml	Asthma (age 1-8)	No
	Pulmicort Nebuamp®	Inhalation suspension	0.125 mg/ml 0.25 mg/ml 0.5 mg/ml	Asthma (age ≥ 3 months)	No
Flunisolide	AeroBid® AeroBid-M®	MDI MDI-menthol	250 mcg/puff	Asthma (age ≥ 6)	No
	AeroSpan®	HFA	80 mcg/puff+		No
	Bronalide®++	MDI	250 mcg/puff	Asthma (age ≥ 4)	N/A
Fluticasone propionate	Flovent®	HFA	44 mcg/puff 50 mcg/puff* 110 mcg/puff 125 mcg/puff* 220 mcg/puff 250 mcg/puff*	Asthma (age ≥ 4)	No
	Flovent Rotadisk®++	DPI	50 mcg/dose 100 mcg/dose 250 mcg/dose	Asthma (age ≥ 12)	N/A
	Flovent Diskus®*	DPI	50 mcg/dose+ 100 mcg/dose* 250 mcg/dose* 500 mcg/dose*	Asthma (age ≥ 4 yrs)	No
Mometasone furoate	Asmanex Twisthaler®	DPI	220 mcg/dose	Asthma (age ≥ 4)	No
Triamcinolone acetonide	Azmacort®	MDI – with spacer mouthpiece	75 mcg/dose		No
Leukotriene modifiers					
Montelukast	Singulair®	Tablets Chewable tablets Granules	10 mg+ 4 mg, 5 mg+ 4 mg/packet+	Asthma (age ≥ 1)	No
Leukotriene receptor antagonists					

Zafirlukast	Accolate®	Tablets	10 mg+ 20 mg+	Asthma (age ≥ 5 yrs in US); (age ≥ 12 yrs in Canada)	No
5- lipoxygenase inhibitor					
Zileuton	Zyflo® Zyflo CR®	Tablets Extended release tablets	600 mg 600 mg	Asthma (age ≥ 12 yrs)	No
Long-Acting Beta-2 Agonists					
Arformoterol	Brovana®	Inhalation solution	15 mcg/2ml	Not approved for asthma (COPD only)	Yes
Formoterol fumarate/ Eformoterol	Foradil Aerolizer®	DPI	12 mcg/capsule+	Asthma (age ≥ 5 yrs)	Yes
	Oxeze Turbuhaler®*	DPI	6 mcg/capsule* 12 mcg/capsule*	Asthma (age ≥ 6 yrs)	Yes
	Oxis Turbohaler®#	DPI	6 mcg/puff 12 mcg/puff	Asthma (age ≥ 6 yrs)	Yes
Salmeterol xinafoate	Serevent Diskus®	DPI	50 mcg/blister+	Asthma (age ≥ 4 yrs)	Yes
	Serevent Diskhaler®*	DPI	50 mcg/blister+	Asthma (age ≥ 4 yrs)	Yes
Anti-IgE medications					
Omalizumab	Xolair®	Powder for subcutaneous injection	202.5 mg (delivers 150 mg/1.2ml)	Asthma (age ≥ 12 yrs)	Yes
Combination products					
Fluticasone propionate/ Salmeterol xinafoate	Advair Diskus®	HFA	100mcg/50mcg+ 250mcg/50mcg+ 500mcg/50mcg+	Asthma (age ≥ 4 yrs)	Yes
	Advair HFA	HFA	45mcg/21mcg 115mcg/21mcg 125mcg/25mcg* 230mcg/21mcg 250mcg/25mcg*	Asthma (age ≥ 12 yrs)	Yes
Budesonide/ formoterol	Symbicort®	HFA	80mcg/4.5mcg 160mcg/4.5mcg	Asthma (age ≥ 12 yrs)	Yes
	Symbicort Turbuhaler®*	DPI	100mcg/6mcg* 200mcg/6mcg*	Asthma (age ≥ 12 yrs)	Yes

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

*This product is available in Canada only.

+This product is available in the US & Canada.

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

++This product has been discontinued by the manufacturer

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 1). 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 1). 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 1). 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 1).

Quality of the Evidence

For quality of evidence the EPC and subcommittee took into account the number of studies, the total number of patients in each study, the length of the study period and the endpoints of the studies. Statistical significance was an important consideration. The subcommittee utilized the EPC's ratings of "good, fair or poor" for grading the body of evidence. Overall quality ratings for an individual study were based on the internal and external validity of the trial.

Internal validity of each trial was based on:

- 1) Methods used for randomization
- 2) Allocation concealment and blinding

- 3) Similarity of compared groups at baseline and maintenance of comparable groups
- 4) Adequate reporting of dropouts, attrition, and crossover
- 5) Loss to follow-up
- 6) Use of intention-to-treat analysis

External validity of trials was assessed based on:

- 1) Adequate description of the study population
- 2) Similarity of patients to other populations to whom the intervention would be applied
- 3) Control group receiving comparable treatment
- 4) Funding source that might affect publication bias.

Weighing the Evidence

A particular randomized trial might receive two different ratings: one for efficacy and another for adverse events. The overall strength of evidence for a particular key question reflects the quality, consistency, and power of the body of evidence relevant to that question.

We rate the overall strength of evidence as low, moderate, high, or insufficient using a modified GRADE approach established by the Evidence-based Practice Centers.

High strength of evidence indicates high confidence in the estimate of effect and that the evidence reflects the true effect; further research is unlikely to change our confidence.

Moderate strength of evidence indicates moderate confidence that the evidence reflects the true effect; further research may change our confidence in the estimate and may change the estimate.

Low strength of evidence indicates low confidence that the evidence reflects the true effect; further research is likely to change our confidence in the estimate and is likely to change the estimate.

Insufficient indicates that evidence is unavailable or does not permit estimation of an effect.

Scope and Key Questions

To identify relevant citations, the EPC searched MEDLINE®, the Cochrane Database of Systematic Reviews®, and the Cochrane Central Register of Controlled Trials® and the International Pharmaceutical Abstracts (through April 2008). They limited the electronic searches to “human” and “English language”. They attempted to identify additional studies through hand searches of reference lists of included studies and reviews. In addition, the EPC 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, they searched dossiers submitted by pharmaceutical companies for the current review.

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 participating organizations of DERP are responsible for specifying the scope of the review so that it reflects the populations, drugs, and outcome measures of interest to them.

The participating organizations approved the following key questions to guide this review:

Key Questions:

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

Conclusions:

The literature search for this report included MEDLINE®, the Cochrane Database of Systematic Reviews®, and the Cochrane Central Register of Controlled Trials® and the International Pharmaceutical Abstracts (through April 2008).

Limitations of the evidence:

1. No study was characterized as an effectiveness trial; many included efficacy studies were conducted in narrowly defined populations or were limited to less than one year of follow-up.
2. Relatively few studies reported exacerbations, healthcare utilization (hospitalizations, emergency visits), or quality of life outcomes. Most outcomes were symptom related.

Conclusions:

Key Question 1: Efficacy/ Effectiveness

Intra-class comparisons

1. Efficacy studies provide moderate strength 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.
2. In children, head-to-head trials support the conclusion that ICSs do not differ in their impact on health outcomes, but data was only available for three comparisons: beclomethasone compared with budesonide, beclomethasone compared with fluticasone, and budesonide compared with fluticasone.
3. One 12 week (n=40) fair quality trial of montelukast and zafirlukast in adults with mild persistent asthma showed no statistically significant difference between groups in rescue

medicine use and quality of life. There was no evidence that met inclusion criteria for children. There were no comparative studies that met inclusion criteria for zileuton.

4. There is moderate strength 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.
5. One study of patients ranging in age from 6-17 years (n=156), found no difference between the LABA's for nocturnal awakenings, exacerbations, quality of life, missed work (parents), missed school, or compliance.
6. There were no studies that met inclusion criteria that compared omalizumab to the other included medications.
7. High strength of evidence indicates there is no difference in efficacy between fluticasone/ salmeterol vs. budesonide/ formoterol in individuals age 12 years or greater in studies up to 6 months in duration. There was no evidence that met inclusion criteria for individuals less than 12 years of age.

Inter-Class comparisons

1. For monotherapy in patients 12 years of age or greater, high strength indicates that inhaled corticosteroids are more efficacious than leukotriene modifiers.
2. Long acting beta agonists are not currently recommended as monotherapy.
3. Low to moderate strength evidence indicates that adding a leukotriene modifier to the same or increased dose of inhaled corticosteroid does not improve efficacy in patients age 12 years or greater.
4. High strength evidence supports addition of a LABA to ICS vs. increasing the dose of ICS in patients age 12 or greater with persistent asthma.
5. Moderate to high strength evidence indicates that inhaled corticosteroid plus a long acting beta agonist are more efficacious than leukotriene modifier monotherapy.
6. Moderate strength evidence indicates that fluticasone plus salmeterol is more efficacious than montelukast for treatment of persistent asthma in children under 12 years of age.
7. There is insufficient evidence to determine a comparative difference for inhaled corticosteroid plus a long acting beta agonist vs. a leukotriene modifier plus a long acting beta agonist or a leukotriene modifier plus a long acting beta agonist in individuals under 12 years of age.

Key Question 2: Harms

Intra-class comparisons

1. Moderate strength evidence indicates no difference in adverse events or withdrawals for inhaled corticosteroids, long acting beta agonists or combination products in individuals greater than 12 years of age.
2. Fair quality evidence indicates short-term growth velocity is reduced slightly less with fluticasone than with beclomethasone or budesonide. This reduction in growth velocity appears to primarily occur in the first year of treatment.
3. There is insufficient evidence to determine if treatment with ICS leads to a reduction in final adult height.

4. Evidence suggests that zileuton has an increased risk of liver toxicity compared to montelukast or zafirlukast.
5. In clinical studies malignant neoplasms were seen in 0.5% of patients treated with omalizumab compared with 0.2% in control patients. The majority of patients were observed for less than one year.

Inter-class comparisons

1. Long acting beta agonists are not currently recommended as monotherapy due to evidence suggesting increased risk of asthma related deaths or life threatening incidents.
2. Evidence suggests that there is no significant difference in adverse events or withdrawals for:
 - a. ICS + LABA vs. ICS (same dose) for patients 12 years old or greater.
 - b. ICS + LABA vs. ICS (increased dose) in patients 12 years old or greater.
 - c. ICS + LM vs. ICS (same dose) in patients 12 years old or greater.
 - d. ICS + LABA vs. ICS + LM in patients 12 years old or greater.

Key Question 3: Subgroups

1. Limited evidence suggests an increased risk in African-Americans for asthma related deaths or life threatening events when treated with salmeterol compared to placebo.
2. There was insufficient evidence to determine a difference between the included medications for based on gender, comorbidities, drug-drug interactions, pregnancy and genetics (genetic polymorphisms eg. Beta-2 adrenoreceptor gene, ADRB2).

Supporting Evidence:

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)

We found 2 systematic reviews with meta-analyses and 30 head-to-head RCTs (29 publications). Four of the head-to-head RCTs included children < 12. 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. Asthma severity ranged from mild persistent to severe persistent. Four studies did not report the severity or it was unable to be determined. Smoking status was not reported for eight studies (27%), including the four studies in pediatric populations. Among the others, twelve studies (40%) excluded individuals with a recent or current history of smoking and 10 (33%) allowed participants to smoke. Among the studies that allowed and reported smoking status, 5% to 34% of participants were current smokers. Other asthma medications were often allowed if maintained at a constant

dose; all trials allowed the use of a short-acting beta-agonist. Most trials enrolled patients who were currently being treated with ICS.

A. Inhaled Corticosteroids

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

1. Beclomethasone compared with budesonide

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

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

The majority of crossover trials had significant design flaws, so the results should be viewed with caution.

For asthma patients not treated with OCS, crossover studies showed no significant difference between treatments for symptom measures (variety of symptom scores reported) or rescue medication use. There was no significant difference between BDP and BUD for daytime breathlessness, morning breathlessness, and daily symptom scores (6 studies, 256 subjects; standardized mean difference (SMD) 0.06, 95% CI: -0.18, 0.31). Nor was there a significant difference in night-time breathlessness and evening breathlessness scores (3 studies, 134 subjects; SMD -0.09, 95% CI: -0.43, 0.25). Similarly, for asthma patients not treated with OCS, parallel group studies showed no significant differences in rescue medication use or withdrawals due to asthma exacerbations. For asthma patients treated with OCS, one crossover study assessed OCS-sparing effects and three evaluated other outcomes. The outcomes for those that did not assess OCS sparing effects were pooled (3 studies, 144 subjects) and found no significant difference between BDP and BUD for daytime or night-time breathlessness scores, sleep disturbance scores, or rescue medication use.

