Therapeutic Class Overview
β-Agonists: Combination Products

Therapeutic Class

- **Overview/Summary:** The combination inhaled corticosteroid (ICS)/long-acting β_2-agonist (LABA) products include Advair® (fluticasone propionate/salmeterol), Breo Ellipta® (fluticasone furoate/vilanterol), Dulera® (mometasone/formoterol) and Symbicort® (budesonide/formoterol), with fluticasone furoate/vilanterol being the most recent agent to be approved by the Food and Drug Administration (FDA). Fluticasone propionate/salmeterol, mometasone/formoterol and budesonide/formoterol are approved for the treatment of asthma; however, only fluticasone propionate/salmeterol, fluticasone furoate/vilanterol and budesonide/formoterol have been approved for the treatment of chronic obstructive pulmonary disease. The ICSs exert their anti-inflammatory effect by binding to the glucocorticoid receptors with a subsequent activation of genes involved in anti-inflammatory processes, as well as via the inhibition of pro-inflammatory genes involved in the asthmatic response. The LABAs have selective action on β_2 receptors which stimulate adenyl cyclase, thereby increasing intracellular cyclic adenosine monophosphate level, and subsequently relaxing bronchial smooth muscles. The LABA medications also inhibit the release of mediators that are involved in immediate hypersensitivity. All of the combination products are associated with similar adverse events, precautions and contraindications.[1-5] Moreover, the labeling for all of the combination products have been revised to reflect the results of an analysis which reported an increased risk of asthma exacerbations and hospitalizations in pediatric and adult patients, as well as death in some patients treated with LABA-containing medications.[6] The combination ICS/LABA products appear to be equally efficacious for their respective indications, with the products differing in available dosage forms, dosing frequency (one vs two inhalations twice daily), pharmacokinetic profiles and ages for their FDA-approved indications.[1-5]

Table 1. Current Medications Available in the Therapeutic Class[1-5]

Generic (Trade Name)	Food and Drug Administration-Approved Indications	Dosage Form/Strength	Generic Availability
Budesonide/ formoterol (Symbicort® HFA)	Maintenance treatment of airflow obstruction in patients with chronic obstructive pulmonary disease including bronchitis and/or emphysema* and treatment of asthma in patients ≥12 years of age	Meter dose aerosol inhaler (HFA) (60 or 120 actuations): 80/4.5 µg 160/4.5 µg	-
Fluticasone propionate/ salmeterol (Advair Diskus®, Advair HFA®)	Maintenance treatment of airflow obstruction in patients with chronic obstructive pulmonary disease including bronchitis and/or emphysema (Advair Diskus®)†, treatment of asthma in patients four years of age and older (Advair Diskus®) and treatment of asthma in patients 12 years of age and older (Advair HFA®)	Dry powder inhaler (60 blisters): 100/50 µg 250/50 µg 500/50 µg Meter dose aerosol inhaler (HFA) (60 or 120 actuations): 45/21 µg 115/21 µg 230/21 µg	-
Fluticasone furoate/ vilanterol (Breo Ellipta®)	Maintenance Treatment of Airflow Obstruction in Patients with Chronic Obstructive Pulmonary Disease	Dry Powder Inhaler (30 dose strips): 100 µg/25 µg	
Mometasone/ formoterol (Dulera®)	Treatment of asthma in patients 12 years of age and older	Meter dose aerosol inhaler (HFA) (120 actuations):	-

		100/5 µg 200/5 µg	

HFA=hydrofluoroalkane
* Symbicort® 160/4.5 µg is the only strength Food and Drug Administration (FDA) approved for this indication.
† Advair Diskus® 250/50 µg is the only strength FDA approved for this indication.

Evidence-based Medicine

- The safety and efficacy of mometasone/formoterol were established in two randomized, double-blind, parallel-group, multicenter trials of 12 and 26 week duration (N=1,509).
    - After 26 weeks of treatment, mometasone/formoterol was more effective than monotherapy with the individual components in controlling asthma and reducing the risk of asthma deteriorations in patients with persistent asthma uncontrolled on medium-dose inhaled corticosteroids (ICSs).[7]
    - After 12 weeks of treatment, mometasone/formoterol was more effective than mometasone monotherapy in improving asthma control and reducing nocturnal awakenings.
        - Patients poorly controlled on high-dose ICSs experienced significant improvements in asthma control, lung function and symptoms when treated with mometasone/formoterol compared to mometasone monotherapy.[8]
    - A long term safety trial demonstrated that treatment with mometasone/formoterol for up to one year is well tolerated.[9]
- A single prospective head-to-head trial comparing mometasone/formoterol to fluticasone propionate/salmeterol demonstrated noninferiority of mometasone/formoterol in regard to the forced expiratory volume in 1 second (FEV_1) area under the curve from 0 to 12 hours. Mometasone/formoterol treatment was also associated with a significantly quicker onset of action and increase in FEV_1 five minutes post dose compared to fluticasone propionate/salmeterol.[10]
- Numerous trials have evaluated the combination ICS/ long-acting β2-agonist (LABA) products to their respective individual components as monotherapy, and results have generally demonstrated that administration of the combination product is more effective than monotherapy for improving lung function and achieving control of asthma symptoms. Moreover, there is similar efficacy between the administration of the combination ICS/LABA products to their individual components used in combination.[11-36]
- Head-to-head trials comparing budesonide/formoterol and fluticasone propionate/salmeterol have been conducted but failed to consistently demonstrate "superiority" of one product over the other.[37-46]
- One study comparing fluticasone propionate/salmeterol and fluticasone furoate/vilanterol did not demonstrate significant differences in improvement of 0 to 24 hour FEV_1.[47]

Key Points within the Medication Class

- According to Current Clinical Guidelines:[48-51]
    - Inhaled corticosteroids (ICSs) and β_2-agonists are well established treatment options in the management of both asthma and chronic obstructive pulmonary disease (COPD).
    - The addition of a long-acting β_2-agonist (LABA) is the preferred treatment option in asthma patients who fail to achieve adequate control with a low to medium dose ICS.
    - β_2-agonists are among the principal bronchodilators used in the treatment of COPD, and LABAs are more effective and convenient than short-acting bronchodilators.
    - ICSs are recommended as adjunctive agents to long-acting bronchodilators to decrease exacerbation frequency in patients with an FEV_1 ≤60% predicted and repeated exacerbations.
    - ICS/LABA products are more effective than either component alone in reducing exacerbations or improving lung function in COPD patients.
    - No one ICS/LABA product is preferred over another for the treatment of asthma or COPD.
- Other Key Facts:
    - All LABA-containing medications carry a Black Box Warning regarding an increased risk of asthma-related deaths associated with their use.

- Budesonide/formoterol and Fluticasone furoate/vilanterol have a quicker onsets of action (15 and 16 minutes) compared to fluticasone propionate/salmeterol (30 to 60 minutes). The onset of action of mometasone/formoterol has not been reported.[1-5]
- All ICS/LABA products are available for twice daily dosing, except fluticasone furoate/vilanterol which is administered once daily.[1-5]
- For the treatment of asthma, Advair® HFA (fluticasone propionate/salmeterol), Dulera® (mometasone/formoterol), Symbicort® (budesonide/formoterol) are approved for use in patients 12 years of age and older, while Advair Diskus® is approved for use in patients four years of age and older.
- No generic products are available in this therapeutic class.

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β-Agonists: Combination Products

Overview/Summary

Symbicort® (budesonide/formoterol), Advair® (fluticasone propionate/salmeterol), Breo Ellipta® (fluticasone furoate/vilanterol) and Dulera® (mometasone/formoterol) are the available combination inhaled corticosteroid (ICS) and long-acting β_2-agonist (LABA) products. Budesonide/formoterol, fluticasone propionate/salmeterol and mometasone/formoterol are Food and Drug Administration (FDA)-approved for the treatment of asthma, while budesonide/formoterol, fluticasone propionate/salmeterol and fluticasone furoate/vilanterol are FDA-approved for the treatment of chronic obstructive pulmonary disease (COPD).[1-5] None of the combination ICS/LABA products are available generically.

Corticosteroids have a wide range of inhibitory activities against multiple cell types (e.g., mast cells, eosinophils) and mediators (e.g., histamine, cytokines) which are involved in the asthmatic response. The ICSs exert their anti-inflammatory effect by binding to the glucocorticoid receptors with a subsequent activation of genes involved in anti-inflammatory processes, as well as via the inhibition of pro-inflammatory genes involved in the asthmatic response. Inflammation is also a component of COPD pathogenesis.[1-5] The LABAs are also useful for long-term control of persistent asthma and COPD, and have been proven to help control nocturnal symptoms. These agents have selective action on β_2 receptors which stimulate adenyl cyclase, resulting in an increased intracellular cyclic adenosine monophosphate level, which subsequently triggers bronchial smooth muscles relaxation. The LABA medications also inhibit the release of mediators that are involved in immediate hypersensitivity.[1-5]

The products differ in their available dosage forms, dosing frequency and in their pharmacokinetic profiles. Budesonide/formoterol (Symbicort®) and fluticasone furoate/vilanterol (Breo Ellipta®) have a faster onsets of action, at 15 and 16 minutes, compared to 30 to 60 minutes with fluticasone propionate/salmeterol (Advair®). The onset of action of mometasone/formoterol (Dulera®) has not been reported. Fluticasone propionate/salmeterol is available as a dry powered inhaler (DPI) and as a hydrofluoroalkane (HFA) metered dose inhaler (MDI) which are dosed as one inhalation twice-daily (DPI) and two inhalations twice daily (MDI), respectively. Budesonide/formoterol and mometasone/formoterol are only available as HFA MDIs, and both are dosed as two inhalations twice daily. Fluticasone furoate/vilanterol (Breo Ellipta®) is available as a DPI and is dosed once daily. [1-5]

Adverse events are similar among the combination ICS/LABA products with headache, nasopharyngitis, pharyngitis and upper respiratory tract infections being the most commonly reported.[1-5] Of note, all LABA-containing medications contain a Black Box Warning regarding an increased risk of asthma-related deaths. In February 2010, results from a meta-analysis demonstrated that LABAs were associated with an increased risk of asthma exacerbations and hospitalizations in pediatric and adult patients, as well as death in some patients. Based on the findings, the FDA now requires the product labeling of all LABA-containing medications to include information regarding these risks. In addition, the use of LABAs is now contraindicated without the presence of an asthma controller medication in the therapeutic regimen. The FDA also recommends that LABAs should only be used long-term in patients whose asthma cannot be adequately controlled on asthma controller medications, and that LABAs should be used for the shortest duration of time to achieve asthma control. Moreover, the FDA recommends the use of a combination ICS/LABA product in pediatric and adolescent patients who require LABA therapy to ensure compliance with both medications.[6]

There has been a single head-to-head trial comparing mometasone/formoterol (Dulera®) to fluticasone propionate/salmeterol (Advair®) which demonstrated mometasone/formoterol (Dulera®) to be non inferior to fluticasone propionate/salmeterol (Advair®) in regard to an improvement in change in forced expiratory volume in 1 second (FEV_1) area under the curve from 0 to 12 hours.[7] One trial comparing fluticasone propionate/salmeterol (Advair®) and fluticasone furoate/vilanterol (Breo Ellipta®) did not demonstrate a significant difference in change in FEV_1. Head-to-head trials comparing budesonide/formoterol (Symbicort®) and fluticasone propionate/salmeterol (Advair®) have not demonstrated consistent "superiority" of one product over the other.[9-18] Trials have compared these agents for standard asthma

maintenance. Moreover, a fixed dose fluticasone propionate/salmeterol regimen has been compared to a patient/prescriber adjustable dose budesonide/formoterol combination regimen. Other trials have evaluated the budesonide/formoterol regimen as both maintenance and as needed treatment. This regimen is also known as Symbicort® Maintenance and Reliever Therapy (SMART). Of particular importance regarding this regimen is that it has not been approved by the FDA. This dosing regimen has reported significantly greater reductions in the overall number of exacerbations and in severe exacerbations compared to regular maintenance dosing regimens of both budesonide/formoterol and fluticasone propionate/salmeterol; however, the SMART dosing regimen demonstrated equal efficacy to both standard dose budesonide/formoterol and fluticasone propionate/salmeterol in lung function parameters, symptom reduction, and as needed reliever medication.[9-18]

Current treatment guidelines published by the National, Heart, Lung, Blood Institute (NHLBI) recommend against the use of a LABA as monotherapy for long-term asthma maintenance or for acute symptom treatment or exacerbations. These agents should be used in combination with an ICS for long-term control and prevention of symptoms in patients with moderate to severe persistent asthma. Of the adjunctive therapies available, LABAs are the recommended option to be used in combination with an ICS in patients ≥12 years of age that have not had adequate asthma symptom control with a low dose ICS. The guidelines recommend that for patients five to 11 years of age with moderate persistent asthma or asthma not controlled adequately on low-dose ICS, the option of a LABA should be weighed equally to potentially increasing the ICS dose. Additionally, the combination of a LABA with an ICS is recommended as preferred therapy in children with severe persistent asthma. The NHLBI guidelines do not specifically select one combination ICS/LABA product as being preferred over the others.[19] The Global Initiative for Asthma (GINA) guidelines also recommend the use of a LABA as add on therapy as the preferred treatment option after the patient has failed to achieve adequate control with medium dose ICS monotherapy. The GINA guidelines also recommend against the use of LABAs as monotherapy. It should be noted that the GINA guidelines recommend that budesonide/formoterol (Symbicort®) can be utilized as both a maintenance and rescue medication; however, use of this agent as a rescue medication is not approved by the FDA. The GINA guidelines also do not specifically select one combination ICS/LABA product as being preferred over the others.[20]

The Global Initiative for Chronic Obstructive Lung Disease guidelines on COPD recommend that if an initial, as-needed, short-acting bronchodilator is not effective for symptom relief, then the use of long-acting bronchodilator should be initiated. Principle bronchodilators include β_2-agonists and anticholinergics and the use of long-acting bronchodilators is more effective and convenient than short-acting bronchodilators. Combining bronchodilators of different pharmacological classes may improve efficacy and decrease adverse effects compared to increasing dose of a single bronchodilator. In patients with an FEV_1 <60% of the predicted value, regular treatment with ICS improves symptoms, lung function and quality of life as well as reduces exacerbations. However, long term therapy ICS as monotherapy is not recommended. Like the NHLBI and GINA guidelines, according to the GOLD guidelines, no one combination ICS/LABA product is preferred over the other.[21] The National Institute for Clinical Excellence (NICE) COPD guidelines recommend the use of long-acting bronchodilators (LABAs and/or anticholinergics) to control symptoms in patients who continue to experience symptoms despite the use of a short-acting bronchodilator agent. In patients with stable COPD and an FEV_1 ≥50%, who remain breathless or who have exacerbations despite management with a LABA, consideration of the addition of an ICS (in a combination inhaler) or a long-acting muscarinic antagonist (when ICSs are not tolerated or declined) should be made. No preferred combination ICS/LABA product is provided within the current NICE guidelines.[22]

Medications

Table 1. Medications Included Within Class Review

Generic Name (Trade name)	Medication Class	Generic Availability
Budesonide/formoterol (Symbicort® HFA)	Inhaled corticosteroid/long-acting β_2-agonist	-
Fluticasone propionate/salmeterol (Advair Diskus®, Advair HFA®)	Inhaled corticosteroid/long-acting β_2-agonist	-

Generic Name (Trade name)	Medication Class	Generic Availability
Fluticasone furoate/vilanterol (Breo Ellipta®)	Inhaled corticosteroid/long-acting β_2-agonist	-
Mometasone/formoterol (Dulera®)	Inhaled corticosteroid/long-acting β_2-agonist	-

HFA=hydrofluoroalkane.

Indications

None of the combination inhaled corticosteroid/long-acting β_2-agonist products are indicated for the relief of acute bronchospasm.[1-5]

Table 2. Food and Drug Administration Approved Indications[1-5]

Generic Name	Treatment of Asthma in Adults and Children ≥4 Years of Age	Treatment of Asthma in Adults and Children ≥12 Years of Age	Maintenance Treatment of Airflow Obstruction in Patients with Chronic Obstructive Pulmonary Disease*
Budesonide/formoterol		✔	✔ †
Fluticasone propionate/ salmeterol	✔ (Advair Diskus®)	✔ (Advair HFA®)	✔ ‡ (Advair Diskus®)
Fluticasone furoate/vilanterol			✔
Mometasone/formoterol		✔	

HFA=hydrofluoroalkane.
*Including bronchitis and/or emphysema.
†Symbicort® 160/4.5 µg is the only strength Food and Drug Administration (FDA) approved for this indication.
‡Advair Diskus® 250/50 µg is the only strength FDA-approved for this indication.

Pharmacokinetics

Table 3. Pharmacokinetics[1-5,]

Generic Name	Onset (minutes)	Duration (hours)	Renal Excretion (%)	Active Metabolites	Serum Half-Life (hours)
Budesonide/formoterol	15	12	60/59 to 62	None	4.7/7.9
Fluticasone propionate/salmeterol	30 to 60	12	<5/25 to 60	None	5.33 to 7.65/5.50
Fluticasone furoate/vilanterol	16	Not reported	1 to 2/70	Yes (with reduced activity)	24/21.3
Mometasone/formoterol	Not reported	Not reported	8/59 to 62	None	25/9 to 11

Clinical Trials

The clinical trials demonstrating the safety and efficacy of the combination inhaled corticosteroid (ICS)/ long-acting β_2-agonist (LABA) products for their Food and Drug Administration (FDA)-approved indications are outlined in Table 4.[7-18,23-95] Numerous trials have evaluated the combination ICS/LABA products to their respective individual components as monotherapy, and in general, results have demonstrated that administration of the combination product is more effective than monotherapy for improving lung function and achieving control of asthma symptoms.[23-33,35,48-56,64] Additionally, there is similar efficacy between the administration of the combination ICS/LABA products to their individual components used in combination.[23,27,31,37,46-49] A single head-to-head trial, described below, has been conducted comparing mometasone/formoterol (Dulera®) and fluticasone propionate/salmeterol (Advair®); however, more head-to-head trials comparing budesonide/formoterol (Symbicort®) and fluticasone propionate/salmeterol (Advair®) have been conducted. Additionally, one trial has compared fluticasone furoate/vilanterol (Breo Ellipta®) and fluticasone propionate/salmeterol (Advair®). Overall the results of these trials were inconsistent in demonstrating efficacy "superiority" of one product over the other.[7,9-18]

In an open label, non inferiority study by Bernstein et al, 722 patients ≥12 years of age with persistent asthma received mometasone/formoterol (Dulera®) or fluticasone propionate/salmeterol (Advair®) for 12 weeks following a two week run in period with mometasone. The primary endpoint was the change in forced expiratory volume in 1 second (FEV_1) area under the curve from 0 to 12 hours ($AUC_{0\ to12h}$) after 12 weeks. At the end of treatment, the change in FEV_1 $AUC_{0\ to12h}$ associated with mometasone/formoterol (Dulera®) was non inferior to improvements observed with fluticasone propionate/salmeterol (Advair®) (3.43 vs 3.24 L/h, respectively; 95% Confidence Interval, -0.40 to 0.76). Moreover, mometasone/formoterol (Dulera®) was associated with a significantly quicker onset of action (*P*<0.001) and a greater least squares mean change in FEV_1 (200 vs 90 mL; *P*≤0.001) compared to fluticasone propionate/salmeterol (Advair®).[7] There were no differences between the two treatment groups in regard to 24-hour asthma symptom scores, the number of symptom-free days and nights or asthma deterioration over 12 weeks (*P* values not reported).

A 12 week, randomized-controlled trial (N=528) compared fluticasone furoate/vilanterol (Breo Ellipta®) and fluticasone propionate/salmeterol (Advair®). The primary endpoint was the weighted mean change from baseline in 0 to 24 hour FEV_1. There was no significant difference in improvement from baseline between the fluticasone propionate/salmeterol (108±221 mL) and fluticasone furoate/vilanterol (130±222 mL) groups (P=0.282).[8]
The safety and efficacy of mometasone/formoterol, was established in two randomized, double-blind, parallel-group, multicenter clinical trials (N=1,509). Enrolled patients were ≥12 years of age with persistent asthma uncontrolled on medium or high dose ICSs. All patients underwent a two to three week run-in period with mometasone to establish a certain level of asthma control.[65,66]

The first trial was a 26 week, placebo-controlled trial (N=781) that compared mometasone/formoterol 100/5 µg, mometasone 100 µg, formoterol 5 µg and placebo. A primary endpoint of FEV_1 $AUC_{0\ to12h}$ demonstrated that patients receiving combination therapy had significantly higher increases from baseline at week 12 compared to mometasone (the primary treatment comparison) (*P*<0.001) and placebo (*P*<0.001). These differences were maintained through 26 weeks of treatment. A second primary endpoint in this trial was clinically judged deteriorations in asthma or reductions in lung function (any of the following: a 20% decrease in FEV_1, a 30% decrease in peak expiratory flow on two or more consecutive days or emergency treatment, hospitalizations or treatment with systemic corticosteroids or other asthma medications not allowed per protocol) for mometasone/formoterol compared to formoterol. A smaller proportion of patients receiving combination therapy (30%) reported an event (54% with formoterol; *P*<0.001).[65]

The second trial was a 12 week, double-blind trial (N=728) that compared the efficacy of mometasone/formoterol 200/5 µg, mometasone/formoterol 100/5 µg and mometasone 200 µg. In this trial, the primary endpoint was the mean change in FEV_1 $AUC_{0\ to12h}$ from baseline to week 12. Patients receiving both doses of combination therapy had significantly greater increases from baseline at day one in mean FEV_1 $AUC_{0\ to12h}$ compared to mometasone (*P* values not reported); the difference was maintained over 12 weeks of treatment. A greater increase in the mean trough FEV_1 from baseline to week 12 was also observed for the higher dose of combination therapy (0.19) compared to the lower dose of combination therapy (0.14; *P* value not reported) and to mometasone (0.10; *P* value not reported). Fewer patients in both combination therapy groups reported clinically judged deterioration in asthma or a reduction in lung function compared to mometasone (12 vs 18%; *P* value not reported).[66]

Table 4. Clinical Trials

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Asthma				
Rosenhall et al[23] Budesonide/formoterol 160/4.5 µg, 2 inhalations BID via MDI vs budesonide 160 µg, 2 inhalations BID via DPI plus formoterol 4.5 µg, 2 inhalations BID via DPI	MC, OL, RCT Patients with moderate persistent asthma (average age, 45)	N=586 6 months	Primary: Safety and efficacy (FEV_1, Mini AQLQ, ACQ, exacerbations Secondary: Not reported	Primary: Patients in both treatment groups had a mean FEV_1 increase of five to six percent from baseline (*P* value not reported). There was no significant change in response using the Mini AQLQ and the ACQ from baseline in both treatment groups. Both treatment groups were well tolerated, with asthma exacerbations occurring at a low frequency (*P* value not reported). The withdrawal rate in both groups was also similar (*P*=0.085). Secondary: Not reported
Canonica et al[24] Budesonide/formoterol 80/4.5 µg, 2 inhalations BID via MDI-FD vs budesonide/formoterol 160/4.5 µg, 2 inhalations BID via MDI-FD vs budesonide/formoterol 80/4.5 µg, 2 inhalations BID via MDI-AMD vs budesonide/formoterol	RCT Patients with persistent asthma	N=2,358 12 weeks	Primary: Frequency of asthma exacerbations and changes in asthma symptom severity Secondary: Asthma control, safety and health economics	Primary: Both FD and AMD budesonide/formoterol treatment groups had similar low frequency of exacerbations, as well as improved comparable lung function. However, results did not reach statistical significance (*P* value not reported). Secondary: Both treatment groups had improved lung function, less asthma symptoms and fewer nighttime awakenings compared to the mean value of the run-in period (*P* value not reported). Patients in the AMD budesonide/formoterol dose group utilized 24% less of the study drug in comparison to those in the FD group (2.95 vs 3.86 daily inhalations, respectively; *P*<0.0001).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
160/4.5 µg, 2 inhalations BID via MDI-AMD				
Lalloo et al[25] Budesonide/formoterol 80/4.5 µg, 1 inhalation BID via DPI vs budesonide 200 µg, 1 inhalation BID Inhaled terbutaline or salbutamol was used as a reliever medication depending on patient preference.	DB, MC, PG, RCT Patients >18 years of age with a diagnosis of asthma assessed by the following: FEV_1 60 to 90% of predicted normal value and >12% reversibility of basal FEV_1 within 15 minutes of terbutaline or salbutamol inhalation; all patients received ICSs of any brand at a constant dose of 200 to 500 µg/day for ≥1 month prior to study entry	N=467 12 weeks	Primary: Morning and evening PEF values Secondary: FEV_1/FVC measurements, symptom free days, reliever free days, nighttime awakenings, time to first mild and severe exacerbation, and safety	Primary: Morning and evening PEF values increased for both treatment groups; however, significantly larger increases were seen with combination therapy than with monotherapy (*P*=0.002 and *P*<0.001, respectively). Secondary: Mean FEV_1 scores increased in both groups but no significant difference was found, additionally, FVC showed no change from baseline. The incidence of asthma control days, symptom free days and reliever medication use (*P*=0.025) all favored combination therapy. Asthma control days favored combination therapy (17 vs 10%; *P*=0.002). Symptom free days were similar between groups (16 vs 10%; *P*=0.007). A reduction of 24 vs 6% and 23 vs 14% favored combination therapy for asthma symptom score and nighttime awakenings, respectively (*P* values not reported). Fewer patients experienced a mild exacerbation (110/230) in the combination group than the monotherapy group (136/237; *P* value not reported). Nighttime awakenings also favored combination therapy (75 vs 105; *P* value not reported). The monotherapy group showed a shorter time to first mild exacerbation compared to the combination group (*P*=0.02). The risk of having a mild exacerbation was estimated to be 26% lower in the combination group (*P*=0.02). The chance of having a severe exacerbation was six percent lower in the combination group (*P*=0.85). No between group differences were noted for the profile and frequency of adverse events. Both treatment groups commonly reported respiratory infection, pharyngitis, and rhinitis. Overall, there were seven severe adverse events, five occurred with combination therapy and two with

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				monotherapy.
Tal et al[26] Budesonide/formoterol 80/4.5 µg, 2 inhalations BID via DPI vs budesonide 100 µg, 2 inhalations BID via MDI	DB, DD, MC, PG, RCT Children 4 to 17 years of age with a diagnosis of asthma for ≥6 months, FEV_1 40 to 90% of predicted value at visit 1, >15% reversibility of FEV_1 within 15 minutes of inhalation of a SABA, 6 weeks constant dosing with an ICS (budesonide, fluticasone or beclomethasone)	N=286 12 weeks	Primary: Morning PEF Secondary: FEV_1, FEV_1 over a 12 hour time period, rescue inhaler use, comparison of nocturnal asthma symptoms, and safety	Primary: Combination therapy resulted in a significantly greater increase in morning PEF than monotherapy (*P*<0.001). Results were similar for evening PEF (*P* value not reported). Secondary: FEV_1 scoring (*P*<0.05), mean improvement of FEV_1 over 12 hours after one dose (*P*<0.05) and mean improvement of FEV_1 ten minutes after first dose (*P*<0.05) favored combination therapy. A decrease in rescue inhaler use from 0.71 to 0.60 inhalations/day was seen in the combination therapy group, and a change of 0.50 to 0.41 inhalations was seen with the monotherapy group. There was no statistical significance between the groups (*P* value not reported). A decrease in the number of nights awakening with asthma symptoms was seen in both groups with no significant difference (combination therapy decreased from 7.2 to 5.5% and monotherapy decreased from 8.5 to 6.6%; *P* value not reported). Reported adverse events between the two groups were comparable and reported as combination vs monotherapy. Pharyngitis (8 vs 12%), respiratory infection (8 vs 6%), rhinitis (7 vs 4%), coughing (5 vs 5%), headache (6 vs 4%), viral infection (7 vs 3%), fever (6 vs 2%) and aggravated asthma (5 vs 3%). In the combination therapy group, 4.7% of patients had serious adverse side effects.
Zangrilli et al[27] Budesonide/formoterol 160/4.5 µg, 2 inhalations BID via DPI vs budesonide 160 µg, 2	AC, DB, MC, RCT Hispanic patients ≥12 years of age with asthma for ≥6 months and a pre-bronchodilator FEV1 of 45 to 85% of predicted	N=150 12 weeks	Primary: Mean change from baseline in morning (AM) PEF Secondary: Predefined asthma events (decreased FEV_1 ≥20% from	Primary: The morning PEF value increased from baseline during randomized treatment, in both treatment groups but there was no significant difference between treatments (25.4 vs 19.9% in the combination and monotherapy groups, respectively; *P*≥0.428). Secondary: Patients who received combination therapy experienced fewer asthma events compared to patients receiving monotherapy, although the

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
inhalations BID via MDI	normal and reversibility of ≥12% with albuterol administration and a documented daytime or nighttime asthma symptom scores ≥0 on 3 or more days within 7 consecutive days during a 2-week run-in period on budesonide 160 µg BID		randomization or FEV_1 <40% of predicted normal, ≥12 inhalations of albuterol per day, decreased morning PEF ≥20% from baseline on ≥3 of seven consecutive days after randomization, ≥2 nocturnal asthma awakenings requiring rescue medication within seven days after randomization, or a clinical exacerbation requiring emergency treatment, hospitalization, or use of an excluded asthma medication) and withdrawals caused by these events, pulmonary function assessments and diary-based measures of asthma control	difference was not statistically significant (25.2 vs 31.7%; *P* value not reported). Similarly, 3.1 and 6.5% of patients in the combination and monotherapy treatment groups withdrew from the study due to asthma related events, although the differences in discontinuation rates were not significant (*P* value not reported). There was no significant difference between patients receiving combination treatment or monotherapy, in regard to the change in daily asthma symptom score, daytime symptom score or nighttime symptom score (*P*≥0.181 for all comparisons). Rescue medication use decreased, and the percentage of symptom-free days, awakening-free nights, and rescue medication-free days increased in both treatment groups, but no differences in these outcomes were observed between the treatment groups (*P* values not reported).
Pohl et al[28] Budesonide/formoterol 160/4.5 µg, 2 inhalations BID, via MDI-AMD vs budesonide 320 µg, 2 inhalations BID, via DPI-	DB, PG, RCT Patients >19 years of age with asthma, FEV_1 reversibility of ≥15% (or 200 mL) within 1 month prior to enrollment, FEV_1	N=133 20 weeks	Primary: Number of patients/ treatment group with ≥1 treatment failure (defined as hospitalization, oral steroids, nebulized β_2-agonists, withdrawal due to lack of efficacy or life-threatening condition)	Primary: The rate of treatment failures were comparable between the two treatment groups with five out of the 63 patients in the budesonide/formoterol group and two out of the 63 patients in the budesonide group experiencing treatment failure throughout the duration of the study. Secondary: Patients in the budesonide/formoterol group had a statistically significant improvement in health-related quality of life and treatment satisfaction (for patients and physicians) vs those in the budesonide group (*P*<0.05).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
AMD	40 to 85% of predicted normal, requirement with an ICS or ICS/LABA combination within given starting dose range		Secondary: Health-related quality of life measured by the SF-36, dose of study medication, days of reliever medication use, and treatment satisfaction	Patients in the budesonide/formoterol group also had a lower use of daily inhalations of study drug vs budesonide (*P*=0.024). Both groups had minimal use of reliever medications.
Kuna et al[29] Budesonide/formoterol 80/4.5 µg, 2 inhalations every evening via MDI vs budesonide/formoterol 80/4.5 µg, 1 inhalation BID via MDI vs budesonide 200 µg, 1 inhalation every evening via DPI	AC, DB, DD, PG, RCT Adult patients with mild to moderate persistent asthma who were not optimally controlled on an ICS dose of 200 to 500 µg/day, mean predicted FEV_1 at baseline was 78.5%	N=617 12 weeks	Primary: Morning PEF Secondary: Evening PEF, symptom-free days, reliever-free days, asthma control days, and adverse events	Primary: Patients in both budesonide/formoterol regimens showed greater improvements in morning PEF (*P*<0.05). Secondary: Patients in both budesonide/formoterol regimens showed greater improvement in evening PEF, symptom-free days, reliever-free days and asthma-control days compared to the budesonide regimen (*P*<0.05). Both budesonide/formoterol regimens were similar in all efficacy variables, except for evening PEF which was higher with the BID regimen (18.3 vs 9.6 L/minute; *P*<0.05). There were no between-group differences in nighttime awakenings due to asthma, or in the number and nature of adverse events.
Morice et al[30] Budesonide/formoterol 160/4.5 µg via DPI vs budesonide/formoterol 160/4.5 µg via MDI	DB, DD, MC, PG, RCT Outpatients ≥12 years of age with asthma for ≥6 months with inadequate control on an ICS alone, FEV_1 of 50 to	N=680 12 weeks	Primary: Change from baseline in morning PEF Secondary: Changes from baseline in evening PEF, nighttime awakenings, asthma symptom score, symptom-free days and	Primary: Patients in the budesonide/formoterol DPI and budesonide/formoterol MDI groups had improved morning PEF compared to those in the budesonide group by 31.4 and 28.6 L/minute, respectively (*P*<0.001). Secondary: Patients in the budesonide/formoterol groups had greater improvements observed compared to those in the budesonide group. End points were similar between the two budesonide/formoterol devices,

