

# Drug Class Review

## Drugs to Treat Asthma and Chronic Obstructive Pulmonary Disease (COPD)

Final Update 1 Report

June 2016

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

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## STRUCTURED ABSTRACT

### Purpose

To compare the efficacy and safety of inhaled corticosteroids (ICSs), long-acting beta-2 agonists (LABAs), leukotriene modifiers (LMs), long-acting anticholinergics, phosphodiesterase-4 inhibitors, and combination products for people with persistent asthma or chronic obstructive pulmonary disease.

### Data Sources

To identify published studies, we searched MEDLINE, The Cochrane Library, International Pharmaceutical Abstracts, and reference lists of included studies through November Week 1 2015. We also requested dossiers of information from pharmaceutical manufacturers. This streamlined update is limited to direct comparisons and did not include placebo-controlled trials.

### Review Methods

Study selection, data abstraction, validity assessment, grading the strength of the evidence, and data synthesis were all carried out according to standard Drug Effectiveness Review Project methods. Strength of evidence for specific comparisons and outcomes was assessed as low, moderate, high, or insufficient (findings rated insufficient not reported in the abstract).

### Results

Ninety studies (35 this update) were included in this review. In intra-class comparisons, few differences were found between drugs, with low- to moderate-strength evidence. In adults or children with asthma, ICSs at equipotent doses did not differ in asthma symptoms, exacerbations, rescue medication, quality of life, or adverse events. While **growth velocity in children with asthma was less affected with fluticasone propionate (FP) than beclomethasone dipropionate (BEC), and height increase was less affected with ciclesonide (CIC) than budesonide (BUD)**, comparative impact on adult height is not known. Similarly, in patients with asthma differences were not found between LABAs in benefits or harms, except that **olodaterol hydrochloride (OLO) resulted in better quality of life than formoterol fumarate (FOR)**. Evidence on long-acting muscarinic antagonists (LAMAs) in patients with chronic obstructive pulmonary disorder (COPD) indicated no differences in benefit or harm outcomes (low-strength evidence). Evidence on LMs in patients with asthma was insufficient to draw conclusions. Comparisons of ICSs/LABAs with each other in patients with asthma or COPD found no differences. Most comparisons found no differences in adverse event outcomes, however, **FP/salmeterol (SAL) was associated with increased risk of pneumonia and pneumonia-related death compared with BUD/FOR**.

Inter-class comparisons found statistically significant differences between classes in multiple instances, with mostly low- and moderate-strength evidence. In patients with COPD, there was no difference in benefits between ICSs and LABAs but **pneumonia was more frequent with ICSs than LABAs**. In patients with asthma, **ICSs resulted in better outcomes than LMs**, with no difference in adverse event outcomes. In patients with asthma there were no differences between LABAs and LAMAs in outcomes, but in patients with COPD evidence was

mixed - there were **more exacerbations and withdrawals due to adverse events with SAL (LABA) than tiotropium (TIO) (LAMA)** but not indacaterol (IND) (LABA) than TIO (LAMA), but there were no differences in hospitalizations or quality of life. Limited evidence suggested that in patients with asthma, more patients taking roflumilast (PDE-4 inhibitor) experienced exacerbations and withdrawals due to adverse events than those taking beclomethasone. In patients with asthma, differences between an ICS/LABA and a different ICS were not found. In patients with COPD, switching to IND may result in fewer serious adverse events than staying on FP/SAL. In patients with asthma, **ICS/LABA (FP/SAL) resulted in fewer exacerbations than LM (montelukast [MON])**, but no difference were seen in adverse events. In patients with COPD there was no difference in outcomes between ICS/LABAs and LABAs and there was mixed evidence between ICS/LABAs and LAMAs. In patients with asthma, **LABAs/ICSs had fewer exacerbations and more serious adverse events, but no difference in quality of life or other adverse event outcomes than LMs/ICSs. LM/LABA had shorter time to treatment failure than ICS/LABA in patients with asthma.** In patients with COPD, LABA/LAMA compared with ICS/LABA, there were no differences between umeclidinium bromide (UME)/vilanterol (VIL) and FP/SAL. Evidence on variation in effectiveness or harms in subgroups of populations with asthma or COPD was insufficient to draw conclusions.

## Conclusions

Within classes of medications used to treat asthma or COPD, there were no consistent differences in benefits or harms outcomes. Between classes of medications used to treat asthma or COPD, there were mostly no consistent differences in benefits or harms at the class level, although some differences in specific outcomes were evident between specific drug comparisons.

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*Published in a separate document.*

## EVIDENCE TABLES

*Published in 2 separate documents: Original and Update 1 Report Evidence Tables (A), which is available on the DERP Clearinghouse for the Draft Report, and Update 1 Report Evidence Tables (B). References throughout this report identify the respective documents as Evidence Tables A or B.*

**Shading** indicates new information for the streamlined update.

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## INTRODUCTION

Asthma is a chronic lung disease characterized by reversible airway obstruction, inflammation, and increased airway responsiveness. Symptoms include wheezing, difficulty breathing, or coughing. Asthma may have a genetic component, often begins early in life, and has variable symptoms regardless of classification.<sup>1</sup> The Expert Panel of the National Asthma Education and Prevention Program (NAEPP) has identified intermittent asthma and persistent asthma as the 2 main severity categories. Persistent asthma is further subdivided into mild, moderate, or severe;<sup>1</sup> however, exacerbations can be severe in any category. Table 1 lists the criteria used to classify asthma severity. The burden of asthma is substantial. In 2014, the number of people affected by asthma worldwide was estimated to be as high as 334 million.<sup>2</sup> In the United States, approximately 22.7 million individuals suffer from asthma and 3,630 deaths were attributed to this condition in 2013.<sup>3</sup>

**Table 1. Classification of asthma severity<sup>1</sup>**

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

Chronic obstructive pulmonary disease (COPD) is a chronic, progressive lung disease characterized by persistent airflow limitation and is commonly seen in individuals over the age of 40. Smoking is the most common risk factor, interacting with genetic predisposition. COPD typically becomes more severe over time, and is usually associated with an increased inflammatory response to smoke and other airborne particles. Chronic inflammation may destroy lung tissue, causing emphysema, and/or lead to small airway damage and obstruction. However, the current COPD definition from the Global Initiative for Chronic Obstructive Lung Disease (GOLD) does not describe emphysema and chronic bronchitis as COPD subtypes, as has been done in the past (<http://goldcopd.org/>). Rather, emphysema is 1 of several pathologic changes in the lungs that may occur. Chronic bronchitis is a clinical term describing the symptoms associated with COPD: cough, sputum production, and dyspnea (shortness of breath). However, chronic bronchitis may develop before or after the changes in airflow that characterize COPD.<sup>4</sup> As in asthma, exacerbations may also occur as a result of COPD. Table 2 shows the GOLD classification of the severity of airflow obstruction in patients with COPD. Assessment of COPD is based on the patient's level of symptoms, future risk of exacerbations, the severity of airflow obstruction, and the identification of comorbidities.<sup>4</sup> COPD affects over 24 million people in the United States,<sup>5</sup> and in 2010, the death rate was 40.8 per 100,000.<sup>6</sup>



**Table 2. Classification of airflow obstruction in chronic obstructive pulmonary disorder<sup>4</sup>**

In patients with FEV <sub>1</sub> /FVC <0.70		
Airflow limitation	GOLD Classification	Percent of predicted FEV <sub>1</sub>
Mild	GOLD 1	≥80%
Moderate	GOLD 2	≥50% to <80%
Severe	GOLD 3	≥30% to <50%
Very severe	GOLD 4	<30%

Abbreviations: GOLD, Global Initiative for Chronic Obstructive Lung Disease.

Many of the drugs used to treat asthma and COPD overlap, although dose and schedule may vary by indication. The goal of treatment is to control symptoms on a day-to-day basis, and to prevent exacerbations. Related to these, are the goals of improved functioning and reduced risk of serious adverse events related to disease progression. Drugs used to treat asthma can be categorized into those that are used to control symptoms (i.e., maintenance) and those used to treat acute symptoms (i.e., rescue medications). This report focuses on the following controller medications: inhaled corticosteroids (ICSs), long-acting beta-2 agonists (LABAs), leukotriene modifiers (LMs), long-acting anticholinergics (and long-acting muscarinic antagonists [LAMAs]), phosphodiesterase-4 inhibitors (PDE-4 inhibitors), and fixed-dose combination products. LMs and PDE-4 inhibitors are oral agents; the remaining drugs are inhaled and delivered through metered dose inhalers (MDIs), dry powder inhalers (DPIs), and nebulizers. ICSs are first line therapy for long-term control in all stages of persistent asthma.<sup>1</sup>

According to the GOLD guidance, initial therapy for COPD is guided by individualized assessment of symptom and exacerbation risk via questionnaires implemented in clinical settings. LAMA or LABA therapies are first-line for patients with moderate disease, while patients with severe or very severe disease are recommended combination therapy of an ICS plus a LABA or LAMA. Second line treatments include various combination therapies and PDE-4 inhibitors (i.e., roflumilast), depending on patient-specific characteristics.

This review is an update of the May 2014 Original Report on drugs to treat asthma and chronic obstructive pulmonary disease, which incorporated 2 previous reports on asthma (completed in 2011) and ICS (completed in 2006).

## Scope

We compared the efficacy, effectiveness, and harms of controller medications used in the treatment of persistent asthma and COPD, and also looked for subgroups that may differ in these areas. We compared outcomes both within and between the major classes of controller drugs. Comparative effects of rescue medications are not included. The Pacific Northwest Evidence-based Practice Center wrote preliminary key questions, identifying the populations, interventions, and outcomes of interest, and based on these, the eligibility criteria for studies. These were reviewed and revised by representatives of organizations participating in the Drug Effectiveness Review Project. The participating organizations approved the following key questions to guide this review:

## Key Questions

1. What is the comparative *within-class* and *across-class* efficacy and effectiveness of long-acting inhaled and long-acting oral medications used to treat outpatients with asthma or chronic obstructive pulmonary disease (COPD)?
2. What is the comparative *within-class* and *across-class* tolerability and frequency of adverse events of long-acting inhaled and long-acting oral medications used to treat outpatients with asthma or chronic obstructive pulmonary disease (COPD)?
3. Are there subgroups of patients [e.g. groups defined by demographics (age, racial groups, gender), asthma or COPD severity, comorbidities, other medications (drug-drug interactions), smoking status, genetics, or pregnancy] for which asthma or COPD controller medications differ in efficacy, effectiveness, or frequency of adverse events?

## Inclusion Criteria

### Populations

- Adult or pediatric (12 months to 18 years) patients with persistent or chronic asthma.
- Adult patients with COPD ( $\geq 18$  years).

### Included Drugs

**Table 3. Included interventions**

Drug type	Active ingredient(s)	Abbreviation	Trade name	Dosage Form
Long-acting beta-2 agonists	Arformoterol tartrate	ARF	Brovana	Solution; Inhalation (nebulized)
	Formoterol fumarate (formerly eformoterol)	FOR	Foradil Perforomist, Aerolizer and Certihaler	Powder; Inhalation (DPI) Solution; Inhalation (nebulized) Powder; Inhalation (DPI)
	Indacaterol maleate	IND	Arcapta	Powder; Inhalation (DPI)
	Olodaterol hydrochloride	OLO	Striverdi Respimat	Soft-mist Spray, Metered (SMI)
	Salmeterol xinafoate	SAL	Serevent	Powder; Inhalation (DPI)
Long-acting muscarinic antagonists <sup>a</sup>	Aclidinium	ACL	Tudorza Pressair	Powder; Inhalation (DPI)
	Glycopyrrolate bromide <sup>b</sup>	GLY	Seebri Breezhaler	Powder; Inhalation (DPI)
	Tiotropium bromide	TIO	Spiriva Spiriva Respimat	Powder; Inhalation (DPI) Soft-mist Spray, Metered (SMI)
	Umeclidinium bromide	UME	Incruse Ellipta	Powder; Inhalation (DPI)
Inhaled corticosteroids	Beclomethasone dipropionate	BEC	QVAR	Aerosol, Metered; Inhalation (MDI)
	Budesonide	BUD	Pulmicort Respules Pulmicort Flexhaler	Suspension; Inhalation (nebulized) Powder, Inhalation (DPI)
	Ciclesonide	CIC	Alvesco	Aerosol, Metered; Inhalation (MDI)
	Flunisolide hemihydrate	FLUN	Aerospan	Aerosol, Metered; Inhalation (MDI)
	Fluticasone furoate	FF	Arnuity Ellipta	Powder; Inhalation (DPI)
	Fluticasone propionate	FP	Flovent DISKUS Flovent HFA	Powder; Inhalation (DPI) Aerosol, Metered; Inhalation (MDI)
	Mometasone furoate	MOM	Asmanex Twisthaler Asmanex HFA	Powder; Inhalation (DPI) Aerosol, Metered; Inhalation (MDI)

Drug type	Active ingredient(s)	Abbreviation	Trade name	Dosage Form
Fixed-dose combination products	<b>ICS/LABA</b>			
	Formoterol/budesonide	FOR	Symbicort	Aerosol, Metered; Inhalation (MDI)
	Formoterol/mometasone furoate	FOR/MOM	Dulera	Aerosol, Metered; Inhalation (MDI)
	Salmeterol xinafoate/fluticasone propionate	SAL/FP	Advair Diskus Advair HFA	Powder; Inhalation (DPI) Aerosol, Metered; Inhalation (MDI)
	Vilanterol/fluticasone furoate	VIL/FF	Breo Ellipta	Powder; Inhalation (DPI)
	<b>LABA/LAMA</b>			
	Indacaterol/glycopyrrolate	IND/GLY	Utibron Neohaler	Powder; Inhalation (DPI)
	Olodaterol hydrochloride/tiotropium bromide	OLO/TIO	Stiolto Respimat	Soft-mist Spray, Metered (SMI)
	Umeclidinium bromide/vilanterol trifenate	UME/VIL	Anoro Ellipta	Powder; Inhalation (DPI)
	Leukotriene modifiers	Montelukast sodium	MON	Singular
Zileuton		SIL	Zyflo Zyflo CR	Tablet Tablet, Extended Release
Zafirlukast		ZAR	Accolate	Tablet
Phosphodiesterase-4 inhibitor		Roflumilast	ROF	Daliresp

Abbreviations: DPI, dry powder inhaler; ICS, inhaled corticosteroid; LABA, long-acting beta-2 agonists; LAMA, long-acting muscarinic antagonists MDI, metered dose inhaler; SMI, soft mist inhaler.

<sup>a</sup> The LAMA category includes anticholinergic drugs as well as those specific for muscarinic receptors.

<sup>b</sup> Note, the active ingredient is glycopyrronium. 15.6 mg of glycopyrrolate bromide = 12.5 mg glycopyrrolate.

Excluded: short-acting drugs, combination products containing a short-acting drug, oral corticosteroids.

Shading indicates drugs newly approved since the last report.

The list of included drugs in Table 3 is limited to formulations and brand names available in the United States, and in general we have included only studies of these drugs. In some cases however, we have included evidence from outside the United States, where we judge that a similar product is available here. For example, a fixed-dose product combining budesonide and formoterol in an MDI is available in the United States (Symbicort<sup>®</sup>), while in other countries the same combination is also available in a DPI (Symbicort<sup>®</sup> Turbohaler<sup>®</sup> or Turbuhaler<sup>®</sup>). Budesonide and formoterol are each available individually via DPI in the United States and could be used to deliver the equivalent drug combination and doses; we have therefore included Turbuhaler<sup>®</sup> evidence, as noted in Results below. Similarly, we have included doses that are available for use in the United States, and eliminated doses that are either not available or have been explicitly deemed unsafe or ineffective.

### Comparisons

- Head-to-head.
- One drug, 2 devices.
- *Excluded: add-on therapy (e.g. comparing fixed-dose combination A/B to either included drug [A or B but not both]), FDCP vs. components at same dose (A/B vs. A+B).*

### Efficacy and Effectiveness Outcomes

- Asthma and COPD control (e.g., exacerbations, days/nights frequency of symptoms, frequency of rescue medication use, courses of oral steroids).
- Quality of life assessed using validated scales.
- Ability to participate in work, school, sports, or physical activity, improved sleep.

- Emergency department/urgent medical care visits.
- Hospitalization (all-cause, unless otherwise specified).
- Decreasing mortality.

### **Adverse Event Outcomes**

- Overall adverse events reported.
- Withdrawals due to adverse events.
- Specific adverse events (e.g., growth suppression, bone mineral density, osteoporosis/fractures, ocular toxicity, suppression of the HPA axis, pneumonia, anaphylaxis, death).

### **Study Designs**

- Efficacy/Effectiveness:
  - Randomized controlled clinical trials of at least 12 weeks duration and  $N \geq 100$ .
    - Head-to-head trials only (*placebo-controlled trials excluded*).
  - Recent comparative good-quality systematic reviews.
    - Search dates May 2014 or later.
- Adverse Events:
  - Randomized controlled clinical trials of at least 12 weeks duration and  $N \geq 100$ .
    - Head-to-head trials only.
  - Recent comparative good-quality systematic reviews.
    - Search dates May 2014 or later.
  - Observational studies of at least 6 months duration and  $N \geq 1,000$ .

### *Excluded:*

- *Placebo-controlled trials, active controlled trials (included drug is compared with a non-placebo medication which is not an included drug), non-comparative observational studies, non-comparative systematic reviews.*
- *Studies that compare one class of drug against another without comparing the individual drug products will be excluded.*

### **Setting**

- Enrolled in study as outpatients (will not exclude for prior hospitalization).
- *Excluded: patients studied while hospitalized or while having an acute asthma or COPD exacerbation.*

## **METHODS**

### **Literature Search**

To identify relevant citations, we searched MEDLINE<sup>®</sup>, the Cochrane Database of Systematic Reviews<sup>®</sup>, the Cochrane Central Register of Controlled Trials<sup>®</sup> through November Week 1 2015 using terms for included drugs, indications, and study designs (see Appendix C for complete search strategies). We limited the electronic searches to “human” and “English language.” We also searched reference lists of included studies, the US Food and Drug Administration’s Center for Drug Evaluation and Research for medical and statistical reviews (of drugs approved since

the last report), and we requested dossiers of published and unpublished studies (or study data) from the relevant pharmaceutical companies for this review. All citations were imported into an electronic database (Endnote<sup>®</sup> X7, Thompson Reuters).

## **Study Selection**

Selection of included studies was based on the inclusion criteria created by the Drug Effectiveness Review Project participants, as described above. Titles and abstracts of citations identified through literature searches were assessed for inclusion by one reviewer and a second reviewer checked all citations excluded by the first reviewer. Full-text articles of potentially relevant citations were retrieved and assessed for inclusion by 2 reviewers. Disagreements were resolved by consensus.

## **Data Abstraction**

We abstracted information on population characteristics, interventions, subject enrollment, and discontinuation and results for efficacy, effectiveness, and harms outcomes for trials, observational studies, and systematic reviews. Data abstraction was performed by one reviewer and independently checked by a second reviewer and differences were resolved by consensus. Throughout the text, we use total daily doses, and do not report the schedules for brevity. Schedules are reported in the evidence tables.

## **Validity Assessment (Quality Assessment)**

We assessed the internal validity (quality) of trials based on the predefined criteria of the Drug Effectiveness Review Project.<sup>7</sup> We rated the internal validity of each trial based on the methods used for randomization, allocation concealment, and blinding; the similarity of compared groups at baseline; maintenance of comparable groups; adequate reporting of dropouts, attrition, crossover, adherence, and contamination; loss to follow-up; and the use of intent-to-treat analysis. The criteria used to rate observational studies of adverse events reflect aspects of the study design that are particularly important for assessing adverse event rates. Studies that had a fatal flaw were rated poor quality; trials that met all criteria were rated good quality; the remainder were rated fair quality. A fatal flaw is reflected by failure to meet combinations of items of the quality assessment checklist. Included systematic reviews were rated for quality based on a clear statement of the question(s); reporting of inclusion criteria; methods used for identifying literature (the search strategy), validity assessment, and synthesis of evidence; and details provided about included studies. Again, these studies were categorized as good when all criteria were met. Two reviewers independently assessed the quality of each study and differences were resolved by consensus.

## **Data Synthesis**

We constructed evidence tables showing the study characteristics, quality ratings, and results for all included studies. Where outcomes were not reported as relative risk or odds ratios, but sufficient data were provided, we calculated these. In addition to discussion of the findings of the studies overall and relative to each other, quantitative analyses were conducted using meta-

analyses on outcomes for which a sufficient number of studies reported and for studies which they were homogeneous enough such that combining their results can be justified. We conducted meta-analyses only for the same subset of outcomes for which we graded the strength of the evidence: exacerbations, quality of life, mortality, number of people with serious adverse events, and withdrawals due to adverse events. Random effects models were used for the estimation of pooled effects.<sup>8</sup> Forest plots were generated to graphically summarize the study results and the pooled results.<sup>9</sup> Forest plots are available upon request. The I<sup>2</sup> statistic (the proportion of variation in study estimates due to heterogeneity) was calculated to assess heterogeneity between the effects from the studies.<sup>10,11</sup> Potential sources of heterogeneity were examined with subgroup analysis by factors such as study design, study quality, variations in interventions, and patient population characteristics. Meta-analyses were conducted using Stats Direct Cam Code, Altrincham UK) software, or STATA 10.1 (StataCorp, College Station, Texas). When meta-analyses could not be performed, the data are summarized qualitatively.

## Grading the Strength of Evidence

We graded strength of evidence based on the guidance established for the Evidence-based Practice Center Program of the Agency for Healthcare Research and Quality.<sup>12</sup> Developed to grade the overall strength of a body of evidence, this approach incorporates 4 key domains: risk of bias (includes study design and aggregate quality), consistency, directness, and precision of the evidence. Strength of evidence is graded for each key outcome measure. We graded the following outcomes: exacerbations, quality of life, mortality, number of people with serious adverse events, and withdrawals due to adverse events. Table 4 describes the grades of evidence that can be assigned. Grades reflect the strength of the body of evidence to answer key questions on the comparative effectiveness, efficacy and harms of controller drugs for asthma and COPD. Grades do not refer to the general efficacy or effectiveness of the drugs. Two reviewers independently assessed each domain for each outcome and differences were resolved by consensus.

**Table 4. Strength of evidence grades and definitions<sup>12</sup>**

Grade	Definition
High	<b>We are very confident that the estimate of effect lies close to the true effect for this outcome.</b> The body of evidence has few or no deficiencies. We believe that the findings are stable, i.e., another study would not change the conclusions.
Moderate	<b>We are moderately confident that the estimate of effect lies close to the true effect for this outcome.</b> The body of evidence has some deficiencies. We believe that the findings are likely to be stable, but some doubt remains.
Low	<b>We have limited confidence that the estimate of effect lies close to the true effect for this outcome.</b> The body of evidence has major or numerous deficiencies (or both). We believe that additional evidence is needed before concluding either that the findings are stable or that the estimate of effect is close to the true effect.
Insufficient	<b>We have no evidence, we are unable to estimate an effect, or we have no confidence in the estimate of effect for this outcome.</b> No evidence is available or the body of evidence has unacceptable deficiencies, precluding reaching a conclusion.

## Peer Review

We received peer review of the report from 1 content expert. Their comments were reviewed and, where possible, incorporated into the final document. All comments and the authors' proposed actions were reviewed by representatives of the participating organizations of the Drug Effectiveness Review Project before finalization of the report.

## Public Comment

This report was posted to the Drug Effectiveness Review Project website for public comment. We received comments from 3 pharmaceutical companies.

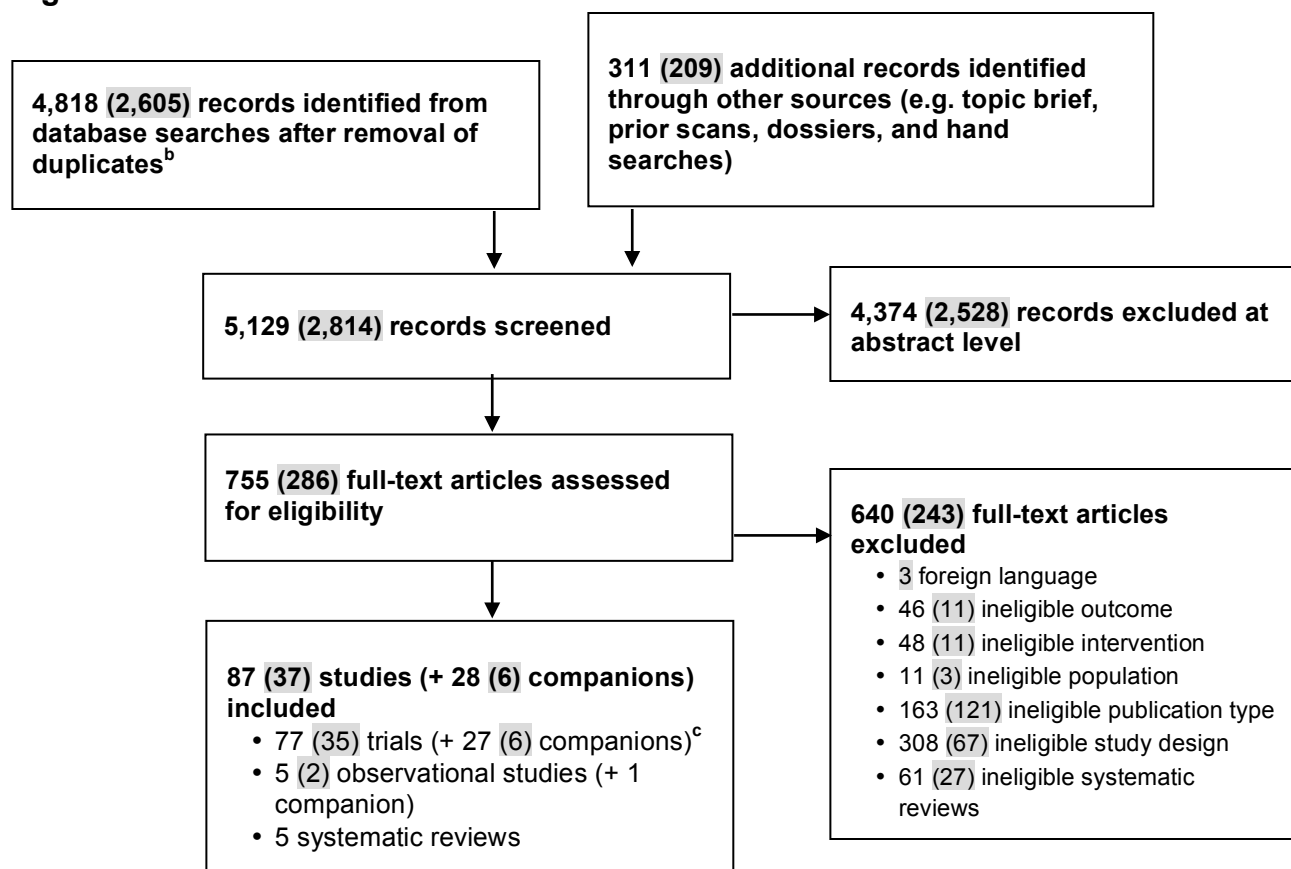
# RESULTS

## Overview

A total of 5,129 citations (2,814 this update) were identified. By applying the eligibility and exclusion criteria to titles and abstracts of all identified citations, we identified 755 potentially includable citations (286 this update). After reapplying the criteria to the full texts of these citations, we ultimately included 87 studies (37 this update).<sup>13-49</sup> Seventy-seven were trials (35 this update)<sup>13-29,31-41,43-49</sup> with 27 companion publications (6 this update),<sup>50-55</sup> 5 were observational studies (2 this update)<sup>30,42</sup> with 1 companion publication, and 5 were systematic reviews. We received dossiers from 6 pharmaceutical manufacturers: Merck, Sunovion, Novartis, Boehringer Ingelheim, GlaxoSmithKline, and AstraZeneca. Figure 1 illustrates the flow of studies through the selection process.

Throughout the text, we use total daily doses, and do not report dosing schedules (schedules are reported in evidence tables).

**Figure 1. Results of literature search<sup>a</sup>**



<sup>a</sup> DERP uses a modified PRISMA flow diagram.<sup>64</sup>

<sup>b</sup> The numbers in the flow chart pertain to streamlined Original Report and Update 1 report. Shading indicate studies identified in Update 1. Unshaded study counts are cumulative.

<sup>c</sup> Of the included trials, 3 trials and 4 companion publications have not been synthesized separately as they are included as part of the systematic reviews.

## **Key Question 1. What is the comparative *within-class* and *across-class* efficacy and effectiveness of long-acting inhaled and long-acting oral medications used to treat outpatients with asthma or chronic obstructive pulmonary disease (COPD)?**

### ***I. Intra-class Comparisons (within a class)***

#### **a. Monotherapy**

##### ***a. Inhaled corticosteroids***

### **Summary of findings**

#### ***Asthma***

- Overall, studies provided low- to moderate-strength evidence that for most comparisons inhaled corticosteroids (ICSs) do not differ in asthma symptoms, exacerbations, rescue medication, or quality of life at equipotent doses
  - Beclomethasone dipropionate (BEC) compared with mometasone furoate (MOM): No difference for all outcomes (moderate-strength evidence)



- Budesonide (BUD) compared with ciclesonide (CIC): No difference for all outcomes (moderate-strength evidence)
- Ciclesonide (CIC) compared with fluticasone propionate (FP): No difference for all outcomes (high-strength evidence)
- Evidence on fluticasone furoate (FF) compared with fluticasone propionate (FP) based on only 1 small, fair-quality trial, was insufficient to draw conclusions.
- Differences found are limited to:
  - BUD compared with MOM: No difference for symptoms, MOM better than BUD for rescue medication use (low-strength evidence)
  - BEC compared with BUD: Nocturnal awakening: BEC better than BUD (low-strength evidence)
  - FP compared with BEC: lower risk of exacerbation: RR 0.71 (0.51 to 0.99) (low-strength evidence) Nocturnal awakening: No difference (moderate-strength evidence)
  - FP compared with BUD: Functional capacity: FP better than BUD (low-strength evidence).
- Evidence was not found for comparisons of BEC versus CIC, or flunisolide (FLUN), BUD, versus FLUN, CIC versus MOM or FLUN versus FP or MOM.
- In children, head-to-head trials supported the conclusion that ICSs do not differ in their impact on health outcomes, but data were only available for 5 comparisons (3 systematic reviews and 5 RCTs): BEC compared with BUD, BEC compared with FP, BUD compared with CIC, BUD compared with FP, and CIC compared with FP.

## ***COPD***

- We did not find any head-to-head trials comparing one ICS with another.

## **Detailed assessment**

### ***Asthma***

We found 3 systematic reviews with meta-analyses<sup>65-67</sup> and 44 head-to-head randomized controlled trials (RCTs) including a total of 15,173 asthma patients.<sup>29,35,68-114</sup> Five head-to-head RCTs included children <12 years.<sup>84,87,104,105,111</sup> No study was characterized as an effectiveness trial; all included efficacy studies were conducted in narrowly defined populations. One systematic review with meta-analysis and 2 RCTs compared BEC with BUD; 2 systematic reviews with meta-analyses and 7 RCTs compared BEC with FP; 2 RCTs compared BEC with MOM; 5 RCTs compared BUD with CIC; 1 meta-analysis and 5 RCTs compared BUD with FP; 1 RCT compared BUD with MOM; 9 RCTs compared CIC with FP; 2 RCTs compared FP with MOM; and 1 compared FF with FP in patients with asthma). Thirteen studies compared MDI to MDI; 8 studies compared DPI to DPI; 12 studies compared MDI to DPI; 1 study compared both DPI to DPI and MDI to DPI.<sup>80</sup> Most trials received a quality rating of fair. The method of randomization and allocation concealment were rarely reported. Most studies were funded by pharmaceutical companies.

Most studies were conducted in adult populations. Five studies<sup>84,87,104,105,111</sup> were conducted primarily in pediatric populations. Seven studies (20%) were conducted in the United States. Asthma severity ranged from mild persistent to severe persistent: 5 studies (14%) were conducted in patients with mild to moderate persistent asthma, 8 (25%) in patients with mild to severe persistent asthma, 5 (16%) in patients with moderate persistent asthma, 7 (22%) in

patients with moderate to severe persistent asthma, and 3 (9%) in patients with severe persistent asthma. Six studies did not report the severity. 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.

Based on National Asthma Education and Prevention Program equipotent dose estimates, 37 head-to-head RCTs included equipotent comparisons for some arms (some included additional arms with non-equipotent comparisons that are not considered here)<sup>68,77,90,97,100,102,115,116</sup> and 10 RCTs (compared only non-equipotent doses).<sup>76,80,82,88,92,94,108,110,117</sup> Of the 24 head-to-head trials that compared equivalent doses, 6 compared high dose to high dose, 5 compared medium dose to medium dose, and 8 compared low dose to low dose. The assessment of the evidence below is based only on equivalent dose-comparisons.

#### *Beclomethasone dipropionate (BEC) compared with budesonide (BUD)*

One good systematic review<sup>65</sup> and 2 more recent fair head-to-head RCTs<sup>99,114</sup> comparing BEC to BUD met our inclusion criteria. The systematic review<sup>65</sup> included 24 studies (1174 subjects); 18 of these were in adults. Twelve studies (50%) had treatment periods of between 2 and 4 weeks and 10 studies (42%) had treatment periods of between 6 and 12 weeks. The longest study had an effective treatment period of 2 years. For inclusion in the review, all studies had to compare equal nominal daily doses of BEC and BUD. Results were stratified by whether patients were stratified by oral corticosteroid use, and by study design (parallel or crossover).

For asthma patients not treated with oral corticosteroids, in crossover studies there was no significant difference between treatments for symptom measures (variety of symptom scores reported) including daytime breathlessness, morning breathlessness, and daily symptom scores (6 studies, 256 subjects [SMD 0.06, 95% CI -0.18 to 0.31]) and night-time breathlessness and evening breathlessness scores (3 studies, 134 subjects [SMD -0.09, 95% CI -0.43 to 0.25]). There was also no difference in withdrawals due to exacerbations or rescue medication use in parallel design studies. For asthma patients treated dependent on oral corticosteroids, 3 crossover studies, 144 subject, found no significant difference between BEC and BUD for daytime or night-time breathlessness scores, sleep disturbance scores, or rescue medication use.