The first RCT²² was a 12-week parallel group trial (N = 460) with stratification for LABA use (2:1 yes: no) that compared treatment with three inhaled corticosteroids: BDP extrafine aerosol (Qvar Autohaler 800 mcg/d, N = 149), BUD Turbuhaler (1600 mcg/d, N = 162), and fluticasone Diskus (1000 mcg/d, N = 149).²² It enrolled patients with moderate to severe persistent asthma who were not controlled with a regimen that included ICS, with or without LABAs. Overall asthma control, assessed by the French version of the Juniper asthma control questionnaire, was improved in all groups with no significant difference between groups (mean change from baseline for BDP compared with BUD: -1.0 compared with -0.8; 95% CI of the difference: - 0.29, 0.08). Among the individual components of control included in the questionnaire (nocturnal awakenings,

morning discomfort, limitation of activity, dyspnea, wheezing, and consumption of short-acting beta-agonist) there were no significant differences except for improvement in nocturnal awakenings favoring BDP (-1.0 compared with -0.7; 95% CI of difference: -0.43, -0.05; $P = 0.045$).

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

2. Beclomethasone compared with fluticasone

One systematic review and 10 head-to-head RCTs comparing fluticasone (FP) to BDP met our inclusion criteria.

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

Ten trials, one good-rated²⁸ and nine fair-rated^{22, 24-27, 29-32} head-to-head RCTs, comparing BDP to FP met the inclusion/exclusion criteria for our review.

The single good-rated trial compared BDP 400 mcg/day (MDI-HFA) to FP 400 mcg/day (MDI) in 172 adults with mild to severe persistent asthma for 6 weeks; both were medium potency doses.²⁸ The trial was conducted in 30 general practice sites in the United Kingdom and Ireland. There were no significant differences in the improvement of asthma symptoms, sleep disturbance, rescue medicine use, or quality of life (AQLQ mean change from baseline) between the two groups.

Of the nine fair-rated RCTs that compared BDP to FP,^{22, 24-27, 29-32} just two included children and adolescents <12 years of age. One was conducted exclusively in a population of children and adolescents aged 4-11²⁶ and one included children, adolescents, and young adults aged 4-19.²⁹ Asthma severity ranged from mild- to severe-persistent. Doses ranged from low to high; all studies included comparisons of equipotent doses of BDP and FP. Study duration ranged from 6 to 52 weeks. All but one trial³⁰ assessed asthma symptoms and rescue medicine use.

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

3. Beclomethasone compared with mometasone

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

4. Beclomethasone compared with triamcinolone

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

5. Budesonide compared with flunisolide

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

6. Budesonide compared with fluticasone

One previously described systematic review and six head-to-head RCTs comparing FP to BUD met our inclusion criteria. The systematic review²¹ included studies comparing FP compared with BDP or BUD. Of the 71 studies included in this review, 37 compared FP to BUD (six of those 37 were included in our review). Comparisons were stratified by FP: BDP/BUD dose ratios of 1:2 or 1:1. The pooled treatment effect of FP was compared to the pooled treatment effect for BDP and BUD. For the studies conducted at dose ratios of 1:2, pooled estimates indicate that FP-treated patients had fewer symptoms, required less rescue medication than those treated with BDP or BUD.

There was no difference in exacerbations. For the studies conducted at dose ratios of 1:1, individual studies and pooled estimates suggest no difference in symptoms, rescue medicine use, or the number of asthma exacerbations. Although we rated the quality of this review as good, the comparison of FP to the combined effect of beclomethasone and budesonide limits possible conclusions regarding the *specific* comparison of BUD to FP. Six fair-rated head-to-head RCTs meeting our inclusion criteria compared budesonide to fluticasone.^{22, 38-42} Trial duration ranged from six to 24 weeks. Two were conducted in children and adolescents;^{39, 41} five were conducted in patients with moderate and/or severe persistent asthma and one was conducted in patients with mild to moderate persistent asthma.⁴¹ Three trials compared nonequivalent doses with FP given at a higher relative dose than BUD.^{38, 40, 41} All but one study³⁸ used dry powder formulations of

both medications. All six trials evaluated outcomes for asthma symptoms and rescue medicine use.

Overall, the evidence from these studies supports the conclusion that there is no difference between equipotent doses of BUD and FP. Three of the trials^{22, 39, 42} that compared equipotent doses and one⁴¹ that compared medium- with low-doses of BUD and FP found no difference for symptoms, exacerbations, or rescue medicine use. In addition, one trial³⁸ comparing two high-doses of FP (1000 mcg/d and 2000 mcg/d) with medium-dose BUD (1600 mcg/d) found no difference between the lower of the two high doses and medium-dose BUD for symptoms, exacerbations, and rescue medicine use. The remaining trial⁴⁰ compared nonequivalent 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.

7. Budesonide compared with mometasone

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

8. Budesonide compared with triamcinolone

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

9. Flunisolide compared with fluticasone

We found two RCTs reported in one publication⁴⁶ that compared flunisolide and fluticasone meeting our inclusion/exclusion criteria. Both were fair-quality trials comparing non-equipotent doses that randomized patients to high-dose FP MDI (500 mcg/d) or medium-dose flunisolide MDI (1000 mcg/d). One was an 8-week double-blind RCT (N = 321) and the other was a 6-week open-label RCT (N = 332). There was a trend toward greater improvement in symptom-free days for patients treated with high-dose FP (P NR for either).

10. *Fluticasone compared with mometasone*

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

11. *Fluticasone compared with triamcinolone*

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

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

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

B. Leukotriene Modifiers

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

1. *Montelukast compared with Zafirlukast*

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

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

We did not identify any systematic reviews or head-to-head trials that compared formoterol to arformoterol or salmeterol to arformoterol.

Formoterol was formerly known as eformoterol in the UK and these are generally considered to be the same medicine. The studies are discussed as they were originally published.

Head-to-head comparisons

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

Two fair-quality RCTs meeting our inclusion/exclusion criteria compared eFM with SM.^{52, 53} Both enrolled patients not adequately controlled on ICSs and were conducted in the UK and Republic of Ireland. The first was an 8-week trial that enrolled 469 adolescents and adults ≥ 12 years of age with mild to moderate persistent asthma.⁵² The other was a 12-week trial that enrolled 156 children and adolescents between six and 17 years of age with moderate persistent asthma.⁵³ Both trials assessed asthma symptoms, nocturnal awakenings, and exacerbations. One trial also reported hospital admission or visits to A&E⁵² while the other study also reported rescue medication use, quality of life, missed work, missed school, and compliance as well.⁵³ The trials found no difference between those treated with eFM and those treated with SM for all outcomes except for rescue medicine use: one trial⁵³ found a greater decrease in rescue medicine use in those treated with eFM than in those treated with SM.

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

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

D. Anti-IgE Therapy

Head-to-head comparisons

As there is only one drug in this category no head to head comparisons were found (or possible).

Placebo controlled evidence

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. One RCT conducted in children reported nocturnal awakenings.⁶² No studies reported mortality or adherence. The EPC conducted meta-analyses on these outcomes when sufficient data was reported by multiple studies.

The five trials in adolescent and adult populations reported statistically significant differences favoring omalizumab in overall symptom scores. The pediatrics study, however, reported “little change” in scores and “minimal difference” between omalizumab and placebo (data NR).⁶² Two trials reported the proportion of “low symptom days.”^{57, 64, 68} Both studies used the term “asthma-free days” but defined the concept to allow for some daily symptoms and daily use of rescue-medication, which essentially means “low symptom” days. The EPC’s meta-analysis found a significant

increase (mean increase of 23.2%) in the proportion of low symptom days in omalizumab-treated patients compared to placebo-treated patients (SMD = 0.232, 95% CI: 0.112, 0.353; $P < 0.001$, 2 studies). There was no significant heterogeneity between studies ($P = 0.3992$).

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

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

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

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

E. Combination Products

ICS+LABA compared with ICS+LABA

Head-to-head comparisons

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

All four trials reported asthma symptoms and exacerbation. Two trials reported each of the following: nocturnal awakenings,^{73, 75} rescue medicine use,^{72, 73} and

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

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

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

Head-to-head comparisons

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

We conducted meta-analyses for six outcomes that were reported with sufficient data in multiple trials. These included symptom-free days, symptom scores, nocturnal awakenings, exacerbations, rescue-free days, and rescue medicine use (puffs/day). We found no statistically significant differences in symptom-free days (SMD = 0.0026, 95% CI: -0.0397, 0.0449, 3 studies contributing 4 comparisons), symptom scores (SMD = -0.0363, 95% CI: -0.0859, 0.0133, 3 studies contributing 4 comparisons), nocturnal awakenings (SMD = -0.0533, 95% CI: -0.1220, 0.0154, 3 studies contributing 4 comparisons), rescue-free days (SMD = -0.0276, 95% CI: -0.0700, 0.0148, 3 studies contributing 4 comparisons), or rescue medicine use (SMD = -0.0656, 95% CI: -0.1337, 0.0026; 4 studies contributing 5 comparisons). Sensitivity analyses indicate that removing one of the comparisons⁷³ would result in outcomes favoring BUD/FM for maintenance and relief for symptom scores and for rescue medicine use. For the other outcomes

sensitivity analyses indicate no difference in overall meta-analysis conclusions with any single study removed. There was no significant heterogeneity between studies for these outcomes with the exception of nocturnal awakenings ($P = 0.049$) and rescue medicine use ($P = 0.012$). However, those treated with BUD/FM for maintenance and relief had fewer exacerbations (SMD = -0.1216, 95% CI: -0.1595, -0.0837; 4 studies contributing 5 comparisons). Sensitivity analyses indicate no difference in overall meta-analysis conclusions with any single study removed. There was no significant statistical heterogeneity between studies ($P = 0.842$).

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

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

We found one good-⁷³ and one fair-quality RCTs^{76, 78} for this comparison. Both trials reported asthma symptoms, nocturnal awakenings, exacerbations, and rescue medicine use. One trial also reported missed work, hospitalizations, and emergency visits⁷³. The results are mixed but show a trend favoring the BUD/FM for maintenance and relief for several outcomes. Both reported statistically significant differences in exacerbations favoring BUD/FM for maintenance and relief, but reported no difference in symptoms. One trial reported fewer nocturnal awakenings in those treated with BUD/FM for maintenance and relief.^{76, 78} The single study reporting missed work, hospitalizations, and emergency visits found no difference between groups.⁷³ None of the trials reported any outcomes favoring the BUD/FM for maintenance and SABA for relief.

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

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

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

II. Inter-class comparisons (Between classes)

A. Monotherapy

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

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. Those treated with ICSs had a greater increase in the proportion of days free from rescue medication (SMD -0.232, 95% CI: -0.286, -0.177, $P < 0.001$, 11 studies), greater reduction in rescue medicine use per day (SMD -0.214, 95% CI: -0.289, -0.139, $P = 0.001$, 12 studies), greater increase in percent of symptom free days (SMD -0.216, 95% CI: -0.276, -0.157, $P < 0.001$, 13 studies), greater improvement in symptom score (SMD -0.243, 95% CI: -0.310, -0.176, $P < 0.001$, 7 studies), less frequent exacerbations (SMD 0.216, 95% CI: 0.127, 0.305, $P < 0.001$, 12 studies), and a greater increase in quality of life (AQLQ scores; SMD -0.153, 95% CI: -0.234, -0.072, $P < 0.001$, 7 studies) than those treated with leukotriene modifiers. For all six meta-analyses, sensitivity analyses indicate no difference in overall meta-analysis conclusions with any single study removed. In addition, there was no significant heterogeneity between studies. When looking at montelukast alone compared with ICSs, our meta-analysis again shows that patients treated with ICSs had a greater increase in the proportion of days free from rescue medication use (SMD -0.202, 95% CI: -0.267, -0.137, $P < 0.001$), greater reduction in rescue medicine use per day (SMD -0.160, 95% CI: -0.258, -0.063, $P = 0.001$), greater increase in the proportion of symptom free days (SMD -0.189, 95% CI: -0.265, -0.113, $P < 0.001$), greater improvement in symptom score (SMD -0.230, 95% CI: -0.304, -0.156, $P < 0.001$), fewer exacerbations (SMD 0.216, 95% CI: 0.127, 0.305, $P < 0.001$), and greater improvement in quality of life (AQLQ score: SMD -0.141, 95% CI: -0.227, -0.055, $P < 0.001$) than those treated with montelukast.