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
vs budesonide 200 µg via MDI	90% predicted normal, reversibility of >12% after inhalation of terbutaline 1 mg, and daily ICS use history ≥3 months		asthma control days	with the exception of symptom-free and asthma control days, which were slightly improved with the DPI.
Jenkins et al[31] Budesonide/formoterol 320/9 µg, 2 inhalations BID via DPI (treatment 1) vs budesonide 400 µg, 2 inhalations BID plus formoterol 9 µg, 2 inhalations BID (treatment 2) vs budesonide 400 µg, 2 inhalations BID (after 12 weeks this group was randomized to either treatment 1 or 2) Terbutaline 0.5 mg was used throughout the study for as-needed relief.	DB, DD, MC, RCT Outpatients >12 years of age with a diagnosis of asthma for ≥6 months, FEV_1 40 to 85% of predicted, >15% reversibility in increase from baseline FEV_1 after inhalation of a bronchodilator (for patients >18 years of age an increase of >200 mL, 15 to 30 minutes post bronchodilator); all patients used ICSs for >4 months before study entry at a daily dose >750 µg for >4 weeks, patients required an asthma	N=456 24 weeks	Primary: Morning and evening PEF Secondary: Adherence to therapy, FEV_1, symptom free days and nights, total number of reliever inhalations recorded in diary, daytime/nighttime symptom scores via diary, and safety	Primary: Patients receiving combination therapy had greater increases from baseline PEF scoring in both the morning and evening with 37.4 and 4.5 L/minute respectively (*P*<0.001). There was no significant difference between either of the combination therapies (*P* value not reported). Secondary: FEV_1 increased over time for all three treatment groups. However, those receiving combination therapy compared to monotherapy showed significant improvement (0.30 vs 0.14 L, respectively; *P*<0.001). Combination therapy reduced asthma symptom scores significantly better than monotherapy alone (*P*=0.0051). Patients receiving combination therapy had 16% more symptom free days than budesonide alone (*P*<0.001), used 0.97 inhalations of reliever medication/day compared to 1.61 for budesonide alone (*P*<0.001), had 19% more reliever free days (*P*<0.001) compared to budesonide alone, and resulted in 16% more asthma-control days, which is approximately 58 more days a year with asthma control (*P*<0.001) compared to budesonide alone. Combination therapy reduced the risk for mild exacerbation by 36% (*P*=0.0032). Combining budesonide/formoterol in one inhaler reduced the risk of mild exacerbation by 17% compared to separate inhaler therapy (*P*=0.13).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
	symptoms score of >1 for ≥4 of 7 days of the run-in period			
Eid et al[32] Budesonide/formoterol 40/4.5 µg, 2 inhalations BID via MDI vs budesonide/formoterol 80/4.5 µg, 2 inhalations QD via MDI vs budesonide 80 µg, 2 inhalations QD via MDI All patients discontinued their current asthma therapy and received budesonide/formoterol 40/4.5 µg, 2 inhalations BID via MDI and as needed rescue albuterol during a 4 to 5 week run-in period.	AC, DB, MC, PG, RCT Patients 6 to 15 years of age with a documented asthma diagnosis for ≥6 months, stable disease based on consistent previous therapy, a pre bronchodilator FEV_1 60 to 90%, bronchodilatory reversibility of ≥12% and ≥0.20 L in FEV_1 and mild to moderate asthma based on ICS use and pulmonary function	N=521 12 weeks	Primary: Evening PEF Secondary: Morning PEF, daytime and nighttime asthma severity scores, nighttime awakenings attributable to asthma, daytime and nighttime rescue medication use, physician and caregiver assessment of overall level of asthma control, PAQLQ, PACQLQ, and safety	Primary: Both combination therapies maintained evening PEF significantly more than monotherapy (*P*≤0.027 for both). For combination therapy, mean evening PEF values steadily improved from baseline values with BID administration, whereas they were maintained at the baseline level with QD administration; however, mean changes from baseline were not significantly difference between the two groups (*P* value not reported). Secondary: For morning PEF, both combination therapies were significantly more effective than monotherapy (*P*≤0.010), and there were no significant differences noted between the combination therapies (*P*<0.05). Morning PEF was well maintained during the treatment period with both combination therapies; improvement from baseline values were observed for BID administration. For daytime and nighttime asthma symptoms, symptom-free days, awakening-free nights and asthma control days, the level of asthma control established during the run-in period was well maintained in all treatment groups, and there were no significant between group differences observed. Compared to monotherapy, treatment with combination therapy BID resulted in significantly less daytime and nighttime rescue medication use and more rescue medication-free days (*P*≤0.023). For combination therapy, daytime rescue medication use increased and rescue medication-free days decreased with QD administration compared to BID administration (*P*≤0.039). The percentage of caregivers whose responses indicated improvements in asthma symptoms or the ease of asthma management was similar across treatment groups (56.7 to 60.4%). Similar results were observed for

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				comparisons of the percentages of physicians whose responses indicated improvements in the patient's asthma symptoms (70.0 to 77.8%). However a significantly greater percentage of physicians' responses indicated improvements in the ease of asthma management with combination therapy BID vs monotherapy (75.0 vs 64.4%; *P*=0.035), but not those receiving combination therapy QD (70.4%; *P*=0.362). Neither the magnitude of mean changes within each group nor the magnitude of the mean differences between the groups was considered clinically meaningful according to the predefined minimal important difference of 0.5 for any of PAQLQ or PACQLQ overall or domain scores. All treatments were generally well tolerated, with most adverse events being of mild to moderate intensity. The incidence of overall adverse events was similar across the treatment groups.
Kerwin et al[33] Budesonide/formoterol 160/4.5 µg, 2 inhalations QD via MDI vs budesonide/formoterol 80/4.5 µg, 2 inhalations QD via MDI vs budesonide/formoterol 80/4.5 µg, 2 inhalations BID via MDI vs budesonide 160 µg, 2	AC, DB, PG, RCT Patients ≥12 years of age with asthma for ≥6 months, mild to moderate asthma based on pulmonary function and ICS use, received an ICS or ICS/LABA therapy for ≥4 weeks before screening, with a FEV_1 60 to 90% and demonstrated reversibility of FEV_1 ≥12% and ≥0.20 L from baseline within 15	N=619 12 weeks	Primary: Evening pre-dose FEV_1 Secondary: Morning and evening pre-dose PEF, daytime and nighttime asthma symptom scores, daytime and nighttime rescue medication use, nighttime awakenings due to asthma, symptoms-free days, awakening-free nights, asthma control days, rescue medication-free days, patient withdrawals due to predefined criteria for worsening asthma, AQLQ, and safety	Primary: Budesonide/formoterol QD (320/9 µg/day) was significantly more effective than budesonide for evening pre-dose FEV_1 and evening PEF (*P*≤0.004). For combination therapy, changes in evening pre-dose FEV_1 and evening PEF were significantly more favorable for BID administration vs QD administration (320/9 µg/day) (*P*<0.001). Mean morning PEF was maintained throughout the study with budesonide/formoterol QD (320/9 µg/day). Budesonide/formoterol QD (160/9 µg/day) was significantly more effective than budesonide in maintaining evening pre-dose FEV_1 and morning PEF during treatment (*P*≤0.016). For combination therapy, changes in evening pre-dose FEV_1 and evening PEF were significantly more favorable for BID administration vs QD administration (160/9 µg/day) (*P*<0.001). Across all efficacy variables, differences between the two combination therapy QD groups were small and of questionable clinical relevance. The only significant difference noted between the two groups was for evening pre-dose PEF (least squares mean difference, 0.05 L; 95% CI, 0.00 to 0.10) which favored the higher dose QD group (320/9 µg/day) (*P*=0.031).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
inhalations QD via MDI All patients discontinued their current asthma therapy and received SB budesonide/formoterol 80/4.5 µg, 2 inhalations BID via MDI during a 4 to 5 week run-in period.	to 30 minutes of SABA use			Secondary: Results for morning and evening pre-dose PEF are reported in the primary outcome section. Changes in rescue medication use and symptom-related variables significantly favored budesonide/formoterol QD (320/90 µg/day) vs budesonide (*P*≤0.045), except awakening-free nights, asthma control days and daytime rescue medication use. For combination therapy, QD administration (320/9 µg/day) and BID administration were similarly effective for diary variables reflective of the 12 hour period after evening dosing (nighttime asthma symptoms, awakening-free nights and nighttime rescue medication use), with significantly more favorable results for BID administration compared to QD administration (320/9 µg/day) for all other symptom-related and rescue medication use variables. Changes in symptom-related variables were significantly more favorable for budesonide/formoterol QD (160/9 µg/day) compared to budesonide (*P*≤0.023), except symptom-free days and daytime rescue medication use. For combination therapy, BID administration was significantly more effective than QD (160/9 µg/day) administration for all symptom-related and rescue medication use variables (*P*<0.01), except those that reflected the 12 hour period after evening dose. For combination therapy, results for asthma control days significantly favored BID administration compared to QD administration (320/9 and 160/9 µg/day) (*P*≤0.005). The percentages of patients withdrawing due to worsening asthma were as follows: 4.6, 6.6, 3.3 and 6.6% for budesonide/formoterol QD (320/9 µg/day), budesonide/formoterol QD (160/9 µg/day), budesonide/formoterol BID and budesonide (*P* values not reported). Mean changes in AQLQ overall and domain scores were small in all groups and less than the clinically meaningful difference. These changes were significantly more favorable for budesonide/formoterol BID vs budesonide (*P*≤0.018), but similar among the combination groups (except

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				for the AQLQ symptoms domain, which significantly favored BID administration vs QD [160/9 µg/day] administration; *P*=0.034). All treatments were generally well tolerated, with most adverse events being of mild to moderate intensity.
Berger et al[34] Budesonide/formoterol 80/4.5 µg, 2 inhalations BID via MDI vs budesonide/formoterol 160/4.5 µg, 2 inhalations QD via MDI vs budesonide/formoterol 80/4.5 µg, 2 inhalations QD via MDI vs budesonide 160 µg, 2 inhalations QD via MDI vs placebo All patients discontinued their current asthma therapy and received SB treatment with	AC, DB, DD, MC, PC, RCT Patients ≥16 years of age with a documented diagnosis of asthma for ≥6 months, mild to moderate persistent asthma based on ICS use and pulmonary function, previous use of low to medium dose ICS during the month prior to enrollment and a pre bronchodilator FEV_1 60 to 90%, with bronchodilator reversibility to albuterol of ≥12% and ≥0.20 L in FEV_1	N=752 12 weeks	Primary: Pulmonary function (evening PEF as primary outcome) Secondary: Daytime and nighttime symptom scores, nighttime awakenings, rescue medication use, events of and patient withdrawals from the trial because of predefined criteria for worsening asthma control, and AQLQ	Primary: For pulmonary function variables (evening PEF and evening pre-dose FEV_1) at the end of QD administration, all combination therapy groups were significantly (*P*<0.001) more effective than placebo. Compared to budesonide, results for evening PEF significantly favored combination therapy (*P*<0.001), whereas results for evening pre-dose FEV_1 significantly favored budesonide/formoterol BID (*P*<0.001). For both evening PEF and evening pre-dose FEV_1, significant differences were observed between the budesonide/formoterol BID and QD groups, favoring BID administration (*P*≤0.010). There were no significant differences in pulmonary function variables between the two combination therapy QD groups. Secondary: Changes from baseline in all rescue medication use and symptom-related variables were significantly better for all combination therapy groups vs placebo (*P*<0.001 for all). Compared to budesonide, significantly (*P*≤0.045) better results were observed for all rescue medication use and symptom-related variables with the combination therapy BID and QD (320/9 µg/day) groups. Over the 12 week period, the percentage of patients with a symptom-free day was greater in all combination therapy groups compared to budesonide and placebo. Nighttime asthma control variables were similar in the budesonide/formoterol QD and BID groups; however, BID administration showed significantly better results than QD (160/9 µg/day) administration for all other asthma control variables (*P*≤0.020). For combination therapy, significant differences in favor of BID administration compared to QD administration (320/9 µg/day) were

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
budesonide/formoterol 80/4.5 µg, 2 inhalations BID via MDI and rescue albuterol as needed during a 4 to 5 week run-in period.				observed for asthma control days (*P*=0.030) and daytime rescue medication use (*P*=0.050). Significant differences in favor of the higher QD dose (320/9 µg/day) compared to the lower (160/9 µg/day) QD dose were observed for symptom-free days, asthma control days and rescue medication-free days (*P*≤0.040). The percentage of patient with events of or withdrawals due to worsening asthma control were significantly lower for all combination therapy groups compared to placebo (*P*<0.001 for all), and for budesonide/formoterol BID and QD (160/9 µg/day) compared to budesonide (*P*≤0.028). In addition, significantly fewer patients in the budesonide/formoterol BID, budesonide/formoterol QD (320/9 µg/day) and budesonide groups met the criterion of clinical asthma exacerbation compared to placebo (*P*<0.01). Results were not significantly different between the combination therapy groups for these variables. Mean changes from baseline in AQLQ overall and all domain scores were significantly more favorable (*P*≤0.010), and differences were clinically meaningful, for all combination therapy groups compared to placebo, with the exception of the environmental exposure domain, for which clinically meaningful differences between placebo were observed only for budesonide/formoterol BID.
Corren et al[35] Budesonide/formoterol 80/4.5 µg, 2 inhalations BID via MDI vs budesonide 80 µg, 2 inhalations BID via MDI vs formoterol 4.5 µg, 2	DB, DD, MC, PC, RCT Patients ≥12 years of age with predominantly mild to moderate persistent asthma treated with an ICS for ≥4 weeks before screening and with a pre bronchodilator FEV_1 60 to 90% of	N=480 12 weeks	Primary: Changes from baseline in morning pre-dose FEV_1 and 12-hour mean FEV_1 after morning dose Secondary: Morning and evening pre-dose PEF, daytime and nighttime symptom scores, nighttime awakenings, daily rescue medication use, and worsening asthma	Primary: The mean change from baseline in pre-dose FEV_1 was greater in patients who received budesonide/formoterol compared to those who received budesonide, formoterol or placebo (*P*<0.005). Observed mean changes from baseline in 12-hour FEV_1 were greater in patients who received budesonide/formoterol compared to those who received budesonide or placebo (*P*<0.001). There was no evidence of diminution of the 12-hour bronchodilatory effect of budesonide/formoterol during the study period. Secondary: Patients who received treatment with budesonide/formoterol had greater mean increases from baseline in morning and evening pre-dose PEF

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
inhalations BID via DPI vs placebo	predicted normal on ICS at screening			compared to budesonide or formoterol (*P*<0.001). Mean decreases in symptom scores were greater with budesonide/ formoterol compared to formoterol and placebo (*P*<0.046). Active treatments were associated with greater mean increases in awakening-free nights compared to placebo (*P*<0.012). Patients who received budesonide/formoterol had a greater mean reduction from baseline in daily rescue medication use compared to formoterol (*P*=0.006). The percentage of patients experiencing worsening asthma was reduced with budesonide/formoterol compared to formoterol or placebo (*P*≤0.01).
Murphy et al[36] Budesonide/formoterol 80/4.5 µg, 2 inhalations BID via MDI vs budesonide 80 µg, 2 inhalations BID via MDI vs formoterol 4.5 µg, 2 inhalations BID via DPI vs placebo	DB, DD, MC, PC, RCT Patients ≥18 years of age with predominantly mild to moderate persistent asthma	N=405 12 weeks	Primary: AQLQ, MOS Sleep Scale, asthma control variables (daily asthma symptom score, percentage of symptom free days, percentage of rescue medication free days, percentage of asthma control days), and PSAM Secondary: Not reported	Primary: A significantly greater improvement from baseline in AQLQ overall and domain scores, MOS Sleep Scale domain scores and asthma control variables was seen in the budesonide/formoterol group compared to placebo (*P*<0.033). A significantly greater improvement from baseline in AQLQ overall and domain scores, daily asthma symptom score, percentage of symptom free days, percentage of rescue medication free days and percentage of asthma control days was seen in the budesonide/formoterol group compared to formoterol (*P*<0.042). Significantly greater PSAM scores were reported in the budesonide/ formoterol group compared to all other treatment arms (*P*<0.004). Secondary: Not reported
Noonan et al[37] Budesonide/formoterol 160/4.5 µg, 2 inhalations	DB, DD, MC, PC, RCT Patients ≥12 years	N=596 12 weeks	Primary: Mean change from baseline in morning pre-dose FEV_1 and mean	Primary: Greater improvements in morning pre-dose FEV_1 were obtained in patients treated with budesonide/formoterol (0.19 L) than those treated with budesonide (0.10 L), formoterol (-0.12 L) or placebo (-0.17 L;

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
BID via MDI vs budesonide 160 µg, 2 inhalations BID via MDI plus formoterol 4.5 µg, 2 inhalations BID via DPI vs budesonide 160 µg, 2 inhalations BID via MDI vs formoterol 4.5 µg, 2 inhalations BID via DPI vs placebo	of age, documented diagnosis of asthma for ≥6 months, moderate to high ICS use for ≥4 weeks, pre bronchodilator FEV_1 45 to 85% of predicted normal		change from baseline in 12-hour FEV_1 after administration of morning dose Secondary: PEF, asthma symptoms, rescue medications use, and worsening asthma	*P*≤0.049). Patients who received budesonide/formoterol also demonstrated a greater improvement in 12-hour FEV_1 than budesonide, formoterol and placebo at two weeks and end of treatment (*P*≤0.001). Fewer patients receiving budesonide/formoterol than the individual products or placebo met worsening asthma criteria. Secondary: Budesonide/formoterol treatment resulted in greater improvements in morning and evening PEF, daytime and nighttime symptoms, worsening asthma and percentage of symptom-free days than budesonide, formoterol and placebo (*P*≤0.05). Patients receiving budesonide/formoterol demonstrated reduction in asthma symptoms, use of rescue medication and improvement in PEF within the first day and effects were maintained over the course of the 12-week study. Significant reductions in the use of rescue medication were observed in patients with budesonide/formoterol treatment compared to formoterol (*P*<0.001) and placebo but not with budesonide (*P*=0.066). Awakenings due to asthma were not significantly different between active treatment groups. Similar results were obtained for treatment arms with combination budesonide/formoterol and concurrent administration of the individual components. No clinically significant differences in adverse events were observed between treatment groups. Patients who received budesonide/formoterol had clinically significant bronchodilation, defined as >15% improvement in FEV_1, within 15 minutes and effect was maintained over 12 hours.
Bateman et al[38] Budesonide/formoterol 160/4.5 µg, 1 inhalation BID via DPI	DB, DD, PG, RCT Patients with asthma (average age of 42 years,	N=373 12 weeks	Primary: Morning PEF Secondary: Evening PEF, clinic	Primary: Patients in the budesonide/formoterol group had significantly greater increases in morning PEF than those in the fluticasone group (27.4 vs 7.7 L/minute, respectively; *P*<0.001).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
vs fluticasone 250 µg, 1 inhalation BID via DPI There was a 2 week run-in period in which patients received budesonide 200 µg BID.	FEV_1 78% predicted, reversibility 21%)		FEV_1, use of reliever medication, symptom-free days, asthma control days, night-time awakenings, and risk of having an exacerbation	Secondary: Those in the budesonide/formoterol group had a significant improvement in their evening PEF and FEV_1 compared to the fluticasone group (*P* values not reported). Also, patients in the budesonide/formoterol group utilized less reliever medication (*P*=0.04) and had a greater proportion of reliever-free days (*P*<0.001). Patients in the budesonide/formoterol group had a 32% risk reduction of having an exacerbation compared to those in the fluticasone group (*P*<0.05). Although not statistically significant, patients in the budesonide/formoterol group had improvements in regards to symptom-free days, asthma control days and nighttime awakenings vs those in the fluticasone group (60.4 vs 55.5%, 57.8 vs 52.4% and 7.9 vs 9.6%, respectively; *P* values not reported).
Papi et al[39] Budesonide/formoterol 200/6 µg, 2 inhalations BID via DPI vs beclomethasone/ formoterol 100/6 µg, 2 inhalations BID via MDI There was a 2 week run-in period in which patients were allowed to continue their stable dose of ICS and use salbutamol as needed, except ≥6 hours prior to pulmonary function test.	DB, DD, MC, PG, RCT Patients 18 to 65 years of age with moderate to severe persistent asthma, an FEV_1 of 50 to 80% of predicted normal, previously treated with an ICS <1,000 µg/day of BDP equivalent, uncontrolled asthma symptoms	N=219 12 weeks	Primary: Morning pre-dose PEF measured by patients (weeks 11 to 12) Secondary: FEV_1, FVC, PEF, $MEF_{50\%}$, symptom scores, and time to first exacerbation	Primary: There was no significant difference in morning pre-dose PEF observed between beclomethasone/formoterol and budesonide/formoterol (difference between adjusted means, 0.49 L/minute; CI, –11.97 to 12.95). Secondary: Patients in the beclomethasone/formoterol and budesonide/formoterol groups had a significant improvement from baseline in their morning PEF (mean increase, 29.43±52.80 L/minute; 95% CI, 19.31 to 39.54; mean increase, 28.63±43.40 L/minute; 95% CI, 20.39 to 36.87). There was no significant difference in evening PEF between the two treatment groups (*P* value not reported). Patients in both treatment groups had significant improvements in FEV_1, FVC, PEF and $MEF_{50\%}$ from baseline beginning at week two of treatment and continuing throughout the study period (*P* value not reported). There was no statistically significant difference reported between the two treatment groups at the end of the study (*P* value not reported). There were statistically significant improvements in both daytime and

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				nighttime symptom scores from baseline observed between the two treatment groups (*P*<0.001), Patients in the beclomethasone/formoterol and budesonide/formoterol groups had a reduction in the daily use of rescue medication in the last week of the run-in period to the last two weeks of the treatment period (2.16±1.15 to 0.76±0.92 puffs/day and 2.28±1.50 to 0.87±1.04 puffs/day, respectively). There was no statistically significant difference in the time to first exacerbation observed between the two groups (*P* value not reported).
Scicchitano et al[40] Budesonide/formoterol 160/4.5 µg, 2 inhalations QD with additional inhalations as needed via MDI vs budesonide 160 µg, 2 inhalations BID via DPI and terbutaline 0.4 mg inhalations as needed	DB, PG, RCT Patients 11 to 80 years of age with symptomatic asthma, mean FEV_1 70% of predicted, mean ICS dose 746 µg/day	N=1,890 12 months	Primary: Time to first severe exacerbation (defined as hospital/emergency room visit, oral steroids or fall in morning PEF to <70% of baseline for two consecutive days) Secondary: Number of severe exacerbations, use of as needed medication, mean daily ICS dose, and number of asthma control days	Primary: Patients in the budesonide/formoterol group had prolonged time to first exacerbation, and a 39% lower risk of having a severe exacerbation compared to the budesonide group (*P*<0.001). Secondary: Patients in the budesonide/formoterol group had 45% fewer severe exacerbations resulting in medical interventions/patient compared to those in the budesonide group (*P*<0.001). Patients in the budesonide/formoterol group also had less utilization of as-needed medication (*P*<0.001), and a lower mean daily ICS dose (466 vs 640 µg/day, respectively) compared to those in the budesonide group. Overall, those in the budesonide/formoterol group experienced 31 more asthma control days and 12 more undisturbed nights/patient-year vs those in the budesonide group (*P* value not reported).
Rabe et al[41] Budesonide/formoterol 80/4.5 µg, 2 inhalations every evening and additional inhalations as needed via MDI	AC, DB, MC, PG, RCT Patients 11 to 79 years of age with an asthma diagnosis for ≥6 months, FEV_1 60	N=697 6 months	Primary: Morning PEF Secondary: FEV_1, evening PEF, as needed inhalations, as needed medication-free days, asthma symptom	Primary: Patients in the budesonide/formoterol group had greater improvements in morning PEF from baseline than those in the budesonide group and was maintained throughout the six month treatment period (34.5 vs 9.5 L/minute, respectively; *P*<0.001). Secondary: Both treatment groups were associated with an increase in mean FEV_1,

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
vs budesonide 160 µg, 2 inhalations every evening via DPI and terbutaline 0.4 mg as needed There was a 14 to 18 day run-in period in which patients received budesonide 100 µg BID and terbutaline 0.5 mg as needed, both via DPI.	to 100% predicted normal, >12% reversibility of baseline FEV_1 15 minutes after terbutaline 1 mg inhalation, all patients had received an ICS 200 to 500 µg/day for ≥3 months at a constant dose for ≥30 days prior to study and were required to have had ≥7 inhalations of as-needed medication during the last 10 days of the run-in period but <10 inhalations on any single day		score, nighttime awakenings, symptom free days, asthma control days, and risk of exacerbation	but those in the budesonide/formoterol group had statistically significant greater improvements compared to those receiving budesonide alone (*P*<0.001). Patients in the budesonide/formoterol group also had greater improvements in evening PEF from baseline than those in the budesonide group. Patients in the budesonide/formoterol group had statistically significantly lower asthma symptom scores in comparison to those who were receiving budesonide (*P*<0.001). There was also a statistically significant improvement in both symptom free days and asthma control-days observed in the budesonide/formoterol group vs those in the budesonide group (*P*<0.01). Those in the budesonide/formoterol group had less utilization of as-needed medication, along with eight percent more as-needed medication-free days vs those in the budesonide group (*P*<0.001). Patients in the budesonide/formoterol had a 54% lower risk in having an exacerbation in comparison to those in the budesonide group (*P*=0.0011), as well as 90% fewer hospitalizations/emergency department treatments vs those in the budesonide group (*P*=0.026).
Louis et al[42] Budesonide/formoterol 160/4.5 µg, 1 inhalation BID with additional inhalations as needed via MDI vs conventional best practice (CBP) treatment (multiple controller	MC, OL, PG, RCT Patients ≥12 years of age with an asthma diagnosis for >3 months and prescribed ICS at a dose of ≥500 µg/day beclomethasone dipropionate equivalent with or without other	N=908 26 weeks	Primary: Time to first severe asthma exacerbation (defined as deterioration in asthma leading to hospitalization, emergency room visit, or equivalent) or oral steroid treatment for ≥3 days. Secondary: Number of severe	Primary: There was no difference in the time to first severe asthma exacerbation for patients treated with budesonide/formoterol compared to CBP (*P*=0.75). Secondary: Only 2.7% of patients who received budesonide/formoterol and 4.1% of patients treated according to CBP experienced a severe asthma exacerbation during treatment. Twelve patients in the budesonide/formoterol group experienced a total of 14 exacerbations, and 19 patients in the CBP group experienced a total of 25 exacerbations (annual rate including all patients: 0.074 vs 0.13 per patient-year; *P*=0.09). A similar percentage of patients in both groups had ≥1 day during which at

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
therapies allowed, ICS and ICS/LABAs at any dose and add-on oral leukotriene antagonist or xanthenes if warranted) The CBP group was treated in a stepwise approach in accordance with the Global Initiative for Asthma guidelines.	controller therapies, if a patient was using ICS monotherapy, they needed to use ≥3 inhalations of as-needed medication for symptom relief during the last 7 days before enrolment.		asthma exacerbations, the mean use of as-needed medication (reliever medication) and prescribed asthma medications and scores on ACQ5, SATQ,	least one dose of an as-needed medication was required (58.5 and 63.5% for budesonide/formoterol and CBP groups, respectively; *P* value not reported). The mean daily dose of inhaled steroid was significantly lower in the budesonide/formoterol group compared to the CBP group (482 vs 589 µg daily, *P*<0.0001). In the budesonide/formoterol group, the mean ACQ5 score assessing symptom control and activity limitation during the treatment period, decreased by -0.30 compared to -0.17 in the CBP group (*P*<0.01). Both groups showed similar overall treatment satisfaction (improvement in SATQ overall score) from enrolment to the end of the study (*P* value not reported).
Akamatsu et al[43] Budesonide/formoterol 160/4.5 µg, 2 inhalations BID vs Fluticasone/salmeterol 250/50 µg, 1 inhalation BID	AC, RCT Patients >18 years of age with asthma for ≥6 months who were able to perform expiratory maneuvers and were receiving fluticasone/ salmeterol for ≥8 weeks	N=66 12 weeks	Primary: ACQ5, pulmonary function tests and exhaled NO parameters Secondary: Not reported	Primary: There was no change in ACQ5 between patients treated with budesonide/formoterol and fluticasone/salmeterol; however, the proportion of patients with an improvement in ACQ5 was significantly higher in the budesonide/formoterol group compared to the fluticasone/salmeterol group (51.6 vs 16.7%; *P*=0.003). The minimum PEF and maximum PEF significantly improved (*P*=0.021 and *P*=0.0054, respectively) in patients treated with budesonide/formoterol but not for patients in the fluticasone/salmeterol group; however, there was no significance between the two treatment groups overall (*P*=0.573 and *P*=0.092, respectively). The changes in exhaled NO parameters after 12 weeks of treatment demonstrated significant improvements in CANO (*P*=0.007) and CANOcorr (*P*=0.008) in the budesonide/formoterol group but not in the fluticasone/salmeterol group. The differences between the treatment groups were statistically significant, favoring budesonide/formoterol (*P*=0.047 and *P*=0.037, respectively). Secondary: Not reported

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Cates et al[44] Budesonide/formoterol vs ICS plus reliever therapy vs current best practice	MA (13 RCTs) Adults and children with chronic asthma	N=13,152 At least 12 weeks	Primary: Exacerbations requiring hospitalization, exacerbations requiring oral corticosteroids, serious adverse events (including mortality and life-threatening events) and growth (in children) Secondary: Severe exacerbations (composite outcome of hospitalization/ emergency room visit/oral steroid course), morning and evening PEF, FEV_1, rescue medication use per day, symptoms/symptom-free days, nocturnal awakenings and quality of life	Primary: *Exacerbations of asthma causing hospital admissions* Twenty one adults and adolescents treated with budesonide/formoterol 160/4.5 µg experienced an exacerbation leading to hospitalization compared to 26 patients treated with current best practice (Peto OR, 0.81; 95% CI, 0.45 to 1.44). Compared to ICS with a separate reliever medication, there was no statistically significant difference in exacerbations of asthma causing hospital admissions with budesonide/formoterol (Peto OR, 0.56; 95% CI, 0.28 to 1.09). Significantly fewer children treated with budesonide/formoterol were hospitalized for asthma exacerbations compared to those treated with higher doses of ICS (OR, 0.33; 95% CI, 0.15 to 0.77). *Exacerbations of asthma treated with oral corticosteroids* There was a statistically significant reduction between treatment with budesonide/formoterol 160/4.5 µg and current best practice with regard to the risk of asthma exacerbation requiring treatment with oral corticosteroids (Peto OR, 0.83; 95% CI, 0.70 to 0.98). The NNT was 90. There was a significant reduction in the number of patients requiring a course of steroids with budesonide/formoterol compared to ICS plus a separate reliever medication (OR, 0.54; 95% CI, 0.45 to 0.64). The NNT was 14. *Serious adverse events* No significant differences were reported between budesonide/formoterol 160/4.5 µg and current best practice in the risk of fatal or non-fatal serious adverse events (fatal events: Peto OR, 1.95; 95% CI, 0.53 to 7.21; non-fatal events: OR, 1.20; 95% CI 0.90 to 1.60). The overall number of events was too small to rule out the possibility of a clinically important increase or decrease in serious adverse events.

