Inhaled Corticosteroid and Long-Acting β₂-Agonist Combination Inhalers

AFHS classifications: Adrenals 68:04, Selective β₂-Adrenergic Agonists 12:12.08.12

Budesonide/formoterol (Symbicort)
Fluticasone propionate/salmeterol (Advair Diskus, Advair HFA, Airduo Respliclick)
Fluticasone furoate/vilanterol (Breo Ellipta)
Mometasone/formoterol (Dulera)

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Executive Summary

Introduction: Combination products containing inhaled corticosteroids (ICSs) and long-acting β2-agonists (LABAs) are indicated for the long-term treatment of patients with asthma. Some ICS/LABA combinations are also approved for the management of chronic obstructive pulmonary disease (COPD).

The 2007 National Heart, Lung, and Blood Institute (NHLBI) guideline and the 2017 Global Strategy for Asthma Management and Prevention (GINA) guideline recommend the use of short-acting β2-agonists (SABAs) as needed (quick relief medications) plus ICS/LABA combinations (controller medications) in certain patients with persistent moderate to severe asthma not adequately controlled with low- or medium-dose ICS. For these patients, several clinical trials demonstrated greater improvements in lung function and asthma control when LABA was added to ICS compared to increasing the ICS dose.

Regarding COPD management, the updated 2017 Global Initiative for Chronic Obstructive Lung Disease (GOLD) guideline recommends LABA/long-acting muscarinic antagonist (LAMA) fixed-dose combinations (FDCs) as preferred treatment options in patients with moderate to severe COPD. Combination ICS/LABA FDC products are second-line therapies. Clinical trials in COPD patients demonstrated superior efficacy of LABA/LAMA compared to LABA/ICS combinations in terms of lung function and exacerbation risk.

Currently, 6 ICS/LABA FDC products, available in a single inhaler, are approved by the Federal Drug Administration (FDA): one budesonide and formoterol (BUD/FM) metered-dose inhaler, 3 fluticasone propionate and salmeterol (FP/SAL) products (2 available as dry powder inhalers and one available as metered-dose inhaler), one fluticasone furoate and vilanterol (FF/VI) dry powder inhaler, and one mometasone and formoterol (M/FM) metered-dose inhaler. The 6 FDCs are available with different corticosteroid concentrations to accommodate different levels of asthma severity and different age groups. They are administered twice daily, with the exception of FF/VI products that are administered once daily. Device characteristics and inhalation techniques also differ between products. Single inhalers may simplify asthma/COPD management and facilitate patient adherence to treatment.

Systematic reviews/meta-analyses (SR/MA) and randomized controlled trials (RCTs) assessing head-to-head efficacy and safety comparisons between the aforementioned combination products are included in this report.

Clinical Efficacy: Comparative evidence included 26 efficacy/safety articles containing 5 SR/MA, 21 RCTs, and 2 mixed treatment comparisons (MTCs). Three safety articles containing one SR/MA and 2 RCTs were also evaluated. The majority of the evidence pertained to asthma. Limited evidence is available for COPD and asthma/COPD overlap. Nomenclature used in this
report includes a slash (\slash/) to separate the different active substances contained in a FDC product and a plus sign (\textplus/) to define two separate products used in combination.

For the management of asthma, 5 SR/MA, 16 RCTs and one MTC were identified:

1. BUD/FM versus BUD+FM (4 RCTs): similar efficacy and safety profiles were reported between BUD/FM pMDI (U.S product) or BUD/FM DPI (non-U.S. product) compared to BUD+FM in children 4 to 11 years, adolescents, and adults. One long-term trial (12-months) in adult patients indicated a lower withdrawal rate with BUD/FM DPI than BUD+FM.

2. FP/SAL versus FP+SAL (1 SR/MA, and 5 RCTs): Results differed among the 5 RCTs. Kawai et al demonstrated similar bronchodilator effect between FP/SAL and FP+SAL groups in adult patients. Van der Berg et al, Chapman et al, and Aubier et al reported improvements in lung function, asthma control, and symptoms at week 12 that did not significantly differ between treatment groups in patients ≥ 4 years old.

   In adolescent and adult patients, Bateman et al. showed superiority of SAL/FP DPI 50/100 µg versus the same doses administered individually for lung function at week 12 (primary endpoint). Chapman et al. reported superiority of SAL/FP DPI 50/250 µg vs. SAL+FP for lung function values at other time points (week 3 and 4). One SR/MA included 4 of the 5 RCTs identified, and showed statistically significant differences between FP/SAL and the mono-components; however, a proper discussion about the clinical relevance of the results was lacking.

3. FP/SAL hydrofluoroalkane (HFA) metered-dose inhaler (MDI) versus FP/SAL dry powder inhaler (DPI) (3 RCTs): No significant differences between the two different inhalers were reported. Low-, medium- and high-doses of fluticasone plus SAL were evaluated.

4. BUD/FM versus FP/SAL (3 SR/MA, 3 RCTs): Three SR/MA reported no significant differences in terms of efficacy (reduction in exacerbations requiring oral corticosteroids or hospitalizations) and safety (asthma-related serious adverse events) between BUD/FM pMDI or DPI compared to FP/SAL MDI or DPI. Three RCTs reported faster onset of bronchodilator action and faster improvements in forced expiratory volume in one second (FEV\textsubscript{1}) with BUD/FM pMDI or DPI compared to SAL/FP DPI.

5. FF/VI versus FP/SAL (1 SR/MA containing one RCT of interest): No statistically significant differences were found between FF/VI DPI 100/25 µg compared to FP/SAL DPI 250/50 µg for the primary endpoints (change in health-related quality of life, severe asthma exacerbations, and serious adverse events), and secondary endpoints (lung function and asthma symptoms). However, authors highlighted the limited comparative efficacy and safety information available to make a robust decision about the preference of FF/VI over FP/SAL. Further research was considered required.

6. FF/VI versus FP/SAL and BUD/FM (1 MTC): One network meta-analysis included 31 RCTs to assess the probability of non-inferiority of once-daily FF/VI vs. twice-daily FP/SAL and BUD/FM in asthma patients ≥ 12 years old. Despite known limitations of network meta-
analyses, results suggested similar lung function improvements with FF/VI 100/25 µg and FF/VI 200/25 µg compared to corresponding doses of FP/SAL and BUD/FM. Health status outcomes were comparable between once-daily FF/VI 100/25 µg compared to twice-daily FP/SAL 250/50 µg and BUD/FM 320/9 µg.

7. M/FM versus FP/SAL (1 RCT): One trial compared M/FM MDI 200/10 µg to FP/SAL DPI 250/50 µg. Non-inferiority was demonstrated for the primary endpoint (improvement in lung function) and most of the secondary endpoints (asthma control, quality of life and symptoms). The onset of bronchodilator action was faster with M/FM than FP/SAL DPI.

For the management of COPD, 4 RCTs and one MTC were identified. The main results are described below:

1. BUD/FM versus FP/SAL (1 RCTs): One trial showed faster onset of bronchodilator effect with BUD/FM compared to FP/SAL.
2. FF/VI versus FP/SAL (3 RCTs): Three trials reported statistically, but not clinically significant differences between FF/VI 100/25 µg and medium-dose FP/SAL (250/50 µg).
3. FF/VI versus FP/SAL and BUD/FM (1 MTC): One network meta-analysis included 33 RCTs to assess the probability of non-inferiority of once daily FF/VI 100/25 µg compared to twice daily FP/SAL 500/50 µg and BUD/FM 400/12 µg in COPD patients ≥ 12 years old. Despite limitations of indirect comparisons, results suggested similar lung function and health status improvements with FF/VI compared to FP/SAL and BUD/FM.

For the management of asthma-COPD overlap, only one RCT comparing FF/VI DPI 200/25 µg versus FP/SAL DPI 500/50 µg was identified. Although no between-group differences were reported, authors mentioned the need for further research due to the study limitations identified.

**Adverse Drug Reactions:** The majority of adverse drug reactions to LABA/ICS combinations are tolerable and manageable. The most common adverse events reported with ICS/LABA combinations are headache, upper respiratory tract infections, pharyngitis, pneumonia, dizziness, oral candidiasis, bronchitis, cough, headaches, musculoskeletal pain, nausea and vomiting. The increased risk of pneumonia in patients with COPD and adrenal suppression are related to the adverse effect profile of inhaled corticosteroids. A main safety warning and class effect for all LABAs is the increased risk of asthma-related death, and the higher risk of asthma-related hospitalizations in children and adolescents.

**Summary:** The identified comparative evidence indicates that the FDA-approved ICS/LABA combination products tend to be similar to each other in terms of efficacy and safety outcomes. ICS/LABA products improve lung function, increase quality of life, and reduce asthma or COPD exacerbation rates. Safety profiles remain similar and manageable when both ICS and LABA are combined.
For the management of asthma, direct comparisons reported no significant differences for 1) FP/SAL compared to BUD/FM, FF/VI, or M/FM; and 2) FP/SAL HFA MDI compared to FP/SAL DPI. Similar efficacy and safety profiles were reported for BUD/FM compared to the mono-components administered concomitantly (BUD+FM). FP/SAL has been shown to be similar to FP+SAL; however, some studies suggest superiority of FP/SAL compared to FP+SAL. For the management of COPD, similar results were reported for FP/SAL compared to FF/VI. Nonetheless, further direct head-to-head comparisons involving ICS/LABA combinations are required to contrast the potential benefits of one FDC over another in patients with asthma, COPD, and asthma/COPD overlap.

Clinician’s decisions on one single ICS/LABA inhaler over another should be based on the specific inhaler technique and patient skills to appropriately use the prescribed ICS/LABA inhaler, the individual patient’s preference, co-morbidities, adverse events, and cost.
Introduction

ICS/LABA combination products are indicated for the management of asthma and COPD. Asthma is a chronic inflammatory disease of the airways caused by the exposure to asthma triggers such as occupational allergens, tobacco smoke, chemical irritants, exercise and stress.\textsuperscript{1,4} It is not a curable condition but can be effectively treated with the available pharmacological options.\textsuperscript{1,4} The main goals of treatment are to control asthma symptoms and reduce the risk of exacerbations. Current clinical guidelines recommend long-term treatment for the management of asthma including reliever medications to quickly control exacerbations (i.e. inhaled short-acting $\beta_2$-agonists), and controller medications as maintenance treatment to reduce inflammation and future risk of exacerbations (e.g. inhaled corticosteroids or inhaled corticosteroids and long-acting $\beta_2$-agonist combinations). For patients with severe asthma, add-on therapies may be required (e.g. long-acting muscarinic antagonists, leukotriene modifiers, theophylline, anti-immunoglobulin E, anti-interleukin 5 or oral corticosteroids).\textsuperscript{1,4}

Inhaled corticosteroids (ICSs) have been extensively studied and are considered by the National Heart, Lung, and Blood Institute (NHLBI) the most potent and effective long-term anti-inflammatory drugs in patients with persistent asthma, including adults and children.\textsuperscript{4} Patients discontinuing or not receiving ICS have a higher risk of asthma exacerbations and reduced lung function than those receiving ICS.\textsuperscript{5,6} Therefore, ICSs are the mainstay in the long-term control of persistent asthma. In some patients with moderate to severe asthma not responding to low doses of ICS alone, the addition of a long-acting $\beta_2$-agonist (LABA) to an ICS improves asthma symptoms and lung function, while reducing the incidence of exacerbations in comparison to simply increasing the ICS dose.\textsuperscript{4}

ICS/LABA combinations are also approved for the management of moderate to severe COPD. These combination products are alternative therapies to LABA/LAMA combination products (preferred therapy) because they have demonstrated superior improvement in lung function, health status and exacerbation risk than the individual components, but not versus LABA/LAMA combinations.\textsuperscript{1,4}

This report evaluates the clinical efficacy and safety of the ICS/LABA combination products based on systematic reviews/meta-analyses (SR/MA) and randomized controlled trials (RCTs) assessing head-to-head comparisons between these combination products. Currently, 6 ICS/LABA fixed-dose combination products, available in a single inhaler, are approved by the Federal Drug Administration (FDA) in the United States: one budesonide and formoterol (BUD/FM\textsuperscript{7}) metered-dose inhaler, 3 fluticasone propionate and salmeterol (FP/SAL\textsuperscript{8-10}) products (2 available as dry powder inhalers and one available as metered-dose inhaler), one fluticasone furoate and vilanterol (FF/VI\textsuperscript{11}) dry powder inhaler, and one mometasone and formoterol (M/FM\textsuperscript{12}) metered-dose inhaler. The 6 FDCs are available with different corticosteroid concentrations to accommodate different levels of asthma severity and different age groups.\textsuperscript{4,7-12}
Nomenclature used in this report includes a slash (‘/’) to separate the different active substances contained in a FDC product and a plus sign (‘+’) to define two separate products used in combination.

Inhaler devices allow the drug to be directly delivered to the airways, increasing local concentrations and reducing the incidence of systemic adverse events. Several types of inhaler devices are available including pressurized metered-dose inhalers (pMDIs), dry powder inhalers (DPIs), and soft-mist inhalers (SMIs). Budesonide/formoterol and mometasone/formoterol are delivered with pMDIs, whereas fluticasone furoate/vilanterol is delivered via DPI. Fluticasone propionate/salmeterol is available in both types of devices, pMDI and DPI. Inhalers have a high impact in the efficiency of drug delivery. Although patients require skills-training for the optimal use of inhalation devices, the simplicity and intuitive use of inhalers play an important role in patient adherence to treatment, especially in children and the elderly. DPIs are deemed to be easier to use compared to MDIs. Yet, for an individual with severe limitations in the force they can generate to inhale a dry powder product, a MDI may be more appropriate. Inhaler device selection should be individualized in order to achieve the highest asthma improvement for each patient.

Budesonide/formoterol was approved in the US in 2006 at two different dosages (80/4.5 and 160/4.5 mcg, 2 inhalations twice daily) for the treatment of asthma in patients 12 years of age and older. Later, the indication was extended to include treatment of asthma in patients 6 years of age and older, as well as treatment of patients with COPD. This FDC is formulated as a HFA-propelled pMDI. Three FDCs containing salmeterol and different concentrations of fluticasone propionate are available. Advair Diskus is a DPI approved for the management of asthma (≥ 4 years old) and COPD. Advair HFA (MDI) and Airduo Respiclick (DPI) are only approved for asthma management in adolescents and adults. Mometasone/formoterol (pMDI) is also indicated for asthma management in adolescents and adults. Fluticasone furoate/vilanterol (DPI) is approved for both asthma (only adults) and COPD management, and is the only one administered once daily (versus twice daily administration with the rest of the FDCs).

The use of singe inhalers provides some advantages versus using separate inhalers. First, the lower dosing-frequency, the avoidance of learning two complex and different inhaler techniques, and the high level of patient satisfaction may improve patient adherence, achieve better control of asthma, and increase quality of life. Secondly, single inhalers may reduce the risk of increased asthma-related deaths associated with use of LABA inhalers alone (black box warning of LABAs). Lastly, the cost of a single inhaler is typically lower than separate inhalers administered together. A 2016 FDA safety announcement recommended use of a fixed-dose combination of ICS and LABA in one single inhaler in order to enhance adherence to asthma treatment in children and adolescents.
<table>
<thead>
<tr>
<th>Active Substances (Brand Name)</th>
<th>Dosage Form(s) and Strengths</th>
<th>Mechanism of Action</th>
<th>Indication</th>
<th>Recommended dose</th>
</tr>
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<tbody>
<tr>
<td>Budesonide/formoterol (HFA pMDI) (Symbicort)</td>
<td>Inhalation Aerosol</td>
<td>Budesonide: ICS Formoterol: LABA</td>
<td>• Treatment of asthma in patients 6 years of age and older &lt;br&gt; • Maintenance treatment of airflow obstruction in patients with COPD including chronic bronchitis and emphysema (160/4.5 mcg dosage)</td>
<td>• Asthma (6 to &lt; 12 years): 2 inhalations of Symbicort 80/4.5 BID &lt;br&gt; • Asthma (≥12 years): 2 inhalations of Symbicort 80/4.5 or 160/4.5mcg BID. Starting dose depends on the severity &lt;br&gt; • COPD: 2 inhalations of Symbicort 160/4.5 BID MAX: 2 inhalations BID</td>
</tr>
<tr>
<td>Fluticasone propionate/salmeterol (Advair Diskus (DPI))</td>
<td>Inhalation Powder</td>
<td>Fluticasone: ICS Salmeterol: LABA</td>
<td>• Treatment of asthma in patients aged 4 years and older &lt;br&gt; • Maintenance treatment of airflow obstruction and reducing exacerbations in patients with COPD (250/50 mcg dosage)</td>
<td>• Asthma (4 to 11 years): 1 inhalation of Advair Diskus 100/50 BID &lt;br&gt; • Asthma (≥12 years): 1 inhalation of Advair Diskus 100/50, 250/50, or 500/50 BID. Starting dosage is based on asthma severity &lt;br&gt; • COPD: 1 inhalation of Advair Diskus 250/50 BID MAX: 1 inhalation BID</td>
</tr>
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* Equivalent to 100/6 mcg and 200/6 mcg metered doses, respectively
* Equivalent to 93/45 mcg, 233/45 mcg, and 465/45 mcg delivered doses per blister, respectively
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<th>Active Substances (Brand Name)</th>
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<tbody>
<tr>
<td><strong>Advair HFA</strong>&lt;br&gt;(pMDI)&lt;br&gt;<strong>Approval date:</strong>&lt;br&gt;June 2006&lt;br&gt;(GlaxoSmithKline)</td>
<td>Inhalation Aerosol&lt;br&gt;- 45/21: FP 45 mcg and SAL 21 mcg <em>&lt;br&gt;- 115/21: FP 115 mcg and SAL 21 mcg</em>&lt;br&gt;- 230/21: FP 230 mcg and SAL 21 mcg*&lt;br&gt;* Equivalent to 50/25 mcg, 125/25 mcg, and 250/25 mcg metered doses, respectively</td>
<td>Fluticasone:&lt;br&gt;ICS&lt;br&gt;Salmeterol:&lt;br&gt;LABA</td>
<td>• Treatment of <strong>asthma</strong> in patients aged 12 years and older.&lt;br&gt;&lt;br&gt;<strong>Limitation:</strong> Not indicated for relief of acute bronchospasm</td>
<td>Use 2 inhalations of Advair HFA 45/21, 115/21, or 230/21 BID. Starting dosage is based on asthma severity</td>
</tr>
<tr>
<td><strong>Airduo Respiclick</strong>&lt;br&gt;(DPI)&lt;br&gt;<strong>Approval date:</strong>&lt;br&gt;January 2017&lt;br&gt;(Teva)</td>
<td>Inhalation Powder&lt;br&gt;- 55/14: FP 55 mcg and SAL 14 mcg* per actuation&lt;br&gt;- 113/14: FP 113 mcg and SAL 14 mcg* per actuation&lt;br&gt;- 232/14: FP 232 mcg and SAL 14 mcg* per actuation&lt;br&gt;* Equivalent to 49/12.75 mcg, 100/12.75 mcg, and 202/12.75 mcg delivered doses, respectively</td>
<td>Fluticasone:&lt;br&gt;ICS&lt;br&gt;Salmeterol:&lt;br&gt;LABA</td>
<td>• Treatment of <strong>asthma</strong> in patients aged 12 years and older.&lt;br&gt;&lt;br&gt;<strong>Limitation:</strong> Not indicated for relief of acute bronchospasm</td>
<td>Use 1 inhalation of Airduo Respiclick 55/14 mcg, 113/14 mcg, or 232/14 mcg BID. Starting dosage is based on prior asthma therapy and disease severity</td>
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<tr>
<td>Active Substances (Brand Name)</td>
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<td>Fluticasone furoate/ vilanterol (DPI) (Breo Ellipta)</td>
<td>Inhalation Powder</td>
<td>Fluticasone: ICS Vilanterol: LABA</td>
<td>• Once-daily treatment of <strong>asthma</strong> in patients aged 18 years and older&lt;br&gt;• Long-term, once-daily, maintenance treatment of airflow obstruction and reducing exacerbations in patients with <strong>COPD</strong> (100/25 mcg dosage)</td>
<td><strong>Asthma</strong>: 1 inhalation of Breo Ellipta 100/25 or 200/25 QD&lt;br&gt;<strong>COPD</strong>: 1 inhalation of Breo Ellipta 100/25 QD&lt;br&gt;&lt;br&gt;* Equivalent to 92/22 mcg and 184/22 mcg delivered doses, respectively</td>
</tr>
<tr>
<td>Mometasone/ formoterol (pMDI) (Dulera)</td>
<td>Inhalation Aerosol</td>
<td>Mometasone: ICS Formoterol: LABA</td>
<td>• Treatment of <strong>asthma</strong> in patients 12 years of age and older&lt;br&gt;&lt;br&gt;<strong>Limitation</strong>: Not indicated for the relief of acute bronchospasm</td>
<td>Use 2 inhalations BID of Dulera 100 mcg/5mcg or 200mcg/5mcg.&lt;br&gt;Starting dosage is based on prior asthma therapy&lt;br&gt;&lt;br&gt;* Equivalent to 115/5.5 mcg and 225/5.5 mcg metered doses, respectively</td>
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</table>