Two more recent trials that were not included in the systematic review were included here. An open-label RCT (6 months, N=225) of adult patients with mild to severe persistent asthma randomized steroid naïve patients to equipotent low doses of FP 125 mcg per day, BEC 200 mcg per day and BUD 200 mcg per day via MDI according to their disease severity based on GINA guidelines.<sup>116</sup> Exacerbations were similar between groups (44 vs. 48). Quality of life was significantly different across the 3 drugs on the St. George Respiratory Questionnaire (SGRQ) at 6 months (endpoint,  $P=0.006$ ).<sup>116</sup> Mean changes from baseline for BEC and BUD were -58 and -56.8 ( $P=NR$ ).

Additionally, a non-inferiority 12-week parallel group trial (N=460), with stratification for LABA use, compared treatment with 3 inhaled corticosteroids: BEC extrafine aerosol (800 mcg/day, N=149), BUD (1600 mcg/day, N=162), and FP (1,000 mcg/day, N=149).<sup>99</sup> Overall asthma control was improved in all groups with no significant difference between groups, establishing non-inferiority of BECx compared with BUD (-1.0 vs. -0.8, 95% CI -0.30 to 0.07).<sup>99</sup> There was low-strength evidence that BECx had statistically significantly greater change in nocturnal awakening on the Juniper asthma control questionnaire compared with BUD (-1.0 vs. -0.7, 95% CI -0.43 to -0.05).

*Beclomethasone dipropionate (BEC) compared with fluticasone propionate (FP)*

Two systematic reviews and 11 head-to-head RCTs comparing FP to BEC met our inclusion criteria. One systematic review<sup>66</sup> included studies comparing FP with either BEC or BUD. Of the 71 studies included in this review, 33 compared FP to BEC (9 of those 33 were included in our review). Comparisons were stratified by FP: BEC/BUD dose ratios of 1:2 or 1:1. The pooled treatment effect of FP was compared with the pooled treatment effect for BEC and BUD. 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. The other systematic review<sup>67</sup> compared either CFC or HFA-propelled FP with HFA-propelled extrafine BEC. The review included 9 studies (1,265 participants) and found no statistically significant difference between treatments for symptom scores and quality of life.

Of the 7 RCTs that compared BEC to FP,<sup>74,84,85,96,99,103,106,116</sup> 1 was conducted exclusively in a population of children and adolescents aged 4-11.<sup>84</sup> Asthma severity ranged from mild- to severe-persistent. Doses ranged from low to high; all studies included comparisons of equipotent doses of BEC and FP. Study duration ranged from 6 to 52 weeks. All but 2 trials<sup>96,103,116</sup> assessed asthma symptoms and rescue medicine use.

Two fair-quality RCTs<sup>85,96</sup> of 1-year duration compared high doses of FP to BEC in adult patients with moderate to severe asthma. One compared BEC 1,500 mcg/day and FP 1,500 mcg/day taken via MDI<sup>85</sup> while the other compared 1,000 mcg FP/day to 2,000 mcg per day BEC via MDI.<sup>96</sup> Exacerbations defined as increase in asthma symptoms leading to change in therapy other than beta<sub>2</sub>-agonist occurred in 16% and 28% of patients taking FP and BEC ( $P < 0.05$ )<sup>85</sup> and in 39% and 48% of patients respectively ( $P = \text{NS}$ ).<sup>96</sup> There is low-strength evidence in adults that FP is better than BEC in proportion of patients with exacerbation (RR 0.71; 95% CI 0.51 to 0.99). Two studies of 3<sup>74</sup> and 6<sup>116</sup> months duration in adults reported higher number of exacerbations in FP compared with BEC. Evidence for exacerbations is insufficient in children (16% treated with FP experienced an exacerbation vs. 19% of children treated with BEC) based on a single study.<sup>84</sup> There is also insufficient-strength evidence to draw any conclusions regarding comparative efficacy of FP or BEC in quality-of-life outcomes. Only 1 study reported on quality of life in adult patients with mild to severe asthma. Treatment with FP resulted in improved St. George's Respiratory Questionnaire (SGRQ) total score at 6 months compared with BEC.<sup>116</sup> The mean change from baseline in total SGRQ total score was -59.3, -58 for FP, and BEC respectively.

There was moderate-strength evidence from two 12-week trials that FP is similar to BEC in nighttime awakening. One study of non-smoking adults compared low and medium doses of FP 88 mcg and 200 mcg or BEC 168 mcg and 336 mcg/day in patients with mild to and severe asthma.<sup>106</sup> Comparison of combined drug effect of FP vs. BEC found no significant difference between groups. The second trial compared high doses of BEC extrafine aerosol, Qvar Autohaler 800 mcg/day, BUD Turbuhaler 1600 mcg/day, and FP Diskus 1,000 mcg/day with stratification for LABA use (2:1 yes:no) indicated non-inferiority for BEC compared with FP in nocturnal awakening assessed by French Version of Juniper Asthma Control Questionnaire (95% CI -0.30 to 0.80).<sup>99</sup>

There is insufficient evidence on mortality associated with FP or BEC to draw conclusions. A 12-month study of patients with moderate to severe asthma receiving high dose 1,500 mcg FP/day MDI reported 2 deaths compared with 1 death in patients taking 1500 mcg BEC/day MDI (RR 1.86; 95% CI 0.25 to 14.11).<sup>85</sup>

*Beclomethasone dipropionate (BEC) compared with mometasone furoate (MOM)*

Two fair-quality RCTs<sup>73,100</sup> compared treatment with BEC and MOM for 12 weeks. Both compared medium-dose BEC MDI (336 mcg/day) and multiple doses of MOM DPI (low-dose 200 mcg/day and medium-dose 400 mcg/day in both studies, and high-dose 800 mcg/day in 1 study),<sup>73</sup> in patients at least 12 years old with persistent asthma. Both studies found no statistically significant differences between BEC and MOM for symptoms, nocturnal awakenings, and rescue medicine use.

*Budesonide (BUD) compared with ciclesonide (CIC)*

Three fair-quality, 12-week, multicenter RCTs meeting our inclusion criteria compared BUD with CIC.<sup>76,90,108,111,118</sup> One was conducted in children age 6-11<sup>111</sup> and 1 in adolescents 12-17 years old.<sup>118</sup> All studies used dry powder formulations of BUD and HFA-MDI for CIC and were non-inferiority trials. All 3 studies reported similar improvement in symptoms,<sup>90,111,118</sup> rescue medication use,<sup>90,111,118</sup> and quality of life<sup>111,118</sup> for subjects treated with CIC and those treated with BUD, finding CIC to be non-inferior to BUD.

*Budesonide (BUD) compared with fluticasone propionate (FP)*

One previously-described systematic review and 5 head-to-head RCTs comparing FP to BUD met our inclusion criteria. The systematic review<sup>66</sup> included studies comparing FP with BEC or BUD. Of the 90 studies included in this review, 37 compared FP to BUD. Comparisons were stratified by FP: BEC/BUD dose ratios of 1:2 or 1:1. The pooled treatment effect of FP was compared with the pooled treatment effect for BEC and BUD. For the studies conducted at dose ratios of 1:1, individual studies and pooled estimates suggest no difference in symptoms, rescue medication use, or the number of asthma exacerbations.

Three fair-quality trials comparing equipotent doses of FP and BUD did not find any difference between drugs in symptoms and rescue medication use.<sup>87,92,99,107,116</sup> Trial duration ranged from 12 to 26 weeks. One was conducted in children and adolescents;<sup>87,93</sup> 4 were conducted in patients with moderate and/or severe persistent asthma,<sup>87,92,99,107</sup> while 1 was conducted in patients with mild, moderate and severe asthma.<sup>116</sup> All used dry powder formulations of both medications.

A fair-quality, 12-week RCT compared high doses of FP to high doses of BUD<sup>92,107</sup> in adult patients with moderate to severe asthma. Although more patients taking BUD reported exacerbations compared with FP, the difference was not statistically significant.

A 20-week double blind, double dummy trial in children 4-12 years with moderate to severe asthma receiving medium doses of FP 400 mcg/day DPI or BUD 800 mcg/day DPI reported similar results with no statistically significant difference between 2 groups in exacerbations (RR 0.25, 95% CI 0.06 to 1.03) although the point estimate favored FP.<sup>87</sup> Evidence for exacerbations in both adults and children is insufficient to support any conclusions about comparative effectiveness of BUD and FP.

Another trial of 6 months duration in 225 patients experiencing mild to severe asthma reported number of exacerbations.<sup>116</sup> Patients received FP 125 mcg/day or 200 mcg/day, BEC or BUD via MDI according to the disease severity based on GINA guidelines. Higher number of exacerbations were reported in patients taking BUD compared with FP (44 vs. 34,  $P=NR$ ). The same study reported quality of life using SGQL and found greater improvement with FP

compared with BUD ( $P=NR$  between groups).<sup>116</sup> This evidence was insufficient to draw conclusions on the comparative efficacy of FP and BUD regarding quality of life.

#### *Budesonide (BUD) compared with mometasone furoate (MOM)*

One fair-quality 12-week RCT<sup>77</sup> compared BUD and MOM. The study randomized 730 people 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) MOM.<sup>77</sup> There were no statistically significant differences between medium-dose BUD and medium-dose MOM for symptoms or nocturnal awakenings, but patients treated with medium-dose MOM had a greater decrease in rescue medicine use than those treated with medium-dose BUD ( $-90.66$  mcg/day vs.  $-33.90$  mcg/d;  $P<0.05$ ).

#### *Ciclesonide (CIC) compared with fluticasone propionate (FP)*

Eight fair-quality RCTs compared CIC with FP using equipotent doses.<sup>29,71,75,79,83,94,98,104,105</sup> While 7 were 12 to 24 weeks in duration, 1 was 6 months.<sup>71</sup> Two enrolled children.<sup>104,105</sup> Three were conducted in subjects with mild to severe persistent asthma; 3 in subjects with moderate persistent asthma;<sup>75,79</sup> and 1 each in mild to moderate<sup>83</sup> and moderate to severe persistent asthma.<sup>71</sup> Five of the trials comparing equipotent doses compared low dose CIC with low-dose FP; 1 compared medium doses<sup>75</sup> and 1 compared high doses.<sup>71</sup> All but 1 trial used HFA-MDI for delivery of both medications.<sup>75</sup> Seven RCTs were funded by the manufacturer of CIC, and 1 study from Iran did not report funding.<sup>29</sup>

We conducted meta-analyses of these studies for exacerbations, symptoms, and rescue medication use and found no statistically significant differences between CIC and FP. There was no statistically significant difference between CIC and FP for exacerbations requiring treatment with oral steroids (OR 0.97, 95% CI 0.50 to 1.88), improvement in symptom scores (SMD 0.016, 95% CI  $-0.05$  to 0.08), or change in rescue medication use (SMD 0.03, 95% CI  $-0.03$  to 0.09). There was no significant statistical heterogeneity for any of these analyses ( $I^2=0$  for all). One more recent study reported that 0.9% (1 of 115) patients taking CIC via MDI withdrew from the study due to an asthma exacerbation, compared with 2.6% (3 of 115) on FP (Evidence-based Practice Center calculated RR 0.33, 95% CI 0.03 to 3.16).<sup>29</sup>

Four of 5 studies assessing quality of life found no difference between groups. The 1 exception was reported in a 12-week trial of 474 subjects, which found greater improvement in quality of life with CIC compared with FP (mean change from baseline in AQLQ: 0.29 vs. 0.11,  $P=0.005$  for 1-sided superiority).<sup>75</sup> The same trial reported non-inferiority or no statistically significant difference between medications for symptoms.

#### *Fluticasone furoate (FF) compared with fluticasone propionate (FP)*

A single fair-quality trial (N=343) compared equipotent doses of FF (100 mcg daily via DPI) and FP (250 mcg twice daily via DPI) in patients 12 years and older with asthma (severity not specified for enrollment).<sup>35</sup> A placebo arm was also included but not reported here. Mean age was 41 years and mean duration of asthma was 18 years. The number of severe exacerbations was similar in both groups (3% with FF and 2% with FP). The difference in percent rescue-free periods per 24 hours, compared with placebo, was also similar between FF (14.8%) and FP (17.9%). Quality of life, as measured by the difference in the AQLQ compared with placebo was similar between drugs at 12 weeks 0.24 for FF and 0.28 for FP. At 24 weeks, the difference compared with placebo was larger and still statistically significant FF (0.33, 95% CI 0.09 to

0.57). For FP, the difference compared with placebo was smaller at 24 weeks and no longer statistically significant (0.16; 95% CI –0.08 to 0.41). Due to the limited evidence, these findings are insufficient to draw conclusions.

#### *Fluticasone propionate (FP) compared with mometasone furoate (MOM)*

Three fair-quality trials compared FP with MOM in adults with asthma.<sup>38,91,102,112</sup> Two compared medium doses of FP (500 mcg daily) with low (200 mcg daily) and medium (400 mcg daily) doses of MOM<sup>38,102</sup> while one compared high dose MOM (800 mcg/day) with high dose FP (1,000 mcg/day).<sup>91</sup>

A fair-quality dose-ranging study (N=733) compared medium-dose FP (500 mcg/day) to low-, medium-, and high-dose MOM (200, 400, and 800 mcg/day, respectively) in 733 patients 12 years and older with moderate persistent asthma for at least 12 weeks.<sup>102</sup> The investigators found no statistically significant differences at endpoint between patients treated with medium-dose FP and those treated with medium- and high-dose MOM with respect to wheeze and cough scores, nighttime awakenings, or rescue medication use ( $P>0.05$  for all). In addition, patients on medium-dose FP had significantly better morning difficulty breathing scores than did patients on either low- or medium-dose MOM ( $P<0.05$ ). A second study (N=566) compared low and medium-dose MOM (200 and 400 mcg per day) DPI with medium-dose FP (500 mcg per day) MDI in adults with mild-moderate persistent asthma who did not receive ICS for >3 months, for 52 weeks.<sup>38</sup> This study was designed to measure bone mineral density changes, and while use of rescue medications was collected it was not reported adequately for comparison purposes.

The multinational trial (N=203) that compared high dose MOM (800 mcg/day) with high dose FP (1,000 mcg/day) for 12 weeks, reported no statistically significant differences at endpoint with respect to rescue medication use, symptoms, and exacerbations.<sup>91</sup>

#### *b. Leukotriene modifiers (LMs)*

##### **Summary of findings**

###### ***Asthma***

- Montelukast (MON) compared with zafirlukast (ZAF)
  - One very small trial provided insufficient evidence to draw conclusions.
- Montelukast (MON) compared with zileuton (ZIL)
  - Evidence from a single study; insufficient evidence to draw conclusions.

###### ***COPD***

- No eligible studies. LMs are approved only for use in patients with asthma.

##### **Detailed assessment**

###### ***Asthma: head-to-head comparisons***

###### *Montelukast (MON) compared with zafirlukast (ZAF)*

One fair-quality, 12-week,<sup>119</sup> head-to-head trial comparing MON to zafirlukast in patients with asthma met the inclusion/exclusion criteria for our review. The trial compared the effect of MON (10 mg/day) and ZAF (40 mg/day) on quality of life and rescue medication use and enrolled 40 adults with mild persistent asthma from a subspecialty respiratory pathophysiology center in Italy. At endpoint, improvement in beta-agonist use was not significantly different between MON- and ZAF-treated patients. Improvements in asthma-related quality of life (AQLQ) also

appeared similar between the 2 treatment groups, but a statistical comparison was not reported and given the small sample size evidence was insufficient to compare quality of life between the 2 drugs (Appendix E, Table E-2).

#### *Montelukast (MON) compared with zileuton (ZIL)*

A somewhat larger, fair-quality trial<sup>120</sup> compared MON with ZIL in adults in India with mild to moderate chronic asthma. Effects of 12 weeks of treatment with ML (10 mg/day, 1 daily dose) or ZIL (2,400 mg/day, two 600 mg tablets twice daily) on symptoms and the use of rescue medications were assessed. The effect of symptoms on activities and sleep was measured on a 4-point scale for each of 4 asthma symptoms, with an overall score summed across symptoms (range 0 to 16 points, where 0 indicates no symptoms). Between baseline and 12 weeks, overall scores for subjects treated with ZIL dropped 5.0 points (95% CI 4.6 to 5.4), and those for MON 4.2 points (95% CI 3.8 to 4.7); though CIs overlapped ( $P=0.018$ ). Decline in rescue medicine use did not differ between the 2 treatment groups ( $P=0.445$ ).

### *c. Long-acting beta-2 agonists (LABAs)*

#### **Summary of findings**

##### ***Asthma***

- Results from 3 efficacy studies provided moderate evidence (Appendix E, Table E-3) that LABAs do not differ in their ability to control asthma symptoms, prevent exacerbations, improve quality of life, and prevent hospitalizations or emergency visits in patients with persistent asthma not controlled on ICSs alone.

##### ***COPD***

- *Arformoterol (ARF) compared with formoterol (FOR)*
  - One fair-quality trial provided low-strength evidence that exacerbation rates and improvements in quality of life did not differ between groups, though for lower-dose ARF there was an increase in exacerbation rates that was borderline statistically significant (RR 1.44; 95% CI 0.99 to 2.10).
- *Formoterol (FOR) nebulized compared with formoterol (FOR) via DPI*
  - Low-strength evidence from 1 fair-quality trial showed that exacerbation rates and changes in quality of life did not differ between treatment arms.
- *Indacaterol (IND) compared with formoterol (FOR)*
  - Low-strength evidence from 1 fair-quality trial showed that exacerbation rates and changes in quality of life did not differ between treatment arms.
- *Indacaterol (IND) compared with salmeterol (SAL)*
  - One fair-quality trial provided low-strength evidence that patients given indacaterol were more likely to experience a clinically important improvement in quality of life after 12 weeks than those given SAL (OR 1.59; 95% CI 1.12 to 2.25).
- *Olodaterol (OLO) compared with formoterol (FOR)*
  - Two replicate trials provided low-strength evidence that OLO at a dose of 10 mcg daily did not change exacerbation rates compared with FOR at 24 mcg daily.
  - Moderate-strength evidence from 2 replicate trials showed that patients given OLO were more likely to report clinically important improvement in quality of

life than were those given formoterol, regardless of OLO dose (OLO 5 mcg/day vs. FOR, RR 1.28, 95% CI 1.10 to 1.48; OLO 10 mcg/day vs. FOR, RR 1.26, 95% CI 1.09 to 1.46).

## Detailed assessment

### *Asthma*

We found 3 fair-quality RCTs in patients with asthma<sup>121-124</sup> that included head-to-head comparisons of 1 LABA with another LABA and met our inclusion/exclusion criteria. All were published before 2010, when the US Food and Drug Administration issued a boxed warning against use of LABAs as monotherapy in patients with asthma (see Key Question 2). For the original Asthma/COPD report and for Update 1, we found no new trials comparing LABAs in patients with asthma.

Two trials compared FOR with SAL<sup>121,122</sup> and 1 compared FOR with SAL.<sup>123,124</sup> Of note, FOR was formerly known as eformoterol (eFOR) in the UK, and these are generally considered the same drug. Study duration ranged from 8 weeks to 6 months. Two were conducted primarily in adult populations,<sup>121,123,124</sup> and 1<sup>122</sup> in a pediatric and adolescent population (age 6-17). All 3 trials enrolled subjects that were not adequately controlled on ICSs. Two of the 3 trials were funded by pharmaceutical companies; 1 trial did not report the source of funding, but at least 1 author had a primary affiliation with a pharmaceutical company.

#### *Arformoterol (ARF) compared with formoterol (FOR)*

We did not identify any good- or fair-quality systematic reviews or head-to-head trials that compared ARF to FOR in patients with asthma.

#### *Formoterol (FOR) compared with salmeterol (SAL)*

Two fair-quality RCTs meeting our inclusion/exclusion criteria compared FOR with SAL.<sup>121,122</sup> 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  $\geq 12$  years of age with mild to moderate persistent asthma.<sup>121</sup> The other was a 12-week trial that enrolled 156 children and adolescents between 6 and 17 years of age with moderate persistent asthma.<sup>122</sup>

Both trials assessed asthma symptoms, nocturnal awakenings, and exacerbations. One trial also reported hospital admission or visits to A&E (accident and emergency departments)<sup>121</sup> while the other study also reported rescue medication use, quality of life, missed work, missed school, and compliance.<sup>122</sup> The trials found no difference between those treated with eFOR and those treated with SAL for all outcomes except for rescue medicine use: 1 trial<sup>122</sup> found a greater decrease in rescue medicine use in those treated with eFOR than in those treated with SAL.

#### *Formoterol (FOR) compared with salmeterol (SAL)*

One fair-quality open-label 6-month RCT meeting our inclusion/exclusion criteria compared FOR with SM in 482 adults  $\geq 18$  years of age with moderate to severe persistent asthma.<sup>123,124</sup> 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 FOR than those treated with SAL.



## **COPD**

We found 7 new trials comparing LABAs in patients with COPD.<sup>33,125-129</sup> Three trials<sup>128-130</sup> compared IND with SAL, and another compared IND with FOR.<sup>125</sup> One trial<sup>131</sup> compared ARF with FOR, one compared FOR delivered with a nebulizer to FOR via dry powder inhaler, and the final trial compared the newer LABA olodaterol (OLO; US Food and Drug Administration-approved in 2014) to FOR.<sup>33</sup> Another trial, with open-label design comparing FOR and SAL over 6 months, was rated poor for efficacy but fair for harms and is discussed in Key Question 2 below.<sup>132</sup> The durations of the COPD trials ranged from 12 weeks to 1 year. Many patients were current smokers, ranging from 34% to 52% of subjects in the 5 studies that reported these data. All 7 studies in COPD patients were funded by pharmaceutical companies.

### *Arformoterol (ARF) compared with formoterol (FOR)*

One fair-quality trial<sup>131</sup> compared ARF with FOR in patients with COPD. The trial recruited 444 patients age 35 and older from 62 centers in the United States. During 6 months of treatment subjects received ARF 30 mcg daily or 50 mcg daily, administered with a nebulizer, or 24 mcg of FOR via DPI. The trial provided low-strength evidence that exacerbation rates were similar between ARF and FOR patients (Appendix E, Table E-3). Patients taking ARF had a somewhat higher risk of 1 or more exacerbations than those taking FOR, with RR 1.44 (95% CI 0.99 to 2.10) for 30 mcg and RR 1.36 (95% CI 0.93 to 2.01) for 50 mcg of ARF; however, differences were not statistically significant. Quality of life, measured by the St. George's Respiratory Questionnaire, improved between baseline and the end of treatment by 6.8 points for patients taking FOR and 3.7 points for those taking either ARF dose, but CIs overlapped between the 3 arms. Rescue medicine use declined and dyspnea symptoms improved to a similar degree in all 3 treatment arms. The trial provided insufficient evidence to compare mortality between the groups; only 1 death occurred in the study, in a patient taking 50 mcg ARF (Appendix E, Table E-3).

### *Formoterol (FOR): nebulized compared with dry powder inhaler*

A 12-week fair-quality trial<sup>126</sup> in 237 United States COPD patients compared FOR administered with a nebulizer to FOR via dry powder inhaler, and provided low-strength evidence that the efficacy of the 2 formulations is comparable. The trial administered 40 mcg daily of FOR via nebulizer or 24 mcg via DPI. Exacerbations occurred in 5 patients using nebulizers (4.1%) and 7 using DPIs (6.1%). Quality of life improved in both treatment arms, with SGRQ scores declining by about 5.5 points with nebulized FOR and 4.1 points with the DPI, and the difference was not statistically significant. No deaths occurred in either group. Results were similar between the 2 groups for rescue medication use, which declined from baseline in both groups.

### *Formoterol (FOR) compared with indacaterol (IND)*

The INVOLVE Study<sup>125</sup> is a multinational randomized trial of COPD patients comparing 2 doses of the new LABA IND with FOR. This fair-quality trial was funded by a pharmaceutical company and recruited 1,300 patients from outpatient sites in 25 countries, not including the United States. The doses of IND were 300 mcg and 600 mcg per day, greater than the 75 mcg per day approved by the US Food and Drug Administration. Patients were randomized to 52 weeks of treatment with either 24 mcg/day of FOR, 300 mcg/day of IND, or 600 mcg/day of IND, all via DPI. The study provided low-strength evidence that the efficacy of IND is

comparable to that of FOR for exacerbations and quality of life, with some clinical outcomes favoring IND.

The INVOLVE trial reported mortality, exacerbations, quality of life, and other outcomes. Exacerbations occurred in 126 patients taking FOR, 133 taking 300 mcg of IND, and 116 taking 600 mcg IND; differences were not statistically significant, and the results provided low-strength evidence that FOR and IND are comparable for preventing exacerbations. Quality of life scores were also very similar between the 3 groups, with SGRQ scores of 37.3 for FOR, 36.6 for IND 300 mcg, and 36.7 for IND 600 mcg (differences not statistically significant), again providing low-strength evidence that FOR and IND have comparable effects. At 12 weeks, dyspnea scores were better with IND than with FOR, but at 52 weeks differences were not statistically significant. Rescue medication use decreased from baseline more with IND than with FOR, and IND patients had fewer days when they needed salbutamol. Patients taking IND also had more nights with no awakenings than did FOR patients, with the difference statistically significant for the higher IND dose. The trial provided insufficient evidence on comparative mortality.

#### *Indacaterol (IND) compared with salmeterol (SAL)*

Three fair-quality RCTs in COPD patients compared the effects of IND with those of SAL. The INSIST Study<sup>128</sup> recruited 1,123 patients from 144 centers in 8 countries including the United States. Patients received either 150 mcg of IND or 100 mcg of SAL daily via DPI for 12 weeks. The INFLIGHT-2 Study<sup>129</sup> was smaller (N=667) but of longer duration (26 weeks). Patients from outpatient sites and clinical research centers in 15 non-United States countries participated, and the same daily doses of IND and SAL as in the INSIST Study were given via DPI. The third trial was a small, unpublished study of 186 patients at 37 centers in Japan, comparing a higher daily dose of IND (300 mcg) to the same dose of SAL (100 mcg) used in the larger trials. It should be noted that the dose of IND used in this study is greater than the dose currently approved in the United States.

None of the 3 trials reported exacerbations or hospitalizations. All 3 did report mortality, but there were few deaths in any trial and evidence was insufficient to establish a difference between the 2 drugs.

INFLIGHT-2 also reported quality of life, and reported that SGRQ scores improved more for IC than for SM after 12 weeks' treatment ( $P<0.05$ ). The minimum clinically important difference is 4 points on the SGRQ scale, and at 12 weeks IND patients were more likely to achieve this clinically-important improvement than were SAL patients (OR 1.59, 95% CI 1.12 to 2.25). By 26 weeks, the gap between SGRQ scores had narrowed and was no longer statistically significant. Dyspnea scores were better in IND than SAL patients at 12 weeks in both studies (statistically significant in both trials), but by the end of the 26-week INFLIGHT-2 trial differences were no longer significant. In both studies IND patients had fewer days requiring salbutamol as a rescue medication; INSIST also showed fewer puffs per day of salbutamol, though INFLIGHT-2 did not.

#### *Olodaterol (OLO) compared with formoterol (FOR)*

Two replicate fair-quality 48-week trials reported in 1 publication compared 2 doses of OLO (5 or 10 mcg daily) given via SMI to FOR 24 mcg daily by DPI.<sup>33</sup>

Of the 1,378 participants across the 2 trials (excluding those given placebo only), 79% were male, the mean age was 64 years, and all had a smoking history of more than 10 pack-

years. Results for exacerbations at the 5 mcg OLO dose were inconsistent across the 2 studies, providing insufficient evidence to compare treatment arms. Results were also somewhat inconsistent across studies for the higher OLO dose, but we rated the strength of this evidence as low for no difference in exacerbation rates between OLO 10 mcg and FOR 24 mcg daily (RR 1.07, 95% CI 0.83 to 1.39).

The same 2 studies<sup>33</sup> reported quality of life using a responder analysis for the St. George's Respiratory Questionnaire (SGRQ), where an improvement from baseline score of at least 4.0 points at 24 weeks was defined as clinically important. Data were reported pooled across the 2 studies, so we could not assess consistency of their results. However, we assessed the strength of evidence as moderate that response rates were better with OLO at either dose than with FOR (RR 1.28, 95% CI 1.10 to 1.48 for OLO 5 mcg vs. FOR, and RR 1.26, 95% CI 1.09 to 1.46 for OLO 10 mcg vs. FOR daily).

#### *d. Long-acting muscarinic agonists (LAMAs)*

##### **Summary of findings**

###### ***Asthma***

- Neither the prior report nor the present update identified any studies compared LAMAs with each other in patients with asthma.

###### ***COPD***

- Three trials comparing GLY to TIO found no differences in rates of exacerbations, use of rescue medication, or quality of life (low-strength evidence).
- Two trials comparing UME to TIO found no differences in rates of exacerbations, use of rescue medication, or quality of life (low-strength evidence).

##### **Detailed assessment**

###### ***COPD***

The prior report did not include any studies comparing LAMAs with each other in patients with COPD. We identified 5 trials that reported efficacy and effectiveness outcomes: 3 trials compared GLY to TIO<sup>19,24,32</sup>, and 2 trials compared UME to tiotropium.<sup>21,50</sup> All trials included adults aged  $\geq 40$  years with COPD, a smoking history of  $\geq 10$  pack-years, and an FEV1/FVC ratio  $< 0.7$ . The duration of 1 trial was 52 weeks,<sup>32</sup> while the remainder were 12-week studies. Sample sizes ranged from 437 to 1,066. Mean ages of participants ranged from 63.5 to 68.0 years, and the proportions of females ranged from 26% to 36%. In all studies, GLY was delivered via the BreezeHaler DPI, UME was delivered via the Ellipta DPI, and TIO was delivered via the HandiHaler DPI. Four trials were rated fair quality,<sup>21,24,32,50</sup> while the remaining trial was good quality.<sup>19</sup> All trials were pharmaceutically-funded.

###### ***Glycopyrrolate (GLY) compared with tiotropium (TIO)***

Three trials compared GLY 50  $\mu\text{g}$  (= 62.4 mcg glycopyrrolate bromide) with TIO 18  $\mu\text{g}$ ; patients in 1 of these trials were receiving SAL/FP as background therapy. The trials reported no differences between groups in COPD exacerbations (rates ranging from 7.5% to 11.3%), use of rescue medication, or quality of life. The dose of GLY is greater than the US Food and Drug Administration-approved dose (31.2 mcg glycopyrrolate/25 mcg glycopyrronium daily).

### *Umeclidinium (UME) compared with tiotropium (TIO)*

Two trials (1 unpublished) compared UME with TIO. These trials reported no significant differences between groups in COPD exacerbations (rates ranging from 6.5% to 11.7%), use of rescue medication, or quality of life.

### b. Combination therapy compared with combination therapy

#### a. *Inhaled corticosteroid (ICS) and long-acting beta-2 agonist (LABA) compared with inhaled corticosteroid (ICS) and long-acting beta-2 agonist (LABA)*

## Summary of findings

### **Asthma**

- *Beclomethasone/formoterol extrafine (BECx/FORx) compared with fluticasone propionate (FP)/salmeterol (SAL)*
  - Evidence on comparative efficacy was insufficient.
- *Budesonide (BUD)/formoterol (FOR) compared with fluticasone propionate (FP)/formoterol (FOR)*
  - Evidence on comparative efficacy was insufficient.
- *Budesonide (BUD)/formoterol (FOR) compared with fluticasone (FP)/salmeterol (SAL)*
  - Moderate-strength evidence from 4 fair-quality trials showed no difference in exacerbation rates between therapies.
- *Mometasone furoate (MOM)/formoterol (FOR) compared with fluticasone propionate (FP)/salmeterol (SAL)*
  - Moderate-strength evidence from 2 fair-quality trials (1 with duration 12 weeks, one 52 weeks) showed no difference in exacerbation rates between groups treated with ICS/LABA with medium-dose ICS.
  - Low-strength evidence from 1 fair-quality 52-week trial showed no difference in exacerbation rates between groups treated with ICS/LABA with high-dose ICS.
- *Fluticasone propionate (FP)/salmeterol (SAL) compared with fluticasone furoate (FF)/vilanterol (VIL)*
  - One good-quality trial provided low-strength evidence of no difference in quality of life between treatment arms.

### **COPD**

- *Beclomethasone (BEC)/formoterol (FOR) compared with fluticasone propionate (FP)/salmeterol (SAL)*
  - Low-strength evidence from a fair-quality 12-week trial suggested no difference between groups in exacerbations, symptoms, 6-minute walk-test, or use of rescue medication. Evidence on quality of life was insufficient.
- *Budesonide (BUD)/formoterol (FOR) compared with beclomethasone (BEC)/formoterol (FOR)*
  - Evidence from a single good-quality, 48-week trial (N=718) indicated no differences in quality of life (moderate-strength evidence) or total exacerbations, exacerbations requiring an emergency department visit or hospitalization, or exacerbations requiring corticosteroid treatment (low-strength evidence).

- *Fluticasone furoate (FF)/vilanterol (VIL) compared with fluticasone propionate (FP)/salmeterol (SAL)*
  - FF/VIL 100 mcg/25 mcg daily compared with FP/SAL 500 mcg/100 mcg daily: moderate-strength evidence from 3 good-quality 12-week trials found no difference in exacerbations or rescue-free days.
  - FF/VIL 100 mcg/25 mcg daily compared with FP/SAL 1,000 mcg/100 mcg daily: low-strength evidence from a single good-quality 12-week trial suggested no difference in rescue-free days or quality of life.

## Detailed assessment

### *Asthma*

We found 10 RCTs with 14 publications<sup>16,17,20,56,57,63,115,133-139</sup> that compared the combination of an ICS plus a LABA with another ICS/LABA combination for controller therapy treatment of asthma. None of the trials included children younger than 12 years of age. Two of the trials were good quality, and the rest were fair quality. Almost all the trials were either funded by pharmaceutical companies or had industry authors, though 1 trial did not report this information.<sup>20</sup> Also, in some studies patients were treated with a fixed-dose combination of BUD/FOR via DPI. This fixed-dose combination product is not available in the United States, but because the same drugs are available individually in DPI formulations, we included evidence from several such studies.<sup>20,56-63</sup>

### *Beclomethasone/formoterol extrafine (BECx/FORx) compared with fluticasone propionate (FP)/salmeterol (SAL)*

We identified 1 trial comparing fixed-dose BECx/FORx with fixed-dose FP/SAL.<sup>17</sup> BECx/FORx was formulated as extrafine particles of each drug delivered via pressurized MDI at a daily dose of 400/24 mcg, while FP/SAL 500/100 mcg per day was delivered via DPI. All patients had controlled asthma by GINA definitions with FP/SAL treatment before enrollment, and results were reported for 416 participants.