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				No significant difference was observed in either fatal (Peto OR, 0.37; 95% CI, 0.05 to 2.62) or non-fatal adverse events (OR, 0.97; 95% CI, 0.73 to 1.29) between budesonide/formoterol and ICS plus a separate reliever medication. Secondary: *Severe exacerbations requiring medical intervention* In seven studies, there was no significant reduction in the time to a severe exacerbation between patients treated with budesonide/formoterol 160/4.5 µg or current best practice (HR, 0.94; 95% CI, 0.85 to 1.04). There was a significant reduction in the time to a serious exacerbation with budesonide/formoterol compared to high dose ICS plus a separate reliever therapy (HR 0.59; 95% CI 0.49 to 0.70). *Change in morning PEF and FEV_1* Data were not available for this outcome for budesonide/formoterol 160/4.5 µg treatment compared to current best practice. There was a significant increase in PEF in the budesonide/formoterol group compared to treatment with a higher dose of budesonide (mean difference, 22.29 L/min; 95% CI, 17.62 to 26.95). There was an increase in FEV_1 with budesonide/formoterol compared to higher doses of budesonide (mean difference, 0.10 L; 95% CI, 0.07 to 0.13). There was no significant difference in PEF for FEV_1 between patients treated with budesonide/formoterol compared to higher doses of ICS. *Rescue medication use* One study evaluated rescue medication use and reported a difference of -0.16 puffs/day (95% CI, -0.27 to -0.05) with budesonide/formoterol 160/4.5 µg compared to current best practice. There was a reduction in rescue medication use in favor of

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				budesonide/formoterol compared to higher doses of budesonide (mean difference, -0.37 puffs per day; 95% CI, -0.49 to -0.25). *Quality of life* On average, children treated with budesonide/formoterol experienced two fewer nocturnal awakenings per night compared to children treated with higher doses of ICS (95% CI, -3.33 to -0.67). *Annual height gain* The mean increase in height over one year in the budesonide/formoterol group was 5.3 cm (range 1 to 14 cm), significantly higher compared to 4.3 cm (range -2 to 15 cm) in the ICS treatment group.
You-Ning et al[45] Fluticasone/salmeterol 125/25 µg, 2 inhalations BID via HFA MDI vs fluticasone/salmeterol 250/50 µg, 1 inhalation BID via Diskus	MC, OL, PG, RCT Patients 18 to 70 years of age with diagnosis of asthma, receiving stable doses of budesonide or beclomethasone up to 1,200 µg/day or fluticasone up to 600 µg per/day for ≥1 month, or required therapy with ICSs, total score of ≥8 for daytime and nighttime symptoms and ≥15% reversibility and 200 mL elevation in FEV_1 following albuterol	N=270 4 weeks	Primary: Morning PEF Secondary: Rescue medication use, daytime and nighttime symptom scores, evening PEF, FEV_1 and patient self-evaluation of efficacy	Primary: Morning PEF improved significantly in both the fluticasone/salmeterol HFA and Diskus groups compared to baseline (P<0.05), but the differences between groups was not significant (P>0.05). Secondary: All secondary endpoints improved significantly compared to baseline in both the fluticasone/salmeterol HFA and Diskus groups (P<0.05), but the difference between groups was not significant for any secondary endpoint (P>0.05) except patient self-evaluation of efficacy at visit three which was significantly higher in the Diskus group compared to the HFA group (P<0.05).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Chapman et al[46] Fluticasone/salmeterol 250/50 µg, 1 inhalation BID via Diskus plus placebo vs fluticasone 250 µg, 1 inhalation BID via Diskus plus salmeterol 50 µg, 1 inhalations BID via Diskus	DB, DD, RCT Individuals 13 to 75 years of age with symptomatic asthma	N=371 28 weeks	Primary: Change in PEFR Secondary: Mean daytime symptom score and FEV_1	Primary: Over weeks one to 12, PEFR was 43 L/minute for the combination therapy group and 36 L/minute for the concurrent therapy group respectively. The difference between the two treatment groups was 6 L/minute (CI, -13 to 0; *P*=0.114), which was within the predefined criteria for clinical equivalence. Secondary: Over weeks one to 12, 35% of the combination therapy group had a mean daytime symptom score of zero compared to 31% of the concurrent therapy group. No statistically significant difference in FEV_1 between the combination and concurrent therapy groups was noticed (*P* value not reported).
Nelson et al[47] Fluticasone/salmeterol 50/100, 50/250 or 50/500 µg, 1 inhalation BID plus placebo vs salmeterol 50 µg, 1 inhalation BID plus fluticasone 100, 250 or 500 µg, 1 inhalation BID	MA (4 DB, DD, MC, RCTs) Individuals ≥4 years of age diagnosed with asthma	N=1,375 All trials were 12 weeks in duration	Primary: Change from baseline in mean PEF over 12 weeks Secondary: Mean change in evening PEF and clinic FEV_1, median percentage of symptom-free days, nights or both, and rescue inhaler free	Primary: A significant advantage (5.4 L/minute) was seen for PEF in the combination therapy over the 12 week treatment period (*P*=0.006). Secondary: There was a difference in favor of the combination therapy in the mean difference in FEV_1 (0.04 L) compared to the concurrent therapy (*P*=0.054). The difference was statistically significant (6.11 L/minute) in the mean evening PEF in favor of the combination therapy (*P*<0.001). There was no significant difference seen in the percentage of symptom-free and/or rescue inhaler free days and nights between treatment groups (*P*=0.165 and *P*=0.635).
Perrin et al[48] Fluticasone/salmeterol 125/25 µg, 2 inhalations BID vs	RCT Patients 16 to 65 years of age with a diagnosis of asthma currently taking an ICS at a stable dose with	N=111 24 weeks	Primary: Adherence during the final six week period (number of doses taken as a percentage of those prescribed) Secondary:	Primary: During the final six weeks of therapy, the mean (SD) percent adherence was 73.7 (36.0), 76.7 (30.5) and 82.4% (24.5) for fluticasone, salmeterol and combination therapy. There was no significant difference between combination therapy and fluticasone (-8.7%; 95% CI, -10.6 to 3.3) or combination therapy and salmeterol (-5.6%; 95% CI, -16.4 to 5.1). Secondary:

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
fluticasone 125 µg, 2 inhalations BID plus salmeterol 25 µg, 2 inhalations BID At each visit, adherence data from each of the three inhalers were uploaded to a computer; therefore, adherence to the individual inhalers could be recorded. Adherence to the combination ICS/LABA inhaler was compared to the adherence to the fluticasone inhaler and to the salmeterol inhaler.	or without a separate LABA inhaler		Adherence in the first, second and third six week periods; percentage of days on which patients were fully adherent in each six week period; the proportion of patients who took >50, >80 or >90% of doses prescribed in each six week period; overuse	The point estimates of adherence were consistently higher for combination therapy compared to fluticasone or salmeterol in all four six week periods; however, the differences were not statistically significant (*P* values not reported). There were no significant differences between the different medications (fluticasone/salmeterol, fluticasone and salmeterol) when adherence was expressed as the percentage of days on which patients were fully adherent, taking the prescribed two doses BID. Throughout the study, patients were fully adherent about four days/week. The proportion of patients who took >50, >80 and >90% of medication as prescribed was not significantly different among the different medications, although the point estimates consistently favored the combination regimen (*P* values not reported). Extra doses of medication were taken on about one day/week, with no significant differences among the three medications. Likewise, when expressed as the mean number of extra doses, there was no significant difference among the three medications.
Marceau et al[49] Fluticasone/salmeterol or budesonide/formoterol (all strengths) vs ICS (beclomethasone, budesonide or fluticasone) plus a LABA (formoterol or salmeterol)	RETRO Individuals 16 to 44 years of age who have not been on combination or concurrent ICS and LABA therapy within the past year	N=5,118 1 year	Primary: Number of prescription renewals during the first year of treatment Secondary: The rate of moderate to severe asthma exacerbations (defined as a filled prescription of an ICS, an emergency department visit or hospitalization for asthma) during the first year of treatment, and weekly number of doses	Primary: An estimation of 44.2% of patients started on combination therapy and 51.5% of patients started on concurrent therapy did not renew their prescription during the first year of treatment (*P*=0.0001). The number of prescriptions filled on average during the first year after treatment initiation was 3.5 for combination therapy and 2.7 for concurrent therapy (*P* value not reported). Secondary: Concurrent users had more exacerbations (1.1 vs 0.7; *P*<0.0001), emergency department visits (0.4 vs 0.2; *P*<0.0001), hospitalizations (0.03 vs 0.01; *P*=0.78) and mean number of doses/week of SABAs (7.0 vs 5.7; *P*<0.0001) compared to combination users.

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
			of SABAs	
Gappa et al[50] Fluticasone/salmeterol 100/50 µg, 1 inhalation BID vs fluticasone 200 µg, 1 inhalation BID All patients received fluticasone 100 µg BID during a 2 week run-in period.	DB, DD, MC, PG, PRO, RCT Patients 4 to 16 years of age with symptomatic persistent seasonal or perennial asthma and prior treatment with an ICS with continuous treatment with an ICS for ≥4 weeks, consent to change ICS treatment to BID inhalations of fluticasone 100 µg and consent to no use of a SABA or anticholinergic on a regular basis	N=441 8 weeks	Primary: Change in morning PEF Secondary: Patient diaries for asthma symptoms, patient diaries for morning and evening PEF recordings, spirometry	Primary: Combination therapy was demonstrated to not be inferior to fluticasone with respect to the change in mean morning PEF after eight weeks of therapy compared to baseline (*P*<0.0004). The mean increase in morning PEF was 30.4±34.1 and 16.7±35.8 L/minute in the two treatment groups. Secondary: Combination therapy resulted in significantly better asthma control and less frequent symptoms compared to fluticasone therapy. During the eight weeks, combination therapy patients achieved an average of 3.4±2.7 weeks of good asthma control, and had 8.0 to 8.7% more days without asthma symptoms or without use of SABA than the fluticasone therapy patients (*P* values not reported). After eight weeks, patients receiving combination therapy had no asthma symptoms and required no SABA rescue medication use on more than 60% days. Asthma symptoms scores during the night and day improved in both groups with no significant differences between them (*P* value not reported). PEF increased in both treatment groups with statistically "superior" results in the combination therapy group compared to the fluticasone group (*P* value not reported). The percentage of days with a peak flow variability ≥20% was -4.7±12.5 and -1.9±12.5 for the combination therapy and monotherapy groups (-1.9; 95% CI, -4.1 to 0.25). Spirometry revealed a significantly larger increase in PEF after combination therapy (6.1 L/minute; 95% CI, 1.8 to 10.4), whereas FEV_1 and FVC increased to a comparable extent in both treatment groups.
Vaessen-Verberne et al[51] Fluticasone 200 µg, BID vs fluticasone/salmeterol 100/50 µg, BID	DB, MC, PG, RCT Patients 6 to 16 years of age with asthma who are still symptomatic on conventional doses of ICSs	N=158 26 weeks	Primary: Percentage of symptom-free days during the last 10 weeks of treatment Secondary: Not reported	Primary: The percentage of symptom-free days did not differ between the two treatment groups in any of the treatment periods (zero to six, six to 16 and 16 to 26 weeks). The mean adjusted difference in symptom-free days between fluticasone and combination therapy during the last 10 weeks was 2.6% (95% CI, -8.1 to 13.4; *P*=0.63) in the per-protocol analysis and 0.4% (95% CI, -9.1 to 9.9; *P*=0.93) in the intent-to-treat analysis.

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
All patients received fluticasone 100 µg BID during a 4 week run-in period. A SABA was used for symptom relief during this period.				Secondary: Not reported
Bateman et al[52] Fluticasone/salmeterol 100/50 µg, 1 inhalation BID via Diskus vs fluticasone 100 µg, 1 inhalation BID via Diskus All patients "stepped up" every 12 weeks until asthma was totally controlled or the highest dose was reached (fluticasone/salmeterol 500/50 µg or fluticasone 500 µg BID).	DB, MC, PG, RCT Individuals ≥12 years of age, categorized into one of three strata based up previous corticosteroid use	N=3,421 12 months	Primary: Asthma control (minimal [ideally no] chronic symptoms, minimal [infrequent] exacerbations, no emergency visits, minimal [ideally no] use of as needed β_2-agonist, no limitations on activities including exercise, PEF <20% [near] normal and minimal [or no] adverse effects from medication) symptoms and rescue albuterol use Secondary: Dose of ICS, and exacerbations	Primary: In the fluticasone/salmeterol group 71% of the patients achieved well controlled asthma compared to 65% in the fluticasone group (*P* value not reported). Compared to fluticasone, individuals in the fluticasone/salmeterol group were significantly faster to achieve asthma control (*P*≤0.002). Secondary: At a lower corticosteroid dose with fluticasone/salmeterol, control was achieved more rapidly than with fluticasone. There were a significantly lower amount of exacerbations requiring oral corticosteroids and or hospitalizations or emergency visits in the fluticasone/salmeterol group in each stratum (*P*≤0.009).
Bateman et al[53] Fluticasone/salmeterol 100/50 µg, 1 inhalation BID via Diskus	DB, MC, PG, RCT Patients 12 to 80 years of age with ≥6 month history of asthma treated	N=484 12 weeks	Primary: Mean morning PEF Secondary: Asthma control (minimal [ideally no] chronic	Primary: Patients in the fluticasone/salmeterol group maintained the improved PEF values achieved in the OL treatment period compared to those in the fluticasone group, whose PEF values decreased. The difference between the groups (63 L/minute) was statistically significant (*P*<0.001).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
vs fluticasone 250 µg, 1 inhalation BID via Diskus All patients were stabilized on fluticasone/salmeterol 250/50 µg, 1 inhalation BID via Diskus during OL treatment for 12 weeks and were "stepping down" therapy.	with only a β_2-agonist over the last 6 months; patients had to have ≤10 pack year smoking history, FEV_1 60 to 80% predicted, reversibility in lung function, combined daytime and nighttime symptom scores of ≥2 on ≥4 of the last 7 days of the run-in period and no exacerbations in the run-in period		symptoms, minimal [infrequent] exacerbations, no emergency visits, minimal [ideally no] use of as needed β_2-agonist, no limitations on activities including exercise, PEF <20% [near] normal and minimal [or no] adverse effects from medication) symptoms, and rescue albuterol use	Secondary: The portion of patients with well controlled asthma remained higher in fluticasone/salmeterol group compared to the fluticasone group (*P* value not reported). The odds of a patient achieving total control of their asthma was 62% greater in fluticasone/salmeterol group compared to the fluticasone group (*P*=0.017). Statistically significant difference in daytime symptom score, daytime and nighttime rescue use, percent symptom free and rescue-free days and nights were in favor of fluticasone/salmeterol (*P*<0.05).
Bateman et al[54] Fluticasone/salmeterol 50/25 µg, 2 inhalations BID via HFA MDI and placebo via Diskus vs fluticasone/salmeterol 100/50 µg, 1 inhalation BID via Diskus and placebo via HFA MDI vs fluticasone 50 µg, 2	DB, DD, PG, RCT Patients ≥12 years of age with diagnosis of reversible airway obstruction, smoking history of <10 pack-years, using ICSs (beclomethasone, budesonide or flunisolide at a dose of 400 to 500 µg/day or fluticasone 200 to 250 µg/day) for ≥4	N=497 12 weeks	Primary: Mean morning PEF Secondary: Evening PEF, daytime and nighttime symptom scores, albuterol use, and clinic FEV_1 values	Primary: Mean morning PEF values were equivalent between the fluticasone/ salmeterol HFA and Diskus groups (*P* value not reported). There was a significant improvement in mean morning PEF values in the fluticasone/salmeterol HFA group compared to the fluticasone CFC group (*P*<0.001). Comparisons were not made between the fluticasone/ salmeterol Diskus and the fluticasone CFC groups. Secondary: Mean evening PEF improved in all three groups compared to baseline with the greatest improvements seen in the fluticasone/salmeterol HFA and Diskus groups, and the difference was significant in the fluticasone and salmeterol HFA group compared to the fluticasone CFC group (*P*<0.001). The number of symptom free days and nights increased in all three treatment groups. The proportion of symptom free days and nights were

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
inhalations BID via CFC MDI and placebo via Diskus	weeks prior to randomization, mean morning PEF 50 to 85% of value measured after albuterol during the last 7 days of the run-in period, symptomatic for the last 7 days of the run-in period, taking albuterol ≤800 µg/day and FEV_1 >50% of predicted value			similar in the fluticasone/salmeterol HFA and Diskus groups. The fluticasone/salmeterol HFA group reported significantly more symptom free days compared to the fluticasone CFC group (*P*=0.001). The fluticasone/salmeterol HFA group reported more symptom free nights compared to the fluticasone CFC group, but this difference was not significant (*P*=0.063). The increase in albuterol free days and nights was similar in the fluticasone/salmeterol HFA and Diskus groups. The increase in albuterol free days and nights was significantly higher in the fluticasone/salmeterol HFA group compared to the fluticasone CFC group (*P*<0.033) for every assessment period except for weeks five through eight (*P*=0.093). Clinic FEV_1 values improved in all three treatment groups and the differences between groups was not significant (*P* value not reported).
Pearlman et al[55] Fluticasone/salmeterol 44/21 µg, 2 inhalations BID via HFA MDI vs fluticasone 44 µg, 1 inhalation BID via CFC MDI vs salmeterol 21 µg, 1 inhalation BID via CFC MDI	DB, PC, PG, RCT Patients ≥12 years of age diagnosed with asthma requiring pharmacotherapy over the last 6 months, FEV_1 40 to 85% of predicted value, ≥15% increase in FEV_1 within 30 minutes of albuterol administration	N=360 12 weeks	Primary: For fluticasone/ salmeterol HFA vs fluticasone CFC: AUC of the 12-hour serial FEV_1 relative to baseline For fluticasone/ salmeterol HFA vs salmeterol CFC: morning pre-dose FEV_1 at endpoint and the probability of patients remaining in the study without being withdrawn for worsening of asthma	Primary: At week 12, the average percent change in serial FEV_1 compared to baseline was significantly greater for fluticasone/salmeterol HFA compared to fluticasone CFC, salmeterol CFC and placebo (*P*≤0.007). The AUC of the 12-hour serial FEV_1 was significantly higher on day one (baseline) and week 12 for the fluticasone/salmeterol HFA group compared to the fluticasone CFC and placebo groups (*P*<0.001), and at week 12 only for the salmeterol CFC group (*P*=0.006). There was a significant improvement in morning pre-dose FEV_1 from baseline in the fluticasone/salmeterol HFA group compared to the fluticasone CFC, salmeterol CFC and placebo groups (*P*≤0.0112). There were significantly fewer patients withdrawn due to worsening of asthma in the fluticasone/salmeterol group compared to the salmeterol CFC and placebo groups (*P*<0.001). The difference was not significant

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
vs placebo HFA MDI Patients were stratified into 2 groups based on asthma therapy at baseline: Group 1-history of an ICS ≥3 months with no change in regimen for ≥1 month prior to screening at the following daily doses: beclomethasone 252 to 336 µg, triamcinolone 600 to 800 µg, flunisolide 1,000 µg, fluticasone 176 µg of MDI or 200 µg of DPI or budesonide 400 to 600 µg. Group 2-β_2-agonist use for only for 1 week prior to screening (ineligible if treated with an ICS within last month).			Secondary: Morning and evening PEF, patient-rated asthma symptom scores, albuterol use, nighttime awakenings requiring albuterol, and AQLQ scores	when comparing the fluticasone/salmeterol HFA group and the fluticasone CFC group (*P* value not reported). Secondary: There was a significant increase in mean change from baseline in morning and evening PEF in the fluticasone/salmeterol HFA group compared to the fluticasone CFC, salmeterol CFC and placebo groups (*P*≤0.006). There was a significantly greater percentage of days without asthma symptoms in the fluticasone/salmeterol HFA group compared to the fluticasone CFC, salmeterol CFC and placebo groups (*P*<0.001). There was a significant decrease in nighttime awakenings in patients in the fluticasone/salmeterol HFA group compared to the fluticasone CFC, salmeterol CFC and placebo groups (*P*≤0.007). There was a significant reduction in the need for albuterol in the fluticasone/salmeterol HFA group compared to the fluticasone CFC, salmeterol CFC and placebo groups (*P*≤0.002). There were no results reported for AQLQ.
Nathan et al[56] Fluticasone/salmeterol 110/21 µg, 1 inhalation BID via HFA MDI vs	DB, PC, PG, RCT Patients ≥12 years of age diagnosed with asthma requiring pharmacotherapy over the last 6	N=365 12 weeks	Primary: For fluticasone/ salmeterol HFA vs fluticasone CFC: AUC of the 12-hour serial FEV_1 relative to baseline For fluticasone/	Primary: The AUC of the 12-hour serial FEV_1 was significantly higher on day one (baseline) and week 12 for the fluticasone/salmeterol HFA group compared to the fluticasone CFC and placebo groups (*P*<0.001), and at week 12 when compared to the salmeterol CFC group (*P*≤0.020). There was a significantly greater improvement in morning pre-dose FEV_1 at endpoint in the fluticasone/salmeterol HFA group compared to the

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
fluticasone 110 µg,1 inhalations BID via CFC MDI vs salmeterol 21 µg, 1 inhalation BID via CFC MDI vs placebo	months, FEV_1 40 to 85% of predicted value, ≥15% increase in FEV_1 within 30 minutes of albuterol administration, history of an ICS ≥3 months with no change in regimen for ≥1 month prior to screening at the following daily doses: beclomethasone 378 to 840 µg, triamcinolone 900 to 1,600 µg, flunisolide 1,250 to 2,000 µg, fluticasone 440 to 660 µg of MDI or 400 to 600 µg of DPI or budesonide 800 to 1,200 µg		salmeterol HFA vs salmeterol CFC: morning pre-dose FEV_1 at endpoint and the probability of patients remaining in the study without being withdrawn for worsening of asthma Secondary: Morning and evening PEF, asthma symptom scores, albuterol use, and nighttime awakenings requiring albuterol use	improvements in the fluticasone CFC and salmeterol CFC groups ($P \leq 0.001$). There was a significant decrease in morning pre-dose FEV_1 in patients in the placebo group ($P \leq 0.001$). Significantly fewer patients in the fluticasone/salmeterol HFA group withdrew due to worsening of asthma compared to the salmeterol CFC and placebo groups ($P < 0.001$). The difference was not significant when comparing the fluticasone/salmeterol HFA group and the fluticasone CFC group (*P* value not reported). Secondary: There was a significant increase in mean change from baseline in morning and evening PEF in the fluticasone/salmeterol HFA group compared to the fluticasone CFC, salmeterol CFC and placebo groups ($P \leq 0.001$). There was a significant improvement in asthma symptom scores in the fluticasone/salmeterol HFA group compared to the placebo group ($P < 0.001$), but the difference when compared to the fluticasone CFC and the salmeterol CFC groups was not significant (*P* value not reported). There was a significant increase in the proportion of days with no asthma symptoms in the fluticasone/salmeterol HFA group compared to the placebo group ($P < 0.001$), but the difference when compared to the fluticasone CFC and the salmeterol CFC groups was not significant (*P* value not reported). The number of nighttime awakenings decreased in the fluticasone/salmeterol HFA group and increased in the fluticasone CFC, salmeterol CFC and placebo groups, but only the difference between the fluticasone/salmeterol HFA and placebo groups was statistically significant ($P < 0.001$). There was a significant reduction in the need for albuterol use in the fluticasone/salmeterol HFA group compared to the fluticasone CFC and placebo groups ($P \leq 0.005$), but there was no significant difference when compared to the salmeterol CFC group (*P* value not reported).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Lundback et al[57] Fluticasone/salmeterol 250/50 µg, 1 inhalation BID via Diskus vs fluticasone 250 µg, 1 inhalation BID via Diskus vs salmeterol 50 µg, 1 inhalation BID via Diskus	DB, PG, RCT Patients 18 to 70 years of age with mild to moderate asthma, symptoms ≥2 times/week and ≥1 of the following: airway hyper-responsiveness, diurnal variability in PEF ≥20% in >3 days during the last 14 days of the run-in, ≥30% difference between the highest and second highest PEF reading during any 7 days of the run-in or reversible increase of ≥15% in FEV_1 or PEF after β_2-agonist administration	N=282 12 months	Primary: Number of patients requiring an increase in study medication Secondary: Number of patients experiencing ≥2 asthma exacerbations during 12 months, clinic lung function tests (FEV_1 and FVC), airway hyper-responsiveness, diary card data containing information on morning PEF, rescue medication use, and daytime and nighttime asthma symptom scores	Primary: Statistically significant lower percentage of patients in the fluticasone/ salmeterol group required an increase in study medication compared to fluticasone and salmeterol monotherapy (*P*<0.001). Secondary: Statistically significant lower number of patients having ≥2 asthma exacerbations in the fluticasone/salmeterol group compared to the fluticasone monotherapy (*P*<0.01) and salmeterol monotherapy groups (*P*<0.001). Statistically significant improvement in morning PEF values in the fluticasone/salmeterol group compared to the fluticasone and salmeterol monotherapy groups (*P*<0.001). Statistically significant improvement in FEV_1 (*P*<0.001) and FVC (*P*<0.05) from baseline in the fluticasone/salmeterol group compared to the salmeterol monotherapy group. No statistically significant difference in FEV_1 or FVC from baseline in the fluticasone/salmeterol group compared to the fluticasone monotherapy group (*P* value not reported). Statistically significant improvement in airway hyper-responsiveness in the fluticasone/salmeterol group compared to the fluticasone monotherapy (*P*<0.05) and salmeterol monotherapy groups (*P*<0.001). Statistically significant increase in symptom-free days in the fluticasone/salmeterol group and the fluticasone monotherapy group than in the salmeterol monotherapy group (*P*<0.05). Statistically significant increase in symptom-free nights in the fluticasone/ salmeterol group and the fluticasone monotherapy group than in the salmeterol monotherapy group (*P*<0.001).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				Statistically significant increase in rescue-medication-free days in the fluticasone/salmeterol group and the fluticasone monotherapy group compared to the salmeterol group (*P*<0.05). Rescue-medication-free nights was 100% for all treatment groups.
Nelson et al[58] Fluticasone/salmeterol 88/42 µg, 1 inhalation BID via HFA MDI vs fluticasone 88 µg, 1 inhalation BID via CFC MDI vs salmeterol 42 µg, 1 inhalation BID via CFC MDI	DB, MC, PG, RCT Patients diagnosed with persistent asthma uncontrolled with an as-needed SABA alone	N=283 12 weeks	Primary: Area under the FEV_1 curve relative to baseline, withdrawal due to asthma exacerbation, and morning and evening PEF Secondary: Not reported	Primary: Morning pre-dose FEV_1 was significantly improved in the fluticasone/ salmeterol HFA group compared to the fluticasone CFC and salmeterol CFC groups (*P*≤0.016). Fewer patients in the fluticasone/salmeterol HFA group withdrew due to worsening of asthma compared to the fluticasone CFC and salmeterol CFC groups (*P*=0.024). Morning and evening PEF values were significantly increased in the fluticasone/salmeterol HFA group compared to the fluticasone CFC and salmeterol CFC groups at endpoint (*P*≤0.002). Secondary: Not reported
Postma et al[59] Fluticasone/salmeterol 100/50 µg, 1 inhalation BID vs ciclesonide 160 µg, 1 inhalation daily in the afternoon vs	DB, DD, PC, PG, MC, RCT Patients aged 12 to 75 years with a diagnosis of mild persistent asthma (FEV_1 ≥80% predicted four hours after rescue medication use (only SABA as required for two months before the	N=657 52 weeks	Primary: Time to the first severe asthma exacerbation Secondary: Percentage of asthma symptom-free days, asthma symptom scores, rescue medication use, rescue medication-free days, FEV1, PEF, AQLQ	Primary: The time to the first severe asthma exacerbation was significantly prolonged with combination therapy compared to placebo (*P*=0.0002) but there was no different between combination therapy and ciclesonide (*P*=0.24). Secondary: Patients in the ciclesonide and combination treatment groups experienced significantly fewer poorly controlled asthma days than placebo-treated patients (0.8 and 0.6% vs 1.7%, respectively; *P≤0*.0016, for both); however, there was no difference between the two treatments (*P*=0.14). The median percentages of asthma symptom-free days were significantly higher with ciclesonide and combination treatment compared to placebo

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
placebo No ICS, LABA OR other than study medications were permitted for two months prior to randomization and the 12-month study period.	start of the study) and randomized to treatment if after a two-week run-in period, they had an FEV_1 ≤80% predicted, reversible airway obstruction (change in FEV_1 ≤12% or ≥200 mL) after salbutamol inhalation, no nocturnal asthma symptoms, and a total daytime asthma symptom score of 2 to 10			(91.5 and 93.6% vs 85.2%, respectively; *P*≤0.001), but there were no significant differences between the treatment groups. (*P*>0.05). Both active treatments provided significantly more asthma symptom-free days than placebo (*P*≤0.008, one-sided), rescue medication-free days (*P*=0.0005), and days with asthma control (*P*≤0.003), without significant differences between the active treatment groups. Both ciclesonide and combination therapy provided significant reductions from baseline in asthma symptom scores (-0.31 and -0.32 vs -0.21 points, respectively; *P*≤0.0015). There was no difference in the scores between the active treatments (*P*=0.75). Patients receiving combination treatment had a significant improvement from baseline in FEV_1 compared to placebo (0.127 vs -0.022 L; *P*<0.001), but not compared to the ciclesonide group (*P*=0.15). Patients receiving combination treatment had a significant improvement from baseline in morning PEF compared to placebo (30.16 vs -9.73 L/min; *P*<0.0001), but not compared to the ciclesonide group (*P*=0.80). Patients receiving combination treatment had a significant improvement from baseline in evening PEF compared to placebo (15.26 vs -15.56 L/min; *P*<0.0001), but not compared to the ciclesonide group (*P*=0.86). Overall, AQLQ scores increased significantly more in both the combination and ciclesonide treatment groups compared to placebo (*P*≤0.0017 for both). Compared to combination treatment, ciclesonide was associated with higher AQLQ scores over the course of treatment (*P*<0.0001).
Nguyen et al[60] Fluticasone/salmeterol 100/50 or 250/50 µg, 1 inhalation BID via Diskus vs	DB, RCT Pediatric patients 4 to 17 years of age with asthma, parent reported emergency room	N=39 12 months	Primary: Reducing the number of emergency department visits and hospitalizations in minority inner-city children	Primary: Statistically significant decrease in the number of emergency department visit/year in the study group compared to the control group (1.2 to 0.8; *P*=0.017). The risk of experiencing at least one hospitalization was reduced by 43% in the treatment group compared to the placebo group (risk ratio, 0.57;

