Formoterol for the Treatment of Chronic Obstructive Pulmonary Disease

Abstract: Bronchodilators, including long-acting β₂-agonists and long-acting muscarinic antagonists, are the mainstay for treatment of patients with chronic obstructive pulmonary disease (COPD) to prevent exacerbations or reduce symptoms. Formoterol is a highly selective and potent β₂-agonist that relaxes airway smooth muscle to significantly improve lung function. Inhaled formoterol works within 5 minutes of administration and provides improvements in spirometry measurements over 12 hours. The lipophilicity of formoterol allows it to form a depot within the smooth muscle to provide a prolonged duration of action. Following therapeutic doses, plasma concentrations are very low or undetectable. Determination of the pharmacokinetics of formoterol following high-dose administration to healthy volunteers revealed that the drug was rapidly absorbed and excreted unchanged in the urine with a half-life of 10 hours. Inhaled formoterol, as monotherapy or in combination with other agents, is an effective and safe treatment option for patients with moderate to severe COPD. Clinical studies have demonstrated improvements in lung function and COPD symptoms, particularly dyspnea; reductions in the risk of exacerbations; and improvement in patients’ health status. The adverse event profile of inhaled formoterol is similar to that of placebo, with few adverse cardiovascular events. Formoterol is a valuable bronchodilator used in the maintenance treatment of COPD. This review describes the mechanism of action, pharmacodynamics, and pharmacokinetics of inhaled formoterol. It also reviews the results of large, randomized, controlled clinical trials that evaluated the use of formoterol as monotherapy and in combination with inhaled corticosteroids, long-acting muscarinic antagonists, and triple therapy regimens in the treatment of patients with moderate to severe COPD.

Keywords: formoterol fumarate, long-acting β₂-agonists, COPD, bronchodilator

Plain Language Summary
COPD leads to substantial illness and mortality in the older population and is characterized by uncomfortable or difficult breathing and frequent use of health-care resources. Bronchodilators represent a key treatment for patients with COPD because they help to open the airways and ease breathing. This effect reduces episodes of worsening COPD symptoms and may improve patients’ quality of life. Formoterol is a bronchodilator that can be used alone or combined with other medicines that can improve lung function in patients with COPD. Many clinical studies have evaluated the efficacy and safety of formoterol in patients with different degrees of COPD symptoms and severity. These studies consistently show the benefits of formoterol and the ability to combine formoterol with other treatments that lead to further benefits without significant safety concerns. This article reviews the clinical studies and the scientific data about how formoterol affects and moves through the body. With decades of experience, formoterol is an important treatment option.
for patients with COPD to improve their symptoms and reduce the limitations and burdens of disease.

Introduction

Chronic obstructive pulmonary disease (COPD) is a major cause of morbidity and mortality that is currently the fourth leading cause of death in the world and was projected to be the third leading cause of death by 2020.\(^1\) Long-acting β\(_2\)-agonists (LABAs) such as formoterol are a mainstay of COPD treatment alone or in combination with long-acting muscarinic antagonists (LAMAs) and/or inhaled corticosteroids (ICS), depending on patients’ symptoms and exacerbation history.\(^1\) Formoterol has been used to treat COPD since the early 1990s and has high selectivity and very high affinity for the β\(_2\)-adrenoceptor.\(^2\) Its long duration of action stems from the lipophilic and basic nature of the drug that allows it to remain in the airway smooth muscle over time.\(^3\) The long-acting bronchodilators (LABAs and LAMAs) improve lung function, as measured by forced expiratory volume in 1 second (FEV\(_1\)), and reduce symptoms of disease by widening the airways and reducing the number of exacerbations.\(^1\) LAMAs are preferred as monotherapy for exacerbation prevention. The objectives of this review article are to describe the pharmacokinetics and pharmacodynamics of formoterol in relation to COPD and other β\(_2\)-agonists and to review clinical trial findings for efficacy and safety of formoterol alone and in fixed-dose combinations with ICS and/or LAMAs in patients with COPD.

Pharmacokinetics and Pharmacodynamics of Formoterol

Description and Pharmacokinetics

Formoterol is an inhaled, selective β\(_2\)-adrenergic receptor agonist formulated as the fumarate salt and as a racemic mixture of two enantiomers.\(^2\) Formoterol has relatively high water solubility and moderate lipophilicity, allowing rapid delivery to bronchial smooth muscle cells for rapid bronchodilation.\(^2,3\) From the depot within the smooth muscle, formoterol progressively leaches out to interact with the active site of the β\(_2\)-receptor, providing its prolonged duration of action. Plasma concentrations following therapeutic doses are very low and difficult to detect. Following inhalation of high-dose formoterol (120 µg) in healthy volunteers, formoterol was rapidly absorbed, with a half-life of approximately 10 hours and urinary excretion of unchanged drug.\(^4\)