When looking at zafirlukast alone compared with ICSs, our meta-analysis again shows that patients treated with ICSs had a greater increase of the proportion of days free from rescue medication use (SMD -0.307, 95% CI: -0.408, -0.207, $P < 0.001$), greater increase of the Proportion of symptom free days (SMD -0.291, 95% CI: -0.391, -0.191, $P < 0.001$), greater change in symptom score (SMD -0.298, 95% CI: -0.451, -0.145, $P < 0.001$), and fewer exacerbations (SMD 0.207, 95% CI: 0.107, 0.307, $P < 0.001$) than those treated with zafirlukast.

A previously published good quality systematic review with meta-analysis compared licensed doses of LTRAs with ICSs.⁸⁰ It included 3 trials testing a higher ICS dose; 3 trials testing a lower ICS dose; and the 21 remaining trials using equal nominal daily

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

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

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

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

We found nine fair quality RCTs that compared ML with FP^{86-89, 97-102} that met our inclusion criteria. Our meta-analyses of outcomes from these trials show that patients treated with FP had a greater increase in the proportion of days free from rescue medication use (SMD -0.232, 95% CI: -0.307, -0.157, $P < 0.001$, 6 studies), greater reduction in rescue medicine use per day (SMD -0.204, 95% CI: -0.317, -0.091, $P < 0.001$), greater increase in the proportion of symptom-free days (SMD -0.258, 95% CI: -0.336, -0.180, $P < 0.001$, 7 studies), greater improvement in symptom score (SMD -0.244, 95% CI: -0.337, -0.151, $P < 0.001$, 4 studies), fewer exacerbations (SMD 0.151, 95% CI: -0.225, -0.021, $P < 0.001$, 5 studies), and greater improvement in quality of life (AQLQ scores: SMD -0.123, 95% CI: -0.225, -0.021, $P = 0.019$, 5 studies) than those treated with ML.

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

Five fair quality RCTs^{82-85, 90, 96} meeting our inclusion criteria compared montelukast with beclomethasone. Most of the outcomes reported favored BDP over ML or found no difference between groups. In general, the results comparing BDP with ML appear to be consistent with the overall results comparing ICSs with LTRAs. Our meta-analyses of outcomes reported with sufficient data in multiple trials shows those treated with BDP had a greater proportion of rescue free days than those treated with ML (SMD -0.108, 95% CI: -0.208, -0.008, $P = 0.034$) and a trend toward a greater proportion of symptom-free days that did not reach statistical significance (SMD -0.118, 95% CI: -0.247, -0.011, $P = 0.073$). Further details of the RCTs can be found in the DERP report, but we will include results of the only trial enrolling children < 12 years of age.⁹⁶ The trial was a fair-rated multinational, multi-center RCT in children (N = 360) comparing ML 5 mg/day (N = 120) compared with medium dose BDP 400 mcg/day (N = 119) compared with placebo (N = 121) for 56 weeks. Subjects with mild persistent asthma, age 6.4 – 9.4 for boys and 6.4 – 8.4 for girls were enrolled worldwide (from most continents). The primary objective of the trial was to assess the effects of ML and BDP on linear growth, however some of our primary outcomes of interest were also reported. Fewer subjects treated with ML or BDP had asthma reported as an adverse experience compared to those treated with placebo, but the difference between groups was not statistically significant (36.7% compared with 42.9% compared with 50.4%, $P = NS$ for ML compared with BDP). There were no statistically significant differences in the percentage of patients requiring oral steroids (25% compared with 23.5%), the percentage requiring more than one course of oral steroids (5.8% compared with 5.9%), or the percentage of days of beta-agonist use (10.55% compared with 6.65%) between those treated with ML and those treated with BDP.

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

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

5. Fluticasone (FP) compared with Zafirlukast

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

< 0.001, 2 studies), and fewer exacerbations (SMD 0.207, 95% CI: 0.107, 0.307, $P < 0.001$, 4 studies) than those treated with zafirlukast.

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

Head-to-head comparisons

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

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

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

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

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

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

Three fair-quality RCTs compared BDP with SM.¹¹⁵⁻¹¹⁷ One¹¹⁵ enrolled adolescents and adults ≥ 12 years of age; the other two studies enrolled children and adolescents aged 6-14¹¹⁶ or 6-16.¹¹⁷ Study duration ranged from 26 weeks to 12 months. All three compared SM with medium-dose BDP. All three trials reported exacerbations and rescue medicine use; two reported symptoms^{115, 117} and nocturnal awakenings;^{115, 116} one reported missed school.¹¹⁶ With the exception of one trial that reported greater improvement in the percentage of rescue-free days for those treated with SM (36% compared with 28%, $P = 0.016$),¹¹⁵ all three trials reported no differences or better outcomes for those treated with BDP than for those treated with SM.

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

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

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

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

Leukotriene modifiers compared with Long-Acting Beta-2 Agonists (LABAs) for Monotherapy

Head-to-head comparisons

1. Montelukast compared with Salmeterol

One fair-rated RCT (N = 191) compared ML 10 mg/day (N = 97) compared with SM 100 mcg/day (N = 94) as monotherapy for 8 weeks.¹¹⁸ Subjects with chronic asthma and evidence of exercise-induced bronchoconstriction age 15 to 45 were enrolled from multiple centers in the United States. The trial was designed to evaluate exercise-induced bronchoconstriction and most of the outcomes reported were intermediate outcomes that are not included in our report. The trial also reported mortality as an outcome, with no deaths in the ML group and one in the SM group ($P = \text{NR}$).

2. Montelukast compared with Eformoterol

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

B. Combination therapy

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

1. ICS+LABA compared with ICS

The results of the six individual trials are described below under the appropriate drug comparisons. The EPC conducted meta-analyses for outcomes that were reported with sufficient data in multiple trials. These included symptom-free days, symptom scores, rescue medicine-free days, and rescue medicine use (puffs/day). We found statistically significant differences favoring those treated with ICS+LABA for all four outcomes. Those treated with ICS+LABA had greater improvement in the percentage of symptom-free days (SMD = 0.262, 95% CI: 0.123, 0.40; $P < 0.001$, 5 studies), greater improvement in symptom scores (SMD = 0.347, 95% CI: 0.174, 0.521; $P < 0.001$, 3 studies), greater improvement in the percentage of rescue-free days (SMD = 0.076, 95% CI: 0.198, 0.496; $P < .001$, 3 studies), and greater reduction in rescue medicine use (SMD = 0.074, 95% CI: 0.23, 0.52; $P < 0.001$, four studies). For all four meta-analyses, sensitivity analyses indicate no difference in overall meta-analysis conclusions with any single study removed. In addition, there was no significant heterogeneity between studies.

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

Four fair-quality RCTs (1,062 subjects) compared FP+SM with FP alone^{107, 109, 121, 122}. All four compared the combination of FP and SM administered in a single inhaler with FP alone. Three of the four used low dose FP; one used medium dose FP.¹²¹ Three were 12-week trials and one was a 24-week trial.¹²² All were conducted in populations of ≥ 12 or 18 years of age. All four trials reported outcome measures for symptoms and rescue medicine use, two trials reported nocturnal awakenings,^{107, 109} and one reported exacerbations.¹²² Three trials reported greater improvements in symptoms for those treated with FP/SM combination products than for those treated with FP alone. Just one trial found no difference in symptoms.¹⁰⁹ All four trials reported statistically significantly better outcomes for most measures of rescue medicine use (puffs/day, % of rescue-free days, % of rescue-free nights, episodes of use) for those treated with FP/SM. Just one trial reported no statistically significant difference for one of its measures of rescue medicine use, but there was a trend toward greater improvement for those treated with FP/SM (mean improvement in puffs/24 hours: -2.4 compared with -1.8).¹⁰⁹ The trials reporting nocturnal awakenings and exacerbations found no difference between groups.

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

Two fair-quality RCTs (1,036 subjects) compared BUD+FM with BUD alone.^{123, 124} Both compared BUD+FM administered in separate inhalers with low-dose BUD alone. One was a 12-week Russian trial that enrolled 338 adults.¹²³ The other was a 1-year multinational trial that enrolled 1970 adolescents and adults ≥ 12 years of age.¹²⁴ The two trials reported some conflicting results. The 12-week trial reported better improvement in symptoms and rescue medicine use for subjects treated with BUD+FM, but no difference in quality of life. The 1-year trial reported no statistically significant differences between the two groups for symptoms, nocturnal awakenings, exacerbations, or rescue medicine use.

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

Head-to-head comparisons

1. *ICS + LABA compared with higher dose ICS*

Using data from the 27 head-to-head RCTs that met our inclusion criteria, we conducted meta analyses for five outcomes that were reported with sufficient data in multiple trials. These included symptom-free days, symptom scores, exacerbations, rescue-free days, and rescue medicine use (puffs/day). Subjects treated with ICS+LABA had greater improvement in the percentage of symptom-free days (SMD = 0.191, 95% CI: 0.133, 0.248; $P < 0.001$, 16 studies contributing 17 comparisons), greater improvement in symptom scores (SMD = 0.176, 95% CI: 0.066, 0.287; $P = 0.002$, 10 studies contributing 11 comparisons), greater improvement in the percentage of rescue-free days (SMD = 0.214, 95% CI: 0.114, 0.301; $P < 0.001$, 9 studies contributing 10 comparisons), and greater reduction in rescue medicine use (SMD = 0.196, 95% CI: 0.138, 0.253; $P < 0.001$, 15 studies contributing 16 comparisons) than those treated with a higher dose ICS alone. However, there was no statistically significant difference in the percentage of subjects with exacerbations, but the point estimate favors those treated with ICS+LABA (SMD = -0.042, 95% CI: -0.095, .010; $P = 0.111$, 18 studies contributing 19

comparisons). For all five meta-analyses, sensitivity analyses indicate no difference in overall meta-analysis conclusions with any single study removed. There was no significant heterogeneity between studies for these outcomes. Additional sensitivity analyses removing all five studies enrolling subjects that were well controlled on current therapy^{99, 128, 130, 133, 144} found no difference in overall meta-analysis.

One good systematic review¹²⁶ compared the addition of any LABA to any ICS (ICS+LABA) with increasing the ICS dose. The review included 30 trials (3 of them in pediatric populations) that included a total of 9,509 subjects. Trial duration ranged from four to 54 weeks. Most studies (N = 26) were less than or equal to 24 weeks. All but one study required subjects to be taking ICS for some time prior to randomization. Eight examined ICSs+LABAs delivered via a single device and 22 tested the combination therapy delivered by separate devices. The systematic review reported no significant difference between groups for the primary outcome, the rate of patients with exacerbations requiring systemic corticosteroids (RR 0.88, 95% CI: 0.77, 1.02, N = 15). They also reported no significant difference in nocturnal awakenings, quality of life, and some measures of symptoms (daytime symptoms at endpoint, nighttime symptoms, % of symptom-free nights at endpoint, and nighttime awakenings) and rescue medicine use (number of daytime rescue inhalations, nighttime rescue inhalations, % overall rescue-free days, or change in nighttime inhalations). However, they reported more favorable results for some measures of symptoms (daytime symptom score, overall 24 hour symptom score, % symptom-free days at endpoint), rescue medicine use (change in daytime rescue inhalations, rescue inhalations over 24 hours), and withdrawals for those treated with ICSs+LABAs .