**Limitation**: Not indicated for relief of acute bronchospasm

**Unlabeled indication**: COPD

Abbreviations: BID, twice daily; BUD, budesonide; COPD, chronic obstructive pulmonary disease; DPI, dry powder inhaler; FM, formoterol; FF, fluticasone furoate; FP, fluticasone propionate; HFA, hydrofluoroalkane; ICS, Inhaled Corticosteroids; LABA, long-acting β₂-adrenergic agonist; LAMA, long-acting antimuscarinic agent; M, mometasone furoate; MAX: maximum dose; MDI, metered dose inhaler; pMDI, pressurized metered dose inhaler; SAL, salmeterol; VI, vilanterol
Disease Overview and Clinical Guidelines

A) Asthma

Disease Overview

Asthma is a chronic inflammatory disease of the airways that affects all age groups and may be life-threatening.\(^{20}\) It is characterized by bronchoconstriction, airway wall thickening and increased mucus production. Asthma symptoms include wheezing, shortness of breath, chest tightness, and night or early morning cough.\(^{21}\) These symptoms are usually accompanied by expiratory airflow limitation.\(^{1}\) Asthma may be resolved spontaneously or require treatment.\(^{1}\) Sporadic and occasionally fatal asthma exacerbations, attacks or flares may occur, especially in those patients at high-risk or with uncontrolled asthma.\(^{21}\) This may result in productivity loss at work or school, family disruption and activity limitations.\(^{1}\) Risk factors for asthma include endogenous factors (e.g. genetic predisposition, atopy, gender), environmental factors (e.g. indoor or outdoor allergens, occupational sensitizers, passive smoking, respiratory infections, diet), and triggers (e.g. allergens such as pollution, tobacco smoke, pollen, and house dust mites, upper respiratory tract viral infections, exercise and hyperventilation, cold air, sulfur dioxide and irritant gases, stress, irritants and some drugs such as beta-blockers, aspirin and nonsteroidal anti-inflammatory drugs).\(^{20,21}\) Patients may have persistent or intermittent asthma, and the severity and frequency of attacks differ from person to person.\(^{2}\)

According to the World Health Organization (WHO), it is estimated that 235 million people worldwide suffer from asthma, with children being the most affected age group.\(^{2}\) In December 2016, 380,000 deaths worldwide were attributed to asthma.\(^{2}\) The majority of deaths occurred in older adults and those living in lower and middle income countries.\(^{2}\) Asthma is a treatable disease whose prevalence is rising, especially in many developing countries due to the increase of people living in urban areas.\(^{20,21}\) In the United States, statistical data from the 2001 to 2010 period indicate an increase in asthma prevalence from 1 in 14 (7%) in 2001 to 1 in 12 (8%) in 2010.\(^{22}\) Data from 2015 show that around 25 million Americans were diagnosed with asthma, with a higher prevalence in children (8.4% children and 7.6% adults), females (9.1% females vs 6.5% male), black people (10.3% black, 7.8% white and 6.6% Hispanic) and those living below the federal poverty threshold.\(^{23}\) Among adults, women are more likely to have asthma compared to men, whereas among children, boys are diagnosed more commonly than girls.\(^{3}\) In the US, the number of asthma-related emergency department visits was 1.6 million in 2013.\(^{24}\) The number of office-based physician visits with asthma as the primary diagnosis was 10.5 million in 2012,\(^{25}\) and a total of 439,435 people were hospitalized in 2010.\(^{26}\) In 2015, the total number of asthma-deaths was 3,615 (219 children, 3,396 adults).\(^{27}\)

In Utah, the Centers for Disease and Control (CDC) reported a prevalence in 2008 of 8.4% for adults and 6.6% for children compared to national rates of 8.5% and 9.0%, respectively.\(^{28}\)
The Utah prevalence in men and women was 7.4% and 9.5%, respectively. In children, the prevalence was 7.1% for boys and 6.2% for girls. The majority of hospitalizations occurred in children between 0 and 4 years, followed by children between 5 to 9 years and adults older than 65 years.\textsuperscript{28}

Asthma is under-diagnosed and under-treated, causing a high health burden on the general population, with an increase in healthcare costs mainly due to hospitalizations, followed by death, emergency department visits, loss of productivity, and school absences.\textsuperscript{3,22,29} The total annual cost to society from medical expenses, loss of productivity and premature death was approximately $56 billion in 2007,\textsuperscript{3} with direct cost (mostly hospital stays due to exacerbations) accounting for $50.1 billion.\textsuperscript{13,29}

\textit{Diagnosis}

Diagnosis of asthma is primarily based on two features: a) a history of respiratory symptoms (i.e. wheeze, shortness of breath, chest tightness and cough), b) evidence of variable expiratory airflow limitation (forced expiratory volume in one second [FEV\textsubscript{1}] measured by spirometry test or peak expiratory flow [PEF] measured with reversibility test).\textsuperscript{30} Once a diagnosis is confirmed, treatment should be initiated as soon as possible.\textsuperscript{1}

\textit{Asthma severity and control}

According to NHLBI guidelines, the initiation of asthma therapy should be based on the assessment of asthma severity stratified by level of impairment (e.g. symptoms, FEV\textsubscript{1}, SABA use; etc.) and risk of exacerbations requiring oral corticosteroids. Asthma is classified in 4 levels of severity with corresponding treatment steps: intermittent asthma (treatment step 1), persistent mild asthma (treatment step 2), persistent moderate asthma (treatment step 3 or 4), and persistent severe asthma (treatment step 5 or 6). \textbf{Table 3} includes asthma severity features and treatment strategies for patients $\geq$12 years of age.

Asthma control should be evaluated 2-6 weeks after initiation of asthma therapy with modifications made, as indicated. Once stabilized, patients should be regularly assessed (at least once a year) for asthma control, treatment-related issues (e.g. adherence, inhaler technique, adverse events), control of environmental factors, and comorbidities that may worsen asthma. This assessment approach will help health professionals to determine whether treatment remains appropriate or should be modified (step down whenever possible or step up if required).\textsuperscript{4}

\textit{Asthma Management}

The goal of long-term asthma management is to \textbf{reduce impairment} (i.e. reduce disease symptoms, reduce the use of inhaled SABAs, improve lung function and activity levels), and \textbf{reduce the risk} of asthma exacerbations, hospitalizations, emergency care visits, adverse effects from medications, and progressive loss of lung function.\textsuperscript{1,4} Several pathways should be
considered in order to achieve these goals: a) administering a reliever and a controller asthma medication, b) treating modifiable risk factors, c) using non-pharmacological therapies and strategies, and d) patient training concerning asthma self-management (e.g. adherence, inhaler technique, written asthma action plan, etc.).\textsuperscript{1,4}

Asthma medications are classified in 2 categories:

1. **Quick-relief medications** to treat acute symptoms and exacerbations (e.g. short-acting $\beta_2$-agonists [SABAs], anticholinergics, systemic corticosteroids).\textsuperscript{4} According to NHLBI and GINA guidelines, SABA as needed is the preferred choice for all patients with asthma symptoms.\textsuperscript{1,4}

2. **Long-term control medications** to achieve and control persistent asthma symptoms (e.g. inhaled or systemic corticosteroids, cromolyn sodium, immunomodulators, leukotriene modifiers, LABAs, and methylxanthines).\textsuperscript{4} Current guidelines recommend inhaled corticosteroids (ICS) or ICS/LABA combination products as preferred controller therapies.\textsuperscript{1,4}

See Table 2 for further information on guideline recommendations. In general, administration of an ICS should be initiated as soon as possible, even if patients do not have asthma symptoms. The decision to use low-, medium- or high-dose ICS, a combination of ICS with a LABA, or other additional treatment(s) will depend on the frequency of symptoms, waking times per week or month and risk factors for exacerbations.\textsuperscript{1,4} Doses of ICS may be increased (step up strategy) when asthma is uncontrolled with the asthma controller initially prescribed. When asthma is well-controlled for 3 months step-down therapy may be considered.\textsuperscript{1,4}

**Adherence**

Patient inhaler skills should be reinforced to assure a correct use of the device. Different inhalers require different techniques for effective use and adequate patient education is crucial to successfully manage asthma.\textsuperscript{1,4} Adherence to treatment should be encouraged in order to avoid uncontrolled asthma symptoms, exacerbations, and possible death.\textsuperscript{1,4}

Unless asthma is appropriately managed, the number of emergency department visits, hospitalizations and deaths may increase.\textsuperscript{22} Therefore, asthma control through understanding the features of an asthma attack, avoiding the exposure to asthma triggers, and considering the instructions given from the doctor is essential.\textsuperscript{1,4}

**Clinical Guidelines for the Management of Asthma**

Several guidelines for the treatment of asthma have been identified. The most recent evidence-based guideline is the 2017 Global Strategy for Asthma Management and Prevention (GINA),\textsuperscript{1} developed by a network of individuals, organizations, and public health officials from all around. The most relevant American guideline in clinical practice was published in 2007 by
the National Heart, Lung, and Blood Institute ("Guidelines for the Diagnosis and Management of Asthma").\textsuperscript{4} Comparative information including treatment recommendations of the two aforementioned guidelines is included in Table 2. Regarding ICS/LABA combination products, both guidelines consider low/medium/high-doses ICS plus LABA as preferred options in adolescents and adults with moderate to severe asthma (treatment step 3 onward). Some variations between guidelines in children of 11 years old and younger are identified. In step 3, NHLBI considers medium-dose ICS or low-dose ICS/LABA as treatment options in children aged 5 years and older, whereas the GINA guideline recommends medium-dose ICS in this population. The GINA guideline includes 4 steps for the management of asthma in children $\leq 5$ years and 5 steps for children $\geq 6$ years, adolescents, and adults. NHLBI guideline contains 6 steps for all age groups.

According to the NHLBI guidelines, ICS/LABA combinations demonstrated greater improvement in lung function, asthma control, and less use of SABA in comparison to ICS alone (baseline doses or increasing ICS doses), LABA alone or ICS/LTRA.\textsuperscript{4} NHLBI states: "For patients inadequately controlled on low-dose ICS, the option to increase the ICS dose should be given equal weight to the addition of a LABA. For patients who have more severe persistent asthma (i.e., those who require step 4 care or higher), the Expert Panel continues to endorse the use of a combination of LABA and ICS as the most effective therapy".\textsuperscript{4}
## Table 2. Clinical Guidelines - Treatment Steps for the Management of Asthma

<table>
<thead>
<tr>
<th>Asthma Severity</th>
<th>Preferred Reliever</th>
<th>Preferred Controller Choice*</th>
</tr>
</thead>
<tbody>
<tr>
<td>NHLBI and GINA</td>
<td>NHLBI 2007*</td>
<td>GINA 2017b</td>
</tr>
<tr>
<td>STEP 1</td>
<td>SABA PRN</td>
<td>None</td>
</tr>
<tr>
<td>STEP 2</td>
<td>SABA PRN</td>
<td>All ages: low-dose ICS</td>
</tr>
<tr>
<td>STEP 3</td>
<td>SABA PRN or Low dose ICS/FMc</td>
<td><strong>Age 0-4</strong>: medium-dose ICS  &lt;br&gt;<strong>Age 5-11</strong>:  - Low-dose ICS + (LABA, LTRA or theophylline) OR - Medium-dose ICS  &lt;br&gt;<strong>Age ≥12</strong>:  - Low-dose ICS + LABA OR - Medium-dose ICS  &lt;br&gt;* Consider consultation with asthma specialist</td>
</tr>
<tr>
<td>STEP 4</td>
<td>SABA PRN or Low dose ICS/FMc</td>
<td><strong>Age 0-4</strong>: medium-dose ICS + (LABA or montelukast)  &lt;br&gt;* Consult with asthma specialist</td>
</tr>
<tr>
<td>STEP 5</td>
<td>SABA PRN</td>
<td><strong>Age 0-4</strong>: High-dose ICS + (LABA or montelukast)  &lt;br&gt;<strong>Age 5-11</strong>: High-dose ICS + LABA  &lt;br&gt;<strong>Age ≥12</strong>: High-dose ICS + LABA (and consideromalizumab for patients who have allergies)  &lt;br&gt;* Consult with asthma specialist</td>
</tr>
<tr>
<td>STEP 6</td>
<td>SABA PRN</td>
<td><strong>Age 0-4</strong>: High-dose ICS + (LABA or montelukast) + OCS  &lt;br&gt;<strong>Age 5-11</strong>: High-dose ICS + LABA + OCS  &lt;br&gt;<strong>Age ≥12</strong>: High-dose ICS + LABA + OCS (and consideromalizumab for patients who have allergies)  &lt;br&gt;* Consult with asthma specialist</td>
</tr>
</tbody>
</table>


**Abbreviations:** FM, formoterol; ICS, inhaled corticosteroids; ICS/LABA, fixed-dose combination of inhaled corticosteroids and long acting beta2-agonists; LTRA, leukotriene receptor antagonists; N/A, not applicable; OCS, oral corticosteroids; PRN, pro re nata; SABA, short-acting beta2-agonists

* Only preferred options are included, but alternative options also exist (e.g. LTRA, low dose ICS +LTRA, medium dose ICS+LTRA or theophylline, anti-IgE, or refer to specialist)


b GINA, Global Strategy for Asthma Management and Prevention (GINA), 2017

c Low dose ICS/FM as maintenance and reliever therapy (recommended by GINA guidelines only). Not approved in the U.S.

**Note:**
- Evidence A (well-conducted RCTs with substantial number of patients). NHLBI: step 1, 2 and 3 (Evidence A)4
- Evidence B (RCTs with limited number of patients, post hoc or subgroup analysis). NHLBI: step 4 and 5 (Evidence B)4
Table 3. Asthma Severity and Treatment Strategies for the Management of Asthma in patients ≥12 years of age (NHLBI Guidelines)⁴

<table>
<thead>
<tr>
<th>Asthma severity</th>
<th>Symptoms</th>
<th>Awakenings at Night</th>
<th>Use of SABA</th>
<th>Lung function (FEV₁)</th>
<th>Interference with Activity limits</th>
<th>Flare-ups</th>
<th>Quick Reliever</th>
<th>Preferred Controller Option</th>
<th>Alternative Controller Options</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>INTERMITTENT ASTHMA</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>STEP 1</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intermittent asthma</td>
<td>≤2 d/w</td>
<td>≤2 x/mo</td>
<td>≤2 d/w</td>
<td>Normal (FEV₁ &gt;80)</td>
<td>None</td>
<td>0-1/y</td>
<td>SABA PRN</td>
<td>No controller</td>
<td>Consider low dose ICS</td>
</tr>
<tr>
<td><strong>PERSISTENT ASTHMA</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>STEP 2</td>
<td></td>
<td></td>
<td></td>
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<td></td>
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<tr>
<td>Mild asthma</td>
<td>&gt;2 d/w</td>
<td>3-4 x/mo</td>
<td>&gt;2 d/w</td>
<td>Normal (FEV₁≥80)</td>
<td>Minor</td>
<td>≥2/y</td>
<td>SABA PRN</td>
<td>Low-dose ICS</td>
<td>Cromolyn, LTRA, nedocromil or theophylline</td>
</tr>
<tr>
<td>STEP 3</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Moderate asthma</td>
<td>Daily</td>
<td>1 x/w</td>
<td>Daily</td>
<td>FEV₁: 60-80%</td>
<td>Some limitation</td>
<td>≥2/y</td>
<td>SABA PRN</td>
<td>Low-dose ICS + LABA OR Medium-dose ICS</td>
<td>Low dose ICS + (LTRA, theophylline or zileuton)</td>
</tr>
<tr>
<td>STEP 4</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Moderate asthma</td>
<td>Throughout the day</td>
<td>7 x/w</td>
<td>Several times/day</td>
<td>FEV₁&lt; 60%</td>
<td>Extremely limited</td>
<td>≥2/y</td>
<td>SABA PRN</td>
<td>Medium-dose ICS + LABA</td>
<td>Medium-dose ICS + (LTRA, theophylline or zileuton)</td>
</tr>
<tr>
<td>STEP 5</td>
<td></td>
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<td></td>
<td></td>
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<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Severe asthma</td>
<td>Throughout the day</td>
<td>7 x/w</td>
<td>Several times/day</td>
<td>FEV₁&lt; 60%</td>
<td>Extremely limited</td>
<td>≥2/y</td>
<td>SABA PRN</td>
<td>High-dose ICS + LABA (and consider omalizumab for patients who have allergies)</td>
<td>Not defined</td>
</tr>
<tr>
<td>STEP 6</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Severe asthma</td>
<td>Not defined</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>SABA PRN</td>
<td>High-dose ICS + LABA + OCS (and consider omalizumab for patients who have allergies)</td>
<td>Not defined</td>
</tr>
</tbody>
</table>

Abbreviations: d, day; FEV₁, forced expiratory volume in one second; FM, formoterol; ICS, inhaled corticosteroids; ICS/LABA, inhaled corticosteroids and long acting beta₂-agonists; LTRA, leukotriene receptor antagonists; mo, month; NHLBI, National Heart, Lung and Blood Institute; OCS, oral corticosteroids; PRN, pro re nata (as needed); SABA, short-acting beta₂-agonists; w, week; x, times; y, years
B) Chronic Obstructive Pulmonary Disease (COPD)

Disease Overview

“Chronic Obstructive Pulmonary Disease (COPD) represents an important public health challenge and is a major cause of chronic morbidity and mortality throughout the world.”

Around 16 million Americans have been diagnosed with COPD and the mortality rate due to COPD has doubled since 1969. COPD was the third leading cause of death in the United States in 2014 and the World Health Organization (WHO) has estimated that COPD will rise from the fourth to the third leading cause of mortality worldwide by 2030. According to the National Heart, Lung and Blood Institute and COPD National Action Plan, COPD kills more than 135,000 Americans each year. Smoking accounts for 80% of COPD-related deaths although 25% of cases were not related to cigarette smoking. Between 2000 and 2014, the overall incidence of COPD-related deaths declined for both men and women ≥25 years, but increased for the population subsets of men and women aged 45-64 and women aged ≥85. The number of people with COPD is increasing “because of continued exposure to risk factors and aging of the population”. Several million people are likely to have undiagnosed COPD due to patient underreporting of symptoms and under-diagnosis by practitioners. According to estimates based on the Behavioral Risk Factor Surveillance System (BRFSS, 2015), 79,200 (3.8%) people ≥ 18 years old have COPD in Utah. Data provided by the Bureau of Epidemiology of the Utah Department of Health showed “a slow but steady increase in the rate of emergency department visits due to COPD, asthma, and hypersensitivity pneumonitis” from 2000 to 2011, with a monthly rate (higher during winter months) between 3 to 14 people per 100,000 Utahn’s. Monthly hospitalizations rates (4 to 15 people/100,000/month) and death rates (1 to 4 people/100,000/month) due to the above three respiratory diseases remained constant from 2000 to 2011.