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
usual care control group (all patients received ICSs at some point during the study)	visits ≥5 in the past 2 years or 2 to 3 in the past 2 months, enrolled in Medicaid in Tennessee, Mississippi or Arkansas		Secondary: Not reported	95% CI, 0.19 to 1.71; *P*=0.31). The risk of experiencing an asthma exacerbation was reduced by 23% in the treatment group compared to the placebo group (*P*=0.09). Secondary: Not reported
Ringdal et al[61] Fluticasone/salmeterol 100/50 µg, 1 inhalation BID plus oral placebo vs fluticasone 100 µg, BID plus montelukast 10 mg, QD	DB, DD, MC, PG RCT Patients 14 to 79 years of age with a diagnosis of asthma, history of receiving ICSs for ≥4 weeks prior to randomization, reversible airway obstruction, ≥15% increase in FEV_1 after β_2-agonist use, mean morning PEF 50 to 85% predicted, cumulative symptom score ≥8 during last 7 days of run-in period and symptoms on ≥4 of last 7 days of run-in	N=806 14 weeks	Primary: Mean morning PEF value Secondary: Evening PEF values, β_2-agonist use, daytime and nighttime symptom scores, changes in asthma medications, FEV_1, incidence and severity of asthma exacerbations, patient assessment of satisfaction with treatment, and physician assessment of effectiveness of treatment	Primary: Statistically significant improvement in morning PEF values in the fluticasone/ salmeterol group compared to the fluticasone plus montelukast group (361 vs 191 L/minute; *P*<0.05). Secondary: Statistically significant improvement in FEV_1 values in the fluticasone/ salmeterol group compared to the fluticasone plus montelukast group (mean treatment difference, 0.11 L; *P*<0.05). The fluticasone/salmeterol group was significantly more likely to have a symptom-free day compared to the fluticasone plus montelukast group (OR, 1.32; 95% CI, 1.05 to 1.65; *P*<0.05). The fluticasone/salmeterol group was significantly more likely to have a rescue free day compared to the fluticasone plus montelukast group (OR, 1.29; 95% CI, 1.02 to 1.63; *P*=0.03), but rescue-free nights did not reach statistical significance. A significantly lower number of patients in the fluticasone/salmeterol group had an asthma exacerbation compared to patients in the fluticasone plus montelukast group (9.6 vs 14.6%; *P*<0.05), but no significant difference between the groups in percentage of patients having moderate or severe asthma exacerbation (*P*=0.07) was noted. The time to first exacerbation was longer in the fluticasone/salmeterol group compared to the fluticasone plus montelukast group (*P*<0.05).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				Patient and physician satisfaction and assessment of treatment was higher in the fluticasone/salmeterol group compared to the fluticasone plus montelukast group (P<0.05).
Lemanske et al[62] Fluticasone 250 µg, BID (ICS step up therapy) vs fluticasone/salmeterol 100/50 µg, BID (LABA step up therapy) vs fluticasone 100 µg BID plus montelukast 5 or 10 mg/day (LTRA step up therapy) All patients received fluticasone 100 µg BID during a 2 to 8 week run-in period. A treatment period was ranked as better than another if the total amount of prednisone received during treatment was ≤180 mg, if the number of annualized asthma control days during the final 12 weeks of the period was	DB, RCT, XO Patients 6 to 17 years of age with mild to moderate asthma diagnosed by a physician, the ability to perform reproducible spirometry, an FEV_1 ≥60% before bronchodilation, an increase in the FEV_1 ≥12% (bronchodilator reversibility) or a methacholine provocation concentration causing a 20% fall in the FEV_1 of ≤12.5 mg/mL	N=182 48 weeks	Primary: Differential response to each of the three step up therapies on the basis of fixed threshold criteria for the following three asthma-control measures: the need for treatment with oral prednisone for acute exacerbations, the number of asthma control days and FEV_1 Secondary: Not reported	Primary: *Differential response to the three step up therapies* A differential response occurred in 161/165 (98%) patients. The percentage of asthma control days differed according to season in all study groups, ranging from 71 to 79% in the winter and summer months. Asthma exacerbations were most frequent during winter months. The average FEV_1 varied by less than one percent across seasons. In pairwise comparisons, the proportion of patients who had a better response to LABA step up therapy was higher than the proportion with a better response to LTRA step up therapy (52 vs 34%; P=0.02), and the proportion with a better response to LABA step up therapy was higher than the proportion of with a better response to ICS step up therapy (54 vs 32%; P=0.004), whereas the response to LTRA and ICS step up therapies were similar. The primary outcome of the trial, a three-way comparison of step-up therapy with the use of rank-ordered logistic regression, predicted that the response to LABA step up was significantly more likely to be the best response, as compared to the response to LTRA step up (relative probability, 1.6; 95% CI, 1.1 to 2.3; P=0.004) and the response to ICS step up therapy (relative probability, 1.7; 95% CI, 1.2 to 2.4; P=0.002). Secondary: Not reported

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
increased by ≥31 days or if the FEV_1 at the end of the period was ≥5% higher. If the prednisone threshold was met, the number of asthma control days and FEV_1 were ignored. If the threshold for asthma control days was met, the FEV_1 was ignored. Otherwise the order of response was determined by the FEV_1.				
Dahl et al[9] Fluticasone/salmeterol 250/50 µg, 1 inhalation BID via Diskus vs budesonide/formoterol 200/6 µg, 2 inhalations BID via DPI	DB, DD, MC, PG RCT Patients >18 years of age with a documented clinical history of asthma for ≥6 months, receiving 1,000 to 2,000 µg/day beclomethasone or equivalent, reversible increase of >12%, 15 minutes after receiving	N=1,769 24 weeks	Primary: Asthma exacerbation rate Secondary: Morning PEF, FEV_1, percentage of symptom-free days, percentage of symptom-free nights, and percentage of rescue- free days	Primary: The adjusted mean rate of all exacerbations over 24 weeks was similar in both treatment groups (2.69 vs 2.79; *P*=0.571). The rate of moderate to severe exacerbations between the treatment groups became significant favoring the fluticasone/salmeterol group (0.105) when compared to the budesonide/formoterol group (0.244) at week 17 to 24 (*P*=0.006). Fluticasone/salmeterol was associated with a 57% reduction in the rate of moderate to severe exacerbations compared to budesonide/formoterol. Secondary: The change from baseline in morning PEF was not statistically different between fluticasone/salmeterol (41.8 L/minute) and budesonide/formoterol (41.4 L/minute; *P* value not reported). The change from baseline in FEV_1 was not statistically different between fluticasone/salmeterol (0.29 L) and budesonide/formoterol (0.27 L; *P* value

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
	salbutamol, asthma symptom score of ≥2 on ≥4 of 7 days of the run-in period			not reported). The change from baseline in percent symptom-free days, nights and rescue free days was not statistically different between fluticasone/salmeterol (63, 85 and 82%) and budesonide/formoterol (60, 86 and 81%; *P* values not reported). The number of patients who achieved a well controlled week of asthma symptoms was 70% in both treatment groups; the difference was not significant (*P*=0.391). Both treatments were shown to be safe and well tolerated, and the incidence of adverse events was similar in both groups. The proportion of patients with at least one side effect that started during treatment was 55% in the fluticasone/salmeterol group and 54% in the budesonide/formoterol group. One percent of patients in each group reported oral candidiasis; overall only one adverse event was thought to be related to the medications and was hoarseness/dysphonia in the budesonide/formoterol group.
Bousquet et al[10] Fluticasone/salmeterol 500/50 µg, 1 inhalation BID via Diskus and terbutaline as needed vs budesonide/formoterol 160/4.5 µg, 2 inhalations BID and as needed via DPI	DB, MC, PG, RCT Patients ≥12 years of age with symptomatic asthma, FEV_1 ≥50%, and had experienced an asthma exacerbation in the previous year	N=2,309 6 months	Primary: Time to first severe exacerbation (defined as asthma deterioration leading to hospitalization or emergency room visit or use of oral corticosteroids for ≥3 days) Secondary: Rate of severe exacerbations, risk of first hospitalization, rate of hospitalization, FEV_1, morning and evening PEF, as needed	Primary: The time to first severe exacerbation was not statistically different between the treatment groups (HR, 0.82; *P*=0.12). Secondary: There was a 21% reduction in the overall exacerbation rate in the budesonide/formoterol group compared to the fluticasone/salmeterol group (25 vs 31 events/100 patients/year). The difference between groups was significant (*P*=0.039). The risk of hospitalization or emergency room visit was decreased in the budesonide/formoterol group when compared to the fluticasone/salmeterol group (HR, 0.64; *P*=0.031). There was a 31% reduction in the rate of hospitalization with budesonide/formoterol compared to fluticasone/salmeterol (9 vs 13 events/100 patients/year; *P*=0.046).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
			medication utilization, asthma control days, symptom free days, and safety	FEV_1 increased in both groups from 2.29 to 2.52 L in the budesonide/formoterol group and from 2.70 to 2.49 L in the fluticasone/salmeterol group. There was no difference between the treatments (*P* value not reported). Morning and evening PEF scores improved in both treatment groups (for budesonide/formoterol there was an increase from 330.1 to 359.5 L/minute in the morning PEF and an increase from 336.7 to 362.3 in evening PEF; for fluticasone/salmeterol there was an increase from 329.0 to 359.4 in the morning PEF and an increase from 337.7 to 361.7 in the evening PEF; a difference that was not statistically significant (morning; *P*=0.67, evening; *P*=0.42 evening). Use of high number as needed medication inhalations of >4, >6 and >8 inhalations/day was reported in 29, 13 and 4% of patients using the fluticasone/salmeterol treatment and in 27, 9 and 3% using the budesonide/formoterol treatment. The differences were not significant (*P*=0.36). Asthma control days increased in both treatment groups from 6.3 and 5.8% at baseline to 44.0 and 44.9% in the budesonide/formoterol and fluticasone/salmeterol groups respectively. The difference was not statistically significant (*P*=0.37). Symptom free days improved from 10.7 and 11.2 at baseline to 47.2 and 48.1 in the budesonide/formoterol and fluticasone/salmeterol groups respectively. The difference was not statistically significant (*P*=0.73). Adverse events were reported in 39 and 40% of patients in the budesonide/formoterol and fluticasone/salmeterol groups respectively. Serious adverse events were three percent in both groups. There were 11 and 20 patients who discontinued the study due to adverse events in the budesonide/formoterol and fluticasone/salmeterol groups respectively. One death occurred in the study due to typhoid fever; however, it was not linked to the study medications.

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
FitzGerald et al[11] Fluticasone/salmeterol 250/50 µg, 1 inhalation BID via Diskus vs budesonide/formoterol 200/6 µg, 2 inhalations BID via DPI	DB, DD, RCT Individuals 18 to 70 years of age, with an documented clinical history of asthma and an FEV_1 between 60 to 90% of projected normal	N=706 1 year	Primary: Percentage of symptom-free days Secondary: Daily asthma symptom scores, morning PEF, percentage of days free of rescue medication use, and nighttime awakenings due to asthma	Primary: The percentage of symptom-free days was higher with fluticasone/salmeterol compared to budesonide/formoterol (58.8 vs 52.1%; *P*=0.034). The percentage of symptom-free days was significantly higher with fluticasone/salmeterol compared to budesonide/formoterol during weeks five through 52 (73.8 vs 64.9%; *P*=0.030). Secondary: In the fluticasone/salmeterol group there was a significant difference in the adjusted annual mean exacerbation rate compared to the budesonide/formoterol group (0.18 vs 0.33; *P*=0.008). The median value for the percentage of days free of rescue medication over weeks five through 52 was 94.5% in the fluticasone/salmeterol group compared to 90.7% in the budesonide/formoterol group (*P*=0.008). Over the 52-week treatment period the mean morning PEF was significantly higher in the fluticasone/salmeterol group compared to the budesonide/formoterol group (400.1 vs 390.6 L/minute; *P*=0.006).
Price et al[12] Fluticasone/salmeterol 250/50 µg, 1 inhalation BID via Diskus-FD vs budesonide/formoterol 200/6 µg, 2 inhalations BID via DPI-AMD During weeks 1 to 4, patients received either 1	DB, DD, MC, PG, RCT Outpatients 18 to 70 years of age, with a clinical asthma history, an FEV_1 60 to 90% predicted normal, had received an ICS dose equal to 200 to 500 µg/day of beclomethasone	N=688 1 year	Primary: Symptom-free days (defined as symptom score of zero in a 24-hour period) Secondary: Rate of exacerbations	Primary: Patients in the fluticasone/salmeterol group had a significantly greater percentage of symptom/free days (58.8%) over the entire year, compared to patients in the budesonide/formoterol group (52.1%; *P*=0.034). Secondary: The adjusted annual mean exacerbation rate was also significantly lower in the fluticasone/salmeterol group compared to the budesonide/formoterol group (47%; *P*=0.008)

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
inhalation of fluticasone/ salmeterol 250/50 µg BID or 2 inhalations of budesonide/formoterol 200/6 µg and during weeks 5 to 52, those who met the criteria, received budesonide/formoterol-AMD or fluticasone/ salmeterol-FD.	and LABA, or an ICS alone at dose equal to >500 to 1,000 µg beclomethasone (≥12 weeks prior to enrollment)			
Ringdal et al[13] Fluticasone/salmeterol 250/50 µg, 1 inhalation BID via Diskus vs budesonide 800 µg, 1 inhalation BID via DPI and formoterol 12 µg, 1 inhalation BID via DPI	DB, DD, PG, RCT Patients 16 to 75 years of age with a clinical history of reversible airway obstruction, symptomatic on 1,000 to 1,600 µg/day of budesonide, beclomethasone or flunisolide, or 500 to 800 µg/day of fluticasone, FEV_1 50 to 85%, increased symptom scores or reliever use	N=428 12 weeks	Primary: Mean morning PEF (during week 12 of treatment) Secondary: Morning and evening PEF, day and nighttime symptom scores, nighttime awakenings, FEV_1, rate and severity of exacerbations, and use of rescue medication, withdrawals from study	Primary: Patients in the per-protocol population had an increase in mean morning PEF of 343 to 386 L/minute with fluticasone/salmeterol compared to an increase of 348 to 389 L/minute observed with budesonide/formoterol (-3.2 L/minute mean difference; 95% CI, -15.0 to 8.6; *P*=0.593). Similar results in mean morning PEF were seen in the intent-to-treat population for both treatment groups. Secondary: The mean rate of exacerbation/patient/84 days of treatment was significantly lower in the fluticasone/salmeterol group in comparison to the budesonide/formoterol group with a risk reduction of 36% (0.472 vs 0.735, respectively; 95% CI, 0.51 to 0.80; *P*<0.001). Over the entire treatment period, patients in the fluticasone/salmeterol group had a statistically significant greater percentage of nights with no awakenings, without symptoms and a symptom score of <2 in comparison to those in the budesonide/formoterol group (*P*=0.02, *P*=0.04 and *P*=0.03, respectively). There was no significant difference in morning and evening PEF, clinic-measured FEV_1, improvement in day-time symptoms and use of relief medication (salbutamol) between the two treatment groups.
Busse et al[14]	MC, OL, RCT,	N=1,225	Primary: Number of	Primary: There was no significant difference seen in the treatment groups and the

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Treatment period I: Fluticasone/salmeterol 250/50 µg, 1 inhalation BID via Diskus vs budesonide/formoterol 160/4.5 µg, 2 inhalations BID via MDI (FD) Treatment period II: fluticasone/salmeterol 250/50 µg, 1 inhalation BID via Diskus vs budesonide/formoterol 160/4.5 µg, 2 inhalations BID via MDI (FD) vs budesonide/formoterol 160/4.5 µg AMD (adjustable from 2 inhalations BID to 2 inhalations QD or 4 inhalations BID all via Diskus)	Patients ≥12 years of age with an asthma diagnosis for ≥6 months and who are in stable condition, required to have a pre bronchodilator FEV_1 ≥50% of predicted normal and to have been maintained on a daily medium dose ICS or ICS/LABA for ≥12 weeks before screening	Treatment Period I: 1 month Treatment Period II: 6 months	exacerbations/patient-treatment year, percentage of patients with ≥1 exacerbations, and time from first dose to first exacerbation Secondary: Predose FEV_1, morning PEF, morning and evening asthma symptom scores, nighttime awakenings, daily rescue medication use, average daily symptom scores, symptom-free days, rescue medication-free days, and safety	time to first exacerbation (*P* value not reported). There was no significant difference seen in the treatment groups and the percentage of patients with at least one exacerbation, for the AMD budesonide/formoterol group the percentage was 8.0%, 8.8% in the FD budesonide/formoterol group and 9.2% in the fluticasone/salmeterol group (*P* value not reported). There was no significant difference seen in the treatment groups and the total number of exacerbations/patient treatment year, for the AMD budesonide/formoterol group the value was 0.196, 0.240 in the FD budesonide/formoterol group and 0.189 in the fluticasone/salmeterol group (*P* value not reported). Secondary: No statistically significant differences were seen in predose FEV_1, for the AMD budesonide/formoterol group the change was 0.13 L, 0.15 L in the FD budesonide/formoterol group and 0.16 L in the fluticasone/salmeterol group (*P* value not reported). No statistically significant differences were seen in morning PEF, for the AMD budesonide/formoterol group the change was 34.73 L/minute, 30.86 L/minute in the FD budesonide/formoterol group and 33.59 L/minute in the fluticasone/salmeterol group (*P* value not reported). No statistically significant differences were seen in morning and evening asthma symptom scores, for the AMD budesonide/formoterol group the change was -0.39, for the FD budesonide/formoterol group the score was -0.37 and -0.35 L in the fluticasone/salmeterol group (*P* value not reported). No statistically significant differences were seen in nighttime awakenings. For the adjustable dose budesonide/formoterol group the percent change was 10.03%, 10.02% in the FD budesonide/formoterol group and 7.73% in the fluticasone/salmeterol group (*P* value not reported). No statistically significant differences were seen in the percentage of

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				symptom-free days, for the AMD budesonide/formoterol group the percent change was 26.59%, 25.80% in the FD budesonide/formoterol group and 25.39% in the fluticasone/salmeterol group (*P* value not reported). No statistically significant differences were seen in the percentage of rescue medication-free days, for the AMD budesonide/formoterol group the percent change was 41.84%, 41.24% in the FD budesonide/formoterol group and 38.85% in the fluticasone/salmeterol group (*P* value not reported). All treatment groups were well tolerated. Adverse events were in general mild (56.1%) or moderate (38.4%), and no study medication adverse events were considered serious.
Kuna et al[15] Fluticasone/salmeterol 125/25 µg, 2 inhalations BID vs budesonide/formoterol 320/9 µg, 1 inhalation BID vs budesonide/formoterol 160/4.5 µg, 1 inhalation BID and additional inhalations as needed Both FD treatment groups also had terbutaline as an as needed reliever	DB, DD, PG, RCT Patients ≥12 years of age with an asthma diagnosis ≥6 months, using an ICS ≥3 months, FEV_1 ≥50% predicted normal, and ≥12% reversibility following terbutaline and ≥1 asthma exacerbation in previous 1 to 12 months	N=3,335 6 months	Primary: Time to first severe exacerbation (defined as asthma deterioration resulting in hospitalization or emergency room visit or the need for oral steroids ≥3 days) Secondary: Exacerbation rates, total number of severe exacerbations, number of patients having ≥1 hospitalization, number of mild exacerbation days, asthma symptom total score, morning and evening PEF, FEV_1, asthma symptom score, asthma induced night-awakenings, symptom-	Primary: The budesonide/formoterol 160/4.5 µg group prolonged the time to first severe exacerbation when compared to the fluticasone/salmeterol (*P*=0.0034) and budesonide/formoterol 320/9 µg groups (*P*=0.023). There was a 33% reduction in the HR for a first severe exacerbation with the budesonide/formoterol 160/4.5 µg group compared to the fluticasone/salmeterol group (*P*=0.003), and a 26% reduction when compared to the budesonide/formoterol 320/9 µg group (*P*=0.026). Secondary: Exacerbation rates were 19, 16 and 12 events/100 patients/six months for the fluticasone/salmeterol group, the budesonide/formoterol 320/9 µg group and the budesonide/formoterol 160/4.5 µg group. The difference between the budesonide/formoterol 160/4.5 µg group, the fluticasone/salmeterol group (*P*<0.001) and the budesonide/formoterol 320/9 µg group (*P*=0.0048) were statistically significant. However the difference between the fluticasone/salmeterol group and the budesonide/formoterol 320/9 µg group was not statistically significant (*P*=0.1). The total number of severe exacerbations were 208, 173 and 125 in the fluticasone/salmeterol, budesonide/formoterol 320/9 µg and budesonide/formoterol 160/4.5 µg groups, respectively (*P* value not

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
medication.			free days, as-needed medication free days, asthma-control days, number of mild exacerbations (defined as a day with any of one the following: morning PEF ≥20% below baseline, daily as-needed medication use ≥2 inhalations or a night with asthma-related awakenings), and safety	reported). The percentage of patients having at least one hospitalizations/emergency room visit was 6, 5 and 4% in the fluticasone/salmeterol, budesonide/formoterol 320/9 µg and budesonide/formoterol 160/4.5 µg groups, respectively. The difference was significant between the budesonide/formoterol 160/4.5 µg group and the fluticasone/salmeterol group (*P*=0.047), but not between the two budesonide/formoterol groups or between the budesonide/formoterol 320/9 µg and fluticasone/salmeterol groups (*P*=0.066). There were no significant differences seen between the three treatment groups in the number of mild exacerbation days. Overall 59, 63 and 61% in the fluticasone/salmeterol group, the budesonide/formoterol 320/9 µg group and the budesonide/formoterol 160/4.5 µg group experienced a mild exacerbation (*P* value not reported). There were no significant differences between all three treatment groups in asthma symptom total score (1.03,1.07 and1.06), percentage of symptom-free days (46.0, 44.6 and 44.2%), percentage of asthma-control days (43.7, 42.2 and 41.3%), percentage of night-time awakenings (14.0,14.6 and 14.1%), total number of inhalations/day (0.96,1.05 and 1.02) for the fluticasone/salmeterol, the budesonide/formoterol 320/9 µg and the budesonide/formoterol 160/4.5 µg groups, respectively (*P* values not reported). There were no significant differences found between all three treatment groups in FEV_1 (2.67, 2.66 and 2.69 L), morning PEF (367, 362 and 363 L/minute), evening PEF (370, 366 and 368 L/minute) for the fluticasone/salmeterol, the budesonide/formoterol 320/9 µg and the budesonide/formoterol 160/4.5 µg groups, respectively (*P* values not reported). All three treatment groups reported no significant differences in the number or severity of adverse events. The most frequently reported adverse events were upper respiratory tract infection, pharyngitis and

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				nasopharyngitis.
Aalbers et al[16] Fluticasone/salmeterol 250/50 µg, 1 inhalation BID via Diskus-FD vs budesonide/formoterol 160/4.5 µg, 2 inhalations BID via DPI-AMD vs budesonide/formoterol 160/4.5 µg, 2 inhalations BID via DPI-FD During a 4 week DB period, the budesonide/ formoterol AMD and FD groups received 2 inhalations BID, and those in the fluticasone/salmeterol group received 1 inhalation BID. During a 6 month extension period, all FD groups remained the same and the budesonide/formoterol AMD group could decrease dose to 1	DB (4 weeks), ES (6 months), OL Patients with moderate-severe asthma, mean symptom score 1.5, mean FEV_1 84% predicted, mean ICS dose 735 µg/day	N=658 4 week DB period plus a 6 month OL extension	Primary: Odds of achieving a WCAW Secondary: Exacerbation rate and use of reliever medication	Primary: There was no difference in the OR pertaining to WCAW observed in the FD treatment groups (*P* value not reported). There was a significant increase in the odds of achieving WCAW observed in the budesonide/formoterol AMD group in comparison to the budesonide/formoterol FD group during the open period, regardless of a 15% decrease in the average use of study drug (OR, 1.335; 95% CI, 1.001 to 1.783; *P*=0.049). Secondary: Patients in the budesonide/formoterol AMD group had a significantly lower exacerbation rate (40%) compared to those in the fluticasone/salmeterol group, and a 32% lower exacerbation rate compared to those in the budesonide-formoterol FD group (*P*=0.018 and *P* value not significant, respectively). Patients in the budesonide/formoterol AMD group used significantly less reliever medication during the open study period vs those in the budesonide/formoterol and the fluticasone/salmeterol FD groups (*P*=0.001 and *P*=0.011, respectively).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
inhalation BID, or increase dose up to 4 inhalations BID for 7 to 14 days based on asthma symptoms.				
Palmqvist et al[17] Fluticasone/salmeterol 250/50 µg, 1 inhalation via Diskus vs budesonide/formoterol 160/4.5 µg, 1 inhalation via DPI vs budesonide/formoterol 160/4.5 µg, 2 inhalations via DPI vs placebo	DB, PC, RCT, XO Adult asthmatic patients (mean predicted FEV_1 of 78%, mean reversibility of 19%)	N=30 4 days	Primary: Mean FEV_1 at 15 minutes after inhalation Secondary: Time to bronchodilation (defined as >15% increase in FEV_1 from baseline), absolute FEV_1 at three minutes, and FEV_1 at time points ≤60 minutes	Primary: Both budesonide/formoterol doses demonstrated improvements in FEV_1 compared to fluticasone/salmeterol and placebo at 15 minutes postdose (P<0.001). Secondary: At one hour, bronchodilation was achieved in 47% of patients in the fluticasone/salmeterol group, 73% of those in the budesonide/formoterol one inhalation group and 77% of those in the budesonide/formoterol two inhalations group. Both doses of budesonide/formoterol also demonstrated significant improvements in FEV_1 at three minutes (P<0.001) and at 60 minutes (P values not reported) compared to fluticasone/salmeterol and placebo.
O'Connor et al[18] Month 1: Budesonide/formoterol 160/4.5 µg, 2 inhalations BID via PMDI vs fluticasone/salmeterol	OL, Phase III, RCT Patients ≥12 years of age with moderate to severe asthma	N=1,225 7 months	Primary: AQLQ, ACQ, ATSM and OEQ Secondary: Not reported	Primary: For AQLQ, no differences were observed between treatment groups in the percentages of patients with clinical meaningful improvements (≥0.5) in overall score. Although improvements were statistically significantly greater (P≤0.04) in the majority of domains for AMD vs either FD regimens, no clinically meaningful between group differences were noted. There were no statistically significant differences between FD regimens in mean improvement from baseline for overall or individual domain scores at the end of treatment.