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

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

Ten fair-quality RCTs (4,025 subjects) compared FP+SM with a higher dose of FP^{48, 99, 128-135}. Seven administered FP+SM in a single inhaler device^{99, 128-130, 132-134} and three tested the combination delivered by separate inhalers. Only one study⁹⁹ included any children ≤ 12 years of age. Study duration was 12 weeks for five trials, 16 weeks for one trial, and 24 weeks for four trials. The majority of trials assessed asthma symptoms (all 10 trials) and rescue medicine use (nine trials). Five trials also reported exacerbations and two reported quality of life. For these outcomes, all 10 trials either reported no difference or outcomes favoring FP+SM combination therapy over the increased dose of FP. No trial reported a statistically significant difference in favor of FP alone for any of these outcomes. For subjects treated with FP+SM compared to those treated with FP alone, six trials reported fewer symptoms or better improvement in symptoms,^{128, 129, 131, 132, 134, 135} seven trials reported a greater decrease or less frequent use of rescue medicine,^{48, 128-132, 135} one trial reported a trend toward fewer exacerbations,¹²⁹ and one trial reported greater improvement in nocturnal awakenings.¹³¹ The two trials reporting quality of life found no statistically significant difference in overall quality of life measures^{99, 134}.

Meta-analyses of these 10 trials shows no statistically significant difference in the percentage of subjects with exacerbations, but the point estimate favors those treated with

FP+SM (SMD = -0.0922, 95% CI: -0.1946, 0.0102; $P = 0.0776$, 5 studies). Sensitivity analyses indicate that removing one study¹³⁵ would have resulted in a statistically significant difference in favor of FP+SM ($P = 0.0473$). There was no significant heterogeneity between studies ($P = 0.770$).

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

Six fair quality RCTs (5,752 subjects) compared BUD+FM with a higher dose of BUD^{76, 78, 124, 136-139}. Four administered BUD+FM in a single inhaler device^{76, 78, 136, 137} and two tested the combination delivered by separate inhalers. Two of the trials^{76, 78} included children ≤ 12 years of age. One enrolled children with mild to moderate persistent asthma between the ages of four and 11.⁷⁶ The other enrolled subjects with moderate persistent asthma between the ages of four and 80.⁷⁸ Study duration was 12 months for five trials and 12 weeks for one trial.¹³⁷ All trials assessed asthma symptoms, exacerbations, and rescue medicine use. Four trials also reported nocturnal awakenings. For these outcomes, the majority of trials reported no difference or outcomes favoring BUD+FM combination therapy. For subjects treated with BUD+FM compared to those treated with BUD alone, four of six trials reported fewer symptoms or better improvement in symptoms,^{76, 78, 137-139} one trial (of five reporting) found greater reduction in nocturnal awakenings,¹³⁷ and three trials reported a greater decrease or less frequent use of rescue medicine.^{78, 137-139} Four trials found no difference in exacerbations.^{76, 78, 136, 137} The remainder of trials reported no difference for these outcomes except for one trial reporting a trend toward fewer exacerbations in subjects treated with the increased dose of BUD than those treated with BUD+FM^{138, 139}.

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

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

Six fair quality RCTs (2,574 subjects) compared BDP+SM with a higher dose of BDP¹⁴⁰⁻¹⁴⁶. All six administered BDP+SM in separate inhalers. One trial¹⁴⁴ enrolled children and adolescents between the ages of four and 18. The remainder were conducted in populations ≥ 12 years of age. Study duration was 12 weeks for one trial, ¹⁴⁵ 21-24 weeks for four,^{140-143, 146} and one year for one.¹⁴⁴ All trials assessed asthma symptoms, exacerbations, and rescue medicine use. Four trials also reported nocturnal awakenings and two reported quality of life outcomes. For each of these outcomes, the majority of trials reported no difference or outcomes favoring BDP+SM combination therapy; none reported a statistically significantly greater improvement for those treated with BDP alone. For symptoms, three trials reported no difference^{140, 141, 144, 145} and three found results favoring BDP+SM.^{142, 143, 146} For nocturnal awakenings, one trial reported no difference¹⁴³ and three found results favoring BDP+SM.^{140-142, 146} For exacerbations, five trials reported no difference^{140-143, 145, 146} and one reported a

trend toward fewer exacerbations requiring steroids for those treated with BDP alone.¹⁴⁴ All but one trial^{140, 141} reported a greater decrease or less frequent use of rescue medicine for those treated with BDP+SM than for those treated with BDP alone. The two trials reporting quality of life found no significant difference between the groups^{140, 141, 145}. Meta-analyses of these six trials showed trends consistent with the overall ICS+LABA compared with higher dose ICS meta-analyses. Subjects treated with BDP+SM had statistically significantly greater reduction in rescue medicine use (SMD = 0.179, 95% CI: 0.048, 0.31; $P < 0.007$, 4 studies; $P = 0.290$ for heterogeneity) and trended toward greater improvement in the percentage of symptom-free days (SMD = 0.136, 95% CI: -0.011, 0.282 ; $P = 0.07$, 2 studies) than those treated with a higher dose BDP alone. There was no statistically significant difference in the percentage of subjects with exacerbations (SMD = -0.0185, 95% CI: -0.095, 0.058; $P = 0.64$, 5 studies contributing 6 comparisons; $P = 0.768$ for heterogeneity).

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

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

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

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

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

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

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

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

improvement in symptoms, nocturnal awakenings, and rescue medicine use for those treated with FP+SM than for those treated with TAA alone.

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

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. Those treated with ICS+LABA had a greater increase in the proportion of days free from rescue medication (SMD 0.271, 95% CI: 0.195, 0.347, $P < 0.001$, 17 comparisons), greater reduction in rescue medicine use per day (SMD -0.324, 95% CI: -0.389, -0.259, $P < 0.001$, 17 comparisons), greater increase in percentage of symptom free days (SMD 0.260, 95% CI: 0.206, 0.314, $P < 0.001$, 24 comparisons), greater improvement in symptom score (SMD -0.298, 95% CI: -0.360, -0.235, $P < 0.001$, 15 comparisons), and a greater increase in quality of life (AQLQ scores; SMD 0.206, 95% CI: 0.083, 0.328, $P = 0.001$, 4 comparisons) than those treated with ICS alone. For all five meta-analyses, sensitivity analyses indicate no difference in overall meta-analysis conclusions with any single study removed. In addition, there was no significant heterogeneity between studies.

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

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

Two good^{157, 167} and 11 fair RCTs^{110, 124, 138, 156, 160-163, 165, 169, 170} (7,881 subjects total) compared the addition of FM to BUD with continuing the same dose of BUD. One of these trials reported using eformoterol (eFM).¹⁶³ Five trials administered BUD+FM in a single inhaler device,^{156, 161, 165, 169, 170} three tested the combination delivered by separate inhalers,^{124, 138, 163} and five administered them both as a single inhaler and in separate inhalers to different study groups.^{110, 157, 160, 162, 167} Three trials included children ≤ 12 years of age.^{162, 165, 169} Study duration was 12 weeks for ten trials, 32 weeks for one trial,¹⁶³ and one year for two trials.^{124, 138} The majority of trials assessed asthma symptoms (all 13 trials), nocturnal awakenings (11 trials), exacerbations (eight trials), and rescue medicine use (all 13 trials). Four trials also assessed quality of life and one assessed missed work or school. For these outcomes, all 13 trials either reported no difference or outcomes favoring BUD+FM combination therapy over the same dose of BUD. No trial reported a statistically significant difference in favor of BUD alone for any of these outcomes. For subjects treated with BUD+FM compared to those treated with BUD alone, nine trials (69%) reported fewer symptoms or better improvement in symptoms,^{105, 106, 108, 110-112, 124, 132, 138, 139, 144, 154-}

161, 163, 164, 166-168 six trials (of seven reporting the outcome) reported fewer exacerbations or a lower risk exacerbations, 124, 138, 156, 163, 165, 170 and nine trials (69%) reported a greater decrease or less frequent use of rescue medicine. 105, 106, 108, 111, 112, 124, 132, 138, 139, 144, 154-161, 163-168 For three of the eleven trials reporting nocturnal awakenings, results favored the BUD+FM group. 156, 157, 161 The other eight reported no difference. 110, 124, 160, 162, 165, 167, 169, 170 Three 162, 163, 169 of the four trials reporting quality of life found no statistically significant difference in overall quality of life measures and one 161 reported greater improvement in those treated with BUD+FM. The single trial reporting missed work or school found no significant difference between groups. 163

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

Seven fair quality RCTs (2,405 subjects) compared the addition of SM to FP with continuing the same dose of FP 105, 106, 108, 111, 132, 154, 159. All seven administered FP+SM in a single inhaler device. None tested the combination delivered by separate inhalers. None of the trials included children ≤ 12 years of age. Study duration was 12 weeks for four trials, 105, 108, 111, 154 24 weeks for one trial, 132 and 12 months for two trials. 106, 159 The majority of trials assessed asthma symptoms (all trials), exacerbations (five trials), and rescue medicine use (all trials). Three trials also reported nocturnal awakenings and one reported quality of life. For these outcomes, all seven trials either reported no difference or outcomes favoring FP+SM combination therapy over the same dose of FP. No trial reported a statistically significant difference in favor of FP alone for any of these outcomes. For subjects treated with FP+SM compared to those treated with FP alone, five trials (71%) reported fewer symptoms or better improvement in symptoms, 105, 111, 132, 154, 159 three trials (of five reporting) reported fewer patients having exacerbations or withdrawn due to exacerbations, 105, 106, 111 and six trials (86%) reported a greater decrease or less frequent use of rescue medicine. 105, 108, 111, 132, 154, 159 Two of the three trials reporting nocturnal awakenings found no difference between groups, 105, 108 one reported a higher percentage of awakening-free nights for the FP+SM group. 111 The single trial reporting quality of life measures reported a trend toward better scores on the activities limitation domain of the AQLQ, but no difference in other domains (*activities limitation*: 1.0 compared with 0.62, $P = \text{NR}$). 111

4. ICS+Salmeterol (SM) compared with ICS

Three fair quality RCTs (835 subjects) compared the addition of SM to any ICS with continuing the same dose of ICS (plus placebo) 155, 158, 164. All three administered ICS+SM by separate inhalers. One trial included children, enrolling 210 subjects between the ages of 4 and 16. 164 Study duration was 12 weeks for two trials 155, 164 and 14 weeks for one. 158 All three trials reported symptoms and rescue medicine use, one reported exacerbations, 155 and one reported quality of life measures. 158 In all three trials, those treated with ICS+SM had greater improvements in symptoms (in one trial the difference was only statistically significant for nighttime symptoms) 155 and rescue medicine use. The single trial reporting exacerbations found no statistically significant difference in the number of patients requiring a course of oral steroids (19 compared with 15, $P = 0.19$). 155 The trial reporting quality of life found no statistically significant difference in overall quality of life, but there was a trend toward greater improvement in the ICS+SM group (AQLQ global score, mean change from baseline: 1.08 compared with 0.61, $P = 0.47$). 158

5. ICS+Formoterol (FM) compared with ICS

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

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

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

ICS+LTRA compared with ICS

Head-to-head comparisons

1. ICS+LTRA compared with ICS

One good systematic review with meta-analysis¹⁷¹ compared LTRA plus ICS with the same dose of ICS, same dose of ICS with taper, or increased doses of ICS. The systematic review included 27 studies (5871 subjects); two of the studies were in children and 25 were in adults. Sixteen of the 27 trials reported data in a way that allowed meta-analysis. Three of these included trials met our inclusion criteria.^{90, 172-174} Many were excluded for wrong medication (pranlukast) or short duration (less than six weeks). Thirteen of the studies (two in children) compared an LTRA plus an ICS with the same doses of an ICS; seven studies compared an LTRA plus an ICS with increased doses of an ICS; and seven studies compared an LTRA plus an ICS with the same doses of ICS with tapering. The LTRAs included montelukast, zafirlukast, and pranlukast. Many trials used higher than licensed doses of LTRAs. Most trials used BDP with a dosing range from low (≤ 400 mcg/day BDP or equivalent) to high (> 800 mcg/day BDP or equivalent) potency, with each trial ensuring same ICS dosing for both groups.

A. 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 agonist 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).

B. 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).

B. ICS+LTRA compared with same ICS (tapering).

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

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

We found one fair RCT¹⁷⁴ comparing the combination of BUD+ML with the same dose of BUD. This fair-rated RCT (N = 639), the CASIOPEA study, compared low to high dose BUD (400 to 1600 mcg/day) plus placebo (N = 313) with low to high dose BUD (400 to 1600 mcg/day) + ML 10 mg/day (N = 326) for 16 weeks.¹⁷⁴ Subjects age 18 to 70 with poorly controlled mild to severe asthma currently being treated with a stable dose of ICS for at least 8 weeks were enrolled from hospital centers in Spain. At endpoint, there were no statistically significant differences in asthma symptom scores or quality of life. However, those treated with BUD+ML had fewer nocturnal awakenings, more asthma free days, fewer days with exacerbations, and greater decrease in rescue medicine use. The differences were reportedly independent of BUD dose.

