## *Therapeutic Class Overview*
## *Long-Acting Inhaled $\beta_2$-Agonists (Single Entity)*

**Therapeutic Class Overview/Summary:**

Respiratory $\beta_2$-agonists are primarily used to treat reversible airway disease. The long-acting $\beta_2$-agonists (LABAs) are all Food and Drug Administration (FDA)-approved for chronic obstructive pulmonary disease with some agents also being approved for asthma maintenance therapy and exercise-induced asthma/bronchospasm.[1-7] Respiratory $\beta_2$-agonists act preferentially on the $\beta_2$-adrenergic receptors. Activation of these receptors on airway smooth muscle leads to the activation of adenylyl cyclase and an increase in intracellular cyclic-3',5'-adenosine monophosphate (cyclic AMP). The increase in cyclic AMP leads to activation of protein kinase A and the inhibition of myosin phosphorylation resulting in lower intracellular ionic calcium and smooth muscle relaxation. Increased cyclic AMP levels also inhibit the release of mediators from mast cells in the airways.[1-6] The respiratory $\beta_2$-agonists can be divided into two categories: short-acting and long-acting. Only the inhaled long-acting $\beta_2$-agonists will be covered in this review and they include: arformoterol, formoterol, indacaterol salmeterol, and the newest agent olodaterol. Respiratory $\beta_2$-agonists elicit a similar biologic response in patients suffering from reversible airway disease, but differ in their dosing requirements, pharmacokinetic parameters and potential adverse events.[1-6] Guidelines do not recommend one long-acting agent over another.[8-11] In addition, head-to-head clinical trials have been inconclusive to determine "superiority" of any one agent .[12-60] There are currently no generic formulations for the LABAs.

**Table 1. Current Medications Available in the Therapeutic Class**[1-6]

| Generic (Trade Name) | Food and Drug Administration Approved Indications | Dosage Form/Strength | Generic Availability |
|---|---|---|---|
| Arformoterol (Brovana®) | Bronchoconstriction in patients with chronic obstructive pulmonary disease, including chronic bronchitis and emphysema; maintenance treatment | Solution for nebulization: 15 µg (2 mL) | - |
| Formoterol (Foradil®, Perforomist®) | Asthma (including nocturnal asthma) and bronchospasm prevention as concomitant therapy with a long-term asthma control medication†; bronchoconstriction in patients with chronic obstructive pulmonary disease, including chronic bronchitis and emphysema; maintenance treatment‡ exercise-induced bronchospasm prophylaxis, acute† | Capsule for inhalation: 12 µg<br><br>Solution for nebulization: 20 µg/2 mL | - |
| Indacaterol (Arcapta Neohaler®) | Bronchoconstriction in patients with chronic obstructive pulmonary disease, including chronic bronchitis and emphysema; maintenance treatment§ | Capsule for inhalation: 75 µg | - |
| Olodaterol (Striverdi Respimat®) | Bronchoconstriction in patients with chronic obstructive pulmonary disease, including chronic bronchitis and emphysema; maintenance treatment§ | Solution for inhalation (breath activated, metered-dose inhaler): 2.5 µg | - |
| Salmeterol (Serevent Diskus®) | Asthma (including nocturnal asthma) and bronchospasm prevention as concomitant therapy with a long-term asthma control medication; bronchoconstriction in patients with chronic obstructive pulmonary disease, including chronic bronchitis and emphysema; maintenance treatment‡; | Dry powder inhaler: 50 µg (28 or 60 inhalations) | - |

| Generic (Trade Name) | Food and Drug Administration Approved Indications | Dosage Form/Strength | Generic Availability |
|---|---|---|---|
| | bronchoconstriction in patients with chronic obstructive pulmonary disease, including chronic bronchitis and emphysema; maintenance treatment | | |

COPD=chronic obstructive pulmonary disease
*Generic available in at least one dosage form or strength.
†Dry powder inhaler only
‡Twice-daily
§Once-daily

**Evidence-based Medicine**

- Clinical trials have demonstrated the efficacy long-acting $\beta_2$-agonists in providing relief from asthma, COPD exacerbations and exercise induced asthma .[12-60]
- Salmeterol and formoterol have been found to improve $FEV_1$ in patients with mild to moderate asthma who require persistent use of SABAs. In a meta-analysis by Salpeter et al, salmeterol and formoterol both demonstrated an increase in severe exacerbations that required hospitalization, life threatening exacerbations and asthma-related deaths in adults and children alike when compared to placebo.[13]
- A systematic review concluded that in patients with COPD, there was no difference in rate of mild exacerbation between patients treated with an ICS or LABA (odds ratio, 1.63; 95% confidence interval [CI], 0.49 to 5.39) or in the rate of moderate or severe COPD exacerbations (relative risk, 0.96; 95% CI, 0.89 to 1.02).[42]
- Overall, data from published clinical trials demonstrate that treatment with indacaterol consistently results in significantly higher mean trough $FEV_1$ after 12 weeks of treatment compared to placebo, formoterol, salmeterol and tiotropium. Patients treated with indacaterol also achieved significant improvements in COPD symptoms, as well as health-related quality of life compared to those treated with placebo.[42-52]
- The safety and efficacy of olodaterol were evaluated in eight unpublished placebo- and/or active-controlled confirmatory clinical trials in patients with COPD. Results from four 48-week studies showed 5 µg olodaterol provided significant improvements in $FEV_1$ and $FEV_1$ $AUC_{0\text{-}3hr}$ at weeks 12 and 24 when compared with placebo (no *P* value provided) . In addition, four 6-week cross-over studies showed that $FEV_1$ $AUC_{0\text{-}12hr}$ and $FEV_1$ $AUC_{12\text{-}24hr}$ was significantly improved with olodaterol when compared with placebo at the conclusion of the studies (no *P* value provided). No data was provided showing the results of the active comparators (formoterol and/or tiotropium) or whether the results were significantly different than olodaterol or not.[4]

**Key Points within the Medication Class**

- According to Current Clinical Guidelines:
  - Short-acting $\beta_2$-agonists are recommended for patients in all stages of asthma, for symptomatic relief of reversible airway disease and for exercise-induced bronchospasm.[8,9]
  - Short-acting $\beta_2$-agonists should be used on an as-needed or "rescue" basis. [8,9]
  - In the chronic management of asthma, the long-acting $\beta_2$-agonists should be used as add-on therapy in patients not adequately controlled on an inhaled corticosteroid. [8,9]
  - Long-acting $\beta_2$-agonists should not be used as monotherapy for the long-term control of asthma. [8,9]
  - Long-acting $\beta_2$-agonists can be used for exercise-induced bronchospasm and provide a longer period of coverage compared to short acting $\beta_2$-agonists. [8,9]
  - Long-acting $\beta_2$-agonists have a role in the treatment of chronic obstructive pulmonary disease (COPD), for patients who remain symptomatic even with current treatment with short-acting bronchodilators. [8,9]
  - Long-acting $\beta_2$-agonists can be added to other COPD treatment regimens, including an anticholinergic agent, in efforts to decrease exacerbations.[10,11]
- Other Key Facts:

- The role of the short- and long-acting respiratory $\beta_2$-agonists in the treatment of asthma and COPD has been well established.
- Studies have failed to consistently demonstrate significant differences between products.
- None of the long-acting respiratory $\beta_2$-agonists are currently available generically.

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# *Therapeutic Class Review*
# *Long-Acting Inhaled $\beta_2$-Agonists (Single Entity)*

**Overview/Summary**

Respiratory long-acting $\beta_2$-agonists (LABA) are primarily used to treat reversible airway disease. All LABAs are Food and Drug Administration (FDA)-approved for the treatment of chronic obstructive pulmonary disease (COPD) with several agents also FDA-approved for use in asthma maintenance therapy with a long-term asthma control medication and also the prevention of exercise-induced asthma/bronchospasm.[1-7] Activation of $\beta_2$-adrenergic receptors on airway smooth muscle leads to the activation of adenylyl cyclase and an increase in intracellular cyclic-3',5'-adenosine monophosphate (cyclic AMP). The increase in cyclic AMP leads to activation of protein kinase A and the inhibition of myosin phosphorylation, ultimately resulting in lower intracellular ionic calcium and smooth muscle relaxation. Increased cyclic AMP levels also inhibit the release of mediators from mast cells in the airways.[1-6] The $\beta_2$-agonists are classified as short- and long-acting agents. Only the inhaled long-acting $\beta_2$-agonists will be covered in this review and they include: arformoterol (Brovana®), formoterol (Foradil®, Perforomist®), indacaterol (Arcapta Neohaler®) and salmeterol (Serevent Diskus®), and the newest agent olodaterol (Striverdi Respimat®). The $\beta_2$-agonists elicit a similar biologic response in patients suffering from reversible airway disease, but differ in their dosing requirements, pharmacokinetic parameters and potential adverse events.[1-6] There are currently no generic formulations for the LABAs.

According to the National Heart, Lung, and Blood Institute (NHLBI) and the Global Initiative for Asthma, inhaled corticosteroids (ICSs) are the most effective long-term control medications used for the treatment of asthma for patients of all ages. The LABAs should not be used as monotherapy for the management of asthma; however, they are considered the most effective adjunctive therapy in patients who are not adequately controlled with an ICS alone. Leukotriene modifiers, mast-cell stabilizers and methylxanthines may also be used as adjunctive therapies but are less effective than LABAs. Chronic administration of systemic corticosteroids is reserved for severe, difficult-to-control asthma patients and the use of immunomodulators is only indicated in asthma patients with severe disease and allergies.[8,9] The guidelines state that SABAs are the medication of choice for the relief of bronchospasm during acute exacerbations of asthma.[8,9] Anticholinergics may also be used for the treatment of acute exacerbations but are considered less effective than SABAs. The addition of a systemic corticosteroid may be required if patients do not respond immediately to treatment with a SABA or if the exacerbation is severe. According to the NHLBI, the use of LABAs to treat acute symptoms or exacerbations of asthma is not recommended.[8,9]

According to the Global Initiative for Chronic Obstructive Lung Disease (GOLD) guidelines, agents used to manage stable chronic obstructive pulmonary disease include inhaled bronchodilators and corticosteroids. The choice between bronchodilators, which are central to COPD symptom management, depends on patient response, the incidence of adverse events and availability. Bronchodilators, which include LABAs and SABAs, anticholinergics and methylxanthines, should be administered as needed or on a scheduled basis to relieve intermittent or worsening symptoms or to prevent or reduce persistent symptoms. Long-acting bronchodilators are more effective than short-acting bronchodilators; however, short-acting bronchodilators should be considered initial empiric therapy.[10] According to the National Institute for Clinical Excellence, long-acting bronchodilators should be used to control symptoms of COPD in patients who continue to experience problems despite the use of short-acting bronchodilators.[11] Also, a combination of bronchodilators from different pharmacologic classes may increase the efficacy of the treatment regimen. The addition of an ICS to a treatment regimen reduces exacerbations and improves lung function.[10] Long-term treatment with oral corticosteroids is not recommended for the management of stable COPD.[10,11] Current GOLD guidelines also recommend the use of bronchodilators and corticosteroids for the management of acute COPD exacerbations.[10] An increase in the dose and/or frequency of short-acting bronchodilators as well as the addition of an anticholinergic is recommended until symptoms improve. The use of antibiotics in COPD is only recommended for the treatment of infectious exacerbations.

## Medications

**Table 1. Medications Included Within Class Review**

| Generic Name (Trade name) | Medication Class | Generic Availability |
|---|---|---|
| Arformoterol (Brovana®) | $\beta_2$-agonist | - |
| Formoterol (Foradil®, Perforomist®) | $\beta_2$-agonist | - |
| Indacaterol (Arcapta Neohaler®) | $\beta_2$-agonist | - |
| Olodaterol (Striverdi Respimat®) | $\beta_2$-agonist | - |
| Salmeterol (Serevent Diskus®) | $\beta_2$-agonist | - |

*Generic available in at least one dosage form or strength.

## Indications

**Table 2. Food and Drug Administration-Approved Indications**[1-6]

| Indication | Arformoterol | Formoterol | Indacaterol | Olodaterol | Salmeterol |
|---|---|---|---|---|---|
| Asthma (including nocturnal asthma) and bronchospasm prevention as concomitant therapy with a long-term asthma control medication | | a * | | | a |
| Bronchoconstriction in patients with chronic obstructive pulmonary disease, including chronic bronchitis and emphysema; maintenance treatment | a † | a † | a ‡ | a ‡ | a † |
| Bronchoconstriction in patients with chronic obstructive pulmonary disease, including chronic bronchitis and emphysema; maintenance treatment | | a * | | | a |

* Dry powder inhaler only
† Twice-daily
‡ Once-daily

## Pharmacokinetics

**Table 3. Pharmacokinetics**[1-6]

| Generic Name | Onset of Action (minutes) | Duration of Action (hours) | Renal Excretion (%) | Active Metabolites | Serum Half-Life (hours) |
|---|---|---|---|---|---|
| Arformoterol | 7 to 20 | Not reported | 63 to 67 | No | 26 |
| Formoterol | Not reported (inhaler)* 12 to 13 (nebs) | 8 to 12 | 1.1 to 28.0 | No | 7 to 10 |
| Indacaterol | 15 | ~24 | 1.2 <2 | Not reported | 40 to 56 |
| Olodaterol | 10 to 20 | Not reported | 19 | No† | 7.5 |
| Salmeterol | 10 to 20 | 12 | 25 | No | 5.5 |

* Onset of action described as similar to albuterol 180 mcg by meter dose inhaler
†Of the six metabolites, the unconjugated demthylation product does binds the beta2-receptor, but it is not detected in plasma after chronic inhalation of the recommended therapeutic doses.

**Clinical Trials**

Clinical trials have demonstrated the safety and efficacy of long-acting $\beta_2$-agonists in the prevention of asthma, COPD exacerbations and exercise induced asthma.[12-60]

Salmeterol and formoterol have been found to improve $FEV_1$ in patients with mild to moderate asthma who require persistent use of SABAs. Results from the SMART trial found that salmeterol treatment was associated with significantly more occurrences of combined respiratory-related deaths or respiratory-related life-threatening experiences compared to placebo ($P$<0.05).[20] In a meta-analysis by Salpeter et al, salmeterol and formoterol both demonstrated an increase in severe exacerbations that required hospitalization, life threatening exacerbations and asthma-related deaths in adults and children when compared to placebo.[13] Due to the results of these studies, the labeling of long-acting inhaled $\beta_2$-agonists now include a black box warning stating that these agents may increase the risk of asthma related deaths.[1-6]

The results of a systematic review demonstrated that in patients with COPD, there was no statistically significant difference in the rate of mild exacerbation between patients treated with an inhaled corticosteroid (ICS) or LABA (odds ratio, 1.63; 95% confidence interval [CI], 0.49 to 5.39) or in the rate of moderate or severe COPD exacerbations (relative risk, 0.96; 95% CI, 0.89 to 1.02).[32] In two studies, patients diagnosed with COPD were treated with arformoterol, salmeterol or placebo. Both arformoterol and salmeterol significantly improved morning trough $FEV_1$ throughout the 12 weeks of daily treatment compared to placebo ($P$<0.001 in both trials).[34,35] In a head-to-head study against salmeterol, formoterol was associated with a greater change from baseline in $FEV_1$ at five minutes postdose on day 28 ($P$=0.022).[37]

The safety and efficacy of indacaterol were evaluated in randomized controlled trials compared to placebo and other agents used in the management of COPD.[42-52] Notably, these trials evaluated indacaterol in doses of 150, 300 and 600 µg once-daily, but not the Food and Drug Administration (FDA)-approved dosing (75 µg once-daily).[42-52] According to the FDA-approved labeling, dose selection for indacaterol in COPD was based on three dose ranging clinical trials, one of which included an asthmatic population. In the two COPD dose ranging trials (18.75, 37.5, 75 and 150 µg/day and 75, 150, 300 and 600 µg/day), a dose-response relationship in $FEV_1$ was observed; however, the effect did not clearly differ between the various doses.[4] Overall, data from published clinical trials demonstrate that treatment with indacaterol consistently results in significantly higher mean trough $FEV_1$ after 12 weeks of treatment compared to placebo, formoterol, salmeterol and tiotropium. Patients treated with indacaterol also achieved significant improvements in COPD symptoms, as well as health-related quality of life compared to those treated with placebo. Compared to placebo, indacaterol significantly reduces the use of rescue medications, increases the days of no rescue medication use and improves diary card-derived symptom variables (e.g., nights with no awakenings, days with no daytime symptoms, days able to perform usual activities). In general, treatment with indacaterol is favored over other long acting bronchodilators for these outcomes, but significant “superiority” is not consistently achieved.[42-52] Placebo-controlled trials demonstrate that within five minutes after administration of indacaterol, significant improvements in bronchodilation are achieved.[47-50] These results have also been observed when comparing indacaterol to salmeterol, salmeterol/fluticasone and tiotropium.[45,50,51]

The safety and efficacy of olodaterol were evaluated in several dose-ranging trials in asthma and COPD patients and eight unpublished confirmatory trials in patients with COPD. The eight confirmatory trials were four pairs of replicate, randomized, double-blind, placbo-controlled trials in 3,533 patients with COPD (5 µg dose, N=1,281; 10 µg dose, N=1,284). Patients were included if they were at least 40 years of age, had at least a 10 pack-year history of smoking and moderate to very severe pulmonary impairment. The first two pairs were 48 week studies with the second pair having an active control of formoterol in addition to placebo. In all four studies, olodaterol the 5 µg dose demonstrated significant improvments in $FEV_1$ and $AUC_{0\text{-}3hr}$ compared with placebo at weeks 12 and 24 (no $P$ value provided). The 10 µg dose did not show any additional benefit over the 5 µg dose (data not shown). No results that compared olodaterol to formoterol in the second pair of trials was reported. The dosing intervals were evaluated in the third and fourth pair of clinical trials. There trials were 6 week cross-over trials with

placebo- and active-control (formoterol and tiotropium). In all four trials, the primary endpoints were change from pre-treatment baseline in $FEV_1$ $AUC_{0\text{-}12hr}$ and $FEV_1$ $AUC_{12\text{-}24hr}$ after 6 weeks. In the four cross-over studies, olodaterol demonstrated significant improvements in $FEV_1$ $AUC_{0\text{-}12hr}$ and $FEV_1$ $AUC_{12\text{-}24hr}$ compared with placebo at the conclusion of the study (no *P* value provided). The results that compared olodaterol to the active controls formoterol and tiotropium were not reported.[5]