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
250/50 µg, 1 inhalation BID via DPI Months 2 to 7: Patients receiving fluticasone/salmeterol continued therapy (FD), whereas those who received budesonide/ formoterol were randomized to continue budesonide/formoterol 160/4.5 µg, 2 inhalations BID via MDI (FD) OR to budesonide/ formoterol 160/4.5, 2 inhalations QD or 4 inhalations BID (AMD). All patients received their usual asthma therapy for 10 to 14 days prior to randomization.				At the end of treatment, the mean change from baseline for all treatment groups exceeded the minimum important difference (0.5) for the ACQ, with no statistically significant or clinically meaningful between group changes noted (*P* values not reported). As indicated by the ATSM overall score at the end of treatment, patients reported significantly greater treatment satisfactions with AMD vs FD fluticasone/salmeterol (*P*=0.020); there was no significant between group differences between the budesonide/formoterol FD and fluticasone/salmeterol FD groups. Patients in both budesonide/formoterol groups reported significantly greater treatment satisfaction than those in the fluticasone/salmeterol group for the attributes of timely relief of symptoms (*P*≤0.037) and feel medication working (*P*≤0.020). Patients in the budesonide/formoterol AMD group reported significantly greater treatment satisfaction for the attribute of dosing management than patients in the fluticasone/salmeterol FD group (*P*<0.001), and reported significantly greater treatment satisfaction of the attributes of daily activity, leisure activity and dosing management than patients in the budesonide/formoterol group FD (*P*≤0.048). For the predefined item “During the past week, you could feel your study medication begin to work right away”, 71, 71 and 59% of patients in the budesonide/formoterol AMD, budesonide/formoterol FD and fluticasone/salmeterol FD groups responded positively at the end of treatment. The differences observed between the budesonide/formoterol groups and the fluticasone/salmeterol groups were statistically significant (*P*≤0.002). For the predefined item “During the past week, you were satisfied with how quickly you felt your study medication begin to work”, 78, 80 and 73% of patients in the budesonide/formoterol AMD, budesonide/formoterol FD and fluticasone/salmeterol FD groups responded positively at the end of treatment. The difference between the FD budesonide/formoterol and fluticasone/salmeterol groups was small but statistically significant (*P*=0.025). Secondary: Not reported

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Vogelmeier et al[63] Budesonide/formoterol 160 mg/4.5 µg, 2 inhalations BID via Turbuhaler SMART™ [plus additional inhalations as needed] vs fluticasone/salmeterol 250/50 µg, 1 inhalation BID via Diskus [plus salbutamol as needed] Maintenance doses could be titrated by clinicians after the first four weeks.	PH, SA Asian outpatients ≥12 years of age with asthma for ≥6 months that used ≥500 µg/day of budesonide or fluticasone propionate (or ≥1,000 µg of another ICS) for ≥1 month prior to study entry, had pre-terbutaline FEV_1 40 to 90% of predicted and at least one severe exacerbation >2 weeks and ≤12 months before study start. Patients also had used as-needed medications on ≥4 of the past 7 days of run-in	N=404 12 months	Primary: Time to first severe exacerbation (defined as asthma deterioration resulting in hospitalization or emergency room visit, the need for oral steroids ≥3 days or unscheduled visit leading to treatment change) Secondary: Asthma control (assessed using ACQ-5), quality of life (using AQLQ(S))	Primary: The time to the first severe exacerbation was significantly longer in patients treated with maintenance plus as-needed budesonide/formoterol compared to patients treated with fluticasone/salmeterol plus as-needed salbutamol (230 vs 45 days, *P*=0.024). Patients treated with the adjusted budesonide/formoterol regimen had a 44% reduction in risk of a first exacerbation compared to patients treated with fluticasone/salmeterol plus salbutamol (95% CI, 0.32 to 0.95; *P*=0.033). The rate of severe exacerbations was lower in the maintenance plus as-needed budesonide/formoterol treatment group (0.16/patient/year) compared to the fluticasone/salmeterol plus salbutamol treatment group (0.26/patient/year) (RR, 0.62/patient/year; 95% CI, 0.41 to 0.94; *P*=0.024). Secondary: The mean changes in overall ACQ-5 scores for the maintenance plus as-needed budesonide/formoterol treatment group and the fluticasone/salmeterol plus as-needed salbutamol treatment group were -0.702 and -0.655, respectively, although this difference was not statistically significant. The mean change in overall AQLQ(S) scores for the maintenance plus as-needed budesonide/formoterol treatment group and the fluticasone/salmeterol plus as-needed salbutamol treatment group were 0.843 and 0.727, respectively, although this difference was not statistically significant. A total of 33 serious adverse events occurred, 14 in the maintenance plus as-needed budesonide/formoterol treatment group and 19 in the fluticasone/salmeterol plus as-needed salbutamol treatment group. Headache occurred more frequently in the fluticasone/salmeterol plus as-needed salbutamol treatment group compared to the budesonide/formoterol treatment group (5 vs 2%; *P*=0.033). The most commonly reported adverse events included upper respiratory

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				tract infections, nasopharyngitis, pharyngolaryngeal pain, headache and hoarseness. With the exception of headache, the rates of adverse events were similar in both groups.
Edwards et al[64] Fluticasone/salmeterol vs budesonide/formoterol vs budesonide/formoterol-AMD vs budesonide	MA (15 trials) Patients with moderate to severe asthma	N=not reported 12 to 52 weeks	Primary: Treatment failure Secondary: Hospitalizations, emergency visits, use of oral steroids	Primary: Patients in the budesonide/formoterol group demonstrated 50% less treatment failure in comparison to those who received budesonide monotherapy (RR, 1.50; 95% CI, 1.12 to 2.02; *P*=0.007). Although there seemed to be a favorable trend in the reduction of treatment failure observed in the budesonide/formoterol-AMD group vs the budesonide/formoterol group, there was no significant difference detected (RR, 0.88; 95% CI, 0.77 to 1.02; *P*=0.09). There was no significant difference observed between those in the budesonide/formoterol group and those in the fluticasone/salmeterol group in regards to treatment failure (*P*=0.86). Secondary: Patients in the fluticasone/salmeterol group had a 49% greater risk of hospitalizations/accident and emergency visits compared to those in the FD budesonide/formoterol group (RR, 1.49; 95% CI, 1.07 to 2.08; *P*=0.02). Patients in the budesonide/formoterol-AMD treatment group had a 28% risk reduction in hospitalizations/accident and emergency visits vs those treated with FD budesonide/formoterol (RR, 0.72; 95% CI, 0.52 to 0.99; *P*=0.04). Budesonide alone, was associated with a greater risk (51%) in the use of oral steroids in comparison to budesonide/formoterol (RR, 1.51; 95% CI, 1.10 to 2.09; *P*=0.01). Patients in the budesonide/formoterol-AMD group had a lower requirement for oral steroids than those in the budesonide-formoterol group (RR, 0.81; 95% CI, 0.70 to 0.95; *P*=0.01). Patients in the budesonide/formoterol-AMD treatment group experienced a 19% decreased risk in use of oral steroids vs those in the budesonide/formoterol group (RR, 0.81; 95% CI, 0.70 to 0.95; *P*=0.01).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Nathan et al[65] Mometasone/formoterol 200/10 µg, 2 inhalations BID via MDI vs mometasone 200 µg, 2 inhalations BID vs formoterol 10 µg, 2 inhalations BID vs placebo All patients entered a 2 to 3 week OL, run-in period with mometasone MDI 200 µg, BID.	DB, DD, MC, PC, PG, RCT Patients ≥12 years of age with a documented history of asthma for ≥12 months on a stable asthma regimen for ≥2 weeks at screening and with a history of a medium dose ICS for ≥12 weeks, with or without a LABA who met ≥1 of the following: an increase in FEV_1 ≥12% or a volume increase of ≥200 mL after about 15 to 20 minutes of albuterol/ salbutamol administration or of a nebulized SABA, PEF variability ≥20% or a diurnal variation of PEF ≥20%	N=781 26 weeks	Primary: Time to first asthma deterioration for combination therapy vs formoterol and bronchodilatory effect of combination therapy vs mometasone Secondary: Change from baseline AQLQ total score for combination therapy vs placebo, ACQ total score for combination therapy vs placebo and proportion of nocturnal awakenings due to asthma requiring SABA rescue medications; trough FEV_1; changes from baseline in AM PEF and symptom scores; total 24-hour SABA usage; time to first moderate asthma exacerbation; safety and tolerability	Primary: A total of 341 patients experienced asthma deteriorations at some point during the study. The median times to first deterioration were 92 and 131 days for formoterol and placebo, respectively. Because <50% of patients in the combination and mometasone groups experienced a deterioration, median times could not be determined. Significantly fewer patients receiving combination therapy (30.4%) and mometasone (33.9%) experienced an asthma deterioration compared to formoterol (54.0%) and placebo (55.6%) (*P*<0.001 for all). FEV_1 $AUC_{0\ to\ 12h}$ improved more with combination therapy compared to mometasone (*P*<0.001) or placebo (*P*<0.001) at all time points throughout the study, and to formoterol at week 12 (*P*=0.017). Secondary: There was a statistically significantly greater mean improvement in baseline AQLQ total scores for combination therapy compared to formoterol (*P*<0.001) and placebo (*P*=0.004). There was a statistically significant and clinically important improvement in the ACQ total scores for combination therapy (-0.52 vs -2.0 for formoterol vs -0.22 for placebo; *P*<0.001 for both). At end of treatment, 24 hour asthma symptoms scores were significantly more improved from baseline levels with combination therapy compared to both formoterol and placebo (*P*<0.001); mean changes from baseline were -0.50, -0.41, 0.11 and 0.09 for combination therapy, mometasone, formoterol and placebo, respectively. Both combination therapy and mometasone exhibited “superior” changes from baseline for nocturnal awakenings compared to formoterol (*P*<0.001 for both) and placebo (*P*<0.001 and *P*=0.003). Mean trough FEV_1 values were balanced across the groups at baseline and mean changes from baseline at week 12 were combination therapy,

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				0.13 L; mometasone, 0.07 L; formoterol, 0.00 L and placebo, -0.05 L. Combination therapy was significantly better than treatment with formoterol after week one (*P*≤0.001) and placebo at all time points (*P*≤0.006). Combination therapy was also statistically better than treatment with mometasone at several time points, including week 26 (*P*=0.023). At end of treatment, the mean changes from baseline in morning PEF values were 7.0, 3.2, -2.9 and -6.0% for combination therapy, mometasone, formoterol and placebo, respectively. The changes were significantly greater for combination therapy compared to the other groups (*P*≤0.008). End of treatment 24 hour SABA use was significantly reduced from baseline levels in both the combination therapy (-61.1%) and mometasone (-22.1%) groups compared to either the formoterol (184.1%) and placebo (79.1%) groups (*P*≤0.001). Reductions were seen in the proportion of patients who experienced moderate asthma exacerbations: 46.1. 50.0, 67.3 and 70.9% (*P*<0.001 for both combination therapy and mometasone vs formoterol and placebo). The most common treatment-emergent adverse events were nasopharyngitis (6.3, 7.8, 6.4 and 3.6%), upper respiratory tract infection (5.8, 8.3, 5.9 and 8.7%) and headache (4.7, 5.2, 3.0 and 3.6%).
Bernstein et al[66] Mometasone/formoterol 100/10 µg, 2 inhalations BID via MDI vs mometasone 100 µg, 2 inhalations BID vs	DB,DD, MC, PC, PG, RCT Patients ≥12 years of age with asthma for ≥12 months who were on a stable asthma regimen (unchanged dose >2 weeks prior to screening) and	N=746 26 weeks	Primary: Time to first asthma deterioration (severe asthma exacerbation, defined as lung function reduction or clinically judged deterioration), Mean change in FEV_1 $AUC_{0\ to\ 12h}$ Secondary: Change from baseline in	Primary: Fewer patients treated with mometasone/formoterol experienced an asthma deterioration event compared to patients treated with formoterol alone (17 vs 45%; *P*<0.001). In addition, the mometasone/formoterol combination treatment was associated with lower rates of deterioration compared to mometasone monotherapy and placebo (17 vs 28 and 46%, respectively; *P*≤0.006). There were fewer asthma deterioration events in the mometasone group compared to formoterol alone (28 vs 45%; *P*≤0.002). Improvements from baseline in lung function for both mometasone/formoterol and formoterol groups were apparent as early as

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
formoterol 10 µg, 2 inhalations BID vs placebo All patients entered a 2 to 3 week OL, run-in period with mometasone MDI 100 µg, BID.	had a history of low-dose ICS use >12 weeks with or without LABA		morning FEV_1 pre-dose assessment (trough FEV1) at each visit and end-point, change in AQLQ total score, change in ACQ total score, change from baseline in proportion of nights with nocturnal awakenings due to asthma requiring SABA use and 24-hr SABA usage	five minutes post-dose, peaked at two hours and were sustained throughout the 12 hour evaluation. The mometasone/formoterol combination was associated with a greater mean FEV_1 $AUC_{0 \text{ to } 12h}$ improvement from baseline at week 12 compared to mometasone alone (4.00 vs 2.53 L/h, respectively; *P*=0.001). Formoterol was associated with a significantly greater mean improvement in FEV_1 $AUC_{0 \text{ to } 12h}$ (3.83 L/h) compared to mometasone and placebo (2.53 and 1.11 L/h, respectively; *P*≤0.004). Treatment with mometasone/formoterol and mometasone also resulted in a significantly greater mean improvement in FEV_1 $AUC_{0 \text{ to } 12h}$ at week 12 compared to placebo (*P*≤0.002).Mean FEV_1 AUC $AUC_{0 \text{ to } 12h}$ improvements at week 12 in placebo, formoterol, mometasone and mometasone/formoterol treatment groups corresponded to mean increases in FEV_1 of 0.09 L (4.1%), 0.32 L (12.3%), 0.21 L (9.0%) and 0.33 L (13.8%), respectively. Secondary: Mometasone/formoterol improved morning pre-dose (trough FEV_1) lung function compared to fluticasone alone during treatment (*P*=0.029). Also, mean percentage changes from baseline in morning PEF values were -5.3, 1.4, 1.6 and 5.2% for placebo, formoterol alone, mometasone alone and mometasone/formoterol groups, respectively (*P*≤0.03 for all groups compared to placebo). Treatment with mometasone/formoterol resulted in a significantly greater mean improvement in ACQ total score at week 26 compared to formoterol and placebo (-0.40 vs -0.12 and -0.11, respectively, *P*≤0.001) but not mometasone monotherapy (-0.32). Similarly, treatment with mometasone/formoterol was associated with significantly greater changes from baseline in total AQLQ(S) score at week 26 compared to formoterol monotherapy and placebo (0.44 vs 0.15 and 0.06, respectively; *P*≤0.003) but not mometasone alone (0.39). Treatment with mometasone/formoterol, mometasone monotherapy and formoterol monotherapy reduced the proportion of nocturnal awakenings requiring SABA use compared to placebo (*P*≤0.015). Treatment with

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				mometasone/formoterol reduced nocturnal awakenings more than formoterol alone *P*=0.035), but mometasone monotherapy did not (*P*=0.742). SABA use over 24 hours was significantly reduced from baseline with mometasone/formoterol and mometasone alone compared to placebo (*P*≤0.004). In addition, mometasone alone reduced SABA use significantly more than formoterol alone (*P*=0.049).
Weinstein et al[67] Mometasone/formoterol 200/10 µg, BID via MDI vs mometasone/formoterol 400/10 µg, BID via MDI vs mometasone 400 µg, BID via MDI All patients entered a 2 to 3 week OL, run-in period with mometasone MDI 400 µg, BID.	DB, MC, PG, RCT Patients ≥12 years of age with asthma for ≥12 months uncontrolled on high dose ICSs (>1,000 mg beclomethasone equivalent) with or without LABA for 12 weeks before screening	N=728 12 weeks	Primary: Mean change in FEV_1 $AUC_{0\ to\ 12h}$ for combination therapy (800/20 µg) vs mometasone Secondary: Change from baseline in ACQ, AQLQ, proportion on nocturnal awakenings requiring SABA rescue medication, trough FEV1, evening PEF and number of asthma deteriorations (any one of the following: ≤80% of baseline FEV_1, a ≤70% of baseline PEF for at least two consecutive days or a clinically judged deterioration resulting in emergency treatment, hospitalization, or treatment with additional asthma medication such	Primary: A significant improvement from baseline to week 12 for mean change in FEV_1 $AUC_{0\ to\ 12h}$ occurred with both doses of combination therapy compared to mometasone alone (4.19 and 3.59 L/hour vs 2.04 L/hour; for the combination therapy doses of 200/10 µg, 400/10 µg and mometasone 400 µg, respectively; *P*<0.001). Both doses of combination therapy resulted in rapid (five minutes) and sustained improvement in lung function throughout 12 weeks. Secondary: Both doses of combination therapy were associated with lower ACQ scores after 12 weeks of treatment compared to mometasone alone (*P*≤0.014), indicating an improvement in asthma control. The mean AQLQ scores increased in all three treatment groups indicating less impairment on activities; however, differences between the groups were not statistically significant. Both doses of combination therapy significantly reduced the number of nocturnal awakenings due to asthma that required SABA use compared to mometasone alone (*P*≤0.006). Mean changes from baseline to week 12 were 0.10, 0.14 and 0.19 L for mometasone 400 µg monotherapy, 200/10 µg combination therapy and 400/10 µg combination therapy, respectively. The 400/10 µg combination dose was significantly more effective at improving trough FEV_1 at week 12 (*P*=0.006) and at all other time points (*P*≤0.04) compared to monotherapy, whereas the 200/10 µg combination dose was more effective than

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
			as systemic glucocorticoid steroids	monotherapy only at week 4 (*P*=0.027). The improvement from baseline in evening PEF was 11.8, 13.3, and 6.6% for the 200/10 µg and 400/10 µg combination doses, and 400 µg of monotherapy, respectively. Improvements from baseline in evening PEF were also significantly greater for both combination treatment groups compared to mometasone monotherapy at all time points (*P*≤0.004). Patients receiving the 200/10 µg dose of combination therapy had significantly fewer asthma deteriorations compared to the mometasone monotherapy group (*P*=0.038). The difference between the 400/10 µg combination treatment group and the mometasone monotherapy group was not significant (*P*=0.053). A combined analysis of both doses of (400/10 µg and 200/10 µg) showed that combination treatment was significantly better than mometasone monotherapy for reducing asthma deteriorations (*P*=0.029).
Bernstein et al[7] Mometasone/formoterol 200/10 µg, 2 inhalations BID via MDI for 12 weeks vs fluticasone/salmeterol 250/25 µg, 2 inhalations BID via MDI for 12 weeks All patients entered a 2 to 4 week run-in period with mometasone MDI 100 µg, BID.	AC, EB, MC, NI, OL Patients ≥12 years of age with persistent asthma for ≥12 months, previous treatment with a medium-dose ICS, alone or with LABA, for ≥12 weeks before screening, stable asthma treatment regimen for ≥2 weeks before screening; history of ≥2 unscheduled asthma-related	N=722 12 weeks	Primary: Mean change in FEV_1 $AUC_{0\ to\ 12h}$ Secondary: Onset of action (change from baseline in FEV_1 at 5 minutes post dose on day 1), patient-reported outcomes and asthma deterioration on treatment.	Primary: At week 12, the change in FEV_1 $AUC_{0\ to\ 12h}$ with mometasone/formoterol treatment was NI to fluticasone/salmeterol (3.43 vs 3.24 L/h, respectively; 95% CI, -0.40 to 0.76). Non inferiority was demonstrated as early as day one of treatment (3.66 vs 3.29 L/h, respectively; 95% CI, -0.11 to 0.84). Secondary: Mometasone/formoterol on FEV_1 was significantly greater than the effect of fluticasone/salmeterol at all time points measured up to 30 minutes post dose (*P*<0.001). Treatment with mometasone/formoterol was NI to fluticasone/salmeterol at both week 4 and week 12 in mean total ACQ and AQLQ score changes from baseline. In both groups, ACQ scores improved to levels that were below the “uncontrolled” threshold. Both groups had the same LS mean baseline proportion of nights with nocturnal awakenings due to asthma that required the use of a SABA. There was no significant difference between treatments in reducing SABA

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
	visits to a physician or emergency department within the past year, or ≥3 unscheduled asthma-related visits within the past 2 years; FEV_1 60 to 90% predicted at screening and baseline, an increase in absolute FEV_1 of ≥12% and ≥200 mL within 15 to 20 minutes after administration of SABA or PEF variability >20%			use by >65% at week 12 (-65.5 vs -69.8% for mometasone/formoterol and fluticasone/salmeterol, respectively; *P* value not reported). There was no significant difference between mometasone/formoterol and fluticasone/salmeterol in total LS mean 24-hour asthma symptom scores. Both treatments improved (reduced) LS mean symptom scores by ≥40% at week 12 (-40.0 vs -49.9%, respectively; *P* value not reported). The proportion of symptom-free days and nights was not significantly different between the two treatment groups. The percentage of patients with asthma deterioration defined as defined as asthma resulting in emergency treatment, hospitalization, or treatment with additional (excluded) asthma medications was similar between the two treatment groups (5.7%).
Maspero et al[68] Mometasone/formoterol 100/10 µg, 2 inhalations BID via MDI vs mometasone/formoterol 200/10 µg, 2 inhalations BID via MDI vs fluticasone/salmeterol	MC, OL, PG, RCT, SB Patients ≥12 years of age with persistent asthma for ≥12 months, an FEV_1 ≥50%, receiving medium to high dose ICSs with or without a LABA for ≥12 weeks before screening, on a stable regimen for	N=404 52 weeks	Primary: Number and percentage of patients who reported adverse events Secondary: Assessment of impact on HPA axis function	Primary: The number and percentage of patients reporting any adverse event in each group were as follows: mometasone/formoterol 22/100 µg, 109 (77.3%); fluticasone/salmeterol 250/50 µg, 56 (82.4%); mometasone/formoterol 400/10 µg, 103 (79.2%) and fluticasone/salmeterol 500/50 µg, 50 (76.9%) (*P* values not reported). No noticeable differences in the nature or frequency of adverse events were observed between the groups. The most common adverse event categories were infections and infestations; nervous system disorders; gastrointestinal disorders and respiratory, thoracic and mediastinal disorders. The majority of adverse events were of mild to moderate severity and about one third of adverse events in each group were judged as likely related to treatment.

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
125/25 µg, 2 inhalations BID via MDI vs fluticasone/salmeterol 250/25 µg, 2 inhalations BID via MDI Patients were stratified at baseline according to their previous ICS dose (medium or high).	≥2 weeks before screening, with evidence of β_2-reversibility and normal electrocardiogram; clinical laboratory tests and chest radiograph and adequate contraceptive precautions for women of childbearing age			A total of 21 patients (5.2%) reported severe or life-threatening adverse events (mometasone/formoterol 200/10 µg, 8 [5.7%]; fluticasone/salmeterol 250/50 µg, 4 [5.9%]; mometasone/formoterol, 400/10 µg, 5 [3.8%] and fluticasone/salmeterol, 4 [6.2%]). Secondary: Compared to baseline, there were sustained statistically significant reductions in plasma cortisol $AUC_{0\ to\ 24h}$ in all treatment groups (P≤0.043) at weeks 26 and 52, with the exception of a nonsignificant reduction for fluticasone/salmeterol 250/50 µg at week 52 (P=0.076). At week 26, the extents of decreases were 37.5, 28.8, 33.3 and 22.3% for mometasone/formoterol 200/10 µg, fluticasone/salmeterol 250/50 µg, mometasone/formoterol 400/10 µg and fluticasone/salmeterol 500/50 µg. At week 52, the corresponding decreases were 2.2, 16.7, 29.6 and 32.2%.
Nelson et al[69] Salmeterol 42 µg, 1 inhalation BID via MDI vs placebo Both groups received this treatment as a supplement, not a replacement to current treatment.	DB, MC, PC, PG, RCT Individuals ≥12 years of age with asthma diagnosis and currently using medication to treat it	N=26,355 28 weeks	Primary: Occurrence of combined respiratory related deaths or respiratory related life-threatening experiences Secondary: All-cause deaths, combined asthma-related deaths or life-threatening experiences, asthma-related deaths, respiratory-related deaths, combined all-cause deaths or life-threatening experiences, and all-cause hospitalizations	Primary: There were three asthma-related deaths and 22 combined asthma-related deaths or life-threatening experiences in subjects receiving placebo compared to 13 and 37 in subjects receiving salmeterol, a difference that was statistically significant (P<0.05). Secondary: There was no statistically significant difference seen in Caucasians in the primary or secondary end points (P value not reported). For the primary and two of the secondary end points there were a statistically significant difference in African Americans receiving salmeterol compared to placebo (P<0.05). Between the treatment groups there was a statistically significant difference for time to first serious adverse event causing discontinuation (placebo survival rate, 96.18%; salmeterol survival rate, 95.61%; P=0.022).
Salpeter et al[70] LABAs	MA (19 DD, PC, RCTs)	N=33,826 All trials were	Primary: Severe asthma exacerbations requiring	Primary: LABAs (formoterol and salmeterol) when compared to placebo resulted in an increase in severe exacerbations that required hospitalization (OR, 2.6;

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
vs placebo	Asthma diagnoses,15% of the participants were African American	at least 3 months	hospitalizations, life-threatening, asthma exacerbations, and asthma-related deaths Secondary: Not reported	95% CI, 1.6 to 4.3), life-threatening exacerbations (OR, 1.8; 95% CI, 1.1 to 2.9) and asthma-related deaths (OR, 3.5; 95% CI, 1.3 to 9.3), with similar risks seen in adults and children. Secondary: Not reported
Sorkness et al[71] Montelukast 5 mg QD at bedtime vs fluticasone 100 µg BID vs fluticasone/salmeterol 100/50 µg QD in the morning and salmeterol 50 µg QD at bedtime vs placebo	DB, RCT Patients ages 6 to 14 years of age with mild-moderate persistent asthma, with an FEV_1 of ≥80% predicted normal at screening and ≥70% predicted normal at randomization	N=285 48 weeks	Primary: The percent of asthma control days Secondary: Percent of episode-free days, time to first exacerbation requiring prednisone, time to treatment failure, number of treatment failures, ACQ score, FEV_1%, FEV_1/FVC, morning and evening PEF and growth	Primary: The percent of asthma control days were 64.2% for the fluticasone monotherapy group, 59.6% for the fluticasone/salmeterol group and 52.5% for the montelukast group. The difference between the fluticasone monotherapy and the montelukast group was significant (*P*=0.004). The difference between the fluticasone/salmeterol group and montelukast was not significant (*P*=0.08). Secondary: The percent of episode-free days were 26.4% in the fluticasone group, 26.8% in the fluticasone/salmeterol group, and 17.8% in the montelukast group. The differences were significant between the fluticasone group and the montelukast group *(P*=0.040) and between the fluticasone/salmeterol and montelukast groups (*P*=0.032). Kaplan-Meier survival curves showed significant “superiority” of fluticasone compared to montelukast mono therapies in favor of fluticasone in both time to first exacerbation requiring prednisone (*P*=0.002) and time to treatment failure (*P*=0.015). Twenty-eight total treatment failures occurred, five with fluticasone, eight with fluticasone/salmeterol and 15 with montelukast. The difference between fluticasone monotherapy and montelukast was significant (*P*=0.04). ACQ score improved by -0.69 in the fluticasone monotherapy group, -0.55 in the fluticasone/salmeterol group and by -0.45 in the montelukast group. There was no significant difference between the fluticasone monotherapy and fluticasone plus salmeterol therapy in ACQ score improvement;

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				however, the difference between fluticasone monotherapy and montelukast was significant (*P*=0.018*)*. The mean change in FEV_1 was 6.32% with fluticasone monotherapy, 3.62% with fluticasone/salmeterol and -0.58% with montelukast. The differences were significant between both the fluticasone monotherapy (*P*<0.001) and fluticasone/salmeterol (*P*=0.010) therapy when compared to montelukast. The mean change for FEV_1/FVC was 3.95% for the fluticasone monotherapy group, 1.76% for the fluticasone/salmeterol group and 0.07% for the montelukast group. The difference was significant between the fluticasone monotherapy group and montelukast (*P*<0.001). Morning PEF values improved by 5.18% in the fluticasone monotherapy group, 5.33% in the fluticasone/salmeterol group and by 0.65% in the montelukast group. The differences were significant between both the fluticasone monotherapy (*P*=0.002) and fluticasone/salmeterol (*P*=0.001) therapy when compared to montelukast. Evening PEF values improved by 2.95% in the fluticasone monotherapy group, 4.31% in the fluticasone/salmeterol group and worsened by -0.57% in the montelukast group. The differences were significant between both the fluticasone monotherapy (*P*=0.017) and fluticasone/salmeterol (*P*<0.001) therapy when compared to montelukast. The mean increase height from baseline was 5.3 cm with fluticasone monotherapy and fluticasone/salmeterol. The increase in height was 5.7 cm in the montelukast group; however, the differences did not reach significance (*P*<0.001) for both groups compared to montelukast.
Calhoun et al[72] Montelukast 10 mg QD vs	DB, DD, MC, RCT Patients 15 to 72 years of age diagnosed with asthma for at least	N=423 12 weeks	Primary: Change from baseline in pre-dose FEV_1 values Secondary: Morning and evening	Primary: A statistically significant improvement in the percent change from baseline in FEV_1 in the fluticasone/salmeterol group was observed compared to the montelukast group (*P*<0.001). Secondary:

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
fluticasone/salmeterol 100/50 µg BID	six months and had been treated with oral or inhaled β_2-agonists for at least six weeks prior to study, FEV_1 values of between 50 to 80% of predicted value and an increase in FEV_1 of at least 12% within 30 minutes of inhaled albuterol		PEF values, asthma symptom score, percentage of symptom-free days, β_2-agonist use, percentage of rescue-free days, percent of nights with no asthma-related awakenings, percentage of nights with no asthma-related awakenings in patients with >2 awakenings/week at baseline and nights/ week with no awakenings	A statistically significant improvement in all secondary endpoints for the fluticasone/salmeterol group was observed compared to the montelukast group (*P*<0.001).
Maspero et al[73] Montelukast 5 mg QD vs fluticasone/salmeterol 100/50 µg BID	DB, DD, MC, PG, RCT Patients 6 to 14 years of age with a diagnosis of asthma for ≥6 months, a FEV_1 between 55 to 80% of predicated normal with ≥12% FEV_1 reversibility and were not on any asthma control medications except for a SABA	N=548 12 weeks	Primary: Morning PEF values Secondary: FEV_1, evening PEF values, levels of symptoms and rescue medications, assessment of asthma control, asthma exacerbations, and safety	Primary: The mean change from baseline in morning PEF was 45.8 L/minute in the fluticasone/salmeterol group, and 28.7 L/minute in the montelukast group (*P*<0.001). Secondary: The mean change from baseline in evening PEF was 46.2 L/minute in the fluticasone/salmeterol group, and 28.0 L/minute in the montelukast group (*P*<0.001). The mean change from baseline in FEV_1 was 0.47 L in the fluticasone/salmeterol group, and 0.30 L in the montelukast group (*P*<0.001). The fluticasone/salmeterol group had significantly greater improvements in percentage of symptom free (*P*=0.025) and rescue free (*P*<0.001) 24-hour periods compared to the montelukast group. Asthma control was higher in the fluticasone/salmeterol group (88.3%)

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				than in the montelukast group (66.7%; *P*<0.001). Twice as many patients in the montelukast group (23.2%) had asthma exacerbations than in the fluticasone/salmeterol group (10.3%). Fifty five percent of patients in the fluticasone/salmeterol group and 57% in the montelukast group reported an adverse event during treatment. The most common adverse event reported in both groups was headache (23% in the fluticasone/salmeterol group and 27% in the montelukast group).
Wilson et al[74] Montelukast 10 mg QD or zafirlukast 20 mg BID (LTRA Group) vs salmeterol or formoterol or fluticasone/salmeterol or budesonide/ formoterol (doses not specified) (ICS Group)	CE Patients 12 to 80 years of age with asthma insufficiently controlled with ICS	N=361 24 months	Primary: MiniAQLQ, ACQ, HR-QOL instrument (EQ-5D) and resource use and costs Secondary: Not reported	Primary: The cost to society was significantly higher in the LTRA group compared to the ICS group (adjusted difference, £214; 95% CI, 2 to 411). Patients receiving LTRAs experienced a non-significant incremental gain of 0.009 QALYs (95% CI, -0.077 to 0.103). Secondary: Not reported
Ducharme et al[75] Montelukast 10 mg QD or zafirlukast 20 mg BID (LTRA and ICS group) vs salmeterol 50 µg BID or formoterol 12 µg BID or fluticasone/salmeterol (varying doses) or fluticasone plus salmeterol (varying	MA Children or adults with recurrent or persistent asthma	N=6,030 Varying duration (4 to 48 weeks)	Primary: Number of patients with asthma exacerbations requiring short-term courses of systemic corticosteroids Secondary: Severity of exacerbations, changes in pulmonary function tests, symptom scores, days and/or nights without symptoms,	Primary: The risk of having an exacerbation requiring systemic corticosteroids was 17% lower with the use of LABA and ICS compared to LTRA and ICS (RR, 0.83; 95% CI, 0.71 to 0.97). The type of LTRA used did not affect the primary outcome. The effect of children vs adults could not be evaluated. Secondary: Overall, LABA and ICS significantly improved morning PEF compared to LTRA and ICS (WMD, 15.66 L/minute; 95% CI, 13.21 to 18.11). Overall, LABA and ICS significantly improved evening PEF compared to

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
doses) (LABA and ICS Group) All participants remained on a stable dose of ICS of average 400 to 560 µg/day of beclomethasone or equivalent. Other long-term control medications were allowed provided the dose remained stable during the intervention.			quality of life, use of rescue inhalers, patient satisfaction, changes in measures of inflammation, adverse effects and withdrawal rates	LTRA and ICS (WMD, 12.09 L/minute; 95% CI, 9.26 to 14.92). The combined overall estimate for improvement in FEV_1 was significantly in favor of LABA and ICS compared to LTRA and ICS (WMD, 0.08 L; 95% CI, 0.06 to 0.10). One study reported a significant percent change from baseline in FEV_1 in favor of LTRA and ICS in 40 patients. The combined overall estimate for percent of rescue free days showed a significant difference in favor of LABA and ICS compared to LTRA and ICS (WMD, 8.96%; 95% CI, 4.39 to 13.53), but there was significant heterogeneity in the pooled estimate. The combined overall estimate showed a significant improvement in the global asthma quality of life with LABA and ICS (WMD, 0.11; 95% CI, 0.05 to 0.17). The combined overall estimate showed a significant increase in percentage of symptom free days in favor LABA and ICS (WMD, 6.75%; 95% CI, 3.11 to 10.39). There was significant heterogeneity observed in the montelukast group. One study reported improvement in nighttime symptom score with LABA and ICS compared to LTRA and ICS (N=429). Overall combined improvement in daytime symptoms score favored LABA and ICS (SMD, -0.18; 95% CI, -0.25 to -0.12). The combined overall estimate was in favor of less awakenings with LABA and ICS (WMD, -0.12; 95% CI, -0.19 to -0.06). One study evaluated change in percentage of rescue free nights and no significant difference between groups was observed. The overall estimate showed a significant reduction in the risk of

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				withdrawal with LABA and ICS (RR, 0.93; 95% CI, 0.73 to 0.95). The overall estimate showed no significant difference between groups on the risk of withdrawal due to an adverse event (RR, 1.02; 95% CI, 0.80 to 1.32). The overall estimate showed no significant difference between groups on the risk of withdrawal due to poor asthma control or exacerbation (RR, 0.87; 95% CI, 0.49 to 1.56). Heterogeneity was present. No significant difference was observed between groups in patients with one or more exacerbations requiring hospitalizations (RR, 1.31; 95% CI, 0.58 to 2.98).
Chronic Obstructive Pulmonary Disease				
Welte et al[76] Budesonide/formoterol 320/9 µg, 1 inhalation BID vs placebo Before enrollment, patients stopped their LABA and ICS medications. During a 2 week run-in period all patients used tiotropium 18 µg QD and a reliever medication.	DB, MC, PG, RCT Patients with COPD, eligible for ICS/LABA combination therapy, with a pre bronchodilator FEV_1 ≤50% and a history of exacerbations requiring systemic steroids and/or antibiotics	N=660 12 weeks	Primary: Change in pre-dose FEV_1 Secondary: Pre- and post-dose spirometry measurements, SGRQ-C, morning lung function, COPD symptoms and morning activities, reliever use, exacerbations, and tolerability	Primary: Treatment with budesonide/formoterol improved FEV_1 to a greater extent than placebo. Over the course of the treatment period, the increase in pre-dose FEV_1 was six percent higher (P<0.001) at clinic visits, corresponding to an absolute difference of 65 mL compared to placebo. Secondary: Budesonide/formoterol increased post-dose FEV_1 compared to placebo, by 123 and 131 mL at five and 60 minutes post-dose, respectively. Improvements in pre- and post-dose FVC and inspiratory capacity were also observed with combination therapy. Over the study period, SGRQ-C total scores improved by 3.8 units with budesonide/formoterol compared to 1.5 units with placebo (mean difference, -2.3; 95% CI, -4.23 to -0.32; P=0.023). Improvements in SGRQ-C total score by more than four units were seen in 49.5 and 40.0% of patients in the combination therapy and placebo groups (P=0.016); a similar proportion of patients in each arm had a deterioration in SGRQ-C total scores by more than four units (27.6 and 29.7%, respectively). Similar to what was observed in clinic visits, lung function measurements at home showed significant improvements in pre- and post-treatment (five

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				and 15 minutes) morning FEV_1 and PEF with budesonide/formoterol compared to placebo after one week of treatment. The improvements in FEV_1 were maintained to week 12 (*P*<0.001 for all). Treatment difference were demonstrated in all COPD symptom scores (breathlessness, nighttime awakenings, chest tightness and cough) from run-in to full treatment period (day and night) in favor of budesonide/formoterol compared to placebo (*P*<0.001 for all). Significant improvements in morning, nighttime and daytime reliever use were seen with budesonide/formoterol compared to placebo (*P* values not reported). These effects were seen after the first week of treatment and were stable over time. Severe exacerbations were experienced by 25 (7.6%) patients in the budesonide/formoterol group compared to 61 (18.5%) in the placebo group. Combination therapy decreased the rate of severe exacerbations by 62% (rate ratio, 0.38; 95% CI, 0.25 to 0.78; *P*<0.001) and decreased the number of hospitalizations/emergency room visit by 65% (rate ratio, 0.35; 95% CI, 0.16 to 0.78; *P*=0.011) compared to placebo. Time to first severe exacerbation (HR, 0.39; 95% CI, 0.24 to 0.62; *P*<0.001) and time to first hospitalization/emergency room visit (HR, 0.39; 95% CI, 0.17 to 0.89; *P*=0.026) were also prolonged with combination therapy. In addition, six and 12% of combination therapy and placebo patients required a prescription of antibiotics for the reason "exacerbation of COPD" (*P* value not reported). Both treatment arms were well tolerated and the overall incidence and severity of adverse events were comparable between groups. There were three cases of pneumonia within each group.
Rennard et al[77] Budesonide/formoterol 160/4.5 µg, 2 inhalations BID via MDI	MC, PC, RCT Patients ≥40 years of age with moderate to severe COPD and	N=1,964 12 months	Primary: Mean improvement in baseline pre-dose FEV_1 and one-hour post-dose FEV_1	Primary: The budesonide/formoterol 160/4.5 µg treatment group, demonstrated significantly greater improvements in pre-dose and one hour post-dose FEV_1 when compared to the formoterol monotherapy group (*P*≤0.023). Secondary:

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
vs budesonide/formoterol 80/4.5 µg, 2 inhalations BID via MDI vs formoterol 4.5 µg, 2 inhalations BID via DPI vs placebo	a mean percent predicted FEV_1 at baseline ranging from 33.7 to 35.5%		Secondary: Improvement in morning and evening PEF, exacerbation rates, BCS scores, sleep scores, awakening free nights, use of rescue medications, and safety	Both budesonide/formoterol dose treatment groups had significantly greater improvements in morning and evening PEF when compared to both the formoterol and placebo treatment groups (*P*≤0.017). Exacerbation rates were significantly reduced by 25 to 30% in both the budesonide/formoterol dose treatment groups when compared to the formoterol treatment group, and by 40% when compared to placebo (*P*≤0.004). Both budesonide/formoterol treatment groups had significantly greater improvements in the sleep score and rescue medication when compared to the formoterol treatment group (*P*<0.038). Only the budesonide/formoterol 160/4.5 µg treatment group had a significantly greater improvement in the BCS scores compared to the formoterol treatment group (*P* value not reported), and only the budesonide/formoterol 80/4.5 µg treatment group had a significant improvement in the awakening-free nights compared to formoterol *(P*<0.038). Both budesonide/formoterol were well tolerated compared to both formoterol and placebo. The incidence of pneumonia related adverse events were similar for all active treatment arms, when compared to placebo. The most common adverse events seen in the budesonide/formoterol treatment groups were oral candidiasis, dysphonia and muscle spasms.
Tashkin et al[78] Budesonide/formoterol 160/4.5 µg, 2 inhalations BID via MDI vs budesonide/formoterol 80/4.5 µg 2 inhalations BID via MDI	MC, PC, RCT Patients ≥40 years of age with moderate to severe COPD and a mean percent predicted FEV_1 at baseline ranging from 33.5 to 34.7%	N=1,704 6 months	Primary: Mean improvement in baseline pre-dose FEV_1 and one-hour post-dose FEV_1 Secondary: Improvement in morning and evening PEF, BCS scores, sleep scores, awakening free nights, use of rescue	Primary: The budesonide/formoterol 160/4.5 µg treatment group demonstrated a significantly greater improvement from baseline in pre-dose FEV_1 (0.08 L, 10.7%) when compared to the formoterol monotherapy group (0.04 L, 6.9%; *P*=0.026) and placebo group (0.01, 2.2%; *P* value not reported). Patients receiving the budesonide/formoterol 80/4.5 µg combination therapy did not report a significantly greater improvement in pre-dose FEV_1 when compared to the formoterol monotherapy group. Both combination budesonide/formoterol treatment arms demonstrated a significantly greater improvement in pre-dose FEV_1 and one hour post-

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
vs budesonide 160 µg, 2 inhalations BID via MDI and formoterol 4.5 µg, 2 inhalations BID via DPI vs budesonide 160 µg 2 inhalations BID via MDI vs formoterol 4.5 µg 2 inhalations BID via DPI vs placebo			medications when compared to placebo, and safety	dose FEV_1 when compared to the budesonide monotherapy treatment arm (*P*<0.001). The budesonide/formoterol 160/4.5 µg treatment group demonstrated a significantly greater improvement from baseline in one hour post-dose FEV_1 (0.20 L, 22.6%; *P* value not reported) when compared to the budesonide monotherapy group (0.03 L, 4.9%; *P*<0.001*)* and placebo (0.03 L, 4.1%; *P* value not reported). Secondary: Improvements in both morning and evening PEF values were significantly greater in both budesonide/formoterol combination treatment arms, when compared to the budesonide monotherapy, formoterol monotherapy and placebo groups (*P*≤0.016). Both budesonide/formoterol treatment groups significantly improved BCS scores, sleep scores, awakening free nights and use of rescue medications when compared to placebo (*P*<0.028). Both budesonide/formoterol treatment doses were well tolerated for the six months of treatment. The most common adverse events reported were oral candidiasis, dysphonia and headache. The incidences of pneumonia-related adverse events were similar across for all active treatment groups compared to placebo.
Larsson et al[79] Budesonide/formoterol vs fluticasone/salmeterol	OS, RETRO Patients with COPD	N=9,893 Duration not reported	Primary: COPD exacerbations, emergency visits, utilization of steroids or antibiotics and utilization of other medications used in managing COPD Secondary: Not reported	Primary: The COPD exacerbation rates were 0.80 and 1.09 per patient-year in the budesonide/formoterol and fluticasone/salmeterol treatment groups, respectively, representing a 26.6% reduction in exacerbation rate in the budesonide/formoterol group (rate ratio, 0.74; 95% CI, 0.69 to 0.79; *P*<0.0001). This corresponded to a NNT of 3.4 with budesonide/formoterol compared to fluticasone/salmeterol to prevent one exacerbation per patient-year. In budesonide/formoterol-treated patients, the yearly rate of COPD-related hospitalizations was 0.15 compared to 0.21 in patients treated with fluticasone/salmeterol (*P*<0.0001), a difference of 29.1% (rate ratio, 0.71;

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				95% CI, 0.65 to 0.78; *P*<0.0001). The NNT to prevent one COPD-related hospitalization per patient-year was 16 with budesonide/formoterol compared to fluticasone/salmeterol. There were 27% fewer days in the hospital due to exacerbations of COPD with budesonide/formoterol compared to fluticasone/salmeterol (0.63 vs 0.95 days/year; rate ratio, 0.66; 95% CI, 0.62 to 0.71; *P*<0.0001). There were 21% fewer emergency visits in the budesonide/formoterol treatment group compared to the fluticasone/salmeterol group (0.027 vs 0.034 events/patient-year; rate ratio, 0.79; 95% CI, 0.71 to 0.89; *P*=0.0003). Patients treated with budesonide/formoterol experienced 26% fewer courses of oral steroids (0.63 vs. 0.85 events per year; rate ratio, 0.74; 95% CI, 0.68 to 0.81; *P*<0.0001) and 29% fewer antibiotic courses (0.38 vs. 0.54 events per year; rate ratio, 0.70; 95% CI, 0.66 to 0.75; *P*<0.0001) than patients treated with fluticasone/salmeterol. The number of patients who required tiotropium in addition to the ICS/LABA combination was 16% lower for the budesonide/formoterol group compared to fluticasone/salmeterol group (rate ratio, 0.84; 95% CI, 0.79 to 0.89; *P*<0.0001). Secondary: Not reported
Mansori et al[80] Salmeterol 50 µg, BID vs fluticasone/salmeterol 250/50 µg, BID All patients received theophylline sustained release 200 mg BID and	RCT Male COPD patients with FEV_1 <65%, an FEV_1/FVC <70%, >2 COPD exacerbations within the previous 2 years, with a smoking history >20 packs/year	N=40 3 months	Primary: Pulmonary function tests, SABA use, and six minute walk distance Secondary: Not reported	Primary: Changes in six minute walk distance, FVC, FEV_1, PEF and the frequency of using a SABA with fluticasone/salmeterol were significantly greater compared to those receiving salmeterol (*P*<0.01 to *P*<0.001). The number of exacerbations during 90 days in the last year before the trial was not statistically different between the two groups; however, the number of exacerbations during the 90 day treatment period in patients treated with fluticasone was significantly lower compared to the other patients (*P*<0.001). Secondary: Not reported

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
ipratropium 40 µg QID before starting the trial.	but were ex-smokers in the last 2 years			
Kurashima et al[81] Tiotropium 18 µg QD vs fluticasone 200 µg and salmeterol 50 µg BID	OL, RCT, XO Patients ≥40 years of age with COPD and stable airway obstruction with post-bronchodilator FEV_1/FVC <70%, predicted FEV_1 30 to 80%, and smoking history of >10 pack-years	N=78 4 months (2 months/ treatment arm)	Primary: Post-bronchodilator FVC and FEV_1 Secondary: HRQL using the SGRQ	Primary: Both treatments significantly improved FVC and FEV_1 compared to baseline values (*P*<0.0001). The increase in post-bronchodilator FVC was greater with tiotropium as compared to fluticasone and salmeterol (*P*=0.0021). Secondary: Significant improvements in SGRQ scores were observed in both groups compared to baseline, though no significant differences were observed between groups.
Rabe et al[82] Tiotropium 18 µg QD plus formoterol 12 µg BID vs fluticasone 500 µg BID plus salmeterol 50 µg BID	DB, MC, PG, RCT Patients ≥40 years of age with a diagnosis of COPD, >10 pack-years smoking history, a post-bronchodilator FEV_1 <80% predicted and FEV_1/FVC <0% at visit 1, and predose FEV_1 ≤65% predicted at visit two	N=605 6 weeks	Primary: FEV_1 $AUC_{0-12,}$ peak FEV_1 Secondary: Morning predose FEV_1	Primary: After six weeks, the FEV_1 AUC_{0-12} mean difference was 78 mL higher (95% CI, 34 to 122) with treatment with tiotropium plus formoterol compared to treatment with fluticasone plus salmeterol (*P*=0.0006). The difference in peak FEV_1 was 103 mL (95% CI, 55 to 150) in favor of tiotropium plus formoterol (*P*<0.0001). Secondary: The difference in predose FVC after six weeks favored tiotropium plus formoterol (95% CI, 11 to 147; *P*<0.05).
Dal Negro et al[83] Fluticasone/salmeterol 250/50 µg, 1 inhalation	DB, PC, PG, RCT Patients 53 to 78 years diagnosed	N=18 52 weeks	Primary: FEV_1, morning PEF values, COPD symptom scores, number of	Primary: Increase in FEV_1 percent predicted noted in the fluticasone/salmeterol group but this increase was not significant (49.9 to 53.4%; *P*=0.07). However, if the increase is expressed as a percent over baseline value, it

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
BID via Diskus vs salmeterol 50 µg, 1 inhalation BID via Diskus vs placebo	with moderate COPD who were naïve to ICSs, FEV_1 ≤80% predicted value but >800 mL, FEV_1/FVC ratio ≤70% predicted value, FEV_1 change of ≤12% following β_2-agonist administration, receiving regular treatment with oral theophylline 200 mg BID, SABA as needed current or ex-smokers with history of ≥10 pack years		exacerbations, and β_2-agonist use Secondary: Not reported	is significant in the fluticasone/salmeterol group (1.1 to 6.6; *P*<0.001), but not in the salmeterol group (*P*=0.79). Statistically significant increase in morning PEF values in the fluticasone/salmeterol group compare to the placebo group (180 L/minute to 255.4 L/minute compared to 160.6 L/minute to 173.3 L/minute; *P*<0.001) but values did not change in the salmeterol and placebo groups. Statistically significant reduction in daily symptom scores in the fluticasone/salmeterol group (*P*=0.008), but not in the salmeterol group (*P* value not reported). Statistically significant reduction in β_2-agonist use in the fluticasone/salmeterol group (4.2 to 1.9; *P*<0.001), but not in the salmeterol group (4.1 to 4.2; *P* value not reported). Statistically significant decrease in exacerbations in fluticasone/salmeterol group (*P*<0.001), but not in salmeterol group (*P* value not reported). Secondary: Not reported
Hanania et al[84] Fluticasone/salmeterol 250/50 µg, 1 inhalation BID via Diskus vs fluticasone 250 µg, 1 inhalation BID via Diskus vs salmeterol 50 µg, 1 inhalation BID via Diskus	DB, MC, PC, RCT Patients 40 to 87 years of age, current or former smokers with ≥20 pack year history, diagnosed with COPD, FEV_1/FVC ratio of ≤70%, baseline FEV_1 of <65% predicted normal value but >0.70 L (or if ≤0.70 L, then	N=723 24 weeks	Primary: Morning pre-dose FEV_1 and two hour post-dose FEV_1 Secondary: Morning PEF values, transition dyspnea index, CRDQ, CBSQ, exacerbations, and supplemental albuterol use	Primary: Statistically significant increase in pre-dose FEV_1 in the fluticasone/salmeterol group compared to the salmeterol group (91 mL; *P*=0.012) and placebo (1 mL; *P*<0.001). No significant difference between the fluticasone/salmeterol group and the fluticasone group (*P* value not reported). Statistically significant increase in two hour post-dose FEV_1 in the fluticasone/salmeterol group compared to the salmeterol group (281 vs 200 mL; *P*<0.001), placebo (281 vs 58 mL; *P*<0.001) and fluticasone group (281 vs 147 mL; *P*<0.001). Secondary: Statistically significant increase in morning PEF values in the fluticasone/salmeterol group compared to the salmeterol, placebo and

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
vs placebo	>40% predicted)			fluticasone groups ($P \leq 0.034$), though improvements were also seen from baseline in the salmeterol and fluticasone monotherapy groups ($P<0.001$). Statistically significant improvements in dyspnea index observed in the fluticasone/salmeterol group ($P=0.023$) compared to the placebo group, in addition to improvements in the fluticasone ($P=0.057$) and salmeterol ($P=0.043$) monotherapy groups compared to the placebo group (NOTE: difference in the fluticasone monotherapy group not significant; *P* value not reported). Statistically significant reduction in supplemental albuterol use in the fluticasone/salmeterol group compared to the fluticasone monotherapy group (-1.0 vs -0.2; $P=0.036$) and placebo (-1.0 vs 0.1; $P=0.002$). Numerical reduction in supplemental albuterol use in the fluticasone/salmeterol group compared to the salmeterol monotherapy group. Statistically significant increase in CBSQ scores in the fluticasone/salmeterol group and the fluticasone monotherapy group compared to placebo ($P \leq 0.017$). There was significant difference between treatment groups in terms of exacerbations or time to first exacerbation (*P* value not provided).
Vestbo et al[85] Fluticasone/salmeterol 500/50 µg, 1 inhalation BID vs fluticasone 500 µg, 1 inhalation BID vs	DB, PC, PG, RCT Patients diagnosed with COPD, pre-dose FEV_1 25 to 70% predicted, <10% increase in FEV_1 after β_2-agonist use, pre-bronchodilator FEV_1/FVC ratio	N=1,465 12 months	Primary: Time to first observation of treatment effects in each arm of study, analyzed for the first 14 days after initial treatment Secondary: Not reported	Primary: Significant increases in PEF in the fluticasone/salmeterol and salmeterol monotherapy groups over placebo after one day ($P<0.001$). This was also observed in the fluticasone group on day two ($P<0.001$). Increase in PEF values in the fluticasone/salmeterol group was significantly better than the other treatment groups after day one ($P<0.001$). No other mention of comparison between groups. Significant increase in FEV_1 values in all treatment groups compared to placebo by day 14 ($P<0.001$ for the salmeterol monotherapy and fluticasone/salmeterol groups and $P=0.016$ for the fluticasone

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
salmeterol 50 µg, 1 inhalation BID vs placebo	≤70%, smoking history of ≥10 pack years, history of chronic bronchitis, ≥1 COPD exacerbation/year for previous 3 years, and 1 of them requiring oral corticosteroids, antibiotics, or both			monotherapy group). No mention of comparison between groups. Secondary: Not reported
Calverley et al[86] Fluticasone/salmeterol 500/50 µg, 1 inhalation BID via Diskus vs fluticasone 500 µg, 1 inhalation BID via Diskus vs salmeterol 50 µg, 1 inhalation BID via Diskus vs placebo	DB, PC, PG, RCT Patients diagnosed with COPD, pre-dose FEV_1 25 to 70% predicted, <10% increase in FEV_1 after β_2-agonist use, pre-bronchodilator FEV_1/FVC ratio ≤70%, smoking history of ≥10 pack years, a history of chronic bronchitis, ≥1 COPD exacerbation/year for previous 3 years, and ≥1 exacerbation in previous year	N=1,465 12 months	Primary: Pre-dose FEV_1 after 12 months of treatment and after abstaining from bronchodilators for ≥6 hours and from study medication by ≥12 hours Secondary: Pre-dose FVC, post-bronchodilator FEV_1 and FVC, morning PEF, use of relief medication, symptom scores, nighttime awakenings, acute COPD exacerbations and SGRQ scores	Primary: Statistically significant improvement in pre-dose FEV_1 in all treatment groups compared to placebo (P<0.001 for salmeterol, P=0.0063 for fluticasone and P<0.001 for fluticasone/salmeterol) and statistically significant improvement in the fluticasone/salmeterol group compared to the fluticasone and salmeterol monotherapy groups (P<0.001). Secondary: Predose FVC improved significantly in all groups compared to placebo (P=0.0004 for salmeterol, P=0.013 for fluticasone and P<0.001 for fluticasone/salmeterol) and there was a statistically significant improvement in pre-dose FVC in the fluticasone/salmeterol group when compared to the fluticasone and salmeterol monotherapy groups (P=0.006 for salmeterol and P<0.001 for fluticasone). Postbronchodilator FEV_1 improved significantly in the fluticasone and fluticasone/salmeterol groups compared to the placebo group (P=0.013 for fluticasone and P<0.001 for fluticasone/salmeterol), and there was a statistically significant difference between the fluticasone/salmeterol group compared to the salmeterol and fluticasone monotherapy groups (P=0.039 and P=0.0014, respectively). Statistically significant improvement in PEF in all treatment groups

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
	requiring oral corticosteroids, antibiotics, or both			compared to placebo (*P*<0.001), and there was a statistically significant improvement in the fluticasone/salmeterol group compared to the fluticasone and salmeterol monotherapy groups (*P*<0.001). All active treatment groups significantly decreased the number of exacerbations per patient/year compared to placebo (*P*=0.003), but there was no significant difference between the groups (*P* values not reported). Statistically significant reduction in the use of relief medication in the fluticasone/salmeterol group compared to the placebo and other treatment groups (*P*<0.001 for placebo, *P*=0.004 for salmeterol and *P*=0.003 for fluticasone). Statistically significant reduction in nighttime awakenings in the fluticasone/salmeterol group compared to the placebo and salmeterol groups (*P*=0.006 and *P*=0.011, respectively), but there was no significant difference between the fluticasone/salmeterol and fluticasone monotherapy groups (*P*=0.591). Fluticasone/salmeterol combination therapy showed significant improvement in SGRQ scores compared to placebo and fluticasone (*P*=0.0003 and *P*=0.021 respectively), but no difference between fluticasone/salmeterol and salmeterol monotherapy (*P*=0.071).
Partridge et al[87] Budesonide/formoterol 320/9 µg, 1 inhalation BID plus placebo vs salmeterol/fluticasone 50/500 µg, 1 inhalation BID plus placebo The treatment periods	DB, DD, RCT, XO Patients ≥40 years of age with a clinical diagnosis of COPD, symptoms for ≥2 years, ≥1 COPD exacerbation requiring oral steroids and/or antibiotics in the previous 12	N=442 2 weeks	Primary: PEF five minutes post-morning dose Secondary: PEF and FEV_1 before and at five and 15 minutes after morning dose and before evening dose, CDLM, CCQ, and SGRQ-C	Primary: The estimated increase from baseline in PEF five minutes post-morning dose was 15.1 vs 14.2 L/minute for the two groups (mean difference, 1.01 L/minute; 95% CI, -2.7 to 4.7; *P*=0.603). Secondary: Mean morning FEV_1 improved more with budesonide/formoterol at five minutes post dose (0.12 vs 0.09 L, respectively; *P*=0.090), and significantly at 15 minutes post dose (0.14 vs 0.10 L, respectively; *P*<0.05). There were no statistically significant differences in morning pre-dose lung function (i.e., PEF measurements). e-Diary recorded morning PEF and FEV_1 showed greater improvements for budesonide/formoterol, indicating a more rapid onset of effect.

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
were separated by a 1 to 2 week washout period during which the patients used their prescribed ICS in the same manner as during the run-in period.	months, a current or previous smokers with a smoking history of ≥10 pack years, FEV_1 ≤50% and FEV_1/vital capacity <70% pre-bronchodilator and who had previously used a short-acting bronchodilator as reliever medication			At five and 15 minutes post-dose, budesonide/formoterol had numerically greater improvements in both symptom variables (breathlessness and chest tightness), with no statistical significance (data not shown). Comparing patients' abilities to perform morning activities, treatment with budesonide/formoterol resulted in statistically significant improvements (total CDLM score, 0.22 vs 0.12, respectively; mean difference, 0.10; 95% CI, 0.01 to 0.19; *P*<0.05). In addition, numerically greater improvements with budesonide/formoterol were observed for the individual morning activities that comprised the total score (getting washed, dried, dressed; eating breakfast, walking around the house early and walking around the house later). Although statistically significant, the observed mean difference between treatments (0.10) was below the minimal important differences of 0.20. Overall CCQ scores and SGRQ-C total scores were comparable between the two groups (data not shown).
Make et al[88] Fluticasone/salmeterol 250/50 µg, 1 inhalation BID vs ipratropium/albuterol 36/206 µg, 1 inhalation QID	DB, DD, MC, PG, RCT Patients 40 to 85 years of age diagnosed with moderate to severe COPD, FEV_1/FVC ratio ≤70%, FEV_1 >0.70 L and ≤70% predicted normal value (or if ≤0.70 L, then ≥40% predicted), smoking history of ≥10 pack years, use of inhaled short acting	N=361 8 weeks	Primary: Morning pre-dose FEV_1 Secondary: Morning PEF values, six-hour FEV_1 AUC, percentage of symptom free nights, dyspnea, and overall combined daytime symptom score	Primary: Statistically significant improvement in morning pre-dose FEV_1 in the fluticasone/salmeterol group compared to the ipratropium/albuterol group (change from baseline, 126 vs -1 mL; *P*<0.001). Secondary: Statistically significant improvement in mean FEV_1 AUC in the fluticasone/salmeterol group at week eight compared to the ipratropium/albuterol group (change from baseline, 0.38 vs -0.18; *P*=0.002). Statistically significant improvement in morning PEF values in the fluticasone/salmeterol group compared to the ipratropium/albuterol group at week one and throughout study (change from baseline, 33 vs 1 L/minute; *P*<0.001). Mean post-administration FEV_1 values significantly higher in the ipratropium/albuterol group at one half, one and two hours compared to the fluticasone/salmeterol group (*P*<0.001), but higher in the

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
	bronchodilator for COPD for ≥30 days			fluticasone/salmeterol group at six hours (*P*=0.003). Dyspnea scores significantly higher in the fluticasone/salmeterol group compared to the ipratropium/albuterol group (*P*=0.026), though improvements over baseline observed in both groups. Significantly greater reduction in overall daytime symptom score in the fluticasone/salmeterol group compared to the ipratropium/albuterol group (change from baseline, -46.7 vs -28.1; *P*=0.024). Statistically significant increase in albuterol-free nights in the fluticasone/salmeterol group compared to the ipratropium/albuterol group (change from baseline, 19.0 vs 7.3%; *P*<0.001), and a similar increase in albuterol-free days (change from baseline, 34.7 vs 26.7%; *P*=0.021).
Martinez et al.[89] Fluticasone furoate/vilanterol 100/25 µg QD vs fluticasone furoate/vilanterol 200/25 µg QD vs fluticasone furoate 200 µg QD vs fluticasone furoate 100 µg QD	DB, MC, PC, PG, RCT Patients aged ≥40 years of age with stable, moderate to severe COPD, a smoking history of ≥10 pack-years, a post-bronchodilator FEV_1/FVC ratio of ≤0.70, a post-bronchodilator FEV_1 ≤70% predicted and a score of ≥2 on the mMRC Dyspnea Scale	N=1,224 24 weeks	Primary: Zero to four hour weighted mean postdose-FEV_1 and trough-FEV_1 Secondary: CRQ-SAS, peak FEV_1, time to ≥100 mL improvement from baseline in FEV_1 on day one, time to ≥12% improvement in FEV_1 over the first four hours post-dose on day one, use of rescue medications, nighttime awakenings and safety parameters	Primary: The 100/25 µg and 200/25 µg combination regimens were associated with improvement in weighted mean postdose-FEV_1 compared to placebo (214 mL; 95% CI, 161 mL to 266 mL for the 100 µg dose comparison; and 209 mL; 95% CI, 157 mL to 261 mL for the 200 µg dose comparison, respectively) and fluticasone furoate monotherapy (168 mL; 95% CI, 116 mL to 220 mL for the 100 µg dose comparison; 168 mL; 95% CI, 117mL to 219 mL for the 200 µg dose comparison, respectively). In addition, the combination regimens were associated with an increase in trough FEV_1 compared to placebo (144 mL; 95% CI, 91 mL to 197 mL for the 100 µg dose comparison; and 131 mL; 95% CI, 80 mL to 183 mL for the 200 µg dose comparison, respectively). However, there was no significant difference between the combination regimen and vilanterol alone (45 mL; 95% CI, -8 mL to 97 mL for the 100 µg dose comparison; and 32 mL; 95% CI, -6 mL to 102 mL for the 200 µg dose comparison, respectively) Secondary: From day one of the study postdose-FEV_1 and trough-FEV_1 were greater with fluticasone furoate/vilanterol and vilanterol compared with fluticasone furoate and placebo. Both parameters increased rapidly from day 1 to day 14 and were generally maintained thereafter.

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
vs vilanterol 25 µg QD vs placebo Albuterol was allowed for use as symptom relief, as was ipratropium bromide provided the dose was a stable dosing regimen from the screening visit onward.				Over six months, scores on the dyspnea domain of the CRQ-SAS declined relative to placebo with both strengths of fluticasone furoate, but improved with both strengths of fluticasone furoate/vilanterol and with vilanterol alone. In the fluticasone furoate 100 µg and 200 µg arms adjusted mean peak FEV_1 was 24 mL (95% CI, -6 to 55) and 7 mL (95% CI, -23, to 37) respectively, greater than placebo while for vilanterol the adjusted mean increase from placebo was 147 mL (95% CI, 117 to 177). The equivalent values for fluticasone furoate/vilanterol 100/25 µg and 200/25 µg were 152 mL (95% CI, 122 to 182) and 141 ml (95% CI, 111 to 171), respectively. Other efficacy comparisons generally favored the use of fluticasone furoate/vilanterol compared to placebo. No increase was seen in on-treatment adverse events or serious adverse events, with active therapy vs. placebo. Exacerbations were infrequent but occurred more often in the placebo arm (21 events) than in any active treatment arm and more frequently in the vilanterol arm (18 events) than in the fluticasone furoate-containing arms (14 events).
Kerwin et al.[90] Fluticasone furoate/vilanterol 50/25 µg QD vs fluticasone furoate vilanterol 100/25 µg QD vs	DB, MC, PC, PG, RCT Patients aged ≥40 years of age with stable, moderate to severe COPD, a smoking history of ≥10 pack-years, a post-bronchodilator FEV_1/FVC ratio of	N=1,030 24 weeks	Primary: Zero to four hour weighted mean postdose-FEV_1 and trough-FEV_1 Secondary: CRQ-SAS, peak FEV_1, time to ≥100 ml improvement from baseline in FEV_1 on day one, time to ≥12% improvement in FEV1 over the first four	Primary: The 100/25 µg combination regimen was associated with improvement in weighted mean postdose-FEV_1 compared to placebo (173 mL; 95% CI, 123 mL to 224 mL) and fluticasone furoate monotherapy (120 mL; 95% CI, 70 mL to 170 mL).). In addition, the combination regimen was associated with an increase in trough FEV_1 compared to placebo (115 mL; 95% CI, 60 mL to 169 mL). However, there was no significant difference between the combination regimen and vilanterol alone (48 mL; 95% CI, -6 mL to 102 mL). Similar results were observed with the 50 µg/25 µg compared to placebo. Secondary: For FEV_1 at other time points over 24 weeks, both strengths of fluticasone furoate/vilanterol showed rapid and sustained improvements over placebo,

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
fluticasone furoate 200 µg QD vs vilanterol 25 µg QD vs placebo Albuterol was allowed for use as symptom relief, as was ipratropium bromide provided the dose was a stable dosing regimen from the screening visit onward.	≤0.70, a post-bronchodilator FEV1 ≤70% predicted and a score of ≥2 on the mMRC Dyspnea Scale		hours post-dose on day one, use of rescue medications, nighttime awakenings and safety parameters	and were greater than the vilanterol monotherapy arm at all time points from day 14. Similarly, both combination strengths and vilanterol showed rapid and sustained effects on trough FEV_1 compared with placebo, and both combination strengths provided greater lung function effects than vilanterol at days 7, 28, 56, 84, 140 and 168, but only the 50 µg/25 µg strength provided greater lung function effects at day 2, day 112 and day 169, and only the 100 µg/25 µg strength provided greater lung function effects at day 14. Both fluticasone furoate/vilanterol arms showed greater improvements compared with placebo in diary card symptoms, rescue use or rescue-free 24-h periods, nighttime awakenings and morning peak flow. The incidence of on-treatment adverse events was higher with active therapy compared to placebo, but the reports of serious adverse events were similar across arms. Reported adverse events included nasopharyngitis, local steroidal effects (candidiasis, oropharyngeal pain) and upper respiratory tract infection.
Agusti et al[8] Fluticasone propionate/ salmeterol 500/50 µg BID vs fluticasone furoate/ vilanterol 100/25 µg QD	DB, DD, MC, PG, RCT Patients aged ≥40 years of age with a smoking history of ≥10 pack-years, a post-bronchodilator FEV_1/FVC ratio of ≤0.70, a post-bronchodilator FEV_1 ≤70% predicted and at least one moderate COPD exacerbation	N=528 12 weeks	Primary: 24-hour effect on lung function after 12 weeks assessed by change from baseline in weighted mean FEV_1 Secondary: Time to 100 mL increase from baseline from zero to four hours on day one, change from baseline in trough FEV_1 on day 85 and change in health status	Primary: On day 84, there was no significant difference in improvement from baseline between the fluticasone propionate/salmeterol (108±221 mL) and fluticasone furoate/vilanterol (130±222 mL) groups (P=0.282). Secondary: Because statistical significance was not achieved for the primary endpoint, statistical significance in the secondary endpoints could not be inferred. The mean change from baseline in trough FEV_1 on day 85 was 88 mL in the fluticasone propionate/salmeterol group compared to 111 mL in the fluticasone furoate/vilanterol (mean treatment different, 23 mL; 95% CI, -21 to 66). The median time to reach an increase of ≥100 mL in FEV_1 was 28 minutes in the fluticasone propionate/salmeterol group compared to 16 minutes in the fluticasone furoate/vilanterol.

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
	within the last 2 years.			There was no significant difference in the proportion of rescue free 24-hour periods between the groups. The rate of adverse events was similar between the groups.
Lee et al[91] Exposure to ICSs, ipratropium, LABAs, theophylline and SABAs	Nested case-control Patients treated in the United States Veterans Health Administration health care system	N=145,020 Cohort identified between October 1, 1999 and September 30, 2003 and followed through September 30, 2004	Primary: All-cause mortality, respiratory mortality, and cardiovascular mortality Secondary: Subgroup analyses of primary outcomes	Primary: After adjusted for differences in covariates, ICSs and LABAs were associated with reduced odds of death. An adjusted OR of 0.80 (95% CI, 0.78 to 0.83) for ICSs and 0.92 (95% CI, 0.88 to 0.96) for LABAs was observed. Ipratropium was associated with an increased risk of death (OR, 1.11; 95% CI, 1.08 to 1.15). Theophylline exposure was associated with a statistically significant increase in respiratory deaths compared to the unexposed group (OR, 1.12; 95% CI, 1.46 to 2.00). An increase in the odds of respiratory death was observed with LABAs (OR, 1.12; 95% CI, 0.97 to 1.30); however, the increase did not reach statistical significance. In addition, a decrease in the odds of respiratory death was observed with ICSs (OR, 0.88; 95% CI, 0.79 to 1.00), however, this also did not reach statistical significance. Exposure to ipratropium was associated with a 34% increase in the odds of cardiovascular death (OR, 1.34; 95% CI, 0.97 to 1.47), whereas ICS exposure was associated with a 20% decrease (OR, 0.80; 95% CI, 0.72 to 0.88). LABAs (OR, 0.97; 95% CI, 0.99 to 1.37) and theophylline (OR, 1.16; 95% CI, 0.99 to 1.37) were not associated with statistically significant risks in cardiovascular deaths. Secondary: In a sensitivity analysis based on dose of medication, higher doses were associated with a larger effect than lower doses, consistent with a dose response to the medication. With current smoking associated with a RR for death of 1.5, these estimates would result in adjusted risk ratios of 0.77 for ICSs, 1.08 for ipratropium and 0.90 for LABAs. Among the medication regimens, those that included theophylline were associated with increased risk for respiratory death. For cardiovascular death, ipratropium alone (OR, 1.42; 95% CI, 1.27 to 1.59) and ipratropium

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				plus theophylline (OR, 1.47; 95% CI, 1.09 to 1.98) were associated with increased risk, whereas the presence of ICSs with ipratropium reduced the risk for cardiovascular death (OR, 1.04; 95% CI, 0.90 to 1.22; *P*<0.001). In the all-cause mortality group, ICS were consistently associated with reduced odds of death when used alone or in combination with other medications, whereas ipratropium and ipratropium plus theophylline were associated with elevated risk for death.
Cope et al[92] Indacaterol 150 mg PO QD vs indacaterol 300 mg PO QD vs budesonide/formoterol 9/160 µg, 1 inhalation BID vs budesonide/formoterol 9/320 µg, 1 inhalation BID vs fluticasone/salmeterol 50/250 µg, 1 inhalation BID	MA (15 PC, RCT) RCTs evaluating patients with COPD who were treated with indacaterol, budesonide/formoterol or salmeterol/fluticasone and reported outcomes of trough FEV_1 (reported predose values) at 12 weeks and 6 months, SGRQ total score at 6 months, and TDI total score at 6 months	N=10,211 Up to 6 months	Primary: Trough FEV_1 at week 12 and 6 months, total scores for St. George's Respiratory Questionnaire SGRQ, and TDI. Secondary: Not reported	Primary: Treatment with indacaterol 150 µg resulted in a greater change from baseline in FEV_1 at 12 weeks compared to budesonide/formoterol 160/9 µg (0.11 L; 95% CI, 0.08 to 0.13; *P* value note reported) and budesonide/formoterol 320/9 µg (0.09 L; 95% CI, 0.06 to 0.11; *P* value not reported). Indacaterol 150 µg was comparable to fluticasone/salmeterol 250/50 µg (0.02 L; 95% CI, -0.04 to 0.08; *P* value not reported) and fluticasone/salmeterol 500/50 µg (0.03 L; 95% CI, 0.00 to 0.06; *P* value not reported). Similar results were observed for indacaterol 300 µg at 12 weeks and indacaterol 150 µg and 300 µg at six months. Indacaterol 150 µg demonstrated a comparable improvement in SGRQ total score at six months compared to both doses of budesonide/formoterol, and a greater improvement compared to fluticasone/salmeterol 500/50 µg (−2.16 point improvement; 95% CI, -4.96 to 0.95; *P* value not reported). Indacaterol 150 and 300 µg demonstrated comparable TDI scores compared to fluticasone/salmeterol 250/50 µg (0.21 points; 95% CI, -0.57 to 0.99; and 0.39; 95% CI, -0.39 to 1.17, respectively; *P* values not reported) and fluticasone/salmeterol 500/50 µg at six months.

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
vs fluticasone/salmeterol 50/500 µg, 1 inhalation BID				
Karner et al[93] Tiotropium and ICS/LABA vs tiotropium vs ICS/LABA	MA 3 RCT's of participants 62 to 68 years of age with severity of COPD varied from moderate to very severe according to GOLD guideline definitions of COPD	N=1,051 Up to 52 weeks	Primary: All cause mortality, hospital admissions, exacerbations, pneumonia and SGRQ scores Secondary: Symptoms, FEV_1, non-fatal serious adverse events, adverse events and withdrawals	Primary: There was no significant difference in mortality rates between patients receiving therapy with ICS/LABA plus tiotropium and tiotropium alone (OR, 1.88; 95% CI, 0.57 to 6.23; *P*=0.30). There were fewer patients admitted to the hospital who received ICS/LABA plus tiotropium (41/474) compared to the tiotropium plus placebo group (50/487); however, the difference between groups was not significant (OR, 0.84; 95% CI, 0.53 to 1.33). The number of patients admitted to hospital with exacerbations was higher in the tiotropium plus placebo group (38/487) compared to the ICS/LABA plus tiotropium group (25/474); however, this difference was not significant (OR, 0.66; 95% CI, 0.39 to 1.13). Two studies examined the effect of ICS/LABA plus tiotropium on exacerbation rates compared to tiotropium alone. One study reported no difference in exacerbations between the treatment groups (OR, 0.89; 95% CI, 0.56 to 1.41), while the other study reported a significant reduction with the triple therapy compared to tiotropium monotherapy (OR, 0.36; 95% CI, 0.22 to 0.60). The risk of developing pneumonia was low, and there was no statistically significant difference between treatment with ICS/LABA plus tiotropium and tiotropium plus placebo (OR, 1.35; 95% CI, 0.31 to 5.99). Changes in SGRQ scores significantly favored ICS/LABA plus ipratropium treatment compared to ipratropium plus placebo after five months (*P*=0.002) and one year (*P*=0.01). Secondary:

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				The addition of tiotropium to ICS/LABA significantly increased FEV_1 (difference, 0.06 L; 95% CI, 0.04 to 0.08), although this was below the threshold of 100 to 140 mL which is considered to be a clinically important increase. There were fewer patients suffering non-fatal serious adverse events in the tiotropium plus ICS/LABA group (12/504) compared to patients taking tiotropium plus placebo (20/517), although the difference was not statistically significant (OR, 0.60; 95% CI, 0.29 to 1.25). A higher number of patients suffered adverse events while treated with tiotropium plus ICS/LABA (140/504) compared to patients tiotropium plus placebo (132/517), although the difference was not significant (OR, 1.12; 95% CI, 0.85 to 1.49). The difference between the number of patients who withdrew from the studies due to adverse events was not significantly different between patients taking tiotropium plus ICS/LABA and tiotropium plus placebo (OR, 0.92; 95% CI, 0.46 to 1.83).
Aaron et al[94] Tiotropium 18 µg QD plus placebo vs tiotropium 18 µg QD plus salmeterol 50 µg BID vs tiotropium 18 µg QD plus fluticasone/salmeterol 500/50 µg BID	DB, MC, PC, PG, RCT Patients ≥35 years of age with ≥1 COPD exacerbation in the last 12 months requiring systemic steroids or antibiotics, history of ≥10 pack-years of cigarette smoking, documented chronic airflow obstruction with	N=449 1 year	Primary: Proportion of patients who experience a COPD exacerbation requiring systemic steroids or antibiotics Secondary: Mean number of COPD exacerbations/patient-year, total number of exacerbations resulting in urgent visits to a health care practitioner or emergency room, number of hospitalizations for	Primary: The proportion of patients who experienced at least one COPD exacerbation in the tiotropium plus placebo group (62.8%) did not significantly differ between the tiotropium plus salmeterol group (64.8%) and the tiotropium plus fluticasone/salmeterol group (60.0%). The absolute risk reduction was -2.0 percentage points (95% CI, -12.8 to 8.8) for the tiotropium plus salmeterol group compared to tiotropium plus placebo (*P*=0.71) and 2.8 percentage points (95% CI, -8.2 to 13.8) for tiotropium plus fluticasone/salmeterol compared to the tiotropium plus placebo group (*P*=0.62). The unadjusted OR risk for exacerbations was 1.03 (95% CI, 0.63 to 1.67) with tiotropium plus salmeterol compared to tiotropium plus placebo and 0.85 (95% CI, 0.52 to 1.38) for tiotropium plus fluticasone/salmeterol compared to tiotropium plus placebo.

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
	an FEV_1/FVC <70% and a post-bronchodilator FEV_1 <65% of the predicted value		COPD, total number of hospitalizations for all causes, changes in HRQL, dyspnea and lung function	Secondary: The mean number of COPD exacerbations/patient-year did not significantly differ between the tiotropium plus placebo group (1.61) and the tiotropium plus salmeterol group (1.75) and the tiotropium plus fluticasone/salmeterol group (1.37). The incidence rate ratio was 1.09 (95% CI, 0.84 to 1.40) for tiotropium plus salmeterol compared to tiotropium plus placebo (*P*=0.51) and 0.85 (95% CI, 0.65 to 1.11) for tiotropium plus fluticasone/salmeterol compared to tiotropium and tiotropium plus placebo (*P*=0.24). Patients treated with tiotropium plus fluticasone/salmeterol had lower rates of severe COPD exacerbations requiring hospitalization than did patients treated with tiotropium plus placebo with an incidence rate ratio of 0.53 (95% CI, 0.33 to 0.86; *P*=0.01). All-cause hospitalizations were reduced in patients treated with tiotropium plus placebo (*P*=0.04). Similar benefits were not seen with tiotropium plus salmeterol compared to tiotropium plus placebo. The one-year change in total score on the SGRQ was -4.5 points in the tiotropium plus placebo group, -6.3 points in the tiotropium plus salmeterol group (*P*=0.02) and -8.6 points in the tiotropium plus fluticasone/salmeterol group (*P*=0.01). Dyspnea scores improved over one year of observation but did not significantly differ among the treatment groups (*P*=0.38). Over 52 weeks, the absolute pre bronchodilator FEV_1 increased by 0.027 L in the tiotropium plus placebo group compared to 0.086 L in the tiotropium plus fluticasone/salmeterol group (*P*=0.049). In addition, the percent predicted FEV_1 increased by 1.3% in the tiotropium plus placebo group compared to 4.6% in the tiotropium plus fluticasone/salmeterol group (P=0.005). Lung function was not significantly better in the tiotropium plus salmeterol group than in the tiotropium plus placebo group.
Make et al[95]	DB, DD, MC, PG, RCT	N=361	Primary: Morning pre-dose FEV_1	Primary: Statistically significant improvement in morning pre-dose FEV_1 in the

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Fluticasone/salmeterol 250/50 µg, 1 inhalation BID vs ipratropium/albuterol 36/206 µg, 1 inhalation QID	Patients 40 to 85 years of age diagnosed with moderate to severe COPD, FEV_1/FVC ratio ≤70%, FEV_1 >0.70 L and ≤70% predicted normal value (or if <0.70 L, then ≥40% predicted), smoking history of ≥10 pack years, use of inhaled short acting bronchodilator for COPD for ≥30 days	8 weeks	Secondary: Morning PEF values, six-hour FEV_1 AUC, percentage of symptom free nights, dyspnea, and overall combined daytime symptom score	fluticasone/salmeterol group compared to the ipratropium/albuterol group (change from baseline, 126 vs -1 mL; *P*<0.001). Secondary: Statistically significant improvement in mean FEV_1 AUC in the fluticasone/salmeterol group at week eight compared to the ipratropium/albuterol group (change from baseline, 0.38 vs -0.18; *P*=0.002). Statistically significant improvement in morning PEF values in the fluticasone/salmeterol group compared to the ipratropium/albuterol group at week one and throughout study (change from baseline, 33 vs 1 L/minute; *P*<0.001). Mean post-administration FEV_1 values significantly higher in the ipratropium/albuterol group at one half, one and two hours compared to the fluticasone/salmeterol group (*P*<0.001), but higher in the fluticasone/salmeterol group at six hours (*P*=0.003). Dyspnea scores significantly higher in the fluticasone/salmeterol group compared to the ipratropium/albuterol group (*P*=0.026), though improvements over baseline observed in both groups. Significantly greater reduction in overall daytime symptom score in the fluticasone/salmeterol group compared to the ipratropium/albuterol group (change from baseline, -46.7 vs -28.1; *P*=0.024). Statistically significant increase in albuterol-free nights in the fluticasone/salmeterol group compared to the ipratropium/albuterol group (change from baseline, 19.0 vs 7.3%; *P*<0.001), and a similar increase in albuterol-free days (change from baseline, 34.7 vs 26.7%; *P*=0.021).

Drug regimen abbreviations: AMD=adjustable maintenance dosing, BID=twice daily, FD=fixed dose, QD=once daily, QID=four times daily
Study abbreviations: AC=active control, CI=confidence interval, DB=double-blind, DD=double-dummy, EB=evaluator blinded, ES=extension study, HR=hazard-ratio, MC=multicenter, MA=meta-analysis, OL=open label, OS=observational study, OR=odds ratio, PC=placebo-controlled, PG=parallel-group, PH=post hoc, PRO=prospective, RCT=randomized controlled trial, RETRO=retrospective, RR=relative risk, SA=subgroup analysis, SB=single blind, SD=standard deviation, XO=crossover
Miscellaneous abbreviations: ACQ=Asthma Control Questionnaire, ACQ-5=five-item version of Asthma Control Questionnaire, AQLQ=standardized Asthma Quality of Life Questionnaire, ATSM=Asthma Treatment Satisfaction Measure, AUC=area under the curve, BCS=breathlessness, cough and sputum scores, CANO=alveolar nitric oxide concentration, CANOcorr= alveolar nitric oxide concentration uncorrected, CBP=conventional best practices, CBSQ=chronic bronchitis symptom questionnaire, CCQ=Clinical COPD Questionnaire, CDLM=Capacity of Daily Living During the

Morning, CFC= chlorofluorocarbon, COPD=chronic obstructive pulmonary disease, CRDQ=chronic respiratory disease questionnaire, CRQ-SAS= Chronic Respiratory Questionnaire Self-Administered Standardized, DPI=dry powder inhaler, FEV_1=forced expiratory volume in 1 second, FVC=forced vital capacity, HFA=hydrofluoroalkane, HPA=hypothalamic-pituitary-adrenal, ICS=inhaled corticosteroid, LABA=long-acting β_2-agonist, LS=least squares, LTRA=leukotriene receptor antagonist, MDI=metered dose inhaler, $MEF_{50\%}$=mid-expiratory flow at 50% vital capacity, mMRC=Modified Medical Research Council, MOS Sleep Scale=Medical Outcomes Study Sleep Scale, NNT=number needed to treat, NO=nitric oxide, OEQ=Onset of Effect Questionnaire, PACQLQ=Pediatric Asthma Caregiver's Quality of Life Questionnaire, PAQLQ=Pediatric Asthma Quality of Life Questionnaire, PEF=peak expiratory flow, PEFR=peak expiratory flow rate, PSAM=Patient Satisfaction with Asthma Medication questioner, SABA=short acting β_2-agonist, SF-36=Short-Form Health Survey, SGRQ=Saint George's Respiratory Questionnaire, SGRQ-C=Saint George's Respiratory Questionnaire for COPD patients, WCAW=well-controlled asthma week

Special Populations

Table 5. Special Populations[1-5]

Generic Name	Population and Precaution				
	Elderly/ Children	Renal Dysfunction	Hepatic Dysfunction	Pregnancy Category	Excreted in Breast Milk
Budesonide/ formoterol	No evidence of overall differences in safety or efficacy observed between elderly and younger adult patients. Safety and efficacy in children <12 years of age have not been established.	Not studied in renal dysfunction.	Not studied in hepatic dysfunction; use with caution.	C	Unknown; use with caution.
Fluticasone propionate/ salmeterol	No dosage adjustment required in the elderly. Safety and efficacy in children <4 years of age have not been established for the dry powder inhaler. Safety and efficacy in children <12 years of age have not been established for the meter dose aerosol inhaler (HFA).	Not studied in renal dysfunction.	Not studied in hepatic dysfunction; use with caution.	C	Unknown; use with caution.
Fluticasone furoate/ vilanterol	No dosage-adjustment required in the elderly; however, greater sensitivity of some individuals cannot be ruled out. No evidence of overall differences in safety or efficacy observed between elderly and younger adult patients. Safety and efficacy in children have not been established.	No dosage adjustment required.	No dosage adjustment required; however, this agent should be used with caution in patients with moderate or severe hepatic impairment due to increased fluticasone systemic exposure.	C	Unknown; use with caution.
Mometasone/ formoterol	No evidence of overall differences in safety or efficacy observed between elderly and younger adult patients. Safety and efficacy in children <12 years of age	No dosage adjustment required.	No dosage adjustment required.	C	Unknown; use with caution.

Generic Name	Population and Precaution				
	Elderly/ Children	Renal Dysfunction	Hepatic Dysfunction	Pregnancy Category	Excreted in Breast Milk
	have not been established.				

HFA=hydrofluoroalkane.

Adverse Drug Events

Table 6. Adverse Drug Events (%)[1-5]

Adverse Event	Budesonide/ Formoterol	Fluticasone Propionate/ Salmeterol	Fluticasone Furoate/ Vilanterol	Mometasone/ Formoterol
Ear, Nose and Throat				
Candidiasis, oral	1.4 to 3.2	1 to 4	-	-
Hoarseness/dysphonia	<3	2 to 5	-	-
Nasal congestion	2.5 to 3.2	-	-	-
Nasopharyngitis	9.7 to 10.5	-	9	4.7
Pharyngitis	<3	10 to 13	-	-
Pharyngolaryngeal pain	6.1 to 8.9	-	-	-
Sinusitis	4.8 to 5.8	4 to 5	-	2.0 to 3.3
Upper respiratory infection	7.6 to 10.5	21 to 27	7	-
Upper respiratory inflammation	-	6 to 7	-	-
Lower Respiratory				
Bronchitis	<4	2 to 8	-	-
Cough	<4	3 to 6	-	-
Viral respiratory infections	-	4	-	-
Neurology				
Headache	6.5 to 11.3	12 to 13	7	2.0 to 4.5
Gastrointestinal				
Gastrointestinal discomfort	1.1 to 6.5	1 to 4	-	-
Diarrhea	-	2 to 4	-	-
Influenza	2.4 to 3.2	-	-	-
Nausea/vomiting	1.4 to 3.2	4 to 6	-	-
Viral gastrointestinal infections	-	<3	-	-
Other				
Back pain	1.6 to 3.2	-	-	-
Candidiasis, unspecified site	-	<3	-	-
Candidiasis, oropharyngeal			5	
Musculoskeletal pain	-	2 to 4	-	-

- Event not reported or incidence <1%.

Contraindications/Precautions

The combination inhaled corticosteroid (ICS)/long-acting β_2-agonist (LABA) products are contraindicated for the primary treatment of status asthmaticus or in any other acute asthma or chronic obstructive pulmonary disease (COPD) episodes where intensive measures might be required. Budesonide/ formoterol (Symbicort®) and mometasone/formoterol (Dulera®) are additionally contraindicated in patients with hypersensitivity to any ingredient that the combination product consists of, and fluticasone propionate/salmeterol (Advair®) and fluticasone furoate/vilanterol (Breo Ellipta®) are further contraindicated in patients with severe milk protein hypersensitivities.[1-5]

All LABA-containing medications are assigned a Black Box Warning (outlined below) regarding an increased risk of asthma-related deaths. In February 2010, results from a meta-analysis demonstrated that LABAs were associated with an increased risk of asthma exacerbations and hospitalizations in

pediatric and adult patients, as well as death in some patients. Use of a LABA medication is contraindicated in patients not receiving an asthma controller medication. Additionally, long-term use of LABA medications is recommended only in patients whose asthma cannot be adequately controlled on asthma controller medications, and LABA medications should be used for the shortest duration of time required to achieve asthma control. Specific to the pediatric and adolescent populations, the use of a combination ICS/LABA product is recommended in these patients who require a LABA in order to ensure compliance with both medications.[1-5,19,21]

The combination ICS/LABA products should not be initiated in patients during rapidly deteriorating or potentially life-threatening episodes of asthma or COPD. In addition, as with other inhaled drugs containing β_2-adrenergic agents, these combination products should not be used more often than recommended, at higher doses than recommended or in conjunction with other medications containing LABAs, as an overdose may result.[1-5]

The development of localized infections of the mouth and pharynx with *Candida albicans* has been reported in patients treated with combination ICS/LABA products. If an infection develops, it should be treated with appropriate local and systemic therapy, while treatment with the combination product continues, but at times therapy with the combination product may need to be interrupted. Patients should be instructed to rinse their mouth after inhalation of a combination ICS/LABA product.[1-5]

Physicians should monitor for the development of pneumonia in patients with COPD who are receiving a combination ICS/LABA product as the clinical features of pneumonia and exacerbations frequently overlap. In addition, patients receiving medications that suppress the immune system are more susceptible to infections than healthy patients. ICSs should be used with caution, if at all, in patients with active or quiescent tuberculosis infections of the respiratory tract; untreated systemic fungal, bacterial, viral or parasitic infections or ocular herpes simplex.[1-5]

Particular care is needed for patients who have been transferred from systemically active corticosteroids to ICSs because deaths due to adrenal insufficiency have occurred. After withdrawal from systemic corticosteroids, a number of months are required for recovery of the hypothalamic-pituitary-adrenal (HPA) function. The fluticasone propionate/salmeterol hydrofluoroalkane inhaler should not be used for transferring patients from systemic corticosteroid therapy. Budesonide, fluticasone propionate and mometasone will often help control asthma symptoms with less suppression of the HPA function than therapeutically equivalent doses of oral prednisone. Since ICSs are absorbed into the circulation and can be systemically active at high doses, the beneficial effects of these agents in minimizing HPA dysfunction may be expected only when recommended dosages are not exceeded and individual patients are titrated to the lowest effective dose. Because of the possibility of systemic absorption of ICSs, patients treated with one of the combination ICS/LABA products should be observed carefully for any evidence of systemic corticosteroid effects.[1-5]

As with any inhaled medication, the combination ICS/LABA products can produce paradoxical bronchospasm, which may be life threatening. If this occurs, it should be treated immediately with an inhaled short-acting bronchodilator, and therapy with the combination product should be discontinued and alternative therapy should be initiated.[1-5]

Excessive β-adrenergic stimulation has been associated with seizures, angina, hypertension or hypotension, tachycardia, arrhythmias, nervousness, headache, tremor, palpitation, nausea, dizziness, fatigue, malaise and insomnia. Therefore, the combination ICS/LABA products should be used with caution in patients with cardiovascular disorders, especially coronary insufficiency, cardiac arrhythmias and hypertension.[1-5]

Decreases in bone mineral density (BMD) have been observed with long term therapy of products containing ICSs. The clinical significance of small changes in BMD with regard to long term consequences such as fracture is unknown. Patients with major risk factors for decreased bone mineral content should be monitored and treated with established standards of care. Assessment of BMD is

recommended prior to starting treatment with fluticasone propionate/salmeterol and periodically thereafter. If significant reductions in BMD are observed and treatment is still required, use of a medication to treat or prevent osteoporosis should be considered.[1-5]

ICSs may cause a reduction in growth velocity when administered in pediatric patients; therefore, growth should be monitored in patients receiving a combination ICS/LABA product. To minimize the systemic effects of an ICS, each patient's dose should be titrated to the lowest dosage that effectively controls their symptoms.

Glaucoma and cataracts have been reported in patients with asthma and COPD following long term administration of ICSs; therefore, close monitoring is warranted in patients with a change in vision or with a history of increased intraocular pressure, glaucoma and/or cataracts.[1-5]

In rare cases, patients receiving a combination ICS/LABA product may present with systemic eosinophilic conditions. These events usually have been associated with the reduction and/or withdrawal of oral corticosteroid therapy following the introduction of an ICS.[1-5]

Like all medications containing sympathomimetic amines, the combination ICS/LABA products should be used with caution in patients with convulsive disorders thyrotoxicosis and in those who are unusually responsive to sympathomimetic amines.[1-5]

β-adrenergic agonist medications may produce significant hypokalemia in some patients which has the potential to produce adverse cardiovascular effects. The reduction in serum potassium is usually transient and does require supplementation. Clinically significant changes in blood glucose and/or serum potassium were seen infrequently during clinical trials with the combination ICS/LABA products.[1-5]

Black Box Warning for Symbicort® (budesonide/formoterol), Advair® (fluticasone propionate /salmeterol) and Dulera® (mometasone/formoterol)[1-3,5]

WARNING
Long-acting β_2 adrenergic agonists may increase the risk of asthma-related death. Data from a large placebo-controlled United States study that compared the safety of salmeterol or placebo added to usual asthma therapy showed an increase in asthma-related deaths in patients receiving salmeterol. This finding with salmeterol is considered a class effect of the long-acting β_2 adrenergic agonists. Currently available data are inadequate to determine whether concurrent use of inhaled corticosteroids or other long-term asthma-control drugs mitigates the increased risk of asthma-related death from long-acting β_2 adrenergic agonists. Available data from controlled clinical trials suggest that long-acting β_2 adrenergic agonists increase the risk of hospitalization in children and adolescents. Therefore, when treating patients with asthma, only prescribe inhaled corticosteroid/ long-acting β_2 adrenergic agonist for patients not adequately controlled on a long term asthma control medication (e.g., inhaled corticosteroids) or whose disease severity clearly warrants initiation of treatment with both an inhaled corticosteroid and long-acting β_2 adrenergic agonist. Once asthma control is achieved and maintained, assess the patient at regular intervals and step down therapy (e.g., discontinue inhaled corticosteroid/ long-acting β_2 adrenergic agonist for) if possible without loss of asthma control, and maintain the patient on a long-term asthma-control medication, such as an inhaled corticosteroid. Do not use inhaled corticosteroid/ long-acting β_2 adrenergic agonist for patients whose asthma is adequately controlled on low or medium dose inhaled corticosteroids.

Black Box Warning for Breo Ellipta® (fluticasone furoate/vilanterol)[4]

WARNING
Long-acting β_2 adrenergic agonists may increase the risk of asthma-related death. Data from a large placebo-controlled United States study that compared the safety of salmeterol or placebo added to usual asthma therapy showed an increase in asthma-related deaths in patients receiving salmeterol. This finding with salmeterol is considered a class effect of the long-acting β_2 adrenergic agonists.

WARNING
The safety and efficacy of fluticasone furoate/vilanterol in patients with asthma have not been established. Fluticasone furoate/vilanterol is not indicated for the treatment of asthma.

Drug Interactions

Table 7. Drug Interactions[1-5]

Generic Name	Interacting Medication or Disease	Potential Result
ICSs (budesonide, fluticasone propionate)	Azole antifungals	ICS effects and toxicity may be increased.
ICSs (budesonide)	Barbiturates	Decreased pharmacologic effects of ICSs may be observed.
ICSs (budesonide)	Hydantoins	Decreased ICS effects may occur within days of phenytoin initiation and persist for three weeks after discontinuation.
ICSs (budesonide)	Rifamycins	Decreased pharmacologic effects of ICSs may be observed.
ICSs (budesonide)	Warfarin	ICSs may reduce the anticoagulant dose requirements and occasionally induce hypercoagulation that could oppose the anticoagulant action of warfarin.
LABAs (formoterol, salmeterol)	B-blockers	Pharmacologic effects of sympathomimetic β-agonists may be antagonized by β-blockers, resulting in bronchospasm.
ICSs (budesonide. fluticasone, mometasone) and vilanterol	CYP 450 3A4 inhibitors	Concomitant administration of a potent CYP-3A4 inhibitor increases the systemic exposure to these agents. Caution should be advised when using these combinations.

ICS=inhaled corticosteroid, LABAs=long-acting β-agonists

Dosage and Administration

Table 8. Dosing and Administration[1-5]

Generic Name	Adult Dose	Pediatric Dose	Availability
Budesonide/ formoterol	Treatment of asthma in adults and children >12 years of age: Meter dose aerosol inhaler (HFA): initial, two inhalations BID, with the starting dose based upon the patient's asthma severity; maintenance, for patients who do not respond adequately to the starting dose after one to two weeks with 80/4.5 µg, consideration to using 160/4.5 µg can be made to provide additional asthma control; maximum, 160/4.5 µg BID Maintenance treatment of airflow obstruction in patients with chronic obstructive pulmonary disease*†: Meter dose aerosol inhaler (HFA): 160/4.5 µg, two inhalations BID	Safety and efficacy in children <12 years of age have not been established.	Meter dose aerosol inhaler (HFA) (60 or 120 actuations): 80/4.5 µg 160/4.5 µg
Fluticasone	Treatment of asthma in adults and	Treatment of asthma in	Dry powder

Generic Name	Adult Dose	Pediatric Dose	Availability
propionate/ salmeterol	children >12 years of age: Dry powder inhaler: initial, one inhalation BID, with the starting dose based upon the patient's asthma severity; maintenance, failure to respond to the starting dosage after two weeks of therapy warrants consideration to using a higher strength to provide additional improvement in asthma control; maximum, 500/50 µg BID Meter dose aerosol inhaler (HFA): initial, two inhalations BID, with the starting dose based upon the patient's asthma severity; maintenance, failure to respond to the starting dosage after two weeks of therapy warrants consideration to using a higher strength to provide additional improvement in asthma control; maximum, 230/21 µg two inhalations BID Maintenance treatment of airflow obstruction in patients with chronic obstructive pulmonary disease*‡: Dry powder inhaler: 250/50 µg one inhalation BID	children >4 years of age: Dry powder inhaler: 100/50 µg one inhalation BID (initial dose is indicated for patients not currently on an inhaled corticosteroid and whose treatment warrants the initiation of two maintenance therapies) Safety and efficacy in children <4 years of age have not been established for the dry powder inhaler. Safety and efficacy in children <12 years of age have not been established for the meter dose aerosol inhaler (HFA).	inhaler (60 blisters): 100/50 µg 250/50 µg 500/50 µg Meter dose aerosol inhaler (HFA) (60 or 120 actuations): 45/21 µg 115/21 µg 230/21 µg
Fluticasone furoate/vilanterol	Maintenance treatment of airflow obstruction in patients with chronic obstructive pulmonary disease: Dry powder Inhaler: initial, maintenance and maximum, one inhalation QD	Safety and efficacy in children have not been established.	Dry Powder Inhaler (30 dose strips): 100 µg/25 µg
Mometasone/ formoterol	Treatment of asthma in adults and children >12 years of age: Meter dose aerosol inhaler (HFA): initial, 100/5 µg two inhalations BID if previous therapy with medium dose inhaled corticosteroid or 200/5 µg two inhalations BID if previous therapy with high dose inhaled corticosteroid; maintenance, two inhalations BID; maximum, 200/5 µg two inhalations BID	Safety and efficacy in children <12 years of age have not been established.	Meter dose aerosol inhaler (HFA) (120 actuations): 100/5 µg 200/5 µg

BID=twice daily, HFA=hydrofluoroalkane, QD=once daily
*Including bronchitis and/or emphysema.
†Symbicort® 160/4.5 µg is the only strength Food and Drug Administration (FDA) approved for this indication.
‡Advair® 250/50 µg is the only strength FDA-approved for this indication.

Clinical Guidelines

Table 9. Clinical Guidelines

Clinical Guidelines	Recommendations
Global Initiative for Chronic Obstructive Lung Disease: **Global Strategy for the Diagnosis, Management, and Prevention of Chronic Obstructive Pulmonary Disease (2014)**[21]	Diagnosis • A clinical diagnosis of chronic obstructive pulmonary disease (COPD) should be considered in any patient who has chronic cough, dyspnea, excess sputum production, or history of exposure to risk factors including smoking. • A diagnosis of COPD should be confirmed by spirometry. • COPD patients typically display a decrease in both Forced Expiratory Volume in one second (FEV_1) and FEV_1/ Forced Vital Capacity (FVC) ratio. • The presence of a post-bronchodilator $FEV_1/FVC < 0.70$ confirms the presence of persistent airflow limitation and COPD. • A detailed medical history should be obtained for all patients suspected of developing COPD. • Severity of COPD is based on the level of symptoms, the severity of the spirometric abnormality, and the presence of complications. • Chest radiograph may be useful to rule out other diagnoses. • Arterial blood gas measurements should be performed in advanced COPD. • Screening for α_1-antitrypsin deficiency should be performed in patients of Caucasian decent who develop COPD at 45 years of age or younger. • Differential diagnoses should rule out asthma, congestive heart failure, bronchiectasis, tuberculosis, diffuse panbronchiolitis, and obliterative bronchiolitis. Treatment • Patients should be instructed to avoid the exacerbating exposure. This includes assisting the patient in smoking cessation attempts and counseling the patient on how to avoid pollutant exposures. • The management of COPD should be individualized to address symptoms and improve the patient's quality of life. • None of the medications for COPD have been shown to modify long-term decline in lung function. Treatment should be focused on reducing symptoms and complications. • Administer bronchodilator medications on an as needed or regular basis to prevent or reduce symptoms and exacerbations. • Principle bronchodilators include β_2-agonists, anticholinergics and theophylline used as monotherapy or in combination. • The use of long-acting bronchodilators is more effective and convenient than short-acting bronchodilators. • For single-dose, as needed use, there is no advantage in using levalbuterol over conventional nebulized bronchodilators. • Combining bronchodilators of different pharmacological classes may improve efficacy and decrease adverse effects compared to increasing dose of a single bronchodilator. • In patients with an FEV_1 <60% of the predicted value, regular treatment with inhaled corticosteroids (ICS) improves symptoms, lung function and quality of life as well as reduces exacerbations. • Long term therapy ICS as monotherapy is not recommended. • Chronic treatment with systemic corticosteroids should be avoided due to an unfavorable risk-benefit ratio. • COPD patients should receive an annual influenza vaccine.

Clinical Guidelines	Recommendations
	• The pneumococcal polysaccharide vaccine is recommended for COPD patients ≥65 years old or for patients <65 years old with an FEV_1 <40% of the predicted value. • Exercise training programs should be implemented for all COPD patients. • Long-term administration of oxygen (>15 hours/day) increases survival in patients with chronic respiratory failure. Management of exacerbations • The most common causes of an exacerbation are respiratory tract infections. • Inhaled short-acting β_2-agonists, with or without short-acting anticholinergics are the preferred bronchodilators for treatment for exacerbations of COPD. • Roflumilast may also be used to reduce exacerbations for patients with chronic bronchitis, severe to very severe airflow limitation and frequent exacerbations not adequately controlled by long-acting bronchodilators. • Antibiotics are recommended in patients with increased dyspnea, increased sputum volume or increased sputum purulence; or increase sputum purulence and increased dyspnea or increased sputum volume, or patients that require mechanical ventilation.
National Institute for Health and Clinical Excellence: **Chronic Obstructive Pulmonary Disease: Management of Chronic Obstructive Pulmonary Disease in Adults in Primary and Secondary Care (partial update) (2010)**[22]	Diagnosis • Diagnosis should be considered in patients >35 years of age who have a risk factor for the development of COPD and who present with exertional breathlessness, chronic cough, regular sputum production, frequent winter bronchitis or wheeze. • The primary risk factor is smoking. • Spirometry is diagnostic of airflow obstruction. Airflow obstruction is defined as FEV_1 <80% predicted and FEV_1/FVC <70%. Treatment • Smoking cessation should be encouraged for all patients with COPD. • SABAs, as necessary, should be the initial empiric treatment for the relief of breathlessness and exercise limitation. • Long-acting bronchodilators ($beta_2$ agonists and/or anticholinergics) should be given to patients who remain symptomatic even with short-acting bronchodilators. • Once-daily, long-acting anticholinergics are preferred compared to four-times-daily short-acting anticholinergics in patients with stable COPD who remain breathless or who have exacerbations despite the use of short-acting bronchodilators as required and in whom a decision has been made to begin regular maintenance bronchodilator therapy with an anticholinergic. o FEV_1 ≥50% predicted: LABA or long-acting anticholinergic. o FEV_1 <50% predicted: either LABA with an ICS in a combination inhaler or a long-acting anticholinergic. • In patients with stable COPD and FEV_1 ≥50% who remain breathless or have exacerbations despite maintenance therapy with a LABA, consider adding an ICS in a combination inhaler or a long-acting anticholinergic when ICSs are not tolerated or declined. • Consider a long-acting anticholinergic in patients remaining breathless or having exacerbations despite therapy with LABAs and ICSs and vice versa. • Choice of drug should take in to consideration the patient's symptomatic response, preference, potential to reduce exacerbations, adverse events

Clinical Guidelines	Recommendations
	and costs. • In most cases, inhaled bronchodilator therapy is preferred. • Oral corticosteroids are not normally recommended and should be reserved for those patients with advanced COPD in whom therapy cannot be withdrawn following an exacerbation. • Theophylline should only be used after a trial of LABA and SABA or if the patient is unable to take inhaled therapy. Combination therapy with β_2-agonists and theophylline or anticholinergics and theophylline may be considered in patients remaining symptomatic on monotherapy. • Pulmonary rehabilitation should be made available to patients. • Noninvasive ventilation should be used for patients with persistent hypercapnic respiratory failure. <u>Management of exacerbations</u> • Patients with exacerbations should be evaluated for hospital admission. • Patients should receive a chest radiograph, have arterial blood gases monitored, have sputum cultured if it is purulent, and have blood cultures taken if pyrexial. • Oral corticosteroids should be used in all patients admitted to the hospital who do not have contraindications to therapy. The course of therapy should be no longer than 14 days. • Oxygen should be given to maintain oxygen saturation above 90%. • Patients should receive invasive and noninvasive ventilation as necessary. • Respiratory physiotherapy may be used to help remove sputum. • Before discharge, patients should be evaluated by spirometry. • Patients should be properly educated on their inhaler technique and the necessity of usage and should schedule a follow up appointment with a health care professional.
American College of Physicians, American College of Chest Physicians, American Thoracic Society, and European Respiratory Society: **Diagnosis and Management of Stable Chronic Obstructive Pulmonary Disease: A Clinical Practice Guideline Update from the American College of Physicians, American College of Chest Physicians, American Thoracic Society, and European Respiratory**	<u>Diagnosis</u> • Targeted use of spirometry for diagnosis of airflow obstruction is beneficial for patients with respiratory symptoms, particularly dyspnea. • Evidence is insufficient to support the use of inhaled therapies in asymptomatic individuals who have spirometric evidence of airflow obstruction, regardless of the presence or absence of risk factors for airflow obstruction. <u>Treatment</u> • For stable COPD patients with respiratory symptoms and an FEV_1 between 60 and 80% predicted, inhaled bronchodilators may be used. There is, however, conflicting evidence regarding the benefit of inhaled bronchodilators in these patients. • For stable COPD patients with respiratory symptoms and FEV_1 <60% predicted, treatment with inhaled bronchodilators is recommended. • Patients who benefit the most from inhaled bronchodilators (anticholinergics or long-acting β-agonists) are those who have respiratory symptoms and airflow obstruction with an FEV_1 <60% predicted. The mean FEV_1 was <60% predicted in the majority of the trials that evaluated the management of COPD. This recommendation does not address the occasional use of short-acting inhaled bronchodilators for acute symptom relief. • Monotherapy with long-acting inhaled anticholinergics or long acting inhaled β-agonists for symptomatic patients with COPD and FEV_1 <60% predicted are recommended due to their ability to reduce exacerbations and improve

Clinical Guidelines	Recommendations
Society (2011)[96]	health-related quality of life. • The specific choice of monotherapy should be based on patient preference, cost, and adverse effect profile. • There is inconclusive evidence regarding the effect of inhaled agents (anticholinergics and long-acting β-agonists) on mortality, hospitalizations, and dyspnea. • ICSs are superior to placebo in reducing exacerbations but are not recommended as preferred monotherapy in patients with COPD. Concern over their adverse event profile (thrush, potential for bone loss, and moderate to severe easy bruisability) and less biologic rationale for their use. • Combination therapy with inhaled agents (long-acting inhaled anticholinergics, long-acting inhaled β-agonists, or inhaled corticosteroids) may be used for symptomatic patients with stable COPD and FEV_1 <60% predicted. The combination therapy that has been most studied to date is long-acting inhaled β-agonists plus inhaled corticosteroids. • Pulmonary rehabilitation is recommended for symptomatic patients with an FEV_1 <50% predicted. • Pulmonary rehabilitation may be considered for symptomatic or exercise-limited patients with an FEV_1 <50% predicted. • Continuous oxygen therapy is recommended in patients with COPD who have severe resting hypoxemia (PaO2 ≤55 mm Hg or SpO2 ≤88%).
The National Heart, Lung, and Blood Institute/National Asthma Education and Prevention Program: **Guidelines for the Diagnosis and Management of Asthma (2007)**[19]	<u>Diagnosis</u> • To establish a diagnosis of asthma, a clinician must determine the presence of episodic symptoms or airflow obstruction, partially reversible airflow obstruction and alternative diagnoses must be excluded. • The recommended methods to establish a diagnosis are a detailed medical history, physical exam focusing on the upper respiratory tract, spirometry to demonstrate obstruction and assess reversibility and additional studies to exclude alternative diagnoses. • A diagnosis of asthma should be considered if any of the following indicators are present: wheezing, history of cough, recurrent wheeze, difficulty breathing or chest tightness, symptoms that occur or worsen with exercise or viral infections and symptoms that occur or worsen at night. • Spirometry is needed to establish a diagnosis of asthma. • Additional studies such as pulmonary function tests, bronchoprovocation, chest x-ray, allergy testing and biomarkers of inflammation may be useful when considering alternative diagnoses. <u>Treatment</u> • Pharmacologic therapy is used to prevent and control asthma symptoms, improve quality of life, reduce the frequency and severity of asthma exacerbations and reverse airflow obstruction. • The initial treatment of asthma should correspond to the appropriate asthma severity category. • Long-term control medications such as inhaled corticosteroids (ICSs), long-acting bronchodilators, leukotriene modifiers, cromolyn, theophylline and immunomodulators should be taken daily on a long-term basis to achieve and maintain control of persistent asthma. • Quick-relief medications are used to provide prompt relief of bronchoconstriction and accompanying acute symptoms such as cough, chest tightness and wheezing. • Quick relief medications include short-acting β_2-adrenergic agonists

Clinical Guidelines	Recommendations
	(SABAs), anticholinergics and systemic corticosteroids. Long-term control medications • ICSs are the most potent and consistently effective long-term control medication for asthma in patients of all ages. • Short courses of oral systemic corticosteroids may be used to gain prompt control when initiating long-term therapy and chronic administration is only used for the most severe, difficult-to-control asthma. • When patients ≥12 years of age require more than a low-dose ICS, the addition of a long-acting β_2-adrenergic agonist (LABA) is recommended. Alternative, but not preferred, adjunctive therapies include leukotriene receptor antagonists, theophylline, or in adults, zileuton. • Mast cell stabilizers (cromolyn and nedocromil) are used as alternatives for the treatment of mild persistent asthma. They can also be used as preventatively prior to exercise or unavoidable exposure to known allergens. • Omalizumab, an immunomodulator, is used as adjunctive therapy in patients 12 years and older who have allergies and severe persistent asthma that is not adequately controlled with the combination of high-dose ICS and LABA therapy. • Leukotriene receptor antagonists (montelukast and zafirlukast) are alternative therapies for the treatment of mild persistent asthma. • LABAs (formoterol and salmeterol) are not to be used as monotherapy for long-term control of persistent asthma. • LABAs should continue to be considered for adjunctive therapy in patients five years of age or older who have asthma that require more than low-dose ICSs. For patients inadequately controlled on low-dose ICSs, the option to increase the ICS should be given equal weight to the addition of a LABA. • Methylxanthines, such as sustained-release theophylline, may be used as an alternative treatment for mild persistent asthma. • Tiotropium is a long-acting inhaled anticholinergic indicated once-daily for chronic obstructive pulmonary disease (COPD) and has not been studied in the long-term management of asthma. Quick-relief medications • SABAs are the therapy of choice for relief of acute symptoms and prevention of exercise-induced bronchospasm. • There is inconsistent data regarding the efficacy of levalbuterol compared to albuterol. Some studies suggest an improved efficacy while other studies fail to detect any advantage of levalbuterol. • Anticholinergics may be used as an alternative bronchodilator for patients who do not tolerate SABAs and provide additive benefit to SABAs in moderate-to-severe asthma exacerbations. • Systemic corticosteroids are used for moderate and severe exacerbations as adjunct to SABAs to speed recovery and prevent recurrence of exacerbations. • The use of LABAs is not recommended to treat acute symptoms or exacerbations of asthma. Assessment, treatment and monitoring • A stepwise approach to managing asthma is recommended to gain and maintain control of asthma. • Regularly scheduled, daily, chronic use of a SABA is not recommended.

<table>
<tr><th>Clinical Guidelines</th><th>Recommendations</th></tr>
<tr><td></td><td>
Increased SABA use or SABA use more than two days a week for symptom relief generally indicates inadequate asthma control.
• The stepwise approach for managing asthma is outlined below:
<table>
<tr><th>Inter-mittent Asthma</th><th colspan="5">Persistent Asthma: Daily Medication</th></tr>
<tr><th>Step 1</th><th>Step 2</th><th>Step 3</th><th>Step 4</th><th>Step 5</th><th>Step 6</th></tr>
<tr><td><u>Preferred</u>
SABA as needed</td><td><u>Preferred</u>
Low-dose ICS

<u>Alternative</u>
Cromolyn, leukotriene receptor antagonists, nedocromil, or theophylline</td><td><u>Preferred</u>
Low-dose ICS+LABA or medium-dose ICS

<u>Alternative</u>
Low-dose ICS+either a leukotriene receptor antagonists, theophylline, or zileuton</td><td><u>Preferred</u>
Medium-dose ICS+LABA

<u>Alternative</u>
Medium-dose ICS+either a leukotriene receptor antagonists, theophylline, or zileuton</td><td><u>Preferred</u>
High-dose ICS+ LABA and consider omalizu-mab for patients who have allergies</td><td><u>Preferred</u>
High-dose ICS+LABA+ oral steroid and consider omalizumab for patients who have allergies</td></tr>
</table>

<u>Management of exacerbations</u>
• Appropriate intensification of therapy by increasing inhaled SABAs and, in some cases, adding a short course of oral systemic corticosteroids is recommended.

<u>Special populations</u>
• For exercise-induced bronchospasm, pretreatment before exercise with either a SABA or LABA is recommended. Leukotriene receptor antagonists may also attenuate exercise-induced bronchospasm, and mast cell stabilizers can be taken shortly before exercise as an alternative treatment for prevention; however, they are not as effective as SABAs.
• The addition of cromolyn to a SABA is helpful in some individuals who have exercise-induced bronchospasm.
• Consideration of the risk for specific complications must be given to patients who have asthma who are undergoing surgery.
• Albuterol is the preferred SABA in pregnant women because of an excellent safety profile.
• ICSs are the preferred treatment for long-term control medication in pregnant women. Specifically, budesonide is the preferred ICS as more data is available on using budesonide in pregnant women than other ICSs.
</td></tr>
<tr><td>Global Initiative for Asthma:
Global Strategy for Asthma Management and Prevention (2012)[20]</td><td>
<u>Treatment</u>
• Education should be an integral part of all interactions between health care professionals and patients, and is relevant to asthma patients of all ages.
• Measures to prevent the development of asthma, asthma symptoms, and asthma exacerbations by avoiding or reducing exposure to risk factors should be implemented whenever possible.
• Controller medications are administered daily on a long-term basis and include inhaled and systemic corticosteroids, leukotriene modifiers, LABAs in combination with ICSs, sustained-released theophylline, chromones, and anti-immunoglobulin E (IgE).
• Reliever medications are administered on an as-needed basis to reverse bronchoconstriction and relieve symptoms and include rapid-acting inhaled β_2-agonists, inhaled anticholinergics, short-acting theophylline and SABAs.
</td></tr>
</table>

Clinical Guidelines	Recommendations
	Controller medications • ICSs are currently the most effective anti-inflammatory medications for the treatment of persistent asthma for patients of all ages. • ICSs differ in potency and bioavailability, but few studies have been able to confirm the clinical relevance of these differences. • Most clinical benefit from an ICS in adults is achieved at relatively low doses, equivalent to 400 µg of budesonide daily. Higher doses provide little further benefit but increase the risk of adverse events. • To reach clinical control, add-on therapy with another class of controller is preferred over increasing the dose of the ICS. • Leukotriene modifiers are generally less effective than low doses of ICSs therefore may be used as an alternative treatment in patients with mild persistent asthma. • Some patients with aspirin-sensitive asthma respond well to leukotriene modifiers. • Leukotriene modifiers used as add-on therapy may reduce the dose of the ICS required by patients with moderate to severe asthma, and may improve asthma control in adult patients whose asthma is not controlled with low or high doses of ICSs. • Several studies have demonstrated that leukotriene modifiers are less effective than LABAs as add-on therapy. • LABAs should not be used as monotherapy in patients with asthma as these medications do not appear to influence asthma airway inflammation. • When a medium dose of the ICS fails to achieve control, the addition of a LABA is the preferred treatment. • Controlled studies have shown that delivering a LABA and an ICS in a combination inhaler is as effective as giving each drug separately. Fixed combination inhalers are more convenient, may increase compliance, and ensure that the LABA is always accompanied by an ICS. • Although the guideline indicates that combination inhalers containing formoterol and budesonide may be used for both rescue and maintenance, this use is not approved by the Food and Drug Administration (FDA). • Tiotropium has been evaluated in adults with uncontrolled asthma compared to double-dose ICSs and salmeterol. Study results are conflicting and no effect on asthma exacerbations has been demonstrated. • Theophylline as add-on therapy is less effective than LABAs but may provide benefit in patients who do not achieve control on ICSs alone. Furthermore, withdrawal of sustained-release theophylline has been associated with worsening asthma control. • Cromolyn and nedocromil are less effective than a low dose of ICSs. • Oral LABA therapy is used only on rare occasions when additional bronchodilation is needed. • Anti-IgE treatment with omalizumab is limited to patients with elevated serum levels of IgE. • Long-term oral corticosteroid therapy may be required for severely uncontrolled asthma, but is limited by the risk of significant adverse effects. • Other anti-allergic compounds have limited effect in the management of asthma. Reliever medications • Rapid-acting inhaled β_2-agonists are the medications of choice for the relief of bronchospasm during acute exacerbations and for the pretreatment of

<table>
<tr><th>Clinical Guidelines</th><th>Recommendations</th></tr>
<tr><td></td><td>exercise-induced bronchoconstriction, in patients of all ages.
• Rapid-acting inhaled β_2-agonists should be used only on an as-needed basis at the lowest dose and frequency required.
• Although the guidelines state that formoterol, a LABA, is approved for symptom relief due to its rapid onset of action, and that it should only be used for this purpose in patients on regular controller therapy with ICSs, the use of this agent as a rescue inhaler is not approved by the FDA.
• Ipratropium, an inhaled anticholinergic, is a less effective reliever medication in asthma than rapid-acting inhaled β_2-agonists.
• Short-acting theophylline may be considered for relief of asthma symptoms.
• Short-acting oral β_2-agonists (tablets, solution, etc.) are appropriate for use in patients who are unable to use inhaled medication however they are associated with a higher prevalence of adverse effects.
• Systemic corticosteroids are important in the treatment of severe acute exacerbations.

<u>Assessment, treatment, and monitoring</u>
• The goal of asthma treatment is to achieve and maintain clinical control.
• To aid in clinical management, a classification of asthma by level of control is recommended: controlled, partly controlled, or uncontrolled.
• Treatment should be adjusted in a continuous cycle driven by the patient's asthma control status and treatment should be stepped up until control is achieved. When control is maintained for at least three months, treatment can be stepped down.
• Increased use, especially daily use, of reliever medication is a warning of deterioration of asthma control and indicates the need to reassess treatment.
• The management approach based on control is outlined below:
<table>
<tr><th>Step 1</th><th>Step 2</th><th>Step 3</th><th>Step 4</th><th>Step 5</th></tr>
<tr><td colspan="5">Asthma education and environmental control</td></tr>
<tr><td colspan="5">As needed rapid-acting β_2-agonist</td></tr>
<tr><td rowspan="5">Controller options</td><td>Select one</td><td colspan="2">Select one</td><td>Add one or more</td><td>Add one or both</td></tr>
<tr><td>Low-dose ICS</td><td colspan="2">Low-dose ICSs + LABA</td><td>Medium- or high-dose ICS + LABA</td><td>Oral corticosteroid</td></tr>
<tr><td>Leukotriene modifier</td><td colspan="2">Medium- or high-dose ICS</td><td>Leukotriene modifier</td><td>Anti-IgE treatment</td></tr>
<tr><td>-</td><td colspan="2">Low-dose ICS +leukotriene modifier</td><td>-</td><td>-</td></tr>
<tr><td>-</td><td colspan="2">Low-dose ICS +sustained-release theophylline</td><td>-</td><td>-</td></tr>
</table>

<u>Management of exacerbations</u>
• Repeated administration of rapid-acting inhaled β_2-agonists is the best method of achieving relief for mile to moderate exacerbations. Systemic corticosteroids should be considered if the patient does not immediately respond to rapid-acting inhaled β_2-agonists or if the episode is severe.</td></tr>
<tr><td>Joint Task Force on Practice Parameters for Allergy and Immunology: Pathogenesis,</td><td>• In asthmatic patients, frequent exercise-induced bronchoconstriction suggests inadequate asthma control and requires patient reevaluation to determine the need for additional therapy.
• There is both intra-patient and inter-patient variability in responsiveness to pharmacologic therapies for exercise-induced constriction.</td></tr>
</table>

Clinical Guidelines	Recommendations
Prevalence, Diagnosis and Management of Exercise-Induced Broncho-constriction: A Practice Parameter (2010)[97]	• Medications may differ in effectiveness over time because of variability of asthma, environmental conditions, intensity of the exercise stimulus and tachyphylaxis. • Inhaled β_2-agonists are the most effective group of agents for short-term protection against exercise-induced bronchoconstriction and for accelerating recovery of airway obstruction after exercise. • When given as a single-dose or on an intermittent basis, SABAs and LABAs may protect against or attenuate exercise-induced bronchoconstriction. • Daily use of β_2-agonists alone or in combination with ICS would usually lead to tolerance; therefore, monotherapy with adrenergic agents is generally recommended for use only on an intermittent basis for prevention of exercise-induced bronchoconstriction. • Daily therapy with leukotriene receptor antagonists does not lead to tolerance and can be used for intermittent or maintenance prophylaxis. However, its protection against exercise-induced bronchoconstriction may not be complete, and it has no use to reverse airway obstruction when it occurs. • Inhaled cromolyn sodium and nedocromil sodium* can attenuate exercise-induced bronchoconstriction when used shortly before exercise; however, these agents have a short duration of action and have no bronchodilator activity. They may be effective when used alone or as adjunct therapy. • Use of ICS may decrease the frequency and severity of exercise-induced bronchoconstriction but does not eliminate the need for acute therapy. • ICS does not prevent the occurrence of tolerance from daily β_2-agonist use. • The efficacy of ipratropium has been inconsistent in attenuating exercise-induced bronchoconstriction; however, a few patients may respond to this agent. • There have been inconsistent results on the efficacy of medications in other therapeutic classes, including theophylline, antihistamines, calcium channel blockers, inhaled furosemide, heparin and hyaluronic acid. • Preexercise warm-up, reduction in sodium intake and ingestion of fish oil and ascorbic acid supplementation may help to reduce the severity of exercise-induced bronchoconstriction.

Conclusions

The combination inhaled corticosteroid (ICS)/long-acting β_2-agonist (LABA) products, with the exception of fluticasone furoate/vilanterol (Breo Ellipta®), are all Food and Drug Administration (FDA)-approved for the treatment of asthma in adults and children (age varies depending on product). Currently, only budesonide/formoterol (Symbicort®), fluticasone propionate/salmeterol (Advair®) and fluticasone furoate/vilanterol (Breo Ellipta®) are currently FDA-approved for the treatment of chronic obstructive pulmonary disease (COPD).[1-5] The combination ICS/LABA products are not available generically, and the individual components of each of the products are also commercially available solely as branded products.

In regards to the clinical efficacy of the combination ICS/LABA products, trials have demonstrated that the combination products are “superior” to the individual separate components. In addition, head-to-head trials comparing budesonide/formoterol and fluticasone propionate/salmeterol failed to demonstrate that one product is consistently “superior” over the other. A single prospective head-to-head trial comparing mometasone/formoterol (Dulera®) to fluticasone propionate/salmeterol demonstrated non inferiority in regard to forced expiratory volume in 1 second (FEV_1) area under the curve from 0 to 12 hours, in addition to a significantly faster onset of action and increase in FEV_1.[7] While one study comparing fluticasone propionate/salmeterol and fluticasone furoate/vilanterol did not demonstrate significant differences in improvement of 0 to 24 hour FEV_1.[8] The combination products have been compared to the

Symbicort® Maintenance and Reliever Therapy (SMART) dosing regimen. The SMART dosing regimen used in these trials demonstrated a greater decrease in asthma exacerbations and hospitalization rates compared to standard dosing regimens for budesonide/formoterol and fluticasone propionate/salmeterol. Again, it is important to note that the SMART dosing regimen has not been approved by the FDA.[9-18,23-95]

For the treatment of asthma, current guidelines support the use of combination ICS/LABA products for long term control and prevention of symptoms in patients who do not achieve sufficient symptom control with an ICS (low to medium dose) as monotherapy, as LABA medications are the preferred add on therapy in these patients. According to the Global Initiative for Asthma (GINA) guidelines, clinical trials have demonstrated that delivering a LABA and an ICS in a combination inhaler is as effective as giving the two individual agents concomitantly. They also state that fixed combination inhalers are more convenient, may increase compliance and ensure that the LABA is always accompanied by an ICS. A major divergence between the National, Heart, Lung, Blood Institute (NHLBI) and GINA guidelines, is the recommendation of budesonide/formoterol as both maintenance and rescue therapy by the GINA guidelines.[19,20] As mentioned previously, the use of a combination ICS/LABA product for the relief of acute bronchospasm is not approved by the FDA.[1-5] Currently, the NHLBI guidelines recommend that LABA medications should not be used for the treatment of acute asthma symptoms or exacerbation.[19,20] Regarding the treatment of COPD, consensus guidelines from both the Global Initiative for Chronic Obstructive Lung Disease and the National Institute for Health and Clinical Excellence recommend the use of combination ICS/LABA products as second-line, when a patients remain symptomatic and have repeated exacerbations while on an initial short- and long-acting bronchodilator.[21,22] Finally, none of the current asthma or COPD treatment guidelines recommend the use of one combination ICS/LABA product over another; further reinforcing the lack of any significant clinical difference between the products.[19-22]

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