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

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

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

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

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

Combination products compared with Leukotriene Modifiers

Head-to-head comparisons

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

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

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

≤ 0.001), and increase in quality of life (AQLQ overall score, increase: 1.7 compared with 1.2; $P < 0.001$). Exacerbations occurred less frequently in the FP/SM group (3% compared with 6%; $P = \text{NR}$). Compliance was approximately 99% in both groups. The first fair-rated RCT (N = 423) also compared low dose FP/SM (200 mcg/100mcg daily) (N = 211) compared with ML (10mg/day) (N = 212) for 12 weeks.¹⁷⁷ Subjects with uncontrolled asthma treated with oral or inhaled short-acting beta-agonist age 15 or older were enrolled from multiple centers in the United States. At endpoint, results were similar to those in the good quality RCT described above¹⁷⁶ with significant differences for all outcomes favoring FP/SM over ML: including decrease in symptoms, rescue medicine use, and exacerbations (0%, 5%; $P < 0.001$).

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

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

ICS+LABA vs ICS+LTRA

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

Head-to-head comparisons

1. ICS+LABA compared with ICS+LTRA

One good quality systematic review with meta-analysis including 6,030 subjects (11 of 15 included trials contributed to the analyses) compared LABAs with LTRAs as add-on therapy to ICSs.¹⁷⁸ The included trials compared salmeterol (100 mcg/day) or formoterol (24 mcg/day) plus ICS compared with montelukast (10 mg/day) or zafirlukast (40 mg/day) plus ICS. The ICS dose average was 400 to 560 mcg/day of beclomethasone or equivalent.¹⁷⁸ Of the fifteen trials the met inclusion criteria, a total of 80 subjects

were children. Of the 11 trials that contributed to the analyses, 10 were in adults and one was in children. Six of the included trials met our inclusion criteria.^{179-182, 184, 185} Five of the studies included in the analysis did not meet our inclusion criteria. The systematic review included randomized controlled trials conducted in adults or children with persistent asthma where a LABA or LTRA was added to ICS for 4 to 48 weeks. Inhaled Short-Acting Beta-2 Agonists and short courses of oral steroids were permitted as rescue medications. Subjects had to be on a stable dose of ICSs throughout the trials. The meta-analysis reported that LABA plus ICS was significantly better than LTRA plus ICS for all observed outcomes.¹⁷⁸ Six trials contributed to the primary outcome showing a significant decrease in risk of exacerbation requiring systemic steroids for those treated with LABAs (RR 0.83; 95% CI: 0.71, 0.97). The type of LTRA used did not impact the results. The reported number of patients who must be treated with the combination of LABA and ICS instead of LTRA and ICS to prevent one exacerbation over 48 weeks was 38 (95% CI: 23, 247). Subjects treated with LABA+ICS had greater improvement in the percentage of symptom-free days (WMD 6.75%; 95% CI: 3.11, 10.39, 5 studies), daytime symptom scores (SMD -0.18; 95% CI: -0.25, -0.12, 5 studies), nighttime awakenings (WMD -0.12; 95% CI: -0.19, -0.06, 4 studies), percentage of rescue-free days (WMD 8.96%; 95% CI: 4.39, 13.53, 4 studies), rescue medication use per day (WMD -0.49 puffs/day; 95% CI: -0.75, -0.24, 7 studies), overall asthma-related quality of life (WMD 0.11; 95% CI: 0.05, 0.17, 3 studies). There was significant heterogeneity in one of the analyses (percentage of rescue-free days; $I^2 = 61%$; $P < 0.05$). Six of the seven included trials were included in the systematic review with meta-analysis¹⁷⁸ described above. The other fair-rated RCT,¹⁸³ the SOLTA study, compared low dose FP (200 mcg/day) plus SM (100 mcg/day) (N = 33) compared with low dose FP (200 mcg/day) plus ML 10 mg/day (N = 33) for 12 weeks in 66 adults (age 18 to 50) with uncontrolled mild to moderate asthma. The ICS/LABA combination was delivered via a single inhaler. Patients being treated with medium dose ICSs were enrolled from multiple centers in the United Kingdom. At endpoint, there were no statistically significant differences in asthma symptoms, but the trends in direction of the effect sizes favored the ICS/LABA combination (symptoms-free days: mean difference in change from baseline: 13.2%, 95% CI: -1.9%, -32.9%; $P = 0.064$; symptom-free nights: mean difference in change from baseline: 13.3%, 95% CI: -1.5%, -34.5%; $P = 0.055$). There was no significant difference in daytime rescue use (median % rescue free days at endpoint 73% compared with 70%; $P = NS$), but there was a difference in rescue use at night favoring FP/SM (median rescue free nights at endpoint: 93% compared with 82%; $P = 0.01$). We do not describe all of the other included RCTs in detail because they generally found results consistent with the overall conclusions of the meta-analysis. For all of our outcomes of interest, most trials reported favorable results for subjects treated with ICS+LABA; the others reported no statistically significant differences.

LTRA+LABA compared with ICS+LABA

We found one fair quality RCT comparing LTRA plus LABA with ICS plus LABA.¹⁸⁶ The fair-rated, placebo-controlled, multi-center RCT (N = 192) compared ML (10mg/day) plus SM (100 mcg/day) plus placebo ICS (N = 98) compared with low dose BDP (160 mcg/day) plus SM (100 mcg/day) plus placebo LTRA (N = 92) for 14 weeks, washout for 4 weeks, then crossover for another 14 weeks.¹⁸⁶ Subjects age 12 to 65 with

moderate asthma were enrolled from multiple sites in the United States. There was a 4-week run-in period that involved a single-blind treatment with both BDP (160 mcg/day) and ML (10 mg/day). The primary objective of the study was to assess time until treatment failure. The trial was terminated early because the Data and Safety Monitoring Board determined that the primary research question had been answered. Those treated with LTRA+LABA had significantly shorter time to treatment failure than those treated with ICS+LABA ($P = 0.0008$).

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?

Intra-class Evidence (within one class)

1. Inhaled Corticosteroids

Most studies (93%, 28 of 30) that examined the efficacy of one ICS relative to another (described in Key Question 1) also reported tolerability and adverse events. Four head-to-head RCTs that did not report efficacy met our inclusion/exclusion criteria for tolerability or adverse events.¹⁹²⁻¹⁹⁵ Four of the head-to-head RCTs included children < 12.^{26, 39, 41, 192} Placebo-controlled RCTs and observational studies are described below in their respective specific adverse event sections. Methods of adverse events assessment differed greatly. Few studies used objective scales such as the adverse reaction terminology from the World Health Organization (WHO). Most studies combined patient-reported adverse events with a regular clinical examination by an investigator. Often it was hard to determine if assessment methods were unbiased and adequate; many trials reported only those adverse events considered to be related to treatment. Rarely were adverse events prespecified and defined. Short study durations and small sample sizes limited the validity of adverse events assessment in many trials. Many studies excluded eligible participants that did not tolerate treatment during the run-in period, limiting the generalizability of adverse event assessment. Few RCTs were designed to assess adverse events as primary outcomes; most published studies were post hoc analyses or retrospective reviews of databases.

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

The vast majority of studies reported similar results for equipotent ICS doses. Only three studies reported a difference of greater than 5% in overall adverse events for equipotent doses.^{32, 35, 37} Only one study reported a statistically significant difference in overall adverse events between two ICSs (overall AEs (%): 20 compared with 5, $P < 0.001$ for FP compared with TAA, but the study did not compare equipotent doses.⁵⁰ Three studies reported a difference of greater than 5% in withdrawals due to AEs for equipotent doses.^{25, 36, 194} No trial reported a statistically significant difference in withdrawals due to AEs. Most head-to-head trials reported specific adverse events. Oral candidiasis, rhinitis, cough, sore throat, hoarseness, headache, and upper respiratory infection were among the most commonly reported adverse events. In most head-to-head trials oral candidiasis, rhinitis, cough, sore throat, hoarseness, and bronchitis were reported in fewer than 10 percent of ICS-treated patients. Upper respiratory tract infections were reported by 3 to 32% of study participants. For common specific adverse events, just two trials

reported a statistically significant difference between equipotent doses of different ICSs.^{30, 36} One reported a greater incidence of headache in those treated with BDP than those treated with FP (7% compared with < 1%, $P = 0.03$)³⁰ and one reported a greater incidence of upper respiratory tract infection with TAA than with BDP (10.4% compared with 2.7%, $P = 0.027$).³⁶

B. Specific adverse events

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

I. Bone density/osteoporosis

We found two fair quality systematic reviews with meta-analyses that studied the effect of ICSs on markers of bone function and metabolism.^{187,188} One included 14 studies (2,302 subjects) of patients with asthma or COPD (both RCTs and prospective cohort studies) assessing BMD.¹⁸⁷ The other included six studies of asthmatic subjects with median duration of ICS use of at least three years.¹⁸⁸ Pooled results from both meta-analyses showed no statistically significant difference in BMD between patients taking ICSs and controls. The one that included patients with asthma and COPD reported that asthma patients treated with ICSs showed a slight increase in BMD (0.13%) whereas COPD patients showed a slight decrease (-0.42%); however, neither change was statistically significant.¹⁸⁷ Our review includes eight studies: three of the trials^{194, 195, 200} in the systematic reviews, as well as five additional studies.^{196, 198, 199, 201-203} We excluded the remainder of studies from these two reviews because of wrong population (COPD patients), insufficient sample size, and/or poor quality. In total we include one good-rated RCT,^{198, 199} three fair-rated RCTs,¹⁹⁴⁻¹⁹⁶ one fair prospective cohort study,²⁰⁰ one fair case-control study,²⁰¹ one fair retrospective cohort study,²⁰² and one fair cross-sectional study.²⁰³ All eight studies assessed BMD, fracture risk, or both. In total, three studies evaluated the risk of fracture^{195, 201, 202} and six measured BMD as an intermediate outcome of osteoporosis.^{194-196, 198-200, 203} Two studies compared one ICS to another,^{194, 195} three compared one ICS to placebo,^{196, 198, 199, 203} and three studies compared one ICS or any ICS to a population that did not use an ICS.²⁰⁰⁻²⁰² Most studies evaluated the risk of bone weakening over two to six years; no study was designed specifically to assess lifetime or long-term cumulative ICS. Two of the trials were head-to-head RCTs comparing one ICS with another ICS in adult subjects.^{194, 195} One 24-month open-label trial measuring BMD and vertebral fractures randomized 374 adult patients with asthma to beclomethasone, budesonide, or placebo.¹⁹⁵ Patients were titrated to the minimal effective dose following a pre-specified management plan; subjects who required more than three courses of oral corticosteroids were withdrawn. At two years, no significant differences in BMD were reported between the three treatment groups. A smaller trial reporting BMD randomized 69 asthmatic patients to medium and high doses of beclomethasone or fluticasone.¹⁹⁴ At one year, no significant differences in bone mass or metabolism were noted between the two treatment groups. Six studies (two of them in pediatric populations) comparing an ICS-treated population to a population not treated with ICSs provided mixed evidence of an association between ICS use and loss of BMD or osteoporosis;^{196, 198-203} two of

these studies measured bone fractures.^{201,202} Both of the studies conducted in pediatric populations reported no difference in BMD between ICS- and placebo-treated subjects.^{198, 199, 203} Of the remaining studies, one reported a dose-related decline in BMD with ICS-treated subjects,²⁰⁰ one reported a dose-related increase in the risk of vertebral and non-vertebral fractures with ICS,²⁰² and two reported no difference in non-vertebral fracture²⁰¹ or BMD¹⁹⁶ between ICS-treated subjects and controls.