The trial reported asthma exacerbations, but only 7 occurred and we assessed the strength of evidence for this outcome as insufficient (BECx/FORx vs. FP/SAL, RR 0.76, 95% CI 0.19 to 2.99). Symptoms and rescue medication use did not differ across treatment arms. The mean percent of days with no asthma symptoms was 88.5% for BECx/FORx and 88.8% for FP/SAL, and the percent of days with no rescue medicine use was 95.9% for BECx/FORx and 98.0% for FP/SAL ( $P=NS$  for both outcomes).

### *Budesonide (BUD)/formoterol (FOR) compared with fluticasone propionate (FP)/formoterol (FOR)*

Two fair-quality trials, both conducted in Brazil, compared 12 weeks of BUD and FOR to fixed-dose FP/FOR.<sup>16,20</sup> One of the 2 trials<sup>20</sup> used the fixed-dose BUD/FOR combination in a DPI that is not available in the United States (see Methods), while the other<sup>16</sup> used separate capsules of BUD and FOR. All drugs were delivered via dry powder inhaler, with daily doses of BUD/FOR 800/24 mcg and FP/FOR 500/24 mcg. Across the 2 trials a total of 358 patients received one of the combination therapies, and patients in both trials were predominantly female. One trial included patients with mild to moderate asthma, and for about half of participants asthma was controlled at baseline;<sup>16</sup> in the other, asthma was uncontrolled or partially controlled.<sup>20</sup>

Both trials reported asthma exacerbations (as adverse events), but did not show a statistically significant difference between the 2 therapies (BUD/FOR vs. FP/FOR, RR 1.14, 95% CI 0.67 to 1.93). One trial reported exacerbations requiring oral steroids, which also showed no difference between treatments (RR 0.98, 95% CI 0.34 to 2.80).<sup>20</sup> For both outcomes, we rated the strength of evidence as insufficient because events were few and confidence intervals wide. One trial assessed the use of rescue salbutamol use,<sup>20</sup> and found no difference between patients given the 2 combination therapies: the change from baseline to 12 weeks in the mean number of puffs per day for patients given BUD/FOR was  $-0.08$ , and for those given FP/FOR it was  $-0.53$  ( $P=0.29$ ).

*Budesonide (BUD)/formoterol (FOR) compared with fluticasone propionate (FP)/salmeterol (SAL)*

Based on meta-analysis, 4 trials provided moderate-strength evidence of no statistically significant difference between BUD/FOR and FP/SAL in the number of asthma patients with an exacerbations requiring oral steroids: OR 1.11 (95% CI 0.95 to 1.3) or exacerbations requiring emergency visit or hospital admission: OR 0.74 (95% CI 0.53 to 1.03) (Evidence Tables A and B).<sup>63,133-135</sup> Post hoc subgroup analyses of data in patients 16 years old or greater in 2 studies indicated similar findings.<sup>56,57</sup> Several of these trials<sup>56,57,63</sup> used the fixed-dose BUD/FOR combination in a DPI that is not available in the United States (see Methods).

All the trials reported use of rescue medication, with 3 finding no differences between fixed-dose combination treatments.<sup>63,133,134</sup> The only study finding a small difference was a 6-month trial (N=3,335), where the total daily dose of BUD delivered by DPI is considered medium and the total daily dose of FP delivered by pMDI is considered high.<sup>135,138</sup> The authors reported greater improvement in the number of rescue puffs used per day for those treated with FP/SAL (mean difference 0.10, 95% CI 0.01 to 0.19). This study also reported a lower rate of hospitalizations or emergency visits per 100 patients per 6 months for those treated with BUD/FOR (5 vs. 8,  $P=0.013$ ). The total number of hospitalizations or emergency visits was not analyzed for statistical significance, but there were fewer such events in the BUD/FOR arm compared with the FP/SAL arm (72 and 106, respectively). A post-hoc analysis of the original study that was limited to participants ages 16 and above yielded similar results. Other outcomes reported in the study did not indicate statistically significant differences between groups. Although statistical analysis was not reported, a study using equipotent doses<sup>133</sup> reported numerically fewer hospitalizations/ER visits in patients treated with BUD/FOR.

Two trials reported change in the AQLQ scale.<sup>63,135,137</sup> One reported the proportion with meaningful improvement ( $\geq 0.5$  from baseline) as 63% with BUD/FOR MDI and 61.9% with FP/SAL DPI,<sup>137</sup> while the other reported that an increase in AQLQ score of 0.76–0.78 was seen across groups.<sup>135</sup> These studies did not interpret these differences as clinically meaningful although statistical analyses were not reported.

*Fluticasone propionate (FP)/salmeterol (SAL) compared with mometasone furoate (MF)/formoterol (FOR)*

Based on 2 studies, low- to moderate-strength evidence suggests no difference in the rate of exacerbations between MF/FOR and FP/SAL at medium or high doses in patients with asthma. (Evidence Tables A and B). The 2 studies differed in duration by 40 weeks, so data were not pooled. Additionally, both studies reported “asthma deterioration” defined as emergency visits, hospitalizations or the need for additional medications (e.g. steroids) as a combined outcome

rather than exacerbations specifically. In the 12-week trial comparing medium doses of each combination product, the rates were the same between groups: MF/FOR 5.7% and FP/SAL 5.7%.<sup>115</sup> In the 52-week trial, the rates with the medium doses of each combination product were greater than in the shorter trial, but similar to each other; MF/FOR 9.9% compared with FP/SAL 8.8%.<sup>136</sup> However, in this trial the rates with the higher doses of the combination products were much greater than the medium doses (MF/FOR 17.7% vs. FP/SAL 20.0%), although not statistically significantly different to each other (our calculated  $P=0.58$ ). Other eligible effectiveness outcomes were not reported in either study.

*Fluticasone propionate (FP)/salmeterol (SAL) compared with fluticasone furoate (FF)/vilanterol (VIL)*

In a single good-quality trial (N=806), after 24 weeks of treatment, there were no differences found between FP/SAL and FF/VIL in mean improvement in the AQLQ+12 scale in patients with asthma.<sup>139</sup> The difference in final score was 0.09 (95% CI -0.03 to 0.21). Similarly there was no difference between groups in the EQ-5D scores on any dimension or the overall visual analogue score. No exacerbations occurred during the trial. This study provides only low-strength evidence of no differences between the treatments on quality of life outcomes, due to the limitations of not being able to assess consistency, and having an imprecise estimate of effect. The evidence is insufficient for other outcomes.

**COPD**

Six RCTs enrolling a total of 3,523 patients with moderate to very severe COPD were included. Mean age was in the 60's, and more than two-thirds were male. Smoking history was not consistently reported across studies. The studies were good and fair quality, and all had some form of sponsorship from manufacturers.

*Beclomethasone (BEC)/formoterol (FOR) compared with fluticasone propionate (FP)/salmeterol (SAL)*

In a 12-week, fair-quality study of 419 patients with moderate to severe COPD comparing BEC 200mcg/FOR 12 mcg DPI with FP 500 mcg/SAL 50 mcg DPI, there was no difference between groups in exacerbations (2.8% vs. 1.9%; RR 1.48, 95% CI 0.42 to 5.16).<sup>47</sup> There were no differences between groups on measures of symptoms (symptom scores, breathlessness on rising, or symptom-free days), or on 6-minute walk test. Changes in the use of rescue medication (-0.60 puffs compared with 0.63 puffs;  $P=0.80$ ) and quality of life using the SGRQ (-5.92 vs. -3.80;  $P=0.08$ ) were also not statistically significantly different between groups. The proportion of patients achieving a change of at least 4 points on the SGRQ (considered meaningful change) was also not statistically significant (45% in the BEC/FOR group and 36% in the FP/SAL group; RR 1.24, 95% CI 0.98 to 1.57). This evidence is low-strength, except for quality of life which is insufficient to draw conclusions (Appendix E, Table E-5).

*Budesonide (BUD)/formoterol (FOR) compared with beclomethasone (BEC)/formoterol (FOR)*

In a 48-week, multi-country RCT of BEC/FOR 200mcg/12mcg pMDI, BUD/FOR 400mcg/12mcg DPI, or FOR 12mcg DPI alone (all BID) enrolled 718 patients with severe COPD according to the GOLD guidelines, including at least 1 serious exacerbation in the last year no differences were found BUD/FOR and BEC/FOR in total exacerbations, exacerbations requiring an emergency department visit or hospitalization, exacerbations requiring

corticosteroid treatment, or improvement in quality of life (as measured using the St. George Respiratory Questionnaire).<sup>60</sup> This trial used the fixed-dose BUD/FOR combination in a DPI that is not available in the United States (see Methods). Evidence on exacerbations is moderate-strength; evidence on quality of life is low-strength. It was noted that the overall number of exacerbations was lower than expected in this study, given that the enrollment was patients with severe COPD. Post-hoc subgroup analyses were conducted due to concerns over variation across countries in management of exacerbations, and while the rates were slightly lower for BEC/FOR (0.162 events per patient year) than with BUD/FOR (0.180 events per patient year), these differences were not statistically significant.

#### *Fluticasone furoate (FF)/vilanterol (VIL) compared with fluticasone propionate (FP)/salmeterol (SAL)*

Three good-quality trials (N=1,858) comparing FF 100 mcg/VIL 25 mcg once daily with FP 250 mcg/SAL 50 mcg twice daily for 12 weeks in patients with moderate to very severe COPD were published in a single report.<sup>23</sup> Another trial of FF 100 mcg/VIL 25 mcg once daily compared with FF 500 mcg/SAL 50 mcg twice daily for 12 weeks in patients with moderate to very severe COPD was also included (N=528).<sup>15</sup> These studies were designed primarily to measure lung function outcomes, and few clinical outcomes. In the studies of FF 100 mcg/VIL 25 mcg once daily compared with FP 250 mcg/SAL 50 mcg twice daily, there was no statistically significant difference in exacerbations (pooled 3.7% vs. 2.9%; RR 1.25, 95% CI 0.76 to 2.06).<sup>23</sup> There was also no difference in rescue medication use per day (pooled difference 0.06, 95% CI -0.19 to 0.07) or rescue-free days (per 12 weeks; 54 vs. 49). This evidence is moderate strength. The study comparing FF 100 mcg/VIL 25 mcg once daily with FF 500 mcg/SAL 50 mcg twice daily also found similar percentages of rescue-free days at 12 weeks (62.5% vs. 59.8%) and no statistically significant difference in the change in SGRQ total score at week 12 (-4.3 vs. -3.0; least-squares mean difference -1.3, 95% CI -3.5 to 0.8).<sup>15</sup> No exacerbations were reported. This evidence is low strength.

#### *b. Long-acting muscarinic antagonists (LAMAs) and long-acting beta-2 agonists (LABAs) compared with long-acting muscarinic antagonists (LAMAs) and long-acting beta-2 agonists (LABAs)*

### **Summary of findings**

#### ***Asthma***

- No eligible studies.

#### ***COPD***

- *Glycopyrrolate (GLY)/indacaterol (IND) compared with tiotropium (TIO)/formoterol (FOR)*

- Based on a good-quality RCT, there was low-strength evidence that there is not a statistically significant difference in moderate to severe exacerbations or in quality of life measures between drugs. GLY/IND was found non-inferior to TIO/FOR on quality of life.



## Detailed assessment

### Asthma

- No eligible studies.

### COPD

*Glycopyrrolate (GLY)/indacaterol (IND) compared with tiotropium (TIO)/formoterol (FOR)*  
A good-quality 26-week study (QUANTIFY) of GLY 50 mcg / IND 110 mcg daily (in a fixed-dose DPI) compared with TIO 18 mcg/ FOR 24 mcg daily (separate DPI inhalers) enrolled 934 patients with moderate (57%) to severe (42%) COPD.<sup>140</sup> The mean age was 63 years, and 66% were male. This study provides low-strength evidence (Appendix E, Table E-17) of no difference in moderate or severe exacerbations (62% GLY/IND vs. 70% TIO/FOR; RR 0.85, 95% CI 0.62 to 1.17). The study was designed as a non-inferiority trial with health-related quality of life as the primary outcome, using the SGRQ scale. At 26 weeks, the difference between groups in mean change from baseline (−0.69, 95% CI −2.31 to 0.92) was not statistically significantly different between groups and met criteria for non-inferiority. Analysis of the proportion of patients who had improvement of at least 4 points on the SGRQ (deemed the minimum clinically important difference) also a non-statistically significant difference (46.0% GLY/IND vs. 41.5% TIO/FOR; RR 1.11, 95% CI 0.96 to 1.28). This evidence is moderate strength.

## II. Inter-class Comparisons (between classes)

### A. Monotherapy

#### a. Inhaled corticosteroids (ICSs) compared with leukotriene modifiers (LMs)

### Summary of findings

#### Asthma

- *Fluticasone propionate (FP) compared with montelukast (MON)*
  - High-strength evidence showed fewer exacerbations (OR 0.70, 95% CI 0.57 to 0.86; 10 trials) and greater improvement in quality of life (AQLQ −0.15,  $P$ =NS; 9 trials) with FP than with MON.
  - One trial provided low-strength evidence of fewer emergency department visits (0.10 vs. 0.35,  $P$ =0.002) and missed school days (1.4 vs. 2.1,  $P$ <0.001) with FP than with MON, though physician visits and work days did not differ.
- *Beclomethasone (BEC) compared with montelukast (MON)*
  - Six fair-quality trials provided moderate-strength evidence that exacerbation rates were lower with BEC than with MON (SMD −0.15, 95% CI −0.30 to 0.00).
- *Budesonide (BUD) compared with montelukast (MON)*
  - Differences in reported outcomes were either not statistically significant, or favored BUD (low- to moderate-strength evidence).
- *Fluticasone (FP) compared with zafirlukast (ZAF)*
  - Four fair-quality trials provided high-strength evidence of lower exacerbation rates with FP than with ZAF (SMD −0.21, 95% CI −0.31 to −0.11).

## **COPD**

- No eligible studies.

## **Detailed assessment**

### ***Asthma***

We found 25 fair-quality RCTs<sup>38,46,141-166</sup> comparing ICSs with LMs in patients with asthma. Fifteen of the RCTs were in adolescents and adults  $\geq 12$  years of age and 8 (11 articles) were in children  $< 12$ .<sup>141,143,148,149,156,159,161,162,166,167</sup> Most studies were pharmaceutically-funded, with 76% reporting funding from pharmaceutical companies.

### ***Fluticasone propionate (FP) compared with montelukast (MON)***

We found 10 fair-quality RCTs (14 publications) that compared MON with FP<sup>141,146,148,149,155-159,162,163,166,168</sup> in patients with asthma that met our inclusion criteria. Our meta-analyses of outcomes from these trials show that patients treated with FP had greater improvement in quality of life (AQLQ scores: SMD  $-0.15$ , 95% CI  $-0.25$  to  $-0.06$ , 4 studies) and fewer exacerbations (OR 0.70, 95% CI 0.57 to 0.86, 5 studies), than those treated with MON. Patients treated with FP also had a greater increase in the proportion of days free from rescue medication use (7 studies), greater reduction in rescue medicine use per day (5 studies), greater increase in the proportion of symptom-free days (6 studies), greater improvement in symptom score (4 studies), and fewer nocturnal asthma symptoms requiring albuterol (1 study, median 2.0 for FP vs. 6.5 for MON,  $P=0.005$ ).<sup>167</sup> An analysis of a subset of participants<sup>163</sup> from 1 trial<sup>159</sup> of children age 6 to 14 years found that participants treated with FP had fewer emergency department visits and missed school days than those taking MON, and differences were statistically significant. Differences between FP and MON for physician's visits and missed work were not statistically significant, though patients taking FP appeared to miss fewer days of work ( $P=0.06$ ). It was not clear in this population of children under 15 whether it was participants or their caregivers whose work was analyzed. This study included only the monotherapy arms of the larger trial, and also excluded subjects who did not complete the trial or had missing cost-effectiveness data (19.4% excluded from the 2 treatment arms), which could bias its results. Baseline age and sex were comparable, though smoking was not reported.

### ***Beclomethasone (BEC) compared with montelukast (MON)***

Six fair-quality RCTs<sup>142,143,150,152-154,164</sup> meeting inclusion criteria compared MON with BEC. Most of the outcomes reported favored BEC over MON or found no difference between groups. In general, the results comparing BEC with MON appear to be consistent with the overall results comparing ICSs with LMs. Our meta-analysis shows that compared with MON-treated patients, those treated with BEC had fewer exacerbations (SMD  $-0.15$ , 95% CI  $-0.30$  to  $-0.002$ ). The 6 trials also showed a trend toward more rescue free days and symptom-free days with BEC than with MON.

The only trial enrolling children  $< 12$  years of age was a fair-rated multinational, multi-center RCT in children (N=360) comparing MON 5 mg/day (N=120) with medium dose BEC 400 mcg/day (N=119) for 56 weeks.<sup>143</sup> Subjects with mild persistent asthma, age 6.4 to 9.4 for boys and 6.4 to 8.4 for girls were enrolled worldwide. The primary objective of the trial was to assess the effects of MON and BEC on linear growth; however, some of our primary outcomes of interest were also reported. Fewer subjects treated with MON or BEC had asthma reported as an adverse experience compared with those treated with placebo, but the difference between

groups was not statistically significant (36.7% vs. 42.9% vs. 50.4%,  $P=NS$  for MON vs. BEC). There were no statistically significant differences in the percentage of patients requiring oral steroids (25% vs. 23.5%), the percentage requiring more than 1 course of oral steroids (5.8% vs. 5.9%), or the percentage of days of beta-agonist use (10.55% vs. 6.65%) between those treated with MON and those treated with BEC.

#### *Budesonide (BUD) compared with montelukast (MON)*

We found 4 fair-quality RCTs comparing BUD with MON<sup>46,160,161,165</sup> that met most of our inclusion criteria in patients with asthma. Three of the 4 studies enrolled less than the 100 subjects our update inclusion criteria required, but we retained these data since limited evidence was available for this comparison. Too few studies reported sufficient data for meta-analysis of our included outcomes. Of the 4 RCTs, 1 enrolled adult populations,<sup>165</sup> 1<sup>160</sup> enrolled children and adolescents ages 6-18, 1<sup>161,169</sup> enrolled children ages 2 to 8, and 1 enrolled children aged 2 to 18 in India. Most subjects in these trials had mild persistent asthma. Study duration ranged from 12 to 52 weeks. The reported outcomes of interest were either not statistically significantly different between the 2 groups, or favored BUD. For symptoms, 2 trials<sup>160,165</sup> reported no statistically significant differences between groups. One trial found a statistically significant difference for BUD compared with MON in improvement in daytime symptoms that favored BUD (95% CI -0.48 to -0.11, mean days/week with symptoms,  $P=0.03$ ; point estimate NR), but no difference between groups for nighttime symptoms. Two trials reporting exacerbations found more favorable results for those treated with BUD than those treated with MON,<sup>161,165</sup> including results in patients ages 2 to 4 years (see Key Question 3).<sup>169</sup> The single trial reporting quality of life found no difference between the treatments for overall quality of life measures in patients age 2 to 8 years.<sup>161</sup>

#### *Fluticasone propionate (FP) compared with zafirlukast (ZAF)*

We found 4 fair-quality RCTs comparing FP with ZAF<sup>144,145,147,151</sup> that met our inclusion criteria. All 4 trials show similar results favoring FP over ZAF for symptoms, rescue medicine use, and quality of life. Our meta-analysis again showed that subjects treated with FP had fewer exacerbations (SMD 0.21, 95% CI -0.31 to -0.11, 4 studies) than those treated with ZAF.

### *b. Inhaled corticosteroids (ICSs) compared with long-acting beta-2 agonists (LABAs)*

## **Summary of findings**

### ***Asthma***

- *Beclomethasone (BEC) compared with salmeterol (SAL)*
  - Three fair-quality trials provided moderate-strength evidence of no difference between drugs or better outcomes for those treated with BEC.
- *Budesonide (BUD) compared with formoterol (FOR)*
  - Trend toward fewer symptoms, nocturnal awakenings, and exacerbations, and toward less rescue medicine use (moderate-strength evidence from 2 fair-quality trials).
- *Fluticasone propionate (FP) compared with formoterol (FOR)*
  - Two trials provided low-strength evidence of no difference in exacerbations.
- *Fluticasone propionate (FP) compared with salmeterol (SAL)*

- Seven fair-quality trials showed no difference or a trend toward better outcomes in those treated with FP compared with those treated with SAL.
- *Mometasone (MOM) compared with formoterol (FOR)*
  - Moderate-strength evidence from 2 trials suggested fewer asthma deteriorations (RR 0.63, 95% CI 0.50 to 0.79) or clinically judged deteriorations (RR 0.34, 95% CI 0.17 to 0.67) with MOM than with FOR.

## **COPD**

- *Budesonide (BUD) compared with formoterol (FOR)*
  - Low-strength evidence from meta-analysis of 2 studies suggested no difference in mortality or exacerbations between groups. Differences in quality of life scores (SGRQ) or symptoms scores were also not statistically significantly different between drugs.
- *Fluticasone propionate (FP) compared with salmeterol (SAL)*
  - Low-strength evidence based on a meta-analysis of 2 studies suggested that mortality was increased with FP compared with SAL (OR 1.23, 95% CI 1.01 to 1.51). There were no deaths reported in the other 2 studies.
  - Low-strength evidence based on a meta-analysis of 2 studies suggested significantly greater improvement in SGRQ quality of life scores with FP (mean difference -0.77, 95% CI -1.49 to -0.06, 2 studies).
  - Moderate-strength evidence from 3 studies found no differences between groups in exacerbation rates (RR 0.97, 95% CI 0.91 to 1.05) or hospitalizations due to exacerbations (RR 1.07, 95% CI 0.91 to 1.26).
- *Mometasone furoate (MOM) compared with formoterol (FOR)*
  - One good-quality<sup>170</sup> and 1 fair-quality RCT<sup>171</sup> of 26 weeks duration compared MOM 400 mcg with FOR 10 mcg (combined N=915). Combined, the mean age of subjects was 60 years and 77% were male. Approximately 48% were current smokers.
  - Low-strength evidence from 2 trials suggested no difference between MOM and FOR in mean change in SGRQ quality of life scores or exacerbation rates in either study (exact values not reported).

## **Detailed assessment**

### ***Asthma***

We found 17 fair- or good-quality RCTs<sup>41,172-190</sup> that included head-to-head comparisons of 1 ICS with 1 LABA in patients with asthma meeting our inclusion/exclusion criteria. Thirteen of these were multi-arm trials that compared an ICS/LABA combination product with the individual ICS and LABA components.<sup>41,172-181,187-190</sup> In some studies patients were treated with a fixed-dose combination of budesonide and formoterol via DPI. This fixed-dose combination product is not available in the United States, but because the same drugs are available individually in DPI formulations, we included evidence from several such studies.<sup>20,56-63</sup> Most trials were conducted primarily in adult populations. Four studies<sup>41,185,186,188</sup> included pediatric or adolescent populations. Asthma severity ranged from mild to severe persistent but was most commonly not reported. Most studies excluded current smokers or those with a recent history of smoking. Study duration ranged from 12 weeks to 12 months. Of the 17 trials, 14 (82%) reported funding by pharmaceutical companies.

*Fluticasone propionate (FP) compared with salmeterol (SAL)*

Seven fair-quality RCTs compared FP with SAL for monotherapy.<sup>172,174-178,180,181,187</sup> None included children ≤12 years of age. All 7 also included comparisons with an FP/SAL combination product. Study duration was 12 weeks for 6 trials and 12 months for 1 trial.<sup>174</sup> Four compared SAL with low-dose FP and 3 compared SAL with medium-dose FP. Six of the 7 were conducted in the United States; 1 was conducted in Sweden.<sup>174</sup>

The majority of trials assessed asthma symptoms, nocturnal awakenings, exacerbations, and rescue medicine use. Two trials<sup>177,180</sup> reported quality of life. The majority of trials found no difference or a trend toward better outcomes in those treated with FP compared with those treated with SAL (Evidence Tables A and B).

*Beclomethasone (BEC) compared with salmeterol (SAL)*

Three fair-quality RCTs compared BEC with SAL.<sup>184-186</sup> One<sup>184</sup> enrolled adolescents and adults ≥12 years of age; the other 2 studies enrolled children and adolescents aged 6 to 14 years<sup>185</sup> or 6 to 16 years.<sup>186</sup> Study duration ranged from 26 weeks to 12 months. All 3 compared SAL with medium-dose BEC.

All 3 trials reported exacerbations and rescue medicine use; 2 reported symptoms<sup>184,186</sup> and nocturnal awakenings,<sup>184,185</sup> 1 reported missed school.<sup>185</sup> With the exception of 1 trial that reported greater improvement in the percentage of rescue-free days for those treated with SAL (36% vs. 28%,  $P=0.016$ ),<sup>184</sup> all 3 trials reported no differences or better outcomes for those treated with BEC than for those treated with SAL (Evidence Table A).

*Budesonide (BUD) compared with formoterol (FOR)*

Two fair-quality 12-week multicenter RCTs<sup>173,179</sup> compared BUD with FOR in adolescents and adults aged ≥12 years. The results showed trends toward fewer exacerbations and greater improvements in symptoms, nocturnal awakenings, and rescue medicine use for those treated with BUD (Evidence Table A). Whether these trends were statistically significantly different was not reported (the studies focused on comparing BUD/FOR with the other treatments).

*Mometasone furoate (MOM) compared with formoterol (FOR)*

Two fair-quality RCTs compared MOM 100 mcg<sup>189</sup> or 200 mcg<sup>190</sup> twice daily with FOR 10 mcg twice daily for 26 weeks in patients with asthma. Both studies included patients in over 150 sites in North America, Latin America, Europe, and Asia. In 1 trial (N=394, mean age 42 years, 39% male) 34% of MOM patients experienced an asthma deterioration at some point in the study compared with 54% of FOR patients (RR 0.63, 95% CI 0.50 to 0.79,  $P<0.001$ ).<sup>190</sup> Additionally, MOM was superior to FOR on the 7-point asthma quality of life questionnaire (mean change 0.50 vs. 0.31,  $P=0.04$ ) and in proportion of nights with nocturnal awakenings due to asthma requiring SABA use (0.11 for MOM and 0.17 for FOR,  $P<0.001$ ) but there was no difference between groups on a 7-point asthma control questionnaire ( $P=0.13$ ).

In the second trial (N=376, mean age 39 years, 44% male), treatment with MOM was associated with reduced clinically judged deteriorations (hospitalizations, emergency treatment or treatment with corticosteroids) compared with FOR (RR 0.34, 95% CI 0.17 to 0.67,  $P=0.002$ ).<sup>189</sup>

### *Fluticasone propionate (FP) compared with formoterol (FOR)*

We identified 2 good-quality 12-week RCTs with similar design comparing FP 200 mcg daily with FOR 20 mcg daily (both by MDI) in patients with mild to moderate asthma.<sup>41,188</sup> Both trials included a third group given combination therapy, which we do not report here. Together the 2 trials included 477 patients given 1 of the monotherapies. Patients were  $\geq 12$  years old with a mean age of 38 years and 58% were female. Current smokers were excluded, as well as those with a smoking history of at least 10 pack-years. ICS use within the 4 weeks preceding screening was required for one study,<sup>188</sup> and allowed in the other.<sup>41</sup> Exacerbations were similar with FP compared with FOR (RR 0.81, 95% CI 0.58 to 1.13,  $P=0.21$ ; low-strength evidence).<sup>41,188</sup> There was little difference in rescue medication-free days (43.3% vs. 41.9%) and symptom-free days (37.3% vs. 38.0%) when treated with FP compared with FOR, respectively, though statistical significance was not reported for the FP vs. FOR comparison.<sup>188</sup>

### **COPD**

#### *Budesonide (BUD) compared with formoterol (FOR)*

We identified 1 good-quality systematic review of ICS compared with LABA in patients with COPD.<sup>191</sup> The review included 3 RCTs (combined  $N=1,470$ ) that compared BUD with FOR. The daily FOR dose for all studies was 18 mcg; for 2 studies the daily BUD dose was 800 mcg, with a daily dose of 640 mcg in the third study. All studies were multicenter, double-blind RCTs from 6 months to 1 year duration. The mean age of participants was 64 years with 67% to 78% males. In a meta-analysis of 2 studies, there was no difference in mortality between groups, although the pooled estimate favored a reduction with BUD (OR 0.62, 95% CI 0.31 to 1.22). There was also no difference in exacerbation rates also based on the results from 2 studies (RR 0.86, 95% CI 0.73 to 1.03) and a non-significant improvement in SGRQ quality of life scores with BUD (mean difference  $-0.51$ , 95% CI  $-2.63$  to 1.61, 1 study) but a non-significant improvement in symptom scores with FOR (mean difference  $-0.22$ , 95% CI  $-0.47$  to 0.03, 3 studies).

#### *Fluticasone propionate (FP) compared with salmeterol (SAL)*

We identified 1 good-quality systematic review of ICS compared with LABA in patients with COPD.<sup>191</sup> The review included 7 RCTs (combined  $N=5,997$ ) and all met inclusion criteria for this report. All studies were rated unclear to low risk of bias on randomization, allocation concealment, blinding, completeness of data and selective reporting. All studies were multicenter, double-blind RCTs with durations of 6 months to 3 years. The mean age of participants was 64 years with 62% to 78% males. Four studies compared FP with SAL. Three studies compared BUD with FOR. The daily SAL dose for all studies was 100 mcg; for 3 studies, including the largest study, the daily FP dose was 1,000 mcg, with a daily dose of 500 mcg in the fourth study. All studies were multicenter, double-blind RCTs from 6 months to 3 years duration. The mean age of participants was 64 years with 62% to 76% males.

In a meta-analysis of 2 studies, mortality was increased with FP compared with SAL (OR 1.23, 95% CI 1.01 to 1.51). There were no deaths reported in the other 2 studies. Three studies reported exacerbation rates and found no difference between fluticasone groups and SAL groups (risk ratio 0.97, 95% CI 0.91 to 1.05) with no difference in hospitalizations due to exacerbations (risk ratio 1.07, 95% CI 0.91 to 1.26). However, there was significant improvement in SGRQ quality of life scores with fluticasone (mean difference  $-0.77$ , 95% CI  $-1.49$  to  $-0.06$ , 2 studies).

### *Mometasone furoate (MOM) compared with formoterol (FOR)*

One good-quality<sup>170</sup> and 1 fair-quality RCT<sup>171</sup> of 26 weeks duration compared MOM 400 mcg with FOR 10 mcg (combined N=915). Combined, the mean age of subjects was 60 years and 77% were male. Approximately 48% were current smokers. There was no difference between mometasone and FOR in mean change in SGRQ quality of life scores in either study (exact values not reported). Thirty-three percent of patients treated with MOM experienced a COPD exacerbation compared with 40% of patients treated with FOR in 1 study (RR 0.82, 95% CI 0.65 to 1.04,  $P=0.10$ ).<sup>171</sup>

### *c. Leukotriene modifiers (LMs) compared with long-acting beta-2 agonists (LABAs)*

#### **Summary of findings**

##### ***Asthma***

- *Montelukast (MON) compared with salmeterol (SAL)*
  - Evidence from a single trial was insufficient to draw conclusions.
- *Montelukast (MON) compared with formoterol (FOR)*
  - Evidence from a single trial was insufficient to draw conclusions.

#### **Detailed assessment**

##### ***Asthma***

We found 2 fair-quality RCTs (N=249)<sup>192,193</sup> that included head-to-head comparisons of 1 LM with 1 LABA meeting our inclusion/exclusion criteria in patients with asthma. One 8-week trial compared MON with SAL<sup>192</sup> and one 18-week trial compared MON with eFOR.<sup>193</sup> Both were conducted primarily in adult populations. One was conducted in the United States<sup>192</sup> and 1 in Australia.<sup>193</sup> One trial included patients with moderate to severe asthma,<sup>193</sup> while asthma severity was not reported in the second trial.<sup>192</sup> Both trials excluded current smokers or those with more than a 10 to 15 pack-year history.

##### ***Montelukast (MON) compared with salmeterol (SAL)***

One fair-quality RCT (N=191) compared MON 10 mg/day (N=97) with SAL 100 mcg/day (N=94) as monotherapy for 8 weeks.<sup>192</sup> 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 MON group and 1 in the SAL group ( $P=NR$ ).

##### ***Montelukast (MON) compared with formoterol (FOR)***

One fair-quality cross-over RCT (N=58) compared eFOR 24 mcg/day with MON 10 mg/day (6 weeks of treatment, 1-week washout, 6 weeks of treatment with the other medication, 1-week washout, then all subjects received FP 500 mcg/day for 6 weeks).<sup>193</sup> 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 MON and eFOR comparison because the fluticasone propionate portion of the study does not have a comparison. Over the 12 weeks of treatment, subjects treated with eFOR had fewer symptoms (percentage of symptom-free days: 23 vs. 0;  $P=0.01$ ; symptom scores: 1.2 vs. 1.6;  $P=0.02$ ), less rescue medicine use

(percentage of rescue-free days: 40 vs. 30;  $P=0.008$ ), and better quality of life (score: 0.4 vs. 0.6;  $P=0.001$ ) compared with those treated with MON.

*d. Long-acting beta-2 agonists (LABAs) compared with long-acting muscarinic antagonists (LAMAs)*

**Summary of findings**

**Asthma**

- Three trials comparing SAL with TIO found no differences between the groups in rates of exacerbation or quality of life (low-strength evidence)
- One trial comparing SAL with TIO found no difference between groups in asthma symptoms assessed using the Asthma Control Questionnaire (insufficient evidence).

**COPD**

- A systematic review included in the prior report found increased exacerbations associated with SAL than with TIO (36% vs. 32%; pooled OR 1.19, 95% CI 1.09 to 1.30; moderate-strength evidence), with no differences in hospitalizations or quality of life (low-strength evidence)
- One trial of FOR compared with TIO found no difference in rates of exacerbations (insufficient evidence)
- Evidence from 3 trials of IND compared with TIO suggested that IND is associated with more frequent exacerbations (RR 1.11, 95% CI 1.03 to 1.19), with similar effects on mortality (1.4% vs. 1.5%) and quality of life (SGRQ improvement  $\geq 4$  points: OR 1.03, 95% CI 0.88 to 1.21) in patients with severe COPD. In patients with moderate-to-severe COPD, quality of life improved in fewer patients receiving TIO than IND (42% vs. 50%; RD  $-0.08$ , 95% CI  $-0.13$  to  $-0.03$ ), with no differences in hospitalizations or exacerbations (low-strength evidence).

**Detailed assessment**

**Asthma**

*Salmeterol (SAL) compared with tiotropium (TIO)*

The prior review included 2 fair-quality RCTs<sup>194,195</sup> comparing SAL with TIO in patients whose asthma was not adequately controlled by inhaled corticosteroids. Both of these trials found that SAL and TIO had similar effects on exacerbations and quality of life.

We identified 1 additional trial comparing SAL 50  $\mu\text{g}$  and TIO 2.5 or 5  $\mu\text{g}$ .<sup>31</sup> The relatively large (N=2,100), good-quality study enrolled symptomatic adults (mean age, 43.1 years; 59% female) with asthma diagnosed before age 40, FEV1 60% to 90% of predicted, and who were never-smokers or who quit at least 1 year prior with total pack-years  $\leq 10$ . Over 24 weeks of treatment, severe exacerbations were experienced by 4% to 6% of patients in each group, with no significant differences between groups. Quality of life and Asthma Control Questionnaire scores also did not differ between the groups.



## **COPD**

### ***Salmeterol (SAL) compared with tiotropium (TIO)***

The prior report included a good-quality Cochrane review assessing the effectiveness of SAL compared with TIO.<sup>196</sup> Based on data from 4 trials (total N=8,936; durations ranging from 12 weeks to 12 months), the review found that SAL was associated with increased exacerbations compared with TIO (32%; pooled OR 1.19, 95% CI 1.09 to 1.30), with no differences in hospitalizations (5.2% vs. 2.4%; OR 2.22, 95% CI 0.94 to 5.26) or quality of life.

We identified no new evidence for this comparison.

### ***Formoterol (FOR) compared with tiotropium (TIO)***

The prior report included 1 systematic review that included 1 study comparing FOR with TIO. No significant difference was found between groups in rates of exacerbations (OR 1.32, 95% CI 0.68 to 2.55), with no data on hospitalizations or quality of life.

We identified no new evidence for this comparison.

### ***Indacaterol (IND) compared with tiotropium (TIO)***

The prior report included 1 trial comparing indacaterol and tiotropium in patients with severe COPD. The INVIGORATE trial found that exacerbations were more frequent in patients receiving IND than TIO (RR 1.11, 95% CI 1.03 to 1.19), with similar effects on mortality (1.4% vs. 1.5%) and quality of life (SGRQ improvement  $\geq 4$  points: OR 1.03, 95% CI 0.88 to 1.21). The report also included a systematic review of 2 earlier studies conducted in a broader population of patients with moderate-to-severe COPD. Improvements in quality of life were noted in a smaller proportion of patients receiving TIO than IND (42% vs. 50%; RD -0.08, 95% CI -0.13 to -0.03). The review found no differences between groups in hospitalizations or exacerbations.

We identified no new studies for this comparison.

## ***Inhaled corticosteroids (ICSs) compared with phosphodiesterase-4 (PDE-4) inhibitors***

One trial comparing an ICS to a PDE-4 inhibitor in patients with asthma met our inclusion/exclusion criteria (Table 17).<sup>197</sup> The trial included adolescents and adults ages 12 to 70 years in Europe and the UK. Patients taking BDP had fewer exacerbations than those taking roflumilast (RF); we calculated an exacerbation risk 3 times greater for RF than BDP, but the confidence interval was wide (RR 3.16, 95% CI 1.10 to 9.11). The investigators concluded that RF was noninferior to BDP for asthma symptoms and rescue medicine use. We did not find any trials of PDE-4 inhibitors in patients with COPD.

Overall, limited head-to-head evidence from 1 trial<sup>197</sup> suggested RF is noninferior to BDP in reducing symptoms and rescue medicine use in patients with asthma, though there was a trend towards more exacerbations in patients taking RF compared with those taking BDP.

### ***Beclomethasone (BDP) compared with roflumilast (RF)***

One fair-rated trial comparing BDP with RF met our inclusion/exclusion criteria.<sup>197</sup> The trial had a noninferiority design and enrolled 499 patients ages 12 to 70 years with moderate persistent asthma, according to the trial's reported inclusion and exclusion criteria, from centers in Europe and the UK. Effects of 500 mcg/day of RF or 400 mcg/day BDP on exacerbations, symptoms, and rescue medication use were reported.

Fewer patients taking BDP experienced asthma exacerbations, with 4 exacerbations in the BDP group (2% of these patients) and 13 in the RF arm (5%), for a relative risk of 3.2 comparing

RF with BDP (95% CI 1.1 to 9.1, calculated for this review). Improvements in asthma symptom scores and rescue medication use were similar between the 2 treatment arms. BDP reduced rescue medicine use from baseline by 1.15 puffs/day, compared with a decrease of 1.00 puffs/day for RF ( $P=0.0171$ ), but the investigators did not consider the difference clinically meaningful. Asthma symptoms during the day and night were scored on scales from 0 to 4, with higher scores for symptoms disrupting activities and sleep. Symptom scores declined more from baseline for BDP than RF ( $-1.00$  vs.  $-0.82$ ), but the difference was not statistically significant ( $P=0.09$ ). The study investigators concluded that RF was noninferior to BDP for asthma symptoms and rescue medicine use, though they did not comment on the difference in exacerbations reported and whether they would consider it clinically meaningful.

**Table 5. Characteristics of head-to-head studies comparing inhaled corticosteroids and PDE-4 inhibitors in children and adults with asthma**

Study	Study design N Duration	Country Study population Setting	Comparison (total daily dose in mcg/day)	Quality rating
<b>Beclomethasone dipropionate compared with roflumilast</b>				
Bousquet et al. 2006 <sup>197</sup>	RCT  499  12 weeks	France, Germany, Great Britain, and Spain  Age 12-70, moderate asthma, 70% non-smokers, 30% ex- smokers  Multicenter, setting NR	BDP (400) vs. RF (500)	Fair

Abbreviations: BDP, beclomethasone dipropionate; NR, not reported; RCT, randomized controlled trial, RF, roflumilast.

## B. Combination therapy vs. monotherapy

### a. Inhaled corticosteroid (ICS) and long-acting beta-2 agonist (LABA) compared with LABA

#### Summary of findings

##### *Asthma*

- No eligible studies.

##### *COPD*

- Switch to indacaterol (IND) compared with continued salmeterol (SAL)/fluticasone propionate (FP)
  - One good-quality trial provided low-strength evidence that exacerbation rates did not differ between patients switching to IND and those continuing treatment with SAL/FP.

## Detailed assessment

### COPD

The INSTEAD trial<sup>45</sup> enrolled patients with moderate-severity COPD who had been treated before enrollment with SAL/FP 100/1,000 mcg daily by DPI, and compared continued treatment with SAL/FP with switching to IND 150 mcg daily by DPI for 26 weeks. The dose of IND is higher than that approved by the US Food and Drug Administration. All patients enrolled had at least a 10 pack-year smoking history; 69% were men, and the mean age was 66 years. We rated this trial as fair quality for the quality of life outcome, because 17% of patients in the full analysis set were excluded from the analysis; however, for other outcomes we rated the trial as good quality.

INSTEAD provided low-strength evidence that exacerbation rates did not differ between treatment arms (IND vs. SAL/FP, RR 0.86, 95% CI 0.62 to 1.20). The trial provided insufficient evidence to compare the quality of life outcome across treatment arms. There was no statistically significant difference in the percent of days with no rescue medication use between treatment arms (IND vs. SAL/FP: 52.8% vs. 54.6%, -1.8%, 95% CI -7.2 to 3.6).

#### *b. Inhaled corticosteroid (ICS) and long-acting beta-2 agonist (LABA) compared with inhaled corticosteroid (different drug)*

## Summary of findings

### Asthma

- *Budesonide (BUD)/formoterol (FOR) compared with fluticasone propionate (FP)*
  - Evidence from a fair-quality study provided insufficient evidence to draw conclusions on exacerbations. Other eligible outcomes not reported.
- *Fluticasone propionate (FP)/salmeterol (SAL) compared with ciclesonide (CIC)*
  - Evidence from a fair-quality study provided insufficient evidence to draw conclusions on quality of life or exacerbation rates. Other eligible outcomes not reported.
- *Fluticasone furoate (FF)/vilanterol (VIL) compared with fluticasone propionate (FP)*
  - Low-strength evidence from 3 good-quality trials indicated no statistically significant difference in severe exacerbation rates; pooled RR 0.38 (95% CI 0.04 to 3.98).
  - Low-strength evidence from 2 trials did not find important differences between drugs in quality of life scores using the AQLQ.

### COPD

- We found no eligible studies.

## Detailed assessment

### Asthma

We identified 5 RCTs that compared the combination of an ICS and LABA to a different ICS (at any dose), in patients with asthma. One trial compared BUD/FOR with FP, 1 FP/SAL with CIC, and 3 compared FF/VIL with FP. We identified no studies of this comparison in patients with COPD.

*Budesonide (BUD)/formoterol (FOR) compared with fluticasone propionate (FP)*

One fair-quality trial conducted in Brazil compared 12 weeks of BUD/FOR (administered separately) to FP in 163 patients with mild to moderate asthma.<sup>16</sup> The trial also included a comparison with fixed-dose FP and FOR (N=79), reported above with intra-class comparisons of combination products. All drugs were delivered via DPI, with daily doses of BUD/FOR 800/24 mcg and FP 1,000 mcg and 73% of patients were female. The trial reported asthma exacerbations as adverse events, but provided insufficient evidence (Appendix E, Table E-12) to compare them across treatment arms (BUD/FOR vs. FP, 0.96, 95% CI 0.50 to 1.87).

*Fluticasone propionate (FP)/salmeterol (SAL) compared with ciclesonide (CIC)*

We identified 1 fair-quality RCT (N=432) in patients with mild persistent asthma who were randomized to CIC 160 mcg once daily or FP/SAL 200/100 twice daily.<sup>198</sup> Patients were  $\geq 12$  years of age (mean age 30 years), 43% male, non- or ex-smokers with a smoking history of  $< 10$  pack years. Quality of life scores on the AQLQ were significantly improved with CIC compared with FOR/SAL (mean change 0.36 vs. 0.27,  $P < 0.0001$ ) although there was no difference between treatments on asthma symptom-free days or asthma symptom scores ( $P = 0.06$ ,  $P = 0.75$ , respectively). The probability of experiencing a severe asthma exacerbation was significantly greater in the CIC group compared with the FP/SAL group (0.30 vs. 0.18; calculated RR 1.67, 95% CI 1.18 to 2.36). This evidence is low strength (Appendix E, Table E-12).

*Fluticasone furoate (FF) and vilanterol (VIL) compared with fluticasone propionate (FP)*

We identified 3 RCTs that compared FF/VIL 200/25 mcg daily with FP 1,000 mcg daily via DPI.<sup>34,39,199</sup> Two studies also included a third arm of a lower dose of 1 of the drugs, but not the same across the 2 studies. Two studies were good quality<sup>39,199</sup> and 1 was fair quality.<sup>34</sup> The studies ranged in duration from 12 to 52 weeks, had mean percent male of 40%, and a total sample size of 1,204 for the comparison assessed here. The 52-week, good-quality trial was designed to measure adverse events; this study reported serious exacerbations, which are reported here as a measure of relative benefit.

Based on meta-analysis, these studies provide low-strength evidence of no difference in the incidence of severe exacerbations with FF/VIL compared with FP (1.3% vs. 1.8%, RR 0.377, 95% CI 0.04 to 3.98;  $I^2 = 78\%$ ). This evidence is low-strength because there is heterogeneity in the findings (Appendix E, Table E-12). Sensitivity analysis removing the 52-week study resulted in similar findings.

Two of the trials reported change in quality of life using the ASQL scale, with neither finding a statistically significant difference at 12 or 24 weeks.<sup>34,39</sup> At 12 weeks the study in China found least squares mean change from baseline of 0.80 with FF/VIL compared with 0.69 with FP (difference 0.12, 95% CI -0.08 to 0.32).<sup>34</sup> At 24 weeks, the other study found changes from baseline of 0.93 vs. 0.90 (0.03, 95% CI -0.16 to 0.21), respectively.<sup>39</sup> These 2 trials also assessed rescue-free days at 12 and 24 weeks.<sup>34,39</sup> While neither study found a statistically significant difference, the larger, good quality study found that the FF/VIL group had 38.2% rescue-free days, compared with 31.9% in the FP group – close to being a statistically significant difference (6.3%, 95% CI -0.4 to 13.1).<sup>39</sup> This study also assessed symptom-free days, again not finding a statistically significant difference (4.9%, 95% CI -1.6 to 11.3). The other study, conducted in China, found a difference of 1% (95% CI -7.3 to 9.2). This study also assessed

symptom-free days, again not finding a statistically significant difference (4.9%, 95% CI –2.8 to 12.5).<sup>34</sup>

*c. Inhaled corticosteroid (ICS) and long-acting beta-2 agonist (LABA) compared with long-acting muscarinic antagonist (LAMA)*

**Summary of findings**

***Asthma***

- No eligible studies.

***COPD***

- *Tiotropium (TIO) compared with fluticasone propionate (FP)/salmeterol (SAL)*
  - There was low-strength evidence that, compared with TIO, FP/SAL was associated with lower risk of mortality, higher risk of hospitalization and a higher proportion of patients with a clinically significant improvement in quality of life and no difference in effects on exacerbations
- *Tiotropium (TIO) compared with vilanterol (VIL)/fluticasone furoate (FF)*
  - There was low-strength evidence of no statistically significant difference between TIO and FF/VIL in mortality
- *Tiotropium (TIO) compared with fluticasone furoate (FF)/vilanterol (VIL)*
  - There was low-strength evidence that TIO and FF/VIL do not differ in their effects on mortality and insufficient evidence to draw conclusions about hospitalizations, exacerbations and quality of life
- *Tiotropium (TIO) compared with umeclidinium bromide (UME)/vilanterol (VIL)*
  - For the comparison of UME/VIL 62.5/25 mcg versus TIO 18 mcg, 3 unpublished RCTs provided low-strength evidence of no statistically significant difference in risk of mortality or quality of life.

**Detailed assessment**

For the comparison of TIO and FP/SAL, we included a good-quality Cochrane review<sup>200</sup> of 2 eligible RCTs in patients with COPD.<sup>201,202</sup> For the comparison of TIO versus FF/VIL, we included 2 fair-quality, unpublished, 12-week RCTs (N=880).<sup>13,14,203,204</sup>

*Tiotropium (TIO) compared with fluticasone propionate (FP)/salmeterol (SAL)*

We included a good-quality Cochrane review<sup>200</sup> that included 3 RCTs<sup>201,202,205</sup> that compared TIO to FP/SAL in 1528 participants with COPD. Two of these RCTs met our inclusion criteria.<sup>201,202</sup> The third trial did not meet our criteria because it was published in a non-English language; consequently, we do not discuss its results here.<sup>205</sup> The end date of the Cochrane review search was November 2012 and we did not identify any new trials published since that time.

Both eligible trials compared TIO 18 mcg/day to FP/SAL 500/50 mcg/day. The INSPIRE RCT (Investigating New Standards for Prophylaxis in Reduction of Exacerbations) randomized 1,323 participants and had a 2-year follow-up.<sup>201</sup> The unpublished RCT randomized 125 participants and had a 12-week follow-up.<sup>202</sup> Because of the variation in follow-up duration, the Cochrane review authors did not pool data from these RCTs. The Cochrane review authors also

noted that both RCTs had a high risk of attrition bias: they suffered from high and imbalanced rates of withdrawal and they did not collect data on patients who withdrew.

INSPIRE provided low-strength evidence that FP/SAL was associated with a lower risk of mortality (OR 0.55, 95% CI 0.33 to 0.93) and more patients achieved a clinically important improvement in quality of life (increase of 4 or more units on the SGRQ, OR 1.29, 95% CI 1.04 to 1.60), but there was a higher risk of hospitalization (OR 1.32, 95% CI 1.04 to 1.67) with FP/SAL. There was no statistically significant difference between FP/SAL and TIO in exacerbations (OR 1.13, 95% CI 0.91 to 1.41). Data from the unpublished 12-week study did not add any additional evidence.

#### *Tiotropium (TIO) compared with fluticasone furoate (FF)/vilanterol (VIL)*

We included 2 fair-quality, unpublished, 12-week RCTs (N=880) that compared TIO 18 mcg/day to FF/VIL 100/25 mcg/day in patients with COPD who had or were at risk for comorbid cardiovascular disease.<sup>13,14,203,204</sup> These RCTs provide low-strength evidence of no statistically significant difference between TIO and FF/VIL in incidentally reported mortality (0.9% vs. 0%; OR 4.97, 95% CI 0.58 to 42.77). The unpublished reports of these RCTs did not provide any data on any additional effectiveness/efficacy outcomes of interest.<sup>203,204</sup> Both studies are now published.<sup>13,14</sup>

#### *Tiotropium (TIO) compared with umeclidinium bromide (UME)/vilanterol (VIL)*

We included 3 fair-quality, unpublished, 24-week RCTs (N=1,759) that compared UME/VI 62.5/25 mcg to TIO 18 mcg/day in patients with COPD (ZEP117115, DB2113374, DB2113360).<sup>206-208</sup> Data on deaths were available from the Result Summaries from the GSK Clinical Study Register. Deaths were rare, with only 0.3% in the UME/VIL group and 0.2% in the TIO group (OR 1.28, 95% CI 0.24 to 6.7), which provided low-strength evidence of no statistically significant difference between the 2 drugs. Additional unpublished data from studies DB2113374 and DB2113360 (N=1,694) on scores on the COPD Assessment Test (CAT), St. George's Respiratory Questionnaire (SGRQ), Transition Dyspnea Index (TDI) and Shortness of Breath with Daily Activities Questionnaire (SOBDA) and rescue albuterol use were provided by the manufacturer.<sup>209</sup> Data from these 2 trials provided low-strength evidence of no statistically significant differences between UME/VIL 125 mcg/25 mcg (not a US Food and Drug Administration-approved dose), 62.5 mcg/25 mcg or TIO in least squares mean change on the SGRQ Total Score (DB2113360: -9.03 vs. -6.87 vs. -7.62;  $P=0.346$  and  $P=0.607$ ; DB2113374: -10.52 vs. -9.95 vs. -9.78;  $P=0.588$  and  $P=0.904$ ). There were no consistent differences between UME/VIL 125 mcg/25 mcg, 62.5 mcg/25 mcg or TIO on TDI or SOBDA scores. Evaluation of differences between UME/VIL 125 mcg/25 mcg, 62.5 mcg/25 mcg or TIO on CAT scores was not reported. Reductions in number of puffs per day for rescue albuterol use were statistically significant greater for UME/VIL 125 mcg/25 mcg compared with TIO (DB2113374: -3.2 vs. -2.1,  $P<0.001$ ; DB2113360: -2.0 vs. -1.4;  $P=0.031$ ).

#### *d. Inhaled corticosteroids (ICS)/long-acting beta-agonists (LABAs) compared with leukotriene modifiers (LMs)*

### **Summary of findings**

#### ***Asthma***

- *Fluticasone propionate (FP)/salmeterol (SAL) compared with montelukast (MON)*
  - High-strength evidence from a meta-analysis of 5 RCTs found statistically significant fewer exacerbations with FP/SAL than with MON (SMD 0.26, 95% CI 0.16 to 0.35). Those treated with FP/SAL also had greater improvement in the percentages of symptom-free days and rescue medicine-free days than those taking MON.

#### ***COPD***

- No eligible studies.

### **Detailed assessment**

#### ***Asthma***

Five RCTs<sup>141,159,210-212</sup> included a total of 2,188 patients. Two of the RCTs were in adolescents and adults, 1 enrolled subjects over the age of 6<sup>141</sup> (~15% of subjects < 12 years of age), and 2 enrolled children ages 6-14.<sup>159,211</sup> Four trials were rated fair quality and 1<sup>212</sup> was rated good quality. Four studies were conducted in the United States and 1 study<sup>211</sup> was conducted at sites in both Latin America and Turkey. Asthma severity ranged from mild persistent to severe persistent: 2 studies enrolled subjects with mild to moderate persistent asthma, and 3 studies enrolled subjects with any severity of persistent asthma.

#### *Fluticasone propionate (FP)/salmeterol (SAL) compared with montelukast (MON)*

The 5 included studies are described below. We conducted a meta-analysis for exacerbations, and found a statistically significant difference favoring those treated with FP/SAL (SMD 0.26, 95% CI 0.16 to 0.35). Those treated with FP/SAL also had greater improvement in the percentages of symptom-free days and rescue medicine-free days than those taking MON.

The 5 studies included 1 good-quality RCT<sup>212</sup> and 4 fair-quality RCTs.<sup>141,159,210,211</sup> The good-quality RCT (N=432) compared low dose FP/SAL (100 mcg/200 mcg daily) (N=216) with MON (10 mg/day) (N=216) as monotherapy for 12 weeks.<sup>212</sup> Subjects with uncontrolled asthma treated with oral or inhaled short-acting beta-agonists age 15 and older were enrolled from 51 centers in the United States. At endpoint, those treated with FP/SAL showed a greater improvement in all outcomes compared with MON, including a decrease in the combined asthma symptom score (-1 vs. -0.7;  $P \leq 0.001$ ), increase from baseline in percent symptom free days (+40.3% vs. +27%;  $P \leq 0.001$ ), increase from baseline in percent of awakening free nights (+29.8% vs. +19.6%;  $P = 0.011$ ), decrease from baseline in nights/week with awakenings (-2.2 vs. -1.6;  $P \leq 0.001$ ), decrease in puffs/day (-3.6 vs. -2.2;  $P \leq 0.001$ ), and increase in quality of life (AQLQ overall score, increase: 1.7 vs. 1.2;  $P < 0.001$ ). Exacerbations occurred less frequently in the FP/SAL group (3% vs. 6%;  $P = \text{NR}$ ). Compliance was approximately 99% in both groups.

The first fair-quality RCT (N=423) also compared low dose FP/SAL (100/200 mcg daily) (N=211) with MON (10 mg/day) (N=212) for 12 weeks.<sup>210</sup> Subjects with uncontrolled asthma treated with oral or inhaled short-acting beta-agonists age 15 or older were enrolled from multiple centers in the United States. At endpoint, results were similar to those in the good-

quality RCT described above,<sup>212</sup> with significant differences for all outcomes favoring FP/SAL over MON, including decreased symptoms, rescue medicine use, and exacerbations (0%, 5%;  $P<0.001$ ).

The remaining 3 RCTs showed mixed results, with some outcomes favoring FP/SAL and others showing no difference between the 2 regimens. One trial (N=500) compared low-dose FP (200 mcg/day) (N=169) with low-dose FP (100 mcg/day) plus SAL (50 mcg/day) (delivered once daily at night) (N=165) and also with MON (5-10 mg/day) (N=166) for 16 weeks.<sup>141</sup> Subjects were age 6 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 SAL and MON in symptom-free days or rescue medicine use. However, there were significant differences in the percentage of patients with treatment failure (20.4% vs. 30.3%;  $P=0.03$ ) and asthma control (ACQ: 0.71 vs. 0.82;  $P=0.004$ ) favoring FP plus SAL. Adherence was good for all groups (FP/SAL 93.3% vs. MON 90.5%).

Another fair-quality RCT (N=285), the Pediatric Asthma Controller Trial (PACT), compared low dose FP 200 mcg/day via DPI (N=96) with MON 5 mg/day (N=95) and with the “PACT combination” of low dose FP plus SAL (each 100 mcg/day) via DPI, given as FP 100 mcg plus SAL 50 mcg in the morning plus SAL 50 mcg in the evening for 48 weeks (N=94).<sup>159</sup> Of note, the dose of FP/SAL 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. The trial found favorable results for FP/SAL in the change in the percentage of asthma control days from baseline (33.3% vs. 22.3%;  $P=0.011$ ). Nocturnal asthma symptoms requiring albuterol (NASRA) were less for the PACT combination (median 3.0 NASRA per year) than for MON (6.5), but the difference was not statistically significant ( $P=0.16$ ).<sup>167</sup> At endpoint, the trial found no significant difference in the overall percentage of asthma control days (52.5% vs. 59.6%;  $P=0.08$ ). There was no significant difference in asthma control as measured by change in ACQ score from baseline (-0.45 vs. 0.55;  $P=0.42$ ). Adherence was similar between groups (86% vs. 90%;  $P=NR$ ).

A final RCT showing mixed results, the Pediatric Asthma Control Evaluation (PEACE) study, enrolled children ages 6 to 14 with mild to moderate persistent asthma from outpatient centers at 4 sites in Turkey and 23 in Latin America.<sup>211</sup> Using a double-blind, double-dummy design, 281 children treated with FP/SAL 100 mcg/50 mcg twice daily were compared with 267 patients treated with MON 5 mg daily. The results showed significant improvement in the percentage of symptom free days (OR 1.74, 95% CI 1.07 to 2.82) and asthma-controlled weeks (16.7% more in FP/SAL group, 95% CI 8.3 to 16.7). The risk of not achieving well-controlled asthma was 3 times greater for patients taking MON compared with those taking FP/SAL (OR 2.94, 95% CI 1.97 to 4.37, controlling for age and sex).<sup>213</sup> The trial found no difference between groups in the percentage of nights without awakenings due to nocturnal symptoms (OR 2.33, 95% CI 0.73 to 7.47). The mean exacerbation rate and time was significantly reduced with FP/SAL therapy (0.12 vs. 0.3, OR 0.4, 95% CI 0.29 to 0.57) and the number of patients exacerbation-free at 84 days was 89.6% in FP/SAL patients compared with 74.8% in the MON group (treatment difference, 15%; 95% CI 8 to 22,  $P<0.001$ ). In addition, the percentage of rescue free days increased significantly with FP/SAL treatment (OR 3.24, 95% CI 2.09 to 5.02). Quality of life measures, however, demonstrated mixed results. While PACQLQ scores were higher in the FP/SAL group (mean treatment difference 0.54, 95% CI 0.06 to 1.02), no difference was noted between groups with respect to PAQLQ score (mean treatment difference 0.09, 95%



CI -0.12 to 0.30). Finally, while 7.5% of FP/SAL treated patients required some form of unscheduled health care contact during the study period, substantially more patients on MON therapy required medical attention ( $P=NR$ ). Adherence was similar between groups (87% vs. 84%;  $P=NR$ ).

### ***COPD***

No eligible studies.

### ***e. Long-acting muscarinic antagonists (LAMAs) and long-acting beta-2 agonists (LABAs) compared with long-acting muscarinic antagonists (LAMAs) (different drug)***

### **Summary of findings**

#### ***Asthma***

- No eligible studies.

#### ***COPD***

- Three trials comparing UME/VIL combination therapy with TIO found no differences between groups in deaths, quality of life, daily activities, or exacerbations (low-strength evidence); reductions in use of rescue medication were greater for UME/VIL compared with TIO (-3.2 vs. -2.1 in 1 study and -2.0 vs. -1.4 in another) (moderate-strength evidence)
- One trial of UME/VIL combination therapy compared with UME monotherapy reported less frequent rescue medication use in patients receiving UME/VIL (treatment difference, mean puffs per day: -0.6, 95% CI -1.2 to 0.0 for the 62.5/25 µg dose and -1.1, 95% CI -1.7 to -0.5 for the 125/25 µg dose; not currently US Food and Drug Administration-approved) (low-strength evidence).

### **Detailed assessment**

#### ***COPD***

The prior report included 3 fair-quality 24-week unpublished studies (total N=1,759) comparing the combination of UME 62.5 µg and VIL 25 µg with TIO 18 µg in patients with COPD.<sup>206-208</sup>

We identified 2 publications that reported additional efficacy and effectiveness outcomes for these 3 previously included trials of umeclidinium and vilanterol combination product compared with TIO or UME monotherapy.<sup>21,37</sup> All 3 trials enrolled adults aged  $\geq 40$  years with moderate-to-severe COPD. The mean ages of participants ranged from 62.3 to 64.6 years, the proportions of females ranged from 31% to 32.5%, and the proportions of patients in GOLD COPD stages II or III ranged from 87.3% to 88.3%. All 3 trials compared the UME/VIL combination product to TIO; all trials evaluated UME 62.5 µg/VIL 25 µg to TIO 18 µg, while 2 of the trials also evaluated a higher dose (not currently US Food and Drug Administration-approved) UME 125 µg/VIL 25 µg<sup>21</sup> and 1 trial also compared with UME monotherapy.<sup>21</sup> Sample sizes ranged from 846 to 905, and the duration of all studies was 24 weeks. Two of the trials were rated as good quality, while the third trial was fair.

### *Umeclidinium/vilanterol (UME/VIL) compared with tiotropium (TIO)*

The 3 previously included trials found no difference between groups in deaths (OR 1.28, 95% CI 0.24 to 6.7), quality of life, or daily activities. Reductions in use of rescue medication were greater for UME/VIL compared with TIO (–3.2 vs. –2.1 in 1 study and –2.0 vs. –1.4 in another).

Newly identified publications of 2 of these previously included trials reported rates of exacerbations ranging from 4% to 12%, with no differences between groups.

### *Umeclidinium/vilanterol (UME/VIL) compared with umeclidinium (UME)*

One trial compared UME/VIL to UME.<sup>21</sup> As with the TIO comparison, rates of exacerbation and quality of life scores were similar, while UME/VIL treatment resulted in significantly less frequent use of rescue medication for the higher UME/VIL dose only (treatment difference, mean puffs per day: –0.6, 95% CI –1.2 to 0.0 for the 62.5/25 µg dose and –1.1, 95% CI –1.7 to –0.5 for the high dose; 125/25 µg).

## c. Combination therapy compared with combination therapy

### *a. Long-acting beta-2 agonists (LABAs) and long-acting muscarinic antagonists (LAMAs) compared with long-acting beta-2 agonists (LABAs) and inhaled corticosteroids (ICSs)*

#### **Summary of findings**

##### **Asthma**

- No eligible randomized controlled trials.

##### **COPD**

- *Indacaterol (IND)/glycopyrrolate (GLY) compared with fluticasone propionate (FP)/salmeterol (SAL)*
  - Based on a fair-quality RCT, low-strength evidence suggested that high-dose IND/ GLY 110 mcg/50 mcg has a lower risk of moderate to severe exacerbations than FP 100 mcg/SAL 1,000 mcg (rate per year 0.30 vs. 0.46; RR 0.69, 95% CI 0.48 to 1.00). Time to first moderate to severe exacerbation was also longer with IND/GLY than with FP/SAL (HR 0.65, 95% CI 0.44 to 0.95).
  - Differences were not found on other measures, including quality of life, rescue medication use, ability to perform daily activities, and symptom measures.
- *Vilanterol(VIL)/umeclidinium (UME) compared with fluticasone propionate (FP)/salmeterol (SAL)*
  - Based on 2 good-quality RCTs, there is moderate-strength evidence of no difference in exacerbation rates, and high-strength evidence of no difference in quality of life between VIL 25 mcg/UME 62.5 mcg DPI daily and FP 500 mcg/SAL 100 mcg DPI daily in the short term. Differences were also not found in rescue medication use.
  - Based on a good-quality RCT, there is low-strength evidence of no difference in exacerbation rates, and moderate-strength evidence of no difference in quality of life between VIL 25 mcg/UME 62.5 mcg DPI daily and FP 1,000 mcg/SAL 100 mcg DPI daily. Differences were also not found in rescue medication use.

## Detailed assessment

### COPD

#### *Indacaterol (IND)/glycopyrrolate (GLY) compared with fluticasone propionate (FP)/salmeterol (SAL)*

A fair-quality 26 week study conducted in China (LANTERN) compared IND 110 mcg/ GLY 50 mcg daily (high dose) with FP 100 mcg/SAL 1,000 mcg daily in 744 patients with moderate (52%) to severe (46%) COPD (stage II-III by 2010 GOLD criteria).<sup>49</sup> The dose of IND/GLY is greater than is currently approved in the United States. Mean age was 65 years and 90% of patients were male. This study provides low-strength evidence that there is not a statistically significant difference between drugs in exacerbations or quality of life based on the SGRQ. The rates of any exacerbation per year were 0.59 vs. 0.75 for IND/GLY and FP/SAL, respectively, with a rate ratio of 0.79 and 95% CI 0.58 to 1.07. Analysis of moderate to severe exacerbations found IND/GLY to have a lower risk than FP/SAL; the rate per year was 0.30 compared with 0.46 (rate ratio 0.69, 95% CI 0.48 to 1.00,  $P=0.048$ ), with borderline statistical significance. This study also evaluated the time to first exacerbation, and when limiting to moderate to severe exacerbations finds IND/GLY to have a statistically significantly longer time than FP/SAL (hazard ratio 0.65, 95% CI 0.44 to 0.95). This evidence is low strength due to the low numbers of events making the estimate imprecise.

While both groups quality of life improved from baseline there was not a statistically significant difference between groups. There were also no significant differences in other measures (percent of day with no rescue medication at week 26, change in puff per day of rescue medicine, percent of nights with no night time awakening, percent of days with no daytime symptoms, and percent of days able to perform usual daily activities).

#### *Vilanterol (VIL)/umeclidinium (UME) compared with fluticasone propionate (FP)/salmeterol (SAL)*

Two good-quality 12-week RCTs compared VIL 25 mcg/UME 62.5 mcg DPI daily with FP 500 mcg/SAL 100 mcg DPI daily in patients with moderate (50%) to severe (50%) COPD (N=1,403) who had not experienced an exacerbation in the past 12 months.<sup>22</sup> Across the studies mean age was 63 years and 73% were male. The incidence of exacerbations was identical between groups for both studies (3% per group), providing moderate-strength evidence of no differences between drugs (Appendix E, Table E-17). The studies also provide high-strength evidence of no differences in health-related quality of life at 12 weeks based on the EQ5D scale and the SGRQ scale (Appendix E, Table E-17). Consistent with these findings, the study also reports very similar findings for other outcomes. Rescue medication use was similar (Study 1: -1.4 vs. -1.3 puffs/day and Study 2: -1.6 vs. -1.3 puffs/day) and percent rescue-free days was also similar (Study 1: 37% vs. 36% and Study 2: 34% vs. 34%).

A third good-quality 12-week RCT evaluated VIL 25 mcg/UME 62.5 mcg DPI daily with a higher dose FP 1,000 mcg/SAL 100 mcg DPI daily in 717 patients with moderate (55%) to severe (45%) COPD, with no exacerbations in the year prior to study.<sup>48</sup> Mean age was 62 years and 72% were male. This study also provides low-strength evidence of no difference in exacerbations and moderate-strength evidence of no difference in quality of life measures (Appendix E, Table E-17). Rescue medicine use (treatment difference -0.1; 95% CI -0.3 to 0.1) and percent rescue free days (treatment difference -0.1; 95% CI, -0.4 to 0.3) were also not different at 2 weeks.

*c. Long-acting beta agonists (LABAs) plus inhaled corticosteroids (ICSs) compared with leukotriene modifiers (LMs) plus inhaled corticosteroids (ICS)*

**Summary of findings**

***Asthma***

- High-strength evidence from a good-quality systematic review with meta-analyses found that the addition of a LABA to ICS therapy prevents exacerbations in more patients than does the addition of an LM to ICS therapy for adolescents and adults with persistent asthma. This difference held for patients adding SAL to ICS therapy compared with those adding MON. Strength of evidence was also high that the choice of a LABA compared with an LM did not affect quality of life. Quality of life was also the same for those adding SAL compared with MON (moderate-strength evidence) and those adding SAL compared with ZAF (low-strength evidence).

***COPD***

- No eligible studies.

**Detailed assessment**

***Asthma***

We found 1 systematic review with meta-analysis, first published in 2006<sup>214</sup> and updated in 2011,<sup>215</sup> and 8 RCTs<sup>216-223</sup> that met our inclusion/exclusion criteria and that compared the addition of a LABA with the addition of an LM for patients with asthma poorly controlled on ICS therapy. Risk of bias in included studies was generally low. The systematic review included RCTs conducted in patients with persistent asthma where a LABA or LM was added to ICS for 4 to 48 weeks (weighted mean 26 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 ICS throughout the trials. Of the 11 studies we assessed in the updated systematic review,<sup>215</sup> 9 compared 100 mcg/day of SAL plus ICS with 10 mg/day of MON plus ICS. The other 2 trials compared either SAL or FOR with ZAF (40 mg/day) as add-on therapy to ICSs. Most trials (N=7) used low-dose FP as the ICS in both treatment arms. Of the remaining 4 trials, 1 used low-dose BUD in both arms; 1 combined high-dose BEC with MON, and medium to high dose FP with SAL and the last 2 trials had varying ICS drugs and doses.

All of the 11 trials we assessed were conducted in adult populations. Two studies were conducted in the United States, 1 in the United States and Puerto Rico, 1 in France, and 1 in the UK. Three were multinational trials including 6, 19, and 37 countries, and for the remaining 3 trials the study and/or review did not report the country or countries where the trials took place. For most studies the study or review did not report asthma severity; for the 4 where severity was reported, it was either mild to moderate (1 study), moderate (2 studies) or moderate to severe (1 study).

One good-quality systematic review with meta-analysis compared LABAs with LMs as add-on therapy to ICSs in patients with asthma.<sup>214,215</sup> Eleven of the review's trials, including 6,292 patients, contributed data to meta-analyses we report here. Six of these eleven trials met our inclusion criteria,<sup>216-221</sup> and 5 did not.

The systematic review provided high-strength evidence that LABA plus ICS was significantly better than LM plus ICS for preventing exacerbations (Appendix E, Table E-19).<sup>215</sup>

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 to 0.97). The reported number of patients who must be treated with the combination of LABA and ICS instead of LM and ICS to prevent 1 exacerbation over 48 weeks was 38 (95% CI 22 to 244).

Quality of life was also slightly better for patients treated with ICS/LABA. The change in Asthma Quality of Life Questionnaire score from baseline, measured on a 7-point scale, was 0.11 points higher for patients using LABAs as add-on to ICSs, compared with those adding LMs (95% CI 0.05 to 0.17). However, the minimal important difference established for the AQLQ is 0.5 points. The systematic review thus provides high-strength evidence that there is no clinically important difference in quality of life between patients adding LABAs to ICS therapy for asthma and those adding LMs (Appendix E, Table E-19). However, reported symptoms and rescue medicine use all favored LABAs: compared with patients using LMs as add-on therapy, those adding LABAs had fewer symptoms, more symptom-free days, more days when they did not require rescue medicine use, and fewer nighttime awakenings (all differences statistically significant in meta-analyses). There was no significant heterogeneity in any of the meta-analyses we discuss here.

#### *Salmeterol (SAL) and inhaled corticosteroid (ICS) compared with montelukast (MON) and inhaled corticosteroid (ICS)*

The systematic review included sub-analyses grouping trials by specific LABA and LM comparisons in patients with asthma. It provided high-strength evidence from 9 trials that patients adding SAL to ICS had a lower risk of exacerbations than those adding MON. Two trials provided moderate-strength evidence that there were no clinically important differences in quality of life for SAL compared with MON as add-on therapy (Appendix E, Table E-19). These results for exacerbations and quality of life were similar to those for the overall drug classes, since most of the trials in the review compared SM and ML. Four included trials provided data on hospitalizations due to exacerbations, and 1 on mortality, all 5 trials comparing SAL with MON; however, evidence from these trials was insufficient to compare SAL and MON for these outcomes.

#### *Salmeterol (SM) and inhaled corticosteroid (ICS) compared with zafirlukast (ZAF) and inhaled corticosteroid*

For this comparison as well, there were no clinically important differences in quality of life between intervention arms, though strength of evidence was low from the 1 trial reporting this outcome for SAL compared with ZAF, a trial which was included in the systematic review but did not meet our inclusion criteria. The same single trial reported exacerbations, but evidence was insufficient to compare this outcome between patients taking SM compared with ZAF (Appendix E, Table E-19).

#### *c. Leukotriene modifiers (LMs) and long-acting beta-2 agonists (LABAs) compared with inhaled corticosteroids (ICSs) and long-acting beta-2 agonists (LABAs)*

### **Summary of findings**

#### ***Asthma***

- Evidence from a single study was insufficient to draw conclusions.

## **COPD**

- No eligible studies.

### **Detailed assessment**

We found 1 fair-quality RCT comparing LM plus LABA with ICS plus LABA (Appendix E, Table E-18).<sup>224</sup> This fair-rated, placebo-controlled, multi-center RCT (N=192, 110 eligible for primary analysis) compared MON (10 mg/day) plus SAL (100 mcg/day) plus placebo ICS (N=98) with low-dose BEC (160 mcg/day) plus SAL (100 mcg/day) plus placebo LM (N=92) for 14 weeks, washout for 4 weeks, then crossover for another 14 weeks.<sup>224</sup> Subjects age 12 to 65 with moderate asthma were enrolled from multiple sites in the United States. 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. For 29 subjects, ICS/LABA was superior (longer time to treatment failure), and for 8 subjects LM/LABA was superior ( $P=0.0008$ ). The remaining 73 subjects did not experience treatment failure during the trial's 14 weeks of treatment.

## **Key Question 2. What is the comparative *within-class* and *across-class* tolerability and frequency of adverse events of long-acting inhaled and long-acting oral medications used to treat outpatients with asthma or chronic obstructive pulmonary disease (COPD)?**

### ***I. Intra-class Comparisons (within a class)***

#### **A. Monotherapy**

##### ***a. Inhaled corticosteroids (ICSs)***

### **Summary of findings**

#### ***Asthma***

- *Overall adverse events, tolerability, and common adverse events.* Moderate-strength evidence from head to head RCTs suggested no significant differences between ICSs in overall incidence of adverse events and withdrawals due to adverse events for equipotent doses of ICSs in patients with asthma.
- *Osteoporosis and fractures.* There was insufficient evidence to determine potential differences between ICSs in impact of long-term treatment on bone fractures or osteoporosis.
- *Growth.* There was insufficient evidence to determine potential differences between ICSs in impact of long-term treatment on final adult height.
  - Evidence on an intermediate outcome of growth velocity (mm/day) over shorter periods (20 weeks to 1 year) suggests that short-term growth velocity is greater with FP than with BEC or BUD in children with asthma and that CIC results in greater mean height increase than BUD over the short-term (12 weeks).
- *Other adverse outcomes.* There was insufficient evidence from existing studies to draw conclusions regarding the comparative risk of acute adrenal crisis, cataracts, ocular hypertension and open-angle glaucoma with different ICSs.

## **COPD**

- *Pneumonia*. There was insufficient evidence to determine differences in risk of pneumonia between BEC and FP.

## **Detailed assessment**

Most studies that examined the efficacy of 1 ICS relative to another in patients with asthma (described in Key Question 1) also reported tolerability and adverse events. Forty-six head-to-head RCTs and 2 observational studies met our criteria for tolerability or adverse events.<sup>29,35,42,84,87,93,104,105,111,225-229</sup> Six head-to-head RCTs included children < 12 with asthma,<sup>84,87,93,104,105,111</sup> and only 1 observational study of patients with COPD was included.<sup>42</sup>

## **Asthma**

### *Overall adverse events, tolerability, and common adverse events*

Of the 47 head-to-head studies reviewed for this section (all conducted in patients with asthma), most reported frequency of adverse events without tests of statistical significance. The vast majority of studies reported similar results for equipotent ICS doses. Four studies reported a difference of greater than 5% in withdrawals due to adverse events for equipotent doses.<sup>74,78,104,226</sup>

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% of ICS-treated patients. Upper respiratory tract infections were reported by 3% to 32% of study participants. For common specific adverse events, just 3 trials reported a statistically significant difference between equipotent doses of different ICSs.<sup>75,78,96</sup> One reported a greater incidence of headache in those treated with BEC than those treated with FP (7% vs. <1%,  $P=0.03$ );<sup>96</sup> 1 reported a greater incidence of oral candidiasis with FP than with CIC (3.8% vs. 0%,  $P=0.002$ );<sup>75</sup> and 1 reported that a greater proportion of patients experienced local oropharyngeal adverse effects (candidiasis and dysphonia) with FP than with CIC ( $P=0.0023$ ).<sup>71</sup> Meta-analysis of trials reporting “oral candidiasis-thrush” that compared equipotent doses of CIC with FP revealed lower odds of oral candidiasis-thrush for those treated with CIC (OR 0.33, 95% CI 0.17, 0.64).

### *Bone density/osteoporosis*

Three fair-quality RCTs compared an ICS to another in asthma patients.<sup>38,226,227</sup> One 24-month open-label trial measuring bone mineral density and vertebral fractures randomized 374 adult patients with asthma to BEC or BUD.<sup>227</sup> Patients were titrated to the minimal effective dose following a pre-specified management plan; subjects who required more than 3 courses of oral corticosteroids were withdrawn. At 2 years, no significant differences in BMD were reported between the 2 treatment groups. A smaller trial reporting BMD randomized 69 asthmatic patients to medium and high doses of BEC or FP.<sup>226</sup> At 1 year, no significant differences in bone mass or metabolism were noted between the 2 treatment groups.

A fair-quality trial compared low- and medium-dose MOM (200 and 400 mcg per day) DPI with medium-dose FP (500 mcg per day) MDI in adults with mild-moderate persistent asthma who did not receive ICS for >3 months, for 52 weeks.<sup>38</sup> Bone mineral density was measured at 26 weeks, 52 weeks and at study endpoint. At the lumbar spine and the total femur,

density increased very slightly, and differences were not statistically significant. Changes in femoral neck density were 0.4% (MOM 400 mg), -0.2% (MOM 200 mg), and -0.4% (FP); the difference between MOM 400 mg and FP was statistically significant ( $P=0.044$ ).

### *Growth*

Three head-to-head RCTs comparing FP to BEC,<sup>84</sup> FP to BUD,<sup>87</sup> or CIC to BUD<sup>111</sup> assessed differences in growth in asthma patients. A fair-quality, 1-year, multinational head-to-head trial determined differences in growth velocity comparing a medium dose of FP (400 mcg/day) to a medium dose of BEC (400 mcg/day) in 343 pre-pubertal children with asthma.<sup>84</sup> ITT analysis revealed that adjusted mean growth velocity was significantly greater in fluticasone propionate than in BEC-treated patients (+0.70 cm/year; 95% CI 0.13 to 1.26;  $P<0.02$ ). A second RCT compared differences in growth velocity in 333 children treated with a medium dose of FP (400 mcg/day) or a medium dose of BUD (800 mcg/day) over 20 weeks.<sup>87</sup> Linear growth velocity was greater for FP-treated children compared with those treated with BUD (adjusted mean increase in height: 2.51 cm compared with 1.89; difference 6.2 mm (95% CI 2.9 to 9.6,  $P=0.0003$ ). The third RCT compared growth in 621 children (age 6-11) treated with either a low dose of CIC (160 mcg/day) or a low dose of BUD (400 mcg/day) over 12 weeks. Ciclesonide-treated subjects had a greater mean body height increase (1.18 cm vs. 0.70 cm,  $P=0.0025$ ). One fair-quality retrospective observational study in Croatia studied linear growth velocity in prepubertal children aged 4 to 9.5 years with persistent asthma for a period of 23 weeks.<sup>230</sup> Linear growth velocity was 0.187 mm/day with FP (N=502) and 0.194 mm/day with BUD (N=43) (statistical analysis not conducted). Due to local guidelines, the mean age of patients taking BUD was greater than those taking FP (7.16 vs. 6.53 years); the implications are not clear.

### *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 such studies of HPA axis suppression can be extrapolated to assess differences in risks for clinically significant adrenal suppression.

### *Cataracts*

Systemic corticosteroid-induced cataracts typically are located on the posterior side of the lens and are referred to as posterior subcapsular cataracts (PSC). No study compared the risk of developing PSC between an ICS and another. One head-to-head RCT evaluated the effect of CIC and BEC on eye lens opacity in adult patients with asthma and found CIC to be non-inferior to BEC (both delivered at high doses).<sup>228</sup> Both treatments were found to have minimal impact on lenticular opacity development and/or progression.

### *Ocular hypertension and open-angle glaucoma*

No study compared 1 ICS to another for the risk of ocular hypertension or open-angle glaucoma.



## **COPD**

### *Pneumonia*

A good-quality retrospective cohort study evaluated BEC (via breath-actuated inhaler) compared with standard (large-particle) FP via MDI in 668 patients with COPD. The study evaluated a 2-year period, and found that 2.1% (7 of 334) on BEC and 1.2% (4 of 334) on FP had a diagnosis of pneumonia, but the study further reports that they considered 3 in each group to have been adequately confirmed.

### *b. Leukotriene modifiers (LMs)*

#### **Summary of findings**

##### *Asthma*

- There was insufficient evidence to determine differences in tolerability or overall adverse events between the LMs.

## **COPD**

- We identified no comparative trials in patients with COPD.

#### **Detailed assessment**

##### *Asthma*

###### *Overall adverse events*

We found 2 fair-quality head-to-head trials comparing 1 LM with another that met inclusion/exclusion criteria for our review.<sup>119,120</sup> One trial compared quality of life outcomes between MON and ZAF at recommended doses in adults with mild persistent asthma, but did not report whether adverse events occurred in either group. The second trial compared ZIL and MON in patients in India with mild to moderate asthma.<sup>120</sup> No patient in either drug arm reported serious adverse events or withdrew due to adverse events.

###### *Liver toxicity*

In 1 head-to-head trial comparing MON with ZIL in patients with asthma,<sup>120</sup> 2 patients (2%) taking ZIL developed altered liver function tests (LFT), 1 with alanine aminotransferase (ALT) elevation and 1 with total bilirubin elevation. None of the patients taking MON showed such changes. However, the difference between groups was not statistically significant (risk difference calculated for this review: 0.02, 95% CI –0.02 to 0.06, i.e., the incidence of LFT abnormalities in patients taking ZIL increased by 2 per 100 subjects compared with patients taking ML, but the 95% CI included no difference.) In addition, no patient in either group had clinical symptoms or signs of liver toxicity.

### *c. Long-acting beta-2 agonists (LABAs)*

#### **Summary of findings**

##### *Asthma*

- Limited evidence provides no evidence of a difference in tolerability or adverse events between FOR and SAL in patients with asthma, regardless of whether or not corticosteroids are used concurrently.

- It should be noted that due to reports that regular use of LABAs increases the risk of asthma-related death, and that the risk may be significantly higher in African Americans, LABAs are contraindicated for use as monotherapy in patients with persistent asthma (see boxed warning in product labels for details).

## **COPD**

- *Arformoterol (ARF) compared with formoterol (FOR)*
  - One fair-quality trial provided low-strength evidence that withdrawals due to adverse events and serious adverse events did not differ by group.
- *Indacaterol (IND) compared with formoterol (FOR)*
  - Low-strength evidence from 1 fair-quality trial showed that withdrawals due to adverse events did not differ between patients given lower-dose IND and those given FOR, but that withdrawals due to adverse events were lower for patients given higher-dose IND than for those given FOR (RR 0.58, 95% CI 0.36 to 0.94).
- *Indacaterol (IND) compared with salmeterol (SAL)*
  - Low-strength evidence from 1 fair-quality trial suggested an increase in serious adverse events with IND compared with SAL, though statistical significance was borderline (OR 1.51, 95% CI 0.99 to 2.28). There was no difference in withdrawals due to adverse events between groups.

## **Detailed assessment**

### *Arformoterol (ARF) compared with salmeterol (SAL)*

We did not identify any good- or fair-quality systematic reviews or head-to-head trials that compared ARF with SAL in subjects with asthma or COPD.

### **Asthma**

We found 3 fair-quality RCTs in patients with asthma<sup>121-124</sup> that included head-to-head comparisons of 1 LABA with another LABA and met our inclusion/exclusion criteria. All were published before 2010, when the US Food and Drug Administration issued the boxed warning against use of LABAs as monotherapy in patients with asthma. For the original Asthma/COPD report and for Update 1, we found no new trials comparing LABAs in patients with asthma.

### *Formoterol (FOR) or formoterol (FOR) compared with salmeterol (SAL)*

Of the 4 included head-to-head trials, 2 were conducted only in adults,<sup>124,132</sup> 1 enrolled adults and adolescents<sup>121</sup> and 1 enrolled only children and adolescents between 6 and 17 years old.<sup>122</sup> All 4 trials compared FOR (12 mcg twice daily) with SAL (50 mcg twice daily). Only 1<sup>121</sup> of the 4 trials was blinded. Detailed descriptions of these RCTs are provided in the Key Question 1 section of this report with the exception of 1 study that was included for this section but not for efficacy outcomes,<sup>132</sup> which is described in the Evidence Tables.

One open-label RCT conducted in the United States<sup>132</sup> compared FOR (24 mcg/day) to SAL (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% vs. 11.3%) and withdrawals due to adverse events (5.7% vs. 3.4%).

One trial<sup>121,231</sup> randomized 469 patients to blinded eFOR via DPI, SAL via DPI, or SAL via MDI. They found similar rates of hospital admission and emergency department visits and total study withdrawals. Another trial<sup>123</sup> compared FOR administered via DPI with SAL given

via DPI in 482 adult asthmatics. The trial found comparable rates of hospitalizations, study withdrawals, withdrawals due to adverse events, and drug-related adverse events. The only trial enrolling children and adolescents<sup>122</sup> randomized subject (N=156) to FOR or SAL and also found similar rates of study withdrawals and withdrawals due to adverse events.

Two systematic reviews compared SAL and FOR directly. The first review<sup>232</sup> compared the risk of adverse events in patients with chronic asthma who received FOR and corticosteroid compared with SAL and corticosteroid for chronic asthma. One trial compared FOR and BEC to SAL and FP, and the other 7 trials compared FOR and BUD to SAL and FP. The reviewers found no significant differences in any serious adverse events, including all-cause mortality (OR 1.03, 95% CI 0.06 to 16.44), all-cause non-fatal serious adverse events (OR 1.14, 95% CI 0.82 to 1.59), and asthma-related serious adverse events (OR 0.69, 95% CI 0.37 to 1.26). The study using BEC instead of BUD was relatively small (N=228 participants) and reported no deaths or hospital admissions.

The second systematic review<sup>233</sup> compared the risk of adverse events in patients with chronic asthma who received FOR versus SAL, without the addition of ICS. This review was first published in 2009<sup>233</sup> and updated in 2013 with searches through January 2012;<sup>234</sup> however, the update found no new studies to include, and we therefore excluded the 2013 publication from this report. The 2009 review found no statistically significant differences in any serious adverse events, including all-cause mortality (one total death in the SAL group, not attributable to asthma), all-cause serious adverse events in adults (OR 0.77, 95% CI 0.46 to 1.28), all-cause serious events in children (OR 0.95, 95% CI 0.06 to 15.33), and asthma-related serious adverse events in adults (OR 0.86, 95% CI 0.29 to 2.57) and children (no events in either group).

### ***COPD***

We found 7 new trials comparing LABAs in patients with COPD.<sup>33,125-129</sup> Three trials<sup>128-130</sup> compared IND with SAL, and another compared IND with FOR.<sup>125</sup> One trial<sup>131</sup> compared ARF with FOR, 1 compared FOR delivered with a nebulizer to FOR via dry powder inhaler, and the final trial compared the newer LABA olodaterol (OLO; US Food and Drug Administration-approved in 2014) to FOR.<sup>33</sup> Another trial, with open-label design comparing FOR and SAL over 6 months, was rated poor for efficacy but fair for harms and is discussed here.<sup>132</sup>

#### *Arformoterol (ARF) compared with formoterol (FOR)*

One fair-quality trial<sup>131</sup> included 444 patients with asthma from 62 centers in the United States. Patients received 6 months of treatment with either 30 or 50 mcg ARF daily via nebulizer, or 24 mcg/day FOR via DPI. Withdrawals due to harms appeared similar across treatment arms, with 10.1% of patients taking 30 mcg ARF withdrawing, 10.9% of those taking 50 mcg ARF, and 8.2% of those taking FOR, though the study did not report a statistical comparison. Serious adverse events also appeared similar between ARF and FOR, though results differed for the 2 doses of ARF. We calculated RR 1.41 (95% CI 0.75 to 2.66) for patients taking ARF 30 compared with those taking FOR, and RR 0.71 (95% CI 0.33 to 1.52) for those taking 50 mcg of ARF versus FOR; though RRs appeared inconsistent, both 95% CIs included 1.0 (no effect). The study thus provides low-strength evidence that serious harms and withdrawals due to harms do not differ between ARF and FOR.

*Formoterol (FOR) (nebulized) compared with formoterol (FOR) dry powder inhaler (DPI)*

A fair-quality trial<sup>126</sup> compared 2 formulations of FOR, 1 delivered via nebulizer and the other via DPI. The trial enrolled 237 patients with COPD from 38 centers in the United States for 12 weeks of treatment with FOR 40 mcg via nebulizer or 24 mcg via DPI. Few patients experienced serious adverse events (N=4 overall) or withdrew due to adverse events (N=8), and evidence was insufficient to compare these outcomes for the 2 FOR formulations.

*Formoterol (FOR) compared with indacaterol (IND)*

The INVOLVE Study of 1,300 patients in 25 countries outside the United States compared IND with FOR. Over 52 weeks of treatment subjects received 300 mcg/day of IND, 600 mcg/day of IND, or 24 mcg/day of FOR, all via DPI. The study did not report serious adverse events, but for both doses of IND fewer patients withdrew due to adverse events than did patients taking FOR. However, the differences did not reach statistical significance: we calculated RR 0.85 (95% CI 0.56 to 1.30) for withdrawals in patients taking 300 mcg IND and RR 0.58 (95% CI 0.36 to 0.94) for 600 mcg IND, each compared with patients taking FOR.

*Indacaterol (IND) compared with salmeterol (SAL)*

Two fair-quality RCTs<sup>128,129</sup> compared treatment with 150 mcg daily of IND with 100 mcg of SAL in COPD patients, and a third small trial compared 300 mcg daily of IND to 100 mcg of SAL.<sup>130</sup> One trial<sup>120</sup> recruited 1,123 patients from 8 countries including the United States for 12 weeks' treatment; another<sup>129</sup> treated 667 patients from 15 non-United States countries for 26 weeks; and 1 included 186 patients in a 52-week trial in Japan<sup>130</sup> Both serious harms and withdrawals due to harms appeared to favor SAL, though differences were not statistically significant. Our meta-analyses comparing IND with SAL calculated OR 1.19 (95% CI 0.74 to 1.90) for withdrawals due to harms, and OR 1.51 (95% CI 0.99 to 2.28) for serious harms. It should be noted that the dose of IND studied is greater than the 75 mcg daily currently approved in the United States.

*Olodaterol (OLO) compared with formoterol (FOR)*

Two replicate fair-quality 48-week trials reported in 1 publication compared 2 doses of OLO (5 or 10 mcg daily) given via SMI to formoterol 24 mcg daily by DPI.<sup>33</sup> Of the 1,378 participants across the 2 trials (excluding those given placebo only), 79% were male, the mean age was 64 years, and all had a smoking history of more than 10 pack-years. The trials reported serious adverse events and withdrawals due to adverse events, but provided insufficient evidence to compare these outcomes across treatment arms. Deaths and episodes of pneumonia were also reported, but these were infrequent and confidence intervals comparing rates across treatment arms were wide (data not shown).

*d. Long-acting muscarinic antagonists (LAMAs)*

**Summary of findings**

**Asthma**

- No eligible studies.

**COPD**

- *Glycopyrrolate (GLY) compared with tiotropium (TIO)*
  - Low-strength evidence from 3 RCTs suggests no differences in overall adverse events, withdrawal due to adverse events, pneumonia, or death.
- *Umeclidinium (UME) compared with tiotropium (TIO)*
  - Low-strength evidence from 2 RCTs no differences in overall adverse events, withdrawal due to adverse events, pneumonia, or death.
- *Umeclidinium (UME) compared with glycopyrrolate (GLY)*
  - Evidence from a single RCT was insufficient to draw conclusions.

### Detailed assessment

The prior report did not include any studies comparing LAMAs with each other in patients with COPD. We identified 6 trials that reported adverse events outcomes: 3 trials compared GLY to TIO,<sup>19,24,32</sup> 2 trials compared UME to TIO,<sup>21,50</sup> and 1 trial compared UME to GLY.<sup>25</sup> All trials included adults aged  $\geq 40$  years with COPD, a smoking history of  $\geq 10$  pack-years, and an FEV1/FVC ratio  $< 0.7$ . The duration of 1 trial was 52 weeks,<sup>32</sup> while the remainder were 12-week studies. Sample sizes ranged from 437 to 1,066. Mean ages of participants ranged from 63.5 to 68.0 years, and the proportions of females ranged from 26% to 36%. In all studies, GLY was delivered via the BreezeHaler DPI, UME was delivered via the Ellipta DPI, and TIO was delivered via the HandiHaler DPI. Five trials were rated fair quality,<sup>21,24,25,32,50</sup> while the remaining trial was good quality.<sup>19</sup> All trials were pharmaceutically-funded.

#### *Glycopyrrolate (GLY) compared with tiotropium (TIO)*

Three trials<sup>19,24,32</sup> compared GLY 50  $\mu\text{g}$  (glycopyrronium 50 mcg = 62.5 mcg glycopyrrolate) with TIO 18  $\mu\text{g}$ . The trials reported no differences between groups in overall adverse events, withdrawal due to adverse events, pneumonia, or death. The dose of GLY used here is higher than the US Food and Drug Administration-approved dose.

#### *Umeclidinium (UME) compared with tiotropium (TIO)*

Two trials (one unpublished) compared UME with TIO, reporting no significant differences between groups in overall adverse events, withdrawal due to adverse events, pneumonia (reported in 1 trial<sup>50</sup>), or death (reported in 1 trial<sup>21</sup>).

#### *Umeclidinium (UME) compared with glycopyrrolate (GLY)*

One trial that compared UME with GLY reported no differences between groups in overall adverse events, withdrawal due to adverse events, pneumonia, or death.<sup>25</sup>

### B. Combination therapy compared with monotherapy

#### *a. Inhaled corticosteroid (ICS) and long-acting beta-2 agonist (LABA) compared with inhaled corticosteroid (different drug)*

### Summary of findings

#### *Asthma*

- *Budesonide (BUD)/formoterol (FOR) compared with fluticasone propionate (FP)*
  - Evidence from a fair-quality study provided insufficient evidence to draw conclusions on adverse events.

- *Fluticasone propionate (FP)/salmeterol (SAL) compared with ciclesonide (CIC)*
  - Evidence from a fair-quality study provided low-strength evidence that adverse events were reported more frequently with CIC than FP/SAL (RR 1.15, 95% CI 1.01, 1.30).
- *Fluticasone furoate (FF)/vilanterol (VIL) compared with fluticasone propionate (FP)*
  - Low-strength evidence from 3 good-quality trials indicates no statistically significant difference in withdrawals due to adverse events (pooled RR 0.91, 95% CI 0.18 to 4.76,  $I^2=68%$ ); or serious adverse events (pooled RR 0.62, 95% CI 0.21 to 1.85;  $I^2=0%$ ).

## Detailed assessment

### *Asthma*

We identified 5 RCTs that compared the combination of an ICS and LABA to a different ICS (at any dose) in patients with asthma. One trial compared BUD/FOR with FP, 1 FP/SAL with CIC, and 3 compared FF/VIL with FP. We identified no of this comparison in patients with COPD.

#### *Budesonide (BUD)/formoterol (FOR) compared with fluticasone propionate (FP)*

One fair-quality trial conducted in Brazil compared 12 weeks of BUD and FOR to FP in 163 patients with mild to moderate asthma.<sup>16</sup> The daily dose of BUD/FOR was 800 mcg/24 mcg, and that of FP was 1,000 mcg. The trial also included a comparison with fixed-dose FP and FOR (N=79), reported above with intra-class comparisons of combination products. Serious adverse events were reported, but none occurred in these treatment arms (insufficient evidence to compare; Appendix E, Table E-12).

#### *Fluticasone propionate (FP)/salmeterol (SAL) compared with ciclesonide (CIC)*

We identified 1 fair-quality RCT (N=432) in patients with mild persistent asthma who were randomized to CIC 160 mcg once daily or FP/SAL 200/100 twice daily.<sup>198</sup> Patients were  $\geq 12$  years of age (mean age 30), 43% male, non- or ex-smokers with a smoking history of  $< 10$  pack years. Ciclesonide increased the risk of experiencing any adverse event compared with FP/SA, 95% CI 1.01 to 1.30), although most events were considered mild to moderate. This evidence is insufficient to draw conclusions (Appendix E, Table E-12).

#### *Fluticasone furoate (FF)/vilanterol (VIL) compared with fluticasone propionate (FP)*

We identified 3 RCTs that compared FF/VIL 200/25 mcg once daily with FP 500 mcg twice daily via DPI.<sup>34,39,199</sup> Two studies also included a third arm of a lower dose of 1 of the drugs, but not the same across the 2 studies. Two studies were good quality,<sup>39,199</sup> and 1 was fair quality.<sup>34</sup> The studies ranged in duration from 12 to 52 weeks and had a total sample size of 1,204 for the comparison assessed here. All 3 studies found similar proportions of patients reporting adverse events. Pooled analysis indicates no statistically significant difference between groups for withdrawals due to adverse events (RR 0.91, 95% CI 0.18 to 4.76;  $I^2=68%$ ). The risk of experiencing a serious adverse event while on study treatment was also not statistically significantly different after pooling (0.62, 95% CI 0.21 to 1.85;  $I^2=0%$ ). This evidence is low strength. One study reported that 2% (2 of 155) of patients on FF/VIL developed pneumonia after 12 weeks treatment compared with none in the FP group (0/154).<sup>34</sup> Evidence for these findings is low strength (Appendix E, Table E-12).

## C. Combination therapy compared with combination therapy

### a. Long-acting beta-2 agonists (LABAs) and long-acting muscarinic antagonists (LAMAs) compared with long-acting beta-2 agonists (LABAs) and inhaled corticosteroids (ICS)

#### Summary of findings

##### Asthma

- No eligible studies.

##### COPD

- *Glycopyrrolate (GLY)/indacaterol (IND) compared with fluticasone propionate (FP)/salmeterol (SAL)*
  - Based on a fair-quality RCT, there was low-strength evidence that there is not a statistically significant difference between drugs in overall adverse events, withdrawals due to adverse events, pneumonia and adverse events leading to hospitalization.
- *Umeclidinium (UME)/vilanterol(VIL) compared with fluticasone propionate (FP)/salmeterol (SAL)*
  - Based on 2 good-quality trials, there was moderate-strength evidence of no difference in overall adverse events, serious adverse events, and withdrawals due to adverse events or pneumonia between UME 62.5 mcg/VIL 25 mcg DPI daily and FP 500 mcg/SAL 100 mcg DPI daily.
  - Based on a good-quality RCT, there was low-strength evidence of no difference in overall adverse events, withdrawals due to adverse events or pneumonia between UME 62.5 mcg/VIL 25 mcg DPI daily and FP 1,000 mcg/SAL 100 mcg DPI daily.

#### Detailed assessment

##### COPD

###### *Glycopyrrolate (GLY)/indacaterol (IND) compared with fluticasone propionate (FP)/salmeterol (SAL)*

A fair-quality 26-week study (LANTERN) compared GLY 110 mcg/IND 50 mcg daily with FP 100 mcg/SAL 1,000 mcg daily in 744 patients with moderate (52%) to severe (46%) COPD (stage II-III by 2010 GOLD criteria).<sup>49</sup> This dose of GLY/IND is high dose (twice the US Food and Drug Administration approved dose), and the dose for glycopyrrolate is given in glycopyrronium equivalents. Mean age was 65 years and 90% were male. This study provides low-strength evidence that there is not a statistically significant difference between drugs in overall adverse events (149/372, 40.1% vs. 175/369, 47.4%) or withdrawals due to adverse events (12/372, 3.2%) compared with 17/369, 4.6%). There were lower absolute rates of pneumonia and adverse events leading to hospitalization with GLY/IND (0.8% and 4.3%, respectively) than FP/SAL (2.7% and 8, 4%, respectively) but the rates were low and the difference was not statistically significant. There were 2 deaths in the GLY/IND group and 0 in the FP/SAL group.

### *Umeclidinium (UME)/vilanterol (VIL) compared with fluticasone propionate (FP)/salmeterol (SAL)*

Two good-quality 12-week RCTs compared UME 62.5 mcg/VIL 25 mcg DPI daily with FP 500 mcg/SAL 100 mcg DPI daily in patients with moderate (50%) to severe (50%) COPD (N=1,403).<sup>22</sup> Overall, 26% of patients taking UME/VIL had an adverse event compared with 27% taking FP/SAL. Low-strength evidence finds no difference between groups in serious adverse events or withdrawals due to adverse events (Appendix E, Table E-17). Pneumonia was rare and not significantly different between groups.

A third good-quality 12-week RCT evaluated UME 62.5 mcg/VIL 25 mcg DPI daily with a higher dose FP 1,000 mcg/SAL 100 mcg DPI daily in 717 patients with moderate (55%) to severe (45%) COPD, with no exacerbations in the year prior to study.<sup>48</sup> This study found very similar rates of overall adverse events (28% vs. 29%) and withdrawals due to adverse events (2% vs. 1%) and pneumonia (<1% both groups). This is low-strength evidence.

### *b. Long-acting muscarinic antagonists (LAMAs) and long-acting beta-2 agonists (LABAs) compared with long-acting muscarinic antagonists (LAMAs) and long-acting beta-2 agonists (LABAs)*

#### **Summary of findings**

##### **COPD**

- *Glycopyrrolate (GLY)/indacaterol (IND) compared with tiotropium (TIO)/formoterol (FOR)*
  - Based on a good-quality 26-week trial, there is moderate and low-strength evidence that there is not a statistically significant difference in overall adverse events or withdrawals due to adverse events. Pneumonia incidence was also not significantly different at 26 weeks.
- *Umeclidinium(UME)/vilanterol (VIL) compared with tiotropium (TIO)/indacaterol (IND)*
  - Evidence was insufficient to draw conclusions.

#### **Detailed assessment**

##### **COPD**

*Glycopyrrolate (GLY)/indacaterol (IND) compared with tiotropium (TIO)/formoterol (FOR)*  
A good-quality 26-week study (QUANTIFY) of GLY 110 mcg/IND 50 mcg daily (in a fixed-dose DPI) compared with TIO 18 mcg/FOR 24 mcg daily (separate DPIs) enrolled 934 patients with moderate (57%) to severe (42%) COPD.<sup>140</sup> This dose of GLY/IND is high dose (twice the US Food and Drug Administration approved dose), and the dose for glycopyrrolate is given in glycopyrronium equivalents. The mean age was 63 years, and 66% were male. This study provides moderate-strength evidence of no difference in overall adverse events, and low-strength evidence of no difference in withdrawals due to adverse events. In this short-term study, event rates of pneumonia were low but slightly greater with TIO/FOR. The difference is not statistically significant (0.2% [1/476] GLY/IND vs. 1.7% [8/458] TIO/FOR; RR 0.12, 95% CI 0.03 to 0.96). There were 3 deaths in each group, again not statistically significantly different between groups.



*Umeclidinium (UME)/vilanterol (VIL) compared with tiotropium (TIO)/indacaterol (IND)*  
We included 1 unpublished RCT comparing UME 62.5 mcg/VIL 25 mcg DPI daily with TIO 18 mcg/ mcg in separate DPIs daily in patients with moderate to very severe COPD for 14 weeks.<sup>27</sup> The dose of IND is higher than that approved by the US Food and Drug Administration. A total of 961 patients, mean age 64 years, 72% male, with 46% predicted FEV1 at baseline were enrolled. Only adverse event data from this study were eligible for this review (as reported in ClinicalTrials.gov). Withdrawals due to adverse events were not reported, but overall 42% (202/482) in the UME/VIL group and 39% (186/479) in the TIO/IND group reported any adverse event. Within these there were 4% (17/482) and 3% (15/479) with non-fatal serious adverse events. There were 4/482 (0.8%) deaths in the UME/VIL groups and 1/479 (0.2%) in the TIO/IND group. One death in each group was due to pneumonia. The other 3 deaths in the UME/VIL group were due to cardiac arrest, ventricular fibrillation, circulatory collapse and 1 due to respiratory failure. This study was rated poor-quality due to the lack of adequate information in the ClinicalTrials.gov report provided by the manufacturer, and the evidence is insufficient for drawing conclusions.

### *c. Inhaled corticosteroids (ICSs) plus long-acting beta-2 agonists (LABAs) compared with inhaled corticosteroids (ICSs) plus long-acting beta-2 agonists (LABAs)*

#### **Summary of findings**

##### ***Asthma***

- *Beclomethasone/formoterol extrafine (BECx/FORx) compared with fluticasone propionate (FP)/salmeterol (SAL)*
  - Evidence on comparative harms was insufficient.
- *Budesonide (BUD)/formoterol (FOR) compared with fluticasone propionate (FP)/formoterol (FOR)*
  - Evidence on comparative harms was insufficient.
- *Budesonide (BUD)/formoterol (FOR) compared with fluticasone propionate (FP)/salmeterol (SAL)*
  - Four trials provided moderate-strength evidence that withdrawals due to adverse events did not differ between treatment arms.
- *Mometasone furoate (MOM)/formoterol (FOR) compared with fluticasone (FP)/salmeterol (SAL)*
  - Moderate-strength evidence from 2 fair-quality trials (12 weeks and 52 weeks) showed no difference in withdrawals due to adverse events or serious adverse events when comparing moderate doses to each other. Evidence from 1 fair-quality 52-week trial is low strength for a high-dose comparison, but again no differences were found.
  - Low-strength evidence suggested that ocular toxicity is not different between treatments.
- *Fluticasone (FP)/salmeterol (SAL) compared with fluticasone furoate (FF)/vilanterol (VIL)*
  - One trial provided low-strength evidence that withdrawals due to adverse events and serious adverse events did not differ between groups.

## **COPD**

- *Beclomethasone extrafine (BECx)/formoterol (FOR) compared with fluticasone propionate (FP)/salmeterol (SAL)*
  - Evidence on comparative adverse events was insufficient.
- *Budesonide (BUD)/formoterol (FOR) compared with beclomethasone (BEC)/formoterol(FOR)*
  - Evidence on comparative adverse events was insufficient.
- *Fluticasone propionate (FP)/salmeterol (SAL) compared with budesonide (BUD)/formoterol (FOR)*
  - Evidence on the risk of pneumonia was conflicting, depending on length of follow-up.
    - Evidence (2 good-quality observational studies) on the risk of pneumonia was conflicting.
      - A study with mean 3.5 years follow-up found greater risk with FP/SAL than with BUD/FOR (RR 1.73, 95% CI 1.57 to 1.90), event rates per 100 patient-years 11% and 6.4%). Mortality due to pneumonia was also increased (HR 1.8% CI 1.22 to 2.53; crude incidence 3.6% vs. 1.9%).
      - A study with 12 months of follow-up found no difference between the drugs in pneumonia diagnosis (OR 0.92, 95%, CI 0.81 to 1.04; event rates 17.3% vs. 19.0%) for BUD/FPR compared with FP/SAL.
- *Fluticasone furoate (FF)/vilanterol (VIL) compared with fluticasone propionate (FP)/salmeterol (SAL)*
  - FF 100 mcg/VIL 25 mcg daily with FP 500 mcg/SAL 100 mcg daily:
    - There was high-strength evidence from 3 good-quality trials that there is no difference in incidence of overall adverse events and moderate-strength evidence of no difference in pneumonia, withdrawals due to adverse events or serious adverse events.
  - FF 100 mcg/VIL 25 mcg daily compared with FF 1,000 mcg/SAL 100 mcg daily
    - Low-strength evidence from a single good-quality 12-week trial suggested no difference in overall adverse events or withdrawals due to adverse events.

## **Detailed assessment**

### ***Asthma***

We found 10 RCTs with 15 publications<sup>16,17,20,54,56,57,63,115,133-139</sup> that compared the combination of an ICS plus a LABA with another ICS/LABA combination for controller therapy treatment of asthma, and reported adverse events. One trial was good quality and the rest were fair quality.

### ***Beclomethasone/formoterol extrafine (BECx/FORx) compared with fluticasone propionate (FP)/salmeterol (SAL)***

We identified 1 trial comparing fixed-dose BEC and FOR with fixed-dose FP and SAL.<sup>17</sup> BEC/FOR was delivered via MDI at a daily dose of 400/24 mcg, while FP/SAL 500/100 mcg per day was delivered via DPI. Results were reported for 416 participants. The trial reported withdrawals due to adverse events and serious adverse events, but only 11 and 4 events occurred,

respectively, and we assessed the strength of evidence for this outcome as insufficient (BEC/FOR vs. FP/SAL, RR 1.21, 95% CI 0.40 to 3.69 for withdrawals due to adverse events and RR 1.01, 95% CI 0.18 to 5.68 for serious adverse events).

*Budesonide (BUD)/formoterol (FOR) compared with fluticasone propionate (FP)/formoterol (FOR)*

Two fair-quality trials (total N=358), both conducted in Brazil, compared BUD and FOR to fixed-dose FP and FOR, all delivered via DPI, with daily doses of BUD/FOR 800 mcg/24 mcg and FP/FOR 500/24 mcg.<sup>16,20</sup> Both trials reported serious adverse events, but only 7 events occurred and there was no statistically significant difference between the 2 therapies (BUD/FOR vs. FP/FOR, RR 0.77, 95% CI 0.12 to 4.99; insufficient evidence). One trial also reported withdrawals due to adverse events,<sup>20</sup> which were also infrequent (2 events) and showed no difference between treatments (RR 0.98, 95% CI 0.10 to 9.31; insufficient evidence).

*Budesonide (BUD)/formoterol (FOR) compared with fluticasone propionate (FP)/salmeterol (SM)*

Based on meta-analysis, 4 trials provided moderate-strength evidence of no statistically significant difference between BUD/FOR and FP/SM in the number of patients withdrawing from the study due to an adverse event; RR 1.02 (95% CI 0.68, 1.54) (Evidence Tables A and B).<sup>63,133-135</sup> The risk of experiencing a serious adverse event was also not statistically significantly different between the combination products (pooled RR 1.30, 95% CI 0.88 to 1.90). Post hoc subgroup analyses of data in patients 16 years old or greater in 2 studies indicated similar findings.<sup>56,57</sup>

*Fluticasone propionate (FP)/salmeterol (SAL) compared with mometasone furoate (MOM)/formoterol (FOR)*

Based on 2 studies, moderate-strength evidence suggests no difference in the rates of withdrawals due to adverse events, serious adverse events, or ocular toxicity between MOM/FOR and FP/SAL at medium doses. (Evidence Tables A and B).<sup>54,115,136</sup> The 2 studies differed in duration by 40 weeks, so data were not pooled. We calculated the individual relative risks as shown in Table 6 below. Although the high dose comparison indicates a potential for greater risk for both study withdrawal and serious adverse events with high dose MOM/FOR compared with FP/SAL, confidence intervals are not statistically significant. Evidence for the higher doses was rated low strength.

Ocular toxicity was reported in 2014<sup>54</sup> using data from the same trial reported in 2010.<sup>136</sup> It was measured using the validated Lens Opacities Classification System (LOCS) III, used for early detection of cataracts. The Evidence-based Practice Center calculated relative risks for the reported Class 1, Class 2, and Class 3 LOCS III grade changes, and found no statistically significant differences between treatment arms for any class. Results pooled across the 3 classes are shown in Table 5 below, and also show no statistically significant differences between patients treated with MOM/FOR and FP/SAL.

**Table 6. Risk of adverse event outcomes: MF/FOR compared with FP/SM**

Study, dose	Dose	Relative Risk (95% CI)
<i>Serious Adverse Events</i>		
Bernstein 2011	Medium	0.95 (0.29 – 3.03)
Maspero 2010	Medium	0.84 (0.27 – 2.64)

Study, dose	Dose	Relative Risk (95% CI)
Maspero 2010	High	2.0 (0.50 – 8.21)
<i>Withdrawal due to Adverse Events</i>		
Bernstein 2011	Medium	0.95 (0.35 – 2.56)
Maspero 2010	Medium	1.21 (0.28 – 5.32)
Maspero 2010	High	6.54 (0.81 – infinity) <sup>a</sup>

Abbreviations: FOR, formoterol; FP, fluticasone propionate; MF, mometasone furoate; SM, salmeterol.

<sup>a</sup> Zero events in FP/SM group, 0.5 continuity factor used.

### *Fluticasone propionate (FP)/salmeterol (SAL) compared with fluticasone furoate (FF)/vilanterol (VIL)*

In a single good-quality trial (N=806), after 24 weeks of treatment, there were no differences found between FP/SAL and FF/VIL in withdrawal due to adverse events or incidence of serious adverse events.<sup>139</sup> Asthma exacerbation was included as a serious adverse event and occurred in 1 patient. This evidence is low strength due to imprecision and lack of a corroborating study.

### **COPD**

We found 6 RCTs and 3 observational studies comparing adverse event rates in patients with moderate to very severe COPD treated with fixed-dose combination products of an ICS/LABA. Six studies were good quality and 3 were fair quality.

### *Beclomethasone extrafine (BECx)/formoterol (FOR) compared with fluticasone propionate (FP)/salmeterol (SAL)*

In a 12-week, fair-quality, study of 419 patients with moderate to severe COPD comparing BECx 200mcg/FOR 12 mcg DPI with FP 500 mcg/SAL 50 mcg MDI, small numbers of patients withdrew due to adverse events (1.4% vs. 2.4%;  $P>0.05$ ), had pneumonia (3 vs. 0,  $P>0.05$ ), and there was 1 death in the BECx/FOR group and none in the FP/SAL group.<sup>47</sup> Overall adverse event rates were not reported. This evidence is inefficient to draw conclusions.

### *Budesonide (BUD)/formoterol (FOR) compared with beclomethasone (BEC)/formoterol (FOR)*

In the trial of 718 patients with severe COPD, differences in rates of serious adverse events, any adverse events, withdrawals due to adverse events and pneumonia were not different between the groups.<sup>60</sup> Rates for withdrawing due to adverse events were 3.8% with BEC/FOR and 2.5% with BUD/FOR, rates of pneumonia were 2.1% compared with 2.9%, respectively. While 2 patients died in the BEC/FOR group and 4 in the BUD/FOR group none were reported to be related to drug treatment.

### *Budesonide (BUD)/formoterol (FOR) compared with fluticasone propionate (FP)/salmeterol (SAL)*

Two good-quality retrospective cohort studies evaluated BUD/FOR compared with FP/SAL and reported adverse events.<sup>30,62</sup> One of the 2<sup>62</sup> used the fixed-dose BUD/FOR combination in a DPI that is not available in the United States (see Methods). These studies provide conflicting evidence on the risk of pneumonia with these drugs, differentiated by duration of follow-up. A study (N=5,468), based on Swedish primary care medical records and linked databases, provides low-strength evidence of an increased risk of pneumonia and pneumonia-related mortality in patients using FP/SAL compared with BUD/FOR.<sup>62</sup> The study used propensity score matching to reduce confounding. While the follow-up period was up to 10 years, or the end of use of the fixed-dose combination product, emigration or death, the mean duration of follow-up per patient

was 3.5 years. The risk of pneumonia was significantly higher with FP/SAL compared with BUD/FOR; RR 1.73 (95% CI 1.57 to 1.90; event rates 11% and 6.4%). Similar results were found for pneumonia requiring hospitalization (RR 1.74, 95% CI 1.56 to 1.94). Analysis of baseline risk factors indicated that those with greater disease burden had higher rates with FP/SAL than with BUD/FOR. Mortality related to pneumonia was also increased with FP/SAL compared with BUD/FOR; RR 1.76 (95% CI 1.22 to 2.53; crude incidence 3.6% vs. 1.9%).

A second study, using administrative claims data from the United States (N=7,394), also reported on pneumonia.<sup>30</sup> The study used propensity score matching to reduce confounding, and adjusted for potential confounders and followed patients newly starting BUD/FOR or FP/SAL for 1 year. This study provides low-strength evidence of no statistically significant difference in rates of pneumonia diagnosis at 1 year (odds ratio 0.92, 95% CI 0.81 to 1.04; event rates 17.3% vs. 19.0% comparing BUD/FOR with FP/SAL). No other outcomes related specifically to pneumonia were reported, but rates of hospitalization, emergency department visits, and outpatient office visits were also not statistically significantly different between groups. Withdrawals due to or serious adverse events were not reported.

#### *Fluticasone furoate (FF)/vilanterol (VIL) compared with fluticasone propionate (FP)/salmeterol xinafoate (SAL)*

Three good-quality trials (N=1,858) comparing FF 100 mcg/VIL 25 mcg DPI daily with FP 500 mcg/SAL 100 mcg daily for 12 weeks in patients with moderate to very severe COPD were published in a single report.<sup>23</sup> Two of these studies previously had data available for this report only via the results reported in ClinicalTrials.gov.<sup>51,52</sup> These studies provide high-strength evidence that there is no difference between the drugs in the incidence of overall (any) adverse event, and moderate-strength evidence of no differences in the rates of serious adverse events, withdrawals due to adverse events and pneumonia. The publication's pooled analysis reports similar, not statistically significantly different, rates of overall adverse events (27% and 28%;  $P=0.52$ ), serious adverse events (2% and 3%) and withdrawals due to adverse events (2% and 3%). The incidence of pneumonia was 7% with FF/VIL and 4% with FP/SAL.

Another good quality trial of FF 100 mcg/VIL 25 mcg daily compared with FF 1,000 mcg/SAL 100 mcg daily for 12 weeks in patients with moderate to very severe COPD was also included (N=528).<sup>15</sup> Again overall incidence of adverse events for FF/VIL and FP/SAL (27% and 26%), withdrawals due to adverse events (2% and 1%), and severe adverse events (2% and 1%) were low and similar between groups. Pneumonia was not reported. This evidence is low strength.

#### *Fluticasone propionate (FP)/salmeterol (SAL) compared with fluticasone furoate (FF)/vilanterol (VIL)*

Three RCTs with results reported on the ClinicalTrials.gov trial registry provide insufficient-strength evidence on comparative harms for FF/VIL and FP/SAL used for 12 weeks in patients with COPD.<sup>15,235-237</sup> For withdrawals due to adverse events, combining all 3 trials together results in a relative risk of 1.38 (95% CI 0.39 to 4.93) with an  $I^2$  of 53%. Removing 1 trial that used a high dose of FP/SAL (500 mcg/50 mcg twice daily vs. 250 mcg/50 mcg in the other 2 trials) results in a relative risk of 0.09 (95% CI 0.39 to 2.48) and a  $\chi^2$   $P$  of 0.07 ( $I^2$  inestimable). Serious adverse events and mortality rates were low in the trials, and pooled analyses are similarly inconclusive and difficult to interpret due to heterogeneity and imprecise estimates. Using all 3 trials, the risk of serious adverse events was relative risk of 1.03 (95% CI 0.40 to

2.53,  $I^2=23\%$ ), and with removal of the higher dose study became relative risk of 0.69 (95% CI 0.26 to 1.80). Across the 3 trials (N=1,558 total), 2 patients died in the FF/VIL groups and 1 died in the FOR/SAL groups.

## **II. Inter-class Comparisons (between classes)**

### **A. Monotherapy**

#### **a. Inhaled corticosteroids (ICSs) compared with leukotriene modifiers (LMs)**

#### **Summary of findings**

##### ***Asthma***

- Data from 2 good-quality systematic reviews, numerous fair-quality head-to-head RCTs, and 1 observational study provided no evidence of a difference in adverse events between ICSs and LMs.

##### ***COPD***

- No eligible studies.

#### **Detailed assessment**

##### ***Asthma***

We found 2 systematic reviews with meta-analyses<sup>238,239</sup> and 18 RCTs<sup>38,46,141-147,149,151,154-158,161,164-166</sup> that compared ICSs and LMs (described in Evidence Tables A and B and in the Key Question 1 section of this report). Study duration ranged from 6 weeks to 56 weeks. Four RCTs and an observational study not included in these reviews are also included here.<sup>38,46,143,157,230</sup>

One good-quality systematic review with meta-analysis<sup>238,240</sup> provides evidence for adverse events and tolerability in patients with asthma, comparing LM and ICS drug classes. The meta-analysis found the same risk of experiencing any adverse effects in patients taking LMs compared with those taking ICSs (N=22 trials, 3 in children, RR 1.00, 95% CI 0.95 to 1.05). Serious adverse events were not assessed. There was no statistically significant difference in the risk of withdrawing due to adverse events (N=25 trials, 8 in children, 8,518 patients; RR 1.24, 95% CI 0.95 to 1.63). For both overall adverse events and withdrawals due to adverse events, results were similar in subanalyses of adult compared with pediatric patients.

A second systematic review with meta-analysis<sup>239</sup> included 18 studies (N=3,757) enrolling children and adolescents less than 18 years of age, 13 of which compared ICS therapy to that of MON but only 5 trials reported adverse event outcomes. Six of the included trials met our inclusion criteria<sup>149,156,160-162,168</sup> but 7 did not. Intervention drugs included MON (4 to 10 mg) compared with BEC 200-400 mcg/day (0.5 mg nebulized), FP 200 mcg/day, or BUD 200-800 mcg/day. Overall, the meta-analysis reported no difference between ICS- and MON-treated patients with respect to incidence of adverse effects (N=1,767, RR 0.98, 95% CI 0.86 to 1.11,  $P=0.73$ ).

Overall tolerability and adverse events from individual head-to-head trials are summarized in Evidence Tables A and B. Most studies did not find a significant difference between ICSs and LMs. In this update, 2 RCTs found no differences in rates of overall adverse events (in a small trial, N=60, comparing BUD and MON in children and adolescents)<sup>46</sup> or withdrawal due to adverse events (in a larger trial, N=566, in adults comparing both MOM and

FP to MON).<sup>38</sup> Other outcomes reported were not eligible for this review (i.e., bone density and serious adverse events deemed related to study drug).

One fair-quality head-to-head RCT (N=360) compared linear growth rates in prepubertal children treated with MON, BEC, or placebo.<sup>143</sup> The mean growth rate of subjects treated with BDP was 0.81 cm less than that of subjects treated with MON over the study's 56-week duration. In contrast, a retrospective cohort study of 844 children ages 4 to 9.5 years taking MON (N=245), FP (N=502) or BUD (N=43) found no significant difference in linear growth velocity between those taking MON (0.180 mm/day, SE 0.0055) and those taking 1 of the inhaled corticosteroids (0.187 mm/day, SE 0.0044).<sup>230</sup>

## *b. Inhaled corticosteroids (ICSs) compared with long-acting beta-2 agonists (LABAs)*

### **Summary of findings**

#### ***Asthma***

- Although evidence from 16 head-to-head trials (4,773 subjects) provided no evidence of a difference in overall adverse events between ICSs and LABAs in adults and adolescents with asthma, LABAs are not recommended nor approved for use as monotherapy for persistent asthma because they may increase the risk of asthma-related death (see LABA vs. LABA section of Key Question 2).
  - Rates of overall adverse events and withdrawals due to adverse events were similar for those treated with ICSs and those treated with LABAs.

#### ***COPD***

- Based on a good-quality systematic review and meta-analysis of 7 RCTs of FP compared with SAL and BUD compared with FOR, there was moderate-strength evidence of no difference in risk of any adverse event between ICS and LABA (OR 1.12, 95% CI 0.96 to 1.30, 5 studies), but moderate-strength evidence of increased risk of serious pneumonia with ICS compared with LABA (OR 1.48, 95% CI 1.13 to 1.94, 5 studies).
- Low-strength evidence from 2 RCTs of MOM compared with FOR indicates no difference in withdrawals due to adverse events, risk of experiencing an adverse event, and risk of experiencing a serious adverse event.

### **Detailed assessment**

#### ***Asthma***

##### *Fluticasone propionate (FP) compared with salmeterol (SAL)*

Seven fair-quality RCTs compared FP with SAL for monotherapy.<sup>172,174-178,180,181,187</sup> The majority of trials found no difference or a trend toward better outcomes in those treated with FP compared with those treated with SAL (Evidence Tables A and B).

##### *Budesonide (BUD) compared with formoterol (FOR)*

There were no reviews or head-to-head studies comparing BUD with FOR in patients with asthma.

##### *Mometasone furoate (MOM) compared with formoterol (FOR)*

Two fair-quality RCTs of 26 weeks duration compared MOM 200 mcg<sup>190</sup> or MOM 100 mcg<sup>189</sup> with FOR 10 mcg in patients with asthma. The most frequent adverse event in both trials was

upper respiratory infections but did not differ between groups in either trial (*P* values not reported). Severe or serious adverse events were also similar between groups in both RCTs (*P* values not reported).

#### *Fluticasone propionate (FP) compared with formoterol (FOR)*

We identified 2 good-quality 12-week RCTs with similar design comparing FP 200 mcg daily with FOR 20 mcg daily (both by MDI) in patients with mild to moderate asthma.<sup>41,188</sup> Patients were  $\geq 12$  years with a mean age of 38 years and 58% female. Current smokers were excluded, as well as those with a smoking history of at least 10 pack-years. There was no difference between treatment with FP and FOR in study withdrawals due to adverse events (RR 0.65, 95% CI 0.33 to 1.29, *P*=0.22; insufficient evidence), risk of experiencing any adverse event (RR 0.94, 95% CI 0.75 to 1.18, *P*=0.60), or severe adverse event (RR 0.55, 95% CI 0.21 to 1.44, *P*=0.22).

#### **COPD**

We identified 1 good-quality systematic review of ICS compared with LABA in patients with COPD.<sup>191</sup> The review included 7 RCTs (combined *N*=5,997) and all met inclusion criteria for this report. All studies were rated unclear to low risk of bias on randomization, allocation concealment, blinding, completeness of data and selective reporting. All studies were multicenter, double-blind RCTs with durations of 6 months to 3 years. The mean age of participants was 64 years with 62% to 78% males. Four studies compared FP with SAL. Three studies compared BUD with FOR.

#### *Fluticasone propionate (FP) compared with salmeterol (SAL)*

We identified 1 good-quality systematic review of ICS compared with LABA in patients with COPD.<sup>191</sup> The review included 4 RCTs (combined *N*=4,527) that compared FP with SAL. The daily SAL dose for all studies was 100 mcg; for 3 studies, including the largest study, the daily FP dose was 1,000 mcg, with a daily dose of 500 mcg in the fourth study. All studies were multicenter, double-blind RCTs from 6 months to 3 years duration. The mean age of participants was 64 years with 62% to 76% males. The risk of any adverse event of any non-fatal serious adverse event were not different in the FP groups compared with the SAL groups (OR 1.14, 95% CI 0.96 to 1.35, 4 studies; OR 1.17, 95% CI 0.60 to 2.28, 3 studies, respectively). However serious pneumonia adverse events were increased with FP (OR 1.46, 95% CI 1.12 to 1.92, 4 studies).

#### *Budesonide (BUD) compared with formoterol (FOR)*

We identified 1 good-quality systematic review of ICS compared with LABA in patients with COPD. The review included 3 RCTs (combined *N*=1,470) that compared BUD with FOR. The daily FOR dose for all studies was 18 mcg; for 2 studies the daily BUD dose was 800 mcg, with a daily dose of 640 mcg in the third study. All studies were multicenter, double-blind RCTs with durations from 6 months to 1 year. The mean age of participants was 64 years with 67% to 78% males. One study provided data for risk of experiencing any adverse event (*N*=559) and found when treated with BUD compared with FOR (OR 1.03, 95% CI 0.74 to 1.44). Results were similar for serious, non-fatal adverse events based on a pooled analysis of 3 studies (OR 1.01, 95% CI 0.77 to 1.31). One study reported risk of serious pneumonia. While the point estimate favored FOR, the confidence interval was wide (OR 2.82, 95% CI 0.40 to 20.16).



### *Mometasone furoate (MOM) compared with formoterol (FOR)*

One good-quality<sup>241</sup> and 1 fair-quality RCT<sup>171</sup> of 26 weeks duration compared MOM 400 mcg with FOR 10 mcg (combined N=915). Combined, the mean age of subjects was 60 years and 77% were male. Approximately 48% were current smokers. There was no difference between MOM and FOR in withdrawals due to adverse events (RR 0.77, 95% CI 0.29 to 2.08,  $P=0.60$ ,  $I^2=53\%$ ), risk of any adverse event (RR 0.94, 95% CI 0.78 to 1.12,  $P=0.46$ ,  $I^2=0\%$ ), and risk of a serious adverse event (RR 0.98, 95% CI 0.63 to 1.52,  $P=0.92$ ,  $I^2=0\%$ ). Results were similar with the additional data from the 26-week extensions.

### *d. Leukotriene modifiers (LMs) compared with long-acting beta-2 agonists (LABAs)*

#### **Summary of findings**

##### ***Asthma***

- Two small head-to-head trials provide insufficient evidence to draw conclusions.
  - LABAs are not recommended or approved for use as monotherapy for persistent asthma because they may increase the risk of asthma-related death.

##### ***COPD***

- No eligible studies.

#### **Detailed assessment**

We found 2 fair-quality RCTs<sup>192,193</sup> that included head-to-head comparisons of 1 LM with 1 LABA. In both trials, overall adverse events and/or withdrawals due to adverse events were similar between those treated with LMs and those treated with LABAs (Evidence Tables A and B).

### *e. Long-acting muscarinic antagonists (LAMAs) compared with long-acting beta-2 agonists (LABAs)*

#### **Summary of findings**

##### ***Asthma***

- *Tiotropium (TIO) compared with salmeterol (SAL)*
  - There was low-strength evidence of no significant difference between TIO and SAL in withdrawals due to adverse events or the proportion of patient with serious harms.

##### ***COPD***

- *Tiotropium (TIO) compared with salmeterol (SAL)*
  - There was moderate-strength evidence that TIO is associated with fewer patients experiencing a nonfatal serious adverse event and low-strength evidence that TIO is associated with a lower proportion of patients who withdraw due to adverse events compared with SAL.
- *Tiotropium (TIO) compared with indacaterol (IND)*
  - There was low-strength evidence that TIO does not differ from IND in the proportion of patients with nonfatal serious harms or who withdrew due to harms.
- *Tiotropium (TIO) compared with formoterol (FOR)*

- There was low-strength evidence that TIO does not differ from FOR in the proportion of patients with nonfatal serious harms or who withdrew due to harms.

## Detailed assessment

### *Asthma*

#### *Tiotropium (TIO) compared with salmeterol (SAL)*

Two fair-quality RCTs provide low-strength evidence of no statistically significant differences in withdrawals due to harms between TIO and SAL add-on treatment in patients whose asthma was not controlled by inhaled corticosteroids alone (pooled OR 3.13; 95% CI 0.49 to 20.04; 1% vs. 0.3%).<sup>194,195</sup> For patients with the B16-Arg/Arg genotype, there is low-strength evidence of no statistically significant differences between TIO and SAL in rate of serious adverse events (1.6% vs. 5.2%; OR 0.29; 95% CI 0.03 to 1.56).<sup>194</sup> TIO and SAL were comparable on all other harms. The Key Question 1 section of this report describes these RCTs in more detail and results are provided in the Evidence Tables.

### *COPD*

#### *Tiotropium (TIO) compared with salmeterol (SAL)*

Four RCTs in 3 publications with 8936 participants) provided data on harms.<sup>242-244</sup> Compared with SAL, TIO was associated with significant lower proportions of patients with nonfatal serious harms (11.8% vs. 13.6%; OR 0.85; 95% CI 0.75 to 0.96; moderate-strength evidence) and withdrawals due to harms (7.1% vs. 8.6%; OR 0.81; 95% CI 0.69 to 0.95; low-strength evidence).

#### *Tiotropium (TIO) compared with indacaterol (IND)*

Two RCTs with 2,856 participants with moderate to severe COPD provided low-strength evidence of no statistically significant differences between TIO and IND in proportions of patients with nonfatal serious harms (6.0% vs. 5.4%; OR 1.10; 95% CI 0.78 to 1.55) and withdrawals due to harms (3.6% vs. 5.3%; OR 0.72; 95% CI 0.49 to 1.05) after 12 to 26 weeks.<sup>140,245</sup> One RCT with 3,444 participants with severe COPD also provided low-strength evidence that TIO and IND had similar rates of adverse event-related withdrawals (5.6% vs. 5.9%) and rates of any serious adverse event (15% in both groups).<sup>246</sup>

#### *Tiotropium (TIO) compared with formoterol (FOR)*

One RCT with 431 participants provided data on harms for the comparison of TIO and FOR.<sup>247</sup> This RCT provided low-strength evidence of no statistically significant differences between TIO and FOR in proportions of patients with nonfatal serious harms (5.9% vs. 2.9%; OR 2.13; 95% CI 0.74 to 6.94; from good-quality Cochrane review)<sup>196</sup> and withdrawals due to harms (4.5% vs. 3.8%; OR 1.20; 95% CI 0.46 to 3.09).

### *f. Inhaled corticosteroids (ICSs) compared with phosphodiesterase-4 (PDE-4) inhibitors*

## Summary of findings

### *Asthma*

- Evidence from a single trial was insufficient to draw conclusions.

## ***COPD***

- No eligible studies.

### **Detailed assessment**

#### ***Asthma***

The single included trial comparing an ICS to a PDE-4 inhibitor enrolled 499 adolescents and adults with asthma from centers in the UK and Europe, and administered either 400 mcg/day BEC or 500 mcg/day ROF over 12 weeks.<sup>197</sup> Few patients experienced serious harms, only 3 of those taking ROF and 2 taking BEC (1% of patients in each arm), providing insufficient evidence to compare this outcome between the 2 drugs. However, 9 patients in the ROF arm withdrew due to adverse events, compared with just 1 in the BEC arm. We calculated a RR of 8.75 (95% CI 1.45 to 53.25) for withdrawals due to adverse events; though the confidence interval was very wide, it did exclude no difference between the drugs. We did not identify any reviews or head-to-head studies comparing ICS with PDE-4 inhibitors in patients with COPD.

#### ***g. Long-acting beta-2 agonists (LABAs) compared with long-acting muscarinic antagonist (LAMAs)***

### **Summary of findings**

#### ***Asthma***

- Three trials comparing salmeterol (SAL) with tiotropium (TIO) found no differences between the groups in rates of overall adverse events, withdrawal due to adverse events, or specific harms (low-strength evidence).

## ***COPD***

- Three trials from the prior report found increased rates of withdrawal due to adverse events for salmeterol (SAL) compared with tiotropium (TIO) (OR 1.23; 95% CI 1.05 to 1.45) (moderate-strength evidence).
- One trial of formoterol (FOR) compared with tiotropium reported no differences in non-fatal serious adverse events or withdrawal due to adverse events (insufficient evidence)
- One trial of indacaterol (IND) compared with tiotropium (TIO) in severe COPD patients and 2 trials in moderate-to-severe COPD patients found no differences in serious adverse events or withdrawal due to adverse events (low-strength evidence).

### **Detailed assessment**

#### ***Asthma***

##### ***Salmeterol (SAL) compared with tiotropium (TIO)***

The prior review included 2 fair-quality RCTs<sup>194,195</sup> comparing SAL with TIO in patients whose asthma was not adequately controlled by inhaled corticosteroids. Both of these trials found no differences in rates of withdrawal due to adverse events or other harms between SAL and TIO.

We identified 1 additional trial comparing SAL 50 µg and TIO 2.5 or 5 µg.<sup>31</sup> In this 24-week trial, no differences were reported between groups in rates of overall adverse events or withdrawal due to adverse events. For the comparison of SAL 50 µg with TIO 5 µg, the pooled OR for overall adverse events from all 3 trials was 1.11 (95% CI 0.89 to 1.37;  $I^2=0\%$ ).

## **COPD**

### *Salmeterol (SAL) compared with tiotropium (TIO)*

A systematic review included in the prior review compared SAL to TIO in patients with COPD reported harms. SAL was associated with increased rates of nonfatal serious harms (13.6% vs. 11.8%; OR 1.18, 95% CI 1.04 to 1.33) and withdrawal due to adverse events (8.6% vs. 7.1%; OR 1.23, 95% CI 1.05 to 1.45).

We identified no new trials published since the prior comparing SAL to TIO in patients with COPD.

### *Formoterol (FOR) compared with tiotropium (TIO)*

The prior report included 1 trial reporting the harms of FOR compared with TIO. No differences were noted in rates of non-fatal serious adverse events (OR 0.83, 95% CI 0.32 to 2.17) or withdrawal due to adverse events (OR 0.47, 95% CI 0.14 to 1.35).

We identified no new studies for this comparison.

### *Indacaterol (IND) compared with tiotropium (TIO)*

The prior report included 1 trial reporting harms of IND compared with TIO in patients with severe COPD, which found no differences in serious adverse events (15% vs. 15%) or withdrawal due to adverse events (5.6% vs. 5.9%). In addition, the report identified 2 trials conducted in patients with moderate-to-severe COPD, in which no differences were reported in non-fatal serious adverse events (OR 0.91, 95% CI 0.65 to 1.28) or withdrawal due to adverse events (OR 1.39, 95% CI 0.95 to 2.04).

We identified no new studies for this comparison.

## **B. Combination therapy compared with monotherapy**

### ***a. Inhaled corticosteroids (ICSs) and long-acting beta-2 agonists (LABAs) compared with long-acting beta-2 agonists (LABAs)***

#### **Summary of findings**

##### ***Asthma***

- No eligible studies.

##### ***COPD***

- *Switch to indacaterol (IND) compared with continued salmeterol (SAL)/ propionate (FP)*
  - A good-quality trial provided low-strength evidence that rates of serious adverse events were lower with IND than with SAL/FP (RR 0.29, 95% CI 0.11 to 0.74).

#### **Detailed assessment**

##### ***COPD***

The INSTEAD trial<sup>45</sup> enrolled patients with moderate-severity COPD who had been treated before enrollment with SAL/FP 100/1,000 mcg daily by DPI, and compared continued treatment with SAL/FP with switching to IND 150 mcg daily by DPI for 26 weeks. This dose is twice the US Food and Drug Administration approved dose. All patients enrolled had at least a 10 pack-year smoking history; 69% were men, and the mean age was 66 years. The trial provided low-strength evidence that rates of serious adverse events were lower with patients switching to IND

than with those continuing SAL/FP (RR 0.29, 95% CI 0.11 to 0.74). Evidence was insufficient to compare rates of withdrawals due to adverse events between groups.

*b. Inhaled corticosteroids (ICSs) and long-acting beta-2 agonists (LABAs) compared with inhaled corticosteroids (different drug)*

**Summary of findings**

***Asthma***

- *Fluticasone propionate (FP)/salmeterol (SAL) compared with ciclesonide (CIC)*
  - There is low-strength evidence CIC results in an increased risk of experiencing any adverse event compared with FOR/SAL (RR 1.15, 95% CI 1.01 to 1.30).
- *Fluticasone furoate (FF)/vilanterol (VIL) compared with fluticasone propionate (FP)*
  - Low-strength evidence from 2 RCTs finds no difference in withdrawals, any, and serious adverse events.

***COPD***

- No eligible studies.

**Detailed assessment**

*Fluticasone propionate (FP)/salmeterol (SAL) compared with ciclesonide (CIC)*

We identified 1 fair-quality RCT (N=432) in patients with mild persistent asthma who were randomized to CIC 160 mcg once daily or FP/SAL 200/100 twice daily.<sup>198</sup> Patients were  $\geq 12$  years of age (mean age 30), 43% male, non- or ex-smokers with a smoking history of  $< 10$  pack years. Ciclesonide increased the risk of experiencing any adverse event compared with FOR/SAL (RR 1.15, 95% CI 1.01 to 1.30,  $P=0.04$ ), although most events were considered mild to moderate.

*Fluticasone furoate (FF)/vilanterol (VIL) compared with fluticasone propionate (FP)*

We identified 1 good-quality<sup>199</sup> and 1 fair-quality, unpublished RCT<sup>248</sup> that compared FF/VIL with FP via DPI. The good-quality study (N=503, mean age 39 years, 37% male, duration 52 weeks) primarily evaluated safety. Patients were randomized to FF/VIL (200/25 mcg or 100/25 mcg once daily) or FP (500 mcg) twice daily. There were few study withdrawals due to adverse events (8/403 treated with FF/VIL and 6/100 treated with FP (RR 0.66, 95% CI 0.18 to 2.45,  $P=0.54$ ). The risk of experiencing any adverse event was also similar (RR 0.93, 95% CI 0.81 to 1.06), although the risk of any serious adverse event was reduced with FF/VIL (RR 0.14, 95% CI 0.04 to 0.48).

The fair-quality, unpublished study (N=392, mean age 47, 41% male, duration 24 weeks) randomized patients to FF/VIL 200/25 mcg once daily or FP 500 mcg twice daily via DPI. As in the published study, there were few withdrawals due to adverse events (7/197 treated with FF/VIL and 2/195 treated with FP, RR 3.46, 95% CI 0.73 to 16.47,  $P=0.12$ ). The risk of experiencing a non-serious adverse event similar between the FF/VIL and FP groups (RR 0.84, 95% CI 0.64 to 1.11), as was the risk of any serious adverse event (RR 2.97, 95% CI 0.61 to 14.53).

### *c. Inhaled corticosteroids (ICSs) and long-acting beta-2 agonists (LABAs) compared with long-acting muscarinic agonists (LAMAs)*

#### **Summary of findings**

##### *Asthma*

- No eligible studies.

##### *COPD*

- *Tiotropium (TIO) compared with fluticasone propionate (FP)/salmeterol (SAL)*
  - When compared with FP/SAL in patients with COPD, there is low-strength evidence that TIO is associated with a significantly lower proportion of patients with serious harms, but the drugs do not differ in the proportion of patients who withdraw due to adverse events.
- *Tiotropium (TIO) compared with fluticasone furoate (FF)/vilanterol (VIL)*
  - Compared with FF/VIL, there is low-strength evidence that TIO does not differ in the proportion of COPD patients with serious adverse events, but insufficient evidence to draw conclusions about the comparative effect on withdrawals due to adverse events.
- *Tiotropium (TIO) compared with umeclidinium bromide (UME)/vilanterol (VIL)*
  - Compared with UME/VIL, there is low-strength evidence that TIO does not differ in its risk of withdrawal due to adverse events, but insufficient evidence to draw conclusions about the comparative effect on serious harms.

#### **Detailed assessment**

##### *Tiotropium (TIO) compared with fluticasone propionate (FP)/salmeterol (SAL)*

According to a good-quality Cochrane review<sup>200</sup> that included 2 eligible RCTs that compared FP/SAL 500/50 to TIO 18 mcg/day,<sup>201,202</sup> findings from the 2-year INSPIRE trial provided low-strength evidence that FP/SAL had a higher risk of serious harms (OR 1.55; 95% CI 1.21 to 1.98), but similar rates of withdrawals due to adverse events (OR 1.03; 95% CI 0.72 to 1.47) in patients with COPD.<sup>201</sup> Also in INSPIRE, proportions of patients with pneumonia was statistically significantly greater with FP/SAL (OR 2.13; 95% CI 1.33 to 3.40).<sup>200</sup> The unpublished 12-week study provided low-strength evidence that TIO and FP/SAL had similar shorter-term rates of withdrawals due to adverse events (3% vs. 0%) and serious adverse events (3% vs. 2%).

##### *Tiotropium (TIO) compared with vilanterol (VIL)/fluticasone furoate (FF)*

The 2 fair-quality 12-week RCTs (N=880) described above provided low-strength evidence of no statistically significant difference between TIO 18 mcg/day and FF/VIL 100/25 mcg/day in proportions of COPD patients with serious harms (4.3% vs. 3.9%; OR 1.11, 95% CI 0.57 to 2.16). We initially included these studies as unpublished, although they are now published<sup>13,14</sup> The proportion of patients who withdrew due to harms was 5% for TIO and 6% for FF/VIL in GSK study HZC115247 (OR 0.83; 95% CI 0.22 to 2.98) and 4% and 2%, respectively in GSK study HZC115805 (OR 2.02; 95% CI 0.69 to 6.64), but unacceptable inconsistency and imprecision across these findings precluded a conclusion about the pooled estimate of effect for

this outcome (OR 1.38; 95% CI 0.67 to 2.85). The proportion of patients with any adverse event, pneumonia and other specific adverse events were similar for TIO and FF/VIL.

*Tiotropium (TIO) compared with umeclidinium bromide (UME)/vilanterol (VIL)*

We included 3 fair-quality, unpublished, 24-week RCTs (N=1,759) and 1 good-quality, unpublished, 12-week RCT (n=496) that compared UME/VIL 62.5/25 mcg to TIO 18 mcg/day in patients with COPD and provided low-strength evidence of no statistically significant difference in withdrawals due to adverse events (5.4% vs. 3.9%; OR 1.42; 95% CI 0.90 to 2.23).<sup>26,206-208</sup> The proportion of patients with a serious adverse event was 5.1% for UME/VIL and 4.5% for TIO (OR 1.09; 95% CI 0.46 to 2.62), but unacceptable inconsistency and imprecision precluded a conclusion about this outcome.

*d. Inhaled corticosteroids (ICSs) and long-acting beta-2 agonists (LABAs) compared with leukotriene modifiers (LMs)*

**Summary of findings**

***Asthma***

- *Fluticasone propionate (FP)/salmeterol (SAL) compared with montelukast (MON)*
  - Moderate-strength evidence finds that overall, FP/SAL and LMs have similar rates of overall adverse events and withdrawals due to adverse events based on evidence from 4 short-term trials.

***COPD***

- No eligible studies.

**Detailed assessment**

***Asthma***

*Fluticasone propionate (FP)/salmeterol (SAL) compared with montelukast (MON)*

We found 4 RCTs<sup>141,210-212</sup> comparing low dose FP plus SAL with MON in patients with asthma. Two of the RCTs were in adolescents and adults, 1 enrolled subjects over the age of 6<sup>141</sup> (~15% of subjects were <12 years of age) and 1 enrolled only children age 6-14 years.<sup>211</sup>

The trials are described in more detail in the Key Question 1 section of the report. The 4 trials reporting withdrawals due to adverse events reported similar rates for those treated with MON (range 0.6% to 4%) and those treated with FP/SAL (range 0% to 3%); in each case the withdrawal rates in the 2 groups were within 1% of each other. The 3 trials reporting serious adverse events also reported similar, low rates between groups, less than 3% in any intervention group and with differences between FP/SAL and MON groups ranging from 0% to 0.5% (Evidence Tables A and B).

*e. Long-acting muscarinic antagonists (LAMAs) and long-acting beta-2 agonists (LABAs) compared with long-acting muscarinic antagonists (LAMAs)*

**Summary of findings**

***Asthma***

- No eligible studies.

## **COPD**

- *Umeclidinium (UME)/vilanterol (VIL) compared with tiotropium (TIO)*
  - Based on 3 fair-quality trials, low-strength evidence suggests no difference in overall adverse events, serious adverse events, withdrawal due to adverse events death, or pneumonia.
- *Umeclidinium (UME)/vilanterol (VIL) compared with umeclidinium (UME)*
  - Evidence from a single RCT provided insufficient evidence to draw conclusions.

## **Detailed assessment**

### **COPD**

The prior report included 3 fair-quality unpublished studies comparing the UME/VIL combination product with tiotropium in patients with COPD.<sup>206-208</sup>

We identified 4 trials (in 3 publications) that reported harms outcomes for the comparison of the UME/VIL combination therapy with tiotropium<sup>21,26,37</sup>; 3 of these (in 2 publications) are published reports<sup>21,37</sup> of previously included unpublished trials<sup>206-208</sup> that reports additional outcomes. One trial also compared with UME monotherapy.<sup>21</sup> All 4 trials enrolled adults aged  $\geq 40$  years with moderate-to-severe COPD. The mean ages of participants ranged from 62.3 to 64.6 years, the proportions of females ranged from 31% to 34.3%, and the proportions of patients in GOLD COPD stages II or III ranged from 87.3% to 88.3%. Sample sizes ranged from 496 to 905; 3 of the studies were 24 weeks long, while the duration of the fourth trial was 12 weeks. Three of the trials were rated as good quality, while the fourth trial was fair. All trials were funded pharmaceutically.

#### *Umeclidinium (UME)/vilanterol (VIL) compared with tiotropium (TIO)*

The 3 unpublished trials included in the prior report found no differences between groups in serious adverse events (5.1% vs. 4.5%; OR 1.09, 95% CI 0.46 to 2.62) or withdrawal due to adverse events (5.4% vs. 3.9%; OR 1.42, 95% CI 0.90 to 2.23).

Subsequently published reports of these trials, as well as an additional unpublished trial, found no differences between groups in overall adverse events (pooled OR 1.14; 95% CI 0.93 to 1.39;  $I^2=25\%$ ), death, or pneumonia. Consistent with the previously available trials, the additional newly identified unpublished trial also reported no difference between groups in withdrawal due to adverse events.

#### *Umeclidinium (UME)/vilanterol (VIL) compared with umeclidinium (UME)*

Similar to the comparison of UME/VIL with TIO, 1 trial comparing UME/VIL combination therapy with UME monotherapy found no differences between groups in overall adverse events, withdrawal due to adverse events, or death.



## C. Combination therapy compared with combination therapy

### *a. Inhaled corticosteroid (ICS) and long-acting beta-2 agonist (LABA) compared with inhaled corticosteroid and leukotriene modifier (LM)*

#### **Summary of findings**

##### ***Asthma***

- Overall, results from a good-quality systematic review with meta-analysis provided high-strength evidence that there is no difference in withdrawals due to adverse events.
- The review provided moderate-strength evidence that more patients adding LABAs to ICS therapy had serious harms than did patients adding LMs. These results held for trials comparing the specific drugs SAL and MON, both added to ICSs.
- There was insufficient evidence to assess adverse events in children <12 years of age.

##### ***COPD***

- No eligible studies.

#### **Detailed assessment**

##### ***Asthma***

We found 1 systematic review with meta-analysis, first published in 2006<sup>214</sup> and updated in 2011<sup>215</sup> and 6 RCTs<sup>216-221</sup> that compared the addition of a LABA with the addition of an LM for asthma patients poorly controlled on ICS therapy. All 6 of the RCTs meeting our inclusion criteria were also included in the systematic review, and we focus here on the results of the systematic review (described in detail in Key Question 1) Eleven of the trials included in the review (N=6,292) contributed data to meta-analyses we report here.

The systematic review reported no difference in withdrawals due to adverse events in patients with asthma (11 studies, RR 1.01, 95% CI 0.79 to 1.29) comparing drug classes ICS/LABA to LM/ICS; similar results for SAL/ICS vs. MON/ICS). For serious adverse events, the relative risk comparing LABAs with LMs as add-on therapy was 1.35 (95% CI 1.00 to 1.82), with again results very similar for SAL compared with MON as add-on therapy. There was also no significant difference in rates of elevated liver enzymes between patients treated with SAL and MON (1 study, RR 1.13, 95% CI 0.66 to 1.94 comparing ICS/LABA to LM/ICS). The review included 1 study each comparing SAL with ZAF and FOR with ZAF, and evidence was insufficient to compare harms for these specific drugs.

##### ***COPD***

We did not identify any good- or fair-quality systematic reviews or head-to-head trials that compared LABAs and LMs as add-on therapy to ICSs in subjects with COPD.

**Key Question 3. Are there subgroups of patients [e.g. groups defined by demographics (age, racial groups, gender), asthma or COPD severity, comorbidities, other medications (drug-drug interactions), smoking status, genetics, or pregnancy] for which asthma or COPD controller medications differ in efficacy, effectiveness, or frequency of adverse events?**

### ***Summary of findings***

- We did not find any studies that directly compared the efficacy or adverse events of our included drugs between subgroups and the general population in patients with asthma or COPD.
  - In head-to-head comparisons, few subgroups based on age, racial groups, sex, other medications, or comorbidities were evaluated.

### ***Detailed Assessment***

#### **I. Demographics**

##### ***Age***

##### ***Asthma***

Differences in efficacy, tolerability, and adverse events between children <12 years of age and adolescents or adults ≥12 are described in the body of the report (Key Questions 1 and 2) in the appropriate sections. These differences are also noted in the overall summary table. Therefore, they are not discussed here.

Only a few trials have studied the efficacy and safety of asthma medications in very young children (less than 3 years). We found no head-to-head studies comparing the efficacy or safety of our included drugs in very young children with efficacy or safety in older children, adolescents, or adults. We did find 1 trial comparing BUD with MON in children ages 2 to 8 years with mild persistent asthma.<sup>161</sup> A subgroup analysis of patients ages 2-4<sup>169</sup> (Table 7) shows that those taking BUD had 1.35 exacerbations (mild or severe) per patient per year, while those taking MON had 2.30 ( $P=0.003$ ). The difference between treatment groups was greater for children 2 to 4 than in the full population ages 2 to 8, “possibly suggesting that MON is less effective at controlling asthma in the younger subpopulation of patients”. Quality of life was similar between the 2 treatment groups in both age groups, though a measure of the child’s emotional health in the Children’s Health Survey for Asthma favored MON in children age 2 to 4 years. Serious adverse events occurred in 2% of BUD patients age 2 to 4 compared with 6% of MON patients; the difference again was greater than for patients age 2 to 8 years, though the investigators did not comment on differences in adverse effects between the age groups.

##### ***COPD***

In a case control study of elderly patients with COPD, mean age 78 years, the subjects were identified using the Quebec health insurance database and followed-up for 5.4 years to identify rates of serious pneumonia.<sup>249</sup> Serious pneumonia was higher with current users (defined as subjects with last prescription was dispensed within 60 days of the index date) of FP and BUD compared with their control groups. Fluticasone is associated with 2-fold (100%) increase in serious pneumonia (RR 2.01; 95% CI 1.93 to 2.10), with higher dose indicating greater

incidences of pneumonia. Budesonide is associated with 17% increase in rates of serious pneumonia (RR 1.17; 95% CI 1.09 to 1.26) without a dose-response effect.

### *Racial groups*

We did not find any studies that directly compared the efficacy and tolerability of included drugs within 1 racial or ethnic group to efficacy and tolerability in another such group. Two studies performed subgroup analyses in patients with asthma; results may provide indirect evidence of differences between racial groups (Table 7).

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.<sup>250</sup> 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 to 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 vs. 1, RR 7.26, 95% CI 0.89 to 58.94), and Caucasians (6 vs. 1, RR 5.82, 95% CI 0.70 to 48.37).

The Salmeterol Multicenter Asthma Research Trial (SMART),<sup>251</sup> a large 28-week randomized, double-blind study assessed the safety of SAL MDI (42 mcg twice/day) compared with placebo in asthma patients. We excluded placebo-controlled trials from this updated review, and so do not discuss this trial in detail. However, the trial reported statistically significant increases in respiratory-related deaths, asthma-related deaths, and in combined asthma-related deaths or life-threatening experiences for subjects receiving SAL compared with those receiving placebo. The increased risk was thought to be largely attributable to the African-American subpopulation. The US Food and Drug Administration released a safety alert based on the results of the trial, reporting that there were no significant differences in asthma-related events between SAL and placebo in Caucasian patients; however, in African Americans, there was a statistically significantly greater number of asthma-related events, including deaths, in SAL- compared with placebo-treated patients.<sup>252</sup>

A head-to-head trial identified for this 2014 update<sup>131</sup> compared 2 LABAs in COPD patients, and analyzed harms for racial subgroups (Table 7). The trial enrolled 444 patients from 62 United States centers; 63 patients were African American and 375 Caucasian. Patients received 6 months’ treatment with 24 mcg/day FOR via DPI or 1 of 2 doses of ARF (30 mcg or 50 mcg daily). The trial found little difference between drug arms in withdrawals due to adverse events in Caucasians (range 7.9 to 9.5% across treatment arms). For African Americans, though very few withdrawals occurred, it appeared that more patients withdrew due to adverse effects with ARF than with FOR; withdrawals were slightly higher for ARF 30 mcg (14.3%) than for FOR (10.5%), and higher still for the higher ARF dose (21.7%, suggesting a positive dose-response relationship). Consistent with the SMART trial showing higher risks of LABA use in African Americans, rates of withdrawal due to adverse events were higher in each drug arm for African Americans than they were for Caucasians. For serious adverse events, the comparison of ARF and FOR was difficult to interpret for Caucasians, with more patients taking ARF 30 experiencing serious adverse events (13.5%) than patients taking FOR (8.7%), but fewer patients taking ARF 50 experiencing serious adverse events (3.3%, i.e., there was no dose-response relationship for ARF vs. FOR). For African Americans, serious adverse event rates for FOR and

ARF 30 were about the same (15.8% vs. 14.3%), but the rate of serious adverse events in patients taking ARF 50 was higher (26.1%). Again, the African American subgroup in this trial was small and few adverse events occurred overall, so these results should be interpreted with caution.

One fair-quality multicenter trial in patients with asthma compared MON (10 mg/day) plus SAL (100 mcg/day plus placebo ICS) with low dose BEC (160 mcg/day plus SAL 100 mcg/day plus placebo LM) for 14 weeks, washout for 4 weeks, then crossover for another 14 weeks.<sup>224</sup> This study is described in detail in Key Question 1. The LM plus LABA combination led to significantly more subjects having a shorter time to treatment failure compared with ICS plus LABA (29 vs. 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 LM/LABA) was not significantly different from the proportion of African-American subjects ( $P=1.0$ ).

### **Gender**

We found 1 observational study that assessed ICS harms in premenopausal women with asthma, and another that directly compared the efficacy and tolerability of ICSs and LMs between boys and girls ages 4 to 9.5 years.

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

A retrospective cohort study of 844 children with asthma in Croatia<sup>230</sup> compared linear growth velocity between girls and boys taking either MON or the ICSs FP or BUD (Table 7). The study found no significant differences according to sex or age between treatment groups including ICS and non-ICS (MON) groups (ANOVA,  $P>0.05$  for all comparisons). The study actually showed slightly higher mean growth velocity in patients taking ICSs compared with those taking MON, in contrast to negative effects of ICSs on growth more typically reported. This was especially true for BUD among girls; however, because of prescribing practices in Croatia the mean age of patients taking BUD was also higher, which may explain differences in growth rates in this group. The BUD group also represented just 5% of the total cohort, and standard errors were higher in this group.

We identified no evidence for subgroup differences based on gender in patients with COPD.

## **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 asthma 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 1 ICS and another. We identified no evidence for subgroup differences based on comorbidities in patients with COPD.

### III. Other medications

A good-quality Cochrane review<sup>196</sup> reported that 2 RCTs of patients with COPD<sup>243,244</sup> found no statistically significant difference among subgroups that were, or were not, taking inhaled corticosteroids, in the comparison between TIO and SAL in the proportion of patients with 1 or more exacerbations. We did not find any evidence for subgroup differences based on additional medications taken in patients with asthma.

### IV. Smoking status

We found 1 cross-over study comparing asthmatic smokers and nonsmokers.<sup>253</sup> In this study, 44 nonsmokers (total lifetime smoking history of less than 2 pack-years and no smoking for at least 1 year) and 39 “light” smokers (currently smoking 10-40 cigarettes/day and a 2-15 pack-year history) were randomized to BEC (320 mcg/day) or MON (10 mg/day) for 8 weeks of active treatment, an 8-week washout, and then 8 weeks of active treatment with the other medication. Both smokers and non-smokers showed some improvement in change in average quality of life scores. However, the change from baseline was only statistically significant in ML-treated non-smokers. Average change was greater in MON-treated non-smokers compared with smokers than it was in BEC-treated non-smokers compared with smokers. The difference was not based on a direct statistical comparison between the MON and BEC groups and further studies are needed to determine if there are differences in the response to MON and/or BEC based on smoking status.

A randomized trial in 683 current smokers in the UK<sup>157</sup> compared 500 mcg/day of FP to 10 mg/day of MON in patients with asthma. The study did not include a comparison group of non-smokers. Exacerbation rates were lower for FP than MON (OR 0.75, 95% CI 0.43 to 1.31). Though the risk reduction was not statistically significant, it was similar in magnitude to that seen for studies overall (0.70, 95% CI 0.57 to 0.86, Key Question 1; includes this trial in smokers and 4 others in other populations). Adverse events did not differ between FP and MON in this study in smokers, similar to results found overall for ICSs compared with LMs (Key Question 2).

We found no evidence for subgroups differences based on smoking status in patients with COPD.

### V. Pregnancy

Maintaining adequate control of asthma during pregnancy is important for the health and well-being of both the mother and her baby. Inadequate control of asthma during pregnancy has been associated with higher rates of premature birth, intrauterine growth retardation, lower birth weight, perinatal death, and preeclampsia.<sup>1,254,255</sup> Expert opinion recommends ICSs as the preferred treatment for long-term control of asthma symptoms in pregnancy.<sup>1</sup> 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.<sup>1</sup>

US Food and Drug Administration-approved labeling classifies medications by the potential for risk during pregnancy. Budesonide is the only ICS labeled as a pregnancy category B (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 (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.<sup>256</sup>

In general, BUD 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 LMs 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.<sup>1</sup>

We found 1 systematic review and 2 observational studies focusing on ICS use in pregnant asthmatics. We did not identify any studies assessing the efficacy or safety of LABAs, LMs, 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.<sup>257</sup> Studies were eligible for inclusion in this analysis if the included women were exposed to any therapeutic dosage of any FP, BEC, BUD, TAA or FLUN 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 2 studies was 0.96 (95% CI 0.51 to 1.83;  $P=0.9582$ ). The summary OR for preterm delivery in 3 studies was 0.99 (95% CI 0.8 to 1.22;  $P=0.9687$ ). The summary OR for low birth weight delivery in 2 studies was 0.89 (95% CI 0.7 to 1.14;  $P=0.4013$ ). The summary OR for pregnancy-induced hypertension in 3 studies was 0.97 (95% CI 0.84 to 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.

A second observational study<sup>258</sup> aimed to investigate the association between doses of ICSs during the first trimester of pregnancy and the risk of congenital malformations among women with asthma. The study found that women using low to moderate doses of ICSs (>0 to 1,000 mcg/day equivalent BEC) were not at increased risk of having a baby with a malformation than women who did not use ICSs during the first trimester. Women using high doses of ICSs (>1,000 mcg/day) were more likely to have a baby with a malformation than women who used low to moderate doses (adjusted RR, 1.63; 95% CI 1.02 to 2.60). However, these results should be interpreted with caution as confounding by severity of asthma cannot be ruled out as the cause of these findings.

We also identified 1 observational study of 6199 women with asthma giving birth between 1998 and 2008 in Canada (7,376 pregnancies).<sup>259</sup> Women were exposed to ICS (N=4,198 pregnancies), LABA (650 pregnancies), or neither (3,178 pregnancies). FP alone was the most commonly used ICS (76%) followed by BUD alone (14.5%). SAL was the most commonly prescribed LABA (69.7%), followed by FOR (29.2%). All women treated with LABA were also prescribed ICS. Women exposed to LABA and higher-dose ICS were more likely to have diabetes and moderate or severe asthma prior to pregnancy. Exposure during pregnancy to LABA did not significantly affect the odds of low birth weight babies, preterm birth, or babies small for gestational age. The effect of exposure to ICS differed by ICS dose. There was no effect of ICS at lower doses but at the equivalent of 500 mcg/day of FP the odds of having a low birth weight baby was 1.66 (95% CI 1.01 to 2.73) and the odds of having a small for gestational age baby was 1.80 (95% CI 1.19 to 2.71). Exposure to inhaled corticosteroids during pregnancy did not affect the odds of preterm birth even at the highest steroid dose (OR, 1.13, 95% CI 0.65 to 1.97).

Insufficient data exists to determine if risks associated with ICSs differ among ICSs. Additionally we identified no evidence for subgroup differences related to pregnancy in patients with COPD.

## VI. Genetics

Several genes (coding for LM, ICS, or beta-agonist receptors), have been associated with response to medications used in the treatment of asthma.<sup>1,260-264</sup> To date, there is not sufficient evidence to draw conclusions about whether testing for variants in these genes has any clinical utility (insufficient-strength 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.<sup>1,260,261,264,265</sup>

Two studies have prospectively evaluated the effects of drugs to treat asthma in patients with ADRB2 polymorphisms. One RCT (N=544) evaluated therapy with a LABA alone and in combination with an ICS and found no evidence of a pharmacogenetic effect of  $\beta$ -receptor variation on SAL response.<sup>265</sup> It reported no difference over 16 weeks in response to SAL for various ADRB2 genotype (Arg/Arg vs. Gly/Gly vs. Arg/Gly). The second RCT compared 16 weeks of treatment with TIO 5 mcg/day and SAL 50 mcg/day when added to 400 to 1,000 mcg/day of BUD or equivalent in 388 patients with asthma with the B16-Arg/Arg genotype.<sup>194</sup> There were no statistically significant differences between TIO and SAL in exacerbations, quality of life, withdrawals due to adverse events, or serious adverse event outcomes and these findings were comparable to those of another RCT that compared TIO and SAL in a broader patient population.<sup>195</sup>

We identified no evidence for subgroup differences based on genetics in patients with COPD.

### *Salmeterol (SAL) compared with tiotropium (TIO)*

The prior review included a good-quality Cochrane review of SAL with TIO, which analyzed 4 trials including 8,936 patients.<sup>196</sup> We identified 2 subgroup analyses<sup>51,52</sup> of the POET COPD trial, which compared SAL 100  $\mu$ g with TIO 18  $\mu$ g and was included in the previously included systematic review. The good-quality subgroup analyses assessed patients with a polymorphism thought to affect response to LABA treatment<sup>52</sup> and patients at high risk for exacerbations<sup>51</sup>. Patients with the Arg16Arg genotype who received SAL had significantly reduced rates of exacerbation (32.3% vs. 39.8 to 42.1% for other genotypes), while exacerbation risk was not modified by genotype among patients receiving TIO.<sup>52</sup> In patients at increased risk of exacerbation, SAL was associated with more frequent exacerbations than TIO (RR 1.11, 95% CI 1.01 to 1.23).<sup>51</sup>

## VII. Disease severity

The 6-month trial in patients with mild to severe asthma comparing equipotent doses of FP 125 mcg/day, BEC 200 mcg/day or BUD 200 mcg/day according to disease severity found significant improvements in SGRQ total score in favor of FP at 6 months compared with BUD or BEC in mild persistent asthma. For patients with moderate persistent asthma, FP was considered better than BEC and comparable to BUD at 6 months. In patients with severe asthma, there were no statistically significant difference between the 3 groups.<sup>116</sup>

The 1-year Prevention of Exacerbations with Tiotropium in COPD (POET-COPD) trial randomized 7,376 patients with moderate to very severe COPD and found that, compared with SAL 50 mcg twice daily in the overall study population, TIO 18 mcg once daily significantly increased time to first exacerbation and time to first severe exacerbation, reduced annual rates of moderate-to-severe and severe exacerbations, and had similar rates of mortality, withdrawals due to adverse events and proportions of patients with serious adverse events.<sup>244</sup> Other findings for the overall study population are described in more detail in Key Questions 1 and 2. Preplanned subgroup analyses of the POET-COPD trial based on disease severity found that, compared with SAL, TIO also significantly prolonged time to first exacerbation in patients with less severe disease (Global Initiative for Chronic Obstructive Lung Disease [GOLD] Stage II (HR 0.88, 95% CI 0.79 to 0.99) and in patients who were naïve to prior maintenance therapy (HR 0.79, 95% CI 0.65 to 0.97).<sup>266</sup> In the GOLD Stage II subgroup, TIO also significantly prolonged time to first hospitalized exacerbation (HR 0.66, 95% CI 0.48 to 0.91) and significantly reduced the annual rates of hospitalized exacerbations (RR 0.70, 95% CI 0.57 to 0.85), but did not significantly reduce the annual rate of overall exacerbations (RR 0.91, 95% CI 0.81 to 1.01). In the subgroup of maintenance naïve patients, TIO also significantly reduced annual rates of overall exacerbations (RR 0.77, 95% CI 0.63 to 0.94), but did not significantly reduce annual rates of hospitalized exacerbations or significantly prolong time to first hospitalized exacerbation (effect estimates not reported). As with the overall study population, number of deaths were similar for TIO and SAL in both the GOLD stage II and maintenance naïve subgroup (data not reported). Likewise, there was no statistically significant difference between TIO and SAL in incidence of serious adverse events in the GOLD stage II (RR 0.93, 95% CI 0.77 to 1.13) and the maintenance naïve subgroups (RR 0.87, 95% CI 0.63 to 1.18).

**Table 7. Summary of studies evaluating subgroups of patients for whom controller medications may differ in efficacy or frequency of adverse events**

Author, Year Quality	Study design		Comparison	Results
	N	Population		
<b>Age (less than 3 years)</b>				
Szefer et al. 2007 <sup>161</sup> Fair	RCT, open label	Children 2-8, mild persistent asthma, smoking status NR	BUD inhalation suspension (BIS) (0.5 mg) vs. MON (4 or 5 mg)	Exacerbations: BIS 1.23/patient/year, MON 1.63 (P=0.034)
	395  52 weeks		Low dose ICS	QOL: CHQ-P50 and CHSA similar between groups  SAEs: BIS 4 patients (2%), MON 8 (4%)
Szefer et al. 2013 <sup>169</sup> Fair	203	Subgroup analysis: Children ages 2-4		Exacerbations: BIS 1.35/patient/year, MON 2.30 (P=0.003)  QOL: no significant differences in CHQ-PF50 or CHSA, except for the CHSA's patient emotional health subscale which favored MON  SAEs: BIS 2 (2%), MON 6 (6%)
Suissa, 2013 <sup>249</sup> Fair	Case control  218,049	Older adults, 78 years with COPD		Serious pneumonia (vs. control) Current users FP: RR 2.01, (95% CI 1.93 to 2.10)  Current users BUD: RR 1.17; (95% CI 1.09 to 1.26)



Author, Year Quality	Study design		Comparison	Results
	N	Population		
Racial groups				
Walters et al. 2007 <sup>250</sup> Good	Systematic review with meta-analysis 67 RCTs	Adults and children with asthma	Regular inhaled LABA (either SAL or FOR) administered twice daily vs. placebo.	Composite endpoint of respiratory-related death and life threatening adverse events (intubation and mechanical ventilation): Greater in African-Americans than Caucasians (Relative Risk Increase 3.9; 95% CI 1.29 to 11.84).
	42,333			
	≥4 weeks			
Hanania et al. 2010 <sup>131</sup> Fair	RCT  444  6 months	COPD Age ≥ 35, 45% current smokers	ARF NEB (30) vs. ARF NEB (50) vs. FOR DPI (24)	Caucasian: WAEs: FOR N=10 (7.9%), ARF 30 N=12 (9.5%), ARF 50 N=11 (9.0%) SAEs: FOR N=11 (8.7%), ARF 30 N=17 (13.5%), ARF 50 N=4 (3.3%)  Black: WAEs: FOR N=2 (10.5%), ARF 30 N=3 (14.3%), ARF 50 N=5 (21.7%) SAEs FOR N=3 (15.8%), ARF 30 N=3 (14.3%), ARF 50 N=6 (26.1%)
Deykin et al. 2007 <sup>224</sup> Fair	RCT (crossover)  192  14 weeks	Ages 12-65 asthmatics  No current smokers	MON (10 mg/d) + SAL (100 mcg/d) + placebo ICS vs. BEC (160 mcg/d) + SAL (100 mcg/d) + placebo LM  Low dose ICS	No difference in proportion of Caucasian subjects with preferential <sup>a</sup> protection against treatment failure while using ICS + LABA (relative to an LM/LABA) as vs. that in the African-American subjects (P=1.0)
Gender				
Erceg et al. 2012 <sup>230</sup> Fair	Retrospective cohort  844  2y, 3mo of data assessed	Persistent asthma Age 4 to 9.5	Doses NR FP (N=502) vs. BUD (N=43) vs. MON (N=245)  Mean ages(y): FP: 6.53 BUD: 7.16 MON: 6.87	Linear Growth Velocity (mm/day, mean±SE):  Boys: FP: 0.186±0.0058 BUD:0.167±0.0141 ICS: 0.184±0.0055 MON:0.180±0.0066  Girls: FP:0.189±0.0072 BUD:0.236±0.0283 ICS: 0.194±0.0071 MON: 0.181±0.0098
Smoking status				
Lazarus et al. 2007 <sup>253</sup>	RCT, crossover	Age 18-50 asthmatics	Smokers vs. non- smokers	Change in AQOL average score: MON/Non-smoker 0.23 (0.04, 0.42 ; P=0.02) MON smoker 0.07 (-0.19, 0.32; P=NS) BEC Non-smoker 0.13 (-0.06, 0.32; P=NS) BEC Smoker 0.12 (-0.13, 0.37; P=NS)
SMOG study Fair	83  24 weeks			
Price et al. 2013 <sup>157</sup> Fair	RCT  683  6 months	Age 18 to 55, chronic asthma, all subjects active cigarette smokers	FP (500 mcg) vs. MON (10 mg)	Exacerbations (FP vs. MON): 5 studies including Price: OR 0.70, 95% CI 0.57 to 0.86 Price (smokers): OR 0.75, 95% CI 0.43 to 1.31  Adverse events: no evidence of a difference in adverse events between ICSs and LMs overall (KQ2) or for smokers (Price)

Author, Year Quality	Study design		Comparison	Results
	N	Population		
<b>Pregnancy</b>				
Blais et al. 2009 <sup>258</sup> Fair	Cohort  13,280 pregnancies	Pregnant women with asthma	No ICS use (8,734 pregnancies) vs. >0-1,000 mcg/d (4,392 pregnancies) vs. >1,000 mcg/d (154 pregnancies)	Adjusted RRs, all malformations: G1: 1.08 (0.94-1.24) G2: Reference G3: 1.66 (1.02-2.68)  Adjusted RRs, major malformations: G1: 1.06 (0.89-1.26) G2: Reference G3: 1.67 (0.91-3.06)
Norjavaara & Gerhardsson de Verdier, 2003 <sup>267</sup> Fair	Database review  293,948	Pregnant asthmatic women	BUD vs. control (no BUD exposure during pregnancy)	No difference in gestational age, birth weight, length, rate of stillbirths, or multiple births for children born to BUD-treated mothers. Rate of caesarean birth was higher in women taking BUD early in pregnancy (P<0.05)
Cossette, 2013 <sup>259</sup> Fair	Cohort  7,376  pregnancies	Pregnant woman with asthma	ICS vs. ICS/LABA vs. no treatment	LABA use not associated with low birth weight, small for gestational age, or preterm birth; ICS exposure at higher-doses associated with low birth weight and small for gestational age but not preterm birth
Rahimi et al. 2006 <sup>257</sup> Fair	Systematic review with meta-analysis	Pregnant asthmatic women	Any therapeutic dosage of any ICS (FP, BEC, BUD, TAA, FLUN) vs. no ICS exposure	ICSs did not increase the rates of any obstetrical outcomes.  Major malformations: Summary (2 studies) OR=0.96 (95% CI 0.51 to 1.83); P=0.9582  Preterm delivery: Summary (3 studies) OR=0.99 (95% CI 0.8 to 1.22); P=0.9687  Low birth weight delivery: Summary (2 studies) OR=0.89 (95% CI 0.7 to 1.14); P=0.4013  Pregnancy-induced hypertension: Summary (3 studies) OR=0.97 (95% CI 0.84 to 1.2); P=0.9932

Abbreviations: AQOL, average quality of life; BUD, budesonide; CI, confidence interval; DPI, dry powder inhaler; FOR, formoterol; FP, fluticasone propionate; ICS, inhaled corticosteroid; LABA, long-acting beta-2 agonist; LM, leukotriene modifiers; MA, meta-analysis; MON, montelukast; NR, not reported; NS, not statistically significant; OR, odds ratio; QOL, quality of life; RCT, randomized controlled trial; RR, relative risk; SAL, salmeterol; SR, systematic review.

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

## SUMMARY

### Strength of Evidence

The strength of evidence in this report ranges from high-strength evidence based on meta-analysis of multiple fair- and good-quality RCTs, to insufficient evidence primarily where there was a single study for a given comparison with inadequate sample size to confer precision to

estimates, and unknown consistency of findings. For inter-class comparisons there were more opportunities to pool study results, improving the strength of evidence for these findings. Intra-class comparisons suffered from imprecision and unknown consistency – these flaws combined with even fair-quality studies resulted in low or insufficient ratings for many of the comparisons.

### **Limitations of this Report**

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

Methodological limitations of the review within the defined scope included the exclusion of studies published in languages other than English and lack of a specific search for unpublished studies. In addition, the data from most RCTs included in this report have limited utility for assessing real-world adherence to medications. This is largely because they enrolled selected populations, often requiring a high degree of adherence to be included in the trial, and were short-term studies. For example, many of the trials had a run-in period during which adherence was assessed and then only included subjects that met a threshold for good adherence (e.g., adherence to 80% of recommended doses). Unfortunately, for many drugs, there are few or no effectiveness studies and many efficacy studies.

### **Applicability**

The applicability of the results are limited by the scope of the Key Questions and inclusion criteria and by the applicability of the studies included. Most studies included narrowly defined populations of patients who met strict criteria for case definition, had few comorbidities, and used few or no concomitant medications. Minorities, older patients, and the most seriously ill patients were often underrepresented. Additionally, the effectiveness of the inhaled drugs may vary by technique such that use in real-life settings could have different results.

**Table 8. Summary of evidence: Comparative benefits and harms of controller medications for the treatment of persistent asthma or COPD**

Strength of evidence	Conclusions
<i>Intra-class comparisons (within class)</i>	
<b>Monotherapy</b>	
<b>Inhaled corticosteroids (ICSs) compared with ICSs:</b>	
<b>Low to Moderate</b> (≥12 years) 37 RCTs/3 SRs	<p><b>Asthma</b></p> <ul style="list-style-type: none"> <li>For most comparisons ICSs do not differ in asthma symptoms, exacerbations, rescue medication, or quality of life at equipotent doses. Relatively few studies reported exacerbations, healthcare utilization, or quality of life outcomes. Long-term data beyond 12 weeks is lacking for most of the comparisons. Differences are limited to:               <ul style="list-style-type: none"> <li>BUD vs. MOM: No difference for symptoms, MOM better than BUD for rescue medication use. (Low-strength evidence)</li> <li>BEC vs. BUD: Nocturnal awakening: BEC better than BUD. (Low-strength evidence)</li> <li>FP vs. BEC: lower risk of exacerbation (Low-strength evidence) Nocturnal awakening: No difference (Moderate-strength evidence)</li> <li>FP vs. BUD: FP better than BUD on functional capacity. (Low-strength evidence)</li> </ul> </li> <li>The overall incidence of adverse events, withdrawals due to adverse events, and specific adverse events (other than oral candidiasis) are similar for equipotent doses of ICSs.               <ul style="list-style-type: none"> <li>Meta-analysis of equipotent doses of CIC vs. FP found lower risk of oral candidiasis-thrush with CIC (<b>OR 0.33, 95% CI 0.17, 0.64</b>).</li> </ul> </li> </ul>
<b>Moderate</b> (<12 years) 5 RCTs/3 SRs	<ul style="list-style-type: none"> <li>In children, the body of evidence supports the above conclusion, but data was only available for 5 comparisons: BEC vs. BUD, BEC vs. FP, BUD vs. CIC, BUD vs. FP, and CIC vs. FP.</li> <li>3 fair head-to-head trials provide evidence that short-term (20 weeks to 1 year) growth velocity is reduced less with FP than with BEC or BUD. A 4th head-to-head trial found that CIC-treated subjects had a greater mean body height increase than budesonide-treated subjects over 12 weeks. Evidence on final adult height is not available.</li> </ul>
<b>COPD:</b> No eligible studies of ICS vs. ICS in patients with COPD.	
<b>Leukotriene modifiers (LMs) compared with LMs: Insufficient evidence, asthma only</b>	
<b>Long-acting beta-2 agonists (LABAs) compared with LABAs:</b> Contraindicated for monotherapy in Asthma	
<b>Low to Moderate</b>	<p><b>COPD</b></p> <ul style="list-style-type: none"> <li>ARF and FOR had similar exacerbation rates, improvements in quality of life, and rates of serious adverse events and withdrawals due to adverse events.</li> <li>Nebulized FOR is similar to FOR via DPI in exacerbations and quality of life.</li> <li>FOR and IND have similar exacerbations and quality of life. In comparisons of standard dose FOR with high-dose IND, there was not a statistically significant difference in withdrawals due to adverse events, though patients taking an even higher dose of IND were less likely to withdraw due to harms than those taking FOR (<b>RR 0.58, 95% CI 0.36 to 0.94</b>).</li> <li>Important improvement in quality of life was more likely with IND than SAL (<b>OR 1.59, 95% CI 1.12 to 2.25</b>).</li> <li>Greater improvement in quality of life with OLO than FOR (<b>RR 1.28, 95% CI 1.10 to 1.48</b> for 5 mcg OLO, <b>RR 1.26, 95% CI 1.09 to 1.46</b> for 10 mcg).</li> </ul>
<b>Long-acting muscarinic antagonists (LAMAs) compared with LAMAs:</b>	
<b>Low</b>	<p><b>COPD</b></p> <ul style="list-style-type: none"> <li>3 trials of high-dose GLY vs. standard-dose TIO and 2 of UME and TIO found no differences in rates of exacerbations, use of rescue medication, or quality of life.</li> <li>Compared with TIO, no differences in overall adverse events, withdrawal due to adverse events, pneumonia, or death with high-dose GLY or UME.</li> </ul>

**Table 8. Summary of evidence: Comparative benefits and harms of controller medications for the treatment of persistent asthma or COPD**

Strength of evidence	Conclusions
<b>Combination therapy compared with combination therapy</b>	
<b>ICS+LABA compared with ICS+LABA</b>	
<b>Moderate</b> (≥12 years)	<p><b>Asthma</b></p> <p><b>BUD/FOR compared with FP/SAL:</b></p> <ul style="list-style-type: none"> <li>• Large trials up to 6 months in duration find no significant difference in efficacy or quality of life. Meta-analyses show no difference between BUD/FOR and FP/SAL in exacerbations requiring oral steroids, exacerbations requiring ED visit or hospital admission.</li> <li>• Data from 4 large head-to-head trials (5,818 subjects) provide no evidence of a difference in overall adverse events, serious adverse events or withdrawal due to adverse events between BUD/FOR and FP/SAL in adults and adolescents.</li> </ul>
<b>Moderate (standard doses)</b> <b>Low (High doses)</b> (≥12 years)	<p><b>FP/SAL compared with MOM/FOR</b></p> <ul style="list-style-type: none"> <li>• Moderate-strength evidence from 2 trials (12 and 52 weeks) indicated no difference in asthma deteriorations and no difference in withdrawal due to adverse events or risk of serious adverse events at medium ICS doses.</li> <li>• For combinations including higher ICS doses, there is low-strength evidence from a single study that there were no statistically significant differences in exacerbations, withdrawal due to adverse events or incidence of serious adverse events between MOM/FOR and FP/SAL.</li> <li>• Ocular toxicity did not differ between treatments at either dose (low-strength evidence)</li> </ul>
<b>Low</b> (≥12 years)	<p><b>FP/SAL compared with FF/VIL</b></p> <ul style="list-style-type: none"> <li>• Low-strength evidence suggests no difference in quality of life between the treatments.</li> <li>• Low-strength evidence from a single study of fixed- dose combination inhalers of FP/VIL compared with FP/SAL suggests no difference in rates of withdrawal due to adverse events or serious adverse events between drugs.</li> </ul>
<b>Low</b> <b>(Moderate for QOL BUD/FOR vs. BEC/FOR)</b> <b>(6 RCTs)</b>	<p><b>COPD</b></p> <p><b>BEC/FOR compared with FP/SAL</b></p> <ul style="list-style-type: none"> <li>• Low-strength evidence of no difference in exacerbations, symptoms, 6-minute walk-test, use of rescue medication. Evidence on quality of life was insufficient.</li> </ul> <p><b>BUD/FOR compared with BEC/FOR</b></p> <ul style="list-style-type: none"> <li>• No differences in quality of life (moderate-strength evidence) or total exacerbations, exacerbations requiring an emergency department visit or hospitalization, or exacerbations requiring corticosteroid treatment (low-strength evidence).</li> <li>• A single good-quality trial did not suggest differences in adverse events, withdrawals due to adverse events, pneumonia or mortality.</li> </ul> <p><b>F)/VIL compared with FP/SAL</b></p> <ul style="list-style-type: none"> <li>• <b>FF/VIL 100 mcg/25 mcg daily vs. FP/SAL 500 mcg/100 mcg daily.</b> Moderate-strength evidence from 3 good-quality 12-week trials finds no difference in exacerbations (pooled 3.7% vs. 2.9%; RR 1.25, 95% CI 0.76 to 2.06), rescue medication use (pooled difference 0.06 per day, 95% CI -0.19 to 0.07) or rescue-free days (54 vs. 49 per 12 weeks).</li> <li>• <b>FF/VIL 100 mcg/25 mcg daily vs. FP/SAL 1,000 mcg/100 mcg daily.</b> Low-strength evidence from a single good-quality 12-week trial suggests no difference in rescue-free days or quality of life.</li> </ul> <p><b>BUD/FOR compared with FP/SAL:</b></p> <ul style="list-style-type: none"> <li>• Evidence (2 good-quality observational studies) on the risk of pneumonia is conflicting.</li> <li>• After a mean 3.5 years follow-up, greater risk with FP/SAL than with BUD/FOR (RR 1.73, 95% CI 1.57 to 1.90), event rates per 100 patient-years 11% and 6.4%). Mortality due to pneumonia was also increased (HR 1.8% CI 1.22 to 2.53; crude incidence 3.6% vs. 1.9%). A 2nd study with 12 months of follow-up finds no difference between the drugs in pneumonia (OR 0.92, 95%, CI 0.81 to 1.04; event rates 17.3% vs. 19.0%) for BUD/FPR vs. FP/SAL.</li> </ul>
<b>Inter-class Comparisons (between classes)</b>	
<b>Monotherapy</b>	

**Table 8. Summary of evidence: Comparative benefits and harms of controller medications for the treatment of persistent asthma or COPD**

Strength of evidence	Conclusions
<b>ICSs compared with leukotriene modifiers:</b>	
<b>High</b>	<p><b>Asthma</b></p> <ul style="list-style-type: none"> <li>Efficacy studies up to 56 weeks provide consistent evidence favoring ICSs over LMs for both children and adults. ICSs had significantly lower risk of exacerbations than LMs (<b>OR 0.70; 95% CI 0.57 to 0.86</b> for FP vs. MON). Meta-analysis found statistically significant differences in favor of ICSs over LMs for quality of life.</li> <li>No evidence of a difference in risk of withdrawal due to adverse effects (RR 1.24, 95% CI 0.95 to 1.63, 25 trials) comparing LMs with ICSs in adults and children.</li> </ul>
<b>Low</b>	An analysis of a subset of 154 children age 6 to 14 in 1 trial found that those treated with FP had significantly fewer ED visits (0.10 vs. 0.35, $P=0.002$ ) and missed school days (1.4 vs. 2.1, $P<0.001$ ) than those treated with MON.
<b>ICSs compared with LABAs:</b>	
<b>Low to Moderate</b>	<p><b>COPD</b></p> <ul style="list-style-type: none"> <li>No difference in mortality (OR 1.17, 95% CI 0.97 to 1.42; 1 SR of 7 RCTs), exacerbations (OR 0.96, 95% CI 0.89 to 1.02, 1 SR of 4 RCTs), or in hospitalizations due to exacerbations (Risk Ratio 1.07, 95% CI 0.91 to 1.26, 1 study; moderate-strength evidence).</li> <li>No difference in risk of having any adverse event (OR 1.12, 95% CI 0.96 to 1.30). Serious pneumonia AEs were more frequent with ICS than LABA based on a good-quality SR of 5 studies (<b>OR 1.48, 95% CI 1.13 to 1.94</b>)</li> </ul>
<b>ICS compared with PDE-4 inhibitors:</b>	
<b>Low</b>	<p><b>Asthma</b></p> <ul style="list-style-type: none"> <li>More patients taking ROF experienced exacerbations (<b>RR 3.16, 95% CI 1.10 to 9.11</b>) and withdrew due to adverse events (<b>RR 8.75, 95% CI 1.45 to 53.3</b>) than those taking BEC.</li> </ul>
<b>LABAs compared with LAMAs</b>	
<b>Asthma: monotherapy with LABAs contraindicated</b>	
<b>Moderate</b>	<p><b>COPD</b></p> <p><b>SAL compared with TIO</b></p> <ul style="list-style-type: none"> <li>A systematic review found higher risk of exacerbations with SAL than TIO (<b>36% vs. 32%</b>; <b>pooled OR 1.19, 95% CI 1.09 to 1.30</b>) and no differences in hospitalizations or quality of life between SAL and TIO.</li> </ul>
<b>Low</b>	<ul style="list-style-type: none"> <li>3 trials found moderate-strength evidence of increased rates of withdrawal due to adverse events for SAL compared with TIO (<b>OR 1.23, 95% CI 1.05 to 1.45</b>).</li> </ul>
<b>Low</b>	<p><b>IND compared with TIO</b></p> <ul style="list-style-type: none"> <li>Evidence from 3 trials suggested that IND is associated with more frequent exacerbations (<b>RR 1.11, 95% CI 1.03 to 1.19</b>), with similar effects on mortality (1.4% vs. 1.5%) and quality of life (SGRQ improvement <math>\geq 4</math> points: OR 1.03, 95% CI 0.88 to 1.21) in patients with severe COPD.</li> <li>In patients with moderate-to-severe COPD, quality of life improved in fewer patients receiving TIO than IND (<b>42% vs. 50%</b>; <b>RD -0.08, 95% CI -0.13 to -0.03</b>), with no differences in hospitalizations or exacerbations</li> <li>These trials provided low-strength evidence of no differences in serious adverse events or withdrawal due to adverse events.</li> </ul>
<b>Combination therapy compared with monotherapy</b>	
<b>ICS/LABA compared with LABA:</b>	

**Table 8. Summary of evidence: Comparative benefits and harms of controller medications for the treatment of persistent asthma or COPD**

Strength of evidence	Conclusions
<b>Low</b>	<p><b>COPD</b></p> <ul style="list-style-type: none"> <li>One good-quality trial suggested that exacerbation rates did not differ between patients switching to IND and those continuing treatment with SAL and FP.</li> <li>There were significantly lower rates of serious adverse events for patients switching to IND than for those continuing treatment with SAL and FP (RR 0.29, 95% CI 0.11 to 0.74).</li> </ul>
<b>ICS/LABA compared with ICS (different drug)</b>	
<b>Low (5 RCTs)</b>	<p><b>Asthma</b></p> <p><b>FP/VAL compared with FP</b></p> <ul style="list-style-type: none"> <li>3 good-quality trials find no statistically significant difference in severe exacerbation rates. 2 trials do not find important differences between drugs in quality of life scores using the AQLQ</li> <li>Meta-analyses of these trials also find no statistically significant difference in withdrawals due to adverse events; or serious adverse events.</li> </ul> <p><b>FP/SAL compared with CIC</b></p> <ul style="list-style-type: none"> <li>Evidence from a fair-quality study finds that quality of life (AQLQ) was significantly improved with CIC vs. FOR/SAL (<b>mean change 0.36 vs. 0.27, P&lt;0.0001</b>); The risk exacerbations was significantly greater in the CIC group than the FP/SAL group (0.30 vs. 0.18; <b>RR 1.67, 95% CI 1.18 to 2.36</b>).</li> <li>Adverse events more common with CIC than FP/SAL (<b>RR 1.15, 95% CI 1.01, 1.30</b>).</li> </ul>
<b>ICS/LABA compared with LAMA</b>	
<b>Low</b>	<p><b>COPD</b></p> <p><b>FP/SAL compared with TIO</b></p> <ul style="list-style-type: none"> <li>Compared with TIO, FP/SAL was associated with lower risk of mortality, better quality of life, but higher risk of hospitalization. There was no difference in exacerbations.</li> <li>Compared with FP/SAL, TIO is associated with a significantly lower proportion of patients with serious harms, but no difference in withdrawals due to adverse events.</li> </ul> <p><b>FF/VIL compared with TIO</b></p> <ul style="list-style-type: none"> <li>No difference in mortality or serious adverse events.</li> </ul>
<b>ICS/LABA compared with LMs</b>	
<b>High (Moderate for age ≤ 12 years)</b>	<p><b>Asthma</b></p> <ul style="list-style-type: none"> <li>Meta-analysis of 5 RCTs finds FP/SAL to be more efficacious than MON for preventing exacerbations.</li> <li>3 trials find greater efficacy for ICS/LABA in children ages 6 to 14 or a mixed age group with 15% of subjects &lt;12 years of age.</li> </ul>
<b>Low</b>	<ul style="list-style-type: none"> <li>No difference in overall adverse events and withdrawals due to adverse events.</li> </ul>
<b>LABA/LAMA compared with LAMA</b>	
<b>Low to Moderate</b>	<p><b>COPD</b></p> <p><b>UME/VIL compared with UME</b></p> <ul style="list-style-type: none"> <li>1 trial found less frequent rescue medication use in patients receiving UME/VIL than UME alone (difference in mean puffs per day: <b>-0.6, 95% CI -1.2 to 0.0</b> for the 62.5/25 µg dose).</li> </ul> <p><b>UME/VIL compared with TIO</b></p> <ul style="list-style-type: none"> <li>3 unpublished trials found no differences in deaths, quality of life, daily activities, or exacerbations (low-strength evidence) but moderate-strength evidence that reductions in use of rescue medication were greater for UME/VIL vs. TIO (<b>-3.2 vs. -2.1 in 1 study and -2.0 vs. -1.4 in another</b>).</li> <li>There were no differences in serious adverse events, withdrawal due to adverse events, overall adverse events, death, or pneumonia</li> </ul>

**Table 8. Summary of evidence: Comparative benefits and harms of controller medications for the treatment of persistent asthma or COPD**

Strength of evidence	Conclusions
<b>Combination therapy compared with combination therapy</b>	
<b>LABA/LAMA compared with ICS/LABA</b>	
Moderate and High (2 RCTs)	<p><b>COPD</b></p> <p><b>UME/VIL compared with FP/SAL (standard doses)</b></p> <ul style="list-style-type: none"> <li>Based on 2 good-quality 12-week trials, there is moderate-strength evidence of no difference in exacerbation rates (3% each group), and high-strength evidence of no difference in quality of life between UME/VIL and FP/SAL on the EQ5D or SGRQ</li> <li>There was no difference in overall adverse events, serious adverse events, and withdrawals due to adverse events or pneumonia</li> </ul> <p><b>UME/VIL compared with FP/SAL (higher dose ICS)</b></p> <ul style="list-style-type: none"> <li>Based on a good quality 12-week trial, there is no difference in exacerbation rates or rescue medication use, and moderate-strength evidence of no difference in quality of life based on the EQ5D or SGRQ.</li> <li>No difference in overall adverse events, withdrawals due to adverse events or pneumonia.</li> </ul>
Low to Moderate (1 RCT)	
<b>ICS/LABA compared with LM/ICS</b>	
Moderate to High	<p><b>Asthma</b></p> <ul style="list-style-type: none"> <li>For the drug classes overall, fewer patients taking ICS/LABA had exacerbations than those taking LM/ICS (<b>RR 0.83, 95% CI 0.71 to 0.97</b>), but important differences in quality of life were not found (high-strength evidence).</li> <li>No difference in withdrawals due to adverse events between ICS/LABA and LM/ICS (high-strength evidence) but more patients taking LABAs/ICSs had <i>serious</i> adverse events than patients taking LM/ICSs (<b>RR 1.35, 95% CI 1.00 to 1.82</b>; moderate-strength evidence)</li> </ul>
<b>LM/LABA compared with ICS/LABA</b>	
Low $\geq$ 12 years	<p><b>Asthma</b></p> <p><b>LM/LABA had significantly shorter time to treatment failure than ICS/LABA (<math>P=0.0008</math>; 29 vs. 8 subjects failed) in a 12 week trial.</b></p>

Abbreviations: ARF, arformoterol; AQLQ, BEC, beclomethasone; BUD, budesonide; CI, confidence interval; CIC, ciclesonide; COPD, chronic obstructive pulmonary disorder; DPI, dry powder inhaler; ED, emergency department; FF, fluticasone furoate; FOR, formoterol; FP, fluticasone propionate; GLY, glycopyrrolate; ICS, inhaled corticosteroid; IND, indacaterol; LABA, long-acting beta-2 agonist; LAMA, long-acting muscarinic antagonist; LM, leukotriene modifier; MOM, mometasone; MON, montelukast; OLO, olodaterol; OR, odds ratio; RCT, randomized controlled trial; RR, relative risk; RD, risk difference; ROF, roflumilast; SAL, salmeterol; SGRQ, St. George Respiratory Questionnaire; SR; systematic review; TIO, tiotropium; UME, umeclidinium; VIL, vilanterol.



**Table 8. Summary of evidence for controller medications for the treatment of persistent asthma or COPD: Key Question 3**

**Key Question 3. Are there subgroups of these patients based on demographics (age, racial groups, gender), asthma severity, comorbidities (drug-disease interactions, including obesity), other medications (drug-drug interactions), smoking status, genetics, or pregnancy for which asthma controller medications differ in efficacy, effectiveness, or frequency of adverse events?**

Strength of evidence	Conclusions
<b>Insufficient</b>	Evidence on differences based on age, (younger or older), racial groups, gender, pregnancy status, and genetic markers was limited to small subgroup analyses of single trials, or small observational studies. Evidence is briefly summarized below.
<b>Age</b>	<ul style="list-style-type: none"> <li>• One study of 2 to 8 year olds with asthma included a subgroup analysis of patients age 2 to 4 that suggested more exacerbations per patient and more patients with serious adverse events with montelukast than with budesonide.</li> <li>• One case-control study of older adults found 2-fold increased risk of serious pneumonia with FP and BUD compared with controls with a dose-response relationship for FP.</li> </ul>
<b>Racial groups</b>	<ul style="list-style-type: none"> <li>• A trial of 63 African American and 375 Caucasian patients with COPD suggested higher risk of withdrawals due to and serious adverse events among African American patients taking ARF compared with FOR. These differences were not apparent among Caucasians.</li> </ul>
<b>Gender</b>	<ul style="list-style-type: none"> <li>• One observational study suggested that the effects of MON compared with BUD or FP on linear growth velocity do not differ between boys and girls.</li> </ul>
<b>Pregnancy</b>	<ul style="list-style-type: none"> <li>• We did not find any studies that directly compared the included medications. Budesonide is the only ICS labeled pregnancy category B; the other ICSs are category C. LABA and lower dose ICS were not associated with low birth weight, preterm birth or small for gestational age babies. Higher dose ICS increased the risk of having a low birth weight or small for gestational age baby.</li> </ul>
<b>Genetics</b>	<ul style="list-style-type: none"> <li>• One RCT found no difference in response to SAL (+/- ICSs) for people with various ADRB2 (Beta-2 adrenoreceptor gene) genotypes (Arg/Arg vs. Gly/Gly vs. Arg/Gly).</li> <li>• One trial reported fewer exacerbations among patients with the Arg16Arg genotype receiving SAL, while exacerbation risk was not modified by genotype among patients receiving TIO.</li> </ul>

Abbreviations: ARF, arformoterol; BUD, budesonide; COPD, chronic obstructive pulmonary disorder; FP, fluticasone propionate; FOR, formoterol; ICS, inhaled corticosteroid; LABA, long-acting beta-2 agonist; MON, montelukast; RCT, randomized controlled trial; SAL, salmeterol; TIO, tiotropium.

## CONCLUSIONS

In intra-class comparisons, few differences were found between drugs, with low- to moderate-strength evidence. In adults or children with asthma, ICSs at equipotent doses do not differ in asthma symptoms, exacerbations, rescue medication, quality of life or adverse events. While **growth velocity is less affected with fluticasone propionate (FP) than beclomethasone dipropionate (BEC), and height increase was less affected with ciclesonide (CIC) than budesonide (BUD) in children**, evidence on final adult height is not available. Similarly, in patients with asthma differences were not found between long-acting beta-2 agonists (LABAs) in benefits or harms, except that **olodaterol hydrochloride (OLO) resulted in better quality of life than formoterol fumarate (FOR)**. Evidence on long-acting muscarinic antagonists (LAMAs) in patients with COPD indicates no differences in benefit or harm outcomes. Evidence on leukotriene modifiers (LMs) in patients with asthma was insufficient to draw conclusions. Comparisons of ICSs/LABAs with each other in patients with asthma or chronic obstructive pulmonary disorder (COPD), no differences benefits were found and most comparisons found no

differences in adverse event outcomes, however, **FP/salmeterol (SAL) was associated with increased risk of pneumonia and pneumonia-related death compared with BUD/FOR.**

Inter-class comparisons found statistically significant differences between classes in multiple instances, with mostly low- and moderate-strength evidence. In patients with COPD, there was no difference in benefits between ICSs and LABAs but **pneumonia was more frequent with ICSs than LABAs.** In patients with asthma, **ICSs result in better outcomes than LMs,** with no difference in adverse event outcomes. In patients with asthma there were no differences between LABAs and LAMAs in outcomes, but in patients with COPD evidence was mixed - there were **more exacerbations and withdrawals due to adverse events with SAL (LABA) than tiotropium (TIO) (LAMA)** but not indacaterol (IND) (LABA) than TIO (LAMA), but there were no differences in hospitalizations or quality of life. Limited evidence suggested that in patients with asthma, more patients taking roflumilast (PDE-4 inhibitor) experienced exacerbations and withdrawals due to adverse events than those taking beclomethasone.) In patients with asthma, ICS/LABA was not different to a different ICS, but in patients with COPD switching to IND may result in fewer serious adverse events than staying on FP/SAL. In patients with asthma, **ICS/LABA (FP/SAL) resulted in fewer exacerbations than LM (montelukast [MON]),** but no difference adverse events. In patients with COPD there was no difference in outcomes between ICS/LABAs and LABAs and there was mixed evidence between ICS/LABAs and LAMAs. In patients with asthma, **ICS/LABAs had fewer exacerbations and more serious adverse events, but no difference in quality of life or other adverse event outcomes than ICS/LMs. LABA/LM had shorter time to treatment failure than ICS/LABA in patients with asthma.** In patients with COPD, LABA/LAMA compared with ICS/LABA differed based on the specific drugs compared. **GLY/IND had fewer exacerbations and longer time to first exacerbation than FP/SAL,** but there were no differences between umeclidinium bromide (UME)/vilanterol (VIL) and FP/SAL.

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Clinical Study Register: [http://www.gsk-clinicalstudyregister.com/search?study\\_ids=2116961](http://www.gsk-clinicalstudyregister.com/search?study_ids=2116961).

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