COPD is a progressive disease which includes emphysema, chronic bronchitis, and in some cases asthma. It is characterized by chronic coughing (most commonly daily and productive, but also intermittent and unproductive), breathlessness on exertion (initially intermittent and becoming persistent), sputum production (any pattern of sputum production may indicate COPD), and frequent exacerbations of bronchitis. In the United States, the Centers for Disease Control and Prevention (CDC) reports that tobacco smoke is a key factor in the development and progression of COPD, but other factors such as air pollutants in the home and workplace (e.g. occupational dusts, home cooking and biomass fuels), genetic factors, and respiratory infections also contribute to disease progression. Besides genetic factors, abnormal lung development and accelerated aging are also host factors that predispose individuals to develop COPD. In relation to COPD and air pollution, the Utah Department of Health recommends checking the air quality before doing any outdoor activity in order to modify the level of exertion, accordingly. According to the National Heart, Lung and Blood Institute,
COPD most often occurs in people age 40 and over with a history of smoking (either current or former smokers), and several relevant sources report that tobacco smoke is the main risk factor for COPD. According to the CDC, groups more likely to report COPD include people aged 65–74 years, American Indians/Alaska natives and multiracial non-Hispanics, women, individuals who were unemployed, retired, or unable to work, individuals with less than a high school education, people with lower incomes, individuals who were divorced, widowed, or separated, current or former smokers, and those with a history of asthma. In 2010, the annual costs related to COPD for the American health care system were estimated to be more than $32 billion with additional absenteeism costs of $3.9 billion. Medical costs are projected to increase to $49 billion by 2020. The implementation of programs and strategies to prevent COPD are intended to reduce the economic burden of COPD and improve the quality of life of people with COPD.

Spirometry is considered the gold standard for accurate, reproducible, and objective measurement of lung function and it is the best way of making a definitive diagnosis of asthma and COPD. However, the GOLD guidelines state that “despite its good sensitivity, peak expiratory flow measurement alone cannot be reliably used as the only diagnostic test because of its week specificity.” Spirometry measures the volume of air that the patient forcibly expels from the lungs after a maximal inspiration (forced vital capacity or FVC) and the air volume exhaled during the first second (forced expiratory volume in one second or FEV₁). Values are compared with predicted normal values (for age, height, sex, and ethnicity) to determine the severity of airway obstruction (e.g. mild, moderate, or severe disease levels). A post-bronchodilator FEV₁/FVC ratio < 70% confirms the presence of airflow limitation that is not fully reversible. Some other measures such as the Modified Medical Research Council (mMRC) dyspnea scale for measuring breathlessness, exacerbation frequency, body mass index, quality of life assessment, and exercise capacity are used to better understand patient’s airflow status. Jones et al (2014) outlined the validated minimal clinically important differences (MCID) for the most frequently used COPD outcomes in placebo-controlled clinical trials. For the lung function outcome, a MCID of 100 ml for FEV₁ was established for a COPD treatment to be considered effective. An improvement of 1 unit in the Transition Dyspnea Index (TDI) and a reduction of 4 units in the St George’s Respiratory Questionnaire were defined as MCID. No validated MCID is available for the exacerbation rate.

COPD is a preventable disease, but once a patient has developed COPD, it is a chronic disease that is largely incurable. The goal of management is to improve a patient’s functional status and quality of life (reducing symptoms and future risk of exacerbations). Initially, smoking cessation or avoidance of smoke and other air pollutants is fundamental to prevent or slow disease progression. According to the WHO, smoking cessation is the single most effective and cost-effective way to reduce the risk of developing COPD and stop its progression. The WHO states that brief tobacco dependence treatment is effective and
recommends that every tobacco user should be offered this treatment at every health care provider visit. The 2017 GOLD guideline includes several smoking cessation pharmacological strategies, such as nicotine replacement products, varenicline and bupropion, and highlights the utility of behavioral support programs. COPD pharmacotherapy can alleviate symptoms such as wheezing and coughing, decrease the frequency and severity of exacerbations, and increase exercise tolerance (by acting on bronchial smooth muscle contraction, bronchial mucosal congestion and edema, airway inflammation, and increased airway secretions). Currently, no treatment (aside from lung transplantation) has been shown to significantly improve long-term lung function or decrease mortality. Reduction of therapy once symptom control has been achieved is not normally possible in COPD and further worsening of lung function usually requires the introduction of additional treatments. Medications for the management of COPD include oral inhalation β2-agonists (SABA and LABA), oral inhalation anticholinergics (SAMA and LAMA), corticosteroids (inhaled and systemic), methylxanthines, phosphodiesterase-4 inhibitors, and combinations of short-acting bronchodilators (SABA/SAMA), long-acting bronchodilators (LABA/LAMA), and long-acting β2-agonists with inhaled corticosteroids (LABA/ICS). Bronchodilators on an as-needed basis or on a regular basis provide symptomatic relief but do not reduce disease progression. The long-term decline in lung function is one of the hallmarks of the disease. The GOLD pharmacologic treatment algorithm based on group A through D classification (using symptoms and exacerbation history) is discussed in the guideline section.

Patients with COPD often experience acute exacerbations of signs and symptoms which the WHO describes as another hallmark of COPD, and exacerbations and co-morbidities contribute to the overall severity of COPD. An exacerbation can be caused by several factors, but most commonly by respiratory tract infections. Initial recommendations for pharmacological treatment of an exacerbation include short-acting β2-agonists, with or without short-acting anticholinergics, and short courses (5-7 days) of systemic corticosteroids. Antibiotics are also considered for those with clinical signs of airway infection (e.g., increased volume and change of color of sputum, or fever). Methylxanthines, which have a narrow therapeutic index, are not recommended due to their unfavorable safety profiles. GOLD guidelines state that adequate interventions for the prevention of exacerbations should be initiated following an exacerbation, and include bronchodilators (LABAs, LAMAs, LABA+LAMA), corticosteroid-containing regimens (LABA+ICS, LABA+LAMA+ICS), non-steroid anti-inflammatory (roflumilast), anti-infectives (vaccines, long-term macrolides), mucoregulators (N-acetylcysteine, carbocysteine), and others (smoking cessation, rehabilitation, lung volume reduction). Selective inhibitors of isoenzyme phosphodiesterase-4 (PDE-4 inhibitors) increase cyclic adenosine monophosphate (cAMP) in inflammatory and immunomodulatory cells reducing airway inflammation. The only PDE-4 inhibitor currently available in the U.S. is roflumilast (Dairesp), administered orally and once-daily, to reduce the
risk of exacerbations in patients with severe COPD associated with chronic bronchitis and a history of exacerbations (not for the relief of acute bronchospasm). \textsuperscript{54,55} Azithromycin or erythromycin can also be used to reduce exacerbation risk. GOLD guidelines report that a reduction in the exacerbation risk has been demonstrated with the long-term use over 1 year of azithromycin or erythromycin. However, azithromycin may be linked with an increased risk of bacterial resistance and hearing impairment.\textsuperscript{49}

Patient adherence to COPD treatment is a key component to achieve treatment success, improve health-related quality of life, reduce the risk of hospitalizations and diminish health system costs.\textsuperscript{56-58} Treatment adherence may increase by simplifying dosing regimens (i.e. using medications allowing for lower dosing frequencies such as once daily instead of twice daily), employing an easy-to-use\textsuperscript{59} and intuitive inhalation device, and using a single inhaler instead of multiple separate inhalers when dual- or triple-combination therapy is necessary.\textsuperscript{56,57,60}

Patients with COPD may also benefit from supplemental oxygen (if blood oxygen levels are low), nonpharmacological interventions such as exercise,\textsuperscript{38,49,50} and administration of influenza and pneumococcal vaccines to decrease the impact of lower respiratory infections (infections often trigger exacerbations).\textsuperscript{38,49} Treatment programs such as pulmonary rehabilitation teach COPD management strategies on an individualized basis (e.g. breathing strategies, energy-conserving techniques, and nutritional counseling) to increase quality of life.\textsuperscript{38,40} It has been reported that COPD patients with poor nutritional status and low body weight have decreased pulmonary status, reduced diaphragmatic mass, poorer exercise capacity, increased mortality rates and reduced quality of life.\textsuperscript{61}

**Clinical Guidelines for the Management of COPD**

**Diagnosis**

The Global Initiative for Chronic Obstructive Lung Disease (GOLD) assessment guideline for guiding pharmacotherapy in COPD has progressed from a simple spirometric grading system (classified COPD severity into GOLD 1 to 4 groups according to the predicted FEV$_1$) to the “ABCD” assessment tool in 2011 which combined spirometry, clinical symptoms, and frequency of exacerbations per year,\textsuperscript{40,62} and currently to the 2017 guideline in which some refinements were included to address concerns with the 2011 tool while “maintaining consistency and simplicity for the practicing clinician.”\textsuperscript{40,49} In the new guideline, spirometric grades are separated from symptoms and exacerbation history so that patients are first classified as GOLD grades 1-4 (disease severity based on FEV$_1$), and then as Group A-D based on exacerbation history, assessment of symptoms, and risk of future exacerbations.\textsuperscript{40,45,49}

In the current guideline, the GOLD committee recommends, after a confirmed diagnosis by spirometry (post-bronchodilator FEV$_1$/FVC <0.7), further assessment of the patients’ condition by:
1. **Spirometry** to determine the severity of airflow limitation which is graded as GOLD 1=mild (FEV1 ≥80), GOLD 2=moderate (FEV1 50-79), GOLD 3=severe (FEV1 30-49), or GOLD 4=very severe (FEV1 <30)

2. **Assessment of symptoms** using different questionnaires:
   a. the Modified Medical Research Council (mMRC) questionnaire for assessment of dyspnea, i.e. ranging from Grade 0= “I only get breathless with strenuous exercise” to Grade 4= “I am too breathless to leave the house or I am breathless when dressing and undressing.”
   b. the COPD Assessment Test (CAT) for assessment of symptoms.

3. Recording their **history of exacerbations** in the previous year (0-1 or ≥2 exacerbations) and prior hospitalizations

Labelling a patient’s COPD condition includes both a grade and a group e.g. GOLD Grade 4, group B.

As stated in the guideline: “This classification scheme may facilitate consideration of individual therapies (exacerbation prevention versus symptom relief)” and “also help guide escalation and de-escalation therapeutic strategies for a specific patient.”

**Smoking Cessation**

Current Global Initiative for GOLD guidelines stress the importance of smoking cessation, and include a Cochrane systematic review reference of long-term quit success rates of up to 25% if effective resources and time are dedicated. The guideline includes a strategic framework for health care providers to help patients stop smoking. The benefit of vaccinations (influenza and pneumococcal), other non-pharmacological treatments, and recommendations for prescription of supplemental oxygen are also included as pharmacological treatments “should be complemented by appropriate non-pharmacological interventions.”

**Pharmacotherapy**

The GOLD committee recommends that treatment should “be individualized and guided by severity of symptoms, risk of exacerbations, side-effects, comorbidities, drug availability and cost, and the patient’s response, preference and ability to use various drug delivery devices.”

Pharmacologic therapy used in COPD includes β2-agonists, anticholinergics, methylxanthines, phosphodiesterase-4 inhibitors, and combinations (including corticosteroids). In the past, GOLD recommendations were given for initial therapy according to airflow obstruction (FEV1), symptoms and exacerbations. Currently, the 2017 GOLD guidelines include proposed pharmacologic algorithms based on patients’ symptoms and exacerbation rate (i.e. by ABCD group classification) without considering FEV1 measurement. Moreover, recommendations are proposed for initiation of therapy and for subsequent escalation and/or de-
escalation (considering symptoms and exacerbation risk). It is important to note that treatment escalation has not been systematically evaluated and de-escalation strategies only include ICS. The recommendations will be re-evaluated as additional evidence becomes available.

GOLD guideline recommends the following pharmacologic treatment algorithms for each group (A-D):

<table>
<thead>
<tr>
<th>GOLD Groups</th>
<th>Symptom Burden</th>
<th>Exacerbation/previous year</th>
<th>Initial, escalation and de-escalation pharmacological strategiesa</th>
</tr>
</thead>
<tbody>
<tr>
<td>A Low (mMRC 0-1, CAT &lt;10)</td>
<td>0-1 (no hospital admission)</td>
<td>1. Single bronchodilator (short or long-acting bronchodilator) 2. Evaluate and switch to another if necessary;</td>
<td></td>
</tr>
<tr>
<td>B High (mMRC ≥2, CAT ≥10)</td>
<td>0-1 (no hospital admission)</td>
<td>1. LAMA or LABA 2. If symptoms persist: LAMA+LABA</td>
<td></td>
</tr>
<tr>
<td>Cb Low (mMRC 0-1, CAT &lt;10)</td>
<td>≥2 or ≥1 leading to hospitalization</td>
<td>1. LAMA 2. If further exacerbations, switch to:  ( \Rightarrow ) LAMA+LABA (preferred) or  ( \Rightarrow ) LABA+ICS (alternative)</td>
<td></td>
</tr>
<tr>
<td>Db High (mMRC ≥2, CAT ≥10)</td>
<td>≥2 or ≥1 leading to hospitalization</td>
<td>1. LABA+LAMA (preferred); some patients may start with LAMA or LABA/ICS 2. If further exacerbations and symptoms persist: TT (LABA+LAMA+ICS) 3. If further exacerbations occurs:  ( \Rightarrow ) Roflumilast (if FEV₁&lt;50 and chronic bronchitis)  ( \Rightarrow ) Macrolide (in former smokers)c  ( \Rightarrow ) Stop ICS</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: CAT, COPD assessment test; COPD, chronic obstructive pulmonary disease; GOLD, Global Initiative for Chronic Obstructive Lung Disease; ICS, inhaled corticosteroids; LABA, long-acting β₂-adrenergic agonist; LAMA, long-acting antimuscarinic agent; mMRC, modified Medical Research Council; TT, triple therapy;

a Based on efficacy and safety data available. GOLD guidelines note that escalation and de-escalation have not been “systematically tested”

b Treatment recommendations with lack of supporting direct evidence

c Azithromycin is preferred

The 2017 GOLD guidelines recommend a single bronchodilator for initial therapy in those groups with lower risk of exacerbations (i.e. groups A and B). LABA/LAMA combination products are recommended as the preferred option in patients with moderate to severe COPD, when symptoms persist or further exacerbations occur on monotherapy treatment with LAMA or LABA (i.e. group B and C). For group D patients, initiate therapy with a LABA/LAMA combination product (preferred treatment) and escalate to triple therapy (LABA+LAMA+inhaled
corticosteroids) if further exacerbations occur. Roflumilast or a macrolide may be considered, in certain severe patients if appropriate, and require evaluations and individual management.\textsuperscript{40,45,49}

**Comparison data LABA/ICS vs. LABA/LAMA**

Recent evidence from a study published in the New England Journal of Medicine indicates that LABA/LAMA treatment is more effective at reducing exacerbations than LABA/ICS combinations.\textsuperscript{49,65} This study (Wedzicha et al. 2016) was a 52-week non-inferiority trial evaluating LABA/LAMA vs LABA/ICS (LABA indacaterol 110 mug plus the LAMA glycopyrronium 50 mug once daily or the LABA salmeterol 50 mug plus the inhaled glucocorticoid fluticasone 500 mug twice daily). The primary outcome was the annual rate of all COPD exacerbations.\textsuperscript{65} Even though this was a non-inferiority trial, the authors found that indacaterol/glycopyrronium was not only non-inferior, but more effective than salmeterol/fluticasone in decreasing COPD exacerbations in patients with a history of exacerbation during the previous year.\textsuperscript{65} The 2017 GOLD guidance reflects this evidence by including the LABA/LAMA combination as preferred over LABA/ICS combinations (but still keeping it as an alternative).\textsuperscript{40}

**Triple Therapy**

In September 2017, the first single-triple-therapy inhaler was approved in the U.S based on 2 confirmatory trials. It contains fluticasone furoate, umeclidinium, and vilanterol. It is indicated for the long-term, once-daily, maintenance treatment of patients with COPD, including chronic bronchitis and/or emphysema, who are on a fixed-dose combination of fluticasone furoate and vilanterol for airflow obstruction and reducing exacerbations in whom additional treatment of airflow obstruction is desired or for patients who are already receiving umeclidinium and a fixed-dose combination of fluticasone furoate and vilanterol.\textsuperscript{66}

Evidence presented by the GOLD guidelines supporting stepping up to triple therapy, includes (details of evidence referenced by the GOLD guidance was included to improve understanding):

- “The step up in inhaled treatment to LABA plus LAMA plus ICS (triple therapy) can occur by various approaches.”\textsuperscript{40,67}
  - According to Bruselle et al. (2015) “Real-world prescription pathways leading to triple therapy (TT) (inhaled corticosteroid [ICS] plus long-acting beta2-agonist bronchodilator [LABA] plus long-acting muscarinic antagonist) differ from Global initiative for chronic Obstructive Lung Disease [GOLD] and National Institute for Health and Care Excellence treatment recommendations” and they therefore conducted a historical analysis of prescribing pathways in the UK (2002 to 2010). COPD patients without asthma that were receiving TT were identified and pathways from diagnosis to TT were then identified, and LABA plus ICS was identified as the most common
prescription pathway to TT. The authors concluded that “Real life UK prescription data demonstrates the inappropriate prescribing of TT and confirms that starting patients on ICS plus LABA results in the inevitable drift to overuse of TT. This study highlights the need for dissemination and implementation of COPD guidelines to physicians, ensuring that patients receive the recommended therapy.”

- “This may improve lung function and patient reported outcomes.”
  - Welte et al (2009): “budesonide/formoterol added to tiotropium versus tiotropium alone provides rapid and sustained improvements in lung function, health status, morning symptoms and activities, and reduces severe exacerbations.”
  - Singh et al (2008) states that there is little data on triple therapy with salmeterol, fluticasone propionate (SFC) and tiotropium bromide (TIO). They compared the effects of SFC 50/500 mcg twice daily in addition to TIO 18 mcg once daily versus the individual treatments alone, and found greater improvements with triple therapy in terms bronchodilation, as well as advantages in airway conductance, lung volumes, and patient related benefits (improving Transition Dyspnoea Index and use of rescue medication).
  - Jung et al (2012) states that triple therapy with tiotropium and fluticasone propionate/salmeterol (FSC) is commonly used in COPD, “but no study had evaluated the effectiveness of tiotropium plus FSC with 250 mug of fluticasone propionate.” They therefore evaluated “whether tiotropium (18 mug once daily) plus FSC (250/50 mug twice daily) provides better clinical outcomes compared to tiotropium monotherapy” and found that “Over the course of 24 weeks, FSC (250/50 mug twice daily) added to tiotropium provided greater improvement in lung function and quality of life in patients with COPD (FEV(1) <= 65%) than tiotropium alone.”
  - Hanania et al (2012) evaluated the efficacy and safety of triple therapy: “fluticasone/salmeterol (FSC) (250/50 mcg twice daily) when added to tiotropium (18 mcg once daily) (TIO)” and found that it “significantly improves lung function without increasing the risk of adverse events.”