II. Growth

Three head-to-head RCTs comparing fluticasone to beclomethasone²⁶ or fluticasone to budesonide^{39, 192} assessed differences in growth. A fair 1-year multinational head-to-head trial determined differences in growth velocity comparing a medium dose of fluticasone (400 mcg/day) to a medium dose of beclomethasone (400 mcg/day) in 343 pre-pubertal children with asthma.²⁶ ITT analysis revealed that adjusted mean growth velocity was significantly greater in fluticasone than in beclomethasone-treated patients (+0.70 cm/year; 95% CI: 0.13 to 1.26; $P < 0.02$). Another fair RCT compared growth velocity in 60 children treated with either a low dose of fluticasone (200 mcg/day) or a low dose of budesonide (400 mcg/day) over one year.¹⁹² Fluticasone-treated children had less reduction in growth velocity than the budesonide treated group (height standard deviation score: 0.03 compared with 0.23; $P < 0.05$); the authors did not provide absolute numbers in centimeters of differences in growth. The third RCT compared differences in growth velocity in 333 children treated with a medium dose of fluticasone (400 mcg/day) or a medium dose of budesonide (800 mcg/day) over 20 weeks.³⁹ Linear growth velocity was greater for fluticasone-treated children compared to those treated with budesonide (adjusted mean increase in height: 2.51 cm compared with 1.89; difference 6.2 mm (95% CI: 2.9-9.6, $P = 0.0003$). Four additional studies provide general evidence of growth retardation for ICSs. These included two meta-analyses^{189, 190} and three RCTs.^{96, 197-199} A good quality meta-analysis assessed differences in short-term growth velocity in 273 children with mild to moderate asthma treated with either beclomethasone (mean 400 mcg/day) or placebo for 7 to 12 months.¹⁸⁹ The meta-analysis reported a statistically significant decrease in linear growth velocity of children treated with beclomethasone (-1.54 cm per year; 95% CI: -1.15, -1.94) compared to the placebo group. Another good-quality meta-analysis assessed short-term growth velocity in 855 children treated with beclomethasone or fluticasone compared to placebo. Growth velocity was statistically significantly reduced in those treated with beclomethasone (1.51 cm/year; 95% CI: 1.15, 1.87; four studies) and in those treated with fluticasone (0.43cm/year; 95% CI: 0.1, 0.85; 1 study) compared to placebo.¹⁹⁰

The best longer-term evidence of linear growth delay comes from the Childhood Asthma Management Program (CAMP) study, a good quality RCT with median follow-up of 4.3 years that randomized 1,041 asthmatic children to budesonide, nedocromil, or placebo.^{198, 199} The mean increase in height was significantly less in budesonide-treated patients than in placebo-treated patients (-1.1 cm; 22.7 cm compared with 23.8 cm; $P = 0.005$). This analysis was performed on an intent-to-treat basis, providing a more conservative than an “as treated” analysis. The differences in growth occurred, however, primarily during the first year of treatment. After two years of treatment growth velocity was approximately the same between groups. Another placebo controlled trial assessing growth velocity under low-dose fluticasone treatment (100 mcg/day; 200 mcg/d) did not find any significant differences in linear growth compared to placebo after one year of

treatment.^{197, 210} One additional fair quality RCT (N = 360) compared linear growth rates in prepubertal children treated with montelukast, beclomethasone, or placebo over 56 weeks and found that the mean growth rate of subjects treated with beclomethasone was 0.78 cm less than that of subjects treated with placebo and 0.81 cm less than that of subjects treated with montelukast (P < 0.001 for both).⁹⁶

III. Acute adrenal crisis

The use of ICSs includes the risk of altered hypothalamic-pituitary axis (HPA axis) functioning and the rare possibility of resultant adrenal suppression. We did not find any studies meeting our inclusion/exclusion criteria reporting on the comparative frequency of clinical adrenal insufficiency in patients treated with ICSs. However, multiple studies report on adrenal suppression during ICS therapy using urinary or serum cortisol levels and results of stimulation tests as intermediate outcomes. It is unclear to what extent results from sensitive studies of HPA axis suppression can be extrapolated to assess differences in risks for clinically significant adrenal suppression. Various case reports indicate that acute adrenal crisis is an extremely rare but potentially fatal adverse event of ICS treatment.²¹¹⁻²¹³ However, in most cases dosing was likely outside approved labeling. These case reports did not meet eligibility criteria for this report.

IV. Cataracts

Systemic corticosteroid-induced cataracts typically are located on the posterior side of the lens and are referred to as posterior subcapsular cataracts (PSC); we reviewed studies that compared the risk of PSC in ICS-treated populations to non-ICS-treated populations. No study compared the risk of developing PSC between one ICS and another. One placebo-controlled trial^{198, 199} and five observational studies²⁰⁴⁻²⁰⁸ evaluated the risk of developing cataracts between ICS- and non-ICS-treated patients. One RCT^{198, 199} and one observational study²⁰⁴ compared budesonide to placebo; the other studies all compared nonspecific ICS use to no ICS use. Two studies were conducted in pediatric populations,^{198, 199, 204} one in a mixed population of children and adults,²⁰⁷ and three evaluated adult populations (≥ 40 years).^{205, 206, 208} Both trials conducted in children reported no significant differences in the development of PSC between budesonide-treated patients and placebo or matched controls.^{198, 199, 204} One of these was the CAMP study, a good quality RCT with median follow-up of 4.3 years that allocated 1,041 asthmatic children to budesonide, nedocromil, or placebo.^{198, 199} The single study that included a mixed population of adults and children reported no increase in the risk of developing cataracts between ICS-treated patients and controls in persons younger than 40 years; a dose-, duration-, and age-related increase in risk was observed for persons older than 40 years of age.²⁰⁷

Consistent evidence from two case-control studies^{206, 208} and one cross-sectional study²⁰⁵ conducted in adult populations reported an increased risk of cataracts for ICS-treated patients compared to controls. Both case-control studies found the risk of cataracts increased at higher ICS doses and longer duration of treatment; one study reported a higher relative risk for ICS doses greater than 1,600 mcg/day²⁰⁸ and one study reported a higher relative risk for budesonide or beclomethasone doses greater than 1,000 mcg/day.²⁰⁶ Most studies did not control for or did not report previous exposure to systemic corticosteroids, a known cause of cataracts. Only one observational study controlled for previous exposure to systemic corticosteroids; controlling for systemic

corticosteroid use and other potential confounders had little effect on the magnitude of the associations in this study.²⁰⁵

V. Ocular hypertension and open-angle glaucoma

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

2. Leukotriene Modifiers

Direct Evidence

We found just one fair-rated 12-week head-to-head trial comparing one leukotriene modifier with another that met inclusion/exclusion criteria for our review.⁵¹ The trial compared quality of life outcomes between montelukast and zafirlukast at recommended doses in adults with mild persistent asthma and did not report any adverse events in either group.

We found no head-to-head trials for comparisons of other leukotriene modifiers. In addition, we found no head-to-head trials in children.

Indirect Evidence

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

Liver toxicity

Evidence from placebo-controlled trials of zileuton reported an increased risk of hepatic toxicity with increased frequency of elevated liver transaminases (ALT elevations of ≥ 3 times the upper limit of normal: 1.9% compared with 0.2% for zileuton compared with placebo).¹⁰ In patients treated for up to 12 months with zileuton in addition to their usual asthma care, 4.6% developed an ALT of at least three times the upper limit of normal, compared with 1.1% of patients receiving their usual asthma care.¹⁰ Due to the increased risk, monitoring of liver function tests is required with zileuton therapy.¹ Rare cases of liver toxicity have been reported with montelukast (cholestatic hepatitis, hepatocellular liver injury, and mixed-pattern liver injury) and zafirlukast (fulminant hepatitis, hepatic failure, liver transplantation, and death have been reported).¹⁰ Data from safety databases and placebo-controlled trials suggest numerically similar rates of increased transaminases between montelukast (increased ALT: 2.1% compared with 2%; increased AST 1.6% compared with 1.2%) or zafirlukast (increased ALT: 1.5% compared with 1.1%) and placebo.¹⁰

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

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.

Direct Evidence

Of the four included head to head trials, two were conducted only in adults,^{55, 56} one enrolled adults and adolescents⁵² and one enrolled only children and adolescents between 5-18 years old.⁵³ All four trials compared FM (12 mcg twice daily) with SM (50 mcg twice daily). Only one⁵² of the four trials was blinded. Detailed descriptions of these RCTs are provided in the Key Question 1 section of this report with the exception of one study that was included for this section but not for efficacy outcomes.⁵⁶ One open-label RCT conducted in the United States⁵⁶ compared formoterol (24 mcg/day) to salmeterol (50 mcg/day) in 528 adult asthmatics who were already taking low dose ICSs. The duration of the study was 24 weeks and the investigator found similar numbers of total withdrawals (14.5% compared with 11.3%) and withdrawals due to adverse events (5.7% compared with 3.4%). One trial^{52, 217} randomized 469 patients to blinded eFM via DPI, SM via DPI, or SM via MDI. They found similar rates of hospital admission and ED visits and total study withdrawals. Another trial⁵⁴ compared FM administered via DPI with SM given via DPI in 482 adult asthmatics. The trial found comparable rates of hospitalizations, study withdrawals, withdrawals due to adverse events, and drug-related adverse events. The only trial enrolling children and adolescents⁵³ randomized subject (N = 156) to FM or SM and also found similar rates of study withdrawals and withdrawals due to adverse events.

Indirect evidence

Among the systematic reviews with meta-analysis we included for this section, the most recent was published in 2007.²¹⁶ Their review aimed to examine both efficacy and safety outcomes of studies comparing LABAs to placebo in “real world” asthmatic populations in which only some patients were using regular ICSs at baseline. They included 67 studies randomizing a total of 42,333 participants. Salmeterol was used as a long-acting agent in 50 studies and formoterol in 17. The treatment and monitoring period was relatively short (4 -9 weeks) in 29 studies, and somewhat longer (12 -52 weeks) in 38 studies. The systematic review reported that LABAs were generally effective in reducing asthma symptoms in this population, but they noted safety concerns for patients not using ICSs and for African Americans, based on data from the Salmeterol Multicenter Asthma Research Trial (SMART), described below.²¹⁴ From a post-hoc analysis of SMART, their estimate for the relative risk of asthma-related death for those taking ICSs at baseline did not show an increased risk (RR 1.34, 95% CI: 0.30 to 5.97). However, those not taking ICSs at baseline had an increased risk of asthma-related death (RR 18.98, 95% CI: 1.1 to 326). In addition, other asthma-related serious adverse events were increased in LABA-treated patients (OR 7.46, 95% CI: 2.21 to 25.16). For respiratory-related death, they found an increased risk in the total population (RR 2.18, 95% CI: 1.07 to 4.05), but no difference between subgroups of subjects using ICS compared with those not using ICS at baseline (test for interaction $P = 0.84$). Among their findings regarding less severe side effects, they noted that tremor was more common in LABA treated patients (OR 3.86, 95% CI: 1.91 to 7.78). Of the four included systematic reviews with meta-analysis (Table 46), one²¹⁵ was designed specifically to examine risks for life-threatening or fatal