**Table 4. Clinical Trials**

| Study and Drug Regimen | Study Design and Demographics | Sample Size and Study Duration | End Points | Results |
|---|---|---|---|---|
| **Asthma** | | | | |
| Kemp et al[12]<br><br>Albuterol via MDI<br><br>vs<br><br>formoterol via DPI<br><br>vs<br><br>placebo | MA (45 RCTs)<br><br>Studies in which formoterol was administered either with or without an ICS or other adjunct therapy were included in this analysis | N=8,369<br><br>Duration not reported | Primary:<br>Serous asthma exacerbations (asthma-related deaths, intubations and hospitalizations)<br><br>Secondary:<br>Not reported | Primary:<br>Compared to placebo, the risk of a serious asthma exacerbation was highest in the formoterol group receiving 10 to12 µg daily (OR, 3.9; 95% CI, 1.5 to 10.3). Patients receiving formoterol 48 µg and 20/24 µg daily also had a greater risk of severe asthma exacerbations compared to placebo (OR, 2.9; 95% CI, 1.2 to 6.6 and OR, 1.8; 95% CI, 0.8 to 4.0, respectively). The risk of serious asthma exacerbation was also higher with albuterol compared to placebo (OR, 2.6; 95% CI, 1.0 to 6.6).<br><br>In children, the risk of serious asthma exacerbations was higher among patients being treated with formoterol compared to placebo (OR, 8.4; 95% CI, 1.1 to 65.3). Formoterol use in adolescents and adults was not associated with an increased risk of serious asthma exacerbations (OR, 0.30; 95% CI, 0.03 to 3.50 and OR, 1.30; 95% CI, 0.4 to 3.7, respectively).<br><br>Among adults who reported using concomitant ICS at baseline, a trend toward fewer serious asthma exacerbations was seen in those receiving formoterol compared to placebo (adolescents: OR, 0.8; 95% CI, 0.05 to 12.3; adults: OR, 0.6; 95% CI, 0.2 to 2.2). Children receiving concomitant ICS had greater odds of experiencing a serious asthma exacerbation (OR, 7.8; 95% CI, 1.0 to 61.3) when also using formoterol.<br><br>Secondary:<br>Not reported |
| Salpeter et al[13]<br><br>LABAs (formoterol via DPI)<br><br>vs<br><br>placebo | MA (RCTs)<br><br>Individuals diagnosed with asthma (15% of the participants were African American) | N=33,826<br><br>At least 3 months | Primary:<br>Severe asthma exacerbations requiring hospitalizations, life-threatening asthma exacerbations, and asthma-related deaths | Primary:<br>Treatment with LABAs (formoterol and salmeterol) resulted in an increase in severe exacerbations that required hospitalization (OR, 2.6; 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) compared to placebo. The risks seen in adults and children were similar.<br><br>Secondary:<br>Not reported |

| Study and Drug Regimen | Study Design and Demographics | Sample Size and Study Duration | End Points | Results |
|---|---|---|---|---|
| | | | Secondary:<br>Not reported | |
| Boonsawat et al[14]<br><br>Formoterol 18 µg administered at 0, 30, and 60 minutes via DPI<br><br>vs<br><br>albuterol 100 µg administered at 0, 30, and 60 minutes via MDI | DB, DD, PG, RCT<br><br>Individuals 18 to 67 years of age with asthma presenting to the ED with acute bronchoconstriction | N=88<br><br>1 day | Primary:<br>$FEV_1$ and asthma symptoms<br><br>Secondary:<br>Not reported | Primary:<br>A nonsignificant increase in $FEV_1$ at 75 minutes compared to baseline was seen (37% in the formoterol group vs 28% in the albuterol group; *P*=0.18).<br><br>There was a significant increase in the maximum $FEV_1$ between 75 to 240 and 15 to 45 minutes after the first and second dose of the medications in the formoterol group compared to the albuterol group (51 vs 36%; *P*<0.05).<br><br>Subjective symptom score assessments decreased during the course of the study (*P* value not reported).<br><br>Secondary:<br>Not reported |
| Pauwels et al[15]<br><br>Formoterol 4.5 µg administered as needed via DPI<br><br>vs<br><br>albuterol 200 µg administered as needed via MDI | MC, OL, RCT<br><br>Individuals ≥6 years of age with asthma requiring the use of $\beta_2$-agonists as reliever medication | N=18,124<br><br>6 months | Primary:<br>Asthma-related and non-asthma-related serious adverse events, discontinuation due to adverse events, and time to first exacerbation<br><br>Secondary:<br>Rescue reliever mediation | Primary:<br>The number of adverse events reported was not statistically significant between the two groups (*P* value not reported).<br><br>With formoterol there was a significantly higher number of asthma-related discontinuation due to adverse events (1.0 vs 0.5%; *P*<0.001).<br><br>Compared to albuterol, there was a significantly longer time to first asthma exacerbation with formoterol (*P*<0.001).<br><br>Secondary:<br>Rescue inhaler use decreased in both groups over the course of the study with a significantly greater decrease seen in the formoterol group (*P*<0.001). |
| Molimard et al[16]<br><br>Formoterol 12 µg via DPI and albuterol via MDI to | MC, OL, PG, RCT<br><br>Individuals ≥18 years of age with | N=259<br><br>3 months | Primary:<br>The mean change in morning predose PEF for the entire | Primary:<br>Over three months, there was a significantly higher mean increase in the morning PEF in the formoterol group than in the albuterol group (25.7 and 4.5 L/minute (*P*<0.0001). |

| Study and Drug Regimen | Study Design and Demographics | Sample Size and Study Duration | End Points | Results |
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| use as needed (administered as separate products)<br><br>vs<br><br>albuterol 100 µg via MDI to be used throughout the day as needed | moderate persistent asthma | | treatment period<br><br>Secondary:<br>Mean increase in evening predose PEF for the entire treatment period, day and night use of albuterol and scores on the SGRQ | Secondary:<br>At visits three and five, there was a significantly greater improvement in predose $FEV_1$ with formoterol compared to albuterol ($P$<0.01 and $P$<0.05).<br><br>At three months, the mean changes from baseline in the number of puffs of albuterol during the day and night were -0.8 and -0.4 with formoterol and 0.1 and 0.1 for albuterol ($P$<0.0001).<br>There was a significant increase in symptom-free days and nights in the formoterol group compared to albuterol ($P$<0.05 for both).<br><br>A significant decrease was seen in the SGRQ score with formoterol compared to albuterol (-6.4 vs -3.5; $P$=0.05). |
| Pleskow et al[17]<br><br>Formoterol 12 µg BID via DPI<br><br>vs<br><br>formoterol 24 µg BID via DPI<br><br>vs<br><br>albuterol 180 µg QID via MDI<br><br>vs<br><br>placebo | DB, DD, MC, PC, PG, RCT<br><br>Individuals 12 to 75 years of age with mild to moderate asthma | N=554<br><br>12 weeks | Primary:<br>$FEV_1$ at the 12-hour evaluation time point<br><br>Secondary:<br>AUC of $FEV_1$, and percent of predicted $FEV_1$ | Primary:<br>On the final visit at the 12-hour mark, both formoterol groups showed significant improvement in $FEV_1$ compared to placebo and albuterol ($P$<0.001 and $P$<0.002) with no statistical difference between albuterol and placebo at this time.<br><br>Secondary:<br>At the last visit, both formoterol groups showed significant improvement at all time points compared to placebo ($P$<0.001) with the exception of formoterol 12 µg at time zero. Both groups also showed significant improvement against albuterol at time zero, two to six hours, and 10 to 12 hours ($P$<0.001 and $P$<0.002). In the albuterol group there were also a significant difference compared to placebo at all points in time except zero, four to six and 10 to 12 hours ($P$<0.013).<br><br>The AUC of $FEV_1$ was significantly different in favor of both formoterol groups compared to placebo ($P$<0.001), formoterol 24 µg compared to albuterol ($P$<0.001) and albuterol compared to placebo ($P$<0.008) at all visits.<br><br>Both medications were well tolerated with no significant difference between them ($P$ value not reported). |

| Study and Drug Regimen | Study Design and Demographics | Sample Size and Study Duration | End Points | Results |
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| Bouros et al[18]<br><br>Formoterol 12 µg BID via DPI, added to current beclomethasone DPI treatment (500 µg QD; administered as separate products)<br><br>vs<br><br>beclomethasone 1,000 µg QD via DPI | MC, OL, PG, RCT<br><br>Individuals ≥18 years of age who were symptomatic on 500 µg daily of inhaled beclomethasone | N=132<br><br>12 weeks | Primary:<br>Mean PEF during final seven days of treatment<br><br>Secondary:<br>Overall PEF, asthma symptoms, rescue medication and safety | Primary:<br>There was a treatment effect of 20.36 L/minute in the combination group over the patients receiving the double dose of ICS (*P*=0.021).<br><br>Secondary:<br>For the entire treatment period, the combination group had an overall evening premedication PEF that was significantly higher compared to the double dose of ICS (*P*<0.05).<br><br>There was a decrease in day and night symptom scores in both groups but there was a significant difference in favor of the combination group (night; *P*=0.001, day; *P*<0.001).<br><br>In both groups the number of puffs of rescue medication taken decreased during the study, with a significant improvement seen with the combination compared to the double dose of the ICS (night; *P*=0.003, day; *P*<0.001).<br><br>There was no significant difference in adverse events in either group (*P* value not reported). |
| Von Berg et al[19]<br><br>Salmeterol 50 µg BID via DPI<br><br>vs<br><br>placebo<br><br>Both groups received albuterol MDI to use as needed. | DB, PC, PG, RCT<br><br>Individuals 6 to 15 years of age with a documented history of reversible airway obstruction requiring $\beta_2$-agonist treatment for symptomatic control | N=426<br><br>12 months | Primary:<br>Change from baseline in mean morning PEF<br><br>Secondary:<br>Percent of symptom-free nights and days, percent of nights and days with no rescue inhaler and incidence of asthma exacerbations | Primary:<br>Over the first six months of the study, the adjusted mean change above baseline in mean morning PEF was 341 minutes in patients treated with salmeterol compared to 171 minutes for placebo (*P*<0.001). This significant improvement was maintained throughout the second six months of the study (*P*=0.03).<br><br>Over the first six months of the study, the adjusted mean change above baseline in mean evening PEF was 251 minutes in patients treated with salmeterol compared to 121 minutes for placebo (*P*<0.001). This significant improvement was maintained throughout the second six months of the study (*P*=0.05).<br><br>Secondary:<br>Although the number of symptom-free days was high (86%) in both groups, there was no statistically significant difference between the |

| Study and Drug Regimen | Study Design and Demographics | Sample Size and Study Duration | End Points | Results |
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| | | | | groups (*P* value not reported).<br><br>There was a higher frequency distribution of the percentage of nights with no rescue inhaler use in patients receiving salmeterol compared to placebo that was significant throughout the 12-month treatment period (*P*<0.05).<br><br>During the 12-month treatment period there was no statistically significant difference between the treatment in the number of patients with asthma exacerbations (*P*=0.2). |
| Nelson et al[20]<br><br>Salmeterol 42 µg BID via DPI<br><br>vs<br><br>placebo<br><br>Both groups received this treatment as a supplement, not a replacement to current treatment. | DB, MC, OS, PC, PG, RCT<br><br>Individuals ≥12 years of age with asthma and currently using asthma medications | N=26,355<br><br>28 weeks | Primary:<br>Occurrence of combined respiratory related deaths or respiratory related life-threatening experiences<br><br>Secondary:<br>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:<br>There were three asthma-related deaths and 22 combined asthma-related deaths or life-threatening experiences in subjects receiving placebo compared to 13 asthma-related deaths and 37 combined asthma-related deaths or life-threatening experiences in subjects receiving salmeterol, a difference that was statistically significant (*P*<0.05).<br><br>Secondary:<br>There was no statistically significant difference seen in Caucasians in the primary or secondary end points (*P* value not reported).<br><br>For the primary and two of the secondary end points there was a statistically significant difference in African Americans receiving salmeterol compared to placebo (*P*<0.05).<br><br>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). |
| Boulet et al[21] | DB, MC, PG, RCT, | N=228 | Primary:<br>$FEV_1$ | Primary:<br>Salmeterol resulted in a significantly greater mean improvement in $FEV_1$ |

| Study and Drug Regimen | Study Design and Demographics | Sample Size and Study Duration | End Points | Results |
|---|---|---|---|---|
| Salmeterol 50 µg BID via DPI<br><br>vs<br><br>albuterol 200 µg QID via MDI | Individuals ≥12 years of age with mild to moderate asthma for ≥6 months | 15 weeks | Secondary:<br>PEF, symptoms, use of rescue medication, and adverse events | compared to albuterol from hours three to six (*P*<0.001) and 10 to 12 (*P*<0.012) and this effect was maintained throughout the study.<br><br>Secondary:<br>A significant improvement in evening PEF was seen for salmeterol compared to albuterol (34 vs 6 L/minute; *P*<0.001).<br><br>The average percent increase of symptom-free days in the salmeterol group was significantly greater than the albuterol group (29 vs 15%; *P*=0.012).<br><br>There was no significant difference in rescue medication use between the two groups and both treatments were well tolerated (*P* value not reported). |
| Faurschou et al[22]<br><br>Salmeterol 100 µg BID via DPI and as needed albuterol<br><br>vs<br><br>albuterol 400 µg QID via MDI and as needed albuterol<br><br>All patients continued to receive their ICS dose. | DB, DD, MC, PG, RCT<br><br>Individuals ≥18 years of age with chronic asthma currently receiving ICS | N=190<br><br>6 weeks | Primary:<br>PEFR<br><br>Secondary:<br>Symptom scores, use of rescue inhaler, $FEV_1$ and patient and physician assessment of efficacy | Primary:<br>The mean morning PEFR improved by 33 L/minute in the salmeterol group compared to 4 L/minute in the albuterol group at the conclusion of the study (*P*<0.001). There was a significant reduction in diurnal variation in the salmeterol group, from 39 to 22 L/minute compared to the albuterol group with a change from 34 to 37 L/minute (*P*<0.001).<br><br>Secondary:<br>Salmeterol increased $FEV_1$ after three and six weeks compared to baseline significantly more than albuterol (*P*<0.05 for both weeks).<br><br>There was a significant improvement in symptom-free nights in the salmeterol group compared to the albuterol group *(P*<0.001); however, there was no significant difference in symptom-free days.<br><br>There was no difference in the number of rescue-free days between the groups; however, there was an increase in percent of rescue-free nights in the salmeterol group (*P*<0.04). |
| Vervloet et al[23]<br><br>Salmeterol 50 µg BID via DPI | MC, OL, PG, RCT<br><br>Patients ≥18 years of age with | N=482<br><br>6 months | Primary:<br>Mean morning predose PEF during the last seven days | Primary:<br>The 95% CI for the treatment contrast formoterol minus salmeterol was -8.69, 9.84 L/minute during the last seven days of treatment and was included entirely in the predefined range of equivalence (*P* value not |

| Study and Drug Regimen | Study Design and Demographics | Sample Size and Study Duration | End Points | Results |
|---|---|---|---|---|
| vs<br><br>formoterol 12 µg BID via DPI | moderate to severe reversible obstructive airway disease for ≥1 year and currently using regular ICS (no attempt was made to exclude patients with COPD) | | of treatment<br><br>Secondary:<br>Mean morning and evening predose PEF during the last week before each clinic visit, overall mean morning and evening pre-dose PEF, day and night use of rescue medication and time symptoms score | reported).<br><br>Secondary:<br>The estimated treatment contrasts showed a trend towards greater efficacy with formoterol over salmeterol for mean evening predose PEF, which became statistically significant at two, three and four months (*P*<0.05).<br><br>Both treatments resulted in a mean decrease in rescue medication use to less than half compared to baseline and an improvement in mean symptom score but no significant difference between the groups was found (*P* value not reported).<br><br>Both medications were found to be safe and well tolerated (*P* value not reported). |
| Condemi et al[24]<br><br>Salmeterol 50 µg BID via DPI<br><br>vs<br><br>formoterol 12 µg BID via DPI | AC, MC, PG, OL<br><br>Individuals 18 to 75 years of age with moderate to moderately severe asthma diagnosed at least 1 year prior and currently on ICS | N=528<br><br>6 months | Primary:<br>Mean morning PEF measured five minutes after dosing<br><br>Secondary:<br>Mean morning and evening predose PEF, number of episode-free days, use and time of rescue medications, symptom score, overall mean morning predose PEF and safety | Primary:<br>There was a significant increase in mean PEF values measured five minutes after dosing in patients receiving formoterol compared to salmeterol (393.4 vs 371.7 L/minute; *P*<0.001).<br><br>Secondary:<br>Individuals receiving formoterol reported using significantly fewer actuations of rescue medication/week within 30 minutes of dosing (1.4 vs 2.1; *P*<0.005), significantly fewer actuations between morning and evening doses (5.6 vs 7.7; *P*<0.03) and significantly fewer actuations between evening and morning doses (2.8 vs 4.2; *P*<0.03) all compared to salmeterol.<br><br>Patients experienced significantly more episode free days in the formoterol group compared to the salmeterol group (9.5 vs 7.8*; P*<0.04).<br><br>Mean morning predose PEF, mean evening predose PEF and nighttime or daytime symptom scores did not differ significantly between treatments (*P* value not reported). |
| Brambilla et al[25] | MC, OL, PG, RCT | N=6,239 | Primary:<br>Difference in | Primary:<br>A significant increase in mean evening predose PEF was seen in |

| Study and Drug Regimen | Study Design and Demographics | Sample Size and Study Duration | End Points | Results |
|---|---|---|---|---|
| Salmeterol 50 µg BID via DPI and as needed albuterol<br><br>vs<br><br>formoterol 12 µg BID via DPI and as needed albuterol<br><br>vs<br><br>as needed albuterol<br><br>All patients continued to receive their ICS dose. | Patients ≥18 years of age with moderate to severe persistent asthma sub-optimally controlled on ICS with on demand albuterol with or without salmeterol | 4 weeks | evening predose PEF between patients continued on salmeterol and these switched to formoterol<br><br>Secondary:<br>Morning predose PEF, daytime and nighttime asthma symptom score, use of rescue inhaler, and percent days with no asthma symptoms or albuterol use | patients switched to formoterol from salmeterol or albuterol as needed compared to patients staying on salmeterol (402.9 vs 385.5 L/minute; *P*<0.001) and albuterol as needed (409.3 vs 385.0 L/minute; *P*<0.001).<br><br>Secondary:<br>In patients switched to formoterol compared to individuals who continued to receive salmeterol or on-demand albuterol, there was a significant increase in morning predose PEF, a significantly reduction in both daytime and nighttime asthma symptom score, a significant higher percent of symptom-free days, and a significant reduction in rescue medication use (all *P*<0.001).<br><br>There was no significant difference in the incidence of adverse event between groups (*P* value not reported). |
| Martin et al[26]<br><br>Salmeterol 42 µg two inhalations BID via DPI<br><br>vs<br><br>albuterol extended release tablets 4 mg in the morning and 8 mg in the evening | DB, DD, MC, RCT, XO<br><br>Individuals 18 to 65 years of age with $FEV_1$ >50% and 12% improvement following inhaled albuterol | N=56<br><br>8 weeks | Primary:<br>Morning peak flow, $FEV_1$ measurements<br><br>Secondary:<br>Nocturnal symptoms, nights without awakenings, rescue inhaler use, and safety | Primary:<br>Improvements in PEF and $FEV_1$ were significantly improved in both groups (*P*<0.001) but did not differ significantly between groups (*P* value not reported).<br><br>Secondary:<br>A comparison of the adjusted treatment means for the percentage of nights without awakenings demonstrated a significant improvement with salmeterol compared to albuterol (84.6 vs 79.4; *P*=0.021).<br><br>There was no statistical difference between the two groups concerning the percentage of patients who had no nocturnal awakenings (*P* value not reported).<br><br>A significant decrease in baseline puffs/day of a rescue inhaler was observed in both the salmeterol group (4.57 to 1.85; *P*<0.001) and the albuterol group (4.57 to 2.66; *P*<0.001). The decrease with salmeterol was significantly greater (*P*<0.001). |