- “Adding a LAMA to existing LABA/ICS improves lung function and patient reported outcomes, in particular exacerbation risk.”
- “A RCT did not demonstrate any benefit of adding ICS to LABA plus LAMA on exacerbations.”
- “Altogether, more evidence is needed to draw conclusions on the benefits of triple therapy LABA/LAMA/ICS compared to LABA/LAMA.”
C) Asthma and COPD

Disease overview

According to the updated Joint Project of GINA and GOLD (April 2017),76 “asthma-COPD overlap is characterized by persistent airflow limitation with several features usually associated with asthma and several features usually associated with COPD. Asthma-COPD overlap is therefore identified in clinical practice by the features that it shares with both asthma and COPD”. This project includes new recommendations for patients with both COPD and asthma. The correct identification of these patients and adequate treatment decisions remain a challenge. Some patients are borderline between asthma and COPD because they share asthma and COPD symptoms. This is especially common in smokers and the elderly. Given that this condition is considered a combination of asthma and COPD characteristics, the usual term used in previous guideline versions (i.e. “Asthma COPD Overlap Syndrome (ACOS)”) is no longer recommended. Currently, the Joint Project of GINA and GOLD considers that “asthma-COPD overlap” is the most appropriate term.76

Diagnosis of patients with respiratory symptoms is based on a stepwise process including: a) identification of patients with chronic airway disease by clinical history evaluation, physical examination and other investigations, b) differentiation between typical asthma, typical COPD and asthma-COPD overlap by exploring the usual features, c) assessment of airflow limitation by spirometry, and d) referral to a specialist in special situations.76

Clinical Guidelines for the Management of Asthma-COPD Overlap

The treatment recommendations outlined in table 6 are based on limited clinical evidence since studies conducted in this type of population are lacking.76

Table 5. Recommendations for Initial Treatment in Patients with Asthma-COPD Overlap76*

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Symptoms</th>
<th>Initial Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Asthma</td>
<td>Features of asthma</td>
<td>- Asthma drugs (adequate ICS as controller therapy)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- NO LABA monotherapy</td>
</tr>
<tr>
<td>Possible Asthma</td>
<td>Some features of asthma</td>
<td></td>
</tr>
<tr>
<td>Asthma-COPD Overlap</td>
<td>Features of both asthma and COPD</td>
<td>- Low/moderate dose ICS and consider LABA +/- or LAMA</td>
</tr>
<tr>
<td>COPD</td>
<td>Features of COPD</td>
<td>- COPD drugs (bronchodilators or ICS/bronchodilator)</td>
</tr>
<tr>
<td>Possible COPD</td>
<td>Some features of COPD</td>
<td>- NO ICS alone</td>
</tr>
</tbody>
</table>

Abbreviations: COPD, chronic obstructive pulmonary disease; GINA, global initiative for asthma; GOLD, global initiative for chronic obstructive lung disease; ICS, inhaled corticosteroids; LABA, long-acting beta2 agonists; LAMA, long-acting muscarinic antagonist

* See GINA and GOLD guidelines for further information about recommended treatments
Pharmacology

The differing mechanism of action of medications indicated for the management of asthma allows tackling asthma through several pathophysiology aspects. β2-agonists such as albuterol, levalbuterol, formoterol, salmeterol, and vilaterol exert their pharmacologic action via relaxation of bronchial smooth muscles due to the selective activation of β2 receptors. These bronchodilators differ in onset of action and duration of effect. Short-acting β2-agonists (SABAs) including albuterol and levalbuterol have a fast onset of action and short duration, which make these agents useful as quick relievers for asthma attacks. LABAs including salmeterol, vilanterol and formoterol have slower onset of action than SABAs but provide a longer duration of effect. A study reported a bronchodilator effect of longer than 12 hours for salmeterol/fluticasone propionate and budesonide/formoterol, and longer than 24 hours for fluticasone/vilanterol. Among the LABAs, evidence showed that vilanterol has a faster onset of action than salmeterol. ICSs activate glucocorticoid receptors resulting in a delayed onset of action and extended duration of anti-inflammatory activity in the airways. Both LABA and ICS are classified as long-term controller medications for persistent asthma and are available as separate inhalers or may be combined into one single inhaler. When ICS and LABA are combined, complementary and positive benefits are shown in several studies. Regarding the recommended regimen, ICS and LABA are usually used as fixed-dose combination (once daily or twice daily) with SABA administered on as-needed basis for asthma exacerbations.

ICS/LABA fixed-dose combinations are administered via inhalation, are primarily metabolized by the liver via the cytochrome P450 system, and eliminated within 4.7 to 25 hours. Table 6 outlines the main pharmacokinetic characteristics of ICS/LABA combination products. Although no formal drug-drug interaction have been conducted with ICS/LABAs, drug-drug interactions may occur as individual components of the combinations (i.e. glucocorticoids and LABAs) are known to be extensively metabolized by CYP3A4. For instance, vilanterol is a substrate of CYP3A4 and salmeterol hydroxylation is metabolized by the CYP3A4 isoenzyme. Systemic exposure to ICS and LABAs may be increased when they are administered with strong CYP3A4 inhibitors such as ketoconazole, ritonavir, atazanavir, clarithromycin, indinavir,itraconazole, nefazodone, nelfinavir, saquinavir, telithromycin. ICS/LABA combination products should be administered with caution in combination with other adrenergic drugs (LABAs’ effects may be increased), with xanthine derivatives, diuretics or non-potassium sparing diuretics (hypokalemia and electrocardiograph changes produced by LABAs may be worsened), with monoamine oxidase inhibitors, tricyclic antidepressants and QTc-prolonging drugs (LABAs’ cardiovascular events may be potentiated), and with beta blockers (reduced effect of beta-agonists and increased risk of severe bronchospasm). No pharmacokinetic interactions between the two components of the FDCs were identified in pharmacokinetic studies when both drugs were administered concomitantly.
<table>
<thead>
<tr>
<th>Active Substance (Combination Products)</th>
<th>Absorption</th>
<th>Protein binding</th>
<th>Metabolism</th>
<th>Excretion</th>
<th>Elimination (half-life)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Budesonide/formoterol</td>
<td>BUD:</td>
<td>BUD: 85% to 90%</td>
<td>BUD: Liver (extensive), via CYP3A4</td>
<td>BUD: Fecal: as metabolites</td>
<td>BUD: 4.7 hr</td>
</tr>
<tr>
<td></td>
<td>FM:</td>
<td>FM: 31% to 64%</td>
<td>FM: Hepatic; via CYP2D6, CYP2C19, CYP2C9 and CYP2A6; direct glucuronidation (primary pathway), O-demethylation and glucuronide conjugation</td>
<td>FM: Fecal: 32% to 34%</td>
<td>FM: 7.9 hr</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>FM: Renal: 60% approx.</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>FM: Renal: 59% to 62% as metabolites, 6% to 10% unchanged</td>
<td></td>
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<tr>
<td></td>
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<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fluticasone propionate/salmeterol</td>
<td>FP:</td>
<td>FP: 91%</td>
<td>FP: Complete first pass metabolism</td>
<td>FP: Renal (&lt;5%)</td>
<td>FP: 5.33 to 7.65 hr</td>
</tr>
<tr>
<td></td>
<td>SAL:</td>
<td>SAL: 95%</td>
<td>SAL: metabolized extensively via hydroxylation</td>
<td>SAL: Fecal: 25 to 60% in urine</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>SAL: Feces (25 to 60%)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fluticasone furoate/vilanterol</td>
<td>FF:</td>
<td>FF: 99.6%</td>
<td>FF: Hepatic (extensive; via CYP3A4)</td>
<td>FF: Feces: 90% (IV) to 101% (oral)</td>
<td>FF: 24 hr (hepatic impairment: 30.9 to 53.5 hr)</td>
</tr>
<tr>
<td></td>
<td>VI:</td>
<td>VI: 93.9%</td>
<td>VI: via CYP3A4</td>
<td>VI: Renal: 1% (oral) to 2% (IV)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>VI: Urine (70%)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>VI: Feces (30%)</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mometasone/formoterol</td>
<td>MOM:</td>
<td>MOM: 98% to 99%</td>
<td>MOM/FM: Liver (extensive)</td>
<td>MOM: Fecal: 74%</td>
<td>MOM: 25 hr</td>
</tr>
<tr>
<td></td>
<td>FM:</td>
<td>FM: 31% to 38%</td>
<td></td>
<td>FM: Renal: 8% changed</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>FM: Fecal: 32% to 34%</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>VM: Renal: 6.2% to 6.8% unchanged</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: BA, bioavailability; BUD, budesonide; COPD, chronic obstructive pulmonary disease; FF, fluticasone furoate; FM, formoterol; FP, fluticasone propionate; GI, gastrointestinal; min, minute; hr, hour; LABA, long-acting β2-adrenergic agonist; MOM, mometasone; SAL, salmeterol; Tmax, time to peak concentration; VI, vilanterol
Special Populations

Table 7 describes the recommendations for ICS/LABA combination product use in special populations.

Renal and hepatic impairment

No dosage adjustment is required in patients with renal impairment. Caution should be exercised in patients with hepatic impairment.

Pregnant women

No adequate and well-controlled studies of ICS/LABA FDCs are available. The use of these combinations during pregnancy and lactation should be assessed in relation to the benefit for the mother and the risk for the fetus. Beta-agonists may affect uterine contractility. Cautious use is advised when these combinations are administered during labor and delivery.7-12

Pregnant women with asthma should be monitored to avoid uncontrolled asthma. If uncontrolled asthma occurs, asthma attacks should be treated. Budesonide is the preferred ICS by NHLBI because there is more evidence available about this agent than with other ICS.4 The treatment benefits for the mother and fetus outweigh the risk of asthma medication.83

Geriatric patients

In several long-term clinical trials including COPD patients, the incidence of pneumonia in the fluticasone/salmeterol group was higher in patients older than 65 years old than in those patients younger than 65 years old.8

Comorbidities

Patients with asthma may also have comorbidities such as allergic bronchopulmonary aspergillosis, gastroesophageal reflux, obesity, obstructive sleep apnea, rhinitis and sinusitis, stress and depression. Treatment of these conditions may improve asthma control.1,4

Comorbidities associated with COPD include lung cancer, cardiovascular disease (heart failure, arrhythmias, peripheral vascular disease and hypertension), osteoporosis, depression/anxiety and gastroesophageal reflux. Each comorbid disease should be appropriately treated.40,45
<table>
<thead>
<tr>
<th>Active Substance (Combination Products)</th>
<th>Renal Impairment</th>
<th>Hepatic Impairment</th>
<th>Pregnancy and lactation</th>
<th>Pediatric</th>
<th>Geriatric</th>
</tr>
</thead>
<tbody>
<tr>
<td>Budesonide/formoterol fumarate</td>
<td>Not studied (No dosage adjustment proposed)</td>
<td>Not studied. Monitor patients for signs of increased drug exposure</td>
<td><strong>Pregnancy:</strong> No studies in pregnant women. Adverse events were observed in animal reproduction studies using this combination. In women with poorly or moderately controlled asthma, there is an increased risk of several perinatal adverse outcomes such as preeclampsia in the mother and prematurity, low birth weight, and small for gestational age in the neonate. Pregnant women with asthma should be closely monitored and medication adjusted as necessary to maintain optimal asthma control. Given that β-agonists have the potential to affect uterine contractility if administered during labor, the use of this combination during labor should be restricted to those patients in whom the benefits clearly outweigh the risks. <strong>Lactation:</strong> It is not known if formoterol is present in breast milk; budesonide is present in small amounts. Infant risk cannot be ruled out. Weigh the potential benefits of drug treatment against potential risks before prescribing this drug during breastfeeding.</td>
<td>Indicated for children ≥6 years. Safety and effectiveness of SYMBICORT in asthma patients &lt;6 years of age have not been established</td>
<td>No adjustment required. As with other products containing β₂-agonists, special caution should be exercised in elderly patients with cardiovascular disease</td>
</tr>
<tr>
<td>Fluticasone propionate/ Salmeterol</td>
<td>Not studied (No dosage adjustment proposed)</td>
<td>Not studied. Fluticasone and salmeterol are primarily cleared in the liver and may lead to accumulation in patients with hepatic impairment; Monitor patients for signs of increased drug exposure</td>
<td><strong>Pregnancy:</strong> No studies in pregnant women. Adverse events were observed in animal reproduction studies using this combination. Use during pregnancy only if the potential benefit justifies the potential risk to the fetus. <strong>Lactation:</strong> It is not known if fluticasone or salmeterol are present in breast milk. The decision to continue or discontinue breastfeeding during therapy should take into account the risk of infant exposure, the benefits of breastfeeding to the infant, and benefits of treatment to the mother.</td>
<td>Indicated for children aged ≥4 years (Advair Diskus) and children aged ≥12 years (Advair HFA and Airduo Respliclick)</td>
<td>Limited data. Dose selection should be cautious. As with other products containing β₂-agonists, special caution should be exercised in elderly patients with cardiovascular disease</td>
</tr>
<tr>
<td>Fluticasone furoate/ Vilanterol</td>
<td>No dosage adjustment necessary</td>
<td>No dosage adjustment proposed. However, systemic fluticasone exposure may be</td>
<td><strong>Pregnancy:</strong> Insufficient data in pregnant women. Adverse events have not been observed in animal reproduction studies. In women with poorly or moderately controlled asthma, there is an increased risk of several perinatal</td>
<td>Safety and efficacy not established in children</td>
<td>No adjustment required</td>
</tr>
<tr>
<td>Active Substance (Combination Products)</td>
<td>Renal Impairment</td>
<td>Hepatic Impairment</td>
<td>Pregnancy and lactation</td>
<td>Pediatric</td>
<td>Geriatric</td>
</tr>
<tr>
<td>----------------------------------------</td>
<td>------------------</td>
<td>--------------------</td>
<td>------------------------</td>
<td>----------</td>
<td>----------</td>
</tr>
<tr>
<td>Mometasone/Formoterol</td>
<td>Not studied</td>
<td>Not studied</td>
<td>Pregnancy: No studies in pregnant women. In women with poorly or moderately controlled asthma, there is an increased risk of several perinatal adverse outcomes such as preeclampsia in the mother and prematurity, low birth weight, and small for gestational age in the neonate. Pregnant women with asthma should be closely monitored and medication adjusted as necessary to maintain optimal asthma control. Given that β-agonists have the potential to affect uterine contractility if administered during labor, the use of this combination during labor should be restricted to those patients in whom the benefits clearly outweigh the risks. Lactation: Not known whether mometasone and formoterol are excreted in human milk. Evaluate health benefits of breastfeeding versus mother’s clinical need for therapy and any potential adverse effects on the breastfed infant from therapy or from the underlying maternal condition.</td>
<td>Children ≥12 years and adolescents (adult dosing)</td>
<td>No adjustment required. As with other products containing β₂-agonists, special caution should be exercised in elderly patients with cardiovascular disease</td>
</tr>
</tbody>
</table>
Utah Medicaid Utilization Data

According to Utah Medicaid fee-for-service (FFS) data, the number of unique FFS patients with only asthma diagnosis coding from 2013 to 2017 period was 19,449. The number of patients with both asthma and COPD diagnosis coding was 2,955, and those with COPD only was 8,824. The majority of FFS patients filling prescriptions for ICS/LABA combination products were adults. The most commonly prescribed FDC for patients with asthma, COPD, or both asthma and COPD diagnosis coding during 2013-2017 period was fluticasone/salmeterol (specifically Advair Diskus), followed by budesonide/formoterol, mometasone/formoterol, and fluticasone/vilanterol. Some patients filled prescriptions for 2 separate inhalers at the same time instead of using single-inhaler, FDCs. Currently, budesonide/formoterol (Symbicort), fluticasone/salmeterol (Advair Diskus), fluticasone/vilanterol (Breo Ellipta) and mometasone/formoterol (Dulera) are preferred in the Utah Medicaid Preferred Drug List. The remaining 2 fluticasone/salmeterol FDC products (Advair HFA, Airduo Respiclick) are currently non-preferred.84

Table 8. ICS/LABA treatment in Utah Medicaid FFS patients for 2013-2017 period

<table>
<thead>
<tr>
<th>Combination Products*</th>
<th>Unique Patients with Medication Fills</th>
<th>Unique Patients with included diagnoses**</th>
<th>Only COPD Dx Coding (n= 8,824)</th>
<th>Only Asthma Dx Coding (n= 19,449)</th>
<th>Asthma AND COPD Dx Coding (n=2,955)</th>
<th>No COPD/Asthma Dx Coding</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fixed-dose combinations (ICS/LABA)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Budesonide/formoterol</td>
<td>1154</td>
<td>1018</td>
<td>158</td>
<td>602</td>
<td>258</td>
<td>136</td>
</tr>
<tr>
<td>Fluticasone/salmeterol</td>
<td>2311</td>
<td>2073</td>
<td>291</td>
<td>1256</td>
<td>526</td>
<td>238</td>
</tr>
<tr>
<td>Fluticasone/vilanterol</td>
<td>65</td>
<td>50</td>
<td>9</td>
<td>24</td>
<td>17</td>
<td>15</td>
</tr>
<tr>
<td>Mometasone/formoterol</td>
<td>519</td>
<td>447</td>
<td>44</td>
<td>302</td>
<td>101</td>
<td>72</td>
</tr>
<tr>
<td>Separate inhalers in combination*** (ICS+LABA)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Beclomethasone + formoterol</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Beclomethasone + salmeterol</td>
<td>5</td>
<td>4</td>
<td>1</td>
<td>2</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Budesonide + formoterol</td>
<td>17</td>
<td>16</td>
<td>9</td>
<td>1</td>
<td>6</td>
<td>1</td>
</tr>
<tr>
<td>Budesonide + salmeterol</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Fluticasone + formoterol</td>
<td>8</td>
<td>8</td>
<td>5</td>
<td>0</td>
<td>3</td>
<td>0</td>
</tr>
<tr>
<td>Fluticasone + salmeterol</td>
<td>16</td>
<td>14</td>
<td>1</td>
<td>9</td>
<td>4</td>
<td>2</td>
</tr>
<tr>
<td>Mometasone + formoterol</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Mometasone + salmeterol</td>
<td>3</td>
<td>3</td>
<td>0</td>
<td>2</td>
<td>1</td>
<td>0</td>
</tr>
</tbody>
</table>

Abbreviations: COPD, chronic obstructive pulmonary disease; Dx, diagnosis; FDC, fixed-dose combination; FFS, fee-for-service; ICS, inhaled corticosteroid; LABA, long-acting beta-2 agonist
* Via FDCs or via separate inhalers
** Total unique patients with either COPD or asthma diagnosis codes submitted for 2013-2017 period
*** Separate single inhalers filled within 30 days
Methods

Literature Search

Search strategies were developed by an informational scientist for OVID Medline and EMBASE. Strategies consisted of controlled vocabulary, such as MeSH, and keyword phrases. Two methodological filters were used, one for systematic reviews and another for randomized controlled trials (RCTs). Results were limited to English language. Databases were searched from date of inception forward. In EMBASE, we excluded conference abstracts. Searches were conducted in June 2017. We searched for systematic reviews first, and then for RCTs, without any restriction date. The complete search strategies and terms are available in Appendix A.

We also screened the reference lists of related systematic reviews. Likewise, we searched other relevant websites for further information:

1. The National Institute of Health (NIH), The National Heart, Lung, and Blood Institute (NHLBI), the World Health Organization (WHO), the Centers for Disease and Control (CDC), the Global Initiative for Chronic Obstructive Lung Disease (GOLD) and the Global Initiative for Asthma (GINA) websites for the most recent asthma and COPD treatment guidelines.
2. Food and Drug Administration (Drugs@FDA: FDA Approved Drug Products: https://www.accessdata.fda.gov/scripts/cder/daf/) for prescribing information package inserts
3. Evidence-based drug information databases (Micromedex, Lexicomp, and UpToDate)

Screening

At least two review authors screened titles and abstracts. The full texts for all citations receiving two inclusion votes were retrieved; eligibility criteria for inclusion was determined by the lead author. Conflicts were resolved via discussion between reviewers or a third person. Figure 1 shows the PRISMA flow chart85 for the review process.

Inclusion and Exclusion Criteria

Systematic reviews and RCTs providing head-to-head efficacy comparisons between the ICS/LABA combination products were included. For product comparisons where a systematic review provided robust data, we examined only those trials or systematic reviews published after the search date of the robust systematic reviews.

Excluded references met the following exclusion criteria:

• Studies evaluating non-FDA-approved indications or dosages
• Other types of studies (e.g. non-comparative or non-randomized trials, placebo-controlled studies, phase 1 and 2 studies, observational studies, in vitro studies, animal studies, cost-effectiveness studies, etc.)
• Reviews not using a systematic review methodology

A list containing the excluded references is provided in Appendix F.

Figure 1. PRISMA Flow Diagram of the selection process
Clinical Efficacy and Safety

Clinical evidence involving head-to-head comparisons among ICS/LABA combination products is presented for the products currently available in the United States. From a total of 1,381 references identified using the developed search strategy (221 SR/MA and 1,160 RCTs), we selected 26 efficacy/safety articles containing 5 SR/MA, 21 RCTs, and 2 MTCs, and 3 safety articles containing 1 SR/MA and 2 RCTs for our qualitative synthesis. Main results are outlined in Appendixes B, C, D, and E.

Studies including ICS/LABA combinations were mainly performed in patients with persistent asthma that continue suffering symptoms and exacerbations with low- or medium-doses ICS therapy, or in patients with moderate to severe COPD. Regarding asthma management, the most common primary efficacy endpoints include: a) lung function (FEV₁ or peak expiratory flow [PEF] from baseline), b) assessment of asthma symptoms (day and night time symptom score) and use of rescue medications, c) asthma exacerbations, and d) change in health-related quality of life (measured by asthma quality of life questionnaire [AQLQ]). Concerning COPD management, the most frequent primary endpoints include improvement in lung function, exacerbation rate, and health status.

Different inhaler devices delivering the same dose of BUD plus FM are internationally approved. BUD/FM pMDI is available in the U.S. BUD/FM DPI is available in Europe. Two RCTs compared the efficacy and safety of the two aforementioned inhalers showing therapeutic equivalence between them.⁸⁶,⁸⁷ Hence, evidence available evaluating BUD/FM DPI was also included in this report.

1. Single ICS/LABA inhaler versus separate inhalers administered concomitantly (ICS+LABA)

a) Budesonide/formoterol (BUD/FM) versus budesonide plus formoterol (BUD+FM)

[4 articles: 4 RCTs]

Patients with asthma

Clinical trials including the U.S. BUD/FM inhaler (pMDI)

Noonan et al⁸⁸ (2006) conducted a 12-week RCT in patients ≥12 years of age with moderate to severe persistent asthma previously receiving ICS therapy. Patients were treated with BUD/FM pMDI, BUD or FM monotherapy, placebo, or BUD+FM in separate inhalers. Results indicated similar efficacy outcomes in terms of mean changes in FEV₁ and worsening or improvement in asthma symptoms between BUD/FM FDC and the concurrent administration of separate inhalers (BUD+FM). Safety profiles were also considered comparable between groups.
**Clinical trials including the non-U.S. BUD/FM inhaler (DPI)**

Pohunet et al\(^89\) (2006) performed a clinical trial in children between 4 and 11 years old with asthma to compare BUD/FM DPI 80/4.5 µg, 2 inhalations twice daily (Symbicort Turbuhaler), budesonide plus formoterol (100 µg + 4.5 µg, 2 inhalations twice daily), and budesonide 100 µg 2 inhalations twice daily. No differences in efficacy outcomes (morning peak expiratory flow [PEF] and asthma symptom changes) and safety results were observed between groups.

Rosenhall et al\(^90\) 2002 (6-month study, 586 patients) and Rosenhall et al\(^91\) 2003 (6-month extension open label study, 321 patients) evaluated the single inhaler containing BUD/FM DPI 160/4.5 (2 inhalations twice daily) versus BUD and FM administered concomitantly in adult patients with moderate persistent asthma. The 6-month study reported that BUD/FM DPI was similarly effective in terms of lung function, exacerbation rate, asthma control, and health-related quality of life (measured by two different questionnaires) as BUD and FM administered at the same time in separate inhalers. Similar safety profiles were observed between groups. Data from a subgroup of patients completing the 12-month study showed similar efficacy and safety outcomes between groups that were constant until the end of the study. Of note, the proportion of withdrawals over 12 months was higher in the BUD+FM group than BUD/FM DPI group (19.4% vs 9.2%, respectively; \(p=0.008\)). Authors postulated a potential positive impact on adherence to inhalation therapy in those patients using one single inhaler compared to those using separate inhalers.

**b) Salmeterol/fluticasone propionate (SAL/FP) versus salmeterol plus fluticasone propionate (SAL+FP) [6 articles: 1 SR/MA and 5 RCTs]**

**Patients with asthma**

Kawai et al\(^92\) (2007) evaluated SAL/FP DPI 50/250 µg twice daily versus SAL+FP in a 14-day RCT including 18 adult Japanese and 17 Caucasian asthmatic patients. They found no significant differences in terms of FEV\(_1\) and specific airways conductance (sGaw) responses between SAL/FP and the separate inhalers administered concomitantly for total analysis. In addition, similar results were observed in Japanese and Caucasian asthmatic patients.

Van der Berg et al\(^93\) (2000) reported similar efficacy and safety results when SAL/FP DPI 50/100 µg twice daily and SAL+FP DPI administered via separate inhalers were compared in a 12-week study including asthmatic children aged from 4 to 11 years not responding to monotherapy with an ICS. Both treatment groups reported an improvement in lung function, asthma control and symptoms, without significant differences between groups. Although the authors did not measure adherence to inhalation therapy, they commented that a single inhaler may increase adherence.
Bateman et al\textsuperscript{94} (1998), Chapman et al\textsuperscript{95} (1999), and Aubier et al\textsuperscript{96} (1999) conducted 3 RCTs (one each) comparing SAL/FP DPI via single inhaler and FP+SAL administered via separate inhalers in patients \( \geq 12 \) years old with asthma. Three different doses of fluticasone were tested (i.e. 100, 250 and 500 micrograms twice daily). All studies demonstrated that SAL/FP was as effective as SAL+FP with regard to the primary endpoint of lung function (measured by morning PEF rate) at week 12. In addition, Bateman et al showed superiority of SAL/FP 50/100 µg versus SAL+FP for lung function at week 12, and Chapman et al reported superiority of SAL/FP 50/250 µg for lung function values at other time points (week 3 and 4). Similar results were observed between groups for the secondary endpoints (i.e. evening PEF rate, day/night-time symptom scores, use of rescue medication, and safety outcomes).

Nelson et al\textsuperscript{97} (2003) conducted a meta-analysis to compare FP/SAL DPI versus separate inhalers administered concomitantly. Results suggested statistically significantly greater improvements in morning PEF with FP/SAL administered in one single inhaler than separate inhalers. Study limitations and a proper discussion regarding the clinical relevance of the results was lacking.

2. Fluticasone propionate/salmeterol (FP/SAL) DPI versus FP/SAL pMDI [3 articles: 3 RCTs]

**Patients with asthma**

- FP/SAL HFA MDI 50/25 µg vs FP/SAL Diskus 100/50 µg

  Bateman et al\textsuperscript{98} (2001) directly compared two different inhalers (DPI and pMDI) containing FP/SAL in a 12-week multicenter RCT including 497 patients with asthma aged 11-79 years. The treatment arms were FP/SAL Diskus 100/50 µg (one inhalation twice daily) and FP/SAL HFA MDI 50/25 µg (two inhalations twice daily). Results demonstrated clinical equivalence between groups for the primary endpoint (increase in mean morning PEF over weeks 1 to 12), and all secondary endpoints (evening PEF, daytime and night-time symptom scores, use of rescue salbutamol and clinic FEV\textsubscript{1}).

- FP/SAL HFA MDI 125/25 µg vs FP/SAL Diskus 250/50 µg

  You-Ning et al\textsuperscript{99} (2005) performed a RCT to compare FP/SAL HFA MDI 125/25 µg (two inhalations twice daily) vs FP/SAL Diskus 250/50 µg (one inhalation twice daily) in Chinese adult patients with moderate asthma. Both treatment arms reported similar improvements in the primary endpoint (morning PEF) and all secondary endpoints over weeks 1 to 4. Differences between groups were not statistically significant.

- FP/SAL HFA MDI 250/25 µg vs FP/SAL Diskus 500/50 µg

  Van Noord et al\textsuperscript{100} (2001) evaluated FP/SAL HFA MDI 250/25 µg (two actuations twice daily) versus FP/SAL Diskus 500/50 µg (one actuation twice daily) in patients with asthma.
Clinical equivalence was demonstrated between groups for the primary endpoint (mean change in morning PEF over weeks 1 to 12) and for secondary endpoints.

Safety profiles were comparable between groups in the 3 aforementioned RCTs.

3. Budesonide/formoterol (BUD/FM) pMDI or DPI versus fluticasone propionate/salmeterol (FP/SAL) DPI or pMDI [7 articles: 3 SR/MA, 4 RCTs]

Patients with asthma

Two Cochrane reviews performed by Lasserson et al\(^{101}\) (2008) and Lasserson et al\(^{102}\) (2011) assessed the efficacy and safety between FP/SAL pMDI or DPI and BUD/FM pMDI or DPI twice daily in adolescents and adults with chronic asthma. Both reviews included the same 4 published RCTs (Aalbers 2004,\(^{103}\) Busse 2008,\(^{104}\) Kuna 2007 [COMPASS],\(^{105}\) and Dahl 2006\(^{106}\) [EXCEL]). The dose of FP/SAL was 500/100 mcg per day and doses for BUD/FM ranged from 400/12 mcg/day to 800/24 mcg/day. The meta-analysis indicated the following results:

- No statistically significant differences between groups for the primary endpoint (exacerbations requiring oral steroid treatment, exacerbations requiring admission to hospital, and asthma-related serious adverse events) at 6 months
- No statistically significant differences between groups for the secondary endpoint (lung function results, exacerbations requiring emergency department visit/hospital admission, adverse events, and rescue medication use)

Authors mentioned the results were associated with high imprecision due to the width of confidence intervals for the primary endpoint. Authors concluded the need for well-conducted RCTs, especially in children.

Edwards et al\(^{107}\) (2007) performed a meta-analysis to compare the effectiveness of BUD/FM versus ICS alone or other ICS/LABA in patients aged 16 years and older with moderate to severe asthma. Among the 15 studies considered for inclusion in the meta-analysis, 3 compared BUD/FM DPI versus FP/SAL MDI or DPI (Aalbers 2004,\(^{103}\) Kuna 2007 [COMPASS],\(^{105}\) and Dahl 2006\(^{106}\) [EXCEL]). Results for the comparisons of interest are reported below:

- No significant differences between groups for the primary endpoint of “treatment failure”, defined as 1 or more of the following outcomes: asthma-related serious adverse events, oral glucocorticosteroid treatment required, accident or emergency visit and/or admission to hospital, withdrawal due to a need for additional asthma therapy or adverse events.
- The secondary analysis showed no significant differences between groups in the number of exacerbations requiring oral steroid use. However, the risk of exacerbations requiring hospitalizations/A&E visits was statistically significantly higher with FP/SAL than BUD/FM.
Authors discussed several limitations, including primarily the use of an uncommon primary endpoint in this type of trial.

In addition, 3 short-term studies in asthmatic patients compared the onset of bronchodilation between single-inhaler BUD/FM pMDI or DPI and FP/SAL DPI. All showed BUD/FM had a faster onset of action measured by FEV₁ at 3 minutes in comparison to FP/SAL. Moreover, improvements in FEV₁ were more rapidly observed at other time points in those patients on treatment with BUD/FM than those with FP/SAL.

**Patients with COPD**

Regarding the onset of effect of BUD/FM compared to FP/SAL, one study in patients with COPD reported faster onset of bronchodilator effect with BUD/FM compared to FP/SAL.

4. **Fluticasone furoate/vilanterol (FF/VI) versus fluticasone propionate/salmeterol (FP/SAL) and/or BUD/FM** [5 articles: 1 SR/MA, 4 RCTs, 2 MTC]

**Patients with asthma**

One Cochrane review, published by Dwan et al. in 2016, evaluated the efficacy and safety of FF and VI in children and adults with chronic asthma. One 24-week study assessing FF/VI DPI 100/25 mcg once daily versus FP/SAL DPI 250/50 mcg twice daily was identified (Woodcock 2013). A total of 806 patients with persistent asthma uncontrolled with medium-dose ICS were randomized. No statistically significant differences were found between groups for the primary endpoints (change in health-related quality of life, severe asthma exacerbations, and serious adverse events). No statistically significant differences were reported for the secondary endpoints (change in FEV₁ and asthma symptoms). Authors highlighted the limited comparative efficacy and safety information available to make a robust decision about the preference of FF+VI over FP/SAL. The authors state that further research is required.

Svedsater et al. (2016) performed a mixed treatment comparison (MTC) modelling approach, including direct and indirect comparisons (network meta-analysis), to evaluate the probability of non-inferiority of once-daily FF/VI compared to twice-daily ICS/LABA combination therapies. Thirty one RCTs including ICS/LABAs in asthma patients ≥ 12 years old were evaluated using covariate-adjusted Bayesian hierarchical models. Results suggested similar lung function improvements with FF/VI 100/25 µg and FF/VI 200/25 µg compared to corresponding doses of FP/SAL and BUD/FM. Health status outcomes were comparable between once-daily FF/VI 100/25 µg compared to twice-daily FP/SAL 250/50 µg and BUD/FM 320/9 µg. There were insufficient data to measure non-inferiority on health status of FF/VI 200/25 µg and exacerbation rates. Study limitations included: 1) indirect comparisons, 2) low number of RCTs assessing ICS/LABAs, especially those assessing exacerbation rate outcomes,
and 3) heterogeneity in design, outcome definition, population and region between included studies.

**Patients with COPD**

Dransfield et al\(^{115}\) (2014) conducted 3 RCTs in different centers to evaluate the efficacy and safety of FF/VI 100/25 µg once daily compared to medium-dose FP/SAL DPI (250/50 µg) twice daily over 12 weeks in adult patients with moderate to very severe COPD. The pooled analysis of the 3 trials showed statistically significant differences in favor of FF/VI for the endpoint of change in lung function at day 84; however, these results were not clinically relevant. Safety profiles were similar between groups.

Stynes et al\(^{116}\) (2015) performed a MTC, including direct and indirect comparisons (network meta-analysis), to evaluate the probability of non-inferiority of once-daily FF/VI compared to twice-daily ICS/LABA combination therapies. Thirty three RCTs including ICS/LABAs in COPD patients ≥ 12 years old were evaluated using covariate-adjusted Bayesian hierarchical models. Results suggested non-inferiority in terms of lung function and health-related quality of life improvements with FF/VI 100/25 µg compared to FP/SAL 500/50 µg and BUD/FM 400/12 µg. Regarding exacerbation rate outcome, non-inferiority was not demonstrated. Study limitations included: 1) indirect comparisons, 2) low number of RCTs assessing ICS/LABAs, especially those assessing exacerbation rate outcomes, and 3) heterogeneity in design, outcome definition, population and region between included studies.

**Patients with asthma-COPD overlap**

Ishiura et al\(^{117}\) (2015) conducted a 12-week, randomized, open-label cross-over study comparing FF/VI DPI 200/25 µg vs FP/SAL DPI 500/50 µg in 16 patients with asthma-COPD overlap syndrome (ACOS). This study reported the following results:

- Similar improvements in the main spirometry parameters for lung function (i.e. FEV\(_1\), forced expiratory flow, and forced vital capacity) between FF/VI once daily and FP/SAL twice daily in ACOS patients.
- No differences between groups for other parameters measured such as asthma control test and COPD assessment test.

Several limitations were identified including the controversial criteria to diagnose ACOS patients, the lack of evidence about the mechanism of the clinical benefit of FF/VI, and the use of an insufficiently validated method (forced oscillation technique) to measure the respiratory impedance. Authors propose the need of additional studies to confirm the efficacy of FF/VI in this type of patients.
5. Mometasone/formoterol (M/FM) compared to fluticasone propionate/salmeterol (FP/SAL)  
   [1 article: 1 RCT]

*Patients with asthma*

Bernstein et al\textsuperscript{118} 2011 performed a multicenter, 12-week, noninferiority trial to compare the efficacy of M/FM MDI 200/10 μg twice daily versus FP/SAL DPI 250/ 50 μg twice daily in asthmatic patients aged ≥12 years uncontrolled with medium-dose ICS. This study demonstrated the below findings:
- Noninferiority between treatment groups for the primary endpoint (i.e. change from baseline in area under the curve in FEV\textsubscript{1} measured over 0-12 hours postdose), and superiority in favor of M/FM for the secondary endpoint of onset of action (i.e change from baseline in FEV\textsubscript{1} at 5 minutes postdose on day 1)
- No significant differences for the incidence of adverse events and for the rest of secondary efficacy endpoints such as asthma control, quality of life and day/night symptoms.
Safety

The most common AEs reported with ICS/LABA were nasopharyngitis, upper respiratory tract infection or inflammation, dysphonia, oral candidiasis, bronchitis, cough, headaches, nausea and vomiting in patients with asthma, and pneumonia, oral candidiasis, throat irritation, bronchitis, dysphonia, cough, viral respiratory infections, headaches, and musculoskeletal pain in COPD patients. Table 9 includes complete safety information on ICS/LABA combinations. ICS/LABA combination products should not be used in patients with acute episodes of asthma or COPD due to limited clinical data available. One Cochrane review reported similar asthma-related serious adverse events between FP/SAL MDI or DPI and BUD/FM pMDI or DPI. Two RCTs assessed the safety of M/FM versus FP/SAL in patients with asthma: one RCT showed similar reductions in cortisol concentrations in both groups. The other trial reported a similar incidence of treatment-emergent and treatment-related AEs over 1 year between groups.

A Black Box warning and a class effect of all LABAs is the increased risk of asthma-related death. This information comes from the results of a U.S. trial (SMART) comparing salmeterol versus placebo (each combined with usual asthma therapy), which showed an increased risk in death associated with asthma in the salmeterol group (13 deaths/13,176 with salmeterol vs. 3/13,179 deaths with placebo; RR: 4.37 [95% CI: 1.25, 15.34]). A post hoc analysis of SMART reported a higher risk of asthma-related hospitalizations in children and adolescents treated with salmeterol than those receiving placebo (35/1,653 with salmeterol vs 16/1,622 with placebo; RR: 2.1 [95% CI: 1.1, 3.7]). The product labelling specifically highlights the use of ICS/LABA only if patients have uncontrolled asthma with low- or medium-dose ICS. Once patients are controlled with ICS/LABA products, the clinician should step down therapy to ICS. Other important warnings associated with LABA use include paradoxical bronchospasm (a rare but life-threatening AE), and cardiovascular effects (increased heart rate, palpitations and QTc interval prolongation).

Regarding ICS safety, pneumonia, oral candidiasis, immunosuppression, glaucoma and cataracts, hypercorticism and adrenal suppression, decrease in bone mineral density, and reduction in growth are some ICS-related warnings. An increased risk of pneumonia was observed in several long-term clinical trials (2 replicate 1-year studies and one 3-year trial) including patients with COPD. Yang et al conducted a meta-analysis comparing ICS versus placebo in COPD patients. A higher incidence of pneumonia, oral candidiasis, hoarse voice and skin bruising was reported. For the outcome of pneumonia in trials longer than 6 months, the odds ratio (OR) was 1.56 (95% CI 1.30 to 1.86, 6235 participants). For the outcome of oropharyngeal candidiasis, a higher incidence in patients treated with ICS was reported (OR 2.65, 95% CI 2.03 to 3.46, 5586 participants). Nannini et al reported a higher incidence of pneumonia with ICS/LABA compared to salmeterol in COPD patients. A decrease in growth velocity has been reported in children and adolescents due to uncontrolled asthma or use of ICS. However, experts consider the benefits to outweigh the risks. As this AE is dose-dependent, patients should be treated with the lowest efficacious dose.
### Table 9. Adverse Effects and Warnings of ICS/LABA Combination Products

<table>
<thead>
<tr>
<th>Combination Product</th>
<th>Adverse Effects</th>
<th>Black Box, warnings and precautions</th>
</tr>
</thead>
</table>
| **Budesonide/-formoterol fumarate** | >10%:  
  CNS: Headache (7% to 11%)  
  Resp: Nasopharyngitis (7% to 11%), upper respiratory tract infection (4% to 11%)  
  1% to 10%:  
  CNS: Dizziness (<3%)  
  GI: Abdominal distress (1% to 7%), oral candidiasis (1% to 6%), vomiting (1% to 3%)  
  Infection: Influenza (2% to 3%)  
  NMS: Back pain (2% to 3%)  
  Resp: Pharyngolaryngeal pain (6% to 9%), lower respiratory tract infection (3% to 8%), sinusitis (4% to 6%), bronchitis (5%), nasal congestion (3%) | • **Black Box:** ASTHMA-RELATED DEATH associated to LABA component. This is considered a class effect among all LABAs. Available data from controlled clinical trials suggest that LABA may increase the risk of asthma-related hospitalization in pediatric and adolescent patients. When treating patients with asthma, prescribe SYMBICORT only for patients not adequately controlled on a long-term asthma-control medication, such as an inhaled corticosteroid or whose disease severity clearly warrants initiation of treatment with both an inhaled corticosteroid and LABA. Once asthma control is achieved and maintained, assess the patient at regular intervals and step down therapy (e.g. discontinue SYMBICORT) if possible without loss of asthma control, and maintain the patient on a long-term asthma control medication, such as an inhaled corticosteroid |
| **Fluticasone propionate/Salmeterol** | >10%:  
  CNS: Headache (12% to 21%)  
  Resp: Upper respiratory tract infection (16% to 27%), pharyngitis (9% to 13%)  
  >3% to 10%:  
  CNS: Dizziness (1% to 4%), pain (1% to 4%)  
  GI: Nausea (3% to 6%), vomiting (3% to 6%), gastrointestinal infection (≤4%; including viral), diarrhea (2% to 4%), oral candidiasis (1% to 4%)  
  NMS: Musculoskeletal pain (2% to 7%), myalgia (≤4%)  
  Resp: Throat irritation (7% to 9%), bronchitis (2% to 8%), upper respiratory tract inflammation (4% to 7%), lower respiratory tract infection (1% to 7%; COPD diagnosis and age >65 years increase risk), cough (3% to 6%), sinusitis (4% to 5%), viral respiratory tract infection (3% to 5%), hoarseness (1% to 5%)  
  1% to 3%:  
  CV: Cardiac arrhythmia, chest symptoms, edema, myocardial infarction, palpitations, syncope, tachycardia  
  CNS: Migraine, mouth pain, sleep disorder  
  Derm: Dermatitis, diaphoresis, eczema, exfoliation of skin, urticaria, viral skin infection  
  Endo: Fluid retention, hypothyroidism, weight gain  
  GI: Constipation, dysgeusia, oral mucosa ulcer  
  GU: Urinary tract infection | • Not indicated in patients with acute deterioration of disease and acute episodes. Do not initiate in acutely deteriorating asthma or to treat acute symptoms  
• Excessive use of the FDC or use with other LABAs may cause overdose and produce life-threatening CV effects  
• Adrenal suppression: May occur with very high dosages or at the regular dosage in susceptible individuals  
• Immunosuppression  
• Lower respiratory infections (e.g. pneumonia)  
• Oral candidiasis  
• Psychiatric manifestations (depression, euphoria, insomnia)  
• Strong cytochrome P450 3A4 inhibitors (e.g., ritonavir): Risk of increased systemic corticosteroid effects  
• Decreases in bone mineral density  
• Effects on growth  
• Glaucoma and cataracts |
<table>
<thead>
<tr>
<th>Combination Product</th>
<th>Adverse Effects</th>
<th>Black Box, warnings and precautions</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Hema&amp;onco</strong>: Hematoma</td>
<td><strong>HSR</strong>: Hypersensitivity reaction</td>
<td>• Metabolic effects: be alert to eosinophilic conditions, hypokalemia, and hyperglycemia.</td>
</tr>
<tr>
<td><strong>Hepatic</strong>: Abnormal hepatic function tests</td>
<td><strong>Infection</strong>: Candidiasis (≤3%), bacterial infection, viral infection</td>
<td>• Paradoxical bronchospasm (life-threatening): Rarely occurs.</td>
</tr>
<tr>
<td><strong>HSR</strong>: Hypersensitivity reaction</td>
<td><strong>NMS</strong>: Muscle injury (≤3%), arthralgia, bone disease, bone fracture, muscle cramps, muscle rigidity, muscle spasm, ostealgia, rheumatoid arthritis, tremor</td>
<td>• CNS depression: drowsiness, dizziness, and/or blurred vision</td>
</tr>
<tr>
<td><strong>Ophth</strong>: Conjunctivitis, eye redness, keratitis, xerophthalmia</td>
<td><strong>Resp</strong>: Chest congestion, ENT infection, epistaxis, laryngitis, lower respiratory signs and symptoms (hemorrhage), nasal signs and symptoms (irritation), rhinitis, rhinorrhea, sneezing</td>
<td>• Immediate hypersensitivity reactions: angioedema, urticarial or skin rash (discontinue therapy immediately)</td>
</tr>
<tr>
<td><strong>Misc</strong>: Burn, laceration, wound</td>
<td></td>
<td>• CV effects: LABA may increase pulse rate, blood pressure, ECG changes, prolongation of QTc interval</td>
</tr>
<tr>
<td><strong>Fluticasone furoate/ Vilanterol</strong></td>
<td></td>
<td>• Use with caution in patients with: convulsive disorders, thyrotoxicosis, diabetes mellitus, and ketoacidosis</td>
</tr>
<tr>
<td><strong>1% to 10%</strong>:</td>
<td><strong>CV</strong>: Hypertension (≥3%), peripheral edema (≥3%), extrasystoles (≥2%), supraventricular extrasystole (≥2%), ventricular premature contractions (≥2%)</td>
<td><strong>CNS</strong>: Headache (5% to 8%)</td>
</tr>
<tr>
<td><strong>Gl</strong>: Oropharyngeal candidiasis (2% to 5%), diarrhea (≥3%), upper abdominal pain (≥2%)</td>
<td><strong>Infection</strong>: Influenza (≥3%)</td>
<td><strong>NMS</strong>: Arthralgia (2% to ≥3%), back pain (2% to ≥3%), bone fracture (2%)</td>
</tr>
<tr>
<td><strong>Resp</strong>: Nasopharyngitis (6% to 10%), upper respiratory tract infection (≥2% to 7%), pneumonia (2% to 7%), oropharyngeal pain (2% to ≥3%), pharyngitis (2% to ≥3%), chronic obstructive pulmonary disease (≥3%), cough (1% to ≥3%), sinusitis (1% to ≥3%), bronchitis (&lt;1% to ≥3%), acute sinusitis (≥2%), allergic rhinitis (≥2%), rhinitis (≥2%), viral respiratory tract infection (≥2%), voice disorder (2%)</td>
<td><strong>MISC</strong>: Fever (2% to ≥3%)</td>
<td></td>
</tr>
<tr>
<td><strong>Mometasone/Formoterol</strong></td>
<td><strong>1% to 10%</strong>:</td>
<td><strong>CNS</strong>: Headache (≤5%)</td>
</tr>
<tr>
<td></td>
<td><strong>Resp</strong>: Nasopharyngitis (5%), voice disorder (4% to 5%), sinusitis (2% to 3%)</td>
<td><strong>Resp</strong>: Nasopharyngitis (5%), voice disorder (4% to 5%), sinusitis (2% to 3%)</td>
</tr>
</tbody>
</table>

**Abbreviations:** CNS, central nervous system; CV, cardiovascular system; Derm, dermatologic; ECG, electrocardiogram; Endo, endocrine; FDC, fixed-dose combinations; Gl, gastrointestinal system; GU, genitourinary system; Hema&onco, hematologic and oncologic; HSR, hypersensitivity reaction; ICP, intracranial pressure; Immuno, Immunologic system; Metab, metabolic; Misc, miscellaneous; Neur, Neurologic system; NMS, neuromuscular system; Onc, oncologic; Ophth, Ophthalmologic system; Psy, Psychiatric; Resp, respiratory system
Summary

The 6 FDA-approved ICS/LABA combination products are indicated for the long-term management of patients with persistent asthma. Among them, BUD/FM, FP/SAL DPI, and FF/VI are also indicated for the long-term management of COPD. The 6 FDCs are available with different corticosteroid concentrations to accommodate different levels of asthma severity and different age groups. They are administered via single inhaler twice daily, with the exception of FF/VI products that are administered once daily. Device characteristics and inhalation techniques differ between products. Patients should be adequately trained by health professionals to assure the correct use of inhalers. Single inhalers may improve patients’ convenience, adherence to controller mediation, treatment efficacy, health-related quality of life, and health system costs.

With regard to asthma disease, current U.S. and international guidelines (NHLBI and GINA guidelines, respectively) recommend the use of SABAs as needed (quick-relief medications) plus ICS/LABA combinations (controller medication) in certain patients with persistent moderate to severe asthma not adequately controlled with low- or medium-dose ICS. For these patients, several clinical trials demonstrated greater improvements in lung function and asthma control when LABA was added to ICS, rather than increasing the ICS dose.

Regarding COPD management, the updated 2017 Global Initiative for Chronic Obstructive Lung Disease (GOLD) guideline recommends LABA/long-acting muscarinic antagonist (LAMA) fixed-dose combinations (FDCs) as preferred treatment options in patients with moderate to severe COPD. Combination ICS/LABA FDC products are second-line therapies. Clinical trials in COPD patients demonstrated superior efficacy of LABA/LAMA compared to LABA/ICS combinations in terms of lung function and exacerbation risk. These treatment recommendations are not yet reflected in the Medicaid FFS prescription usage patterns. FFS utilization data show that ICS/LABA combinations are prescribed more frequently than LABA/LAMA combinations for moderate to severe COPD.

Comparative evidence included 26 efficacy/safety articles containing 5 SR/MA, 21 RCTs, and 2 mixed treatment comparisons (MTCs). Three safety articles containing one SR/MA and 2 RCTs were also evaluated. Studies assessed head-to-head comparisons between the FDC products, between a FDC and its mono-components administered concomitantly, or between two different inhaler devices containing the same ingredients. The majority of the evidence pertained to asthma. Limited evidence is available for COPD and asthma/COPD overlap.

For the management of asthma, 5 SR/MA, 16 RCTs and one MTC were identified:

1. BUD/FM versus BUD+FM (4 RCTs): similar efficacy and safety profiles were reported between BUD/FM pMDI (U.S product) or BUD/FM DPI (non-U.S. product) compared to BUD+FM in children 4 to 11 years, adolescents, and adults. One long-term trial (12-months) in adult patients indicated a lower withdrawal rate with BUD/FM DPI than BUD+FM.
2. FP/SAL versus FP+SAL (1 SR/MA, and 5 RCTs): Results differed among the 5 RCTs. Kawai et al demonstrated similar bronchodilator effect between FP/SAL and FP+SAL groups in adult patients. Van der Berg et al, Chapman et al, and Aubier et al reported improvements in lung function, asthma control, and symptoms at week 12 that did not significantly differ between treatment groups in patients ≥ 4 years old. In adolescent and adult patients, Bateman et al. showed superiority of SAL/FP DPI 50/100 µg versus the same doses administered individually for lung function at week 12 (primary endpoint). Chapman et al. reported superiority of SAL/FP DPI 50/250 µg vs. SAL+FP for lung function values at other time points (week 3 and 4). One SR/MA included 4 of the 5 RCTs identified, and showed statistically significant differences between FP/SAL and the mono-components; however, a proper discussion about the clinical relevance of the results was lacking.

3. FP/SAL hydrofluoroalkane (HFA) metered-dose inhaler (MDI) versus FP/SAL dry powder inhaler (DPI) (3 RCTs): No significant differences between the two different inhalers were reported. Low-, medium- and high-doses of fluticasone plus SAL were evaluated.

4. BUD/FM versus FP/SAL (3 SR/MA, 3 RCTs): Three SR/MA reported no significant differences in terms of efficacy (reduction in exacerbations requiring oral corticosteroids or hospitalizations) and safety (asthma-related serious adverse events) between BUD/FM pMDI or DPI compared to FP/SAL MDI or DPI. Three RCTs reported faster onset of bronchodilator action and faster improvements in forced expiratory volume in one second (FEV₁) with BUD/FM pMDI or DPI compared to SAL/FP DPI.

5. FF/VI versus FP/SAL (1 SR/MA containing one RCT of interest): No statistically significant differences were found between FF/VI DPI 100/25 µg compared to FP/SAL DPI 250/50 µg for the primary endpoints (change in health-related quality of life, severe asthma exacerbations, and serious adverse events), and secondary endpoints (lung function and asthma symptoms). However, authors highlighted the limited comparative efficacy and safety information available to make a robust decision about the preference of FF/VI over FP/SAL. Further research was considered required.

6. FF/VI versus FP/SAL and BUD/FM (1 MTC): One network meta-analysis included 31 RCTs to assess the probability of non-inferiority of once-daily FF/VI vs. twice-daily FP/SAL and BUD/FM in asthma patients ≥ 12 years old. Despite known limitations of network meta-analyses, results suggested similar lung function improvements with FF/VI 100/25 µg and FF/VI 200/25 µg compared to corresponding doses of FP/SAL and BUD/FM. Health status outcomes were comparable between once-daily FF/VI 100/25 µg compared to twice-daily FP/SAL 250/50 µg and BUD/FM 320/9 µg.

7. M/FM versus FP/SAL (1 RCT): One trial compared M/FM MDI 200/10 µg to FP/SAL DPI 250/50 µg. Non-inferiority was demonstrated for the primary endpoint (improvement in lung function) and most of the secondary endpoints (asthma control, quality of life and symptoms). The onset of bronchodilator action was faster with M/FM than FP/SAL DPI.
For the management of COPD, 4 RCTs and one MTC were identified. The main results are described below:

1. BUD/FM versus FP/SAL (1 RCTs): One trial showed faster onset of bronchodilator effect with BUD/FM compared to FP/SAL.
2. FF/VI versus FP/SAL (3 RCTs): Three trials reported statistically, but not clinically significant differences between FF/VI 100/25 µg and medium-dose FP/SAL (250/50 µg).
3. FF/VI versus FP/SAL and BUD/FM (1 MTC): One network meta-analysis included 33 RCTs to assess the probability of non-inferiority of once daily FF/VI 100/25 µg compared to twice daily FP/SAL 500/50 µg and BUD/FM 400/12 µg in COPD patients ≥ 12 years old. Despite limitations of indirect comparisons, results suggested similar lung function and health status improvements with FF/VI compared to FP/SAL and BUD/FM.

For the management of asthma-COPD overlap, only one RCT comparing FF/VI DPI 200/25 µg versus FP/SAL DPI 500/50 µg was identified. Although no between-group differences were reported, authors mentioned the need for further research due to the study limitations identified.

Additional direct head-to-head comparisons involving ICS/LABA combinations are required to contrast the potential benefits of one fixed-dose combination over another in patients with asthma, COPD, and asthma/COPD overlap.

The majority of adverse drug reactions associated with ICS/LABA combinations are tolerable and manageable. The most common AEs reported with ICS/LABA were upper respiratory tract infection or inflammation, pharyngitis, dysphonia, oral candidiasis, bronchitis, cough, headaches, nausea and vomiting in patients with asthma, and pneumonia, oral candidiasis, throat irritation, dysphonia, viral respiratory infections, headaches, musculoskeletal pain in patients COPD. The increased risk of pneumonia in patients with COPD and adrenal suppression are related to the adverse effect profile of inhaled corticosteroids. A main safety warning and class effect for all LABAs is the increased risk of asthma-related death, and the higher risk of asthma-related hospitalizations in children and adolescents.

In summary, all trials concluded ICS/LABA combination products improve lung function, increase quality of life, and reduce asthma or COPD exacerbation rate. Safety profiles remain similar and manageable when both ICS and LABA are combined.

For the management of asthma, direct comparisons reported no significant differences for 1) FP/SAL compared to BUD/FM, FF/VI, or M/FM; and 2) FP/SAL HFA MDI compared to FP/SAL DPI. Similar efficacy and safety profiles were reported for BUD/FM compared to the mono-components administered concomitantly (BUD+FM). FP/SAL has been shown to be similar to FP+SAL; however, some studies suggest superiority of FP/SAL compared to FP+SAL. For the management of COPD, similar results were reported for FP/SAL compared to FF/VI.
Studies including direct and indirect comparisons suggested similar efficacy profiles with fluticasone and vilanterol compared to fluticasone/salmeterol and budesonide/formoterol in patients with asthma or COPD.

Further direct head-to-head comparisons involving ICS/LABA combinations are required to contrast the potential benefits of one FDC over another in patients with asthma, COPD, and asthma/COPD overlap.

Clinician’s decisions on one single ICS/LABA inhaler over another should be based on the specific inhaler technique and patient skills to appropriately use the prescribed ICS/LABA inhaler, the individual patient’s preference, co-morbidities, adverse events, and cost.
References


44. Spirometry for Health care Providers. Global Initiative for Chronic Obstructive Lung Disease (GOLD); 2010.


55. Taegtmeyer AB, Leuppi JD, Kullak-Ublick GA. Roflumilast--a phosphodiesterase-4 inhibitor licensed for add-on therapy in severe COPD. *Swiss medical weekly.* 2012;142:w13628.
60. Svedsater H, Roberts J, Patel C, Macey J, Hilton E, Bradshaw L. Life Impact and Treatment Preferences of Individuals with Asthma and Chronic Obstructive Pulmonary Disease: Results from Qualitative Interviews and Focus Groups. *Advances in therapy.* 2017.


96. Aubier M, Pieters WR, Schlosser NJ, Steinmetz KO. Salmeterol/fluticasone propionate (50/500 microg) in combination in a Diskus inhaler (Seretide) is effective and safe in the treatment of steroid-dependent asthma. Respiratory medicine. 1999;93(12):876-884.
98. Bateman ED, Silins V, Bogolubov M. Clinical equivalence of salmeterol/fluticasone propionate in combination (50/100 microg twice daily) when administered via a chlorofluorocarbon-free metered dose inhaler or dry powder inhaler to patients with mild-to-moderate asthma. Respiratory medicine. 2001;95(2):136-146.
100. Noord J.A v, H L, Diaz T C, A.P G, P D. Clinical Equivalence of a Salmeterol/Fluticasone Propionate Combination Product (50/500??g) Delivered via a Chlorofluorocarbon-Free Metered-Dose Inhaler with the Diskus?? in Patients with Moderate to Severe Asthma. Vol 212001.


## Appendix A. MEDLINE & EMBASE Literature Search Strategies for ICS/LABA Combination Products

Table 1. Medline Literature Search Strategy (via Ovid) for systematic reviews and randomized controlled trials

<table>
<thead>
<tr>
<th>Ovid MEDLINE(R) Epub Ahead of Print, In-Process &amp; Other Non-Indexed Citations, Ovid MEDLINE(R) Daily, Ovid MEDLINE and Versions(R). Search Strategy Date: June 2017</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>SR Results:</strong> 130; <strong>RCT Results:</strong> 946</td>
</tr>
</tbody>
</table>

1. Budesonide, Formoterol Fumarate Drug Combination/ or (biresp or duoresp or vyaler or vylaer or spiromax* or (budesonid* adj3 formoterol*)) or symbicort).ti,ab,kw,kf,rn. (799)
2. Fluticasone Propionate, Salmeterol Xinafoate Drug Combination/ or (Advair* or fluticason* adj5salmeterol* or Aerivio or airexar or atmadisc or (salmeterol* adj2 (xinafoat* or fluticason*)) or seretide or serflu or viani).ti,ab,kw,kf,rn. (1304)
3. ((fluticason* adj4 furoat* adj4 vilanterol*) or Breo or relovair or relvar or revinty ellipta).ti,ab,kw,kf,rn. or fluticasone furoate-vilanterol trifenate.rs,ps. or (fluticasone and furoate-vilanterol trifenate).nm,rn,rx,px. (133)
4. Mometasone Furoate, Formoterol Fumarate Drug Combination/ or (Dulera or ('formoterol* adj5 'mometason*') or zenhale).ti,ab,kw,kf,rn. (46)
5. 1 or 2 or 3 or 4 [all 4 drug combos] (2015)
6. limit 5 to english language [All 4 drug combos, ENG] (1866)
7. Adrenergic beta-2 Receptor Agonists/ or (('adrenergic beta 2' or 'adrenergic beta2' or 'beta2 adrenergic' or 'beta 2 adrenergic' or 'beta 2 adrenoceptor*' or 'beta2 adrenoceptor*') adj3 (agonist* or stimulant* or stimulator* or stimulating)).ti,ab,kw,kf,rn. or 'beta 2 agonist*'.ti,ab or 'beta2 agonist*'.ti,ab. (9632)
8. exp Glucocorticoids/ or (glucocorticoid* or glucocorticosteroid* or glucocortoid* or glycocorticoid*).ti,ab,kw,kf,rn. (213362)
9. 7 and 8 [all 2 drug classes] (1326)
10. limit 9 to english language [All 2 drug classes, ENG] (1191)
11. exp animals/ not humans.sh. (4416452)
12. (animal? or beaver? or beef or bovine or breeding or bull or canine or castoris or cat or cattle or cats or chicken? or chimp$ or cow or dog or dogs or equine or foal or foals or fish or fish or insect? horse or horses or livestock or mice or monkey? or mouse or murine or plant or plants or pork or porcine or protozoa? or purebred or rat or rats or rodent? or sheep or thoroughbred).ti. or veterinarian$.ti,ab,kw,kf,hw. (2157596)
13. 11 or 12 [animal set] (4900264)
14. ((systematic adj2 review) or (overview adj3 review?)).ti. or (metaanaly$ or meta-analy$).ti,ab,pt. or ((systematic adj2 review) or (metaanaly$ or meta-analy$)).kw,kf. [SR set] (178318)
15. (randomized controlled trial or controlled clinical trial).pt. or randomized.ab. or placebo.ab. or clinical trials as topic.sh. or randomly.ab. or trial.ti. [RCT set] (1144469)
16. 6 not 13 (1831)
17. 16 and 14 [Drug Combos + SR set] (88)
18. **16 and 15 [Drug Combos + RCT set] (946)**
19. 10 not 13 (1128)
20. 19 and 14 [Drug classes + SR set] (69)
21. **19 and 15 [Drug Combos + RCT set] (553)**
22. **17 or 20 [Drug combo or class -- SRs set] (130)**
23. 18 or 19 [Drug combo or class -- RCTs set] (1816)
24. Adrenergic beta-2 Receptor Agonists/ and exp Glucocorticoids/ (311)
25. 14 and 24 (25)
26. 20 not 25 (44)
27. Adrenergic beta-2 Receptor Agonists/ or (('adrenergic beta 2' or 'adrenergic beta2' or 'beta2 adrenergic' or 'beta 2 adrenergic' or 'beta 2 adrenoceptor*' or 'beta2 adrenoceptor*') adj3 (agonist* or stimulant* or stimulator* or stimulating)).ti. or 'beta 2 agonist*'.ti,ab or 'beta2 agonist*'.ti,ab. (7888)
28. exp Glucocorticoids/ or (glucocorticoid* or glucocorticosteroid* or glucocortoid* or glycocorticoid*).ti,ab. (212735)
29. 27 and 28 (1198)
30. limit 29 to english language (1070)
Table 2. EMBASE Literature Search Strategy (via EMBASE.com)

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<th>EMBASE.com. Search Date: June 2017</th>
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<td>No. Query Results</td>
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<td>#23  #18 OR #19</td>
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<tr>
<td>Systematic Reviews</td>
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<td>#21  #10 AND #17 NOT (#13 OR #18 OR #19 AND #20)</td>
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<td>Drug Classes &amp; Indication &amp; Trials</td>
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<td>#20  #6 AND #7 AND #17 NOT (#13 OR #18 OR #19)</td>
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<td>Drug Combinations &amp; Indications &amp; Trials</td>
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</tr>
<tr>
<td>#19  #10 AND #16 NOT #18</td>
<td>35</td>
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<td>Drug Classes &amp; Indication &amp; SR.</td>
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<tr>
<td>#18  #6 AND #7 AND #16</td>
<td>101</td>
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<td>Drug Combinations &amp; Indications &amp; SR.</td>
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</tr>
<tr>
<td>#17  'clinical study'/mj OR 'clinical trial'/mj OR 'controlled clinical trial'/mj OR 'controlled study'/mj OR 'major clinical study'/mj OR 'randomized controlled trial'/mj OR 'control group'/mj OR ((clinical OR randomorm* OR controlled OR multicentre OR multicenter OR *multi centre' OR 'multi center) NEAR/3 (study OR trial)):ti,ab OR placebo:ab,ti OR 'head to head':ti,ab OR placebo:ab,ti 903390</td>
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<td>#16  #14 OR #15</td>
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<td>'systematic review'/mj OR 'meta analysis'/mj</td>
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</tr>
<tr>
<td>#15  metaanaly*,:ti,ab OR 'meta analysis*':ti,ab OR (systematic NEAR/2 review):ti</td>
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<tr>
<td>#13  #11 OR #12</td>
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<tr>
<td>#11  'animal'/exp OR 'invertebrate'/exp OR 'animal experiment'/exp OR 'animal model'/exp OR 'animal tissue'/exp OR 'animal cell'/exp OR 'nonhuman'/de NOT ('animal'/exp OR 'invertebrate'/exp OR 'animal experiment'/exp OR 'animal model'/exp OR 'animal tissue'/exp OR 'animal cell'/exp OR 'nonhuman'/de AND ('human'/exp OR 'human cell'/de))</td>
<td>6229736</td>
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<tr>
<td>#10  #7 AND #8 AND #9 AND [english]/lim NOT 'conference abstract'/it</td>
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<tr>
<td>Drug Classes &amp; Indication</td>
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</tr>
<tr>
<td>#9  'beta 2 adrenergic receptor stimulating agent'/mj OR ('(adrenergic beta 2' OR 'adrenergic beta2' OR 'beta2 adrenergic' OR 'beta 2 adrenergic' OR 'beta 2 adrenoceptor*') OR 'beta2 adrenoceptor*') NEAR/3 (agonist* OR stimulant* OR stimulator* OR stimulating)):ti,ab,rn OR 'beta 2 agonist*':ti,ab,rn OR 'beta2 agonist*':ti,ab,ab5657</td>
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<td>#8  'glucocorticoid'/mj OR 'corticosterone'/mj OR corticosterone*:ab,ti,rn OR glucocorticoid*:ab,ti,rrn OR OR glucocorticoid*:ab,ti,rrn OR glucocorticoid*:ab,ti,rrn OR glucocorticoid*:ab,ti,rrn</td>
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<td>#7  'chronic obstructive lung disease'/mj OR copd:ti,ab OR 'chronic obstructive lung':ti,ab OR 'chronic obstructive pulmonary':ti,ab OR 'asthma'/exp/mj OR asthma*:ab,ti OR 'lung allergy':ab,ti OR 'lung allergies':ab,ti</td>
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<td>#6  #1 OR #2 OR #3 OR #4 OR #5 AND [english]/lim NOT 'conference abstract'/it</td>
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<td>Drug Combinations</td>
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<td>#5  'formoterol fumarate plus mometasone furoate'/de OR dulera:ab,ti,tn OR (formoterol* NEAR/5 mometason*):ab,ti,tn,dn OR zenhale:ab,ti,tn</td>
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<td>#4  'fluticasone furoate plus vilanterol'/de OR breo:ab,ti,tn OR ('fluticasone* NEAR/4 vilanterol*'):ab,ti,tn</td>
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<tr>
<td>OR relvair:ab,ti,tn OR relvar:ab,ti,tn OR 'revinty ellipta':ab,ti,tn</td>
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<td>#3  'fluticasone propionate plus salmeterol xinafoate'/de OR aerio:ab,ti,tn OR airdar:ab,ti,tn OR atmadi:ab,ti,tn OR salmeterol*:ab,ti,tn OR (salmeterol* NEAR/3 xinafoat*):ab,ti,tn,sn OR seretide:ab,ti,tn OR serflu:ab,ti,tn OR vian:ab,ti,tn</td>
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</tr>
<tr>
<td>#2  'fluticasone propionate plus salmeterol'/de OR advair*:ab,ti,tn OR ('fluticasone* NEAR/5 salmeterol*'):ab,ti,tn</td>
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<td>#1  'budesonide plus formoterol'/exp OR biresp:ab,ti,tn OR duoresp:ab,ti,tn OR vyaler:ab,ti,tn OR vylaer:ab,ti,tn OR spiromax*:ab,ti,tn OR (budesonid* NEAR/4 formoterol*):ab,ti,tn OR symbicort:ab,ti,tn</td>
<td>2455</td>
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</tbody>
</table>
### Appendix B. Key Evidence: Cochrane Systematic Reviews of ICS/LABA Combination Products*

<table>
<thead>
<tr>
<th>Study Reference and Search Date</th>
<th>Objective(s)</th>
<th>Treatment Interventions</th>
<th>Clinical Efficacy</th>
<th>Clinical Safety</th>
<th>Limitations</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Dwan et al 2016$^{112}$: Vilanterol and fluticasone furoate for asthma (Cochrane Database of Systematic Reviews 2016)</td>
<td>To compare effects of VI and FF in combination versus placebo, or versus other ICSs and/or LABAs, on acute exacerbations and on health-related quality of life (HRQoL) in adults and children with chronic asthma.</td>
<td>VI + FF 100/25mcg vs FP/SAL 250/50mcg BID (1 study: Woodcock 2013$^{113}$) VI + FF 200/25 mcg versus FP/SAL 500/50 mcg (1 conference abstract with limited information: Hojo 2015)</td>
<td>VI+FF 100/25mcg vs FP/SAL 250/50mcg BID Primary outcomes:  - <em>Change in HRQoL</em> (measured by AQLQ at 24 wk): MD 0.09, 95% CI -0.03 to 0.21 (no significant differences between groups)  - <em>Severe asthma exacerbation</em> (with hospital admission or treatment with a course of oral corticosteroid): OR 0.50, 95% CI 0.05 to 5.52 (no significant differences between groups)</td>
<td>VI+FF 100/25mcg vs FP/SAL 250/50mcg BID Primary outcomes:  - <em>Serious adverse events</em>: OR 0.80, 95% CI 0.21 to 2.99 (no significant differences between groups)</td>
<td>• Only one single study supporting the comparison</td>
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<tr>
<td>2. Lasserson et al 2011$^{102}$: Cochrane Database of Systematic Reviews 2011. Combination fluticasone and salmeterol versus fixed dose combination</td>
<td>To assess the relative effects of FP/SAL and BUD/FM in adults and children</td>
<td>BUD/FM 400 to 800/12 to 24 mcg/day FP/SAL 500/100 mcg/day</td>
<td>Primary outcomes:  - % patients with exacerbations requiring oral steroid treatment (Mean follow-up: 6 months): OR 0.89, 95% CI 0.74 to 1.07 (4 studies)</td>
<td>Primary outcomes:  - <em>Asthma-related SAEs</em> (Mean follow-up: 6 months): OR 1.47, 95% CI 0.75 to 2.86 (3 studies)</td>
<td>• Wide CI for the effect estimated in primary outcomes (imprecision)</td>
</tr>
</tbody>
</table>

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*ICS/LABA: Inhaled Corticosteroids/Large-Aerosol-Breather Agonists*
budesonide and formoterol for chronic asthma in adults and children

- 5 studies (5537 adults and adolescents) included in the review: Aalbers 2004,103 Busse 2008,104 COMPASS or Kuna 2007,105 EXCEL or Dahl 2006106 and one unpublished article
- Literature search conducted in June 2011

<table>
<thead>
<tr>
<th>Study Reference and Search Date</th>
<th>Objective(s)</th>
<th>Treatment Interventions</th>
<th>Clinical Efficacy</th>
<th>Clinical Safety</th>
<th>Limitations</th>
</tr>
</thead>
<tbody>
<tr>
<td>children with asthma</td>
<td>% patients with exacerbations requiring admission to hospital (Mean follow-up: 6 months): OR 1.29, 95% CI 0.68 to 2.47 (4 studies)</td>
<td></td>
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<tr>
<td>Population included:</td>
<td>Secondary outcomes:</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>• Adults and adolescents</td>
<td>• Exacerbations requiring ED visit/hospital admission (composite): OR 1.3, 95% CI 0.94 to 1.8</td>
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</tr>
<tr>
<td>taking regular inhaled steroids before the studies started and with mild or moderate chronic asthma</td>
<td>• Quality of life: Pooled data not available. No statistically significant differences between the treatments were reported in either study</td>
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<tr>
<td></td>
<td>• Diary card peak flow: No significant differences between groups (5 studies)</td>
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<td></td>
<td>• FEV1: No significant differences between groups (5 studies)</td>
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<td></td>
<td>• Rescue medication use: No significant differences between groups (3 studies)</td>
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<td></td>
<td>• Symptoms: No significant differences between groups (3 studies)</td>
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<tr>
<td>Authors’ conclusion: Statistical imprecision in the effect estimates for exacerbations and serious adverse events, which preclude drawing conclusions. Further trials are needed to better determine the relative effects of these drug combinations</td>
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</tr>
</tbody>
</table>

3. Lasserson et al 2008101 This review includes the same studies as in Lasserson et al 2011

Secondary outcomes:

- **AEs**: OR 1.00, 95% CI 0.88 to 1.15 (3 studies):
  - Headache: OR 1.08, 95% CI 0.82 to 1.43
  - Candidiasis: OR 1.64, 95% CI 0.68 to 4.00
  - Upper respiratory tract infection: OR 1.09, 95% CI 0.81 to 1.47
  - Dysphonia: OR 1.45, 95% CI 0.87 to 2.43

- **Withdrawals (AEs)** (Mean follow-up: 6 months): OR 0.94, 95% CI 0.6 to 1.46 (5 studies)

- **Deaths**: 1 death with FP/SAL and 0 deaths with DUB/FM (reported in only one study: COMPASS)

- SAEs too infrequent
- Only adults and adolescents. No data for children

Abbreviations: AQLQ, asthma quality of life questionnaire; AM, morning; BID, twice daily; CI, confidence interval; ED, emergency department; FEV1, forced expiratory volume in one second; FF, fluticasone furoate; FP, fluticasone propionate; HRQoL, health-related quality of life; MD, mean difference; OR, Odds ratio; PEF, peak expiratory flow; RR, risk ratio; SAL, salmeterol; VI, vilanterol; wk, week; µg, micrograms
### Appendix C. Key Evidence: Other Systematic Reviews Including ICS/LABA Combination Products

<table>
<thead>
<tr>
<th>Study Reference and Search Date</th>
<th>Objective(s)</th>
<th>Treatment Intervention</th>
<th>Clinical Efficacy</th>
<th>Clinical Safety</th>
<th>Limitations</th>
</tr>
</thead>
</table>
| 4. **Edwards et al 2007**<sup>107</sup>: Systematic review and meta-analysis of budesonide/formoterol in a single inhaler | To compare the effectiveness of budesonide/formoterol using fixed dosing (BUD/FORM) with inhaled corticosteroid (ICS) alone or alternative ICS and long-acting β<sub>2</sub>-agonist (LABA) regimens for adults with moderate/severe asthma. | BUD/FM and SAL/FP in a single inhaler | **Primary analysis:**  
- No evidence of a difference in **treatment failure** with BUD/FM compared to SAL/FP (RR 0.99; 95% CI: 0.83 to 1.16, p = 0.86)  
**Secondary analysis:**  
- Use of SAL/FP compared with BUD/FM increased the risk of **exacerbations requiring hospitalizations**/ A&E visits by 49% (RR 1.49; 95% CI: 1.07 to 2.08, p = 0.02)  
- There is no evidence of a difference in the number of **exacerbations requiring oral steroid** use with BUD/FM compared to SAL/FP (RR 0.94; 95% CI: 0.79–1.11, p = 0.46). | Withdrawals due to AEs: no differences between groups | • Primary outcome not universally available  
• Lack of blinding in several studies |
| 5. **Nelson et al 2003**<sup>97</sup>: Enhanced synergy between fluticasone propionate and salmeterol inhaled from a single inhaler versus separate inhalers | This meta-analysis aimed to determine the efficacy of FP and SAL inhaled from a single inhaler (combination therapy) or from separate inhalers (concurrent therapy). | FL/SAL vs FL+SAL at the 3 FDA-approved strengths (100/50, 250/50, and 500/50) | **Individual studies:**  
Confirmed equivalence between combination and concurrent therapy on the basis of the primary efficacy measure (morning peak expiratory flow [PEF]). Each study showed a consistent trend in favor of combination therapy.  
**Meta-analysis**  
- A significant advantage for combination therapy compared with concurrent therapy in morning PEF (mean difference between groups in change from baseline over 12 weeks of 5.4 L/min; P = 0.006; 95% CI = 1.5-9.2). |  
• No limitations explained in the article  
• Letter to Editor (by Lipwoth 2003): “this information by Nelson 2003 should not be used as evidence-based |
### Appendix D. Randomized Controlled Trial Included in the Previous Systematic Reviews

<table>
<thead>
<tr>
<th>Study Reference and Design</th>
<th>Objective(s)</th>
<th>Treatment Intervention</th>
<th>Clinical Efficacy</th>
<th>Clinical Safety</th>
<th>Limitations</th>
</tr>
</thead>
</table>
| Woodcock et al113 2013     | To compare the efficacy of FF/VI with fluticasone propionate (FP)/salmeterol (SAL) in patients with persistent asthma uncontrolled on a medium dose of ICS. | FF/VI 100/25 µg QD, FP/SAL 250/50 µg BID | Primary endpoint:  
- Change in 0 to 24-hour FEV₁ after 24 weeks of treatment:  
  FF/VI (341 mL) vs FP/S (377 mL) (not significant)  
Secondary endpoints (all not significant):  
Exacerbation rates, ACT scores, QOL questionnaire scores, unscheduled health care use | AE (%):  
- Nasopharyngitis (53% FF/VI vs. 49% FP/SAL)  
- Headache (34% FF/VI vs. 41% FP/SAL)  
- URTI (26% FF/VI vs. 16% FP/SAL)  
- Cough (15% FF/VI vs. 13% FP/SAL)  
- Sinusitis (12% FF/VI vs. 7% FP/SAL) | Too short-study |

**Abbreviations:** AE, adverse events; FF/VI, fluticasone propionate/vilanterol; FP, fluticasone propionate; FM, formoterol; N/A, not available; PEF, peak expiratory flow; SAE, serious adverse events; SAL, salmeterol; µg or mcg, micrograms; VI, vilanterol
### Appendix E. Randomized Controlled Trial Not Included in the Previous Systematic Reviews

<table>
<thead>
<tr>
<th>Study Reference and Design</th>
<th>Objective(s)</th>
<th>Treatment Interventions</th>
<th>Clinical Efficacy</th>
<th>Clinical Safety</th>
</tr>
</thead>
</table>
| 1. Ishiura et al\(^{117}\) 2015 | To compare the effectiveness of once-daily FF/VI 200/25 μg vs. twice-daily FP/SAL 500/50 μg in 16 patients with stable ACOS (16 males, no females) with a mean age of 74.2 ± 6.7 (±SD) (range 59–87) years | • FF/VI 200/25 μg, DPI  
• FP/SAL 500/50 μg, DPI | Mean changes values for the FEV\(_1\):  
• Run-in period: 1.33 (±0.29) L  
• After the FP/SAL treatment period: 1.38 (±0.39) L  
• After the FF/VI treatment period: 1.47 (±0.38) L | • The heart rate after each treatment did not differ significantly among the treatment periods  
• None of the patients complained of CV or GI symptoms after the administration of FP/SAL or FF/VI |
| 2. Dransfield et al\(^{115}\) 2014 | To compare the lung function effects of FF/VI with those of twice-daily fluticasone propionate/salmeterol (FP/SAL) in patients aged ≥40 years with moderate-to-very severe COPD | • FF/VI 100/25 μg QD in the morning via the ELLIPTA (DPI)  
• FP/SAL 250/50 μg BID via the Accuhaler (DPI) | Primary efficacy end-point:  
• Change from baseline through 0-24 h wm FEV\(_1\) on day 84: Pooled analysis: The treatment difference was statistically but not clinically significant (\(P < 0.001\)) | Pooled AEs (FF/VI 27%; FP/SAL 28%) and serious adverse events (FF/VI 2%; FP/SAL 3%) were similar between treatments. |
| 3. Bernstein et al\(^{118}\) 2011 | To compare the noninferiority of M/FM versus FP/SAL in 722 patients aged ≥12 years with uncontrolled persistent | • M/FM MDI 200/10 μg BID (delivered as 2 inhalations of M/FM MDI 100/5 μg)  
• FP/SAL 250/50 μg BID (delivered as 1 inhalation) | Primary endpoint:  
• Change from BL to week 12 in AUC for FEV\(_1\) measured for 0-12 hours postdose (FEV\(_1\) AUC0-12 h): 3.43 M/FM L×h vs FP/SAL 3.24 L×h (95% CI, -0.40 to 0.76). (M/FM was noninferior to FP/SAL) | Incidence of AEs:  
M/FM: 7.8% (n = 29)  
FP/SAL: 8.3% (n = 29)  
Secondary endpoints:  
• Onset of action: the effect of M/FM occurred significantly faster than the effect of FP/SAL |
<table>
<thead>
<tr>
<th>Study Reference and Design</th>
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<th>Treatment Interventions</th>
<th>Clinical Efficacy</th>
<th>Clinical Safety</th>
</tr>
</thead>
<tbody>
<tr>
<td>noninferiority efficacy and safety trial</td>
<td>asthma previously treated with medium-dose ICS with or without a LABA</td>
<td>Mean increase from BL in FEV₁ at 5 min postdose on day 1: M/FM: 200 ml and FP/SAL: 90 ml (p&lt;0.001)</td>
<td>Asthma control, quality of life, and symptoms: similar between groups</td>
<td></td>
</tr>
<tr>
<td>4. Kawai et al² 2007</td>
<td>• 14-day randomised, double-blind, crossover study</td>
<td>To compare SAL/FP (SAL 50 mcg/FP 250 mcg BID) and SAL+FP (SAL 50 mcg b.i.d.+FP 250 mcg BID) in male and female Japanese (n=18) and Caucasian (n=17) asthmatics</td>
<td>Primary endpoint: 0–12 h specific airways conductance (sGaw; AUC and peak response) in Japanese patients after 14 days: SAL/FP is equivalent to SAL+FP. Secondary endpoints: Similar results between groups at Day 1 in Japanese patients Similar results between groups at Day 1 and Day 14 in Caucasian patients than in Japanese patients No significant ethnic differences in therapeutic response</td>
<td>Comparable safety profiles between groups</td>
</tr>
<tr>
<td>5. Noonan et al 2006⁸⁸</td>
<td>• 12-week, double-blind, double-dummy, placebo-controlled, multicenter study</td>
<td>To compare the efficacy and safety of BUF/FM pMDI with BUD, FM and BUD+FM in separate inhalers in 596 patients ≥12 years of age with moderate to severe persistent asthma previously receiving ICSs.</td>
<td>BUD/FM vs BUD+FM: Primary endpoints: Mean change from baseline in morning predose FEV₁ Mean difference between groups (95% CI): 0.05 (–0.05, 0.15) Mean change from baseline in 12-hour FEV₁ Mean difference between groups (95% CI): At Day 1: –0.01 (–0.07, 0.06) At week 2: 0.01 (–0.07, 0.09) End of treatment: 0.01 (–0.08, 0.09) Secondary measures: % patients with worsening of asthma, improvements in diary variables, % of awakening-free nights, rescue medication use: Similar results between groups</td>
<td>Similar safety profile between groups Oral candidiasis appeared to be higher in the BUD/FM group compared with the other treatment groups</td>
</tr>
<tr>
<td>6. Pohunek et al 2006⁸⁹</td>
<td>• 12 wk, double-blind, double-dummy, randomized, parallel-group, active-controlled</td>
<td>To compare the efficacy and safety of BUF/FM pMDI with BUD, and BUD+FM in separate inhalers in 630 children (4–11 y) with asthma</td>
<td>BUD/FM vs BUD+FM: Primary endpoints: 1. Mean change from baseline in morning PEF No significant difference between groups (p 0.14) Secondary endpoints: change from baseline in: evening PEF; total asthma-symptom score (sum of night-time plus daytime symptom scores); night-time awakenings due to asthma symptoms; use of reliever medication; reliever free days; and symptom-free days. Similar results between groups</td>
<td>Incident of AEs: BUD/FM, 39% vs BUD+FM in separate inhalers, 37% Discontinuations: 2 with BUD+FM and 1 with BUD</td>
</tr>
<tr>
<td>Study Reference and Design</td>
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| multi-centre study (Study 0688)  
- Centers: 80 centers in 8 countries | To evaluate the efficacy and safety of SAL/FP delivered via a HFA-MDI inhaler in Chinese patients (aged 18–70 years) with moderate asthma poorly controlled with ICS                                                                 |  
- **FP/SAL** HFA MDI 125/25 µg (2 puffs, BID)  
- **FP/SAL** 250/50 µg via Diskus (one puff, BID)                                                                                                                                                                                                                                                   | Primary endpoints (morning PEF): No statistically significant differences between groups regarding improvements in morning PEF  
Secondary endpoint (evening PEF, daytime and nighttime symptom score, use of rescue salbutamol, FEV1 and patients self-evaluation): No statistically significant differences between groups                                                                                                                                                  | Incidence of AEs: No statistically significant differences between groups                                                                                                                                                                                                                                                                       |
| 7. You-Ning et al99  
2005 |  
- 4-week randomised, open-label, parallel-group, multicentre study |  
- **BUD/FM** 160/4.5 µg 2 inhalations BID (Symbicort Turbuhaler, DPI)  
- **BUD + FM** (160 µg + 4.5 µg, 2 inhalations BID)  
- A SABA was allowed as reliever                                                                                                                                                                                                 | Fewer patients withdrew from treatment with BUD/FM compared with BUD+FM (9.2% vs 19.4%, p=0.008)  
- No differences in the time to first exacerbation  
- Increases in FEV1 of 4-6% from BL in both groups, and sustained during the 12-month period  
- Overall, no differences in lung function between groups  
- Reduction of approximately 30% in ACQ scores in each group  
- HRQoL: similar improvements between groups  
  
No differences between groups in AEs, vital signs, ECG or laboratory measurements (including morning serum cortisol)  
  
SAE: 3.7% in BUD/FM, 5.8% in BUD+FM  
  
Discontinuations due to asthma worsening: 1.4% in BUD/FM vs 4.9% BUD+FM | No differences between groups in AEs, vital signs, ECG or laboratory measurements (including morning serum cortisol) | | |
| 8. Rosenhall et al91  
2003 |  
- 12 month open, randomized, parallel group study  
- Centre: 29 Swedish centres | To compare long-term safety and efficacy of BUD/FM single inhaler with BUD+FM via separate inhalers in adults with asthma |  
- **BUD/FM** 160/4.5 µg 2 inhalations BID (Symbicort Turbuhaler, DPI)  
- **BUD + FM** (160 µg + 4.5 µg, 2 inhalations BID) | Fewer patients withdrew from treatment with BUD/FM compared with BUD+FM (9.2% vs 19.4%, p=0.008)  
- No differences in the time to first exacerbation  
- Increases in FEV1 of 4-6% from BL in both groups, and sustained during the 12-month period  
- Overall, no differences in lung function between groups  
- Reduction of approximately 30% in ACQ scores in each group  
- HRQoL: similar improvements between groups  
  
No differences between groups in AEs, vital signs, ECG or laboratory measurements (including morning serum cortisol)  
  
SAE: 3.7% in BUD/FM, 5.8% in BUD+FM  
  
Discontinuations due to asthma worsening: 1.4% in BUD/FM vs 4.9% BUD+FM | No differences between groups in AEs, vital signs, ECG or laboratory measurements (including morning serum cortisol) | | |
| 9. Rosenhall et al90  
2002 |  
- 6-month open, randomized, multicenter parallel group study | To compare safety and efficacy of BUD/FM single inhaler with BUD+FM via separate inhalers in adults with asthma |  
- **BUD/FM** 160/4.5 µg 2 inhalations BID (Symbicort Turbuhaler, DPI)  
- **BUD + FM** (160 µg + 4.5 µg, 2 inhalations BID)  
- A SABA was allowed as reliever | Whithdrawal rates were low in both groups  
- No differences in the time to first exacerbation  
- Increases in FEV1 of 5-6% from BL in both groups, and sustained during the 12-month period  
- Overall, no differences in lung function between groups  
- Reduction of approximately 30% in ACQ scores in each group  
- HRQoL: similar improvements between groups  
  
No differences between groups in AEs, vital signs, ECG or laboratory measurements (including morning serum cortisol) | No differences between groups in AEs, vital signs, ECG or laboratory measurements (including morning serum cortisol) | | |
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<th>Clinical Safety</th>
</tr>
</thead>
</table>
| **10. Bateman et al**2001  | To investigate the hypothesis of equivalent efficacy and comparable safety of 2 inhaled presentations of SAL/FP combination products | • SAL/FP HFA MDI 25/50 μg (2 inhalations BID)  
• SAL/FP DPI 50/100 μg (1 inhalation BID, via Diskus) | **Primary endpoints** (mean morning PEF over weeks 1–12):  
Both groups were clinically equivalent  
**Secondary endpoints** (evening PEF, daytime and night-time symptom scores, use of as-required salbutamol and clinic FEV₁):  
Both groups were clinically equivalent | • AEs and serum cortisol levels: No significant difference between groups |
|                            |              |                         |                  |                  |
| **11. Van Noord et al**2001 | To demonstrate equivalent efficacy and comparable tolerability of two inhaled combined formulations of SAL/FP in asthma patients (12 to 82 years) | • SAL/FP HFA MDI 25/250 μg (2 inhalations BID)  
• SAL/FP DPI 50/500 μg (1 inhalation BID, via Diskus) | **Primary endpoints** (change in morning PEF over weeks 1 to 12):  
Adjusted mean increases 50 L/min (with FP/SAL MDI) and 48 L/min (with FP/SAL DPI); treatment difference -2 L/min; 95% CI: -11 to 7 L/min (Clinical equivalence between groups) | • Similar safety profiles between groups |
|                            |              |                         |                  |                  |
| **12. Van der Berg et al**2000 | To compare the efficacy and safety in 257 children (4-11 years) of SAL/FP (50/100 μg BID) via a single Diskus™ inhaler (Seretide™; combination therapy) or concurrently using two separate Diskus™ inhalers (concurrent therapy) | • FP/SAL (50/100 μg BID) via Diskus™ inhaler (Seretide)  
• FP+SAL (50+100 μg BID) via separate inhalers | **Primary endpoint**:  
Adjusted change in Mean Morning PEF (week 1-12):  
SAL/FP: improvement of 33 L/min  
SAL+FP: improvement of 28 L/min  
*Difference between the two treatment arms (concurrent – combination): −5 L/min (90% CI −10, 0 L/min) was within the definition of equivalence; p=0.103. (Criterion for clinical equivalence: 90% CI between ±15 L/min)  
(SAL/FM is clinically equivalent to SAL+FM)  
Adjusted change in Mean Morning PEF (other time interval):  
similar result to that at week 1-12, except difference between groups at week 2 that was statistically significant (−9 L/min; 90% CI, −15, −3 L/min; p=0.017) in favor of fixed dose combination | • Drug-related AEs:  
SAL/FP: 10%  
SAL+FP: 5%  
• Most common AEs: candidiasis, malaise and fatigue, aggression and hostility, and lower respiratory tract events  
• Withdrawals due to AEs: 4 patients (2 in SAL/FP and 2 in SAL+FP)  
• Laboratory value changes (e.g. serum cortisol levels): No significant difference between groups |
<table>
<thead>
<tr>
<th>Study Reference and Design</th>
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<th>Treatment Interventions</th>
<th>Clinical Efficacy</th>
<th>Clinical Safety</th>
</tr>
</thead>
</table>
| **13. Chapman et al**<sup>95</sup> 1999 | To compare the efficacy and safety of a new combination Diskus inhaler containing both SAL 50 μg and FP 250 μg (Seretide) with the two drugs delivered via separate Diskus inhalers in 371 asthma patients (13 to 75 years) | • FP/SAL (250/50 μg BID) via Diskus™ inhaler (Seretide)  
• FP+SAL (250+50 μg BID) via separate inhalers | • Adjusted mean change difference in predicted morning PEF from BL for weeks 1–12 (15% and 13% for the combination and concurrent treatment groups, respectively) (not significant treatment difference, −1%; 90% CI, −4, 1%; p=0.361)  
Secondary endpoints: Similar improvements between groups in lung function, symptom score and rescue medication use | cortisol concentrations): similar between groups |
| **14. Aubier et al**<sup>96</sup> 1999 | To compare the efficacy and safety of a new combination Diskus inhaler containing both SAL 50 μg and FP 500 μg (Seretide) with the two drugs delivered via separate Diskus inhalers | • FP/SAL (500/50 μg BID) via Diskus™ inhaler (Seretide)  
• FP+SAL (500+50 μg BID) via separate inhalers | Primary endpoints:  
• Adjusted mean improvements in morning PEFR from BL (12-week period):  
  SAL/FP: 43 L/min  
  SAL+FP: 36 L/min  
  *Difference between the two treatment arms (concurrent − combination): −6 L/min (90% CI: −13 to 0 L/min; p=0.114). Criterion for clinical equivalence: 90% CI=±15 L/min  
  (SAL/FM is clinically equivalent to SAL+FM)  
• Adjusted mean improvements in morning PEFR from BL (at week 3 and 4):  
  • At week 3: 90% CI: −16 to −2 L/min, p=0.037  
  • At week 4: 90% CI: −16 to −2 L/min, p=0.043  
  (SAL/FM is statistically superior to SAL+FM at week 3 and 4)  
Secondary endpoints:  
• Adjusted mean changes in evening PEFR (12-week period):  
  SAL/FP: 35 L/min  
  SAL+FP: 25 L/min  
  *Difference between groups: −10 L/min (90% CI: −16 to −4 L/min; p=0.008)  
  (SAL/FM is statistically superior to SAL+FM)  
• Daytime and night-time symptom scores, and use of salbutamol as reliever: no differences between groups | Similar safety profile (AEs leading to withdrawal and laboratory values) between groups |
<table>
<thead>
<tr>
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<th>Clinical Safety</th>
</tr>
</thead>
</table>
| double-dummy study         | drugs delivered via separate Diskus inhalers in 503 asthma patients aged ≥12 years | • FP 500 μg BID  
• PBO | (90% CI $-10$ to $4$ L/min; $p=0.535$). Criterion for clinical equivalence: 90% CI=±15 L/min  
($SAL/FM$ is clinically equivalent to $SAL+FM$) |  |
| 15. Bateman et al$^{94}$ 1998 | To compare SAL 50µg and FP 100µg in a single device with the delivery of the two drugs via two separate inhalers in 244 asthma patients (12-78 years) | • FP/SAL (100/50 µg BID) via Diskus™ inhaler (Seretide)  
• FP+SAL (100+50 µg BID) via separate inhalers | Primary endpoints:  
• Adjusted mean improvements in morning PEFR from BL (12-week period):  
SAL/FP: 42 L/min  
SAL+FP: 33 L/min  
*Difference between the two treatment arms (concurrent – combination): −9 L/min  
(90% CI: $−17$, $0$ L/min). Criterion for clinical equivalence: 90% CI=±15 L/min  
($SAL/FM$ is statistically superior to $SAL+FM$) |  |
| 15. Bateman et al$^{94}$ 1998 |  |  | Secondary endpoints:  
• Percentage predicted morning PEFR, actual and percentage predicted evening PEFR: similar between groups  
• Adjusted mean changes in FEV₁ from BL at week 12:  
SAL/FP: 0.20L  
SAL+FP: 0.17L  
*Treatment difference=−0.03L (90% CI: $−0.12$, $0.05$L)  
• Similar improvements between groups in daytime and nighttime symptom scores, percentage symptom free days and nights, and use of rescue salbutamol  
• Compliance: high in both groups  
SAL/FP: 94  
SAL+FP: 93% |  |

Abbreviations: ACOS, Asthma-chronic obstructive pulmonary disease overlap syndrome (ACOS); ACQ, asthma control questionnaire; ACT, asthma control test; AE, adverse event; AUC, area under the curve; CAT, COPD assessment test; CI, confidence interval; COPD, chronic obstructive pulmonary disease; CV, cardiovascular; DPI, dry powder inhaler; HFA, hydrofluoroalkane; FeNO, fractional exhaled nitric oxide; FEF, forced expiratory flow; FM, formoterol; FOT, forced oscillation technique; FP, fluticasone propionate; FVC, forced vital capacity; GI, gastrointestinal; HRQoL, health related quality of life; M, mometasone; MDI, metered-dose inhaler; MiniAQLQ, Mini Asthma Quality of Life Questionnaire; PBO, placebo; PEF, peak expiratory flow; PEFR, peak expiratory flow rate; pMDI, pressurized metered dose inhaler; SABA, short-acting beta₂ agonists; SAE, serious adverse events; S or SAL, salmeterol; µg or mcg, micrograms; VI, vilanterol
List of Excluded References

Wrong comparator (monotherapy, LABA/LAMA, placebo, or non FDA-approved ICS/LABA dosages)


Wrong outcome


Wrong study design


Wrong intervention


Review (not a systematic review, not a randomized controlled trials)


Full text not available


Note: Duplicates (n=4) are not included in this list.