asthma exacerbations associated with LABA. The majority of subjects (about 80%) in the studies included in this review were treated with salmeterol. The meta-analyses found that the risk of hospitalization was increased in LABA treated patients (OR 2.6, CI: 1.6 to 4.3). The estimated risk difference for hospitalization attributed to LABA was 0.7% (CI: 0.1% to 1.3%) over 6 months. Notably, the investigators assessed separately the associations between SM and FM and risk for this outcome. They found an increased risk for hospitalization associated with both salmeterol (OR, 1.7 [CI: 1.1 to 2.7]) and with formoterol (OR, 3.2 [CI: 1.7 to 6.0]). They also estimated the risk for life-threatening asthma attacks and found it to be increased for LABA-treated patients (OR 1.8, CI: 1.1 to 2.9, risk difference 0.12%, CI: 0.01% to 0.3% over 6 months). Lastly, they examined the risk for asthma-related deaths in these studies and found it to be increased for LABA treated patients: (OR 3.5, 95% CI: 1.3 to 9.3; risk difference 0.07%, CI: 0.01% to 0.1% over 6 months). There was significant overlap between the two meta-analyses described above.^{215, 216} Twelve of 14 (86%) published studies included in the 2006 meta-analysis²¹⁵ were also included in the 2007 meta-analysis.²¹⁶ The 2007 analysis included studies of shorter duration, which partially accounted for the greater number of included studies. An older systematic review¹⁵³ evaluated RCTs in which the addition of LABAs to ICS was compared with adding placebo to ICS. They found no differences in overall adverse effects, serious adverse events, or in specific side effects. Comparative safety was examined secondarily, and only one included study reported deaths, with three deaths reported overall. Further, the Salmeterol Multicenter Asthma Research Trial (SMART),²¹⁴ a large 28-week randomized study of the safety of LABAs was categorized as “awaiting assessment” at the time this systematic review was published. SMART included 26,355 subjects and was terminated due to findings in African Americans and difficulties in enrollment.²¹⁴ The trial found no statistically significant difference between those treated with salmeterol and those treated with placebo for the primary outcome, respiratory-related deaths, or life-threatening experiences was low and not significantly different for salmeterol compared with placebo (50 compared with 36; RR 1.40; 95% CI: 0.91 to 2.14). However, the trial reported statistically significant increases in respiratory-related deaths (24 compared with 11; RR 2.16; 95% CI: 1.06 to 4.41) and asthma related deaths (13 compared with 3; RR 4.37; 95% CI: 1.25 to 15.34), and in combined asthma-related deaths or life-threatening experiences (37 compared with 22; RR 1.71; 95% CI: 1.01 to 2.89) for subjects receiving salmeterol compared to those receiving placebo. In addition, subgroup analyses suggest the risk may be greater in African Americans compared with Caucasian subjects. The increased risk was thought to be largely attributable to the African-American subpopulation: respiratory-related deaths or life-threatening experiences (20 compared with 5; RR 4.10; 95% CI: 1.54 to 10.90) and combined asthma-related deaths or life threatening experiences (19 compared with 4; RR 4.92; 95% CI: 1.68 to 14.45) in subjects receiving salmeterol compared to those receiving placebo.²¹⁴ Finally, another systematic review with meta-analysis¹²⁰ examined the efficacy and safety of *initiating* LABA with ICS compared with ICS alone in steroid naïve asthmatics. They found no differences in rates of any adverse effects or in withdrawals due to adverse effects. They did find an increased risk for tremor associated with LABA (RR 5.05; 95% CI: 1.33 to 19.17).

4. Anti-IgE Therapy

Of the six included RCTs, only one⁶² focused on children (6-12 years old); all other RCTs included adolescents and adults ≥ 12 years of age. The systematic review included all six RCTs. These studies are described in detail in the Key Question 1 section of this report. A good quality systematic review with meta-analysis found no difference in headache, urticaria, number of patients with any adverse events, and withdrawals due to adverse events between subcutaneous omalizumab and placebo.⁷⁰ However, injection site reactions were significantly greater in omalizumab patients (OR 2, 95% CI: 1.37 to 2.92).

When looking at the individual studies, we found wide variation in incidence of injection site reaction across studies. Most studies reported the occurrence of injection site reaction as less than 10%. One study, however, reported that the frequency of occurrence was greater than 35% in both the omalizumab and placebo groups. Wide variance in the occurrence of injection site reaction across studies may be explained by the fact that one study interpreted this term more broadly to encompass one or more of a number of symptoms (e.g., burning, itching, warmth, bruising, redness, hive formation, rashes). Other studies limited the term to denote severe reactions, and some studies do not describe how they apply the term. The package insert for omalizumab used a broader definition (injection site reactions of any severity) and reported occurrence rates of 45% and 43% for omalizumab and placebo, respectively.¹⁰ Withdrawals attributed explicitly to adverse events were similar in adult and pediatric patients. However, in the pediatric study, 1.8% of omalizumab- and 1.8% of placebo-treated patients withdrew because of pain or fear of injection.⁶²

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

Most studies that examined the efficacy of one combination treatment relative to another (described in Key Question 1) also reported tolerability and adverse events. All trials included adolescents and adults; one trial also included children.⁷⁸ Study duration ranged from 12 weeks to one year; most trials were six months or greater. Methods of adverse events assessment differed greatly. Few studies used objective scales such as the adverse reaction terminology from the World Health Organization (WHO). Most studies combined patient-reported adverse events with a regular clinical examination by an investigator. Often it was hard to determine if assessment methods were unbiased and adequate; many trials reported only those adverse events considered to be related to treatment. Rarely were adverse events prespecified and defined.

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

Overall adverse events and withdrawals due to adverse events were commonly reported. 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. Frequency of adverse events was similar between those treated with BUD/FM and those treated with FP/SM.

II. Inter-class comparisons (between classes)

A. Monotherapy

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

Direct Evidence

One good quality systematic review with meta-analysis⁸⁰ provides the best evidence for overall adverse events and tolerability. The meta-analysis found no significant difference in the risk of experiencing any adverse effects (N = 15 trials, RR 0.99, 95% CI: 0.93 to 1.04) or of specific adverse events including elevation of liver enzymes, headaches, nausea, or oral candidiasis. In addition, treatment with leukotriene modifiers was associated with a 30% increased risk of overall withdrawals (N = 19 trials, RR 1.3, 95% CI: 1.1 to 1.6), which appeared to be due to poor asthma control (N = 17 trials, RR 2.6, 95% CI: 2.0 to 3.4) rather than due to adverse effects (N = 14 trials, RR 1.2, 95% CI: 0.9 to 1.6). Most studies did not find a significant difference between ICSs and leukotriene modifiers for overall tolerability and adverse events. Specific adverse events reported with ICSs (see Key Question 2 section on ICSs above), such as cataracts and decreased growth velocity, were not found among patients taking LTRAs. One fair quality head-to-head RCT (N = 360) compared linear growth rates in prepubertal children treated with montelukast, beclomethasone, or placebo.⁹⁶ The mean growth rate of subjects treated with beclomethasone was 0.81 cm less than that of subjects treated with montelukast.

Indirect Evidence

Indirect evidence from placebo-controlled trials is described in other sections of this report (see Key Question 2, Inhaled Corticosteroids and Leukotriene Modifiers sections). Evidence from placebo-controlled trials and observational studies suggest that ICSs may increase the risk of cataracts and may decrease short term growth velocity and bone mineral density.

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

We found 11 fair or good quality RCTs¹⁰⁵⁻¹¹⁷ that included head-to-head comparisons of one ICS with one LABA reporting tolerability or overall adverse events. These trials are described in the Key Question 1 section of this report. 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).

Leukotriene modifiers compared with Long-Acting Beta-2 Agonists (LABAs) for Monotherapy

Direct Evidence

We found two fair quality RCTs^{118, 119} that included head-to-head comparisons of one leukotriene modifier with one LABA. In both trials, overall adverse events and/or withdrawals due to adverse events were similar between those treated with leukotriene modifiers and those treated with LABAs.

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).

Combination therapy

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

Direct evidence

We found one good systematic review¹²⁰ and five fair RCTs^{107, 109, 121-124}. Four trials compared fluticasone plus salmeterol with fluticasone alone and two compared budesonide plus formoterol with budesonide alone. The trials are described in the Key Question 1 section of the report. The systematic review reported no significant differences between treatments in overall adverse events (RR 1.1, 95% CI: 0.8, 1.5, 5 trials), withdrawals due to adverse events (RR 1.71, 95% CI: 0.68, 4.27, 3 trials), overall withdrawals (RR 0.9; 95% CI: 0.6 to 1.2, 6 trials), or in any of the specific adverse events (including headache, oral candidiasis, or tremor).¹²⁰ The authors note that the upper confidence interval was high for some adverse events, ruling out complete reassurance that there is no increased risk. The results appear similar for those treated with ICS+LABA and those treated with ICS alone.

Indirect evidence

Indirect evidence described previously in the Key Question 2 Long-Acting Beta-2 Agonists (LABAs) section of this report describes the evidence suggesting the increased risk of asthma related death in patients treated with LABAs.²¹⁴⁻²¹⁶ Of note, the most current (2007) systematic review included a post-hoc analysis of data from the the Salmeterol Multicenter Asthma Research Trial (SMART) that did not show a statistically significantly increased risk of asthma-related death for those taking ICSs at baseline (RR 1.34, 95% CI: 0.30 to 5.97). But, those not taking ICSs at baseline had an increased risk of asthma-related death (RR 18.98, 95% CI: 1.1 to 326).

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

Direct Evidence

We found one systematic review with meta-analysis¹²⁶ and 27 RCTs^{48, 76, 78, 99, 124, 128-152} that included head-to-head comparisons between an ICS+LABA with a higher dose ICS meeting our inclusion/exclusion criteria. These trials compared the addition of a LABA to an ICS with increasing the dose of the ICS. Fifteen of the 27 (56%) administered the ICS and LABA in a single inhaler and twelve (44%) administered the ICS and LABA in separate inhalers. Although four trials^{76, 78, 99, 144} included children, just one enrolled an exclusively pediatric population under 12 years of age.⁷⁶ The trials are described in the Key Question 1 section of the report. The systematic review reported no difference in overall withdrawals (all reasons) (N = 23, RR 0.92, 95% CI: 0.82, 1.03), overall adverse events (N = 15, RR 0.93, 95% CI: 0.84, 1.03), or specific side effects, with the exception of a three-fold increase rate of tremor in the LABA group (N = 10, RR 2.96, 95% CI: 1.60, 5.45). The rate of withdrawals due to poor asthma control favored the combination of LABA and ICS (N = 20, RR 0.69, 95% CI: 0.52,

0.93). The overall adverse events, withdrawals due to adverse events, and specific adverse events for the included RCTs appear consistent with these findings

Indirect evidence

Indirect evidence described previously in the Key Question 2 Long-Acting Beta-2 Agonists (LABAs) section of this report describes the evidence suggesting the increased risk of asthma related death in patients treated with LABAs.[214-216](#) Of note, the most current (2007) systematic review included a post-hoc analysis of data from the the Salmeterol Multicenter Asthma Research Trial (SMART) that did not show a statistically significantly increased risk of asthma-related death for those taking ICSs at baseline (RR 1.34, 95% CI: 0.30 to 5.97). But, those not taking ICSs at baseline had an increased risk of asthma-related death (RR 18.98, 95% CI: 1.1 to 326).

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

Direct Evidence

We found one systematic review with meta-analysis[153](#) and 27 RCTs (29 publications)[105, 106, 108, 110-112, 124, 132, 138, 139, 144, 154-170, 218](#) that included head-to-head comparisons between an ICS+LABA with the same dose ICS meeting our inclusion/exclusion criteria. These trials compared the addition of a LABA to an ICS with continuing the same dose of the ICS. Fourteen of the 27 (52%) administered the ICS and LABA in a single inhaler, nine administered them in separate inhalers, and four studies administered them both as a single inhaler and in separate inhalers to different study groups. Seven studies (26%) included pediatric populations under 12 years of age.[144, 162, 164, 165, 168, 169, 218](#) The trials are described in greater detail in the Key Question 1 section of the report. The systematic review reported no difference between treatments in the risk of overall adverse effects (N = 11, RR 0.98, 95% CI: 0.92 to 1.05), withdrawals due to adverse effects (N = 19, RR 1.29, 95% CI: 0.96 to 1.75), serious adverse events (N = 4 comparisons, RR 1.16, 95% CI: 0.30 to 4.42), or in any of the reported specific side effects including headache (N = 12, RR 1.13, 95% CI: 0.92 to 1.41), hoarseness (N = 3 comparisons, RR 0.71, 95% CI: 0.16 to 3.18), oral thrush (N = 4, RR 1.04, 95% CI: 0.35 to 3.06), tachycardia or palpitations (N = 5, RR 2.13, 95% CI: 0.77 to 5.88), cardiovascular adverse effects such as chest pain (N = 3, RR 0.90, 95% CI: 0.32 to 2.54), or tremor (N = 7, RR 2.48, 95% CI: 0.78 to 7.89). However, the upper confidence interval for some adverse events was high (for example tachycardia, palpitations and tremor). The overall adverse events, withdrawals due to adverse events, and specific adverse events for the included RCTs appear consistent with these findings.

Indirect evidence

Indirect evidence described previously in the Key Question 2 Long-Acting Beta-2 Agonists (LABAs) section of this report describes the evidence suggesting the increased risk of asthma related death in patients treated with LABAs.[214-216](#) Of note, the most current (2007) systematic review included a post-hoc analysis of data from the the Salmeterol Multicenter Asthma Research Trial (SMART) that did not show a statistically significantly increased risk of asthma-related death for those taking ICSs at baseline (RR 1.34, 95% CI: 0.30 to 5.97). But, those not taking ICSs at baseline had an increased risk of asthma-related death (RR 18.98, 95% CI: 1.1 to 326).