Preclinical Pharmacological Profile and Comparisons with Other β\(_2\)-Agonists

Formoterol is highly bronchoselective and potent compared with other β\(_2\)-agonists (Table 1).\(^3\) In guinea pig trachea contracted with prostaglandin F\(_{2α}\), formoterol was approximately 50-fold and 27-fold more potent than salbutamol and salmeterol, respectively.\(^5\) Indeed, compared with salbutamol and salmeterol, formoterol was 10- to 20-fold more potent at inhibiting histamine-induced bronchoconstriction in conscious guinea pigs.\(^5\) In vitro studies of human airway smooth muscle fragments showed that formoterol relaxed the tissue in a concentration-dependent fashion and was the most potent compared with other β\(_2\)-agonists.\(^5\) Results from in vitro studies in human isolated bronchi indicate that formoterol has a greater maximal efficacy than olodaterol.\(^6\)

Although vilanterol is more selective than formoterol for β\(_2\)- versus β\(_1\)- or β\(_3\)- adrenoreceptors, formoterol exhibits greater β\(_2\)-adrenoreceptor intrinsic efficacy and functional potency.\(^7\)

Onset and Duration of Action

Formoterol relaxed both animal and human smooth muscle cells rapidly and comparably to salbutamol, whereas salmeterol was markedly slower.\(^5\) In patients with COPD, formoterol increased FEV\(_1\) within 5 minutes of inhalation (Figure 1), and the effect observed at this early time point

**Table 1** Comparative Pharmacology and Pharmacokinetic Characteristics of LABAs

| Characteristic       | Formoterol       | Indacaterol       | Olopatadine       | Vilanterol       | Salmeterol       |
|----------------------|------------------|-------------------|-------------------|------------------|------------------|
| β\(_2\) agonism       | Full agonist     | Partial agonist   | Nearly full agonist | Partial agonist | Partial agonist |
| Selectivity          | β\(_2\) > β\(_3\) > β\(_1\) | β\(_2\) > β\(_3\) > β\(_1\) | β\(_2\) >> β\(_1\) > β\(_1\) | β\(_2\) >> β\(_1\) > β\(_1\) | β\(_2\) >> β\(_1\) > β\(_1\) |
| Potency              | ++               | ++                | ++                | ++               | ++               |
| Lipophilicity        | ~10 hours        | 40–56 hours       | 7.5 hours         | 21 hours         | 5.5 hours        |
| Elimination half-life| Within 5 minutes | Within 5 minutes  | Within 5 minutes  | Within 5 minutes | Within 5 minutes |
| Onset of action in COPD | 12 hours        | 24 hours          | ≥24 hours         | 22 hours         | 12 hours         |
| Duration of action   |                  |                   |                   |                  |                  |

**Note:** Data from these studies.

**Abbreviations:** COPD, chronic obstructive pulmonary disease; LABA, long-acting β\(_2\)-agonist.
was 80% of the maximal effect of the drug.\textsuperscript{8} Formoterol exhibited faster onset of bronchodilator action within the first 2 hours of administration compared with tiotropium in patients with COPD.\textsuperscript{9} Fluticasone/formoterol had a faster onset of bronchodilator action compared with fluticasone/salmeterol in patients with asthma; similarly, glycopyrro-nium/formoterol also had a faster onset of bronchodilator action compared with umeclidinium/vilanterol.\textsuperscript{10,11} The rapid onset of formoterol in combination with budesonide was confirmed in a study comparing the Turbuhaler\textsuperscript{®} and Spiromax\textsuperscript{®} devices in patients with COPD;\textsuperscript{12} these results are consistent with studies in patients with asthma.\textsuperscript{13,14} With regard to duration of effect, formoterol produced long-lasting inhibition of induced contraction in human bronchial tissues, suggesting retention within the tissues.\textsuperscript{2} The lipophilicity of formoterol and depot effects likely explain the long duration of action following inhalation. In patients with COPD, formoterol significantly improved spirometry over 12 hours.\textsuperscript{15}

**Clinical Efficacy of Inhaled Formoterol in Patients with COPD**

Formoterol is available in a number of different products as monotherapy and in fixed-dose combinations (Table 2). Formoterol monotherapy was approved by the United States Food and Drug Administration (US FDA) in 2001 as an inhalation solution for use in a jet nebulizer, and in powder form for use with the Aerolizer\textsuperscript{®} inhaler (which is no longer available). Fixed-dose combinations include budesonide and formoterol in a pressurized metered-dose inhaler (pMDI) approved in 2006, and glycopyrrolate and formoterol pMDI approved in 2016. The combination of aclidinium bromide and formoterol in a breath-actuated dry powder inhaler (DPI) was approved in 2019, and, more recently, formoterol has been added as a component in triple therapy combinations. Formulations of extrafine particles enable delivery of the drugs to the small airways, thus reducing the dose necessary to achieve efficacy.\textsuperscript{16}

![Graph showing the effect of formoterol and salbutamol on FEV1](image)

**Figure 1** The bronchodilator effect of formoterol occurs rapidly. A single inhalation of medication was administered to 24 patients with stable COPD in a randomized, three-way, crossover study. Reprinted from Respiratory Medicine, Vol 95 (10), Benhamou et al, Rapid onset of bronchodilatation in COPD: a placebo-controlled study comparing formoterol (Foradil Aerolizer) with salbutamol (Ventodisk), pages 817–821, Copyright 2001, with permission from Elsevier.\textsuperscript{9} 

**Abbreviations:** COPD, chronic obstructive pulmonary disease; FEV\textsubscript{1}, forced expiratory volume in 1 second.
Table 2 Available Formoterol Products

| Formoterol Products                  | Brand Name                  | Delivery Method | Approvals     | Dosage                                      |
|-------------------------------------|-----------------------------|-----------------|---------------|---------------------------------------------|
| Monotherapy products                |                             |                 |               |                                             |
| Formoterol                          | Atimos Modulte®             | pMDI            | EU            | 12 µg BID; up to 4 inhalations daily for severe COPD |
| Formoterol inhalation powder        | Foradil Aerolizer®          | Capsule used with Aerolizer inhaler | US 2001 EU | 12 µg every 12 hours                        |
| Formoterol inhalation solution      | Perforist®                  | Nebulizer       | US 2001       | One 20 µg/2 mL vial every 12 hours           |
| Combination with corticosteroid     |                             |                 |               |                                             |
| Mometasone-formoterol              | Dulera®                     | pMDI            | US 2010 (asthma only) | EU | No COPD indication                          |
| Beclomethasone-formoterol          | Fostair® (EU) Fostex® (Poland) | pMDI and DPI | EU            | 100/6 µg per inhalation; 2 inhalations BID  |
|                                    |                             |                 |               | 100/6 µg per inhalation (dosing frequency not specified) |
| Budesonide-formoterol              | Symbicort®                  | pMDI            | US 2006       | 160/4.5 µg per inhalation; 2 inhalations BID |
|                                    | Symbicort Turbuhaler®       | DPI             | EU 2014       | 160/4.5 µg per inhalation; 2 inhalations BID |
|                                    | Fobumix Easyhaler®          | DPI             | EU 2016       | 160/4.5 µg per inhalation; 2 inhalations BID |
| Combination with LAMA               |                             |                 |               |                                             |
| Glycopyrrolate-formoterol           | Bevespi AEROSPHERE®         | pMDI (co-suspension technology) | US 2016 EU 2018 | 9/4.8 µg per inhalation; 2 inhalations BID |
| Acildinium-formoterol               | Duaklir Pressair®           | DPI             | US 2019       | 400/12 µg per inhalation; 1 inhalation BID  |
|                                    | Duaklir Genuair®            | DPI             | EU 2014       | 340/12 µg per inhalation; 1 inhalation BID  |
| Triple therapy (LABA, LAMA, ICS)    |                             |                 |               |                                             |
| Budesonide-glycopyrrolate-formoterol| Breztri AEROSPHERE®         | pMDI            | US 2020       | 160/9/4.8 µg per inhalation; 2 inhalations BID |
| Budesonide-formoterol-glycopyrronium| Trimbow®                   | pMDI            | EU 2017       | 100/6/10 µg per inhalation; 2 inhalations BID |

Note: No longer available.

Abbreviations: BID, twice daily; COPD, chronic obstructive pulmonary disease; DPI, dry powder inhaler; EU, European Union; ICS, inhaled corticosteroid; LABA, long-acting β₂-agonist; LAMA, long-acting muscarinic antagonist; pMDI, pressurized metered-dose inhaler; US, United States.

Formoterol Monotherapy
Bronchodilator therapy with LABA or LAMA monotherapy is recommended as initial treatment for Group A and B patients according to the Global Initiative for Chronic Obstructive Lung Disease (GOLD) guidelines. A 2013 meta-analysis identified 14 studies of formoterol 12 µg twice daily (BID) versus placebo, of which three studies also included a formoterol 24 µg BID group and one study evaluated only formoterol 24 µg BID. Most studies used a DPI (ie, Turbuhaler®) to deliver formoterol. Severe COPD exacerbations were reduced by therapy with formoterol 12 µg (odds ratio [OR], 0.75; 95% confidence interval [CI], 0.55–1.02; p=0.064) and 24 µg (OR, 0.28; 95% CI, 0.11–0.73; p=0.0092). The mean difference in trough FEV₁ versus placebo across studies was 45 mL with formoterol 12 µg BID. In a 12-week, randomized, double-blind trial, formoterol via inhalation solution (20 µg/2 mL) and via DPI (12 µg) demonstrated similar efficacy.

Formoterol in Dual Combination with ICS
For patients with moderate to very severe COPD, combination therapy with LABA and ICS is recommended as an optional treatment for patients with a high risk of COPD exacerbations and elevated eosinophils. Triple therapy represents another treatment option, particularly for
Table 3 Efficacy of Formoterol in Combination with ICS

| Clinical Trial | Patient Population | Treatments and Duration* | Key Findings |
|----------------|--------------------|--------------------------|--------------|
| **SHINE**<sup>19</sup> | Current or ex-smokers (≥10 pack-years) | BUD/FF HFA pMDI 2 doses: 320/9 μg BID (n=277) 160/9 μg BID (n=281) | - BUD/FF 320/9 μg significantly improved predose FEV<sub>1</sub> (p≤0.026) and 1-hour postdose FEV<sub>1</sub> (p≤0.039) vs BUD, FF placebo |
| US, EU, South Africa | Age ≥40 years | vs Monocomponents (BUD [n=275] or FF [n=284]) alone or in combination via separate inhalers BUD + FF [n=287]) vs Placebo (n=300) | - BUD/FF 160/9 μg significantly improved predose FEV<sub>1</sub> (p≤0.002) and 1-hour postdose FEV<sub>1</sub> (p<0.001) vs BUD, placebo |
| | COPD dx and symptoms >2 years | | - FF alone significantly improved predose FEV<sub>1</sub> (p=0.039) and 1-hour postdose FEV<sub>1</sub> vs placebo (p<0.001) |
| | ≥1 COPD exacerbation within 1 year of study | | - Both BUD/FF doses significantly improved COPD-related symptoms and decreased daily rescue medication use vs placebo |
| | Use of SABA as rescue medication | | - Most common AEs: COPD (highest in FF group), nasopharyngitis, oral candidiasis, bronchitis, sinusitis, and diarrhea; no difference in pneumonia between treatment groups |
| | Prebronchodilator FEV<sub>1</sub> ≤50% | | |
| | FEV<sub>1</sub>/FVC <70% | | |
| | mMRC dyspnea ≥2 | | |
| **SUN**<sup>20</sup> | Current or ex-smokers (≥10 pack-years) | BUD/FF HFA pMDI 2 doses: 320/9 μg BID (n=494) 160/9 μg BID (n=494) | - BUD/FF 320/9 μg significantly improved predose FEV<sub>1</sub> and 1-hour postdose FEV<sub>1</sub> vs FF (p≤0.023) and placebo (p<0.001) |
| US, EU, Mexico | Age ≥40 years | vs FF DPI 9 μg BID (n=495) | - BUD/FF 160/9 μg significantly improved predose FEV<sub>1</sub> and 1-hour postdose FEV<sub>1</sub> vs placebo (p<0.001) |
| | COPD dx and symptoms >2 years | vs Placebo (n=481) | - The number of exacerbations per patient-treatment year was reduced by 37% and 41%, respectively, with BUD/FF 320/9 μg and 160/9 μg vs placebo (p<0.001) and by 25% and 29% vs FF alone (p≤0.004) |
| | ≥1 COPD exacerbation within 1 year of study | | - Most common AEs: oral candidiasis, COPD, dyspnea; incidence of pneumonia-related AEs similar between treatment groups |
| | Use of SABA as rescue medication | | |
| | Prebronchodilator FEV<sub>1</sub> ≤50% | | |
| | FEV<sub>1</sub>/FVC <70% | | |
| | mMRC dyspnea ≥2 | | |
| **RISE**<sup>21</sup> | Current or ex-smokers (≥10 pack-years) | BUD/FF pMDI 320/9 μg BID (n=606) | - The annual rate of exacerbations (per patient-year) was significantly reduced by 24% with BUD/FF vs FF (0.85 vs 1.12; p=0.006) |
| US, Mexico, South | Age ≥40 years | vs FF DPI 9 μg BID (n=613) | - Time to first exacerbation was significantly reduced by 22% with BUD/FF vs FF (p=0.0164) |
| America, EU, South | COPD dx and symptoms >1 year | | - BUD/FF also significantly reduced nighttime awakenings and rescue medication use |
| Africa | ≥1 moderate/severe COPD exacerbation within 1 year of study | | |
Table 3 (Continued).