| Study and Drug Regimen | Study Design and Demographics | Sample Size and Study Duration | End Points | Results |
|---|---|---|---|---|
| | | | | Seventy eight percent of the patients treated with albuterol and 75.9% of patients treated with salmeterol listed adverse event during the study (*P* value not reported). |
| Brambilla et al[27]<br><br>Salmeterol 50 µg BID via DPI<br><br>vs<br><br>terbutaline sustained release 5 mg tablets BID | DB, DD, MC, PG, RCT<br><br>Individuals 18 to 67 years of age suffering from chronic asthma with >15% reversibility after inhaled albuterol | N=159<br><br>2 weeks | Primary:<br>Number of awakening-free nights over the last week of treatment<br><br>Secondary:<br>Morning PEF, evening PEF, PEF diurnal variations, and nocturnal and diurnal rescue albuterol intake | Primary:<br>In the salmeterol group the mean number of awakening-free nights over the last week of treatment was significantly higher compared to the terbutaline group (5.3 vs 4.6; *P*=0.006).<br><br>Secondary:<br>No significant difference was found concerning the mean evening PEF; however, salmeterol was more efficacious than terbutaline on morning PEF (*P*=0.04) and PEF daily variations (*P*=0.01).<br><br>A significantly greater percent of individuals in the salmeterol group compared to the terbutaline group stopped using rescue albuterol during the day (30 vs 9%; *P*=0.004); however, there was no significant difference at night (*P* value not reported).<br><br>Significantly fewer patients in the albuterol group reported adverse events (16 vs 29%; *P*=0.04). |
| Estelle et al[28]<br><br>Salmeterol 50 µg BID via DPI<br><br>vs<br><br>beclomethasone 200 µg BID via DPI<br><br>vs<br><br>placebo | DB, PC, PG, RCT<br><br>Individuals 6 to 14 years of age with stable asthma | N=241<br><br>56 weeks | Primary:<br>Airway hyper-responsiveness<br><br>Secondary:<br>PEF, rescue inhaler use, and adverse event | Primary:<br>During months one to two of the study, there was significantly less airway hyperresponsiveness with beclomethasone compared to salmeterol (*P*=0.003) or placebo (*P*<0.001); however, this difference was lost two weeks after discontinuation of treatment.<br><br>Secondary:<br>In the beclomethasone group, the PEF varied significantly less when compared to the salmeterol and placebo groups (*P*=0.002 or *P*=0.02) with the similar effects seen with beclomethasone and salmeterol.<br><br>Compared to the placebo group, individuals receiving beclomethasone required significantly less rescue medication and had fewer withdrawals due to exacerbations (*P*<0.001 or *P*=0.03); however, the difference between salmeterol and placebo was not significant (*P* value not reported). |

| Study and Drug Regimen | Study Design and Demographics | Sample Size and Study Duration | End Points | Results |
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| | | | | Height in the beclomethasone-treated children increased by 3.96 cm during months one to 12, which was significantly less than the height increase in the placebo-treated children (5.04 cm; *P*=0.018) and the salmeterol-treated children (5.40 cm; *P*=0.004). |
| Lazarus et al[29]<br><br>Salmeterol 42 µg BID via MDI<br><br>vs<br><br>triamcinolone 400 µg BID via MDI<br><br>vs<br><br>placebo | DB, MC, PC, PG, RCT<br><br>Individuals 12 to 65 years of age with persistent asthma | N=164<br><br>28 weeks | Primary:<br>Change in morning PEF from the final week of the run in period to the final week of treatment<br><br>Secondary:<br>$FEV_1$, asthma symptom scores, rescue albuterol use, QoL scores, and number of exacerbations | Primary:<br>No significant difference in morning PEF measures was seen between the groups; however, they were both more effective compared to placebo (*P* values not reported).<br><br>Secondary:<br>There was no significant difference between the salmeterol and triamcinolone groups in terms of asthma symptom scores, rescue inhaler use, or QoL; both treatment arms were more effective compared to placebo in these categories (*P* values not reported).<br><br>There were significantly more group treatment failures in the salmeterol group than the triamcinolone group (25 vs 6%; *P*=0.004) as well as more exacerbations (20 vs 7%; *P*=0.04). |
| Tattersfield et al[30]<br><br>Terbutaline 0.5 mg as needed via DPI<br><br>vs<br><br>formoterol 4.5 µg as needed via DPI | DB, PG, RCT<br><br>Patients ≥18 years of age with asthma for ≥6 months and treated with a constant dose of ICS | N=362<br><br>12 weeks | Primary:<br>Time to first severe exacerbation<br><br>Secondary:<br>Morning and evening peak flow rate, $FEV_1$, symptoms, number of inhalations of relief medication and safety | Primary:<br>In the formoterol group, patients experienced a longer time to the first severe exacerbation than in the terbutaline group (*P*=0.013) with the relative risk ratio for having an exacerbation first in the formoterol group compared to the terbutaline group of 0.55.<br><br>Secondary:<br>No significant difference was seen between the groups concerning daytime or nighttime symptoms (*P* value not reported).<br><br>It was documented that pre-bronchodilator $FEV_1$ was greater in the formoterol group than the terbutaline group (*P* value not reported).<br><br>Both groups experienced a decrease in rescue inhalations but it was to a greater extent in the formoterol group (1.15 vs 0.40; *P* value not reported). |
| Hermansson et al[31] | MC, OL, PG, RCT | N=243 | Primary: | Primary: |

| Study and Drug Regimen | Study Design and Demographics | Sample Size and Study Duration | End Points | Results |
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| Terbutaline 500 µg QID via DPI<br><br>vs<br><br>salmeterol 50 µg BID via DPI | Patients ≥18 years of age with mild to moderate asthma | 4 weeks | Morning, evening and diurnal PEF, daytime and nighttime symptoms, use of rescue inhaler and $FEV_1$<br><br>Secondary:<br>Not reported | Over four weeks, salmeterol produced significant improvements over terbutaline in morning and evening PEF and diurnal variation (*P*<0.001, *P*=0.045 and *P*<0.001).<br><br>After four weeks there was a statistically significant difference in favor of the salmeterol group in daytime and nighttime asthma score, and percent of days and nights when a rescue medication was needed (*P*<0.001, *P*=0.008, *P*=0.002 and *P*=0.007).<br><br>After four weeks of treatment there were no significant differences in $FEV_1$ or FVC between the two groups (*P*=0.598 and *P*=0.916).<br><br>Secondary:<br>Not reported |
| **Chronic Obstructive Pulmonary Disease** | | | | |
| Spencer et al[32]<br><br>ICS/LABA combination treatment<br><br>vs<br><br>ICS alone<br><br>Vs<br><br>LABA alone | MA (7 RCT)<br><br>Randomized controlled trials comparing ICS and LABA in the treatment of patients with stable COPD | N=5,997<br><br>6 months to 3 years | Primary:<br>Moderate or severe exacerbations, hospitalization due to exacerbations and incidence of pneumonia<br><br>Secondary:<br>All-cause mortality, mild exacerbations, changes in $FEV_1$, QoL, symptom scores of breathlessness, rescue medication use, all cause hospitalizations and discontinuation rates | Primary:<br>There was no difference in the rate of moderate or severe COPD exacerbations between ICS and LABA monotherapy use (RR, 0.96; 95% CI, 0.89 to 1.02). Moreover, there was no significant difference in the exacerbation risk between studies lasting more or less than one year (*P*=0.75).<br><br>Exacerbations leading to hospitalizations were only reported in a single trial which showed that there was no significant difference in the risk of hospitalization due to exacerbation between treatment with fluticasone and salmeterol (RR, 1.07; 95% CI 0.91 to 1.26).<br><br>Overall, there was an increased risk of pneumonia associated with ICS treatment compared to LABA (OR, 1.38; 95% CI 1.10 to 1.73; *P*=0.005).<br><br>Specifically, there was an increased risk of pneumonia in patients treated with fluticasone compared to salmeterol (OR, 1.43; 95% CI, 1.13 to 1.81; *P*=0.003). There was no difference in the risk of developing pneumonia with budesonide compared to formoterol (OR, 0.84; 95% CI, 0.36 to 1.96; *P*=0.68). |

| Study and Drug Regimen | Study Design and Demographics | Sample Size and Study Duration | End Points | Results |
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| | | | | Secondary:<br>The pooled result showed that there was no significant difference in mortality rates between treatment with an ICS or LABA (OR, 0.98; 95% CI 0.59 to 1.64).<br><br>Mild exacerbation rates were not significantly different between patients treated with an ICS or LABA (OR, 1.63; 95% CI, 0.49 to 5.39).<br><br>There was no difference in the increase in $FEV_1$ with ICS compared to LABA treatment (mean difference, -17.36; 95% CI, -39.54 to 4.82).<br><br>Patients treated with an ICS showed greater improvements in QoL compared to those treated with LABA (mean difference, -0.74; 95% CI, -1.42 to<br>-0.06). This difference was small in relation to the threshold of four units for a clinically significant difference.<br><br>There was no statistically significant difference between ICS and LABA using the four point dyspnea scale.<br><br>There was no difference in the use of rescue medication during the treatment period with formoterol compared to ICS (mean difference, 0.56 puffs/24 h; 95% CI, 0.10 to 1.02).<br><br>None of the included studies reported the number of patients admitted to hospital for any cause.<br><br>There was no significant difference in the number of patients discontinuing therapy between patients on ICS and LABA (OR, 1.02; 95% CI, 0.92 to 1.14). Moreover, no statistically significant differences between fluticasone vs salmeterol (OR, 1.05; 95% CI, 0.92 to 1.18) and budesonide vs formoterol (OR, 0.96; 95% CI, 0.76 to 1.20) were observed. |
| Hanania et al[33] (abstract) | DB, DD, MC, RCT<br><br>Patients with | N=443<br><br>6 months | Primary:<br>Post-treatment adverse events, | Primary:<br>The proportion of patients with post-treatment adverse events in the arformoterol 15 µg, arformoterol 25 µg and formoterol groups was 67.8, |

| Study and Drug Regimen | Study Design and Demographics | Sample Size and Study Duration | End Points | Results |
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| Arformoterol 15 µg BID via nebulizer<br><br>vs<br><br>arformoterol 25 µg BID via nebulizer<br><br>vs<br><br>formoterol 12 µg BID via DPI | COPD | | COPD exacerbations, pulmonary function, dyspnea, use of rescue SABAs and ipratropium, SGRQ<br><br>Secondary:<br>Not reported | 76.2 and 66.7% respectively (*P* value not reported).<br><br>The proportion of patients with COPD exacerbation in the arformoterol 15 µg, arformoterol 25 µg and formoterol groups was 32.2, 30.6 and 22.4% respectively (*P* value not reported).<br><br>Pulmonary function improved for all groups and was maintained throughout the study.<br><br>The mean change from baseline in peak $FEV_1$ in the arformoterol 15 µg, arformoterol 25 µg and formoterol groups was 0.30, 0.34 and 0.26 L respectively (*P* value not reported).<br><br>The mean change from baseline in mean 24 hour trough $FEV_1$ in the arformoterol 15 µg, arformoterol 25 µg and formoterol groups was 0.10 L, 0.14 L and 0.09 L respectively (*P* value not reported).<br><br>The mean change from baseline in respiratory capacity in the arformoterol 15 µg, arformoterol 25 µg and formoterol groups was 0.20, 0.37 and 0.23 L respectively (*P* value not reported).<br><br>Dyspnea and use of rescue SABAs and ipratropium improved in all treatment groups.<br><br>Health status as measured by the SGRQ improved in all treatment groups.<br><br>Secondary:<br>Not reported |
| Baumgartner et al[34]<br><br>Arformoterol 15 µg BID via nebulizer<br><br>vs | DB, MC, PC, RCT<br><br>Patients ≥35 years of age with COPD and $FEV_1$ ≤65% predicted and >0.70 L, with | N=717<br><br>12 weeks | Primary:<br>Mean percentage change from baseline in morning trough $FEV_1$ averaged over 12-weeks | Primary:<br>Patients taking all three doses of arformoterol and salmeterol experienced statistically significant improvements in morning trough $FEV_1$ throughout 12 weeks of daily treatment compared to placebo (*P*<0.001).<br><br>Secondary: |

| Study and Drug Regimen | Study Design and Demographics | Sample Size and Study Duration | End Points | Results |
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| arformoterol 25 µg BID via nebulizer<br><br>vs<br><br>arformoterol 50 µg QD via nebulizer<br><br>vs<br><br>salmeterol 42 µg BID via MDI<br><br>vs<br><br>placebo<br><br>Patients were allowed to use albuterol MDI as a rescue therapy and ipratropium MDI as a supplemental medication as needed. | Medical Research Council Dyspnea Scale Score ≥2, an $FEV_1$/FVC ratio ≤70%, and a minimum smoking history of 15 pack-years at baseline | | Secondary:<br>Percent change from baseline in $FEV_1$ $AUC_{0-12}$ | Arformoterol 15 µg demonstrated significantly greater improvement in the percent change from pre-dose in the 12-hour $FEV_1$ $AUC_{0-12\ h}$ compared to placebo ($P$<0.001). Greater improvement in $FEV_1$ $AUC_{0-12}$ was also observed for the arformoterol group compared to the salmeterol group over the 12 week period ($P$<0.024).<br><br>Compared to the 15 µg dose, higher doses did not provide sufficient additional benefit to support their use.<br><br>Adverse events of the three doses of arformoterol were similar compared to salmeterol and placebo. The most serious adverse events were of respiratory and cardiovascular in nature. |
| Data on file[35]<br><br>Arformoterol 15 µg BID via nebulizer<br><br>vs<br><br>arformoterol 25 µg BID via nebulizer<br><br>vs<br><br>arformoterol 50 µg QD via | DB, PC, MC, RCT<br><br>Patients ≥35 years of age with of COPD and $FEV_1$ ≤65% predicted and >0.70 L, with Medical Research Council Dyspnea Scale Score ≥2, an $FEV_1$/FVC ratio ≤70%, and a minimum smoking | N=739<br><br>12 weeks | Primary:<br>Mean percentage change from baseline in morning trough $FEV_1$ averaged over 12-weeks<br><br>Secondary:<br>Percent change from baseline in 12-hour $FEV_1$ $AUC_{0-12}$ | Primary:<br>Patients taking arformoterol and salmeterol experienced statistically significant improvements in morning trough $FEV_1$ throughout 12 weeks of daily treatment ($P$<0.001).<br><br>Secondary:<br>Arformoterol 15 µg demonstrated significantly greater improvement in the percent change from predose in the 12 hour $FEV_1$ $AUC_{0-12\ h}$ compared to placebo ($P$<0.001).<br><br>Adverse events of the three doses of arformoterol were similar compared to salmeterol and placebo. |

| Study and Drug Regimen | Study Design and Demographics | Sample Size and Study Duration | End Points | Results |
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| nebulizer<br><br>vs<br><br>salmeterol 42 µg BID via MDI<br><br>vs<br><br>placebo<br><br>Patients were allowed to use albuterol MDI as a rescue therapy and ipratropium MDI as a supplemental medication as needed. | history of 15 pack-years at baseline | | | |
| Benhamou et al[36]<br><br>Formoterol 24 µg via DPI<br><br>vs<br><br>albuterol 400 µg via DPI<br><br>vs<br><br>placebo | DB, PC, RCT, XO<br><br>Individuals 40 to 75 years of age with stable, reversible COPD | N=25<br><br>1 dose | Primary:<br>AUC (zero to 30 minutes) of $FEV_1$ in one minute<br><br>Secondary:<br>AUC (zero to one hour) of $FEV_1$ in one minute, AUC (zero to three hours) of $FEV_1$ in one minute, maximal change in $FEV_1$ a percent of predicted value | Primary:<br>There were no significant differences between formoterol (5.89) and salmeterol (6.06) in the primary endpoint, but both were statistically higher than placebo (*P*<0.0001).<br><br>Secondary:<br>There were no statistically significant differences between the two active medication groups in secondary endpoints, and each had a similar onset (five minutes; *P* value not reported).<br><br>No serious adverse events or clinically relevant changes in vital sign were observed in any of the groups (*P* value not reported). |
| Cote et al[37]<br><br>Formoterol 12 µg BID via DPI | AC, MC, OL, PG, RCT<br><br>Patients ≥40 years of age who were | N=270<br><br>28 days | Primary:<br>Change from baseline in $FEV_1$ five minutes postdose on day 28 | Primary:<br>Changes from baseline in $FEV_1$ at five minutes postdose on day 28 favored treatment with formoterol over salmeterol (0.13 vs 0.07 L; *P*=0.022). |

| Study and Drug Regimen | Study Design and Demographics | Sample Size and Study Duration | End Points | Results |
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| vs<br><br>salmeterol 50 µg BID via MDI | current or previous smokers (>10 pack-years) with COPD, a prebronchodilator $FEV_1$ >35% of predicted normal, an $FEV_1$ ≤70% of FVC | | Secondary:<br>Changes from baseline in $FEV_1$ at 30 and 60 minutes postdose on day 28, in distance walked in the 6MWT on day 28, and changes in Borg scores for perception of breathlessness after 6MWT | Secondary:<br>Changes from baseline in $FEV_1$ on day 28 were significantly greater with formoterol compared to salmeterol at 30 and 60 minutes postdose (*P*<0.001 and *P*=0.069, respectively).<br><br>There was no difference between formoterol and salmeterol in regard to the change from baseline in distance walked during the 6MWT (65.2 vs 48.1 feet, respectively; *P*=0.412).<br><br>There was no difference in Borg dyspnea scores after the 6MWT for patients who received formoterol or salmeterol (*P* value not reported). |
| Cazzola et al[38]<br><br>Formoterol 12 µg, 12, and 24 µg via DPI<br><br>vs<br><br>albuterol 200 µg, 200, and 400 µg via MDI<br><br>Doses administered on two consecutive days. | RCT, SB, XO<br><br>Patients 51 to 77 years of age with COPD, having an acute exacerbation defined as sustained worsening of the condition from stable and beyond normal day-to-day variations, $FEV_1$ <70% of personal best that is acute in onset and necessitating a change in the medication regimen | N=16<br><br>2 days | Primary:<br>Maximum $FEV_1$ value during the dose-response curve<br><br>Secondary:<br>Spirometric data (inspiratory capacity and FVC), pulse rate, $SpO_2$ values | Primary and Secondary:<br>There was a significant increase in $FEV_1$, inspiratory capacity, and FVC in both the albuterol and formoterol groups compared to baseline after 48 µg of formoterol and 800 µg of albuterol (*P*<0.05).<br><br>There was no significant difference between $FEV_1$, inspiratory capacity, and FVC values in the formoterol group compared to the albuterol group after 48 µg of formoterol and 800 µg of albuterol.<br><br>There was a significant increase in $FEV_1$ values after 24 µg of formoterol compared to 48 µg of formoterol (*P*=0.022).<br><br>There was no significant difference in pulse rate or $SpO_2$ values compared to baseline after 48 µg of formoterol or 800 µg of albuterol (*P*>0.05).<br><br>$SpO_2$ values decreased below 90% in two patients after the highest dose of formoterol and in one patient after the highest dose of albuterol. The clinical significance of this finding was not reported. |
| Gross et al[39]<br><br>Formoterol 20 µg via nebulizer | DB, MC, PC, PG, RCT<br><br>Patients ≥40 years | N=351<br><br>12 weeks | Primary:<br>Percent change from baseline in the standardized | Primary:<br>The percent change in from baseline in the standardized absolute $AUC_{0-12}$ for $FEV_1$ measured over 12 hours following the morning dose at week 12 was significantly improved in the formoterol nebulizer group |