ICS+LTRA compared with ICS

Direct Evidence

We found one good systematic review with meta-analysis¹⁷¹ and two RCTs¹⁷²⁻¹⁷⁴ meeting our inclusion/exclusion criteria. 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.

One fair 16 week trial¹⁷⁴ (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^{172, 173} (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.

Combination products compared with Leukotriene Modifiers

Direct Evidence

We found three RCTs^{99, 176, 177} comparing low dose fluticasone plus salmeterol with montelukast. Two of the RCTs were in adolescents and adults; one enrolled subjects over the age of six⁹⁹ (~15% of subjects were < 12 years of age). The trials are described in the Key Question 1 section of the report. All three trials reported similar overall rates of withdrawals due to adverse events between those treated with ML and those treated with FP/SM. The two trials reporting overall adverse events also reported similar rates between groups. One trial reported a greater incidence of upper respiratory tract infections for those treated with FP/SM than those treated with ML.

ICS+LABA compared with ICS+LTRA (addition of LABA compared with LTRA to ongoing ICS therapy)

Direct Evidence

We found one systematic review with meta-analysis¹⁷⁸ and six RCTs.¹⁷⁹⁻¹⁸⁴ All six of the RCTs were in adolescents and adults ≥ 12 years of age. Of the included studies, 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, $P = \text{NS}$, 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.

Key Question 3; Subgroups:

Are there subgroups of these patients based on demographics (age, racial groups, gender), asthma severity, comorbidities (drug-disease interactions, including obesity), smoking status, genetics, or pregnancy for which asthma controller medications differ in efficacy, effectiveness, or frequency of adverse events?

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.

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. We found no head-to-head studies comparing the efficacy or safety of our included drugs in very young children with older children, adolescents, or adults. Long-term clinical trials have shown ICS treatment to be effective in this population.¹ Some evidence from placebo-controlled trials suggests that montelukast may be effective in children ages two to five; however, one trial reported that montelukast did not reduce the need for oral systemic corticosteroids to control exacerbations.¹ Most recommendations for treatment are based on limited data and extrapolations from studies in older children and adults.¹ This data, as well as expert opinion, supports the use of ICSs for the treatment for asthma in young children.¹

B. Racial groups

We did not find any head-to-head studies that directly compared the efficacy and tolerability of our included drugs between one ethnic population and another. Two studies performed subgroup analyses; results may provide indirect evidence of differences between racial groups.

A good systematic review examined both efficacy and safety outcomes of studies comparing LABAs to placebo in “real world” asthmatic populations in which only some patients were using regular ICSs at baseline.²¹⁶ This study is described in detail in the Key Question 2 section of this report. A post-hoc subgroup analysis indicated that African Americans may be more likely to experience respiratory-related death and life threatening adverse events than Caucasians (Relative Risk Increase 3.9; 95% CI: 1.29, 11.84). There was, however, no significant difference found in asthma-related deaths

between African Americans and Caucasians; results from life table analyses were not significantly different between African Americans (7 compared with 1; RR 7.26; 95% CI: 0.89, 58.94), and Caucasians (6 compared with 1; RR 5.82; 95% CI: 0.70, 48.37). The Salmeterol Multicenter Asthma Research Trial (SMART),²¹⁴ a large 28-week randomized, double-blind study assessed the safety of salmeterol MDI (42 mcg twice/day) compared with placebo. This study is described in detail in Key Question 2. The trial found no statistically significant difference between those treated with salmeterol and those treated with placebo for the primary outcome, respiratory-related deaths or life-threatening experiences (50 compared with 36; RR 1.40; 95% CI: 0.91, 2.14). However, the trial reported statistically significant increases in respiratory-related deaths (24 compared with 11; RR 2.16; 95% CI: 1.06, 4.41), asthma-related deaths (13 compared with 3; RR 4.37; 95% CI: 1.25, 15.34), and in combined asthma-related deaths or life-threatening experiences (37 compared with 22; RR, 1.71; 95% CI: 1.01, 2.89) for subjects receiving salmeterol compared to those receiving placebo. Subgroup analyses suggest the risk may be greater in African Americans compared with Caucasian subjects. The increased risk was thought to be largely attributable to the African-American subpopulation: respiratory-related deaths or life-threatening experiences (20 compared with 5; RR, 4.10; 95% CI: 1.54, 10.90) and combined asthma-related deaths or life-threatening experiences (19 compared with 4; RR, 4.92; 95% CI: 1.68, 14.45) in subjects receiving salmeterol compared to those receiving placebo.²¹⁴ The FDA released a safety alert based on the results of the trial, reporting that there were no significant differences in asthma-related events between salmeterol and placebo in Caucasian patients; however, in African Americans, there was a statistically significantly greater number of asthma-related events, including deaths, in salmeterol- compared with placebo-treated patients.²¹⁹

One fair quality multicenter trial compared montelukast (10 mg/d plus salmeterol (100 mcg/d plus placebo ICS) with low dose BDP (160 mcg/d plus salmeterol 100 mcg/d plus placebo LTRA) for 14 weeks, washout for 4 weeks, then crossover for another 14 weeks.¹⁸⁶ This study is described in detail in Key Question 1. The LTRA plus LABA combination led to significantly more subjects having a shorter time to treatment failure compared to ICS plus LABA (29 compared with 8; $P = 0.0008$). Subgroup analysis found no difference between races. The proportion of Caucasian subjects with preferential protection against treatment failure while using an ICS + LABA (relative to an LTRA/LABA) was not significantly different from the proportion of African-American subjects ($P = 1.0$).

C. Gender

We did not find any study that directly compared the efficacy and tolerability of our included medications between males and females.

One prospective cohort study (described in detail in Key Question 2) evaluated the risk of osteoporosis in premenopausal women using triamcinolone and found a dose-related decline in BMD.²⁰⁰ Although several other studies conducted in mixed populations of men and women found no relationship between ICS use and BMD, evidence is insufficient to support a differential decline in BMD between male and female patients treated with ICSs.

II. Comorbidities

We did not find any study that directly compared the efficacy, effectiveness, or tolerability of our included drugs in populations with specific comorbidities. Because mixed evidence supports an increased risk of osteoporotic fractures, cataracts, and glaucoma in ICS-treated patients (especially at high doses), ICSs should be used with care in populations at increased risk for these conditions. No evidence reflects different risks between one ICS and another. One study assessed differences in efficacy of montelukast, beclomethasone and placebo in patients with differing BMI (normal, overweight and obese).²²⁰ This study did not meet our eligibility criteria; it was a pooled data analysis that was not based on a systematic literature search. Data were pooled from four trials (3 that are described in detail in Key Question 1 and 1 that was reported as an abstract only) to compare the efficacy of montelukast and beclomethasone in patients with differing BMI. Pooled data included 3,073 patients. Patients with normal BMI treated with placebo had a higher percentage of asthma control days than patients who were overweight or obese (33.91% compared with 25.04% for overweight, $P = 0.002$; 25.80% for obese, $P = 0.026$). The effect of montelukast on asthma control days was similar across all three BMI categories; however, the effect of beclomethasone decreased with increasing BMI.

III. Other medications

We did not find any studies meeting our inclusion/exclusion criteria that examined the impact of other medications on the comparative efficacy, tolerability, or adverse events of our included medications.

Although little documentation supports the clinical relevance of this interaction, the product labeling for budesonide, fluticasone, and mometasone does mention the potential for interaction between ICSs and inhibitors of the cytochrome P450 isoenzyme 3A4 (CYP3A4). Because beclomethasone, flunisolide, and triamcinolone also are metabolized by CYP3A4, the potential for interaction with drugs that inhibit this isoenzyme likely applies to all ICSs. Drugs known to inhibit CYP3A4 include amiodarone, cimetidine, clarithromycin, delavirdine, diltiazem, dirithromycin, disulfiram, erythromycin, fluoxetine, fluvoxamine, indinavir, itraconazole, ketoconazole, nefazodone, nevirapine, propoxyphene, quinupristin-dalfopristin, ritonavir, saquinavir, telithromycin, verapamil, zafirlukast, and zileuton. However, the clinical significance of these “potential” interactions is questionable.

IV. Smoking status

We found one cross-over study comparing asthmatic smokers and nonsmokers.²²¹ In this study, 44 nonsmokers (total lifetime smoking history of less than 2 pack-years and no smoking for at least one year) and 39 “light” smokers (currently smoking 10-40 cigarettes/day and a 2-15 pack-year history) were randomized to BDP (320 mcg/d) or montelukast (10 mg/d) for eight weeks of active treatment, an eight week washout, and then eight weeks of active treatment with the other medication. Both smokers and nonsmokers 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 nonsmokers 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 wellbeing of both the mother and her baby. Inadequate control of asthma during pregnancy has been associated with higher rates of premature birth, intrauterine growth retardation, lower birth weight, perinatal death, and preeclampsia.^{1, 222, 223} Expert opinion recommends ICSs as the preferred treatment for long-term control of asthma symptoms in pregnancy.¹ This preference is based on favorable efficacy data in both non-pregnant and pregnant women and also on safety data in pregnant women; results do not show an increased risk of adverse perinatal outcomes.¹

FDA approved labeling classifies medications by the potential for risk during pregnancy. Budesonide is the only ICS labeled as a pregnancy category B – i.e., no well controlled studies have been conducted in women but animal studies have found little to no risk. Other ICS products are pregnancy category C.– i.e., no well-controlled studies have been conducted in women but animal studies have shown harmful effects on the fetus.

Currently,

ICS product labeling recommends the use of an ICS in pregnancy only when anticipated benefits outweigh potential risk.¹⁰ In general, budesonide is the preferred ICS because more data are available on its use during pregnancy than other ICSs. Minimal published data are available on the efficacy and safety of LTRAs or LABAs during pregnancy, but there is theoretical justification for expecting the safety profile of LABAs to resemble that of albuterol, for which there are data related to safety during pregnancy.¹ We found one systematic review and one database review focusing on ICS use in pregnant asthmatics. We did not identify any studies assessing the efficacy or safety of LABAs, LTSIs, or anti-IgE therapy during pregnancy. One systematic review with meta-analysis showed that ICSs did not increase the rates of any adverse obstetrical outcomes.²²⁵ Studies were eligible for inclusion in this analysis if the included women were exposed to any therapeutic dosage of any fluticasone, beclomethasone, budesonide, triamcinolone or flunisolide during pregnancy. Studies were excluded if either did not have a control group or had a control group comprised of non-asthmatic women. Four studies met inclusion criteria. The summary OR for major malformations in two studies was 0.96 (95% CI: 0.51, 1.83; $P = 0.9582$). The summary OR for preterm delivery in three studies was 0.99 (95% CI: 0.8, 1.22; $P = 0.9687$). The summary OR for low birth weight delivery in two studies was 0.89 (95% CI: 0.7, 1.14; $P = 0.4013$). The summary OR for pregnancy induced hypertension in three studies was 0.97 (95% CI: 0.84, 1.2; $P = 0.9932$). Tests for heterogeneity ($P = 0.9249$, $P = 0.2521$, $P = 0.6146$ and $P = 0.0013$, respectively) indicated that the studies for major malformation, preterm delivery and low birth weight were not significantly heterogeneous and could be combined. ICSs do not increase the risk of major malformations, preterm delivery, low birth weight and pregnancy-induced hypertension. The database review reported no significant differences were observed between ICS- and non-ICS-treated mothers.²²⁶ Compared with infants whose mothers did not use an ICS, infants born to mothers treated with an ICS had no significant differences in gestational age, birth weight, and length. Additionally, the rates of preterm delivery, congenital malformation, and stillbirth were similar for ICS- and non-ICS-treated patients. Insufficient data exists to determine if risks associated with ICSs differ among ICSs or among other medications included in this review.

VI. Genetics

Several genes (coding for LTRA, ICS, or beta-agonist receptors), have been associated with response to medications used in the treatment of asthma.^{1, 101, 227-231} To date, there is not sufficient evidence to draw conclusions about whether testing for variants in these genes has any clinical utility (insufficient strength of evidence). Multiple studies have investigated the impact of polymorphisms of the Beta-2 adrenoreceptor gene (ADRB2) on response to beta-agonist therapy, but none have demonstrated clinical validity or clinical utility of testing for ADRB2 polymorphisms.^{1, 227, 228, 231}

References: