Glucocorticoids, Inhaled
Therapeutic Class Review (TCR)

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FDA-APPROVED INDICATIONS

Drug	Manufacturer	Indication(s)
Glucocorticoids		
beclomethasone HFA inhalation aerosol* (QVAR® Redihaler®)[1]	Teva Specialty	▪ Maintenance treatment of asthma as prophylactic therapy (see indicated ages below for each product) **Indicated Ages** ▪ Pulmicort Respules are used in patients aged 12 months to 8 years ▪ ArmonAir Digihaler, Asmanex Twisthaler, QVAR Redihaler, Flovent HFA, and Flovent Diskus are for use in patients aged 4 years and older ▪ Arnuity Ellipta and Asmanex HFA are for use in patients aged 5 years and older ▪ Pulmicort Flexhaler is for use in patients aged 6 years and older ▪ Alvesco is for use for patients 12 years of age and older
budesonide inhalation powder (Pulmicort Flexhaler®)[2]	AstraZeneca	
budesonide inhalation suspension (Pulmicort Respules®)[3]	generic, AstraZeneca	
ciclesonide inhalation aerosol (Alvesco®)[4]	Covis	
fluticasone furoate inhalation powder (Arnuity® Ellipta®)[5]	GlaxoSmithKline	
fluticasone propionate inhalation aerosol (Flovent HFA®)[6]	generic†, GlaxoSmithKline	
fluticasone propionate inhalation powder* (ArmonAir® Digihaler®)[7]	Teva	
fluticasone propionate inhalation powder (Flovent® Diskus®)[8]	GlaxoSmithKline	
mometasone furoate inhalation aerosol (Asmanex® HFA)[9]	Merck/Organon	
mometasone furoate inhalation powder (Asmanex® Twisthaler®)[10]	Merck/Organon	

* Approved as a New Drug Application (NDA) via the 505(b)(2) pathway. A 505(b)(2) NDA is a Food and Drug Administration (FDA) approval pathway in which at least some of the information required for approval comes from studies not conducted by or for the applicant.[11]

† Authorized generic

FDA-Approved Indications (continued)

Drug	Manufacturer	Indication(s)
Glucocorticoid/Long-Acting Beta$_2$-Agonist (LABA) Combinations		
budesonide/formoterol inhalation aerosol (Symbicort®)[12]	generic†, AstraZeneca	▪ Treatment of asthma in patients 6 years of age and older ▪ Maintenance treatment of airflow obstruction and reducing exacerbations in patients with COPD including chronic bronchitis and emphysema
fluticasone furoate/vilanterol (Breo® Ellipta®)[13]	generic†, GlaxoSmithKline	▪ Long-term, once daily, maintenance treatment of airflow obstruction in patients with COPD, including chronic bronchitis and/or emphysema ▪ To reduce exacerbations of COPD in patients with a history of exacerbations ▪ Treatment of asthma in patients 18 years of age and older
fluticasone propionate/ salmeterol inhalation aerosol (Advair® HFA)[14]	GlaxoSmithKline	▪ Treatment of asthma in patients 12 years of age and older
fluticasone propionate/ salmeterol inhalation powder (Advair® Diskus®)[15]	generic, GlaxoSmithKline	▪ Treatment of asthma in patients 4 years of age and older ▪ Maintenance treatment of airflow obstruction in COPD including chronic bronchitis and emphysema (250/50 mcg only) ▪ To reduce COPD exacerbations in patients with a history of exacerbations (250/50 mcg only)
fluticasone propionate/ salmeterol inhalation powder* (AirDuo® RespiClick®, AirDuo Digihaler)[16,17]	generic†, Teva	▪ Treatment of asthma in patients 12 years of age and older
mometasone/formoterol inhalation aerosol (Dulera®)[18]	Merck/Organon	▪ Treatment of asthma in patients 5 years of age and older
Glucocorticoid/Long-Acting Anticholinergic/Long-Acting Beta$_2$-Agonist (LABA) Combinations		
budesonide/glycopyrrolate/ formoterol fumarate (Breztri Aerosphere®)[19]	AstraZeneca	▪ Maintenance treatment of COPD
fluticasone furoate/ umeclidinium/vilanterol (Trelegy® Ellipta®)[20]	GlaxoSmithKline	▪ Maintenance treatment of COPD ▪ Maintenance treatment of asthma in adults

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† Authorized generic

The manufacturing, sale, and dispensing of chlorofluorocarbon (CFC) containing inhalers have been phased out by the United States (US) Food and Drug Administration (FDA) to comply with the Montreal Protocol.[22] Inhalers utilizing an alternative inhalant technology, as shown above, have emerged to meet the needs of patients left by the void.[23]

For asthma therapy, the combination products budesonide/formoterol (Symbicort), fluticasone propionate/salmeterol (Advair Diskus, Advair HFA, AirDuo RespiClick, AirDuo Digihaler),

mometasone/formoterol (Dulera), and fluticasone furoate/vilanterol (Breo Ellipta) should only be prescribed for patients not adequately controlled on a single-agent long-term asthma control medication, such as an inhaled corticosteroid (ICS), or whose disease severity clearly warrants initiation of treatment with both an ICS and a long-acting beta$_2$ agonist (LABA).

The agents in this review are not indicated for the relief of acute bronchospasms. In addition, budesonide/glycopyrrolate/formoterol fumarate (Breztri Aerosphere) is not approved for asthma.

OVERVIEW

Asthma

Prevalence of asthma in the United States (US) continues to rise. More than 25 million Americans have asthma, and over 4 million of these are children.[24] The National Asthma Education and Prevention Program (NAEPP) has defined asthma as a chronic inflammatory disorder of the airways in which many cells and cellular elements play a role.[25,26] In susceptible individuals, inflammation may cause recurrent episodes of wheezing, breathlessness, chest tightness, and coughing. These episodes are usually associated with airflow obstruction that is often reversible, either spontaneously or with treatment. The inflammation also causes an increase in bronchial hyper-responsiveness to a variety of stimuli.

Medications to treat asthma are classified as controllers or relievers. Controllers are medications taken daily on a long-term basis to maintain asthma control. Relievers are medications used on an as-needed basis that act quickly to reverse bronchoconstriction and relieve symptoms.[27] The mainstay of asthma therapy is the use of inhaled corticosteroids (ICS) alone or in combination with other controller medications.[28,29] Studies have demonstrated the efficacy of ICS in improving lung function, reducing symptoms, reducing frequency and severity of exacerbations, and improving the quality of life (QoL) of patients with asthma.[30,31,32,33,34] The 2007 National Heart, Lung, and Blood Institute (NHLBI) states that ICS are currently the most effective anti-inflammatory medications for the treatment of persistent asthma; the 2022 Global Initiative for Asthma (GINA) full report advises that all patients with asthma should receive ICS-containing controller treatment to reduce risk of serious exacerbations and to control symptoms.[35,36,37,38] Multiple other medications are indicated for the treatment of asthma and information can be found in other class reviews.

The 2022 GINA guidelines offer a control-based management plan to adjust treatment in a continuous cycle of assessment, treatment, and review of the patient's response as it relates to symptom control, future risk of exacerbations, and side effects.[39,40,41] Equally important in this process is identifying the patient's own goals regarding their asthma management to ensure improved outcomes. In patients whose asthma is not adequately controlled on the preferred controller despite good adherence and correct technique, a step up in treatment may be added until control is achieved. This can be a short-term or sustained step up in therapy. If control is maintained for at least 3 months on the current regimen, treatment may be stepped down to the lowest step and dosage that maintains control. Patients should be started on treatment based on symptoms, with infrequent symptoms beginning at Step 1 and patients with the most frequent, severe, or debilitating symptoms beginning at Step 4. The pharmacologic stepwise approach for asthma control in the GINA guidelines is described below. Notably, reliever therapy can be considered for symptom management prior to exercise, if needed. The GINA 2022 guidelines describe 2 treatment tracks: Track 1 and Track 2. In Track 1, the reliever is as-needed low dose ICS-formoterol. In Track 2, the reliever is an as-needed SABA, which is the alternative approach when Track 1 is not an option or is not preferred for patient-specific reasons.

Stepwise Approach to Asthma Control from 2022 GINA Guidelines – Controller and Reliever Therapy in Patients ≥ 12 Years Old[42]

Step	Track 1	Track 2	Other Controller Options
1	▪ As-needed low dose ICS/formoterol	▪ Low dose ICS (whenever SABA is taken) ▪ With as-needed SABA	--
2	▪ As-needed low dose ICS/formoterol	▪ Low dose maintenance ICS ▪ With as-needed SABA	▪ Low dose ICS (whenever SABA is taken) or daily LTRA or add HDM SLIT
3	▪ Low dose maintenance ICS/formoterol ▪ With as-needed low dose ICS/formoterol	▪ Low dose maintenance ICS/LABA ▪ With as-needed SABA	▪ Medium dose ICS or add LTRA or add HDM SLIT
4	▪ Medium dose maintenance ICS/formoterol ▪ With as-needed low dose ICS/formoterol	▪ Medium/high dose maintenance ICS/LABA ▪ With as-needed SABA	▪ Add LAMA or add LTRA or switch to high dose ICS
5	▪ Add on LAMA; refer for phenotypic assessment ± anti-IgE (omalizumab), anti-IL-5/5R (mepolizumab, reslizumab, benralizumab), anti-IL4R (dupilumab), anti-TSLP (tezepelumab) ▪ Consider high dose ICS/formoterol ▪ With as-needed low dose ICS/formoterol	▪ Add on LAMA; refer for phenotypic assessment ± anti-IgE (omalizumab), anti-IL-5/5R (mepolizumab, reslizumab, benralizumab), anti-IL4R (dupilumab) ▪ Consider high dose ICS/LABA ▪ With as-needed SABA	▪ Add azithromycin (adults) or add LTRA or add low dose oral corticosteroid (considering adverse effects)

HDM SLIT = house dust mite sublingual immunotherapy; ICS = inhaled corticosteroid; IgE = Immunoglobulin E; IL = interleukin; LABA = long acting beta$_2$-agonist; LTRA = leukotriene receptor antagonist; SABA = short acting beta$_2$-agonist; TSLP = anti-thymic stromal lymphopoietin

Stepwise Approach to Asthma Control from 2022 GINA Guidelines – Controller and Reliever Therapy in Patients 6 to 11 Years Old[43]

Step	Preferred Controller	Other Controller Options	Reliever
1	▪ Low dose ICS whenever SABA is taken	▪ Daily low dose ICS	▪ As needed SABA
2	▪ Daily low dose ICS	▪ Daily LTRA or low dose ICS whenever SABA is taken	▪ As needed SABA
3	▪ Low dose ICS/LABA or medium dose ICS, or very low dose ICS/formoterol MART	▪ Low dose ICS + LTRA	▪ As needed SABA (or ICS/formoterol for MART)
4	▪ Medium dose ICS/LABA or low dose ICS/formoterol MART; refer for expert advice	▪ Add tiotropium or LTRA	▪ As needed SABA (or ICS/formoterol for MART)
5	▪ Refer for phenotypic assessment; ± higher dose ICS/LABA or add-on therapy (e.g., anti-IgE [omalizumab], anti-IL4R [dupilumab])	▪ Add-on anti-IL-5 or add low dose oral corticosteroid (considering adverse effects)	▪ As needed SABA (or ICS/formoterol for MART)

ICS = inhaled corticosteroid; IgE = Immunoglobulin E; IL = interleukin; LABA = long acting beta$_2$-agonist; LTRA = leukotriene receptor antagonist; MART = maintenance and reliever therapy; SABA = short acting beta$_2$-agonist

***Assessment of Asthma Control from 2022 GINA Guidelines*[44]**

Characteristic	Well Controlled (all of the following)	Partly Controlled (any present in past week)	Uncontrolled
A. Assessment of symptom control (preferably over 4 weeks)			
Daytime symptoms more than twice per week	None of these criteria	1 to 2 of these criteria	≥ 3 of these criteria
Limitations of activities due to asthma			
Nocturnal symptoms/awakening due to asthma			
Need for reliever/rescue treatment with a SABA more than twice per week			
B. Risk factors for poor asthma outcomes			
Assess at diagnosis and periodically at least every 1 to 2 years (and during exacerbations); assess forced expiratory volume in 1 second (FEV_1) after 3 to 6 months of controller treatment, and periodically thereafter			
Independent risk factors for exacerbations include (≥ 1 of these risk factors increases risk for exacerbations despite well-controlled symptoms): ▪ Uncontrolled asthma symptoms, excessive SABA use, inadequate ICS, low FEV_1, exposure to cigarette smoke/allergens, poor adherence, incorrect technique, major psychological or socioeconomic problems, obesity, chronic rhinosinusitis, gastroesophageal reflux disease (GERD), pregnancy, sputum or blood eosinophilia, intensive care unit (ICU) admission or prior intubation for asthma, ≥ 1 severe exacerbation in past year, and high bronchodilator reversibility			
Fixed air flow limitation risk factors include: ▪ Lack of ICS treatment, tobacco/chemical/occupational exposures, hypersecretion of mucus, low weight at birth/pre-term birth, sputum or blood eosinophilia, and low FEV_1.			
Risk factors for medication side effects include: ▪ Frequent oral corticosteroid use, long-term/high-dose ICS, taking cytochrome P450 inhibitors, and poor inhaler technique			

FEV_1 = forced expiratory volume in 1 second; ICS = inhaled corticosteroid; LABA = long-acting beta$_2$-agonist; SABA = short-acting beta$_2$-agonist

A 2020 Expert Panel Report from American College of Chest Physicians (CHEST) on the management of chronic cough due to asthma and non-asthmatic eosinophilic bronchitis (NAEB) in adults and adolescents addresses the role of ICS in these patients.[45] For patients with chronic cough due to asthma as a unique system (cough variant asthma), they recommend ICS as first-line treatment. If this is inadequate, the dose may be increased, treatment can be switched to a leukotriene inhibitor, or an ICS/LABA can be considered (Grade 1B). ICS are also recommended first-line for chronic cough due to NAEB (Grade 2B), although they are not FDA- approved for this use.

The NAEPP Expert Panel Report-3 (EPR-3) report released in 2007 by the NHLBI also recommends a similar classification of asthma severity and control, to guide in the initiation and adjustment of therapy, respectively.[46] A focused update to these guidelines was released in 2020.[47] Asthma severity and control are defined in terms of 2 domains, impairment and risk. The distinction between these domains emphasizes the need to consider separately, asthma's effects on quality of life and functional capacity on an ongoing basis (e.g., in the present), along with risks for adverse events, such as

exacerbations and progressive loss of pulmonary function. The group recommends a stepwise approach to asthma management, which is detailed in the table below. In addition, all asthma patients should have a SABA inhaler for use on an as-needed basis. As needed ICS with formoterol is recommended instead for patients 5 to 11 years of age at steps 3 and 4 (as low-dose or medium-dose, respectively), but a SABA is recommended as an alternative. For combinations of an ICS and a LABA for patients ≥ 5 years of age, the group states a single inhaler is preferable. Additional information on the role of biologics in more severe disease are detailed in another Therapeutic Class Review.

Stepwise Approach for Managing Persistent Asthma from the 2007 NAEPP Expert Panel Report-3 and 2020 Focused Update[48,49]

Severity of Asthma	Adults and Children ≥ 12 Years	Children 5 to 11 Years of Age	Children from Birth to 4 Years of Age
Step 1 Intermittent Asthma	SABA as needed (no daily medications needed)	SABA as needed (no daily medications needed)	SABA as needed (no daily medications needed) Add short course of ICS at start of RTI
Step 2 Persistent Asthma	Low-dose ICS Alternative: cromolyn, LTRA, nedocromil, zileuton (Zyflo®), or theophylline	Low-dose ICS Alternative: cromolyn, LTRA, nedocromil, or theophylline	Low-dose ICS Alternative: cromolyn or montelukast
Step 3 Persistent Asthma	Low-dose ICS + formoterol Alternative: medium-dose ICS, low-dose ICS + LABA, low-dose ICS + LAMA, low-dose ICS + LTRA, low-dose ICS + theophylline, or low-dose ICS + zileuton	Low-dose ICS + formoterol Alternative: low-dose ICS + LABA, low-dose ICS + LTRA, or low-dose ICS + theophylline	Medium-dose ICS
Step 4 Persistent Asthma	Medium-dose ICS + formoterol Alternative: medium-dose ICS + LABA, medium-dose ICS + LAMA, medium-dose ICS and 1 of the following: LTRA, theophylline, or zileuton	Medium-dose ICS + formoterol Alternative: medium-dose ICS + LABA, medium-dose ICS + LTRA, or medium-dose ICS + theophylline	Medium-dose ICS + LABA Alternative: medium-dose ICS + montelukast
Step 5 Persistent Asthma	Medium-dose ICS + LABA + LAMA Alternative: Medium-high-dose ICS + LABA, high-dose ICS + LTRA	High-dose ICS + LABA Alternative: high-dose ICS + LTRA, or high-dose ICS + theophylline	High-dose ICS + LABA Alternative: high-dose ICS + montelukast
Step 6 Persistent Asthma	High-dose ICS + LABA + oral corticosteroid	High-dose ICS + LABA + oral corticosteroid Alternative: high-dose ICS + LTRA + oral corticosteroid, high-dose ICS + theophylline + oral corticosteroid	High-dose ICS + LABA + oral corticosteroid Alternative: high-dose ICS + montelukast + oral corticosteroid

ICS = inhaled corticosteroid; LABA = long-acting beta$_2$-agonist; LTRA = leukotriene receptor antagonist or leukotriene modifier; RTI = respiratory tract infection; SABA = short-acting beta$_2$-agonist

COPD

The 2022 edition of the Global Initiative for Chronic Obstructive Lung Disease (GOLD) guidelines define chronic obstructive pulmonary disease (COPD) as a heterogenous disease characterized by persistent respiratory symptoms and airflow limitation that is due to airway and/or alveolar abnormalities typically caused by exposure to noxious particles or gases.[50] It is estimated that the number of Americans with a COPD diagnosis is approximately 16 million.[51] However, the US Preventive Services Task Force (USPSTF) recommends against routine screening for COPD in asymptomatic adults.[52]

Pharmacotherapy for COPD is used to decrease symptoms, reduce the frequency and severity of exacerbations, and improve health status and exercise tolerance.[53] Bronchodilator therapy (e.g., $beta_2$-agonists, anticholinergics, and methylxanthines) is central to symptom management in COPD, and the inhaled route is preferred. Most studies indicate that the existing medications for COPD do not modify the long-term decline in lung function. Therefore, pharmacotherapy for COPD is mainly used to decrease symptoms and/or complications, potentially improving quality of life.

The 2022 updated GOLD guidelines continue to stress that a diagnosis of COPD should be considered in any individual who has dyspnea, chronic cough/sputum production, and a history of exposure to risk factors specific to the disease.[54] Spirometry is required to effectively establish a clinical diagnosis of COPD. A postbronchodilator forced expiratory volume in 1 second to forced vital capacity ratio (FEV_1/FVC) < 0.7 confirms presence of airflow limitation and a diagnosis of COPD. The guidelines continue to emphasize that FEV_1 alone is a poor descriptor of disease status. Therefore, assessment of the patient's symptoms, future risks of exacerbations, severity of airflow limitation, and comorbidities is essential in guiding therapy. The GOLD Classification of Airflow Limitation, which is divided into 4 grades (GOLD 1 [mild] to GOLD 4 [very severe]), utilizes these airflow limitation grades in addition to the number of exacerbations, including those leading to hospitalizations, to describe a patient's disease severity. A COPD exacerbation is defined as an acute event characterized by worsening of the patient's respiratory symptoms that varies from the normal daily variations and requires a change in medication. Hospitalization for a COPD exacerbation signifies a poor prognosis and increased risk of death. The COPD Assessment Test (CAT, 0 to 40) or the Clinical COPD Questionnaire (CCQ) is recommended for a comprehensive assessment of symptoms. The Modified British Medical Research Council (mMRC) questionnaire may be used but only assesses breathlessness. The St. George's Respiratory Questionnaire (SGRQ) is a comprehensive measure of health status but is considered too complex for routine practice. Notably, GINA uses the term asthma-COPD overlap to describe patients with features of both disease states; however, the GOLD guidelines address them as different disorders, regardless of overlapping symptoms.

Patients are classified separately by both their GOLD severity (airflow limitation) and exacerbation/symptom assessment (e.g., GOLD grade 4, group D).[55] The patient groups are summarized as follows:

- **Assessment of Airflow Limitation:**
  - ❒ GOLD 1: mild, $FEV_1 \geq 80\%$ predicted
  - ❒ GOLD 2: moderate, FEV_1 50% to 79% predicted
  - ❒ GOLD 3: severe, FEV_1 30% to 49% predicted
  - ❒ GOLD 4: very severe, $FEV_1 < 30\%$ predicted

- **Assessment of Exacerbation Risk and Symptoms:**

		Symptoms	
Moderate or Severe Exacerbation History		mMRC grade 0 to 1; CAT< 10	mMRC grade ≥ 2; CAT ≥ 10
	0 to 1 moderate exacerbations per year (not leading to hospitalization)	Group A	Group B
	≥ 2 moderate exacerbations per year or ≥ 1 exacerbation leading to hospitalization	Group C	Group D

The 2022 GOLD guidelines recommend treatment plans for COPD based on the aforementioned patient group categories, identified by symptoms/exacerbation risk, and focus on individualized therapy.[56] Bronchodilator medications continue to be central to symptom management in COPD across all groups. While the guidelines review multiple medications and state that bronchodilators are generally effective, GOLD notes that LAMAs, also known as long-acting anticholinergics, have a greater effect on exacerbation reduction and decreased hospitalizations compared to LABAs (Evidence A and B, respectively). Likewise, they generally state that combination treatment with long-acting bronchodilators (e.g., beta$_2$-agonist and anticholinergic) is more effective than bronchodilator monotherapy. The combination of a SABA and short-acting muscarinic antagonist (SAMA) is superior to either agent alone (Evidence A). GOLD further notes that tiotropium improves the effectiveness of pulmonary rehabilitation on improving exercise performance (Evidence B). In regard to anti-inflammatory therapy, the addition of an ICS to a LABA is more effective than a LABA alone (Evidence A); however, regular treatment with ICS increases the risk of pneumonia especially in those with severe disease (Evidence A). Triple therapy (ICS/LAMA/LABA) is more effective compared to an ICS/LABA, LABA/LAMA, or LAMA monotherapy (Evidence, A). For the treatment of stable COPD with bronchodilators, LABAs and LAMAs are preferred over short-acting agents except in the case of patients with occasional dyspnea (Evidence A). Inhaled therapy is also preferred over oral therapy (Evidence A). Patients may be initiated on either bronchodilator monotherapy or dual bronchodilator therapy (LAMA/LABA); those initiated on monotherapy with persistent symptoms should be escalated to dual bronchodilator therapy (Evidence A). For the treatment of stable COPD with ICS, monotherapy with an ICS is not recommended (Evidence A), but long-term treatment with an ICS may be considered in addition to a LABA in patients with a history of exacerbations despite bronchodilator therapy (Evidence A). GOLD states that a PDE4 inhibitor improves lung function and reduces moderate and severe exacerbations in patients with chronic bronchitis, severe to very severe COPD, and a history of exacerbations (Evidence A). The addition of a PDE4 inhibitor to therapy with long-acting bronchodilators (with or without an ICS) can be considered in patients with severe to very severe airflow limitation, chronic bronchitis, and exacerbations (Evidence B). For the treatment of acute exacerbations, GOLD recommends the use of a SABA with or without a short-acting anticholinergic agent (Evidence C).

Following these general medication recommendations, GOLD provides a treatment algorithm based on the patient's ABCD exacerbation/symptom assessment.[57] Group A patients should be initiated on a bronchodilator (short- or long-acting). Patients in Group B should be initiated on a LABA or LAMA. Patients in Group C should be initiated on a LAMA, and Group D patients should be initiated on a LAMA plus LABA (if highly symptomatic), LAMA monotherapy, or a LABA plus ICS (may be preferred in patients with elevated eosinophils). For subsequent pharmacologic treatment, GOLD bases

recommendations on the predominant treatable trait, either dyspnea or exacerbations. For dyspnea in patients on a LABA or LAMA, the next step is a LABA plus LAMA, and if dyspnea persists, a device or drug switch should be considered, along with investigation and treatment of other causes of dyspnea. For those on a LABA plus ICS, escalation to triple therapy can be considered. Likewise, de-escalation of the ICS component or a switch to LABA plus LAMA may be considered if there is a lack of response to the ICS or adverse effects (e.g., pneumonia). For targeting exacerbations, those on a LABA or LAMA can have treatment escalated to LABA plus LAMA, and subsequently, triple therapy (LABA/LAMA/ICS) in patients with an elevated eosinophil count (≥ 100 cells/µL). For those on a LABA or LAMA with a select eosinophil count (≥ 300 cells/µL or ≥ 100 cells/µL plus ≥ 2 moderate exacerbations or 1 hospitalization), treatment with a LABA plus ICS is recommended, followed by triple therapy if needed. If further escalation is needed or escalation is needed in those with an eosinophil count < 100 cells/µL, the addition of roflumilast (FEV_1 < 50% and chronic bronchitis) or azithromycin (former smokers) can be considered in select patients. Similar to targeting dyspnea, de-escalation also should be considered, particularly of the ICS component or a switch to LABA plus LAMA in those on triple therapy may be considered if there is a lack of response to the ICS or adverse effects (e.g., pneumonia). Inhaler technique and adherence to therapy should be assessed before concluding the current therapy is insufficient.

In 2015, CHEST published a joint guideline with the Canadian Thoracic Society (CTS) regarding the prevention of acute exacerbations of COPD.[58] To prevent moderate to severe exacerbations in patients with moderate to severe COPD, they recommend use of a LABA or a LAMA over no therapy (placebo) (Grade 1B and 1A, respectively). In this same group, they recommend the use of a LAMA over a LABA (Grade 1C) and a LAMA over a SAMA (Grade 1A). To prevent mild to moderate exacerbations in patients with moderate to severe COPD, they recommend use of a SAMA over a SABA (Grade 2C) and a SAMA + LABA over a LABA alone (Grade 2C). In patients with moderate to severe COPD, they recommend use of a SAMA + SABA over SABA monotherapy (Grade 2B) to prevent acute moderate exacerbations and use of a LABA over a SAMA to prevent acute exacerbations (Grade 2C). In patients with stable moderate to very severe COPD, CHEST recommends maintenance therapy with an ICS + LABA over placebo, ICS monotherapy, and LABA monotherapy (Grade 1B, 1B, and 1C, respectively) to prevent acute exacerbations. For patients with stable COPD, they recommend either combination LAMA/LABA therapy or LAMA monotherapy as both are effective for exacerbations (Grade 1C). Likewise, in stable patients, either ICS/LABA or LAMA monotherapy is recommended (Grade 1C) and either a LAMA + ICS + LABA or LAMA monotherapy is recommended to prevent exacerbations (Grade 2C).

In 2020, the ATS released additional guidelines for the pharmacologic management of COPD.[59] These guidelines focus on addressing specific questions developed by an ATS panel regarding significant COPD management issues, including when to use dual and triple therapy and ICS use in COPD patients with blood eosinophilia. The panel strongly recommends the use of dual LABA/LAMA therapy over LABA or LAMA monotherapy in COPD patients who complain of exercise intolerance or dyspnea based on pooled evidence demonstrating decreased hospital admissions and exacerbations and improvements in patient quality of life and dyspnea. Additionally, the ATS suggests triple therapy (ICS/LABA/LAMA) in COPD patients with a history of ≥ 1 exacerbations requiring hospitalization, oral steroids, or antibiotics in the past year who, despite LABA/LAMA dual therapy, complain of exercise intolerance or dyspnea. Further, for patients receiving triple combination therapy who experience no exacerbations over the course of 1 year, they suggest that ICS therapy may be discontinued. The ATS also suggests the addition of ICS therapy in COPD patients with blood eosinophilia (≥ 2% blood eosinophils or ≥ 150 cells/µL) who have

experienced ≥ 1 exacerbations requiring hospitalization, oral steroids, or antibiotics in the past year. Additional management recommendations regarding treatment approaches outside of this therapeutic class review are detailed in the guidelines.

Direct head-to-head studies of combination ICS/LABA and ICS/LAMA are limited, making comparison and differentiation difficult.[60] A Cochrane review suggests no significant difference in mortality or lung function (FEV_1) between tiotropium, a long-acting anticholinergic agent, and LABAs; however, statistically significant differences in the number of patients experiencing 1 or more exacerbations were seen in favor of tiotropium, particularly when compared against salmeterol (odds ratio [OR], 0.86; 95% confidence interval [CI], 0.79 to 0.93).[61] Tiotropium and related anticholinergic products are reviewed under a separate Therapeutic Class Review.

PHARMACOLOGY[62,63,64,65,66,67,68,69,70,71,72,73,74,75,76,77,78,79,80]

Corticosteroids suppress the cytokine generation, recruitment of airway eosinophils, and release of inflammatory mediators. These agents thereby block late-phase reaction to allergens, reduce airway hyperresponsiveness, and inhibit inflammatory cell migration and activation.[81] Because systemic corticosteroids have a high incidence of adverse reactions, inhaled corticosteroids (ICS) are preferred for asthma.

The long-acting $beta_2$ agonists (LABAs), formoterol, vilanterol, and salmeterol selectively bind to the $beta_2$-receptors in the bronchial smooth muscle, leading to bronchial relaxation and a decrease in the release of mediators of immediate hypersensitivity from mast cells. Combination products of an ICS/LABA include budesonide/formoterol (Symbicort), fluticasone furoate/vilanterol (Breo Ellipta), fluticasone propionate/salmeterol (Advair HFA, Advair Diskus, AirDuo RespiClick, AirDuo Digihaler), and mometasone/formoterol (Dulera).

Umeclidinium and glycopyrrolate are anticholinergic agents that antagonize the action of acetylcholine released from the vagus nerve. Inhibition of the muscarinic receptors blocks the cholinergic neurotransmission causing bronchodilation. Umeclidinium is a component of Trelegy Ellipta, which also includes fluticasone furoate and vilanterol; it is a fixed-dose combination of all 3 agents. Glycopyrrolate is a component of Breztri Aerosphere, which also contains budesonide and fluticasone fumarate formulated as a fixed-dose, triple combination inhaler therapy.

Delivery and Deposition

The selection of a delivery system and the patients' ability to properly use the device are critical factors in determining clinical success of ICS therapy. Delivery systems can significantly affect both topical and systemic activity of ICS.[82,83]

Metered dose inhalers (MDIs) are pressurized spray inhalers, available in suspension and solution. The user administers the dose by pressing down on the metal canister to release the medicine while inhaling. MDIs deliver approximately 15% to 35% of the administered dose to the lungs. Spacer chambers can be attached to MDIs to make them easier to use by people who find it hard to coordinate the press-and-inhale action. When using the spacer, the drug is held in the chamber allowing the user can take several breaths to inhale the dose; it is more likely that the proper amount of medicine will reach the airways. MDIs with CFC propellants are no longer manufactured. Products in this review with MDI devices include Advair HFA, Alvesco, Asmanex HFA, Dulera, Flovent HFA, QVAR

Redihaler, Symbicort, and Breztri Aerosphere. QVAR Redihaler differs from conventional MDIs as it is a breath activated MDI device, and it should not be used with a spacer or volume holding chamber.

Dry-powder inhalers (DPIs) are breath-actuated devices that release the medicine in the form of a dry powder when the user inhales. Although DPIs minimize the potential difficulties in coordinating the press-and-breathe action of the MDI, these delivery systems tend to result in more dosage variations than MDIs at low inspiratory flow rates (< 20 L/min). Products in this review with DPI devices include Advair Diskus, AirDuo RespiClick, AirDuo Digihaler, Arnuity Ellipta, ArmonAir Digihaler, Asmanex Twisthaler, Breo Ellipta, Flovent Diskus, Pulmicort Flexhaler, and Trelegy Ellipta.

Nebulizer therapy is not the recommended form of administration for most patients.[84] It is considered inferior to an MDI with spacer because of the inconvenience, higher risk of side effects, and potentially higher cost. It may be considered an alternative in cases where patients lack the coordination to use the MDI with spacer, particularly in the very young and the very old. Pulmicort Respules are administered via a nebulizer.

PHARMACOKINETICS[85,86,87,88,89,90,91,92,93,94,95,96,97,98,99,100,101,102,103]

Several comparative studies have demonstrated that, when given in equipotent anti-inflammatory doses, fluticasone propionate (Flovent) and budesonide (Pulmicort) have less systemic effect than the other agents, as measured by plasma cortisol.[104,105,106,107,108] There is, however, considerable intersubject variability in the rate of absorption of these agents from the lungs.[109]

The NAEPP guidelines provide information regarding the relative potencies and dosages of each of the available agents, as seen in the table below.[110] It should be noted that these are not the FDA-approved doses, but rather those doses shown to be clinically effective and recommended by the NHLBI. Mometasone (Asmanex) for pediatrics and ciclesonide (Alvesco) were approved after the release of the 2007 NAEPP report and are therefore not contained in the following comparative chart. However, since 2008, mometasone and ciclesonide have been included in the GINA guidelines.

NAEPP Expert Panel Report-3 Estimated Comparative Daily Dosages for Inhaled Corticosteroids (mcg/day)[111]

Drug	Adults and Children ≥ 12 Years of Age			Children (5 to 11 Years of Age)		
	Low-dose	Medium-dose	High-dose	Low-dose	Medium-dose	High-dose
budesonide inhalation powder (Pulmicort)	180–600	> 600–1,200	> 1,200	180–400	> 400–800	> 800
budesonide inhaled suspension (Pulmicort Respules)	n/a	n/a	n/a	0.5 mg (ages 5 to 8 years)	1 mg (ages 5 to 8 years)	2 mg (ages 5 to 8 years)
fluticasone propionate HFA inhalation aerosol (Flovent HFA)	88–264	264–440	> 440	88–176	> 176–352	> 352
mometasone inhalation powder (Asmanex Twisthaler)	200	400	> 400	n/a	n/a	n/a

n/a= not available

Most of the agents in this class are recommended for twice daily use. The exceptions to this are mometasone (Asmanex Twisthaler), fluticasone furoate/vilanterol (Breo Ellipta), fluticasone furoate inhalation powder (Arnuity Ellipta), and fluticasone furoate/umeclidinium/vilanterol (Trelegy Ellipta) which can be dosed once daily.

2022 GINA Suggested Total Daily Dosages of Inhaled Corticosteroids (mcg/day)[112]

Drug	Adults and Adolescents (≥ 12 years)			Children (6 to 11 years)		
	Low-dose	Medium-dose	High-dose	Low-dose	Medium-dose	High-dose
beclomethasone HFA inhalation aerosol (QVAR)	100–200	> 200–400	> 400	50–100	> 100–200	> 200
budesonide inhalation powder (Pulmicort)	200–400	> 400–800	> 800	100–200	> 200–400	> 400
budesonide respules (Pulmicort Respules)	n/a	n/a	n/a	250–500	> 500–1,000	> 1,000
ciclesonide inhalation aerosol (Alvesco)	80–160	> 160–320	> 320	80	> 80–160	> 160
fluticasone furoate inhalation powder (Arnuity Ellipta)	100		200	50		n/a
fluticasone propionate inhalation aerosol (Flovent HFA)	100–250	> 250–500	> 500	50–100	> 100–200	> 200
fluticasone propionate inhalation powder (Flovent Diskus)	100–250	> 250–500	> 500	50–100	> 100–200	> 200
mometasone furoate inhalation aerosol (Asmanex HFA)	200–400		400	100		200
mometasone furoate inhalation powder (Asmanex Twisthaler)	200		400	n/a		

Onset of Action

Drug	Onset of action	Maximum benefit
Glucocorticoids		
beclomethasone HFA inhalation aerosol (QVAR Redihaler)	1 to 2 weeks	3 to 4 weeks
budesonide inhalation powder (Pulmicort Flexhaler)	24 hours	1 to 2 weeks
budesonide suspension (Pulmicort Respules)	2 to 8 days	4 to 6 weeks
ciclesonide inhalation aerosol (Alvesco)	--	4 weeks or longer
fluticasone furoate inhalation powder (Arnuity Ellipta)	variable	2 weeks or longer
fluticasone propionate inhalation aerosol (Flovent HFA)	24 hours – variable time to onset	1 to 2 weeks or longer
fluticasone propionate inhalation powder (ArmonAir Digihaler)	variable	1 to 2 weeks or longer
fluticasone propionate inhalation powder (Flovent Diskus)	24 hours – variable time to onset	1 to 2 weeks or longer
mometasone furoate inhalation aerosol (Asmanex HFA)	variable	1 week or longer
mometasone furoate inhalation powder (Asmanex Twisthaler)	1 to 2.5 hours (peak levels) – variable time to onset	1 to 2 weeks or longer
Glucocorticoid/Long-Acting Beta$_2$-Agonist (LABA) Combinations		
budesonide/formoterol inhalation aerosol (Symbicort)	15 minutes for asthma; 5 minutes for COPD	2 weeks or longer (asthma); nr (COPD)
fluticasone furoate/vilanterol (Breo Ellipta)	16 minutes	nr
fluticasone propionate/salmeterol inhalation powder (Advair Diskus)	30–60 minutes	1 week or longer
fluticasone propionate/salmeterol inhalation aerosol (Advair HFA)	30–60 minutes	1 week or longer
fluticasone propionate/salmeterol inhalation powder (AirDuo RespiClick, AirDuo Digihaler)	15 minutes for asthma	1 week or longer
mometasone/formoterol inhalation aerosol (Dulera)	variable	1 week or longer
Glucocorticoid/Long-Acting Anticholinergic/Long-Acting Beta2-Agonist (LABA) Combinations		
fluticasone furoate/umeclidinium/vilanterol (Trelegy Ellipta)	30–60 minutes (fluticasone furoate); 5–15 minutes (umeclidinium, vilanterol)	1 week or longer
budesonide/glycopyrrolate/formoterol fumarate (Breztri Aerosphere)	20-40 minutes (budesonide); 2-6 minutes (glycopyrrolate); 20-60 minutes (formoterol fumarate)	3 days or longer

CONTRAINDICATIONS/WARNINGS[113,114,115,116,117,118,119,120,121,122,123,124,125,126,127,128,129,130,131]

All of the agents in this review are contraindicated in the primary treatment of status asthmaticus or other acute episodes of asthma or COPD where intensive measures are required. Likewise, these agents should not be used in patients with known hypersensitivity to the active ingredient or any other component. The inhalation powder formulations of fluticasone furoate (Arnuity Ellipta), fluticasone propionate (ArmonAir Digihaler, Flovent Diskus), fluticasone furoate/vilanterol (Breo Ellipta), fluticasone propionate/salmeterol (Advair Diskus, AirDuo RespiClick, AirDuo Digihaler), and fluticasone furoate/umeclidinium/vilanterol (Trelegy Ellipta) are contraindicated in patients who have a severe hypersensitivity to milk proteins as these products contain milk proteins.

A boxed warning exists for all long-acting beta$_2$ agonists (LABAs)(e.g., salmeterol, formoterol) when used as monotherapy regarding an increased risk of asthma-related deaths. Previously, the FDA required this for all combination products that contain a LABA [e.g., fluticasone propionate/salmeterol (Advair HFA, Advair Diskus), budesonide/formoterol (Symbicort), fluticasone furoate/vilanterol (Breo Ellipta), fluticasone furoate/umeclidinium/vilanterol (Trelegy Ellipta), mometasone/formoterol (Dulera)], but this warning was modified in 2017.[132] A description of 4 large clinical trials that evaluated the potential for increased risk of asthma-related death with the use of the combination of an ICS and LABA is included in the warnings and precautions section of agents in this class that include a LABA. The 4 trials involve 41,297 patients: 3 trials in patients ≥ 12 years and 1 trial in children 4 to 11 years. The results of the trials demonstrated that the use of LABA and ICS combination therapy does not significantly increase the risk of serious asthma outcomes compared to ICS monotherapy. The trials also demonstrated that ICS/LABA combinations were more effective in decreasing asthma exacerbations compared to ICS monotherapy. Notably, while no longer a boxed warning, the labels still retain a warning related to the increased risk of asthma-related death when LABAs are used without an ICS to treat asthma.

With the exception of budesonide/glycopyrrolate/formoterol fumarate (Breztri Aerosphere), which is not indicated for asthma, the labeling of agents including a LABA also states that when treating patients with asthma these agents should be prescribed for only those patients not adequately controlled on a long-term asthma control medication, such as an ICS, or whose disease severity clearly warrants initiation of treatment with both an ICS and LABA. Once asthma control is achieved and maintained, assess the patient at regular intervals and step-down therapy if possible without loss of asthma control, and maintain the patient on a long-term asthma control medication, such as an ICS. Do not use these agents for patients whose asthma is adequately controlled on low or medium dose ICS.

ICS agents are not indicated for the relief of acute symptoms (e.g., as rescue therapy for the treatment of acute episodes of bronchospasm), and patients should be instructed to contact their physician immediately if episodes of asthma that are not responsive to bronchodilators occur during the course of treatment.

Fluticasone furoate/umeclidinium/vilanterol and budesonide/glycopyrrolate/formoterol fumarate should not be used in patients with rapidly deteriorating, potentially life-threatening episodes, or for the relief of acute symptoms of COPD. As symptoms of a COPD exacerbation may resemble symptoms of pneumonia, patients and prescribers should be vigilant in monitoring for pneumonia. Additionally, labeling for fluticasone furoate/umeclidinium/vilanterol has been updated in regard to its vilanterol

component, as it should be used with caution in those with cardiovascular disorders, especially those with coronary insufficiency, cardiac arrhythmias, and hypertension.

Chronic overdosage of products containing corticosteroids may lead to hypercorticism and adrenal suppression. Likewise, use caution when transitioning patients from chronic oral corticosteroids to inhaled corticosteroids due to the potential of adrenal suppression while using chronic oral corticosteroids. A number of months are required for recovery of hypothalamic-pituitary-adrenal (HPA function). Patients should be slowly weaned (e.g., 2.5 mg decrease in prednisone weekly) from systemic corticosteroids when initiating an inhaled corticosteroid. During severe attacks or stress, oral corticosteroids may need to be resumed.

Decreased bone mineral density (BMD) has been observed with the long-term administration of products containing an ICS.[133] The clinical significance of small changes in BMD with regard to long-term outcomes is unknown. Patients with major risk factors for decreased bone mineral content, such as prolonged immobilization, family history of osteoporosis, postmenopausal status, tobacco use, advanced age, poor nutrition, or chronic use of drugs that can reduce bone mass (e.g., anticonvulsants, oral corticosteroids), should be monitored and treated according to the current standards of care. In addition, ICS products may also cause a reduction in growth velocity when administered to pediatric patients. Patients converted from systemic to inhaled corticosteroids should be monitored cautiously due to the risk of adrenal insufficiency, particularly in those on ≥ 20 mg/day prednisone (or equivalent). Several months may be required for HPA function recovery and precautions, including patient instruction for management, should be taken during recovery. A meta-analysis of published and unpublished literature evaluated the impact of long-term inhaled corticosteroid use on bone density in adult patients with asthma or COPD.[134] The authors found that long-term use was not associated with significant changes in bone density.

There have been postmarketing reports of esophageal candidiasis for various products in this class. Rinsing the mouth with water without swallowing following inhalation may help reduce this risk.

Due to the likelihood of immunosuppression with ICS agents, products should also be used with caution in patients with existing infections such as tuberculosis; fungal, bacterial, viral, or parasitic infection; and ocular herpes simplex as worsening may occur. More serious or even fatal course of chickenpox or measles can occur in susceptible patients.

It is necessary to monitor patients for development of eye disorders (e.g., glaucoma, increased intraocular pressure, blurred vision, cataracts, central serous chorioretinopathy), as these effects have been reported in patients on several products within this class. Referral to an ophthalmologist should be considered in patients who develop ocular symptoms.

Paradoxical bronchospasm may occur with inhaled medications. If the occurs, treat immediately with a short-acting bronchodilator and consider alternative therapy.

Patients on an ICS should be monitored for eosinophilic conditions, hypokalemia, and hyperglycemia. ICSs and medications containing sympathomimetic amines should be used with caution in patients with convulsive disorders, thyrotoxicosis, diabetes mellitus, and ketoacidosis. Some of these patients may have clinical features of vasculitis consistent with Churg-Strauss syndrome. Consider the risks of hyperglycemia in patients with diabetes.

LABAs can produce a clinically significant cardiovascular (CV) effect (e.g., increases in pulse rate and systolic or diastolic blood pressure or cardiac arrhythmias). If these effects occur, the LABA may need to

be discontinued. LABAs should be used with caution in patients with CV disorders (e.g., coronary insufficiency, cardiac arrhythmias, and hypertension). LABAs should not be used more often or at higher doses than recommended. They should also not be used in conjunction with other medicines containing LABA, as an overdose may result.

Umeclidinium and glycopyrrolate (components of Trelegy Ellipta and Breztri Aerosphere, respectively) are anticholinergic agents and should be used with caution in patients with urinary retention. In addition, glaucoma, increased intraocular pressure, and cataracts have been reported in patients using anticholinergics; use with caution in patients with narrow angle glaucoma.

DRUG INTERACTIONS[135,136,137,138,139,140,141,142,143,144,145,146,147,148,149,150,151,152,153]

The main route of metabolism for many corticosteroids is via the cytochrome P450 isoenzyme 3A4. Inhibitors of CYP3A4 (e.g., cobicistat, ritonavir, ketoconazole, itraconazole, clarithromycin, erythromycin) may increase the plasma concentration of inhaled corticosteroids (ICS). As a result, several agents within this class include information in the product labeling on this risk. Labeling for budesonide-, fluticasone-, and mometasone-containing products include a warning regarding this risk. Fluticasone furoate (Arnuity Ellipta, Trelegy Ellipta) and fluticasone propionate (ArmonAir Digihaler, Flovent products) use in combination with ritonavir has been associated with systemic corticosteroid effects (e.g., Cushing's syndrome, adrenal suppression) and cardiovascular adverse effects.

Products containing salmeterol, formoterol, or vilanterol (Advair Diskus, Advair HFA, AirDuo RespiClick, AirDuo Digihaler, Breo Ellipta, Breztri Aerosphere, Dulera, Symbicort, Trelegy Ellipta) should be administered with caution to patients being treated with monoamine oxidase inhibitors, tricyclic antidepressants, or drugs known to prolong the QTc interval or within 2 weeks of discontinuation of such agents, because the action of the long-acting beta$_2$ agonist (LABA), on the cardiovascular system may be potentiated by these agents.

Concomitant treatment with xanthine derivatives or diuretics may potentiate any hypokalemic effect of the LABA. Beta-blockers and diuretics should be used caution with drugs containing a LABA. Beta-blockers may interfere with the bronchodilatory effect of the LABA resulting in bronchospasm. Electrolyte abnormalities, such as hypokalemia, exacerbated by diuretics may be enhanced by concomitant beta-agonist usage.

Avoid coadministration of either umeclidinium (a component of Trelegy Ellipta) or glycopyrrolate (a component of Breztri Aerosphere) with other anticholinergic-containing drugs due to the risk of additive adverse effects.

ADVERSE EFFECTS[154,155,156,157,158,159,160,161,162,163,164,165,166,167,168,169,170,171,172]

Drug	Cough	Headache	Nausea	Oral candidiasis	Pharyngitis	Upper respiratory infection
Glucocorticoids						
beclomethasone inhalation aerosol (QVAR Redihaler)	1–3	1–4	1–3	1–7	3.2	0.8–4
budesonide inhalation powder (Pulmicort Flexhaler)	nr	nr	1.8	1.3	2.7	2.2
budesonide suspension (Pulmicort Respules)	5–9	> 3	nr	nr	> 3	34–38
ciclesonide inhalation aerosol (Alvesco)	< 1	4.9-11	< 1	< 1	7-10.5	4.1–8.7
fluticasone furoate inhalation powder (Arnuity Ellipta)	0–3	10–13	reported	< 1–3	3–6	2–6
fluticasone propionate inhalation aerosol (Flovent HFA)	4–6	5–11	reported	2–5	1–3	16–18
fluticasone propionate inhalation powder (ArmonAir Digihaler)	1.6-3.4	1.6-7.3	nr	3.1-4.8	4.8-5.8	4.7-5.5
fluticasone propionate inhalation powder (Flovent Diskus)	1–5	2–14	1–8	< 1–9	3–22	14–21
mometasone furoate inhalation aerosol (Asmanex HFA)	nr	3–5	reported	reported	5–8	nr
mometasone furoate inhalation powder (Asmanex Twisthaler)	nr	20–22	1–3	4–6	8–13	8–15

Adverse effects are reported as a percentage. Adverse effects are obtained from package inserts and are not meant to be comparative or all inclusive. nr = not reported.

Adverse Effects (continued)

Drug	Cough	Headache	Nausea	Oral candidiasis	Pharyngitis	Upper respiratory infection
Glucocorticoid/Long-Acting Beta2-Agonist (LABA) Combinations						
budesonide/formoterol inhalation aerosol (Symbicort)	reported	6.5–11.3	reported	1.4–6	7.3–10.5	3.5–10.5
fluticasone propionate/ salmeterol inhalation powder (Advair Diskus)	3–6	12–13	4–6	1–4	10–13	21–27
fluticasone propionate/ salmeterol inhalation aerosol (Advair HFA)	reported	21	5	1-3	nr	16
fluticasone propionate/ salmeterol inhalation powder (AirDuo RespiClick, AirDuo Digihaler)	reported	3-6	reported	1-4	4-9	nr
fluticasone furoate/ vilanterol (Breo Ellipta)	nr	5-7	nr	2-5	9-10	7 (nr in asthma)
mometasone/formoterol inhalation aerosol (Dulera)	nr	2–4.5	nr	0.7–0.8	4.7	nr
Glucocorticoid/Long-Acting Anticholinergic/Long-Acting Beta2-Agonist (LABA) Combinations						
fluticasone furoate/ umeclidinium/vilanterol (Trelegy Ellipta)	1	4–9	nr	≥ 1	≥ 1–17	≥ 1–7
budesonide/glycopyrrolate/ formoterol fumarate (Breztri Aerosphere)	2.7	reported	reported	3	nr	5.7

Adverse effects are reported as a percentage. Adverse effects are obtained from package inserts and are not meant to be comparative or all inclusive. nr = not reported.

SPECIAL POPULATIONS[173,174,175,176,177,178,179,180,181,182,183,184,185,186,187,188,189,190,191]

Pediatrics

Safety and effectiveness of ciclesonide (Alvesco) and fluticasone propionate/salmeterol (Advair HFA, AirDuo RespiClick, AirDuo Digihaler) in children under age 12 have not been established.

Safety and effectiveness of budesonide (Pulmicort Flexhaler) and budesonide/formoterol (Symbicort) in children < 6 years of age have not been established. Budesonide respules (Pulmicort Respules) are indicated specifically for children between 12 months and 8 years of age.

Fluticasone furoate (Arnuity Ellipta), mometasone furoate (Asmanex HFA), and mometasone/formoterol (Dulera) use in children < 5 years old has not been proven safe and effective,

while beclomethasone (QVAR Redihaler) use in children < 4 years old has not been proven safe and effective.

Fluticasone propionate/salmeterol (Advair Diskus) and fluticasone propionate (Armonair Digihaler, Flovent HFA, Flovent Diskus) in children < 4 years of age have not been proven safe or effective.

Mometasone (Asmanex Twisthaler) is approved for maintenance treatment of asthma as prophylactic therapy for children aged 4 years and older.

The safety and efficacy of fluticasone furoate/vilanterol (Breo Ellipta), fluticasone furoate/ umeclidinium/vilanterol (Trelegy Ellipta) and budesonide/glycopyrrolate/formoterol fumarate (Breztri Aerosphere) have not been established in pediatric patients.

Pregnancy

Ciclesonide (Alvesco) is assigned Pregnancy Category C.

Beclomethasone dipropionate (QVAR Redihaler), budesonide (Pulmicort Flexhaler, Pulmicort Respules), budesonide/formoterol (Symbicort), fluticasone furoate (Arnuity Ellipta), fluticasone furoate/umeclidinium/vilanterol (Trelegy Ellipta), fluticasone furoate/vilanterol (Breo Ellipta), fluticasone propionate products (ArmonAir Digihaler, Flovent HFA, Flovent Diskus), fluticasone propionate/salmeterol (AirDuo RespiClick, AirDuo Digihaler, Advair Diskus, Advair HFA), mometasone (Asmanex HFA, Asmanex Twisthaler), budesonide/glycopyrrolate/formoterol fumarate (Breztri Aerosphere) and mometasone/formoterol (Dulera) are not assigned a Pregnancy Category based on updated or new prescribing information complying with the Pregnancy and Lactation Labeling Rule (PLLR). There are no adequate randomized clinical studies of beclomethasone dipropionate, budesonide, budesonide/formoterol, fluticasone furoate, fluticasone propionate, fluticasone propionate/salmeterol, fluticasone furoate/vilanterol, fluticasone furoate/umeclidinium/vilanterol, mometasone, budesonide/glycopyrrolate/formoterol fumarate or mometasone/formoterol in pregnant women; thus, a risk versus benefit assessment should be conducted prior to using these agents in pregnant women. Studies of inhaled budesonide in pregnant women have not shown an increased risk of abnormalities.

Hepatic Impairment

Budesonide, fluticasone furoate, fluticasone propionate, formoterol fumarate, and salmeterol are predominantly cleared by hepatic metabolism; therefore, hepatic impairment may lead to their accumulation in the plasma. Patients using products containing any of these agents should be monitored closely for adverse effects if they have impaired hepatic function. Labeling for fluticasone furoate (Arnuity Ellipta), fluticasone furoate/vilanterol (Breo Ellipta), and fluticasone furoate/umeclidinium/vilanterol (Trelegy Ellipta) specifically advise close monitoring in patients with moderate to severe impairment, while the budesonide/glycopyrrolate/formoterol fumarate (Breztri Aerosphere) label recommends close monitoring in those with severe impairment.

Concentrations of mometasone furoate appear to increase with severity of hepatic impairment; although, labeling for products containing mometasone furoate (Asmanex, Dulera) do not stipulate caution with their use in patients with hepatic impairment.

No dosage adjustment of ciclesonide (Alvesco) is required in patients with hepatic impairment.

Effect of hepatic impairment on beclomethasone (QVAR) pharmacokinetics has not been evaluated.

DOSAGES[192,193,194,195,196,197,198,199,200,201,202,203,204,205,206,207,208,209,210]

Drug	Adult Doses		Pediatric Doses		Availability
	Initial	Maximum	Initial	Maximum	
Glucocorticoids					
beclomethasone HFA inhalation aerosol (QVAR Redihaler)	40 mcg to 80 mcg twice daily (previous bronchodilator use alone); 40 mcg to 320 mcg twice daily (previous inhaled corticosteroid therapy)	320 mcg twice daily	Age 4 to 11 years: 40 mcg twice daily (Use adult dosing for ages ≥ 12 years)	Age 4 to 11 years: 80 mcg twice daily	40 mcg and 80 mcg breath activated MDI (120 actuations per 10.6 g canister) Dose counter available for all strengths
budesonide inhalation powder (Pulmicort Flexhaler)	360 mcg twice daily	720 mcg twice daily	Age 6 to 17 years: 180 mcg twice daily	Age 6 to 17 years: 360 mcg twice daily	90 mcg and 180 mcg DPI (60 mcg and 120 actuations per canister, respectively) Dose counter available for all strengths Breath activated device
budesonide inhalation suspension (Pulmicort Respules)	--	--	Age 12 months to 8 years: Prior bronchodilator alone: 500 mcg once daily or 250 mcg twice daily Prior ICS: 500 mcg once daily or 250 mcg to 500 mcg twice daily Prior oral glucocorticoid: 500 mcg twice daily or 1,000 mcg once daily	--	250 mcg, 500 mcg, and 1,000 mcg per 2 mL Respules via jet nebulizer

Dosages (continued)

Drug	Adult Doses		Pediatric Doses		Availability
	Initial	Maximum	Initial	Maximum	
Glucocorticoids *(continued)*					
ciclesonide inhalation aerosol (Alvesco)	80 mcg twice daily (patients who received bronchodilator alone)	160 mcg twice daily	Age 12 years and older: 80 mcg twice daily (patients who received bronchodilator alone)	Age 12 years and older: 160 mcg twice daily	80 mcg and 160 mcg MDI with HFA propellant (60 actuations per 6.1 g canister) Dose counter available for all strengths
	80 mcg twice daily (patients who received inhaled corticosteroid)	320 mcg twice daily	Age 12 years and older: 80 mcg twice daily (patients who received inhaled corticosteroid)	Age 12 years and older: 320 mcg twice daily	
	320 mcg twice daily (patients who received oral corticosteroids)	320 mcg twice daily	Age 12 years and older: 120 mcg twice daily (patients who received oral corticosteroid)	Age 12 years and older: 320 mcg twice daily	
fluticasone furoate inhalation powder (Arnuity Ellipta)	One Inhalation of 100 mcg or 200 mcg once daily (starting dose based on prior asthma therapy and disease severity)	200 mcg daily	Age 5 to 11 years: 50 mcg once daily Age 12 years and older: 100 mcg (initial) to 200 mcg once daily	Age 5 to 11 years: 50 mcg daily Age 12 years and older: 200 mcg daily	50 mcg, 100 mcg, and 200 mcg blister strip of powder for inhalation (each strength is available as a package of 30 blisters) Breath activated device
fluticasone propionate inhalation aerosol (Flovent HFA)	88 mcg twice daily (without prior inhaled corticosteroid); 88–880 mcg twice daily (prior inhaled corticosteroid)	880 mcg twice daily	Age 4 to 11 years: 88 mcg twice daily	Age 4 to 11 years: 88 mcg twice daily	44 mcg, 110 mcg, and 220 mcg MDI with HFA propellant (120 actuations per canister) Dose counter available for all strengths

Dosages (continued)

Drug	Adult Doses		Pediatric Doses		Availability
	Initial	Maximum	Initial	Maximum	
Glucocorticoids *(continued)*					
fluticasone propionate inhalation powder (ArmonAir Digihaler)	55 mcg twice daily (55 mcg to 232 mcg twice daily may be used in patients transitioning from other ICS products)	232 mcg twice daily	Age 4 to 11 years: 30 mcg twice daily (30 mcg to 55 mcg twice daily may be used in patients transitioning from other ICS products) Age 12 years and older: 55 mcg twice daily (55 mcg to 232 mcg twice daily may be used in patients transitioning from other ICS products)	Age 4 to 11 years: 30 mcg to 55 mcg twice daily Age 12 years and older: 55 mcg to 232 mcg twice daily	55 mcg, 113 mcg, and 232 mcg (delivers 51 mcg, 103 mcg, and 210 mcg of fluticasone, respectively) in inhaler devices containing 60 doses each* Dose counter available for all strengths Breath activated device
fluticasone propionate inhalation powder (Flovent Diskus)	100 mcg twice daily (patients who received bronchodilators alone)	500 mcg twice daily	Age 4 to 11 years: 50 mcg twice daily (when prior therapy is with bronchodilator alone or inhaled corticosteroid)	Age 4 to 11 years: 100 mcg twice daily	50 mcg, 100 mcg, and 250 mcg blister units (60 blisters per pack) Dose counter available for all strengths Breath activated device
	100 mcg to 250 mcg twice daily (patients who used ICS)	500 mcg twice daily			
	500 mcg to 1,000 mcg twice daily (patients who used oral corticosteroids)	1,000 mcg twice daily			
mometasone furoate inhalation aerosol (Asmanex HFA)	Based on prior asthma therapy and disease severity: 2 inhalations of 100 mcg or 200 mcg twice daily	400 mcg twice daily	Age ≥ 12 years and older (based on prior asthma therapy and disease severity): 2 inhalations of 100 mcg or 200 mcg twice daily Age 5 to < 12 years: 50 mcg twice daily	Age 12 years and older: 400 mcg twice daily Age 5 to < 12 years: 100 mcg twice daily	50 mg, 100 mcg, and 200 mcg pressurized MDI (120 actuations per unit)

* 30 mcg version has been approved but is not yet available.

Dosages (continued)

Drug	Adult Doses		Pediatric Doses		Availability
	Initial	Maximum	Initial	Maximum	
Glucocorticoids *(continued)*					
mometasone furoate inhalation powder (Asmanex Twisthaler)	220 mcg daily in evening (if on bronchodilator alone or inhaled corticosteroid) or 440 mcg twice daily (if on oral corticosteroid)	440 mcg daily (single or divided doses) or 880 mcg daily	Age 12 years and older: 220 mcg daily in evening (if on bronchodilator alone or inhaled steroid) or 440 mcg twice daily (if on oral corticosteroid) Age 4 to 11 years of age: 110 mcg once daily in the evening	Age 12 years and older: 440 mcg daily (single or divided doses) or 880 mcg daily Age 4 to 11 years of age: 110 mcg once daily in the evening	110 mcg and 220 mcg DPI (110 mcg: 30 actuations per unit; 220 mcg: 30, 60, or 120 actuations per unit) Dose counter available for all strengths Breath activated device
Glucocorticoid/Long-Acting Beta2-Agonist (LABA) Combinations					
budesonide/formoterol inhalation aerosol (Symbicort)	**Asthma:** 2 inhalations twice daily of 80/4.5 mcg or 160/4.5 mcg **COPD:** 2 inhalations twice daily of 160/4.5 mcg	2 inhalations twice daily of 160/4.5 mcg	Age 6 years to 11 years (asthma): 2 inhalations twice daily of 80/4.5 mcg Age 12 years and older (asthma): 2 inhalations twice daily of 80/4.5 mcg or 160/4.5 mcg	Age 12 years and older: 2 inhalations twice daily of 160/4.5 mcg	80/4.5 mcg and 160/4.5 mcg per actuation MDI with HFA propellant (60 or 120 actuations per canister) Dose counter available for all strengths
fluticasone furoate/vilanterol inhalation powder (Breo Ellipta) The recommended starting dosages for asthma are based on prior asthma therapy (ICS)	**Asthma:** Low-to mid-dose ICS: 1 inhalation of 100/25 mcg once daily Mid- to high-dose ICS: 1 inhalation of 200/25 mcg once daily **COPD:** 1 inhalation of 100/25 mcg once daily	**Asthma:** 1 inhalation of 200/25 mcg once daily **COPD:** 1 inhalation of 100/25 mcg once daily	--	--	100/25 mcg and 200/25 mcg per inhalation (30 actuations [60 blisters] per unit) Dose counter available Breath activated device

Dosages (continued)

Drug	Adult Doses		Pediatric Doses		Availability
	Initial	Maximum	Initial	Maximum	
Glucocorticoid/Long-Acting Beta2-Agonist (LABA) Combinations *(continued)*					
fluticasone propionate/salmeterol inhalation aerosol (Advair HFA)	2 inhalations of 45/21 mcg twice daily or 115/21 mcg twice daily or 230/21 mcg twice daily	2 inhalations of 230/21 mcg twice daily	Age 12 years and older: 2 inhalations of 45/21 mcg twice daily or 115/21 mcg twice daily or 230/21 mcg twice daily	Age 12 years and older: 2 inhalations of 230/21 mcg twice daily	45/21 mcg, 115/21 mcg, and 230/21 mcg per actuation MDI with HFA propellant (60 or 120 actuations per canister) Dose counter available for all strengths
fluticasone propionate/salmeterol inhalation powder (Advair Diskus)	**Asthma:** 100/50 mcg twice daily to 500/50 mcg twice daily **COPD:** 1 inhalation twice daily of 250/50 mcg	**Asthma:** 500/50 mcg twice daily	Age 4 to 11 years: 100/50 mcg twice daily Age 12 years and older: 1 inhalation twice daily of 100/50, 250/50, or 500/50 mcg	--	100/50 mcg, 250/50 mcg, and 500/50 mcg per actuation Diskus DPI† (60 blisters/actuations per unit) Dose counter available for all strengths Breath activated device
fluticasone propionate/salmeterol inhalation powder (AirDuo RespiClick, AirDuo Digihaler)	**Asthma:** 1 inhalation (55/14 mcg to 232/14 mcg) twice daily	**Asthma:** 232/14 mcg twice daily	Age 12 years and older: 1 inhalation (55/14 mcg to 232/14 mcg) twice daily	Age 12 years and older: 1 inhalation (55/14 mcg to 232/14 mcg) twice daily	55/14 mcg, 113/14 mcg and 232/14 mcg per actuation (60 actuations per unit) Dose counter available for all strengths Breath activated device Not to be used with a spacer or holding chamber
mometasone/formoterol inhalation aerosol (Dulera)	Based on prior asthma therapy and disease severity: 2 inhalations of 100/5 mcg or 200/5 mcg twice daily	2 inhalations of 200/5 mcg twice daily	Age 12 years and older (based on prior asthma therapy and disease severity): 2 inhalations of 100/5 mcg or 200/5 mcg twice daily Ages 5 to < 12 years: 2 inhalations of 50/5 mcg twice daily	Age 12 years and older: 2 inhalations of 200/5 mcg twice daily Ages 5 to < 12 years: 2 inhalations of 50/5 mcg twice daily	50/5 mcg, 100/5 mcg, and 200/5 mcg per actuation (120 actuations per unit) MDI with HFA propellant Dose counter available for all strengths

† A generic formulation of fluticasone propionate/salmeterol (approved via an Abbreviated New Drug Application [ANDA]) also is available from Mylan under the trade name Wixela® Inhub®.[211]

Dosages (continued)

Drug	Adult Doses		Pediatric Doses		Availability
	Initial	Maximum	Initial	Maximum	
Glucocorticoid/Long-Acting Anticholinergic/Long-Acting Beta2-Agonist (LABA) Combinations					
budesonide/ glycopyrrolate/formoterol fumarate (Breztri Aerosphere)	2 inhalations twice daily	2 inhalations twice daily	-	-	160/9/4.8 mcg per actuation MDI with HFA propellant (120 actuations per unit) Dose counter available
fluticasone furoate/ umeclidinium/vilanterol (Trelegy Ellipta)	**Asthma and COPD:** 1 inhalation of 100/62.5/25 mcg once daily	**Asthma:** 1 inhalation of 200/62.5/25 mcg once daily **COPD:** 1 inhalation of 100/62.5/25 mcg once daily	--	--	100/62.5/25 mcg and 200/62.5/25 mcg per actuation DPI (30 actuations per unit) with dose counter Supplied as inhalation powder in 2 foil blister strips per actuation (1 containing fluticasone furoate, 1 containing umeclidinium/vilanterol) Breath activated device

The starting dosage of an inhaled corticosteroid is based on previous asthma therapy and asthma severity, including consideration of patients' current control of asthma symptoms and risk of future exacerbation.

The ArmonAir Digihaler and the AirDuo Digihaler have a built-in electronic module that transmits data on inhaler events to an app; however, use of the app is not required for medication administration.

CLINICAL TRIALS

Search Strategy

Studies were identified through searches performed on PubMed and review of information sent by manufacturers. Search strategy included the FDA-approved use of all drugs in this class. Randomized, controlled, comparative trials are considered the most relevant in this category. Studies included for analysis in the review were published in English, performed with human participants, and randomly allocated participants to comparison groups. In addition, studies must contain clearly stated, predetermined outcome measure(s) of known or probable clinical importance, use data analysis techniques consistent with the study question, and include follow-up (endpoint assessment) of at least 80% of participants entering the investigation. Despite some inherent bias found in all studies, including those sponsored and/or funded by pharmaceutical manufacturers, the studies in this therapeutic class review were determined to have results or conclusions that do not suggest systematic error in their experimental study design. While the potential influence of manufacturer sponsorship and/or funding must be considered, the studies in this review have also been evaluated for validity and importance.

Asthma

beclomethasone (QVAR) versus placebo

The Treating Children to Prevent Exacerbations of Asthma (TREXA) study was a multi-center, 44-week, randomized, double-blind, placebo-controlled trial conducted in 288 children and adolescents with mild persistent asthma aged 6 to 18 years to evaluate the impact and severity of asthma exacerbations in patients who are receiving various combinations of medications for daily and rescue use.[212] Patients were randomly assigned to 1 of 4 treatment groups: twice daily beclomethasone with beclomethasone plus albuterol as rescue (combined group, n=71); twice daily beclomethasone with placebo plus albuterol as rescue (daily beclomethasone group, n=72); twice daily placebo with beclomethasone plus albuterol as rescue (rescue beclomethasone group, n=71); and twice daily placebo with placebo plus albuterol as rescue (placebo group, n=74). Twice daily beclomethasone treatment was 1 puff of beclomethasone (40 mcg per puff) or placebo given in the morning and evening. Rescue beclomethasone treatment was 2 puffs of beclomethasone or placebo for each 2 puffs of albuterol (180 mcg) needed for symptom relief. The primary outcome was time to first exacerbation that required oral corticosteroids. A secondary outcome measured linear growth. Analysis was by intention to treat. Compared with the placebo group (49%; 95% CI, 37 to 61), the frequency of exacerbations was lower in the daily (28%; 95% CI, 18 to 40; p=0.03), combined (31%; 95% CI, 21 to 43; p=0.07), and rescue (35%; 95% CI, 24 to 47; p=0.07) groups. Frequency of treatment failure was 23% (95% CI, 14 to 43) in the placebo group, compared with 5.6% (95% CI, 1.6 to 14) in the combined (p=0.012), 2.8% (95% CI, 0 to 10) in the daily (p=0.009), and 8.5% (95% CI, 2 to 15) in the rescue (p=0.024) groups. Compared with the placebo group, linear growth was 1.1 cm (standard deviation [SD], 0.3) less in the combined and daily arms (p<0.0001), but not the rescue group (p=0.26). Only 2 individuals had severe adverse events; 1 in the daily beclomethasone group had viral meningitis and 1 in the combined group had bronchitis. The authors concluded that children with mild persistent asthma should not be treated with rescue albuterol alone and the most effective treatment to prevent exacerbations is daily inhaled corticosteroids (ICS). ICS as rescue medication with albuterol might be an effective step-down strategy for children with well controlled, mild asthma because it is more effective at reducing exacerbations than is use of rescue albuterol alone. Use of daily ICS treatment and related side-effects, such as growth impairment, can therefore be avoided. This study was funded by the National Heart, Lung and Blood Institute. This formulation is no longer available.

beclomethasone (QVAR Redihaler) versus placebo

Two randomized, double-blind, parallel-group, placebo-controlled trials established the efficacy and safety of beclomethasone within the Redihaler device for the treatment of asthma in adults and adolescents ≥ 12 years.[213] In study 1, enrolled patients with persistent symptomatic asthma despite low-dose inhaled corticosteroid or non-corticosteroid asthma therapy with a FEV_1 40% to 85% predicted normal and reversible bronchoconstriction of 15% with short-acting inhaled beta-agonist entered a 14 to 21 day run-in period and were randomized to beclomethasone Redihaler 80 mcg/day or 160 mcg/day or placebo (n=270). The primary endpoint was the standardized baseline-adjusted trough morning FEV_1 area under the effect curve (AUC) from time 0 to 12 weeks. Both active treatment groups demonstrated a greater improvement in trough FEV_1 versus placebo (80 mcg/day: least squares mean difference, 0.124 L [95% CI, 0.054 to 0.193]; 160 mcg/day: least squares mean difference, 0.116 [95% CI, 0.048 to 0.186]).

In study 2, adult and adolescent patients with persistent symptomatic asthma despite treatment with non-corticosteroid, inhaled corticosteroids (with or without a LABA), or combination asthma therapy.[214] Enrolled patients entered a 2 to 4 week run-in period and those with persistent symptomatic asthma despite low-dose inhaled corticosteroid or non-corticosteroid asthma therapy with a FEV_1 40% to 85% predicted normal, 15% reversibility with short-acting inhaled beta-agonist, and asthma symptoms were randomized to beclomethasone Redihaler 320 mcg/day or 640 mcg/day, beclomethasone (QVAR) 320 mcg/day (reference treatment group), or placebo (n=425). The primary endpoint was the standardized baseline-adjusted trough morning FEV_1 AUC from time 0 to 6 weeks. Both active treatment groups demonstrated a greater improvement in trough FEV_1 versus placebo (320 mcg/day: least squares mean difference, 0.144 L [95% CI, 0.0807 to 0.2066]; 640 mcg/day: least squares mean difference, 0.15 [95% CI, 0.0868 to 0.2132]). Treatment results with the reference treatment group were similar (least squares mean difference, 0.148 [95% CI, 0.0847 to 0.2114]).

A randomized, double-blind, parallel-group, placebo-controlled, 12-week, global efficacy and safety trial compared the efficacy and safety of beclomethasone Redihaler in patients aged 4 to 11 years old with persistent symptomatic asthma despite treatment with non-corticosteroid or low dose inhaled corticosteroid (with or without a LABA).[215] Patients meeting the inclusion criteria (FEV1 40% to 90% predicted normal, reversible bronchoconstriction of at least 12% with short acting inhaled beta agonist) entered a 14 to 21 day run in period. Those who met the randomization criteria discontinued their asthma therapy and were randomized to beclomethasone Redihaler 40 or 80 mcg, beclomethasone (QVAR) 40 or 80 mcg, or placebo administered as 1 inhalation twice daily (n=568). The primary endpoint was the change from baseline in trough percent predicted FEV_1 AUC from time 0 to 12 weeks. The primary endpoint was not found to be statistically significant; however, the change in weekly average of daily morning peak expiratory flow (PEF) over the 12 week treatment period was significant (PEF: 11.3 L/min [95% CI, 5.58 to 17.06] and 8.5 L/min [95% CI, 2.71 to 14.24] for the 80 mcg/day and 160 mcg/day Redihaler doses, respectively). Similar results were seen with evening PEF.

budesonide/formoterol (Symbicort) versus budesonide (Pulmicort)

A double-blind, randomized, 12-week study conducted in 619 patients ages 12 and older with mild to moderate asthma to evaluate the efficacy and tolerability of once daily budesonide/formoterol versus once daily budesonide in patients stable with twice daily budesonide/formoterol.[216] After an initial 4 to 5 weeks of 2 inhalations twice daily budesonide/formoterol 80/4.5 mcg (daily dose of 320/18 mcg), stable patients were randomized to 1 of 4 treatment groups. These groups included: 2 inhalations of twice daily of budesonide/formoterol 80/4.5 mcg (daily dose 320/18 mcg); 2 inhalations once daily in the evening of budesonide/formoterol 160/4.5 mcg or 80/4.5 mcg (daily dose of 320/9 mcg or 160/4.5 mcg); or 2 inhalations once daily of budesonide 160 mcg (daily dose of 320 mcg). All budesonide/formoterol groups maintained significantly more favorable evening pre-dose forced expiratory volume in 1 second (FEV_1), morning PEF, daytime/nighttime asthma symptoms, nighttime rescue medication use, and rescue medication-free days versus budesonide. Variables evaluated during the end of the once daily dosing interval included evening pre-dose FEV_1, evening PEF, daytime asthma symptoms, and daytime rescue medication use. They significantly favored twice daily budesonide/formoterol versus all treatments. Twice daily budesonide/formoterol demonstrated significantly more favorable results for symptom-free and asthma control days versus all treatments and awakening-free nights versus budesonide. Asthma Quality of Life Questionnaire and Asthma Control Questionnaire (ACQ) results significantly favored twice-daily budesonide/formoterol versus budesonide ($p \leq 0.018$). All treatments were well tolerated.

A double-blind, randomized, 12-week multicenter study was conducted in 521 patients ages 6 to 15 years with mild/moderate persistent asthma to assess the efficacy and tolerability of once daily budesonide/formoterol versus budesonide (primary) and twice daily budesonide/formoterol (secondary) in children/adolescents with asthma who have been stabilized with twice daily budesonide/formoterol.[217] Patients had been stabilized during a 4 to 5 week run-in with 2 inhalations twice daily of budesonide/formoterol 40/4.5 mcg inhalations (160/18 mcg daily). These patients were randomized to either continue on the stabilization regimen, to receive a reduced dose of 2 inhalations once every evening of daily budesonide/formoterol 80/4.5 mcg (160/9 mcg daily), or 2 inhalations once every evening of budesonide 80 mcg (160 mcg daily). The once or twice daily regimens of budesonide/formoterol were more effective than budesonide for evening PEF (primary variable) at the end of the 24 hour once daily dosing interval (p≤0.027). Twice daily budesonide/formoterol demonstrated better efficacy versus once daily treatments for evening pre-dose FEV_1 (p≤0.011), versus budesonide for daytime/nighttime rescue medication (p≤0.023), and versus once daily budesonide/formoterol for daytime rescue medication (last 12 hours of once daily dosing) (p=0.032). There were no significant between-group differences for daytime/nighttime asthma symptoms, nighttime awakenings attributed to asthma, or health-related quality of life. Fewer patients experienced asthma worsening based on predefined criteria with twice daily budesonide/formoterol (8.2%) versus once daily budesonide (15.5%) (p=0.036) or once daily budesonide/formoterol (19.6%) (p=0.002). All treatments were well tolerated.

budesonide/formoterol (Symbicort) versus budesonide MDI (Pulmicort)

In a multicenter, double-blind, 26-week, post-marketing study, patients 12 years of age or older with persistent asthma, receiving daily asthma medication and who had experienced 1 to 4 asthma exacerbations in the previous year were randomized to receive either budesonide/formoterol (n=5,846) or budesonide alone (n=5,847).[218] The primary outcome was the first serious asthma-related event (a composite of adjudicated death, intubation, and hospitalization) and was assessed in a time-to-event analysis. The primary end point of asthma-related events occurred in 43 patients who were receiving budesonide/formoterol and in 40 patients who were receiving budesonide alone (hazard ratio, 1.07; 95% CI, 0.7 to 1.65); budesonide/formoterol was shown to be noninferior to budesonide alone. There were 2 asthma-related deaths, both occurred in the budesonide/formoterol group; and 1 of the 2 patients had undergone an asthma-related intubation. The risk of an asthma exacerbation was 16.5% lower with budesonide/formoterol than with budesonide alone (hazard ratio, 0.84; 95% CI, 0.74 to 0.94; p=0.002). Treatment with budesonide/formoterol was associated with a lower risk of asthma exacerbations than budesonide alone with similar risk of serious asthma-related events with both treatments.

budesonide/formoterol (Symbicort) versus budesonide MDI (Pulmicort) versus formoterol (Foradil) versus budesonide (Pulmicort) + formoterol (Foradil) versus placebo

A 12-week, randomized, double-blind, double-dummy, placebo-controlled study was conducted to compare the efficacy and safety of budesonide/formoterol to each of its individual ingredients [budesonide, formoterol, or budesonide + formoterol] as well as to placebo.[219] Five hundred ninety-six patients ages 12 years and older with moderate to severe persistent asthma and previously receiving an ICS were placed on budesonide 160 mcg twice daily. After 2 weeks, they were randomized to budesonide/formoterol 160/4.5 mcg twice daily; budesonide 160 mcg twice daily + formoterol 4.5 mcg twice daily; budesonide 160 mcg twice daily; formoterol 4.5 mcg twice daily; or placebo twice daily.

The primary efficacy endpoints were mean change from baseline of FEV_1 and mean change from baseline in 12-hour FEV_1. The results were similar in the budesonide/formoterol and the budesonide + formoterol groups in all measures. The budesonide/formoterol group showed greater improvement in FEV_1 ($p \leq 0.049$) than the individual budesonide, formoterol, and placebo. Also, fewer patients on budesonide/formoterol experienced worsening asthma symptoms ($p \leq 0.025$). All of the treatments were well tolerated with similar safety profiles.

A 12-week, randomized, double-blind, double-dummy, placebo-controlled, multicenter trial of 596 adult patients (ages 12 and older) with moderate to severe persistent asthma was conducted to evaluate patient reported outcomes (PROs) related to asthma therapy.[220] Patients received budesonide 160 mcg twice daily for the first 2 weeks. They were then randomized to receive 2 inhalations twice daily of 1 of 5 treatment arms: budesonide/formoterol 160/4.5 mcg; budesonide 160 mcg plus formoterol DPI 4.5 mcg; budesonide 160 mcg; formoterol DPI 4.5 mcg; or placebo. PROs were assessed in 553 patients 18 years or older using the standardized Asthma Quality of Life Questionnaire (AQLQ[S]), Medical Outcomes Survey (MOS) Sleep Scale, Patient Satisfaction with Asthma Medication (PSAM) questionnaire, diary data, and global assessments. Patients receiving budesonide/formoterol reported significantly greater improvements from baseline on the AQLQ(S) and asthma control variables (based on symptoms and rescue medication use; all $p<0.001$) versus placebo. Clinically important improvements (increase of ≥ 0.5 points) from baseline to end of treatment in AQLQ(S) overall scores were achieved by 43.6% of patients receiving budesonide/formoterol versus 22.6% of patients receiving placebo ($p=0.001$). The MOS Sleep Scale scores generally showed no differences among treatment groups. Patients receiving budesonide/formoterol had significantly greater PSAM questionnaire scores and better outcomes on physician-patient global assessments at end of treatment versus placebo (all $p \leq 0.001$).

budesonide/formoterol (Symbicort) versus budesonide MDI (Pulmicort) versus formoterol (Foradil) versus placebo

A 12-week, multicenter, double-blind, randomized, placebo-controlled, double-dummy study was conducted in 480 patients age 12 years or older with mild to moderate persistent asthma treated with ICS for 4 weeks or more and with an FEV_1 of 60% to 90%.[221] After a 2-week washout period, patients received either budesonide/formoterol 80/4.5 mcg twice daily (n=123), budesonide 80 mcg twice daily (n=121), formoterol 4.5 mcg twice daily (n=114), or placebo (n=122). At the end of treatment, greater increases in FEV_1 occurred in the budesonide/formoterol group versus all of the other groups (0.37 versus 0.23, 0.17, and 0.03 L, respectively; $p<0.005$). Fewer patients receiving budesonide/formoterol withdrew due to worsening asthma versus the formoterol (42.1% and 18.4%) and placebo (56.6% versus 32.8%) groups. However, the results were similar, according to the authors, with respect to worsening asthma between the budesonide/formoterol and budesonide groups (21.5% versus 6.6%). The authors determined that in adults and adolescents with mild to moderate persistent asthma that twice daily budesonide/formoterol resulted in improved pulmonary function versus its component ingredients alone. All of the study drugs were well tolerated.

ciclesonide (Alvesco) versus budesonide (Pulmicort)

A 12-week, multicenter, randomized study to compare the efficacy of ciclesonide to budesonide enrolled 544 patients ages 12 to 75 years.[222] Patients were randomized to receive inhaled ciclesonide 80 or 320 mcg daily or budesonide 200 mcg twice daily for 12 weeks. The study was designed in a double-blind manner with respect to the ciclesonide dose and open label for budesonide because a

placebo for budesonide was not available. Efficacy and tolerability assessments were performed at baseline and weeks 4, 8, and 12. The primary endpoint was the change from baseline in FEV_1 at 12 weeks. Secondary endpoints included changes from baseline in morning PEF, asthma symptom scores, and rescue medication use. The results of this study in patients with primarily mild to moderate asthma suggest that patients using either dose of ciclesonide (80 or 320 mcg daily) had similar improvements in pulmonary function, control of asthma symptoms, and reduced need for rescue medications as those patients who received budesonide 200 mcg twice daily.

ciclesonide (Alvesco) versus fluticasone (Flovent)

A 12-week, double-blind, parallel-group study compared the efficacy and safety of once daily ciclesonide and twice daily fluticasone in patients ages 12 to 75 years with persistent asthma.[223] Patients were randomized to once daily ciclesonide 80 mcg (n=278), ciclesonide 160 mcg (n=271), or twice daily fluticasone 88 mcg (n=259). Significant improvements from baseline were seen in all 3 treatment groups for FEV_1, asthma symptom scores, and rescue medication use (all $p<0.0001$). Asthma exacerbation rates were low. Adverse event reporting indicated good tolerability of all treatments.

fluticasone furoate (Arnuity Ellipta) versus fluticasone propionate (Flovent Diskus)

A randomized, double-blind, double-dummy, placebo-controlled, multicenter study, enrolled 343 patients with asthma, aged 12 years or older who were not controlled by their current ICS therapy.[224] The primary endpoint was change from baseline in pre-dose evening FEV1 at the end of the 24-week treatment period. Patients randomly received fluticasone furoate (100 mcg) once daily, placebo once daily, or twice daily administered fluticasone propionate (250 mcg). At week 24, once daily fluticasone furoate and twice daily fluticasone propionate significantly improved pre-dose evening FEV1 (+146 mL; $p=0.009$) compared with placebo (+145 mL; $p=0.011$). The secondary endpoint of percentage rescue-free 24-hour periods, was increased with fluticasone furoate (+14.8%; $p<0.001$) and fluticasone propionate (+17.9%; $p<0.001$) compared to placebo.

fluticasone furoate (Arnuity Ellipta) versus placebo with fluticasone propionate as an active control

A 12-week, multicenter, randomized, double-blind, parallel-group, placebo- and active-controlled study evaluated the efficacy and safety of fluticasone furoate in pediatric patients with inadequately controlled asthma aged 5 to 11 years.[225,226] Following a 4-week run-in period, 593 patients were randomized 1:1:1:1:1 to placebo once daily, fluticasone furoate 25 mcg, 50 mcg, or 100 mcg once daily in the evening, or fluticasone propionate 100 mcg twice daily for 12 weeks. The primary endpoint was the mean change from baseline in daily morning PEF over the 12 weeks of treatment. The difference in the mean change from baseline in daily morning PEF over the 12 weeks of treatment, the primary endpoint, was significant in all active treatment groups versus placebo (differences versus placebo of 18.6 L/min, 19.5 L/min, 12.5 L/min, and 14 L/min in the fluticasone furoate 25 mcg, fluticasone furoate 50 mcg, fluticasone furoate 100 mcg, and fluticasone propionate groups, respectively; $p<0.001$ for all comparisons versus placebo).

fluticasone furoate/vilanterol (Breo Ellipta) versus fluticasone furoate (Arnuity Ellipta)

In two, 12-week randomized, double-blind, parallel-group trials, the efficacy of fluticasone furoate/vilanterol on lung function was compared to fluticasone furoate alone in subjects with asthma not controlled on their current treatments of ICS or ICS/LABA.[227] In both studies, all inhalations were administered once daily. In study 1, 609 patients were randomized to fluticasone furoate/vilanterol 100/25 mcg, fluticasone furoate 100 mcg, or placebo. Weighted mean FEV_1 (0 to 24 hours) was

assessed in a subset of subjects (n=309). At week 12, change from baseline in weighted mean FEV_1 was significantly greater for fluticasone furoate/vilanterol 100/25 mcg compared with placebo (302 mL; 95% CI, 178 to 426; p<0.001); change from baseline in weighted mean FEV_1 for fluticasone furoate/vilanterol 100/25 was numerically greater than fluticasone furoate 100 mcg, but not statistically significant (116 mL; 95% CI, -5 to 236). At week 12, change from baseline in trough FEV_1 was significantly greater for fluticasone furoate/vilanterol 100/25 compared with placebo (172 mL; 95% CI, 87 to 258; p<0.001); change from baseline in trough FEV_1 for fluticasone furoate/vilanterol 100/25 mcg was numerically greater than fluticasone furoate 100 mcg, but not statistically significant (36 mL; 95% CI, -48 to 120). In study 2, 1,039 patients were randomized to fluticasone furoate/vilanterol 100/25 mcg, fluticasone furoate/vilanterol 200/25 mcg, or fluticasone furoate 100 mcg.[228,229] The change from baseline in weighted mean FEV_1 (0 to 24 hours) was significantly greater for fluticasone furoate/vilanterol 100/25 mcg compared with fluticasone furoate 100 mcg (108 mL; 95% CI, 45 to 171; p<0.001) at week 12. Improvements in FEV_1 were numerically greater with fluticasone furoate/vilanterol 200/25 mcg compared to the 100/25 mcg dose but these differences were not statistically significant.

fluticasone furoate/vilanterol (Breo Ellipta) versus fluticasone propionate (Flovent Diskus)

In a 24-week randomized, double-blind, parallel-group trial, patients (n=586) not controlled on their current treatments of ICS or combination therapy consisting of an ICS plus a LABA were randomized to fluticasone furoate/vilanterol 200/25 mcg, fluticasone furoate 200 mcg, or fluticasone propionate 500 mcg.[230] All inhalations were administered once daily, with the exception of fluticasone propionate, which was administered twice daily. The change from baseline in weighted mean FEV_1 (0 to 24 hours) was significantly greater for fluticasone furoate/vilanterol 200/25 mcg compared with fluticasone furoate 200 mcg (136 mL; 95% CI, 1 to 270; p=0.048) at week 24. The change from baseline in trough FEV_1 was significantly greater for fluticasone furoate/vilanterol 200/25 mcg compared with fluticasone furoate 200 mcg (193 mL; 95% CI, 108 to 277; p<0.001) at week 24. Patients receiving fluticasone furoate/vilanterol 200/25 mcg had significantly greater improvements from baseline in percentage of 24-hour periods without need of $beta_2$-agonist rescue medication use and percentage of 24-hour periods without asthma symptoms compared with patients receiving fluticasone furoate 200 mcg.

fluticasone furoate/vilanterol (Breo Ellipta) versus fluticasone propionate/salmeterol (Advair)

In a randomized, double-blind, double-dummy, parallel group study, 403 patients received fluticasone furoate/vilanterol 100/25 mcg once daily in the evening, and 403 patients received fluticasone propionate/salmeterol 250/50 mcg twice daily.[231] Improvements from baseline in weighted mean FEV_1 (0 to 24 hours) were observed with both fluticasone furoate/vilanterol (341 mL) and fluticasone propionate/salmeterol (377 mL); the adjusted mean treatment difference was not statistically significant (−37 mL; 95% CI, −88 to 15, p=0.162). There were no differences between 0 to 4 hour serial weighted mean FEV_1, trough FEV_1, asthma control and quality-of-life questionnaire scores, and reported exacerbations between treatments.

fluticasone propionate (Flovent) versus fluticasone propionate/salmeterol (Advair)

A 1-year, randomized, stratified, double-blind, parallel-group study of 3,421 patients with uncontrolled asthma compared fluticasone propionate and fluticasone propionate/salmeterol in achieving guideline-based measures of control: totally and well-controlled asthma.[232] Treatment was stepped-up until total control was achieved (or maximum 500 mcg corticosteroid twice a day). Significantly more

patients in each stratum (previously corticosteroid-free, low- and moderate-dose corticosteroid users) achieved control with fluticasone propionate/salmeterol than fluticasone propionate. Total control was achieved across all strata in 31% versus 19% of patients after dose escalation (p<0.001) and 41% versus 28% of patients at 1 year for fluticasone propionate/salmeterol and fluticasone propionate, respectively. Asthma became well controlled in 63% versus 50% after dose escalation (p<0.001) and in 71% versus 59% of patients at 1 year. Control was achieved more rapidly and at a lower corticosteroid dose with fluticasone propionate/salmeterol versus fluticasone propionate. Across all strata, 68% and 76% of the patients receiving fluticasone propionate/salmeterol and fluticasone propionate, respectively, were on the highest dose at the end of treatment. Exacerbation rates (0.07 to 0.27 per patient per year) and improvement in health status were significantly better with fluticasone propionate /salmeterol.

A multicenter, randomized, double-blind, 4-week, parallel group trial of 248 pediatric patients (ages 4 to 17 years old) with persistent asthma was conducted to evaluate the effectiveness of fluticasone propionate/salmeterol 100/50 mcg compared to fluticasone propionate 100 mcg for the prevention of airflow limitation triggered by standardized exercise challenge.[233] Exercise challenge tests were performed during screening and approximately 8 hours after administration of the blinded study medication on treatment day 28. After 4 weeks of therapy, both treatments provided protection following exercise challenge. The protection estimated by the maximal fall in FEV_1 was significantly better for fluticasone propionate/salmeterol (9.5 +/- 0.8%) compared with fluticasone propionate alone (12.7 +/- 1.1%, p=0.021). Statistically significant differences were not observed for asthma rescue-free days and asthma symptom-free days.

A multicenter, randomized, parallel-group, double-blind study was performed comparing fluticasone/salmeterol 50/100 mcg twice a day and fluticasone propionate 200 mcg twice a day during a 26 week period to evaluate if the combination is non-inferior regarding symptom control and the effects on asthma control and lung function in children with symptomatic asthma.[234] For children with symptomatic asthma despite low to moderate doses of ICS, evidence is still lacking whether to add a long-acting bronchodilator or to increase the dose of ICS. A total of 158 children age 6 to 16 years old, still symptomatic on fluticasone 100 mcg twice daily, were included in a 4-week run-in period. The percentage of symptom-free days during the last 10 weeks of the treatment period did not differ between treatment groups (per protocol analysis: adjusted mean difference 2.6%; 95% CI, -8.1 to 13.4). Both groups showed substantial improvements of about 25 percentage points in symptom-free days (both p<0.001 from baseline). Lung function measurements (FEV_1, forced vital capacity [FVC], PEF rate, and maximal expiratory flow) did not differ between groups except for a slight advantage in maximal expiratory flow in the fluticasone propionate/salmeterol group at 1 week. No differences were found between fluticasone propionate and fluticasone propionate/salmeterol regarding exacerbation rates, adverse events, or growth.

An international, randomized, double-blind, active-comparator, 26-week trial enrolled children ages 4 to 11 who were receiving daily treatment with asthma medications and had experienced asthma exacerbations in the previous year.[235] Children with a history of life-threatening asthma or unstable asthma were excluded from the trial. A total of 6,208 children were randomized in a 1:1 ratio to receive fluticasone propionate plus salmeterol or fluticasone alone for 26 weeks. The primary safety outcome was the first serious asthma-related event (a composite end point that included death, endotracheal intubation, and hospitalization), as assessed in a time-to-event analysis. Of the 6,208 patients in the intent-to-treat population, 27 patients in the fluticasone/salmeterol group and 21 in the

fluticasone-only group experienced a serious asthma-related event (all of which were hospitalizations); the hazard ratio with fluticasone/salmeterol versus fluticasone alone was 1.28 (95% CI, 0.73 to 2.27), meeting the noninferiority margin for fluticasone/salmeterol (p=0.006). A total of 265 patients (8.5%) in the fluticasone/salmeterol group and 309 (10%) in the fluticasone-only group had a severe asthma exacerbation (hazard ratio, 0.86; 95% CI, 0.73 to 1.01). Based on these results, in children with asthma, salmeterol in a fixed-dose combination with fluticasone was associated with a similar risk of a serious asthma-related events to fluticasone alone.

fluticasone propionate (Flovent Diskus) versus fluticasone/salmeterol (Advair Diskus)

AUSTRI trial: A multinational, multicenter, randomized, double-blind trial in adults and adolescents (≥ 12 years old) with persistent asthma compared fluticasone/salmeterol to fluticasone alone for 26 weeks (n=11,679).[236] Patients were randomized 1:1: to fluticasone/salmeterol (100/50, 250/50, or 500/50 mcg) or fluticasone (100, 250, or 500 mcg) administered twice daily. Rescue medication was allowed. Fluticasone/salmeterol was determined to be non-inferior to fluticasone in serious asthma-related events, the primary outcome (hazard ratio [HR], 1.03; 95% CI, 0.64 to 1.66; p=0.003 for noninferiority). The risk for asthma exacerbation was lower in the fluticasone/salmeterol group than the fluticasone only group (HR, 0.79; 95% CI, 0.7 to 0.89; p<0.001).

fluticasone propionate (ArmonAir RespiClick) and fluticasone propionate/salmeterol DPI (AirDuo RespiClick) versus placebo

Trial 1 and Trial 2, double-blind, parallel-group clinical trials, were conducted with fluticasone propionate/salmeterol DPI (RespiClick device) in adult and adolescent patients aged ≥ 12 years with baseline FEV_1 40% to 85% of predicted normal and with asthma not optimally controlled on their current therapy (n=1,375).[237,238] All treatments were given as 1 inhalation twice a day from the RespiClick inhaler (as either fluticasone propionate or fluticasone propionate/salmeterol) and other maintenance medications were discontinued. Trial 1 was a randomized, placebo-controlled, 12-week, global efficacy and safety trial which compared fluticasone propionate 55 mcg and 113 mcg (1 inhalation twice a day) with fluticasone/salmeterol 55/14 mcg and 113/14 mcg (1 inhalation twice a day) and placebo in patients with persistent symptomatic asthma in spite of prior treatment with low- to mid-dose inhaled corticosteroid or inhaled corticosteroid/LABA therapy. Patients received single-blinded placebo and in the run-in period were switched from their baseline ICS therapy to beclomethasone 40 mcg twice daily. The primary outcome for this trial was the change from baseline in trough FEV_1 at week 12 for all patients and standardized baseline-adjusted FEV_1 $AUEC_{0\text{-}12h}$ at week 12 analyzed for a subset of 312 patients who performed postdose serial spirometry. Patients receiving fluticasone/salmeterol (55/14 mcg and 113/14 mcg) had significantly greater improvements in trough FEV_1 (fluticasone/salmeterol 55/14 mcg, least squares mean change of 0.319 L at 12 weeks; fluticasone/salmeterol 113/14 mcg, least squares mean change of 0.315 L at 12 weeks) as compared to fluticasone propionate 55 mcg (least squares mean change of 0.172 L at 12 weeks), fluticasone propionate 113 mcg (least squares mean change of 0.204 L at 12 weeks), and placebo (least squares mean change of 0.053 L at 12 weeks). Patients receiving fluticasone propionate 55 mcg and 113 mcg had a greater improvement in trough FEV_1 compared to placebo (differences of 0.119 L [95% CI, 0.025 to 0.212] and 0.151 L [95% CI, 0.057 to 0.244 L, respectively). Additionally, there was evidence of efficacy for fluticasone and fluticasone/salmeterol compared with placebo for secondary endpoints, including the weekly average of daily trough morning peak expiratory flow and total daily use of rescue medication.

Trial 2 was a randomized, double-blind, placebo-controlled, 12-week, global efficacy and safety trial that compared fluticasone propionate 113 mcg and 232 mcg (1 inhalation twice a day) with fluticasone and salmeterol 113/14 mcg and 232/14 mcg (1 inhalation twice a day) and placebo in adolescents and adult patients with persistent symptomatic asthma despite inhaled corticosteroid or inhaled corticosteroid/LABA therapy.[239] Patients received single-blinded placebo and were switched during the run-in period from their baseline ICS therapy to fluticasone propionate 55 mcg twice daily. Patients were randomly assigned to receive treatment as follows: 145 patients received placebo, 146 patients received fluticasone propionate 113 mcg, 146 patients received fluticasone propionate 232 mcg, 145 patients received fluticasone propionate/salmeterol 113/14 mcg, and 146 patients received fluticasone propionate/salmeterol 232/14 mcg. The primary outcomes for this trial were the change from baseline in trough FEV_1 at week 12 for all patients and standardized baseline-adjusted FEV_1 $AUEC_{0\text{-}12h}$ at week 12 analyzed for a subset of 312 patients who performed postdose serial spirometry. Baseline FEV_1 measurements were similar across treatments: fluticasone propionate 113 mcg 2.069 L, fluticasone propionate 232 mcg 2.075 L, fluticasone propionate/salmeterol 113/14 mcg 2.157 L, fluticasone propionate/salmeterol 232/14 mcg 2.083 L, and placebo 2.141 L. Similar to Trial 1, patients receiving fluticasone propionate/salmeterol 113/14 mcg and 232/14 mcg had significantly greater improvements in trough FEV_1 (fluticasone propionate/salmeterol 113/14 mcg, LS mean change of 0.271 L at 12 weeks; fluticasone propionate/salmeterol 232/14 mcg, LS mean change of 0.272 L at 12 weeks) compared with fluticasone propionate 113 mcg (LS mean change of 0.119 L at 12 weeks), fluticasone propionate 232 mcg (LS mean change of 0.179 L at 12 weeks), and placebo (LS mean change of -0.004 L at 12 weeks). The estimated mean differences between fluticasone propionate 113 mcg and fluticasone propionate 232 mcg compared to placebo were 0.123 L (95% CI, 0.038 to 0.208) and 0.183 L (95% CI, 0.098 to 0.268), respectively. The estimated mean differences between fluticasone propionate/salmeterol 113/14 mcg and fluticasone propionate/salmeterol 232/14 mcg compared to placebo were 0.274 L (95% CI, 0.189 to 0.36) and 0.276 L (95% CI, 0.191 to 0.361), respectively. The estimated mean difference between fluticasone propionate/salmeterol 232/14 mcg and fluticasone propionate 232 mcg was 0.093 L (95% CI, 0.009 to 0.178). The estimated mean difference between fluticasone propionate/salmeterol 113/14 mcg and fluticasone propionate 113 mcg was 0.152 L (95% CI, 0.066 to 0.237).

A multicenter, randomized, double-blind, placebo-controlled trial evaluated the safety and effectiveness of fluticasone propionate in 841 patients 4 to 11 years of age with persistent asthma treated with a stable asthma regimen (e.g., ICS, ICS/LABA, leukotriene modifier; all other than a SABA alone).[240] Patients were required to have a Childhood Asthma Control Test (C-ACT) score ≤ 19 and then entered a run-in period of 14 to 30 days in which they discontinued all non-study drugs. They were randomized 1:1:1:1 to fluticasone propionate 30 mcg twice daily, fluticasone 55 mcg twice daily, fluticasone propionate/salmeterol twice daily, or placebo. At week 12, the estimated mean differences in percent predicted FEV_1 ($ppFEV_1$) between the 30 mcg and 55 mcg doses versus placebo were 6% predicted (95% CI, 3.2 to 8.8) and 7% (95% CI, 4.1 to 9.8), respectively.

While the ArmonAir Respiclick product is no longer marketed, its clinical data (as described above) were used to support the approval of the ArmonAir Digihaler device.[241]

fluticasone propionate (Flovent Diskus) versus salmeterol (Serevent) versus fluticasone propionate/salmeterol (Advair)

A 12-week, randomized, double-blind study was conducted in patients 12 years and older (n=267) with persistent asthma who were symptomatic while taking as-needed, short-acting $beta_2$-agonists (SABA)

alone.[242] Treatments were administered twice daily via the fluticasone propionate/salmeterol diskus device: salmeterol 50 mcg; low-dose fluticasone propionate 100 mcg; or fluticasone propionate 100 mcg with salmeterol 50 mcg. At endpoint, fluticasone propionate/salmeterol were significantly (p≤0.02) more effective than the individual agents used alone in improving morning and evening PEF rate and asthma symptoms. In addition, fluticasone and salmeterol effectively reduced rescue albuterol use (p≤0.04).

fluticasone propionate/salmeterol (Advair) versus budesonide/formoterol (Symbicort)

A multicenter, parallel group, double-blind, double-dummy, randomized 24-week study was designed to compare the efficacy of salmeterol/fluticasone propionate combination 50/250 mcg 1 inhalation twice daily with formoterol/budesonide combination 6/200 mcg 2 inhalations twice daily in patients (n=1,391) with persistent asthma, currently receiving 1,000 to 2,000 mcg/day of ICS.[243] The primary endpoint, mean rate of all exacerbations over 24 weeks, was similar in both treatment groups (p=0.571). A reduction in the rate of exacerbations over time was observed in both treatment groups. Overall, there was a 30% lower annual rate of moderate/severe exacerbations in the salmeterol/fluticasone propionate group compared with the formoterol/budesonide group (95% CI, 0 to 49; 52% reduction versus 1% increase; p=0.059). Similar improvements in lung function, asthma symptoms, and rescue medication usage were seen with both treatments and both were well tolerated.

fluticasone step-up therapy in patients self-identifying as of African descent

Two randomized, double-blind trials assessed the efficacy of step-up therapy in patients self-identifying as of African descent and with asthma that was inadequately controlled with low-dose ICS (Trial 1: age ≥ 12 years, n=294; Trial 2: 5 to 11 years of age, n=280).[244] Various modifications of therapy were assessed, including the addition of salmeterol to fluticasone, increasing the dose of fluticasone by 2.5-fold, increasing the dose of fluticasone by 2.5-fold and adding salmeterol, and increasing the dose of fluticasone by 5-fold in adults and adolescents and increasing the dose of fluticasone by 2-fold, increasing the dose of fluticasone by 2-fold and adding salmeterol, increasing the dose of fluticasone by 5-fold, and increasing the dose of fluticasone by 5-fold and adding salmeterol in children. Overall, increasing the dose of fluticasone demonstrated an increased response in children, while the addition of salmeterol generally provided a greater response in adolescents and adults. Degree of African ancestry and baseline biomarkers did not predict response to treatment.

fluticasone furoate/umeclidinium/vilanterol (Trelegy Ellipta) versus fluticasone furoate/vilanterol (Breo Ellipta)

The phase 3, multinational, double-blind, randomized, parallel group CAPTAIN trial compared the efficacy of fluticasone furoate/umeclidinium plus vilanterol (triple therapy) to fluticasone furoate/vilanterol alone in patients ≥ 18 years of age with inadequately controlled asthma despite use of an ICS/LABA combination and with an FEV_1 of 30% to < 85% predicted normal (n=2,439).[245] Included patients were randomized 1:1:1:1:1:1 to once-daily inhaled fluticasone furoate/vilanterol DPI 100/25 mcg or 200/25 mcg or to once-daily inhaled fluticasone furoate/umeclidinium plus vilanterol DPI 100/31.25/25 mcg, 100/62.5/25 mcg, 200/31.25/25 mcg, or 200/62.5/25 mcg. The primary outcome was the change from baseline in trough FEV_1 at week 24. Secondary endpoints included annualized moderate and/or severe asthma exacerbation rate, 3-hour post-dose FEV_1, SGRQ score, and ACQ scores at week 24. At baseline, the mean age was 53.2 years (SD, 13.1) and 38% were men. At 24 weeks, the difference in least squares mean improvement in FEV_1 from baseline was 110 mL (95% CI,

66 to 153; p<0.0001) for triple therapy 100/62.5/25 mcg versus the fluticasone furoate/umeclidinium 100/25 mcg and 92 mL (95% CI, 49 to 135; p<0.0001) for triple therapy 200/62.5/25 mcg versus fluticasone furoate/umeclidinium 200/25 mcg. Similarly, at week 24, the difference in least squares mean improvement in FEV_1 from baseline was 96 mL (95% CI, 52 to 139; p<0.0001) for triple therapy 100/31.25/25 mcg versus the fluticasone furoate/umeclidinium 100/25 mcg and 82 mL (95% CI, 39 to 125; p=0.0002) for triple therapy 200/31.25/25 mcg versus fluticasone furoate/umeclidinium 200/25 mcg. Three-hour post-dose FEV_1 results supported these findings. Comparisons for exacerbation rates and SGRQ total scores between groups were not statistically significant. Small differences were seen in the ACQ. Adverse events, including serious adverse events, were similar between groups; however, 1 of 3 total deaths (pulmonary embolism) in the trial occurred in the triple therapy 100/31.25/25 mcg group and was associated with study drug. Notably, only the 100/62.5/25 mcg and 200/62.5/25 mcg triple therapy formulations are approved in the US.

mometasone furoate (Asmanex Twisthaler) versus budesonide (Pulmicort) versus placebo

An 8-week, multicenter, placebo-controlled, double-blind, double-dummy study was conducted in 262 patients (12 years of age or older) with moderate persistent asthma to compare the safety and efficacy of once daily mometasone to budesonide and placebo.[246] Patients were randomized to once daily morning treatment with mometasone 440 mcg, low-dose budesonide 400 mcg, or placebo. The primary efficacy endpoint was percent change in FEV_1 from baseline to the final evaluable visit. At endpoint, the FEV_1 was significantly greater (p<0.01) in the mometasone group (8.9%) than both the budesonide group (2.1%) and placebo group (-3.9%). Secondary efficacy variables including morning and evening PEF rates, albuterol use, percentage of asthma symptom-free days, and physician-evaluated response to therapy were also significantly improved at endpoint in the mometasone group compared with both the placebo and budesonide groups (p<0.05). Both active treatments were well tolerated.

mometasone furoate (Asmanex Twisthaler) versus placebo

The efficacy and safety of mometasone for the treatment of children ages 4 to 11 years were established in three, 12-week, double-blind, parallel-group, randomized, placebo-controlled trials (n=630).[247]

mometasone furoate HFA (Asmanex HFA) versus placebo

The safety and efficacy of mometasone HFA for the treatment of children ages 5 to 11 years were demonstrated in a 12-week, multicenter, randomized, double-blind, placebo-controlled trial (n=583).[248]

mometasone (Asmanex) versus tiotropium (Spiriva Respimat) versus placebo

A 42-week, multicenter, double-blind, randomized, crossover trial compared the efficacy of inhaled mometasone, tiotropium, and placebo in 295 patients ≥ 12 years of age with mild, persistent asthma.[249] Patients were categorized based on their sputum eosinophil level (< 2% [n=221] or ≥ 2% [n=74]). Response, defined by a hierarchical composite of treatment failure, asthma control days, and FEV_1, was the primary endpoint. Patients with a low eosinophil level (< 2%) comprises 73% of the participants, but no significant difference was found between active treatment groups and placebo in this population. A significant difference favoring mometasone was found in those with high eosinophil levels (≥ 2%) compared to placebo (74% [95% CI, 60 to 86] versus 26% [95% CI, 14 to 40]), but no

difference was found when tiotropium was compared to placebo in this population (57% [95% CI, 41 to 72] versus 43% [95% CI, 28 to 59]).

mometasone/formoterol (Dulera) versus mometasone (Asmanex HFA) versus formoterol (Foradil) versus placebo

A 26-week, placebo-controlled trial evaluated 781 patients 12 years of age and older with persistent asthma that were not well controlled on medium doses of ICS.[250] The study compared mometasone/formoterol 100/5 mcg, mometasone furoate 100 mcg, formoterol fumarate 5 mcg and placebo; each administered as 2 inhalations twice daily. All other maintenance therapies were discontinued. The $FEV_{1AUC\ (0\text{-}12hr)}$ was assessed as a co-primary efficacy endpoint to evaluate the contribution of the formoterol component. Patients receiving the combination mometasone/formoterol had significantly higher increases from baseline at week 12 in mean $FEV_{1AUC\ (0\text{-}12\ hr)}$ compared to mometasone furoate and placebo (both $p<0.001$). These differences were maintained through week 26. Clinical deterioration in asthma or reductions in lung function was another primary endpoint to evaluate the contribution of mometasone furoate. Deteriorations in asthma were defined as any of the following: a 20% decrease in FEV_1; a 30% decrease in PEF on 2 or more consecutive days; emergency treatment, hospitalization, or treatment with systemic corticosteroids or other asthma medications not allowed per protocol. Fewer patients who received the combination mometasone/formoterol (30%) reported an event compared to patients who received formoterol (54%) ($p<0.001$).

mometasone/formoterol (Dulera) versus mometasone (Asmanex HFA) versus formoterol (Foradil) versus placebo

A 12-week, double-blind trial evaluated 728 patients ages 12 years and older with persistent asthma that were uncontrolled on high dose ICS.[251] This study compared mometasone/formoterol 200/5 mcg with mometasone/formoterol 100/5 mcg and mometasone furoate 200 mcg, each administered as 2 inhalations twice daily by MDIs. All other maintenance therapies were discontinued. Patients receiving either mometasone/formoterol dosages had significantly greater increases from baseline at day 1 in mean $FEV_{1AUC\ (0\text{-}12\ hr)}$ compared to mometasone furoate. The difference was maintained over 12 weeks of therapy. Mean change in trough FEV_1 from baseline to week 12 was also assessed to evaluate the relative contribution of mometasone furoate to the combination product. A greater numerical increase in the mean trough FEV_1 was observed for the higher strength mometasone/formoterol compared to the lower strength mometasone/formoterol and mometasone monotherapy. Clinical deterioration in asthma or reduction in lung function was assessed as an additional endpoint. Fewer patients who received either strength mometasone/formoterol (12% for each group) compared to mometasone furoate (18%) alone reported an event.

mometasone/formoterol (Dulera) versus mometasone monotherapy

The efficacy and safety of mometasone/formoterol in children ages 5 to 11 years with asthma was demonstrated in a multicenter, randomized trial that compared mometasone/formoterol to mometasone furoate MDI (n=181).[252] Participants receiving the combination product demonstrated a statistically significant change from baseline to week 12 in percent predicted FEV_1 compared to mometasone furoate monotherapy.

mometasone/formoterol (Dulera) versus mometasone monotherapy

A 26-week double-blind, randomized control trial compared the efficacy of mometasone/formoterol to mometasone furoate in 11,729 patients ≥ 12 years of age with asthma.[253] At 26 weeks, the combination product demonstrated noninferiority to mometasone monotherapy in the composite outcome of serious asthma-related events (adjudicated hospitalization, intubation, and death) as assessed by a blinded committee (hazard ratio, 1.22; 95% CI, 0.76 to 1.94). In addition, the hazard ratio of the time to first asthma exacerbation, which was defined as clinical deterioration of asthma associated with systemic corticosteroid use for ≥ 3 consecutive days (or ≥ 1 depot injectable), emergency department visits < 24 hours requiring systemic corticosteroid, or hospital stays of ≥ 24 hours, was 0.89 (95% CI, 0.8 to 0.98); however, this difference was driven primarily by a reduction in systemic corticosteroid use (87% of cases).

COPD

budesonide/formoterol (Symbicort) versus formoterol (Foradil)

Two studies have demonstrated the efficacy of budesonide/formoterol compared to formoterol alone on COPD exacerbation.[254] In both trials, patients were randomized to 160/4.5 or 4.5 mcg, respectively, administered as 2 inhalations twice daily for either 6 months (study 1; n=1,219; exacerbations defined as worsening of ≥ 2 major symptoms [dyspnea, sputum volume, sputum color/purulence] or 1 major symptom with ≥ 1 minor symptom) or 12 months (study 2; n=811; exacerbations defined as requiring oral steroids and/or hospitalization). In study 3, the rate ratio [RR] of budesonide/formoterol compared to formoterol was 0.74 (95% CI, 0.61 to 0.91). In study 4, the RR of budesonide/formoterol compared to formoterol was 0.65 (95% CI, 0.53 to 0.8).

budesonide/formoterol (Symbicort) versus budesonide (Pulmicort) versus formoterol (Foradil) versus placebo

In a 12-month, randomized, double-blind, placebo-controlled, parallel-group study in 812 adults (mean age 64 years, mean FEV_1 36%), patients with moderate to severe COPD received 2 inhalations twice daily of either budesonide/formoterol 160/4.5 mcg, budesonide 200 mcg, formoterol 4.5 mcg, or placebo.[255] Severe exacerbations and FEV_1 were the primary variables. Other variables including peak expiratory flow (PEF), COPD symptoms, health-related quality of life (HRQL), mild exacerbations, use of reliever $beta_2$-agonist, and safety variables were recorded. Budesonide/formoterol reduced the mean number of severe exacerbations per patient per year by 24% versus placebo and 23% versus formoterol. For patients receiving budesonide/formoterol, FEV_1 increased by 15% versus placebo and 9% versus budesonide. Morning PEF improved significantly on day 1 versus placebo and budesonide. After 1 week, morning PEF was improved versus placebo, budesonide, and formoterol. Improvements in morning and evening PEF versus comparators were maintained over 12 months. Budesonide/formoterol decreased all symptom scores and use of reliever $beta_2$-agonists significantly versus placebo and budesonide, and improved HRQL versus placebo. All treatments were well tolerated.

The SHINE trial was a 6-month, double-blind, multicenter trial that evaluated the efficacy and tolerability of budesonide/formoterol in 1,704 patients ages 40 years and older with moderate to very severe COPD.[256] Patients were randomized to receive twice daily treatment with 2 inhalations of budesonide/formoterol 160/4.5 mcg or 80/4.5 mcg, budesonide 160 mcg + formoterol 4.5 mcg, budesonide 160 mcg, formoterol 4.5 mcg, or placebo. Primary outcomes measures included pre-dose

and 1-hour post-dose FEV_1 over the 6-month treatment period. Budesonide/formoterol 160/4.5 mcg twice a day (320/9 mcg) improved both pre-dose and 1-hour post-dose FEV_1 compared to either of the components alone or to placebo ($p \leq 0.039$ for all). At the lower dose of 80/4.5 mcg twice a day (160/9 mcg), there was significantly greater improvement in pre-dose FEV_1 and 1-hour post-dose FEV_1 compared with budesonide and placebo ($p \leq 0.002$ for all), but not compared to formoterol. Budesonide/formoterol had a safety profile comparable with that of the mono components and placebo.

budesonide/formoterol (Symbicort) versus fluticasone propionate/salmeterol (Advair) versus salbutamol versus placebo

In a double-blind, double-dummy, crossover study, 90 patients (age 40 years and older; FEV_1 30% to 70%) were randomized to a single dose (2 inhalations) of budesonide/formoterol 160/4.5 mcg, fluticasone propionate/salmeterol 250/25 mcg, salbutamol 100 mcg, or placebo on 4 visits.[257] Outside the United States albuterol is known as salbutamol. The primary endpoint was change in FEV_1 5 minutes after drug inhalation; secondary endpoints included inspiratory capacity (IC) and perception of onset of effect. Budesonide/formoterol significantly improved FEV_1 at 5 minutes compared with placebo ($p<0.0001$) and fluticasone propionate/salmeterol ($p=0.0001$). Significant differences were first observed at 3 minutes. Onset of effect was similar with budesonide/formoterol and salbutamol. Improvements in FEV_1 following active treatments were superior to placebo after 180 minutes (all $p<0.0001$); both combinations were better than salbutamol at maintaining FEV_1 improvements ($p \leq 0.0001$) at 180 minutes. Active treatments improved IC at 15 and 185 minutes compared with placebo ($p<0.0001$). Maximal IC was greater with budesonide/formoterol than fluticasone propionate/salmeterol ($p=0.0184$) at 65 minutes. Patients reported a positive response to the perceptions of the onset of effect question shortly after receiving active treatments (median time to onset was 5 minutes for active treatments versus 20 minutes for placebo), with no significant difference between active treatments. Budesonide/formoterol has an onset of bronchodilatory effect in patients with COPD and reversible airway obstruction that is faster than fluticasone propionate/salmeterol and similar to salbutamol.

budesonide/glycopyrrolate/formoterol fumarate (Breztri Aerosphere) versus glycopyrrolate/formoterol fumarate (Bevespi Aerosphere) versus budesonide/formoterol fumarate (Symbicort)

The double-blind, multicenter, multinational, phase 3 randomized controlled ETHOS trial established the efficacy and safety of budesonide/glycopyrrolate/formoterol fumarate for the treatment of COPD.[258] The 52-week study included 8,588 patients between the ages of 40 to 80 years with moderate to very severe COPD who remained symptomatic despite ≥ 2 COPD maintenance therapies and had experienced ≥ 1 exacerbations throughout the year preceding study inclusion.[259] Patients were randomized 1:1:1:1 to receive either fixed-dose triple therapy with budesonide/glycopyrrolate/formoterol fumarate 320/18/9.6 mcg or 160/18/9.6 mcg twice daily, fixed-dose dual therapy with glycopyrrolate/formoterol fumarate 18/9.6 mcg twice daily, or fixed-dose budesonide/formoterol fumarate 320/9.6 mcg twice daily. The primary endpoint was the annual rate of moderate or severe COPD exacerbations; a key secondary endpoint was the risk of death from any cause. At 52 weeks, annual rates of moderate or severe exacerbations were significantly reduced by 24% in the budesonide/glycopyrrolate/formoterol fumarate 320/18/9.6 mcg group compared to the glycopyrrolate/formoterol fumarate group (RR, 0.76; 95% CI, 0.69 to 0.83; $p<0.001$). A statistically

significant reduction in annual exacerbation rates of 13% favoring budesonide/glycopyrrolate/formoterol fumarate 320/18/9.6 mcg over budesonide/formoterol fumarate was also demonstrated (RR, 0.87; 95% CI, 0.79 to 0.95; p=0.003). Additionally, treatment with budesonide/glycopyrrolate/formoterol fumarate 320/18/9.6 mcg significantly reduced the risk of all-cause death by 46% versus treatment with glycopyrrolate/formoterol fumarate (HR, 0.54; 95% CI, 0.34 to 0.87). The risk of all-cause death for the budesonide/glycopyrrolate/formoterol fumarate 320/18/9.6 mcg group versus the budesonide/formoterol fumarate group was not statistically significant (HR, 0.78; 95% CI, 0.47 to 1.3). The budesonide/glycopyrrolate/formoterol fumarate 160/18/9.6 mcg dose is not FDA-approved for COPD.

Additional efficacy data for budesonide/glycopyrrolate/formoterol fumarate comes from the double-blind, multicenter, multinational, phase 3 randomized controlled trial KRONOS trial, a 24-week trial that included 1,902 patients ages 40 to 80 years who remained symptomatic despite ≥ 2 COPD maintenance therapies.[260] Patients were randomized 2:2:1:1 to receive budesonide/glycopyrrolate/formoterol fumarate 320/18/9.6 mcg twice daily, glycopyrrolate/formoterol fumarate 18/9.6 mcg twice daily, budesonide/formoterol fumarate 320/9.6 mcg twice daily, or open-label budesonide/formoterol fumarate 400/12 mcg twice daily. The primary endpoints were the change in FEV_1 area under the curve from 0 to 4 hours (AUC_{0-4}) at week 24 and the change in baseline, pre-dose, morning trough FEV_1 values at week 24. Results demonstrated that budesonide/glycopyrrolate/formoterol fumarate produced significant increases in FEV_1 AUC_{0-4} compared to budesonide/formoterol fumarate (least squares mean difference [LSMD], 104 mL; 95% CI, 77 to 131; p<0.0001) and budesonide/formoterol fumarate (LSMD, 91 mL; 95% CI, 64 to 117; p<0.0001). A significant difference was not seen in the comparison against glycopyrrolate/formoterol fumarate. Additionally, budesonide/glycopyrrolate/formoterol fumarate produced statistically significant improvements in changes from baseline morning trough FEV_1 compared to budesonide/formoterol fumarate (LSMD, 74 mL; 95% CI, 52 to 95; p<0.0001). Results were non-inferior to budesonide/formoterol fumarate and no statistical difference was seen compared to glycopyrrolate/formoterol fumarate.

fluticasone propionate (Flovent) versus salmeterol (Serevent) versus fluticasone propionate/salmeterol (Advair)

In a double-blind, parallel-group, placebo-controlled study, 1,465 patients with COPD were randomized to receive salmeterol 50 mcg twice daily, high-dose fluticasone 500 mcg twice daily, fluticasone propionate/salmeterol 500/50 mcg twice daily, or placebo.[261] After 12 months, all active treatments improved lung function, symptoms, and health status and reduced use of rescue medication and frequency of exacerbations. Combination therapy improved pretreatment FEV_1 significantly more than did placebo (treatment difference 133 mL; 95% CI, 105 to 161; p<0.0001), salmeterol (73 mL; 95% CI, 46 to 101; p<0.0001), or fluticasone alone (95 mL; 95% CI, 67 to 122; p<0.0001). Combination treatment produced a clinically significant improvement in health status and the greatest reduction in daily symptoms. All treatments were well tolerated with no difference in the frequency of adverse events, bruising, or clinically significant falls in serum cortisol concentration.

In 2 randomized, double-blind, parallel-group, multinational, 1-year trials, a total of 3,255 COPD patients with a history of exacerbations received once daily treatment with vilanterol alone or combined with various doses of fluticasone furoate.[262] Results from these studies are presented individually and in a pooled analysis. Patients ≥ 40 years of age, with COPD and a history of smoking of 10 or more pack-years, a ratio FEV_1 to FVC of ≤ 0.70 after bronchodilators (and an FEV_1 of ≤ 70% of

predicted) and a documented history of at least 1 exacerbation in the previous year were eligible. Study 1 enrolled 1,622 patients; study 2 enrolled 1,633 patients. After a 4-week run-in period of treatment with open-label fluticasone propionate (250 mcg)/salmeterol (50 mcg) twice daily to establish a stable baseline and adherence, patients were randomized 1:1:1:1 to 25 mcg vilanterol alone or 25 mcg vilanterol combined with either 50 mcg, 100 mcg, or 200 mcg fluticasone furoate once daily in the morning. The primary outcome measure was the yearly rate of moderate and severe exacerbations. Moderate exacerbation was defined as worsening symptoms for ≥ 2 days requiring treatment with oral corticosteroids, antibiotics or both. Severe exacerbations were similar, but patients required hospitalization. In Study 1, the difference in yearly rate of exacerbations between the fluticasone furoate/vilanterol 200/25 mcg group and the vilanterol alone group did not reach significance (least squares mean yearly rate 0.9 fluticasone/vilanterol versus 1.05 vilanterol; p=0.1093). The study design employed a statistical hierarchical testing procedure so comparisons of other dosage groups could not be used to infer significance. In Study 2, the differences in yearly rate of exacerbations between all fluticasone furoate/vilanterol groups and the vilanterol alone group were significant. In the 100 mcg fluticasone furoate/25 mcg vilanterol group (approved dose), the least squares mean yearly rate was 0.9 compared to 1.14 in the vilanterol alone group (p=0.0244). In the pooled analysis, the difference between all doses of fluticasone furoate/vilanterol and vilanterol alone was significant and the combination of fluticasone 100 mcg and vilanterol 25 mcg significantly reduced the yearly rate of moderate and severe exacerbations compared to vilanterol alone (0.81 versus 1.11). In these trials, the difference in exacerbation rate was driven primarily in a reduction in moderate exacerbations; few severe exacerbations occurred and the difference between groups in severe exacerbation rate was not significant. The incidence of fractures and pneumonia was higher with fluticasone furoate/vilanterol than with vilanterol alone. Fractures were reported in 19 (100 mcg fluticasone furoate/25 mcg vilanterol) patients compared to 8 vilanterol patients. Overall, pneumonia occurred at about twice the rate in the fluticasone furoate/vilanterol groups compared to the vilanterol group (100 mcg fluticasone furoate/25 mcg vilanterol: 51 events versus 25 mcg vilanterol: 27 events). One case of pneumonia in the group receiving fluticasone furoate/vilanterol 100/25 mcg and 7 cases of pneumonia in the group receiving fluticasone furoate/vilanterol 200/25 mcg were fatal compared to none in the vilanterol or fluticasone furoate monotherapy groups.

fluticasone furoate/vilanterol (Breo Ellipta) versus fluticasone furoate (Advair Diskus) and vilanterol

SUMMIT: A multicenter, multinational, randomized, double-blind trial compared the efficacy of fluticasone furoate/vilanterol 100/25 mcg to fluticasone furoate 100 mcg and vilanterol 25 mcg alone in 16,590 adults with COPD (FEV_1 50% to 70% predicted).[263] All-cause mortality, the primary outcome, was not statistically different when each component was compared to placebo (HR, 0.88 [95% CI, 0.74 to 1.04]; HR, 0.91 [95% CI, 0.77 to 1.08]; and HR, 0.96 [95% CI, 0.81 to 1.14] for the combination, fluticasone only, and vilanterol only, respectively). Likewise, no difference was found in the composite of cardiovascular events. However, all active treatment groups reduced the rate of moderate and severe exacerbations. The on-treatment rate of FEV_1 decline was 46 mL/year with placebo, 38 mL/year with fluticasone furoate (difference versus placebo, 8 mL; 95% CI, 1 to 14), 47 mL/year with vilanterol (difference versus placebo, -2 mL; 95% CI, -8 to 5), and 38 mL/year with the combination (difference versus placebo, 8 mL; 95% CI, 1 to 15).

fluticasone furoate/vilanterol (Breo Ellipta) versus fluticasone propionate/salmeterol (Advair Diskus)

Three randomized, double-blind, double-dummy, parallel-group, comparative multicenter studies compared the efficacy and safety of fluticasone furoate/vilanterol 100/25 mcg once daily, or fluticasone propionate/salmeterol 250/50 mcg twice daily for 12 weeks in 1,858 patients with moderate to very severe COPD.[264] The primary endpoint of each study was change from baseline trough in 0–24 hour weighted mean FEV_1 ($wmFEV_1$) on day 84, using intent-to-treat population. Improvements in 0–24 hour $wmFEV_1$ were seen with both fluticasone furoate/vilanterol 100/25 mcg and fluticasone propionate/salmeterol 250/50 mcg compared with baseline trough in all 3 studies and in the pooled analysis. In study 1, the treatment difference between fluticasone furoate/vilanterol and fluticasone propionate/salmeterol was statistically significant (80 mL, p<0.001); however, in studies 2 and 3, the difference was not statistically or clinically significant (29 mL p=0.267; 25 mL, p=0.137, respectively). In the pooled analysis of all 3 studies, there was a small statistically significant but clinically insignificant treatment difference of 41 mL (p<0.001); this is below the suggested minimal clinically important difference for lung function. Both treatments were well tolerated with generally similar safety profiles.

fluticasone furoate/umeclidinium/vilanterol (Trelegy Ellipta) as assessed via umeclidinium (Incruse® Ellipta®) plus fluticasone furoate/vilanterol (Breo Ellipta) versus placebo plus fluticasone furoate/vilanterol (Breo Ellipta)

The efficacy of fluticasone furoate/umeclidinium/vilanterol (Trelegy Ellipta) is based primarily on the coadministration of its components in 2 multicenter, randomized, double-blind, parallel-group, 12-week confirmatory trials (Trial 1, n=206; Trial 2, n=206).[265,266] In both trials, patients were randomized to either umeclidinium plus fluticasone furoate/vilanterol or placebo plus fluticasone furoate/vilanterol. The primary endpoint was the change from baseline in trough (predose) FEV_1) at day 85 (defined as the mean of the FEV_1 values obtained at 23 and 24 hours following the previous dose on day 84). Combined baseline demographics included a mean age of 64 years, 92% Caucasian, 66% male, an average smoking history of 48 pack-years, and 50% current smokers. At screening, the mean postbronchodilator percent predicted FEV_1 was 46% (range, 14 to 76) and the mean postbronchodilator FEV_1/FVC ratio was 0.48 (range, 0.21 to 0.7). In Trial 1, the addition of umeclidinium to fluticasone furoate/vilanterol demonstrated a statistically significant increase in mean trough FEV_1 versus placebo (124 mL; 95% CI, 93 to 154). In Trial 2, a similar result was found (mean trough FEV_1, 122 mL; 95% CI, 91 to 152). Similar results were demonstrated for the secondary endpoint of the weighted mean FEV_1 (0 to 6 hours postdose) on day 84 in both trials (Trial 1: 153 mL [95% CI, 118 to 187]; Trial 2: 147 mL [95% CI, 114 to 179]). Less average rescue medication was used with the addition of umeclidinium in both trials and a statistically significant difference was found in health-related quality of life (as measured by the SGRQ) in Trial 2 but not in Trial 1. The effect on exacerbations was not measured in clinical trials comparing the addition of umeclidinium or placebo to fluticasone furoate/vilanterol. Notably, a higher dose of umeclidinium was also assessed in the clinical trial; however, a combination product containing this strength is not available.

fluticasone furoate/umeclidinium/vilanterol (Trelegy Ellipta) versus fluticasone furoate/vilanterol (Breo Ellipta) and umeclidinium/vilanterol (Anoro® Ellipta®)

The IMPACT study, a 52-week, multicenter, randomized, double-blind, parallel-group trial, compared the efficacy of fluticasone furoate/umeclidinium/vilanterol (Trelegy Ellipta) with fixed-dose fluticasone furoate/vilanterol and umeclidinium/vilanterol in 10,355 patients with COPD and a history of ≥ 1

moderate or severe exacerbations in the prior year. Included patients were randomized 2:2:1 to receive fluticasone furoate/umeclidinium/vilanterol 100/62.5/25 mcg, fluticasone furoate/vilanterol 100/25 mcg, or umeclidinium/vilanterol 62.5/25 mcg once daily.[267,268] The primary endpoint was the annual rate of on-treatment moderate and severe exacerbations, defined as ≥ 2 major symptoms (e.g., dyspnea, sputum volume, sputum purulence) or worsening of a 1 major symptom combined with ≥ 1 minor symptom (e.g., sore throat, colds, fever without other cause, increased cough or wheeze) that required systemic corticosteroids and/or antibiotics (moderate) or resulted in hospitalization or death (severe). The mean annual rates of exacerbations per year were 0.91, 1.07, and 1.21 in the fluticasone furoate/umeclidinium/vilanterol, fluticasone furoate/vilanterol, and umeclidinium/vilanterol groups, respectively. This equated to a rate ratio of 0.85 (95% CI, 0.8 to 0.9) or 15% decrease (95% CI, 10 to 20) in exacerbation rate of fluticasone furoate/umeclidinium/vilanterol versus fluticasone furoate/vilanterol (p<0.001) and a rate ratio of 0.75 (95% CI, 0.7 to 0.81) or 25% decrease (95% CI, 19 to 30) in exacerbation rate of fluticasone furoate/umeclidinium/vilanterol versus umeclidinium/vilanterol (p<0.001). A decreased risk of time to first exacerbation was also statistically significant between the groups, favoring fluticasone furoate/umeclidinium/vilanterol over its comparators (p<0.001 for both comparisons). A statistically significant difference was also seen favoring fluticasone furoate/umeclidinium/vilanterol over umeclidinium/vilanterol in annual rate of severe exacerbations (p<0.001); however, the difference was not statistically significant between fluticasone furoate/umeclidinium/vilanterol and fluticasone furoate/vilanterol (p=0.064). After 52 weeks of treatment, the mean change from baseline in trough FEV_1 was 97 mL for fluticasone furoate/umeclidinium/vilanterol versus with fluticasone furoate/vilanterol (95% CI, 85 to 109; p<0.001) and 54 mL for fluticasone furoate/umeclidinium/vilanterol versus with umeclidinium/vilanterol (95% CI, 39 to 69; p<0.001). Similar results were seen at all time points assessed during the 52-week trial.

fluticasone propionate/salmeterol (Advair) versus umeclidinium/vilanterol (Anoro Ellipta)

Two 12-week, multicenter, double-blind, parallel-group, double-dummy, randomized trials compared the efficacy of fluticasone/salmeterol to umeclidinium/vilanterol in patients with moderate to severe COPD (Study 1, n=706; Study 2, n=697).[269] Patients with infrequent exacerbations were randomized 1:1 to twice-daily fluticasone/salmeterol 250/50 mcg or once-daily umeclidinium/vilanterol 62.5/25 mcg. Key endpoints included 0 to 24 hour mean FEV_1 on Day 84 (primary), trough FEV_1 on day 85, dyspnea, and change in SGRQ score. Umeclidinium/vilanterol demonstrated significant improvement in lung function compared to fluticasone/salmeterol; the difference in $FEV_{1(0\text{-}24)}$ on day 84 was 74 mL (95% CI, 38 to 110) in Study 1 and 101 mL (95% CI, 63 to 139 in Study 2; p<0.001 for both). Trough FEV_1 values were also superior with umeclidinium/vilanterol in both trials; however, no difference was seen between groups in dyspnea ratings or SGRQ improvement. Adverse event rates were similar between groups.

Clinical Trials: Safety

There is concern that prolonged treatment with high doses of ICS may have a detrimental effect on bone mineral density (BMD), cause ocular toxicity, suppress the adrenal/pituitary axis, and inhibit vertical growth, among other adverse effects.

budesonide (Pulmicort Respules) versus reference treatments in children or adults

Pooled safety data from budesonide inhalation suspension studies (n=2,356) found there were small differences in short-term growth velocity between children who received budesonide inhalation suspension and those who received reference treatment in 2 of 5 trials that evaluated this variable.[270]

No posterior subcapsular cataracts were reported in any study. The frequencies of oropharyngeal events and infection with budesonide inhalation suspension were comparable with those of reference treatments. No increased risk of varicella or upper respiratory tract infection was apparent, and budesonide inhalation suspension did not cause significant adrenal suppression in studies assessing this variable.

Data from the inhaled Steroid Treatment as Regular Therapy in Early Asthma (START) study evaluated the safety of once daily budesonide use over 3 years in patients aged 5 to 66 years with mild, persistent asthma (n=7,221).[271] The most commonly reported events included respiratory infections, rhinitis, pharyngitis, bronchitis, viral infections, and sinusitis. Fewer asthma-related, serious adverse events were reported with budesonide (2.2%) compared with placebo (3.8%). Oral candidiasis was reported more frequently with budesonide (1.2%) than with placebo (0.5%).

A further analysis of the START trial was conducted to determine whether severe asthma exacerbations are associated with a persistent decline in lung function.[272] This study was a 3-year, randomized, double-blind trial that enrolled 7,165 patients (5 to 66 years of age) with persistent asthma. There were 315 patients who experienced at least 1 severe asthma exacerbation, of which 305 were analyzable, 190 in the placebo group and 115 in the budesonide group. In the placebo group, the change in post-bronchodilator FEV_1 percent predicted from baseline to the end of the study, in patients who did or did not experience a severe exacerbation was -6.44% and -2.43%, respectively ($p<0.001$). A significant difference was seen in both children and in adults, but not in adolescents. In the budesonide group, the change in the post-bronchodilator FEV_1 percent predicted in patients who did or did not experience a severe exacerbation was -2.48% and -1.72%, respectively ($p=0.57$). The difference in magnitude of reduction afforded by budesonide, in patients who experienced at least 1 severe asthma-related event compared with those who did not, was statistically significant ($p=0.042$). Severe asthma exacerbations are associated with a more rapid decline in lung function. Treatment with low doses of ICS is associated with an attenuation of the decline.

budesonide (Pulmicort) versus fluticasone propionate (Flovent)

The systemic effects of high-dose budesonide 1,600 mcg/day and high-dose fluticasone 1,500 mcg/day were compared in a randomized, double-blind, cross-over study of 60 adult patients with moderate to severe asthma not controlled on high-dose beclomethasone or budesonide.[273] HPA axis suppression of the 2 treatment groups was assessed by morning serum cortisol and 12-hour nocturnal urinary cortisol excretion measured at the end of each treatment period. Neither treatment produced significant suppression of either parameter compared to baselines. The ratio between the AUC serum cortisol measured after fluticasone treatment and after budesonide treatment was 0.99, indicating equivalent effects on the HPA axis. Two exacerbations of acute asthma occurred during budesonide treatment, and none occurred during fluticasone treatment. Both treatments were well tolerated.

fluticasone propionate (Flovent) versus budesonide (Pulmicort) in children

Forty children (age 1 to 3 years) with mild asthma were studied in a 3-way crossover, randomized, placebo-controlled, double-blind trial.[274] Treatment with medium-dose fluticasone 200 mcg twice daily was compared with low-dose budesonide 200 mcg twice daily and placebo, all given via a spacer device. Systemic steroid activity was assessed after 1 and 4 weeks of treatment by measured increase in lower-leg length. The increases in lower-leg length during placebo, budesonide, and fluticasone treatments were 85, 45, and 34 mcm/day, respectively. Compared to placebo, the growth in lower-leg length was significantly reduced from both corticosteroid treatments. The differences between

budesonide and placebo (40 mcm/day) and between fluticasone and placebo (51 mcm/day) were statistically significant. The difference between the 2 active treatment groups, fluticasone and budesonide, was not statistically significant.

fluticasone propionate/salmeterol (Advair) and fluticasone propionate (Flovent) in children

A randomized, multicenter, double-blind, active-controlled, parallel-group study in 203 children with persistent asthma who were symptomatic during ICS therapy were examined to compare the safety of twice daily treatment of inhaled fluticasone/salmeterol with that of fluticasone alone.[275] The subjects received either fluticasone/salmeterol (100/50 mcg) or low-dose fluticasone (100 mcg) alone twice daily for 12 weeks. The results of the study showed that the safety profile of fluticasone/salmeterol was comparable to that of fluticasone alone with the overall incidence of adverse events being 59% for fluticasone/salmeterol and 57% for fluticasone. The changes in heart rate, blood pressure, and laboratory variables were infrequent and similar between both groups, and no patients had clinically significant abnormal electrocardiographic findings during treatment. The incidence of withdrawals within the study due to asthma exacerbations was 2% in the fluticasone/salmeterol group and 5% in the fluticasone group. Therefore, the study concluded that in children with persistent asthma, fluticasone/salmeterol twice daily was well tolerated, with a safety profile similar to that of fluticasone used alone.

Bone Mineral Density and Fracture

Several studies have been performed to evaluate the relative effects of the various agents on bone mass and metabolism.

A multicenter, double-blind, parallel-group study randomized 69 adults with mild to moderate asthma to treatment with medium or high doses of fluticasone propionate or beclomethasone.[276] After 1 year, there was no loss of trabecular or integral bone in the distal radius or tibia in any of the patients.

However, a meta-analysis of included randomized controlled trials (16 trials; n=17,513) of budesonide or fluticasone propionate compared to control treatment for COPD greater than 24 weeks duration and controlled observational studies (7 studies; n=69,000) of ICS associated fracture risk.[277] This study reported a modest but statistically significant increase in risk of fracture with long-term use of fluticasone propionate and budesonide.

Linear Growth

Orally ICS may cause a reduction in growth velocity when administered to children and adolescents.[278] A reduction of growth velocity in children and adolescents may occur as a result of poorly controlled asthma or from use of corticosteroids.

Evidence on growth velocity and height over an extended time period is available from the Childhood Asthma Management Program (CAMP) trial that compared budesonide with nedocromil and placebo in 1,041 children followed for 4 to 6 years.[279] A difference consistent with the above magnitude occurred during the first year of the study. However, in long-term follow up, the difference in growth velocity was not maintained, and all groups had similar growth velocity at the end of treatment. There was still a 1 centimeter difference between the study groups at the end of treatment. A slight difference in bone age suggests the potential for catch-up for the ICS group. A follow-on study with 943 of the original 1,041 children showed a statistically significant reduction of 1.2 cm in mean adult height (95% CI, -1.9 to -0.5) for the budesonide arm as compared to the placebo group (p=0.001).[280] This magnitude

height difference is consistent with the results seen after 2 years of treatment (-1.3 cm; 95% CI, -1.7 cm to -0.9 cm).

An ancillary study of the CAMP trial demonstrated that low-dose budesonide 400 mcg/day over a 3-year period had no effects on HPA axis function in children with mild to moderate asthma.[281] Growth in children taking corticosteroids by any route should be carefully monitored.

Pneumonia Risk

In a prespecified subanalysis of the SUMMIT trial, investigators assessed the adverse pneumonia events in COPD patients with moderate airflow limitation and heightened cardiovascular risk.[282] A total of 15,590 subjects with moderate airflow limitation (50% ≤ FEV_1 ≤ 70% predicted) were randomized double-blind 1:1:1:1 to inhaled once-daily vilanterol 25 mcg, fluticasone furoate 100 mcg, vilanterol 25mcg/fluticasone furoate 100 mcg, or matched placebo. Of the 16,568 patients who received medication in the safety population, there were 1017 pneumonia events reported from 842 subjects. There was a reported incidence of pneumonia in the placebo, vilanterol, fluticasone furoate, and vilanterol/fluticasone furoate of 5%, 5%, 4%, and 6%, respectively. A number of risk factors were identified for pneumonia risk which included body mass index (BMI) ≤ 25 kg/m^2, greater airflow limitation (FEV_1 <60% predicted), and prior exacerbation history. At the conclusion of the trial, it was found that there was not an increase in pneumonia risk in subjects with COPD and moderate airflow limitation and heightened cardiovascular risk.

META-ANALYSES

Asthma

In 2007, a meta-analysis was completed of randomized trials in children and adults comparing fluticasone to either beclomethasone or budesonide in the treatment of chronic asthma.[283] Two reviewers independently assessed articles for inclusion and methodological quality. Seventy-one studies (14,602 participants) representing 74 randomized comparisons met the inclusion criteria. When compared at a fluticasone-to-budesonide or beclomethasone dose ratio of 1:2, fluticasone produced an end of treatment FEV_1 that was not statistically different from budesonide or beclomethasone (change in FEV_1, 0.04 L; 95% CI, 0 to 0.07). There was also a lack of a statistical difference in change from baseline in FEV_1 between the treatment groups (change in FEV_1, 0.01 L; 95% CI, -0.02 to 0.04). In contrast the mean difference in change in morning peak expiratory flow (PEF) from baseline at the end of treatment was statistically significant (change in morning PEF, 7.42 L/min; 95% CI, 4.97 to 9.87). However, there was no significant difference in change in evening PEF. This applied to all drug doses, age groups, and delivery devices. No difference between fluticasone and beclomethasone or budesonide was seen for trial withdrawals. Fluticasone led to fewer symptoms and less rescue medication use. There was a greater likelihood of pharyngitis with fluticasone when compared to budesonide or beclomethasone with no difference in the likelihood of oral candidiasis. Comparing these agents in a dose ratio of 1:1, fluticasone produced a statistically significant difference in end of treatment FEV_1 over both budesonide and beclomethasone (change in FEV_1, 0.04 L; 95% CI, 0.01 to 0.07). Although the change from baseline was not significantly different between the treatments (change in FEV_1, 0.01 L; 95% CI, -0.03 to 0.05). There were also significant mean differences in absolute morning and evening PEFs between treatments and the change from baseline in morning PEF but not for the change from baseline in evening PEF between the treatment groups. The effects on

exacerbations were mixed. There were no significant differences in the incidence of hoarseness, pharyngitis, candidiasis, or cough at the equivalent dose ratio.

In 2010, a meta-analysis was published of randomized, controlled trials (RCTs) that compared the strategy of increasing the daily dose of ICS to continuing the same ICS dose in the home management of asthma exacerbations in children or adults with persistent asthma who receive daily maintenance ICS.[284] Five RCTs (4 parallel-group and 1 cross-over) involving a total of 1,250 patients (28 children and 1,222 adults) with mild to moderate asthma were included. The mean daily baseline ICS dose was 555 mcg (range 200 mcg to 795 mcg) and the mean daily ICS dose achieved following the increase was 1,520 mcg (range 1,000 mcg to 2,075 mcg), in beclomethasone dipropionate equivalents. Three parallel-group studies in adults (2 doubling and 1 quadrupling; mean achieved daily dose of 1,695 mcg with a range of 1,420 to 2,075 mcg), involving 1,080 patients contributed data to the primary outcome. There was no significant reduction in the need for rescue oral corticosteroids when patients were randomized to the increased dose of ICS compared to the stable maintenance dose groups (OR 0.85; 95% CI, 0.58 to 1.26). Statistically, there was no significant difference in the overall risk of non-serious adverse events associated with the increased ICS dose strategy, but the wide confidence interval prevents a firm conclusion. No serious adverse events were reported.

In 2011, a meta-analysis that compared 2 or more doses of ICS in pediatric patients (age 3 to 18 years) with persistent asthma was published to assess the dose-response relationship including benefits and harms of ICS in children with persistent asthma.[285] A Medline search was conducted for articles published between 1950 and August 2009. Main outcomes of this analysis included morning and evening PEF, FEV_1, asthma symptom score, $beta_2$ agonist use, withdrawal because of lack of efficacy, and adverse events. Meta-analyses were performed to compare moderate (300 to 400 mcg daily) with low (≤ 200 mcg daily beclomethasone-equivalent) doses of the ICS. Fourteen RCTs that included 5,768 asthmatic children that evaluated 5 different ICS were included in the analysis. The pooled standardized mean difference from 6 trials revealed a small but statistically significant increase of moderate over low doses in improving FEV_1 (standardized mean difference, 0.11; 95% CI, 0.01 to 0.21) among children with mild-to-moderate asthma. There was no significant difference between 2 doses in terms of other efficacy outcomes. Local adverse events were uncommon, and there was no evidence of dose-response relationship at low-to-moderate doses.

A Cochrane review of 33 RCTs assessing the efficacy and safety of adding a LABA to an ICS in 6,381 children and adolescents with asthma found that the LABA addition did not result in a significant reduction in exacerbation rate requiring systemic corticosteroids (risk ratio [RR], 0.95; 95% CI, 0.7 to 1.28; 12 RCTs; 1,669 children; moderate quality evidence) but did find superiority in improving lung function compared to the same or higher doses of ICS monotherapy (FEV_1, morning PEF, reduction in use of daytime rescue inhalations, and reduction in use of nighttime rescue inhalations).[286] No significant differences were found in adverse effects; however, there was greater growth in the ICS/LABA group compared to a higher ICS monotherapy dose.

Another Cochrane review of 41 studies (n=27,951) assessed the safety of ICS with and without salmeterol (a LABA) in adults and adolescents with asthma.[287] No difference was found in death (odds ratio [OR], 0.8; 95% CI, 0.36 to 1.78) or non-fatal serious adverse events in adults (OR, 1.14; 95% CI, 0.97 to 1.33) or children (OR, 1.04; 95% CI, 0.73 to 1.48) when the combination was compared to ICS alone. Notably, most studies were done with co-formulated fluticasone and salmeterol and the authors conceded that the data was limited by overall numbers and duration of studies. A similar Cochrane review assessed mortality with the use of ICS with and without formoterol in adults and children with

asthma (39 studies; n=39,786).[288] No deaths were reported in any of the 4,035 adolescents and children, but 17 deaths occurred in the 18,645 adults taking ICS/formoterol compared to 13 in the 17,106 adults taking ICS alone (odds ratio, 1.25; 95% CI, 0.61 to 2.56; moderate-certainty evidence). The odds ratio for asthma-related death was 1 (95% CI, 0.87 to 1.16; high-certainty evidence). Thus, the authors concluded that the data did not support an increased risk of mortality with the addition of a LABA to an ICS; however, this risk cannot be completely ruled out.

Using Cochrane methodology, another meta-analysis evaluated the efficacy and safety of combined ICS/beta-agonist for as needed treatment in adults and adolescents (≥ 12 years of age) with mild asthma.[289] Only 6 studies met criteria (n=9,657), 5 were included in the meta-analysis (all budesonide/formoterol with or without another treatment option), and 2 were open label. Four of the studies were large multinational studies of budesonide 200 mcg/formoterol 6 mcg as a DPI. Bias was a risk as 4 trials were funded by the same manufacturer and the open label trials were included. Compared to a beta-agonist alone, the budesonide/formoterol combination reduced exacerbations requiring systemic steroids (OR, 0.45 [95% CI, 0.34 to 0.6]; 2 RCT [n=2,997]; high-certainty evidence) and reduced the risk of asthma-related hospital admission or emergency department or urgent care visit (OR, 0.35 [95% CI, 0.2 to 0.6]; 2 RCT [n=2,997]; low-certainty evidence). Compared to an ICS alone, the budesonide/formoterol combination did not have a significant difference on reducing the need for systemic steroids (OR, 0.79 [95% CI, 0.59 to 1.07]; 4 RCT [n=8,065]; low-certainty evidence) but did reduce the risk of asthma-related hospital admission or emergency department or urgent care visit (OR, 0.63; 95% CI, 0.44 to 0.91; 4 RCT [n=8,065]; low-certainty evidence).

COPD

In 2011, a meta-analysis compared the relative effects of ICS compared to LABAs on clinical outcomes in patients with stable COPD in 5,997 patients (7 RCTs).[290] All of the trials compared ICS/LABA combination inhalers with LABA and ICS as individual components. Four of these trials included fluticasone and salmeterol mono components and the remaining 3 included budesonide and formoterol mono components. There was no statistically significant difference in the primary outcome, the number of patients experiencing exacerbations (OR, 1.22; 95% CI, 0.89 to 1.67), or the rate of exacerbations per patient year (RR, 0.96; 95% CI, 0.89 to 1.02) between ICS and LABAs. The incidence of pneumonia, the co-primary outcome, was significantly higher among patients on ICS than on LABAs whether classified as an adverse event (OR, 1.38; 95% CI, 1.1 to 1.73) or serious adverse event (Peto OR, 1.48; 95% CI, 1.13 to 1.93). In terms of the secondary outcomes analysis, mortality was higher in patients on ICS compared to patients on LABAs (Peto OR, 1.17; 95% CI, 0.97 to 1.42), although the difference was not statistically significant. Patients treated with beta$_2$-agonists showed greater improvements in pre-bronchodilator FEV_1 compared to those treated with ICS (mean difference (MD), 18.99 mL; 95% CI, 0.52 to 37.46). However, there were greater improvements in health-related quality of life observed in patients receiving ICS compared to those receiving long LABAs (SGRQ MD, -0.74; 95% CI, -1.42 to -0.06). In both cases, the differences were statistically significant but rather small in magnitude. There were no statistically significant differences between ICS and LABA in the number of hospitalizations due to exacerbations, number of mild exacerbations, PEF, dyspnea, symptoms scores, use of rescue medication, adverse events, all cause hospitalizations, or withdrawals from studies. The authors concluded that their findings support current guidelines advocating LABAs as frontline therapy for COPD, with regular inhaled corticosteroid therapy as an adjunct in patients experiencing frequent exacerbations.

A Cochrane database systematic review evaluated ICS in stable COPD.[291] Fifty-five randomized, placebo-controlled studies, representing 16,154 patients, and 5 different ICS (budesonide, beclomethasone dipropionate, fluticasone propionate, triamcinolone acetonide, mometasone furoate) were included in the analysis. The rate of decline of FEV_1 was not blunted by the extended use (> 6 months) of ICS in COPD patients (generic inverse variance analysis: mean difference [MD], 5.8 mL/year with ICS over placebo [95% CI, -0.28 to 11.88; 2,333 participants]; pooled means analysis: 6.88 mL/year [95% CI 1.8 to 11.96, 4,823 participants]). However, statistically significant reductions were seen in the mean rate of exacerbations (generic inverse variance analysis: MD, -0.26 exacerbations per patient per year [95% CI -0.37 to -0.14; 2,586 participants]; pooled means analysis: MD, -0.19 exacerbations per patient per year [95% CI -0.3 to -0.08; 2,253 participants]) and the rate of decline in quality of life as measured by the SGRQ (MD, -1.22 units/year; 95% CI -1.83 to -0.6; 2,507 participants). Conversely, increased rates of oropharyngeal candidiasis (OR, 2.65; 95% CI, 2.03 to 3.46; 5,586 participants) and pneumonia were observed in patients utilizing ICS. No statistically significant effect on mortality was observed (OR, 0.98, 95% CI, 0.83 to 1.16; 8,390 participants). This review advises clinicians to balance the increased risk of adverse effects (e.g., oropharyngeal candidiasis and pneumonia), when considering the use of ICS in COPD to capture the potential benefits of decreased rates of exacerbations and quality of life decline.

A separate meta-analysis looked at the comparison of ICS/LABA products to LABA alone in patients with COPD.[292] Fourteen randomized, blinded studies enrolling 11,794 individuals met inclusion criteria for the analysis. Risk of mortality did not differ significantly between the 2 therapies (OR, 0.92; 95% CI, 0.76 to 1.11; moderate quality). Pneumonia was more common in the ICS/LABA group as compared to LABA alone (OR, 1.55; 95% CI, 1.2 to 2.01; moderate quality). The other primary outcomes, including rate of hospitalizations and risk of exacerbation, were determined to have low quality evidence by the reviewers; neither outcome demonstrated a significant difference between the 2 groups.

In 2020, a systematic literature review and network meta-analysis compared the relative efficacy of combination budesonide/glycopyrronium/formoterol fumarate (BGF) fixed dose, MDI therapy with other fixed dose and open ICS/LAMA/LABA inhaler combinations in patients with moderate to severe COPD (18 studies).[293] BGF was also compared against numerous open, triple combination inhaler regimens. Endpoints consisted of changes in moderate and severe COPD exacerbations, changes in baseline lung function as measured by FEV_1, and changes in baseline symptoms and quality of life as measured by the SGRQ, Transition Dyspnea Index (TDI), and rescue medication use. Results from the analysis demonstrated comparable efficacy (no significant differences) for BGF compared to other therapies.

SUMMARY

The 2007 National Heart, Lung, and Blood Institute (NHLBI), including its 2020 targeted update, and 2022 Global Initiative for Asthma (GINA) guidelines utilize a classification of level of asthma control to guide asthma therapy and state that inhaled corticosteroids (ICS) are currently the most effective anti-inflammatory medications for the treatment of persistent asthma. The updated 2022 GINA recommendations prefer the use of an as needed low-dose ICS/formoterol over a short-acting $beta_2$-agonists in asthma patients ≥ 12 years old as a reliever medication. Data on use of an ICS as needed as a reliever is most abundant with budesonide/formoterol, although it is not an FDA-approved use.

Bronchodilator therapy is central to symptom management in chronic obstructive pulmonary disease and the inhaled route is preferred. The 2022 Global Initiative for Chronic Obstructive Lung Disease

(GOLD) guidelines emphasize individualized therapy; however, in general, they recommend the addition of ICS to long-acting beta$_2$-agonists (LABA) or long-acting anticholinergic agents for patients with severe to very severe COPD.

When used in equivalent dosages, efficacy among all ICS is similar. There are differences among the agents in dosage frequency and the number of inhalations needed for each dose. Most of these single-product agents are recommended for twice daily use. The exceptions to this are mometasone (Asmanex Twisthaler) and fluticasone furoate (Arnuity Ellipta), which can be dosed once daily. Also, there are 2 agents that act as prodrugs, ciclesonide (Alvesco) and beclomethasone (QVAR Redihaler). They are both converted either during absorption (beclomethasone) or by esterases in the lung (ciclesonide).

The use of a combination LABA and an ICS [e.g., salmeterol/fluticasone propionate (Advair, AirDuo RespiClick, AirDuo Digihaler), formoterol/budesonide (Symbicort), formoterol/mometasone (Dulera), fluticasone furoate/vilanterol (Breo Ellipta)] in a single inhaler is effective in the treatment of asthma and reduces asthma exacerbations. Salmeterol/fluticasone propionate (Advair Diskus), formoterol/budesonide (Symbicort), and fluticasone furoate/vilanterol (Breo Ellipta) are also indicated for the maintenance treatment of airflow obstruction and to reduce exacerbations in patients with COPD; formoterol/mometasone (Dulera) is not approved for this indication. Fluticasone furoate/vilanterol (Breo Ellipta) is dosed once daily while budesonide/formoterol (Symbicort) and fluticasone propionate/salmeterol (Advair, AirDuo RespiClick, AirDuo Digihaler) are dosed twice daily. Two products in this class offer fixed-dose options for triple therapy treatment of COPD, fluticasone furoate/umeclidinium/vilanterol (Trelegy Ellipta), a dry-powder inhaler (DPI) dosed as a single inhalation once daily, and budesonide/glycopyrrolate/formoterol fumarate (Breztri Aerosphere), a metered-dose inhaler (MDI) dosed as 2 inhalations twice daily. Fluticasone furoate/umeclidinium/vilanterol (Trelegy Ellipta) is also approved for the maintenance treatment of asthma in adults.

The FDA recommendations on the safe use of LABA in the treatment of asthma also apply to the combination ICS/LABA products. The FDA recommends against the use of LABA without the use of an asthma controller medication such as an ICS. Also, LABA should be used for the shortest duration of time required to achieve control of asthma symptoms and discontinued, if possible, once asthma control is achieved. LABA should be used long-term only in patients whose asthma is not adequately controlled on other asthma controller medications. When selecting an agent for an individual patient, consideration must be given to the characteristics of the particular delivery device and the necessary technique for its use. This is particularly important for the very young and the very old. For children under 5 years of age, an MDI with a spacer and an optional face mask or mouthpiece may be preferable. If this is not effective, consideration could be given towards nebulizer therapy or a DPI as an alternative for individuals, young and old, who cannot use MDIs due to an inability to coordinate hand and press devices.

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