| Study and Drug Regimen | Study Design and Demographics | Sample Size and Study Duration | End Points | Results |
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| vs<br><br>formoterol 12 µg via DPI<br><br>vs<br><br>placebo | of age with COPD, a current or prior history of ≥10 pack-years of cigarette smoking, a post-bronchodilator $FEV_1$ 30 to 70% of the predicted value, and a $FEV_1$/FVC ratio of <0.70 | | absolute $AUC_{0-12}$ for $FEV_1$ measured over 12 hours following the morning dose at week 12<br><br>Secondary:<br>Change in the QoL from baseline in the total SGQR, symptom and impact scores, and rescue medication use | compared to the placebo group (*P*<0.0001).<br><br>Peak $FEV_1$ remained higher in the formoterol nebulizer group compared to the placebo group throughout the study, with the least square mean difference of 0.247 L at week 12 (95% CI, 0.174 to 0.320; *P*<0.0001).<br><br>The formoterol nebulizer group had similar results to the formoterol DPI group in $FEV_1$ $AUC_{0-12}$, 12-hour $FEV_1$ measurements, peak $FEV_1$, trough $FEV_1$, and FVC across all clinic visits. There were no statistically significant differences between the groups (*P* value not reported).<br><br>Secondary:<br>The formoterol nebulizer group demonstrated statistically significant improvements from baseline in the total SGRQ, symptom and impact scores compared to the placebo group (*P*≤0.03). There were no statistically significant differences between the formoterol nebulizer group and the formoterol DPI group in the total SGRQ or component scores (*P* value not reported).<br><br>Albuterol use remained consistent throughout the study for the placebo group. There was a 42% decrease in albuterol use in the formoterol nebulizer group during the first assessment period, which was maintained throughout the study. The formoterol DPI group had similar results to the formoterol nebulizer group.<br><br>Over half of the patients enrolled in the study reported at least one adverse event. The overall incidence of adverse events was similar across the treatment groups. The most commonly reported adverse events were headache, nausea, diarrhea and COPD exacerbation. |
| Sutherland et al[40] (abstract)<br><br>Formoterol 20 µg BID via nebulizer<br><br>vs | OL, RCT, XO<br><br>Patients with COPD | N=109<br><br>5 weeks | Primary:<br>Morning pre-dose $FEV_1$ trough<br><br>Secondary:<br>Post-dose efficacy at six hours, patient | Primary:<br>Morning pre-dose $FEV_1$ was significantly improved in the formoterol group compared to the ipratropium/albuterol group (*P*=0.0015).<br><br>Secondary:<br>Post-dose efficacy at six hours was maintained in the formoterol group compared to the ipratropium/albuterol group (*P*≤0.0001). |

| Study and Drug Regimen | Study Design and Demographics | Sample Size and Study Duration | End Points | Results |
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| ipratropium/albuterol MDI | | | satisfaction, patient perception of disease control, and dyspnea | Patient satisfaction and perception of disease control were significantly greater in the formoterol group among older, male and more severe subgroups (*P* value not reported).<br><br>Both groups resulted in meaningful changes in dyspnea but no significant differences between groups were observed. |
| Hanania et al[40]<br><br>Fluticasone 250 µg BID via DPI<br><br>vs<br><br>salmeterol 50 µg BID via DPI<br><br>vs<br><br>fluticasone/salmeterol 250/50 µg BID via DPI<br><br>vs<br><br>placebo | DB, MC, PC, RCT<br><br>Patients 40 to 87 years of age, current or former smokers with ≥20 pack year history, diagnosed with COPD, with an $FEV_1$/FVC ratio of ≤70%, baseline $FEV_1$ of <65% predicted normal value but >0.70 L (or if ≤0.70 L, then >40% predicted) | N=723<br><br>24 weeks | Primary:<br>Morning pre-dose $FEV_1$ and two hour post-dose $FEV_1$<br><br>Secondary:<br>Morning PEF values, TDI, CRDQ, CBSQ, exacerbations, and supplemental albuterol use | Primary:<br>There was a statistically significant increase in pre-dose $FEV_1$ in the fluticasone/ salmeterol group compared to the salmeterol (*P*=0.012) and placebo (*P*<0.001) groups. No significant difference between the fluticasone/ salmeterol group and fluticasone group was noted.<br><br>There was a statistically significant increase in two hour post-dose $FEV_1$ in the fluticasone/ salmeterol group compared to the salmeterol group (*P*<0.001), the placebo group (*P*<0.001) and the fluticasone group (*P*≤0.048).<br><br>Secondary:<br>There was a statistically significant increase in morning PEF values in the fluticasone/salmeterol group compared to the salmeterol group, placebo group, and fluticasone group (*P*≤0.034), though improvements were also seen from baseline in the salmeterol and fluticasone monotherapy groups (*P*<0.001).<br><br>Statistically significant improvements in TDI occurred in the fluticasone/salmeterol group (*P*=0.023) compared to placebo, in addition to improvements in the fluticasone (*P*=0.057) and salmeterol (*P*=0.043) monotherapy groups compared to placebo.<br><br>There was a statistically significant reduction in supplemental albuterol use in the fluticasone/salmeterol group compared to the fluticasone monotherapy group (*P*=0.036) and placebo (*P*=0.002).<br><br>There was a numerical reduction in supplemental albuterol use in the fluticasone/ salmeterol group compared to the salmeterol monotherapy |

| Study and Drug Regimen | Study Design and Demographics | Sample Size and Study Duration | End Points | Results |
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| | | | | group.<br><br>There was a statistically significant increase in CRDQ scores in the fluticasone/ salmeterol group compared to placebo (*P*=0.006).<br><br>There was a statistically significant increase in CRDQ scores in the fluticasone monotherapy group compared to placebo (*P*=0.002).<br><br>There were a statistically significant increases in CBSQ scores in the fluticasone/salmeterol group and the fluticasone monotherapy group compared to placebo (*P*≤0.017). |
| Vogelmeier et al[41]<br><br>Salmeterol 50 µg BID<br><br>vs<br><br>tiotropium 18 µg QD<br><br>Patients receiving a fixed-dose ICS/LABA were instructed to switch to inhaled glucocorticoid monotherapy at the start of the treatment phase of the study. Patients were allowed to continue their usual medications for COPD, except for anticholinergic drugs and LABA, during the double-blind treatment phase. | AC, DB, DD, MC, PG, RCT<br><br>Patients ≥40 years of age with a smoking history of ≥10 pack-years, a diagnosis of COPD with a $FEV_1$ after bronchodilation of ≤70% of the predicted value, a $FEV_1$/FVC ratio of ≤70%, and a documented history of ≥1 exacerbation leading to treatment with systemic glucocorticoids or antibiotics or hospitalization | N=7,384<br><br>1 year | Primary:<br>Time to the first exacerbation of COPD<br><br>Secondary:<br>Time-to-event end points, number-of-event end points, serious adverse events and death | Primary:<br>Tiotropium increased the time to first exacerbation by 42 days compared to salmeterol (187 vs 145 days, [time until at least 25% of the patients had a first exacerbation]), resulting in a 17% reduction the risk of exacerbations with tiotropium (HR, 0.83; 95% CI, 0.77 to 0.90; *P*<0.001). Of note, less than 50% percent of patients experienced a COPD exacerbation; therefore it was not possible to calculate the median time to first exacerbation in this population.<br><br>Secondary:<br>Compared to salmeterol, treatment with tiotropium significantly reduced the risk of moderate exacerbations by 14% (HR, 0.86; 95% CI, 0.79 to 0.93; *P*<0.001) and of severe exacerbations by 28% (HR, 0.72; 95% CI, 0.61 to 0.85; *P*<0.001).<br><br>Tiotropium reduced the risk of exacerbations leading to treatment with systemic glucocorticoids by 23% (HR, 0.77; 95% CI, 0.69 to 0.85; *P*<0.001), exacerbations leading to treatment with antibiotics by 15% (HR, 0.85; 95% CI, 0.78 to 0.92; *P*<0.001), and exacerbations leading to treatment with both systemic glucocorticoids and antibiotics by 24% (HR, 0.76; 95% CI, 0.68 to 0.86; *P*<0.001).<br><br>The annual rate of exacerbations was 0.64 in the tiotropium group and |

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| | within the previous year | | | 0.72 in the salmeterol group, representing a 11% reduction in the exacerbation rate with tiotropium (RR, 0.89; 95% CI, 0.83 to 0.96; *P*=0.002). Treatment with tiotropium significantly reduced the annual rate of moderate exacerbations by 7% (0.54 vs 0.59; RR, 0.93; 95% CI, 0.86 to 1.00; *P*=0.048) and the annual rate of severe exacerbations by 27% (0.09 vs 0.13; RR, 0.73; 95% CI, 0.66 to 0.82; *P*<0.001).<br><br>The incidence of a serious adverse event was 14.7% compared to 16.5% in the tiotropium and salmeterol groups, respectively. The most common serious adverse event was COPD exacerbation. There were 64 exacerbations in the tiotropium group and 78 in the salmeterol group during the treatment period (HR for tiotropium, 0.81; 95% CI, 0.58 to 1.13). |
| Feldman et al[42]<br>INLIGHT-1<br><br>Indacaterol 150 µg QD<br><br>vs<br><br>placebo<br><br>Patients previously on LABA/ICS combination products were switched to ICS monotherapy at an equivalent dose.<br><br>Salbutamol was provided for use as needed. | DB, MC, PC, PG, RCT<br><br>Patients ≥40 years of age with moderate to severe COPD, smoking history ≥20 pack years, post-bronchodilator $FEV_1$ <80 and ≥30% predicted and $FEV_1$/FVC <70% | N=416<br><br>12 weeks | Primary:<br>Trough $FEV_1$ at 12 weeks<br><br>Secondary:<br>Trough $FEV_1$ after one dose and at day 29, peak $FEV_1$ at day 1 and week 12, $FEV_1$ AUC five minutes to four hours, five minutes to one hour and one hour to hours after last dose at 12 weeks | Primary:<br>Trough $FEV_1$ at 12 weeks was significantly higher with indacaterol compared to placebo, with a least-squares mean (±SEM) difference of 130±24 mL (*P*<0.001).<br><br>Secondary:<br>Indacaterol achieved significantly higher 24 hour post dose trough $FEV_1$ after the first dose, with a least-squares mean difference from placebo of 80±19 mL (*P*<0.001). Similar results were observed at day 29 (difference, 140±24 mL; *P*<0.001).<br><br>Indacaterol achieved a significantly higher peak $FEV_1$ compared to placebo at day one and week 12, with mean differences of 190±28 mL (*P*<0.001) and 160±28 mL (*P*<0.001), respectively.<br><br>The $FEV_1$ AUC measurements after 12 weeks were all significantly higher with indacaterol compared to placebo, with mean differences of 170±24, 180±24 and 170±24 mL, respectively (*P*<0.001 for all). |
| To et al[43]<br><br>Indacaterol 150 µg QD<br><br>vs | DB, PC, PG, RCT<br><br>Patients ≥40 years of age with moderate or severe | N=347<br><br>12 weeks | Primary:<br>Trough $FEV_1$, TDI, SGRQ at week 12<br><br>Secondary: | Primary:<br>Of the patients included, 59.7% had moderate, and 40.3% had severe COPD. Trough $FEV_1$ at week 12 was 0.19 L and 0.20 L in moderate COPD with indacaterol 150 and 300 µg, respectively and 0.15 L and 0.19 L in severe COPD (*P*<0.001 for both subgroups vs placebo). All of |

| Study and Drug Regimen | Study Design and Demographics | Sample Size and Study Duration | End Points | Results |
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| indacaterol 300 µg QD<br><br>vs<br><br>placebo | COPD, a smoking history of ≥20 pack years, post-bronchodilator $FEV_1$ <80% and ≥30% predicted and $FEV_1$/FVC <70% | | Adverse events | the differences exceeded the pre-specified MCID of 0.12 L.<br><br>TDI total scores for both indacaterol doses vs placebo in both subgroups were statistically significant and clinically meaningful (at least one unit; *P*<0.05). The difference from placebo in SGRQ total score at week 12 exceeded the MCID of four units (-4.3 and -4.2 units for indacaterol 150 µg and 300 µg, respectively) (*P*< 0.01 for both).<br><br>Secondary:<br>Adverse event incidences were comparable between the two strengths of indacaterol and placebo. Both strengths of indacaterol were found to be safe, efficacious in improving lung function and dyspnea. |
| Kornmann et al[44]<br>INLIGHT-2<br><br>Indacaterol 150 µg QD<br><br>vs<br><br>salmeterol 50 µg BID<br><br>vs<br><br>placebo<br><br>Permitted concomitant medications included ICS, if the dose and regimen were stable for 1 month prior to screening.<br><br>Patients previously on LABA/ICS combination products were switched to ICS monotherapy at an equivalent dose. | AC, DB, DD, MC, PC, PG, RCT<br><br>Patients ≥40 years of age with moderate to severe COPD, smoking history ≥20 pack years, post-bronchodilator $FEV_1$ <80 and ≥30% predicted and $FEV_1$/FVC <70% | N=1,002<br><br>26 weeks | Primary:<br>Trough $FEV_1$ at 12 weeks compared to placebo<br><br>Secondary:<br>Trough $FEV_1$ at 12 weeks compared to salmeterol, $FEV_1$ at day two and weeks 12 and 26, health status, diary assessments, dyspnea and safety | Primary:<br>Trough $FEV_1$ at 12 weeks was significantly higher with indacaterol compared to placebo (*P*<0.001).<br><br>Secondary:<br>Trough $FEV_1$ at 12 weeks was significantly higher with indacaterol compared to salmeterol (treatment difference, 60 mL; *P*<0.001). Similar results were observed at 26 weeks (treatment difference, 70 mL; *P*<0.001).<br><br>Indacaterol maintained a clinically significant increase in $FEV_1$ over placebo during the course of the trial, with an increase from 130 mL at day two to 170 mL at week 12 and 180 mL at week 26 (*P*<0.001 for all). The difference between salmeterol and placebo was smaller and did not increase with length of treatment (120, 110 and 110 mL at day two, week 12 and week 26, respectively; *P*<0.001 for all). Indacaterol was "superior" at weeks 12 and 26 compared to salmeterol (*P*<0.001 for both).<br><br>Both indacaterol (treatment difference, -3.6, -4.1, -6.3 and -5.0 at weeks four, eight, 12 and 26; *P*<0.001 for all) and salmeterol (-2.5, -3.6, -4.2 and -4.1; *P*<0.01 for all) significantly improved SGRQ total scores compared to placebo, with the differences between indacaterol and salmeterol significantly favoring indacaterol at 12 weeks (*P*<0.05). The |

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| Salbutamol was provided for use as needed. | | | | odds of indacaterol achieving a clinically important improvement from baseline in SGRQ total scores (at least four units) was significantly greater compared to salmeterol by 12 weeks (OR, 1.59; 95% CI, 1.12 to 2.25; *P*<0.01).<br><br>The mean percentage days of poor COPD control over 26 weeks was 34.10% with both indacaterol and salmeterol compared to 38.10% with placebo (*P*=0.058 and *P*=0.057). Compared to patients receiving salmeterol, patients receiving indacaterol used less salbutamol, had higher morning PEF measurements and had more days when they were able to perform usual activities.<br><br>Adjusted mean total TDI scores at weeks four, eight, 12 and 26 were significantly higher with salmeterol (*P*<0.05) and indacaterol (*P*<0.001) compared to placebo. The mean differences compared to placebo were numerically larger with indacaterol than with salmeterol, with significance achieved at weeks four (0.95 vs 0.55; *P*<0.05) and 12 (1.45 vs 0.90; *P*<0.05). Patients receiving indacaterol were more likely to achieve a clinically important improvement from baseline in TDI total scores at all time points compared to patients receiving placebo (*P*<0.001 for all). The odds of this occurring with salmeterol compared to placebo only reached significance at weeks 12 and 26 (*P*≤0.001).<br><br>The most commonly reported adverse events were COPD worsening, nasopharyngitis, upper and lower respiratory tract infections and back pain. The proportions of patients experiencing serious adverse events were similar among the treatments (8.8, 5.7 and 7.8%). |
| Dahl et al[45]<br>INVOLVE<br><br>Indacaterol 300 µg QD<br><br>vs<br><br>indacaterol 600 µg QD | DB, DD, PC, PG, RCT<br><br>Patients ≥40 years of age with moderate to severe COPD, smoking history ≥20 pack years, | N=129<br><br>1 year | Primary:<br>Trough $FEV_1$ at 12 weeks<br><br>Secondary:<br>Days of poor COPD control, SGRQ score, time to first exacerbation, | Primary:<br>Trough $FEV_1$ at week 12 with both indacaterol doses was significantly higher compared to placebo (treatment difference, 170 mL; *P*<0.001) and formoterol (treatment difference, 100 mL; *P*<0.001). Over the remainder of the trial, improvements with indacaterol compared to placebo were maintained at a similar level, while the difference between formoterol and placebo diminished.<br><br>Secondary: |

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| vs<br><br>formoterol 12 µg BID<br><br>vs<br><br>placebo<br><br>Patients previously on LABA/ICS combination products were switched to ICS monotherapy at an equivalent dose.<br><br>Salbutamol was provided for use as needed.<br><br>Other bronchodilators or ICSs were not allowed unless to treat a COPD exacerbation. | post-bronchodilator $FEV_1$ <80 and ≥30% predicted and $FEV_1$/FVC <70% | | spirometry, TDI score, exacerbation rates, BODE index, safety | Both doses of indacaterol were significantly "superior" to placebo in decreasing the number of days of poor COPD control (treatment difference, -4.7; 95% CI, -8.4 to -1.0; *P*<0.05 and -8.3; 95% CI, -12.0 to -4.6; *P*<0.001). Formoterol was also significantly "superior" to placebo (-4.8; 95% CI, -8.5 to -1.1; *P*<0.05).<br><br>Both doses of indacaterol were significantly "superior" to placebo in improving SGRQ scores at weeks 12 (treatment difference, -3.8; 95% CI, -5.6 to -2.1 and -4.1; 95% CI, -5.9 to -2.3; *P*<0.001 for both) and 52 (-4.7; 95% CI, -6.7 to -2.7 and -4.6; 95% CI, -6.6 to -2.6; *P*<0.001 for both). Formoterol was also significantly "superior" to placebo (-3.2; 95% CI, -5.0 to -1.5 and -4.0; 95% CI, -6.0 to -2.0; *P*<0.001 for both).<br><br>There were too few events to calculate COPD exacerbation free time; however, both doses of indacaterol were significantly "superior" to placebo in improving the time to first COPD exacerbation (HR, 0.77; 95% CI, 0.606 to 0.975 and HR, 0.69; 95% CI, 0.538 to 0.882; *P*<0.05 for both). Formoterol was also significantly "superior" to placebo (HR, 0.77; 95% CI, 0.605 to 0.981; *P*<0.05).<br><br>Both doses of indacaterol were significantly "superior" to placebo in improving change from baseline in morning and evening PEF (treatment difference, 28.3; 95% CI, 22.8 to 33.8; and 31.1; 95% CI, 25.6 to 36.7; *P*<0.001 for both [morning PEF], and 24.6; 95% CI, 19.2 to 30.1; and 28.3; 95% CI, 22.8 to 33.8; *P*<0.001 for both [evening PEF]). Formoterol achieved similar results (*P*<0.001 for both), and both doses of indacaterol were significantly "superior" to formoterol (*P*<0.001 for all comparisons).<br><br>Both doses of indacaterol were significantly "superior" to placebo in improving TDI scores at week 12 (treatment difference, 1.17; 95% CI, 0.76 to 1.58 and 1.13; 95% CI, 0.71 to 1.54; *P*<0.001 for both) and week 52 (1.00; 95% CI, 0.53 to 1.47 and 0.98; 95% CI, 0.51 to 1.46; *P*<0.001 for both). Formoterol was also significantly "superior" to placebo (0.72; 95% CI, 0.300 to 1.013; *P*<0.001 and 0.71; 95% CI, 0.24 to 1.19; *P*<0.01). After 12 weeks, both doses of indacaterol were significantly |

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| | | | | "superior" to formoterol (*P*<0.05 for both doses).<br><br>Exacerbations occurred at a rate of 0.60 (rate ratio, 0.82; 95% CI, 0.63 to 1.06; *P* value not significant vs placebo), 0.57 (0.74; 95% CI, 0.56 to 0.97; *P*<0.05 vs placebo) 0.56 (0.75; 95% CI, 0.58 to 0.99; *P*<0.05 vs placebo) and 0.74 per year with indacaterol 300 µg, 600 µg, formoterol and placebo.<br><br>Both doses of indacaterol were significantly "superior" to placebo (least-squares mean, 2.67 and 2.90) in improving the BODE index at week 12 (treatment difference, -0.40; 95% CI, -0.56 to -0.25; *P*<0.001 and -0.24; 95% CI, -0.40 to -0.08; *P*<0.01) and week 52 (-0.55; 95% CI, -0.73 to 0.37 and -0.49; 95% CI, -0.68 to -0.31; *P*<0.001 for both). Formoterol was also significantly "superior" to placebo (-0.28; 95% CI, -0.43 to -0.12 and -0.53; 95% CI, -0.72 to -0.35; *P*<0.001 for both).<br><br>COPD worsening and nasopharyngitis were the only adverse events reported by >10% of patients with any treatment. Eight patients died during the trial and four died during follow up (two due to cardiac arrest [indacaterol 300 µg and placebo], one due to multiorgan failure [formoterol], one due to respiratory failure [formoterol] and four due to sudden death [one, formoterol; three, placebo]). Tremor was reported in 0.2, 1.9, 1.2 and 0.5% of patients, while tachycardia was reported in 0.9, 0.7, 0.5 and 1.2% of patients. Cough observed within five minutes of drug administration was observed in 19.1, 0.8 and 1.8% of patients receiving indacaterol, formoterol and placebo. (*P* values not reported). |
| Korn et al[46]<br>INSIST<br><br>Indacaterol 150 µg QD<br><br>vs<br><br>salmeterol 50 µg BID<br><br>Permitted concomitant | DB, DD, MC, PG, RCT<br><br>Patients ≥40 years of age with moderate to severe COPD, smoking history ≥10 pack years, post- | N=1,123<br><br>12 weeks | Primary:<br>Change in $FEV_1$ AUC from five minutes post dose to 11 hours and 45 minutes postdose at 12 weeks<br><br>Secondary:<br>Trough $FEV_1$, $FEV_1$ | Primary:<br>$FEV_1$ AUC measurements at 12 weeks were significantly higher with indacaterol compared to salmeterol, with an adjusted mean difference of 57 mL (95% CI, 35 to 79; *P*<0.001). The mean (percent) changes from baseline for indacaterol and salmeterol were 0.19 (16.6%) and 0.13 L (11.4%), respectively.<br><br>Secondary:<br>Trough $FEV_1$ significantly favored indacaterol compared to salmeterol after 12 weeks, (adjusted mean difference, 60 mL; 95% CI, 37 to 83; |

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| medications included ICS, if the dose and regimen were stable for 1 month prior to screening.<br><br>Patients previously on LABA/ICS combination products were switched to ICS monotherapy at an equivalent dose.<br><br>Salbutamol was provided for use as needed. | bronchodilator $FEV_1$ <80 and ≥30% predicted and $FEV_1$/FVC <70% | | AUC five minutes to four hours, five minutes to eight hours and eight to 11 hours at 12 weeks, FVC at 12 weeks; dyspnea; safety | *P*<0.001). Indacaterol maintained significance over salmeterol at all visits (*P*<0.001), except on day two (*P* value not significant).<br><br>Results for other $FEV_1$ AUC measurements after 12 weeks all significantly favored indacaterol over salmeterol (*P*<0.001 for all). The adjusted mean differences were 0.06 (95% CI, 0.03 to 0.08), 0.05 (95% CI, 0.03 to 0.08) and 0.07 L (95% CI, 0.04 to 0.09).<br><br>$FEV_1$ at week 12 with indacaterol was significantly higher compared to salmeterol at all time points (*P*<0.001 for all).<br><br>At 12 weeks, FVC with indacaterol was significantly higher compared to salmeterol at all time points (*P* values not reported).<br><br>With regards to dyspnea, TDI total scores with indacaterol were significantly "superior" compared to salmeterol after 12 weeks (adjusted mean difference, 0.63; 95% CI, 0.30 to 0.97; *P*<0.001). There was also a significantly greater proportion of patients receiving indacaterol that achieved a clinically important improvement from baseline (at least one point) in TDI total score (69.4 vs 62.7%; OR, 1.41; 95% CI, 1.07 to 1.85; *P*<0.05).<br><br>Over the 12 weeks, the use of rescue salbutamol was significantly lower with indacaterol (mean difference, -0.18 puffs/day; 95% CI, -0.36 to 0.00; *P*<0.05) and patients had a greater proportion of days with no rescue medication use (mean difference, 4.4 days; 95% CI, 0.6 to 8.2; *P*<0.05).<br><br>Overall incidences of adverse events were similar between the two treatments; at least one adverse event was reported by 33.8 and 33.5% of patients receiving indacaterol and salmeterol. The most frequently reported adverse events were COPD worsening (4.5 vs 5.7%) and headache (3.6 vs 3.6%). Overall, 3.6 and 2.8% of patients experienced a serious adverse event, with cardiac disorders being the most frequently reported (1.1 vs 0.4%; *P* values not reported). |
| Magnussen et al[47] | DB, DD, PC, RCT, | N=96 | Primary: | Primary: |

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| INPUT<br><br>Indacaterol 300 µg QD in the AM<br><br>vs<br><br>indacaterol 300 µg QD in the PM<br><br>vs<br><br>salmeterol 50 µg BID<br><br>vs<br><br>placebo<br><br>Patients were randomly assigned to one of 12 treatment sequences, each comprising 3 DB, 14 day treatment periods, with each treatment period separated by a 14 day washout period.<br><br>In each treatment sequence, patients received 3 of the 4 treatments listed above.<br><br>Permitted concomitant medications included ICS, if the dose and regimen were stable for 1 month | XO<br><br>Patients ≥40 years of age with moderate to severe COPD, smoking history ≥20 pack years, post-bronchodilator $FEV_1$ <80 and ≥30% predicted and $FEV_1$/FVC <70% | 12 weeks | Trough $FEV_1$ at 14 days<br><br>Secondary:<br>$FEV_1$ at individual time points on day one of each treatment period, trough FVC at 14 days, patient-reported symptom assessment and safety | Trough $FEV_1$ was significantly higher with indacaterol PM (treatment difference, 200 mL; *P*<0.001) and indacaterol AM (200 mL; *P*<0.001) compared to placebo. The difference between indacaterol PM and AM (10 mL) was not significant (*P* value not reported).<br><br>Trough $FEV_1$ was significantly higher with indacaterol PM compared to the evening dose of salmeterol (*P*<0.001). No significant difference between indacaterol AM and the morning dose of salmeterol was observed (*P* value not significant).<br><br>Secondary:<br>For individual time point $FEV_1$ values on day one, all active treatments produced significantly higher measurements compared to placebo at all time points. At five minutes, the differences between indacaterol AM and indacaterol PM compared to placebo were 150 and 140 mL (*P*<0.001 for both). The $FEV_1$ with both indacaterol AM and indacaterol PM was numerically higher compared to salmeterol at all time points. Significance was observed between indacaterol AM and salmeterol at all time points until the second salmeterol dose was administered (*P* values not reported).<br><br>Similar results were observed for trough FVC.<br><br>Over 14 days of treatment, both indacaterol AM and indacaterol PM significantly improved the proportion of nights with no awakenings (*P*<0.001 and *P*<0.01), days with no daytime symptoms (*P*<0.05 for both) and days able to perform usual activities (*P*<0.05 for both) compared to placebo. Improvements in all of these analyses were consistently in favor of indacaterol over salmeterol, with the difference reaching significance for indacaterol PM analysis of proportion of nights with no awakenings (*P*<0.05). No differences were observed between the two indacaterol regimens.<br><br>The overall incidence of adverse events was comparable between treatments (25.0, 23.1, 19.1 and 20.6%), with most being of mild to moderate severity. Cough was the most frequently reported suspected |

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| prior to screening. | | | | drug-related adverse event with indacaterol (5.9 and 7.7% compared to 1.5 and 0.0% with salmeterol and placebo). Serious adverse events were reported in two patients receiving indacaterol; neither was suspected to be drug-related. |
| Balint et al[48]<br>INSURE<br><br>Indacaterol 150 or 300 µg, administered as a single dose<br><br>vs<br><br>salbutamol 200 µg, administered as a single dose<br><br>vs<br><br>salmeterol/fluticasone 50 /500 µg, administered as a single dose<br><br>vs<br><br>placebo<br><br>Permitted concomitant medications included ICS, if the dose and regimen were stable for 1 month prior to screening.<br><br>Patients previously on LABA/ICS combination products were switched to | DB, MC, RCT, XO<br><br>Patients ≥40 years of age with moderate to severe COPD, smoking history ≥20 pack years, post-bronchodilator $FEV_1$ <80 and ≥30% predicted and $FEV_1$/FVC <70% | N=89<br><br>5 single dose treatment periods, separated by a 4 to 7 day washout period | Primary:<br>$FEV_1$ at five minutes compared to placebo<br><br>Secondary:<br>$FEV_1$ at five minutes compared to salbutamol and salmeterol/ fluticasone; $FEV_1$ at other scheduled time points; proportion of patients with ≥10, 12 and 15% increase in $FEV_1$ from baseline to each scheduled time point; proportion of patients with ≥12% and 200 mL increase in $FEV_1$ from baseline to each scheduled time point; safety | Primary:<br>$FEV_1$ was significantly higher with both doses of indacaterol compared to placebo (treatment difference, 100 and 200 mL; *P*<0.001 for both).<br><br>Secondary:<br>$FEV_1$ at five minutes was numerically higher with both doses of indacaterol compared to salbutamol (treatment difference, 10 and 30 mL; *P* value not reported), and significantly higher compared to salmeterol/fluticasone (50 and 70 mL; *P*=0.003 and *P*<0.001).<br><br>$FEV_1$ at all time points were significantly higher with both doses of indacaterol compared to placebo (*P*<0.001 for all) and compared to salmeterol/fluticasone at five and 15 minutes (*P*<0.05 for both). Indacaterol 300 µg achieved significantly higher measurements at 30 minutes (*P* value not reported) and two hours (*P*<0.001) compared to salbutamol.<br><br>The proportion of patients with ≥10, 12 or 15% increase in $FEV_1$ from baseline at five minutes were significantly greater with both doses of indacaterol compared to salmeterol/fluticasone (*P*<0.01 for all), and similar to salbutamol (*P* values not significant). After 30 minutes proportions with both doses of indacaterol were significantly greater compared to placebo (*P*<0.001 for all); however, only indacaterol 300 µg achieved significance compared to salmeterol/fluticasone (*P*<0.01, *P*<0.01 and *P*<0.001).<br><br>The proportion of patients with ≥12% and 200 mL increase in $FEV_1$ from baseline at five minutes with both doses of indacaterol and salbutamol were significantly greater compared to salmeterol/fluticasone and placebo (*P*<0.05 for all).<br><br>Overall, adverse events were reported in 3.5, 3.4, 4.7, 6.8 and 4.6% of |

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| ICS monotherapy at an equivalent dose.<br><br>The following medications were excluded at any time during the trial (unless an arm of the study): long and short acting anticholinergics, LABA/ICS combination products, SABA/short acting anticholinergic combination products, other LABAs, SABAs, xanthine derivatives and parenteral or oral corticosteroids. | | | | patients, respectively. All reported adverse events were mild or moderate in severity and none were suspected of being drug-related. There were no serious adverse events reported. |
| Donohue et al[49]<br>INHANCE<br><br>Indacaterol 150 µg QD<br><br>vs<br><br>indacaterol 300 µg QD<br><br>vs<br><br>tiotropium 18 µg QD<br><br>vs<br><br>placebo<br><br>Patients randomized to tiotropium received OL | DB, PC, RCT<br><br>Patients ≥40 years of age with moderate to severe COPD and a smoking history ≥20 pack years | N=1,683<br><br>26 weeks | Primary:<br>Trough $FEV_1$ at 12 weeks compared to placebo<br><br>Secondary:<br>Trough $FEV_1$ at 12 weeks compared to tiotropium, $FEV_1$ at five minutes on day one, TDI, diary card-derived symptom variables, SGRQ, time to first COPD exacerbation and safety | Primary:<br>The difference between both doses of indacaterol and placebo in trough $FEV_1$ was 180 mL, which exceeded the prespecified MCID of 120 mL (*P* value not reported).<br><br>Secondary:<br>The 40 to 50 mL differences between indacaterol 150 and 300 µg compared to tiotropium in trough $FEV_1$ were significant when tested for superiority ($P \leq 0.01$) and noninferiority ($P < 0.001$).<br><br>$FEV_1$ at five minutes on day one was increased relative to placebo by 120 mL (95% CI, 100 to 140) with both doses of indacaterol and by 60 mL (95% CI, 30 to 80) with tiotropium ($P < 0.001$ for all vs placebo and for indacaterol vs tiotropium).<br><br>TDI total scores significantly increased relative to placebo ($P < 0.001$ for all) at all assessments with both doses of indacaterol and after four, 12 and 16 weeks with tiotropium, with significant differences between indacaterol 300 µg and tiotropium after four, eight and 12 weeks ($P < 0.05$ |

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| treatment.<br><br>Albuterol was permitted for use as needed. | | | | for all).<br><br>Over the 26 weeks, the change from baseline in mean daily number of puffs of as needed albuterol was significantly reduced with both doses of indacaterol compared to placebo (*P*<0.001 for both). Both doses of indacaterol were significantly "superior" to tiotropium (*P*≤0.001 for both). The proportion of days with no use of as needed albuterol was significantly lower with both doses of indacaterol compared to placebo (*P*<0.001 for both) and tiotropium (*P*≤0.001).<br><br>The changes in baseline in morning and evening PEF (L/minute) were significantly greater with both doses of indacaterol compared to placebo (*P*<0.001 for all) and tiotropium (morning; *P*≤0.001 for both, evening; *P*<0.05 and *P*<0.01). The proportion of nights with no awakenings (*P*<0.01 for both), days with no daytime symptoms (*P*<0.05 for both) and days able to perform usual activities (*P*<0.01 for both) were all significantly greater with both doses of indacaterol compared to placebo.<br><br>SGRQ total scores improved relative to placebo with both doses of indacaterol at all assessments (*P*<0.01 for all) but not with tiotropium (*P* value not reported).<br><br>Analysis of time to first COPD exacerbation showed a reduced risk compared to placebo with indacaterol 150 µg (HR, 0.69; 95% CI, 0.51 to 0.94; *P*=0.019). Nonsignificant reductions were observed with indacaterol 300 µg (HR, 0.74; 95% CI, 0.55 to 1.01; *P*=0.05) and tiotropium (HR, 0.76; 95% CI, 0.56 to 1.03; *P*=0.08) compared to placebo.<br><br>The rate of cough as an adverse event did not differ across treatments. Cough within five minutes was observed in an average of 16.6 and 21.3% of patients were receiving indacaterol 150 and 300 µg, 0.8% of patients receiving tiotropium and 2.4% of patients receiving placebo (*P* values not reported). Otherwise, adverse events were similar across treatment. |
| Vogelmeir et al[50] | DB, DD, PC, RCT, | N=169 | Primary: | Primary: |

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| INTIME<br><br>Indacaterol 150 µg QD<br><br>vs<br><br>indacaterol 300 µg QD<br><br>vs<br><br>tiotropium 18 µg QD<br><br>vs<br><br>placebo<br><br>Permitted concomitant medications included ICS, if the dose and regimen were stable for 1 month prior to screening.<br><br>Patients previously on LABA/ICS combination products were switched to ICS monotherapy at an equivalent dose.<br><br>Salbutamol was allowed for use as needed. | XO<br><br>Patients ≥40 years of age with moderate to severe COPD, smoking history ≥10 pack years, post-bronchodilator $FEV_1$ <80 and ≥30% predicted and $FEV_1$/FVC <70% | 12 weeks | Trough $FEV_1$ at 14 days vs placebo<br><br>Secondary:<br>Trough $FEV_1$ at 12 weeks vs tiotropium, trough $FEV_1$ after the first dose, $FEV_1$ at individual time points after the first dose and on day 14, safety | Trough $FEV_1$ was significantly higher with both doses of indacaterol compared to placebo (treatment difference, 170 mL; 95% CI, 120 to 220 and 150 mL; 95% CI, 100 to 200; *P*<0.001).<br><br>Secondary:<br>Both doses of indacaterol not only met the criterion for noninferiority compared to tiotropium, but also achieved numerically higher values, with differences compared to tiotropium of 40 and 30 mL, respectively. The *P* value for the statistical comparison of superiority between indacaterol 150 µg and tiotropium was 0.043, with a mean difference of 50 mL; this did not meet the requirement for superiority.<br><br>$FEV_1$ after the first dose was significantly higher with both doses of indacaterol compared to placebo (*P*< 0.001 for all). No differences were noted between indacaterol and tiotropium (*P* value not reported).<br><br>At all time points on day one and after 14 days, all active treatments achieved significantly higher $FEV_1$ measurements compared to placebo (*P*<0.05 for all). Indacaterol 300 µg achieved higher measurements compared to tiotropium at all time points, while indacaterol 150 µg only achieved higher measurements at the majority of time points. Both doses of indacaterol had a fast onset of action on day one, achieving a significantly higher $FEV_1$ after five minutes compared to placebo (treatment difference, 120 and 130 mL, respectively; *P*<0.001 for both) and tiotropium (50 mL; *P*<0.004).<br><br>The overall incidences of adverse events were similar across all treatments and were predominantly mild or moderate in severity including cough, COPD worsening and nasopharyngitis. |
| Buhl et al[51]<br>INTENSITY<br><br>Indacaterol 150 µg QD<br><br>vs | DB, DD, MC, PG, RCT<br><br>Patients ≥40 years of age with moderate to severe | N=1,593<br><br>12 weeks | Primary:<br>Trough $FEV_1$ at 12 weeks<br><br>Secondary:<br>$FEV_1$ and FVC at | Primary:<br>Trough $FEV_1$ was 1.44 and 1.43 L with indacaterol and tiotropium, respectively (treatment difference, 0 mL; 95% CI, -20 to 20); therefore, indacaterol was determined to be noninferior to tiotropium (*P*<0.001). Subsequent criteria for superiority were not met. |

| Study and Drug Regimen | Study Design and Demographics | Sample Size and Study Duration | End Points | Results |
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| tiotropium 18 µg QD<br><br>Patients previously on LABA/ICS combination products were switched to ICS monotherapy at an equivalent dose.<br><br>Salbutamol was allowed for use as needed.<br><br>No other bronchodilator use was permitted. | COPD, smoking history ≥10 pack years, post-bronchodilator $FEV_1$ <80 and ≥30% predicted and $FEV_1$/FVC <70% | | individual time points, TDI, SGRQ, use of rescue medication, diary card-derived symptom variables and safety | Secondary:<br>After five minutes on day one, $FEV_1$ was higher with indacaterol (treatment difference, 70 mL; 95% CI, 60 to 80; *P*<0.00), and the difference remained significant after 30 minutes (*P*<0.001) and one hour (*P*<0.01). FVC measurements followed a similar pattern and were significantly higher with indacaterol (*P*<0.001, *P*<0.001 and *P*<0.05).<br><br>TDI total scores after 12 weeks revealed a significantly greater reduction in dyspnea with indacaterol (treatment difference, 0.58; *P*<0.001). Patients receiving indacaterol were significantly more likely to achieve a clinically relevant improvement in TDI total scores (OR, 1.49; *P*<0.001).<br><br>SGRQ total scores after 12 weeks revealed significantly better health status with indacaterol (treatment difference, -2.1; *P*<0.001). Patients receiving indacaterol were significantly more likely to achieve a clinically relevant improvement in SGRQ total scores (OR, 1.43; *P*<0.001).<br><br>Patients receiving indacaterol significantly reduced the use of daily, daytime and nighttime use of rescue medications (*P*<0.001), and had a significantly greater proportion of days without rescue medication use (*P*=0.004).<br><br>Diary data revealed that indacaterol and tiotropium resulted in similar increases from baseline of 2.0 and 1.9, respectively, in the proportion of days with no daytime COPD symptoms, 7.5 and 4.6 in the proportion of nights with no awakenings and 6.2 and 3.1 in the proportion of days able to undertake usual activities (*P* values not reported).<br><br>Overall incidences of adverse events were similar between the two treatments, with the most common events generally reflecting the type of disease characteristics of COPD. The incidence of COPD worsening was 10.7 vs 8.3%; most cases were mild to moderate in severity. Serious adverse events were reported in 2.8 and 3.8% of patients receiving indacaterol and tiotropium. (*P* values not reported). |
| Chapman et al[52]<br>INDORSE | DB, ES, MC, RCT | N=415 | Primary:<br>Trough $FEV_1$ at 52 | Primary:<br>Trough $FEV_1$ at week 52 was significantly higher for both indacaterol |

| Study and Drug Regimen | Study Design and Demographics | Sample Size and Study Duration | End Points | Results |
|---|---|---|---|---|
| Indacaterol 150 µg QD<br><br>vs<br><br>indacaterol 300 µg QD<br><br>vs<br><br>placebo | Patients in the extension had completed the 26-week core study for which they were required to have moderate to severe COPD with postbronchodilator $FEV_1$ <80% and ≥30% predicted and postbronchodilator $FEV_1$ /FVC <70% and were aged ≥40 years with a ≥20 pack-years smoking history | 52 weeks (26 week extension) | weeks and time to first COPD exacerbation<br><br>Secondary:<br>$FEV_1$ at other time points, albuterol use, rate of exacerbations and SGRQ total score | groups compared to placebo (170 mL; 95% CI, 110 to 230 mL and 180 mL; 95% CI, 120 to 240 mL, for the 150 µg and 300 µg doses, respectively; *P*<0.001).<br><br>The percent change from baseline in trough $FEV_1$ at week 52 was 120 mL (10%), 130 mL (10%), and -40 mL (-3%) with indacaterol 150 µg, indacaterol 300 µg and placebo, respectively. The differences between indacaterol and placebo in trough $FEV_1$ were maintained at a similar level from week two to the end of the study, with differences of ≥160 mL with both doses compared to placebo at each time point (all *P*<0.001).<br><br>There were not enough events in the study to evaluate the time to first exacerbation. The HR compared to placebo of 0.82 (95% CI, 0.51 to 1.34) and 0.86 (95% CI, 0.53 to 1.39) for indacaterol 150 µg and indacaterol 300 µg, respectively, suggested a trend toward improvement associated with indacaterol treatment but this was not statistically significant.<br><br>Secondary:<br>At five minutes postdose on day one, $FEV_1$ increased relative to placebo by 90 mL (95% CI, 40 to 140) with indacaterol 150 µg, and by 100 mL (95% CI, 50 to 150) with indacaterol 300 µg (both *P*<0.001). This bronchodilation at five minutes post-dosing was maintained at all subsequent assessments, with differences compared to placebo of 150 to 290 mL with indacaterol 150 µg, and 180 to 240 mL with indacaterol 300 µg (*P* value not reported).<br><br>At 52 weeks, the use of daily albuterol decreased from baseline by 1.2 puffs with indacaterol 150 µg, and 1.4 puffs with indacaterol 300 µg, compared to placebo (*P*<0.001 for both comparisons). The proportions of days without albuterol use were 56% and 59% with 150 µg, and 300 µg of indacaterol, respectively, (*P*<0.05) compared to placebo (46% of days without albuterol).<br><br>The mean SGRQ total scores with both indacaterol doses were numerically higher at all assessments, and significantly higher at week |

| Study and Drug Regimen | Study Design and Demographics | Sample Size and Study Duration | End Points | Results |
|---|---|---|---|---|
| | | | | 26 (150 µg, *P*=0.002; 300 µg, *P*=0.025) and week 44 (*P*=0.002 for both doses) compared to placebo. |
| Han et al[53]<br><br>Indacaterol 75 to 300 µg QD<br><br>vs<br><br>placebo | MA (6 RCT)<br><br>Patients with stable COPD who received indacaterol or placebo for 12 weeks or more | N=5,250<br><br>Up to 52 weeks | Primary:<br>Odds of achieving an improvement of at least one point on TDI scale<br><br>Secondary:<br>Not reported | Primary:<br>Patients treated with indacaterol 75 µg were significantly more likely to achieve an improvement in TDI score of at least one point compared to placebo (OR, 1.784; 95% CI, 1.282 to 2.482).<br><br>Patients treated with indacaterol 150 µg were significantly more likely to achieve an improvement in TDI score of at least one point compared to placebo (OR, 2.149; 95% CI, 1.746 to 2.645).<br><br>Patients treated with indacaterol 300 µg were significantly more likely to achieve an improvement in TDI score of at least one point compared to placebo (OR, 2.458; 95% CI, 2.010 to 3.006).<br><br>Secondary:<br>Not reported |
| Wang et al[54]<br><br>Formoterol<br><br>vs<br><br>placebo<br><br>or<br><br>indacaterol<br><br>vs<br><br>placebo<br><br>or<br><br>salmeterol | MA (17 RCT)<br><br>Patients with COPD who were treated with LABA or placebo for at least 24 weeks | N=11,871<br><br>At least 24 weeks | Primary:<br>COPD exacerbations and severe COPD exacerbations or withdrawals due to exacerbations<br><br>Secondary:<br>Not reported | Primary:<br>Compared to placebo, statistically significant reductions in COPD exacerbations occurred with formoterol (OR, 0.83; 95% CI, 0.73 to 0.96), indacaterol (OR, 0.82; 95% CI, 0.69 to 0.97) or salmeterol (OR, 0.79; 95% CI, 0.70 to 0.90).<br><br>Overall, LABA treatment was associated with a significantly lower risk of COPD exacerbation compared to placebo (OR, 0.81; 95% CI, 0.75 to 0.88).<br><br>All LABA treatments significantly reduced COPD exacerbations when both the study arm and the placebo arm were exposed to ICS (OR, 0.79; 95% CI, 0.72 to 0.87).<br><br>When both study arms were not exposed to ICS, there was no statistically significant reduction in COPD exacerbations for patients treated with formoterol compared to placebo (OR, 0.93; 95% CI, 0.75 to 1.15). |

| Study and Drug Regimen | Study Design and Demographics | Sample Size and Study Duration | End Points | Results |
|---|---|---|---|---|
| vs<br><br>placebo | | | | The odds of experiencing a severe COPD exacerbation or withdrawal owing to exacerbations was significantly lower with LABA treatment overall compared to placebo (OR, 0.74; 95% CI, 0.63 to 0.88) and for formoterol (OR, 0.85; 95% CI, 0.68 to 1.06), indacaterol (OR, 0.42; 95% CI, 0.21 to 0.83) and salmeterol (OR, 0.66; 95% CI, 0.49 to 0.89) individually.<br><br>When both arms were exposed to ICS, there was no significant reduction in severe exacerbations or withdrawals owing to exacerbations with salmeterol compared to placebo (OR, 0.78; 95% CI, 0.53 to 1.13). Formoterol reduced severe exacerbations or withdrawals owing to exacerbations compared to placebo, but this reduction did not reach statistical significance.<br><br>Secondary:<br>Not reported |
| Rodrigo et al[55]<br><br>Indacaterol<br><br>vs<br><br>LABA<br><br>or<br><br>tiotropium | SR (5 RCT)<br><br>Patients >40 years of age with moderate to severe COPD | N=5,920<br><br>At least 4 weeks | Primary:<br>Trough $FEV_1$<br><br>Secondary:<br>Use of rescue medication, proportion of patients with an improvement of at least one point on TDI, proportion of patients with a decrease of at least four units on SGRQ, COPD exacerbations, withdrawals, all-cause mortality and adverse events | Primary:<br>In two studies comparing indacaterol to tiotropium, there was no statistically significant difference in trough $FEV_1$ between the treatments (WMD, 0.01; 95% CI, 0.03 to -0.01; *P*=0.27).<br><br>In three studies comparing indacaterol to BID LABA use, the trough $FEV_1$ was significantly higher following treatment with indacaterol (WMD, 0.08; 95% CI, 0.06 to 0.09; *P*=0.00001).<br><br>Secondary:<br>Statistically significant reductions in rescue medication use were reported with indacaterol compared to treatment with tiotropium (WMD, -0.57; 95% CI, -0.37 to -0.77) or BID LABA (WMD, -0.22; 95% CI, -0.42 to -0.02).<br><br>The odds of achieving an improvement in TDI score of at least one point was significantly greater with indacaterol compared to treatment with tiotropium (OR, 1.43; 95% CI, 1.22 to 1.67) or BID LABA use (OR, 1.61; 95% CI, 1.13 to 2.28). |

| Study and Drug Regimen | Study Design and Demographics | Sample Size and Study Duration | End Points | Results |
|---|---|---|---|---|
| | | | | The odds of achieving a decrease in SGRQ score of at least four units was significantly greater with indacaterol compared to tiotropium (OR, 1.43; 95% CI, 1.22 to 1.68) or BID LABA (OR, 1.21; 95% CI, 1.01 to 1.45).<br><br>There was no statistically significant difference in the odds of a COPD exacerbation with indacaterol compared to tiotropium (*P*=0.81) or BID LABA (*P*=0.93).<br><br>There was no statistically significant difference in total withdrawals between patients treated with indacaterol compared to tiotropium (*P*=0.78) or BID LABA treatment (*P*=0.60).<br><br>All-cause mortality was not significantly different between the indacaterol treatment group and the tiotropium (*P*=0.13) or BID LABA treatment groups (*P*=0.86).<br><br>The incidences of any adverse event or serious adverse events were not significantly different between patients treated with indacaterol compared to tiotropium or BID LABA (*P*>0.05 for all). |
| Lee et al[56]<br><br>Exposure to ICS, ipratropium, LABAs, theophylline, and SABAs | Nested case-control<br><br>Patients treated in the United States Veterans Health Administration health care system | N=145,020<br><br>Cohort identified between October 1, 1999 and September 30, 2003 and followed through September 30, 2004 | Primary:<br>All-cause mortality, respiratory mortality, and cardiovascular mortality<br><br>Secondary:<br>Subgroup analyses of primary outcomes | Primary:<br>After adjusted for differences in covariates, ICS and LABAs were associated with reduced odds of death. An adjusted OR of 0.80 (95% CI, 0.78 to 0.83) for ICS 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).<br><br>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 ICS (OR, 0.88; 95% CI, 0.79 to 1.00); however, this also did not reach statistical significance.<br><br>Exposure to ipratropium was associated with a 34% increase in the odds |

| Study and Drug Regimen | Study Design and Demographics | Sample Size and Study Duration | End Points | Results |
|---|---|---|---|---|
| | | | | 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.<br><br>Secondary:<br>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.<br><br>With current smoking associated with a RR for death of 1.5, these estimates would result in adjusted risk ratios of 0.77 for ICS, 1.08 for ipratropium, and 0.90 for LABAs.<br><br>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 plus theophylline (OR, 1.47; 95% CI, 1.09 to 1.98) were associated with increased risk, whereas the presence of ICS with ipratropium reduced the risk for cardiovascular death (OR, 1.04; 95% CI, 0.90 to 1.22; *P*<0.001).<br><br>In the all-cause mortality group, ICSs 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 an elevated risk for death. |
| **Exercise-Induced Bronchospasm** | | | | |
| Shapiro et al[57]<br><br>Albuterol 180 µg prior to exercise challenge via MDI<br><br>vs | DD, XO<br><br>Individuals 12 to 50 years of age with a baseline $FEV_1$ >70% and at least a 20% reduction in $FEV_1$ after 2 | N=20<br><br>4 test sequences | Primary:<br>Maximum percent decrease in $FEV_1$ after each exercise challenge<br><br>Secondary:<br>Length of coverage, | Primary:<br>Both formoterol doses produced significantly greater inhibition of $FEV_1$ decrease compared to placebo at all points in time (*P*<0.01), and compared to albuterol at all points in time with the exception of 15 minutes post dose (*P*<0.01).<br><br>The two formoterol dose groups were not statistically different from each other and the only point in time that the mean maximum percent |

| Study and Drug Regimen | Study Design and Demographics | Sample Size and Study Duration | End Points | Results |
|---|---|---|---|---|
| formoterol 12 µg prior to exercise challenge via DPI<br><br>vs<br><br>formoterol 24 µg prior to exercise challenge via DPI<br><br>vs<br><br>placebo | exercise challenges 4 hours apart | | rescue therapy, and tolerability | decrease in $FEV_1$ with albuterol was statistically different from placebo was 15 minutes post dose ($P$<0.05).<br><br>Secondary:<br>Eighty nine percent to 94% of patients given formoterol and 79% of patients receiving albuterol were protected within 15 minutes of administration. Additionally, 71% of patients receiving formoterol were protected 12 hours after dosing compared to 26% of patients receiving albuterol, a percentage close to the 29% of patients receiving placebo ($P$ values not reported).<br><br>Nineteen percent of the patients treated with albuterol required a rescue inhaler at least once compared to zero patients receiving formoterol ($P$ value not reported).<br><br>There was no statistical difference in the percent of patients experiencing adverse event in all of the groups (no $P$ value reported). |
| Richter et al[58]<br><br>Formoterol 12 µg prior to exercise challenge via DPI<br><br>vs<br><br>salmeterol 50 µg prior to exercise challenge via DPI<br><br>vs<br><br>terbutaline 500 µg prior to exercise challenge via DPI<br><br>vs<br><br>placebo | DB, DD, PC, RCT, XO<br><br>Nonsmoking patients 25 to 48 years of age with mild to moderate asthma, a history of exercise-induced bronchoconstriction and a documented hyper-responsiveness to inhaled methacholine | N=25<br><br>13 visits | Primary:<br>Percent increase in $FEV_1$ between the inhalation of the study medication and the initiation of exercise (five, 30, or 60 minutes), and AUC of percent change in $FEV_1$ from end of exercise to 90 minutes<br><br>Secondary:<br>Not reported | Primary:<br>At five minutes there was a significantly stronger response with terbutaline than salmeterol ($P$<0.001) and at five, 15, 30, and 60 minutes after inhalation, formoterol provided greater bronchodilation than salmeterol ($P$<0.05). There was no significant difference between terbutaline and formoterol at any of the time points.<br><br>Mean pre-exercise $FEV_1$ was significantly larger in all active medication groups compared to placebo at 30 and 60 minute intervals ($P$<0.01) and was significantly larger after terbutaline and formoterol compared to salmeterol and placebo at the five-minute interval ($P$<0.05).<br><br>A statistically significant ($P$<0.01) decrease was seen in AUC with increasing time between inhalation and exercise with terbutaline, formoterol, and salmeterol; however, there was no difference between treatments.<br><br>Secondary:<br>Not reported |

| Study and Drug Regimen | Study Design and Demographics | Sample Size and Study Duration | End Points | Results |
|---|---|---|---|---|
| Edelman et al[59]<br><br>Montelukast 10 mg orally once in the evening<br><br>vs<br><br>salmeterol 100 µg, two inhalations BID via DPI | DB, PG, RCT<br><br>Patients 15 to 45 years of age who had been nonsmokers for at least 1 year and had a smoking history of less than 15 pack-years; patients had a history of chronic asthma and a decrease in $FEV_1$ of at least 20% after a standardized exercise challenge on two occasions during the baseline period | N=191<br><br>8 weeks | Primary:<br>Change from baseline in the maximal percentage decrease in $FEV_1$ at the end of eight weeks of treatment<br><br>Secondary:<br>Change from baseline for maximal percent decrease in $FEV_1$ at days one to three and week four, the time required after maximal decrease to return to within 5% of pre challenge values, AUC at all visits, the number and percent of patients requiring rescue medication during or at the conclusion of exercise test, and the number and percent of patients whose decrease in $FEV_1$ from pre-exercise levels was <10%, 10 to 20%, 20 to 40% and >40% | Primary:<br>In both treatment groups spirometry before exercise resulted in a small, non-significant change from baseline $FEV_1$ at first treatment visit at weeks four and eight, the groups did not differ statistically (*P* value not reported).<br><br>No statistical difference was seen at baseline in the maximal percent decrease in $FEV_1$. Improvement in maximal percent decrease in $FEV_1$ observed was maintained at week eight for the montelukast group, compared to the salmeterol group (*P*=0.002).<br><br>Secondary:<br>No statistical difference was seen at baseline in the post exercise AUC or time to recovery within five minutes. Improvement in maximal percent decrease in $FEV_1$ was similar in both groups between days one to three and was maintained at week four in the montelukast group but not in the salmeterol group (*P*=0.015).<br><br>A similar trend was also seen when evaluating the time required after maximal decrease to return to within 5% of pre challenge values and the AUC at all visits. The effect of salmeterol diminished while that of montelukast was maintained (*P*<0.001, *P*<0.001, *P*=0.010, *P*<0.001).<br><br>Twenty five of 96 (26%) patients in the montelukast group required rescue doses of medication after exercise challenge at any post treatment visit compared to 37 of 93 (40%)patients in the salmeterol group, a difference that was statistically significant (*P*=0.044).<br><br>After eight weeks 62 of 93 (66.7%) of patients in the montelukast group achieved a decrease in $FEV_1$ of <20% after exercise challenging compared to 41 of 90 (45.6%) of patients receiving salmeterol (*P*=0.028).<br><br>Both medications were generally well tolerated. |
| Storms et al[60] | DB, MC, PG, RCT | N=122 | Primary:<br>Effect on the | Primary:<br>The maximum post-rescue medication $FEV_1$ after four weeks improved |

| Study and Drug Regimen | Study Design and Demographics | Sample Size and Study Duration | End Points | Results |
|---|---|---|---|---|
| Montelukast 10 mg orally QD in the evening<br><br>vs<br><br>salmeterol 50 µg BID via DPI<br><br>vs<br><br>placebo | Patients 15 to 45 years of age with at least a 1-year history of asthma, documentation of exercise-induced bronchospasm in the past year, and were uncontrolled on ICS for ≥2 months | 4 weeks | maximum $FEV_1$ after $\beta_2$-agonists administered to patients with four weeks of treatment with placebo, montelukast, or salmeterol<br><br>Secondary:<br>Effects of treatment on pre-exercise $FEV_1$, exercise exacerbation, rescue bronchodilation, time to recovery to pre exercise $FEV_1$ level and average CEAQ | in the montelukast and placebo groups but not in the salmeterol group (1.5, 1.2 and -3.9%). This maximum $FEV_1$ was significantly less in the salmeterol group compared to the montelukast ($P$<0.001) and placebo groups ($P$<0.001). Results were similar to those obtained after one week of therapy and the difference between the montelukast and placebo groups was not significant.<br><br>Secondary:<br>There was a significant improvement in the in the mean change from baseline in pre-exercise $FEV_1$ in the salmeterol group compared to the placebo (at week one; $P$<0.001) and montelukast groups (at weeks one and four; $P$=0.010). In addition, there was no difference between the montelukast and placebo groups.<br><br>Montelukast significantly decreased exercise induced bronchospasm at week four compared to placebo ($P$=0.008), however, there was no significant difference between the salmeterol and placebo groups or the salmeterol and montelukast groups.<br><br>Compared to both placebo and salmeterol, after four weeks of treatment montelukast permitted significantly faster rescue with $\beta_2$-agonists ($P$=0.036, $P$=0.005).<br><br>After four weeks, there was a significant difference in the CEAQ score immediately and 10 minutes after exercise with montelukast compared to placebo ($P$<0.020).<br><br>Both medications were generally well tolerated. |

Drug regimen abbreviations: BID=twice daily, QD=once daily, QID=four times daily, TID=three times daily
Study abbreviations: AC=active control, CI=confidence interval, CR=case review, DB=double-blind, DD=double-dummy, ES=extension study, HR=hazard ratio, IB=investigational blinded, MA=meta-analysis, MC=multicenter, OL=open-label, OR=odds ratio, OS=observational study, PC=placebo-controlled, PG=parallel-group, PRO=prospective, RCT=randomized controlled trial, RETRO=retrospective, RR=relative risk, SB=single blinded, XO=crossover
Miscellaneous abbreviations: 6MWT=six-minute walk test, AUC=area under the curve, BODE index= body-mass index, airflow obstruction, dyspnea, and exercise capacity index, CBSQ=chronic bronchitis symptom questionnaire, CEAQ=clinic exercise-assessment questionnaire, CFC=chlorofluorocarbons, COPD=chronic obstructive pulmonary disease, CRDQ=chronic respiratory disease questionnaire, DPI=dry powered inhaler, ED=emergency department, FEV1=forced expiratory volume in 1 second, FVC=forced vital capacity, HFA=hydrofluoroalkane, ICS=inhaled corticosteroid, LABA=long acting β2-agonists, LOS=length of stay, MCID=minimal clinically important difference, MDI=metered dose inhaler, PAQ=pediatric asthma questionnaire, PEF=peak expiratory flow, PEFR=peak expiratory flow rate, QoL=quality of life, SABA=short acting β2-agonists, SEM=standard error of the mean, SGRQ=St. George's Hospital Respiratory Questionnaire, TDI=total dyspnea index, WMD=weighted mean difference

## Special Populations

**Table 5. Special Populations**[1-6]

| Generic Name | Population and Precaution | | | | |
|---|---|---|---|---|---|
| | Elderly/ Children | Renal Dysfunction | Hepatic Dysfunction | Pregnancy Category | Excreted in Breast Milk |
| **Long Acting $\beta_2$-agonists** | | | | | |
| Arformoterol | No evidence of overall differences in safety or efficacy observed between elderly and younger adult patients.<br><br>Safety and efficacy in children have not been established. | No dosage adjustment required. | Use with caution in patients with hepatic dysfunction. | C | Unknown |
| Formoterol | No evidence of overall differences in safety or efficacy observed between elderly and younger adult patients.<br><br>Approved in children five years of age and older (Foradil®).<br><br>Safety and efficacy in children have not been established (Perforomist®). | Not studied in renal dysfunction. | Not studied in hepatic dysfunction. | C | Unknown |
| Indacaterol | No evidence of overall differences in safety or efficacy observed between elderly and younger adult patients.<br><br>Safety and efficacy in children have not been established. | Not studied in renal dysfunction. | No dosage adjustment required; not studied in severe hepatic dysfunction. | C | Unknown |
| Olodaterol | Dosage adjustment not required in the elderly population. No evidence of overall differences between elderly and younger adult patients were observed.<br><br>Safety and efficacy in children have not been established. | No dosage adjustment required. | No dosage adjustment required for patients with mild to moderate hepatic impairment. Not studied in severe hepatic dysfunction, use with caution. | C | Probable, use with caution. |

| Generic Name | Population and Precaution | | | | |
|---|---|---|---|---|---|
| | Elderly/ Children | Renal Dysfunction | Hepatic Dysfunction | Pregnancy Category | Excreted in Breast Milk |
| Salmeterol | Dosage adjustment not required in the elderly population.<br><br>Approved in children four years of age and older. | Not studied in renal dysfunction. | Not studied in hepatic dysfunction. | C | Unknown |

HFA=hydrofluoroalkan

## Adverse Drug Events

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

| Adverse Event(s) | Arformoterol* | Formoterol† | Formoterol* | Indacaterol† | Olodaterol* | Salmeterol† |
|---|---|---|---|---|---|---|
| **Cardiovascular** | | | | | | |
| Angina | a | a | a | - | - | - |
| Arrhythmias | <2 | a | a | - | - | a |
| Arteriosclerosis | <2 | - | - | - | - | - |
| Chest pain | 7 | 1.9 to 3.2 | - | - | - | - |
| Congestive heart failure | <2 | - | - | - | - | - |
| Heart block | <2 | - | - | - | - | - |
| Hypertension | a | a | a | - | - | 4 |
| Hypotension | a | a | a | - | - | - |
| Myocardial infarction | <2 | - | - | - | - | - |
| Palpitations | a | a | a | - | - | a |
| QT prolongation | <2 | - | - | - | - | - |
| Tachycardia | a | a | a | - | - | a |
| **Central Nervous System** | | | | | | |
| Agitation | <2 | - | - | - | - | - |
| Anxiety | - | 1.5 | - | - | - | ≥1 |
| Asthenia | ≥2 | - | - | - | - | - |
| Cerebral infarct | <2 | - | - | - | - | - |
| Central nervous system stimulation | a | - | - | - | - | - |
| Dizziness | a | 1.6 | 2.4 | - | 2.3 | 4 |
| Fatigue | a | a | a | - | - | - |
| Headache | ≥2 | a | a | 5.1 | - | 13 to 17 |
| Hypokinesia | <2 | - | - | - | - | - |
| Insomnia | a | 1.5 | 2.4 | - | - | - |
| Migraine | - | - | - | - | - | ≥1 |
| Nervousness | ≥2 | a | a | - | - | a |
| Paralysis | <2 | - | - | - | - | - |
| Paresthesia | <2 | - | - | - | - | a |
| Sensory disturbances | - | - | - | - | - | a |

| Adverse Event(s) | Arformoterol* | Formoterol† | Formoterol* | Indacaterol† | Olodaterol* | Salmeterol† |
|---|---|---|---|---|---|---|
| Somnolence | <2 | - | - | - | - | - |
| Tremor | ≥2 | 1.9 | a | - | - | a |
| **Dermatological** | | | | | | |
| Angioedema | - | - | - | - | - | a |
| Contact dermatitis | - | - | - | - | - | a |
| Dry skin | <2 | - | - | - | - | - |
| Eczema | - | - | - | - | - | a |
| Herpes simplex | <2 | - | - | - | - | - |
| Herpes zoster | <2 | - | - | - | - | - |
| Photodermatitis | - | - | - | - | - | >1 |
| Pruritus | - | 1.5 | - | - | - | - |
| Rash | 4 | 1.1 | - | - | 2.2 | 4 |
| Skin discoloration | <2 | - | - | - | - | - |
| Skin hypertrophy | <2 | - | - | - | - | - |
| Urticaria | - | - | - | - | - | 3 |
| **Endocrine and Metabolic** | | | | | | |
| Diabetes | - | - | - | >2 | - | - |
| Hyperglycemia | a | a | a | >2 | - | ≥1 |
| Metabolic acidosis | a | a | a | - | - | - |
| **Gastrointestinal** | | | | | | |
| Abdominal pain | - | a | - | - | - | - |
| Constipation | <2 | - | - | - | >2 | - |
| Diarrhea | 6 | - | 4.9 | - | 2.9 | - |
| Dry mouth | a | 1.2 | 3.3 | - | - | - |
| Dyspepsia | - | a | - | - | - | - |
| Dyspeptic symptoms | - | - | - | - | - | ≥1 |
| Gastritis | <2 | - | - | - | - | - |
| Gastroenteritis | - | a | - | - | - | - |
| Gastrointestinal infections | - | - | - | - | - | ≥1 |
| Hyposalivation | - | - | - | - | - | ≥1 |
| Melena | <2 | - | - | - | - | - |
| Nausea | a | a | 4.9 | 2.4 | - | 3 |
| Oral candidiasis | <2 | - | - | - | - | ≥1 |
| Periodontal abscess | <2 | - | - | - | - | - |
| Rectal hemorrhage | <2 | - | - | - | - | - |
| Taste changes | - | - | - | - | - | - |
| Vomiting | ≥2 | - | 2.4 | - | - | 3 |
| **Genitourinary** | | | | | | |
| Calcium crystalluria | <2 | - | - | - | - | - |
| Cystitis | <2 | - | - | - | - | - |
| Glycosuria | <2 | - | - | - | - | - |
| Hematuria | <2 | - | - | - | - | - |
| Kidney calculus | <2 | - | - | - | - | - |
| Nocturia | <2 | - | - | - | - | - |
| Prostate specific antigen increase | <2 | - | - | - | - | - |

| Adverse Event(s) | Arformoterol* | Formoterol† | Formoterol* | Indacaterol† | Olodaterol* | Salmeterol† |
|---|---|---|---|---|---|---|
| Pyuria | <2 | - | - | - | - | - |
| Urine abnormality | <2 | - | - | - | - | - |
| Urinary tract infection | - | - | - | - | 2.5 | |
| **Hematologic** | | | | | | |
| Leukocytosis | ≥2 | - | - | - | - | - |
| **Laboratory Test Abnormalities** | | | | | | |
| Hyperkalemia | ≥2 | - | - | - | - | - |
| Hypokalemia | a | a | a | - | - | - |
| Liver enzyme elevation | - | a | - | - | - | - |
| Metabolic acidosis | - | a | - | - | - | - |
| **Musculoskeletal** | | | | | | |
| Arthralgia | <2 | - | - | - | 2.1 | >1 |
| Arthritis | <2 | - | - | - | - | - |
| Articular rheumatism | - | - | - | - | - | >1 |
| Bone disorder | <2 | - | - | - | - | - |
| Leg cramps | 4 | 1.7 | - | - | - | - |
| Muscle cramps | a | 1.7 | a | >2 | - | 3 |
| Muscle spasm | - | - | - | - | - | 3 |
| Muscle stiffness | - | - | - | - | - | ≥1 |
| Muscle tightness | - | - | - | - | - | ≥1 |
| Muscle rigidity | - | - | - | - | - | ≥1 |
| Musculoskeletal inflammation | - | - | - | - | - | ≥1 |
| Myalgia | - | a | - | - | - | ≥1 |
| Neck rigidity | <2 | - | - | - | - | - |
| Pain | 8 | - | - | >2 | - | 12 |
| Rheumatoid arthritis | <2 | - | - | - | - | - |
| Tendinous contracture | <2 | - | - | - | - | - |
| **Respiratory** | | | | | | |
| Asthma exacerbation | - | 0.6 to 4.7 | - | - | - | 3 to 4 |
| Bronchitis | ≥2 | 4.6 | - | - | 4.7 | 7 |
| Bronchospasm | - | - | - | - | - | a |
| Carcinoma of the lung | <2 | - | - | - | - | - |
| Chest infection | - | 2.7 | - | - | - | - |
| Chronic obstructive pulmonary disease | ≥2 | - | - | - | - | - |
| Cough | - | - | - | 6.5 | 4.2 | 5 |
| Dysphonia | - | 1 | - | - | - | - |
| Dyspnea | 4 | 2.1 | - | - | - | - |
| Increased sputum | - | 1.5 | - | - | - | - |
| Influenza | - | - | - | - | - | 5 |
| Laryngeal irritation | - | - | - | - | - | ≥1 |
| Laryngeal spasm | - | - | - | - | - | ≥1 |
| Laryngeal swelling | - | - | - | - | - | ≥1 |
| Lung disorder | 2 | - | - | - | - | - |
| Nasal congestion | - | - | - | - | - | 9 |

| Adverse Event(s) | Arformoterol* | Formoterol† | Formoterol* | Indacaterol† | Olodaterol* | Salmeterol† |
|---|---|---|---|---|---|---|
| Nasopharyngitis | - | - | 3.3 | 5.3 | 11.3 | - |
| Oral mucosal abnormality | - | - | - | - | - | ≥1 |
| Oropharyngeal edema | - | - | - | - | - | - |
| Oropharyngeal pain | - | - | - | 2.2 | - | - |
| Pharyngitis | - | 3.5 | - | - | - | 6 |
| Pneumonia | - | - | - | - | >2 | - |
| Rhinitis | - | a | - | - | - | 4 |
| Sinusitis | 5 | 2.7 | - | >2 | - | 4 |
| Throat irritation | - | - | - | - | - | 7 |
| Upper respiratory tract infection | - | 7.4 | - | >2 | 8.2 | ≥3 |
| Viral respiratory infection | - | - | - | - | - | 5 |
| Voice alteration | <2 | - | - | - | - | - |
| **Other** | | | | | | |
| Abnormal vision | <2 | - | - | - | - | - |
| Abscess | <2 | - | - | - | - | - |
| Accidental injury | - | - | - | - | - | - |
| Allergic reaction | - | - | - | - | - | - |
| Alopecia | - | - | - | - | - | - |
| Anaphylaxis | - | - | - | - | - | - |
| Back pain | 6 | 4.2 | - | - | 3.5 | - |
| Blurred vision | - | - | - | - | - | - |
| Chattiness | - | - | - | - | - | - |
| Chills | - | - | - | - | - | - |
| Cold symptoms | - | - | - | - | - | - |
| Conjunctivitis | - | - | - | - | - | ≥1 |
| Digitalis intoxication | <2 | - | - | - | - | - |
| Dilated pupils | - | - | - | - | - | - |
| Ear pain | - | - | - | - | - | - |
| Ear signs | - | - | - | - | - | 4 |
| Edema | - | - | - | >2 | - | ≥1 |
| Emotional lability | - | - | - | - | - | - |
| Eye itch | - | - | - | - | - | - |
| Fever | ≥2 | 2.2 | - | - | >2 | a |
| Flu syndrome | 3 | - | - | - | - | - |
| Glaucoma | <2 | - | - | - | - | - |
| Glossitis | - | - | - | - | - | - |
| Hernia | <2 | - | - | - | - | - |
| Hypersensitivity vasculitis | - | - | - | - | - | - |
| Keratitis | - | - | - | - | - | ≥1 |
| Lymphadenopathy | - | - | - | - | - | - |
| Malaise | a | - | a | - | - | - |
| Neoplasm | <2 | - | - | - | - | - |
| Otitis media | - | - | - | - | - | - |
| Pelvic pain | <2 | - | - | - | - | - |
| Peripheral edema | 3 | - | - | - | - | - |

| Adverse Event(s) | Arformoterol* | Formoterol† | Formoterol* | Indacaterol† | Olodaterol* | Salmeterol† |
|---|---|---|---|---|---|---|
| Retroperitoneal hemorrhage | <2 | - | - | - | - | - |
| Tonsillitis | - | 1.2 | - | - | - | - |
| Trauma | - | 1.2 | - | - | - | - |
| Viral infection | - | 17.2 | - | - | - | - |

a Percent not specified.
- Event not reported.
* Inhalation solution.
† Dry powder inhaler.

**Contraindications/Precautions**

All Long-acting $\beta_2$ adrenergic agonists are contraindicated in patients with asthma without use of a long-term asthma control medication. In addition all $\beta_2$-agonists are contraindicated in patients with a history of hypersensitivity to any components of a particular product.[1-6]

In some patients, the use of $\beta_2$-agonists have been reported to produce electrocardiogram changes such as flattening of the T-wave, prolongation of the QTc interval and ST segment depression. All $\beta_2$-agonists can potentially produce clinically significant cardiovascular effects in some patients (i.e., increase pulse rate and blood pressure).[1-6]

In some patients, the use of $\beta_2$-agonists can produce paradoxical bronchospasm, which may be life threatening. Immediate discontinuation of the medication and alternate therapy is indicated if paradoxical bronchospasm is suspected.[1-6]

Immediate hypersensitivity reactions may occur after administration of $\beta_2$-agonists as demonstrated by anaphylaxis, urticaria, angioedema, rash and bronchospasm.[1-6]

The use of $\beta_2$-agonists alone may not be adequate to control asthma symptoms. Early consideration should be given to adding anti-inflammatory agents to the therapeutic regimen.[1-6]

The use of $\beta_2$-agonists may produce significant hypokalemia in some patients. The decrease is usually transient.[1-6]

The use of $\beta_2$-agonists may aggravate preexisting diabetes mellitus and ketoacidosis and should be used with caution in patients with diabetes.[1-6]

The $\beta_2$-agonists should not be used in patients with acutely deteriorating chronic obstructive pulmonary disease. In addition, $\beta_2$-agonists should not be used in the relief of acute symptoms. Acute symptoms should be treated with an inhaled short acting $\beta_2$-adrenergic agonist.[1-6]

**Boxed Warning for long-acting beta-agonists (Brovana®, Perforomist®, Arcapta NeoHaler®, Striverdi Respimat®)**[1,3,4,5]

| WARNING |
|---|
| Asthma-related death:<br>Long-acting beta-2 adrenergic agonists may increase the risk of asthma-related death.<br><br>A placebo-controlled study with another long-acting beta2-adrenergic agonist (salmeterol) showed an increase in asthma related deaths in patients receiving salmeterol.<br><br>The finding of an increase in the risk of asthma-related deaths with salmeterol is considered a class effect of LABA, including arformoterol (BROVANA), formotorol (PERFOROMIST) indacaterol (ARCAPTA NEOHALER) and olodaterol (STRIVERDI RESPIMAT). The safety and efficacy of these LABA in patients with asthma have not been established. All LABA are contraindicated in patients with asthma without use of a long-term asthma control medication. |

**Boxed Warning for Formoterol (Foradil®)**[2]

| WARNING |
|---|
| Asthma-related death:<br><br>Long-acting beta2-adrenergic agonists (LABA), such as formoterol the active ingredient in FORADIL AEROLIZER, increase the risk of asthma-related death. Data from a large placebo controlled US study that compared the safety of another LABA (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 LABA, including formoterol.<br><br>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 LABA.<br><br>Because of this risk, use of FORADIL AEROLIZER for the treatment of asthma without a concomitant long-term asthma control medication, such as an inhaled corticosteroid, is contraindicated. Use FORADIL AEROLIZER only as additional therapy for patients with asthma who are currently taking but are inadequately controlled on a long-term asthma control medication, such as an inhaled corticosteroid. Once asthma control is achieved and maintained, assess the patient at regular intervals and step down therapy (e.g., discontinue FORADIL AEROLIZER) 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 FORADIL AEROLIZER for patients whose asthma is adequately controlled on low or medium dose inhaled corticosteroids.<br><br>Pediatric and Adolescent Patients:<br><br>Available data from controlled clinical trials suggest that LABA increase the risk of asthma-related hospitalization in pediatric and adolescent patients. For pediatric and adolescent patients with asthma who require addition of a LABA to an inhaled corticosteroid, a fixed-dose combination product containing both an inhaled corticosteroid and LABA should ordinarily be considered to ensure adherence with both drugs. In cases where use of a separate long-term asthma control medication (e.g., inhaled corticosteroid) and LABA is clinically indicated, appropriate steps must be taken to ensure adherence with both treatment components. If adherence cannot be assured, a fixed-dose combination product containing both an inhaled corticosteroid and LABA is recommended. |

**Boxed Warning for Salmeterol (Serevent Diskus)**[6]

| WARNING |
|---|
| Long-acting beta2-adrenergic agonists (LABA), such as salmeterol, the active ingredient in SEREVENT® DISKUS®, increase the risk of asthma-related death. Data from a large placebo-controlled US trial that compared the safety of salmeterol with placebo added to usual asthma therapy showed an increase in asthma-related deaths in subjects receiving salmeterol (13 deaths out of 13,176 subjects treated for 28 weeks on salmeterol versus 3 deaths out of 13,179 subjects on placebo). 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 LABA.<br><br>Because of this risk, use of SEREVENT DISKUS for the treatment of asthma without a concomitant long-term asthma control medication, such as an inhaled corticosteroid, is contraindicated. Use SEREVENT DISKUS only as additional therapy for patients with asthma who are currently taking but are inadequately controlled on a long-term asthma control medication, such as an inhaled corticosteroid. Once asthma control is achieved and maintained, assess the patient at regular intervals and step down therapy (e.g., discontinue SEREVENT DISKUS) 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 SEREVENT DISKUS for patients whose asthma is adequately controlled on low- or medium-dose inhaled corticosteroids.<br><br>Pediatric and Adolescent Patients: Available data from controlled clinical trials suggest that LABA increase the risk of asthma-related hospitalization in pediatric and adolescent patients. For pediatric and adolescent patients with asthma who require addition of a LABA to an inhaled corticosteroid, a fixed-dose combination product containing both an inhaled corticosteroid and a LABA should ordinarily be used to ensure adherence with both drugs. In cases where use of a separate long-term asthma control medication (e.g., inhaled corticosteroid) and a LABA is clinically indicated, appropriate steps must be taken to ensure adherence with both treatment components. If adherence cannot be assured, a fixed-dose combination product containing both an inhaled corticosteroid and a LABA is recommended. |

## Drug Interactions

**Table 7. Drug Interactions**[1-6]

| Generic Name | Interacting Medication or Disease | Potential Result |
|---|---|---|
| $\beta_2$-agonists (all) | Diuretics (i.e., loop diuretics, thiazide diuretics) | Electrocardiogram changes or hypokalemia may potentially be worsened with the addition of a $\beta_2$-agonist, particularly when the recommended dose is exceeded. |
| $\beta_2$-agonists (all) | Monoamine oxidase inhibitors | Monoamine oxidase is an enzyme that metabolizes catecholamines. When given with an indirect acting sympathomimetic, hypertensive crisis may occur. |
| $\beta_2$-agonists (all) | Nonselective $\beta_2$-antagonists | β-blockers inhibit the therapeutic effects of $\beta_2$ agonists and may produce bronchospasm in patients with asthma and chronic obstructive pulmonary disease. |
| $\beta_2$-agonists (all) | Tricyclic antidepressants | Tricyclic antidepressant may potentiate the cardiovascular effects of $\beta_2$-agonists. |

## Dosage and Administration

**Table 8. Dosing and Administration**[1-6]

| Generic Name | Adult Dose | Pediatric Dose | Availability |
|---|---|---|---|
| Arformoterol | Bronchoconstriction in patients with chronic COPD, including chronic bronchitis and emphysema; maintenance treatment:<br>Solution for nebulization: 15 µg BID | Safety and efficacy in children have not been established. | Solution for nebulization:<br>15 µg (2 mL) |
| Formoterol | Asthma (including nocturnal asthma) and bronchospasm prevention as concomitant therapy with a long-term asthma control medication:<br>Capsule for inhalation (Foradil®): 12 µg capsule inhaled BID; maximum, 24 µg/day<br>Bronchoconstriction in patients with chronic COPD, including chronic bronchitis and emphysema; maintenance treatment:<br>Capsule for inhalation (Foradil®): 12 µg capsule inhaled BID; maximum, 24 µg/day<br><br>Solution for nebulization (Perforomist®):<br>20 µg BID; maximum 40 µg/day<br><br>Exercise-induced bronchospasm prophylaxis, acute:<br>Capsule for inhalation (Foradil®): 12 µg capsule inhaled at least 15 minutes before exercise | Asthma (including nocturnal asthma) and bronchospasm prevention as concomitant therapy with a long-term asthma control medication (five years of age and older):<br>Capsule for inhalation (Foradil®): 12 µg capsule inhaled BID; maximum, 24 µg/day<br><br>Exercise-induced bronchospasm prophylaxis, acute (five years of age and older):<br>Capsule for inhalation (Foradil®): 12 µg capsule inhaled at least 15 minutes before exercise (no repeat dose) | Capsule for inhalation:<br>12 µg<br><br>Solution for nebulization:<br>20 µg/2 mL |
| Indacaterol | Bronchoconstriction in patients with chronic COPD, including chronic bronchitis and emphysema; maintenance treatment:<br>Capsule for inhalation: 75 µg QD | Safety and efficacy in children have not been established. | Capsule for inhalation:<br>75 µg |
| Olodaterol | Bronchoconstriction in patients with chronic COPD, including chronic bronchitis and emphysema; maintenance treatment:<br>Solution for inhalation: 2 inhalations (5 µg) once-daily at the same time of the day | Safety and efficacy in children have not been established. | Solution for inhalation (breath activated, metered-dose inhaler):<br>2.5 µg |
| Salmeterol | Asthma (including nocturnal asthma) and bronchospasm | Asthma (including nocturnal asthma) and | Dry powder inhaler:<br>50 µg |

| Generic Name | Adult Dose | Pediatric Dose | Availability |
|---|---|---|---|
| | prevention as concomitant therapy with a long-term asthma control medication:<br>Dry powder inhaler: 1 inhalation BID<br><br>Bronchoconstriction in patients with chronic COPD, including chronic bronchitis and emphysema; maintenance treatment:<br>Dry powder inhaler: 1 inhalation BID<br><br>Exercise-induced bronchospasm prophylaxis, acute:<br>Dry powder inhaler: 1 inhalation at least 30 minutes before exercise | bronchospasm prevention as concomitant therapy with a long-term asthma control medication (four years of age and older):<br>Dry powder inhaler: 1 inhalation BID<br><br>Exercise-induced bronchospasm prophylaxis, acute (four years of age and older):<br>Dry powder inhaler: 1 inhalation at least 30 minutes before exercise | |

BID=two times daily, COPD=chronic obstructive pulmonary disease

## 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)**[10] | Diagnosis<br>· 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.<br>· A diagnosis of COPD should be confirmed by spirometry.<br>· COPD patients typically display a decrease in both Forced Expiratory Volume in one second ($FEV_1$) and $FEV_1$/ Forced Vital Capacity (FVC) ratio.<br>· The presence of a post-bronchodilator $FEV_1/FVC < 0.70$ confirms the presence of persistent airflow limitation and COPD.<br>· A detailed medical history should be obtained for all patients suspected of developing COPD.<br>· Severity of COPD is based on the level of symptoms, the severity of the spirometric abnormality, and the presence of complications.<br>· Chest radiograph may be useful to rule out other diagnoses.<br>· Arterial blood gas measurements should be performed in advanced COPD.<br>· Screening for $\alpha_1$-antitrypsin deficiency should be performed in patients of Caucasian decent who develop COPD at 45 years of age or younger.<br>· Differential diagnoses should rule out asthma, congestive heart failure, bronchiectasis, tuberculosis, diffuse panbronchiolitis, and obliterative bronchiolitis.<br><br>Treatment<br>· 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. |

| Clinical Guidelines | Recommendations |
|---|---|
| | · The management of COPD should be individualized to address symptoms and improve the patient's quality of life.<br>· 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.<br>· Administer bronchodilator medications on an as needed or regular basis to prevent or reduce symptoms and exacerbations.<br>· Principle bronchodilators include $\beta_2$-agonists, anticholinergics and theophylline used as monotherapy or in combination.<br>· The use of long-acting bronchodilators is more effective and convenient than short-acting bronchodilators.<br>· For single-dose, as needed use, there is no advantage in using levalbuterol over conventional nebulized bronchodilators.<br>· Combining bronchodilators of different pharmacological classes may improve efficacy and decrease adverse effects compared to increasing dose of a single bronchodilator<br>· 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.<br>· Long term therapy ICS as monotherapy is not recommended.<br>· Chronic treatment with systemic corticosteroids should be avoided due to an unfavorable risk-benefit ratio.<br>· COPD patients should receive an annual influenza vaccine.<br>· 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.<br>· Exercise training programs should be implemented for all COPD patients.<br>· Long-term administration of oxygen (>15 hours/day) increases survival in patients with chronic respiratory failure.<br><br>Management of exacerbations<br>· The most common causes of an exacerbation are respiratory tract infections.<br>· Inhaled short-acting $\beta_2$-agonists, with or without short-acting anticholinergics are the preferred bronchodilators for treatment for exacerbations of COPD.<br>· 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.<br>· 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. |
| Global Initiative for Asthma: **Global Strategy for Asthma Management and Prevention (2012)**[9] | Treatment<br>· Education should be an integral part of all interactions between health care professionals and patients, and is relevant to asthma patients of all ages.<br>· 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.<br>· 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 |

| Clinical Guidelines | Recommendations |
|---|---|
| | anti-immunoglobulin E (IgE).<br>· Reliever medications are administered on an as-needed basis to reverse bronchoconstriction and relieve symptoms and include rapid-acting inhaled $\beta_2$-agonists, inhaled anticholinergics, short-acting theophylline and short-acting $\beta_2$-adrenergic agonists (SABAs).<br><br>Controller medications<br>· ICSs are currently the most effective anti-inflammatory medications for the treatment of persistent asthma for patients of all ages.<br>· ICSs differ in potency and bioavailability, but few studies have been able to confirm the clinical relevance of these differences.<br>· 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.<br>· To reach clinical control, add-on therapy with another class of controller is preferred over increasing the dose of the ICS.<br>· 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.<br>· Some patients with aspirin-sensitive asthma respond well to leukotriene modifiers.<br>· 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.<br>· Several studies have demonstrated that leukotriene modifiers are less effective than LABAs as add-on therapy.<br>· LABAs should not be used as monotherapy in patients with asthma as these medications do not appear to influence asthma airway inflammation.<br>· When a medium dose of the ICS fails to achieve control, the addition of a LABA is the preferred treatment.<br>· Controlled studies have shown that delivering an ICS and LABA 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.<br>· 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).<br>· 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.<br>· 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.<br>· Cromolyn and nedocromil are less effective than a low dose of ICSs.<br>· Oral LABA therapy is used only on rare occasions when additional bronchodilation is needed.<br>· Anti-IgE treatment with omalizumab is limited to patients with elevated serum levels of IgE.<br>· Long-term oral corticosteroid therapy may be required for severely uncontrolled asthma, but is limited by the risk of significant adverse event. |

| Clinical Guidelines | Recommendations |
|---|---|

- Other anti-allergic compounds have limited effect in the management of asthma.

Reliever medications

- Rapid-acting inhaled $\beta_2$-agonists are the medications of choice for the relief of bronchospasm during acute exacerbations and for the pretreatment of exercise-induced bronchoconstriction, in patients of all ages.
- Rapid-acting inhaled $\beta_2$-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 $\beta_2$-agonists.
- Short-acting theophylline may be considered for relief of asthma symptoms.
- Short-acting oral $\beta_2$-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 event.
- Systemic corticosteroids are important in the treatment of severe acute exacerbations.

Assessment, treatment, and monitoring

- 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:

| Step 1 | Step 2 | Step 3 | Step 4 | Step 5 |
|---|---|---|---|---|
| *Asthma education and environmental control* | | | | |
| *As needed rapid-acting $\beta_2$-agonist* | | | | |
| Controller options | Select one | Select one | Add one or more | Add one or both |
| | Low-dose ICS | Low-dose ICSs + LABA | Medium- or high-dose ICS + LABA | Oral corticosteroid |
| | Leukotriene modifier | Medium- or high-dose ICS | Leukotriene modifier | Anti-IgE treatment |
| | - | Low-dose ICS +leukotriene modifier | - | - |
| | - | Low-dose ICS +sustained-release theophylline | - | - |

Management of exacerbations

- Repeated administration of rapid-acting inhaled $\beta_2$-agonists is the best method of achieving relief for mild to moderate exacerbations. Systemic corticosteroids should be considered if the patient does not immediately respond to rapid-acting inhaled $\beta_2$-agonists or if the episode is

| Clinical Guidelines | Recommendations |
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| | severe. |
| The National Heart, Lung, and Blood Institute/National Asthma Education and Prevention Program: **Guidelines for the Diagnosis and Management of Asthma (2007)**[8] | Diagnosis<br>· 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.<br>· 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.<br>· 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.<br>· Spirometry is needed to establish a diagnosis of asthma.<br>· Additional studies such as pulmonary function tests, bronchoprovocation, chest x-ray, allergy testing and biomarkers of inflammation may be useful when considering alternative diagnoses.<br><br>Treatment<br>· 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.<br>· The initial treatment of asthma should correspond to the appropriate asthma severity category.<br>· Long-term control medications such as 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.<br>· Quick-relief medications are used to provide prompt relief of bronchoconstriction and accompanying acute symptoms such as cough, chest tightness and wheezing.<br>· Quick relief medications include SABAs, anticholinergics and systemic corticosteroids.<br><br>Long-term control medications<br>· ICSs are the most potent and consistently effective long-term control medication for asthma in patients of all ages.<br>· 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.<br>· When patients ≥12 years of age require more than a low-dose ICS, the addition of a LABA is recommended. Alternative, but not preferred, adjunctive therapies include leukotriene receptor antagonists, theophylline, or in adults, zileuton.<br>· 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.<br>· 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 |

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<tr><th>Clinical Guidelines</th><th>Recommendations</th></tr>
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ICS and LABA therapy.<br>
· Leukotriene receptor antagonists (montelukast and zafirlukast) are alternative therapies for the treatment of mild persistent asthma.<br>
· LABAs (formoterol and salmeterol) are not to be used as monotherapy for long-term control of persistent asthma.<br>
· 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.<br>
· Methylxanthines, such as sustained-release theophylline, may be used as an alternative treatment for mild persistent asthma.<br>
· Tiotropium is a long-acting inhaled anticholinergic indicated once-daily for COPD and has not been studied in the long-term management of asthma.<br><br>
Quick-relief medications<br>
· SABAs are the therapy of choice for relief of acute symptoms and prevention of exercise-induced bronchospasm.<br>
· 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.<br>
· 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.<br>
· Systemic corticosteroids are used for moderate and severe exacerbations as adjunct to SABAs to speed recovery and prevent recurrence of exacerbations.<br>
· The use of LABAs is not recommended to treat acute symptoms or exacerbations of asthma.<br><br>
Assessment, treatment and monitoring<br>
· A stepwise approach to managing asthma is recommended to gain and maintain control of asthma.<br>
· Regularly scheduled, daily, chronic use of a SABA is not recommended. Increased SABA use or SABA use more than two days a week for symptom relief generally indicates inadequate asthma control.<br>
· 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>Preferred<br>SABA as needed</td><td>Preferred<br>Low-dose ICS<br><br>Alternative<br>Cromolyn, leukotriene receptor antagonists, nedocromil, or theophylline</td><td>Preferred<br>Low-dose ICS+LABA or medium-dose ICS<br><br>Alternative<br>Low-dose ICS+either a leukotriene receptor antagonists, theophylline, or zileuton</td><td>Preferred<br>Medium-dose ICS+LABA<br><br>Alternative<br>Medium-dose ICS+either a leukotriene receptor antagonists, theophylline, or zileuton</td><td>Preferred<br>High-dose ICS+ LABA and consider omalizu-mab for patients who have allergies</td><td>Preferred<br>High-dose ICS+LABA+ oral steroid and consider omalizumab for patients who have allergies</td></tr>
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Management of exacerbations
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| Clinical Guidelines | Recommendations |
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| | · Appropriate intensification of therapy by increasing inhaled SABAs and, in some cases, adding a short course of oral systemic corticosteroids is recommended.<br><br>Special populations<br>· 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.<br>· The addition of cromolyn to a SABA is helpful in some individuals who have exercise-induced bronchospasm.<br>· Consideration of the risk for specific complications must be given to patients who have asthma who are undergoing surgery.<br>· Albuterol is the preferred SABA in pregnant women because of an excellent safety profile.<br>· 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. |
| 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)**[11] | Diagnosis<br>· 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.<br>· The primary risk factor is smoking.<br>· Spirometry is diagnostic of airflow obstruction. Airflow obstruction is defined as $FEV_1$ <80% predicted and $FEV_1$/FVC <70%.<br><br>Treatment<br>· Smoking cessation should be encouraged for all patients with COPD.<br>· Short-acting bronchodilators, as necessary, should be the initial empiric treatment for the relief of breathlessness and exercise limitation.<br>· Long-acting bronchodilators ($\beta_2$ agonists and/or anticholinergics) should be given to patients who remain symptomatic even with short-acting bronchodilators.<br>· Once-daily long-acting anticholinergic antagonists are preferred compared to four-times-daily short-acting anticholinergic antagonists 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 antagonist.<br>o $FEV_1$ ≥50% predicted: LABA or long-acting anticholinergic.<br>o $FEV_1$ < 50% predicted: either LABA with an inhaled corticosteroid in a combination inhaler or a long-acting anticholinergic.<br>· In patients with stable COPD and $FEV_1$ ≥50% who remain breathless or have exacerbations despite maintenance therapy with a LABA, consider adding an inhaled corticosteroid in a combination inhaler or a long-acting anticholinergic antagonist when ICSs are not tolerated or declined.<br>· Consider a long-acting anticholinergics in patients remaining breathless or having exacerbations despite therapy with LABA and ICSs and vice versa.<br>· Choice of drug should take in to consideration the patient's symptomatic response, preference, potential to reduce exacerbations, and side effects |

| Clinical Guidelines | Recommendations |
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| | and costs.<br>· In most cases, inhaled bronchodilator therapy is preferred.<br>· 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.<br>· Theophylline should only be used after a trial of long-acting and short-acting bronchodilators or if the patient is unable to take inhaled therapy.<br>· Combination therapy with $\beta_2$-agonists or anticholinergics and theophylline may be considered.<br>· Pulmonary rehabilitation should be made available to patients.<br>· Noninvasive ventilation should be used for patients with persistent hypercapnic respiratory failure.<br><br>Management of exacerbations<br>· Patients with exacerbations should be evaluated for hospital admission.<br>· 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.<br>· 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.<br>· Oxygen should be given to maintain oxygen saturation above 90%.<br>· Patients should receive invasive and noninvasive ventilation as necessary.<br>· Respiratory physiotherapy may be used to help remove sputum.<br>· Before discharge, patients should be evaluated by spirometry.<br>· 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. |

**Conclusions**

The single-entity respiratory long-acting $\beta_2$-agonists are Food and Drug Administration (FDA)-approved for the treatment of asthma, chronic obstructive pulmonary disease and/or exercise-induced asthma.[1-6] The long-acting $\beta_2$-agonists are available in a variety of dosage forms, including solution for nebulization, capsule for inhaler, solution for inhalation and dry powder inhaler. There are no generic formulations for the long-acting $\beta_2$-agonists currently available. When used for maintenance treatment of COPD, the long-acting $\beta_2$-agonists are typically dosed twice daily, with the exception of indacaterol (Arcapta Neohaler®) and olodaterol (Striverdi Respimat®), which are administered once daily.[1-6]

Guidelines recommend that in the chronic management of asthma, long-acting $\beta_2$-agonists should be used as add-on therapy in patients not adequately controlled on an inhaled corticosteroid as an alternative to maximizing the dose of the inhaled corticosteroid. Long-acting $\beta_2$-agonists can also be used for exercise-induced bronchospasm and provide a longer period of coverage (typically 12 hours or more) compared to the short-acting $\beta_2$-agonists.[8,9] The Global Initiative for Chronic Obstructive Lung Disease and National Institute for Clinical Excellence guidelines state that long-acting $\beta_2$-agonists also have a role in the treatment of COPD for patients who remain symptomatic even with current treatment with short-acting bronchodilators (i.e., short acting $\beta_2$-agonists and anticholinergics). The long acting $\beta_2$-agonists can be added to other regimens, including an anticholinergic agent, in efforts to decrease exacerbations.[10,11] Guidelines do not recommend one long-acting agent over another, and head-to-head clinical trials have been inconclusive to determine “superiority” of any one agent. However, in the treatment of asthma, long-acting $\beta_2$-agonists should not be used as monotherapy or as rescue medications due to the potential risk of asthma-related deaths.[13,20]

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