| Clinical Trial | Patient Population | Treatments and Duration | Key Findings |
|----------------|--------------------|-------------------------|--------------|
| **TELOS**22<br>US, Canada, EU | • Current or ex-smokers (≥10 pack-years)<br>• Age 40–80 years<br>• Symptomatic COPD (CAT score ≥10) despite treatment with ≥1 bronchodilator for 26 weeks<br>• Post-bronchodilator FEV₁ ≥30% but <80%<br>• FEV₁/FVC <70% | BUD/FF MDI (co-suspension delivery)<br>320/10 μg BID (n=655) vs BUD/FF MDI (co-suspension delivery)<br>160/10 μg BID (n=637) vs BUD MDI 320 μg BID (n=206) vs FF MDI 10 μg BID (n=644) vs BUD/FF DPI 400/12 μg BID (n=219) × 24 weeks | • BUD/FF 320/10 μg significantly improved morning predose trough FEV₁ vs FF (LSM 39 mL; p=0.0018); differences between BUD/FF 160/10 μg vs FF were numerically but not significantly improved<br>• Differences in predose FEV₁ were greater for patients with eosinophils ≥150 cells/μL between BUD/FF 320/10 and 160/10 μg vs FF MDI<br>• BUD/FF 320/9 μg and BUD/FF 160/9 μg significantly improved FEV₁ AUC₀₋₄h vs BUD (p<0.0001)<br>• The adjusted annual rate of exacerbations (per-patient-per-year) was significantly reduced with BUD/FF 320/10 and 160/10 μg vs FF MDI (0.44 and 0.50 vs 0.69; p≤0.0094)<br>• AEs were similar across treatment groups, with a low incidence of pneumonia in all groups |
| **Calverley et al**23<br>EU | • Current or ex-smokers (≥20 pack-years)<br>• Age ≥40 years<br>• COPD dx and symptoms ≥2 years<br>• ≥1 COPD exacerbation within 1 year of study<br>• Post-bronchodilator FEV₁ <30% to 50%<br>• FEV₁/FVC <70% | Extrafine BDP/FF pMDI 200/12 μg BID (n=232) vs BUD/FF DPI 400/12 μg BID (n=238) vs FF DPI 12 μg BID (n=233) × 48 weeks | • BDP/FF and BUD/FF significantly improved predose morning FEV₁ vs FF (77 mL and 80 mL vs 26 mL; p=0.046)<br>• The mean rate of exacerbations (per-patient-per-year) was similar between treatments: BDP/FF, 0.41; BUD/FF, 0.42; and FF, 0.43<br>• Rates of hospitalization due to exacerbation were significantly higher with BDP/FF vs BUD and FF: 0.074, 0.033, and 0.040 (p<0.0008)<br>• AEs were similar between treatment groups; most common AE: COPD exacerbation/worsening |
| **FORWARD**16<br>EU | • Current or ex-smokers (≥10 pack-years)<br>• Age ≥40 years<br>• Severe COPD dx<br>• ≥1 COPD exacerbation within 1 year of study<br>• Post-bronchodilator FEV₁ <30% to 50%<br>• FEV₁/FVC <70% | Extrafine BDP/FF pMDI 200/12 μg BID (n=595) vs FF pMDI 12 μg BID (n=591) × 48 weeks | • The adjusted rate of exacerbations (per patient-year) was significantly reduced by 28% with BDP/FF vs FF (0.80 vs 1.12; p<0.001)<br>• Time to first exacerbation was significantly reduced by 20%<br>• BDP/FF significantly improved predose morning FEV₁ at week 12 vs FF (81 mL vs 12 mL; mean difference, 69 mL; p<0.001)<br>• AEs were similar between groups; the most common AE was oral candidiasis (2.2% vs 0.3%); pneumonia occurred in 3.8% in BDP/FF group and 1.8% in FF group |
elevated eosinophil levels, as discussed below. Table 3 summarizes key clinical studies of formoterol/ICS combination therapy. Two similarly designed, pivotal clinical studies were conducted to evaluate the combination of budesonide and formoterol pMDI administered in two dosage strengths (budesonide/formoterol 320/9 µg BID and 160/9 µg BID). Patients with moderate to very severe COPD were enrolled based on the presence of symptoms for >2 years, including a modified Medical Research Council dyspnea scale score ≥2, history of ≥1 COPD exacerbations treated with a course of oral corticosteroids and/or antibiotics within 1 year of screening, and prebronchodilator FEV₁ ≤50% of predicted normal. In the SHINE study (NCT00206154), budesonide/formoterol pMDI 320/9 µg demonstrated significantly greater improvements in lung function compared with the individual components as monotherapy over 6 months. The second study, SUN (NCT00206167), confirmed the significant benefit of budesonide/formoterol pMDI 320/9 µg on lung function, in addition to demonstrating a significant reduction in the rate of COPD exacerbations for both budesonide/formoterol dose groups versus formoterol alone and placebo. The RISE study (NCT02157935) further evaluated the effect of budesonide/formoterol pMDI on the rate of COPD exacerbations as defined by the US FDA guidance (ie, worsening of ≥2 major symptoms or 1 major symptom in combination with ≥1 minor symptom for ≥2 consecutive days and requiring treatment with systemic corticosteroid for ≥3 days and/or antibiotics [moderate] and/or hospitalization [severe]). Budesonide/formoterol pMDI 320/9 µg significantly reduced the annual rate of moderate and severe exacerbations by 24% (p=0.006) and significantly reduced the risk for time to first moderate or severe exacerbation compared with formoterol DPI (p=0.016; Figure 2).

AEROSPHERE™ inhalers using co-suspension delivery technology were developed to enhance delivery of medication by pMDI to the whole lung and minimize the effects of patient handling errors. The TELOS study (NCT02766608) compared 24 weeks of randomized therapy with one of two doses of budesonide/formoterol pMDI (320/10 µg and 160/10 µg BID) to monocomponents formoterol pMDI 10 µg or budesonide pMDI 320 µg (all delivered by single-dose AEROSPHERE™ inhaler), and open-label budesonide/formoterol DPI 400/12 µg. Enrolled patients had symptomatic, moderate to very severe COPD, with no requirement for a history of
COPD exacerbations. A dose response favoring the higher dosage 320/10 μg pMDI was observed for improvements in lung function and exacerbation outcomes. The budesonide/formoterol pMDI 320/10 μg was noninferior to the budesonide/formoterol DPI formulation.

Formoterol has also been studied in other ICS combinations. Calverley and colleagues evaluated treatment with extrafine beclomethasone dipropionate (BDP) plus formoterol compared with formoterol alone for 48 weeks and found that combination therapy improved lung function and symptoms versus monotherapy. In the FORWARD study (NCT00929851), extrafine BDP/formoterol pMDI significantly reduced the exacerbation rate (rate ratio: 0.72; p<0.001) and improved predose morning FEV1 (mean difference at week 12, 69 mL; p<0.001) compared with formoterol alone. The efficacy and safety of the combination of mometasone furoate (MF) and formoterol in two dosage strengths administered by pMDI (400/10 μg and 200/10 μg) were evaluated in two randomized, 52-week, placebo-controlled studies. MF plus formoterol demonstrated dose-dependent improvements in lung function; both doses reduced exacerbations and improved respiratory health status compared with placebo. However, the fixed-dose combination of MF/formoterol is not approved for the treatment of COPD.

Figure 2 Time to first moderate or severe exacerbation in the RISE study.

Notes: aBetween-treatment difference in time to first moderate or severe exacerbation, p<0.016; Cox regression model. Reprinted from Respiratory Medicine, Vol 132, Ferguson et al, Effect of budesonide/formoterol pressurized metered-dose inhaler on exacerbations versus formoterol in chronic obstructive pulmonary disease: the 6-month, randomized RISE (Revealing the Impact of Symbicort in reducing Exacerbations in COPD) study, pages 31–41. Copyright 2017, with permission from Elsevier. Abbreviations: B/f, budesonide/formoterol; BID, twice daily; DPI, dry powder inhaler; f, formoterol; pMDI, pressurized metered-dose inhaler.

Formoterol in Combination with LAMA
According to guidelines from GOLD, LAMA/LABA combination therapy is currently recommended for patients with COPD who do not respond to initial monotherapy, either because of persistent dyspnea or exacerbations. The Phase III Pinnacle studies compared the combination of glycopyrrrolate and formoterol (GFF) formulated for the AEROSPHERE™ inhaler using co-suspension delivery in

![Figure 2: Time to first moderate or severe exacerbation in the RISE study.](image-url)
Table 4 Efficacy of Formoterol in Combination with LAMAs

| Clinical Trial | Patient Population | Treatments and Duration<sup>a</sup> | Key Findings |
|----------------|--------------------|------------------------------------|--------------|
| Pinnacle-1<sup>30</sup> | Current or ex-smokers (≥10 pack-years) Age 40–80 years Moderate to very severe COPD Postbronchodilator FEV<sub>1</sub> <80% FEV<sub>1</sub>/FVC <70% | GFF pMDI 18/9.6 μg BID (n=526) vs GP pMDI 18 μg BID (n=451) vs FF pMDI 9.6 μg BID (n=449) vs OL tiotropium 18 μg QD (n=451) vs Placebo BID (n=219) × 24 weeks | GFF, GR and FF pMDI significantly improved predose morning trough FEV<sub>1</sub> at week 24 vs placebo (all p<0.0001) GFF showed significant differences of 59 mL and 64 mL vs GP and FF, respectively GFF significantly improved 2-hour postdose change from baseline FEV<sub>1</sub> at week 24 vs monocomponents (all p<0.0001) Across both studies, most common AEs were nasopharyngitis, cough, upper respiratory tract infection, sinusitis, dyspnea; all occurred with similar frequency in active vs placebo groups |
| Pinnacle-2<sup>30</sup> | Same as above | GFF pMDI 18/9.6 μg BID (n=510) vs GP pMDI 18 μg BID (n=439) vs FF pMDI 9.6 μg BID (n=437) vs Placebo BID (n=223) × 24 weeks | GFF, GR and FF pMDI significantly improved predose morning trough FEV<sub>1</sub> at week 24 vs placebo (all p<0.02) GFF showed significant differences of 54 mL and 56 mL vs GP and FF, respectively GFF significantly improved 2-hour postdose change from baseline FEV<sub>1</sub> at week 24 vs monocomponents (all p<0.0001) |
| Pinnacle-3<sup>31</sup> | Extension study of Pinnacle-1, –2 Patients receiving GFF, GP, FF, or tiotropium were eligible to continue Patients receiving placebo were not eligible | GFF pMDI 18/9.6 μg BID (n=1035) vs GP pMDI 18 μg BID (n=888) vs FF pMDI 9.6 μg BID (n=894) vs OL tiotropium 18 μg QD (n=450) × 28 weeks | GFF pMDI significantly improved predose morning trough FEV<sub>1</sub> over 52 weeks vs GP, FF, and tiotropium (p<0.0001) vs GP, FF and p<0.017 vs tiotropium) GFF also significantly improved 2-hour postdose FEV<sub>1</sub> over 52 weeks vs both monocomponents and tiotropium (all p<0.0001) Dyspnea scores improved significantly for GFF vs monocomponents No new safety risks were identified for GFF pMDI vs monocomponents |
| Pinnacle-4<sup>32</sup> | Same as Pinnacle-1 and –2 | GFF pMDI 18/9.6 μg BID (n=555) vs GP pMDI 18 μg BID (n=480) vs FF pMDI 9.6 μg BID (n=483) vs Placebo BID (n=238) × 24 weeks | GFF pMDI significantly improved predose morning trough FEV<sub>1</sub> at week 24 vs GR, FF, and placebo (all p<0.0001) GFF significantly improved 2-hour postdose change from baseline FEV<sub>1</sub> at week 24 vs monocomponents and placebo (all p<0.0001) Significant improvement in TDI over 24 weeks for GFF vs GP (LSM difference, 0.33; p<0.0125) and placebo (LSM difference, 0.80; p<0.001) GFF improved SGRQ total score vs placebo (LSM difference, −5.33; p<0.0011) |
### Table 4 (Continued).

| Clinical Trial       | Patient Population                                                                 | Treatments and Duration | Key Findings                                                                                                                                                                                                 |
|----------------------|------------------------------------------------------------------------------------|-------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| **AUGMENT**<sup>44</sup> North America, Australia, New Zealand | ● Current or ex-smokers (≥10 pack-years)  
● Age ≥40 years  
● Postbronchodilator FEV<sub>1</sub> ≥30% to <80%  
● FEV<sub>1</sub>/FVC <70% | ACL/FF DPI 400/12 μg BID (n=333)  
ACL/FF DPI 400/6 μg BID (n=333)  
ACL DPI 400 μg BID (n=337)  
FF DPI 12 μg BID (n=332)  
Placebo DPI (n=331)  
× 24 weeks | ● Both doses of ACL/FF significantly improved 1-hour postdose FEV<sub>1</sub> from baseline to week 24 vs ACL (LSM difference, 108 mL and 87 mL, respectively p<0.0001)  
● ACL/FF 400/12 μg significantly improved predose morning trough FEV<sub>1</sub> from baseline to week 24 vs FF (LSM difference, 45 mL; p=0.01)  
● Numerically greater improvements in FEV<sub>1</sub> measurements were observed for the higher dose of ACL/FF vs the lower dose  
● TDI focal scores were significantly improved with ACL/FF vs ACL, FF (p<0.01), and placebo (p<0.0001)  
● SGRQ total scores were significantly improved at week 24 for ACL/FF and monocomponents vs placebo (p<0.05)  
● Most common AEs were cough and nasopharyngitis |
| **ACLIFORM-COPD**<sup>35</sup> EUL South Africa, South Korea | ● Current or ex-smokers (≥10 pack-years)  
● Age ≥40 years  
● Postbronchodilator FEV<sub>1</sub> ≥30% to <80%  
● FEV<sub>1</sub>/FVC <70% | ACL/FF DPI 400/12 μg BID (n=385)  
ACL/FF DPI 400/6 μg BID (n=381)  
ACL DPI 400 μg BID (n=385)  
FF DPI 12 μg BID (n=384)  
Placebo DPI (n=194)  
× 24 weeks | ● Both doses of ACL/FF significantly improved 1-hour postdose FEV<sub>1</sub> from baseline to week 24 vs ACL and FF (p<0.001), with the 400/12 μg dose superior to the 400/6 μg dose  
● TDI focal scores improved above 1-unit threshold for both doses of ACL/FF (1.29 and 1.16)  
● Incidences of AEs were similar across combination, monotherapy, and placebo arms |
| **AFFIRM-COPD**<sup>35</sup> EUL Canada, South Africa | ● Current or ex-smokers (≥10 pack-years)  
● Age ≥40 years  
● Postbronchodilator FEV<sub>1</sub> <80%  
● FEV<sub>1</sub>/FVC <70%  
● CAT score ≥10 | ACL/FF DPI 400/12 μg BID (n=468)  
Salmeterol/fluticasone DPI 50/500 μg BID (n=463)  
× 24 weeks | ● Peak FEV<sub>1</sub> was significantly greater with ACL/FF vs salmeterol/fluticasone at week 24, with significant differences observed after first dose (p<0.0001)  
● Mean increase in peak FEV<sub>1</sub> at week 24 was 93 mL greater with ACL/FF  
● No significant differences in changes in TDI scores, CAT total scores, or exacerbations between groups  
● Most common AEs were COPD exacerbation, headache, and nasopharyngitis and were similar between groups |
| **AMPLIFY**<sup>19</sup> EUL Israel, US | ● Current or ex-smokers (≥10 pack-years)  
● Age ≥40 years  
● Postbronchodilator FEV<sub>1</sub> <80%  
● FEV<sub>1</sub>/FVC <70%  
● CAT score ≥10 | ACL/FF DPI 400/12 μg BID (n=314)  
ACL DPI 400 μg BID (n=475)  
FF DPI 12 μg BID (n=319)  
Tiotropium DPI 18 μg QD (n=475)  
× 24 weeks | ● ACL/FF significantly improved 1-hour postdose FEV<sub>1</sub> from baseline at week 24 vs ACL, FF, and tiotropium (all p<0.0001)  
● ACL/FF significantly improved predose morning trough FEV<sub>1</sub> vs FF (p<0.001)  
● SGRQ total score improved vs baseline >MCID for ACL/FF (4.68), ACL (4.95), and tiotropium (5.58); improvement for FF was 3.9%  
● Early morning symptom severity was significantly improved with ACL/FF vs tiotropium (p<0.05)  
● Most common AEs: COPD exacerbation, nasopharyngitis, and headache |

**Abbreviations:** ACL, aclidinium; AE, adverse event; BID, twice daily; CAT, COPD Assessment Test; DPI, dry powder inhaler; EUL, European Union; FEV<sub>1</sub>, forced expiratory volume in 1 second; FF, formoterol fumarate; FVC, forced vital capacity; GFF, glycopyrronium/formoterol fumarate; GP, glycopyrronium; LAMA, long-acting muscarinic antagonist; LSM, least squares mean; MCID, minimal clinically important difference; OL, open-label; pMDI, pressurized metered-dose inhaler; QD, once daily; SGRQ, St. George’s Respiratory Questionnaire; TDI, Transition Dyspnea Index; US, United States.

**Note:** Bold font indicates trial duration.
a pMDI with its monocomponents and placebo (Table 4). The fixed-dose GFF pMDI formulation demonstrated lasting stability, dose uniformity, and pharmacokinetics that fell within bioequivalence bounds for the monocomponents (Figure 3). Phase II dose-ranging studies determined the dose of GFF to be used in combination, although they did not show a dose-response relationship for increasing doses of glycopyrrolate. The pivotal registration trials PINNACLE-1 and −2 (NCT01854645 and NCT01854658, respectively) enrolled patients with moderate to very severe COPD but did not require them to be symptomatic or have a recent exacerbation history. Both studies demonstrated greater benefits on lung function with combination therapy versus the monocomponents and placebo. The PINNACLE-3 (NCT01970878) trial was a 28-week extension study of PINNACLE-1 and −2. Results of the study showed that GFF pMDI BID maintained lung function improvements over 52 weeks versus its monocomponents without additional safety risk (Figure 4).

GFF was also determined to be noninferior to open-label tiotropium. To evaluate the efficacy and safety of GFF pMDI in other populations, the PINNACLE-4 (NCT02343458) trial included Asian and European patients. In this population, GFF pMDI improved lung function and symptoms as well as patient-reported outcomes compared with placebo and glycopyrrolate pMDI.

To determine the benefit of GFF combination therapy in patients with COPD who had a low symptom burden, a pooled analysis was conducted of patients from PINNACLE-1, −2, and −4 who met GOLD category A criteria (ie, COPD Assessment Test [CAT] score ≤10 and either no exacerbations or 1 exacerbation that did not lead to hospitalization in the previous year). Fifteen percent of the patients in the pooled population were GOLD category A, and GFF pMDI improved lung function to a magnitude comparable to that observed in the overall population.

Another LAMA used in combination with formoterol is aclidinium, and several studies have evaluated a fixed-dose

![GFF MDI 14.4/10 μg vs GP MDI 14.4 μg](image)

**Figure 3** Relative bioavailability for glycopyrronium/formoterol combination versus glycopyrronium or formoterol monotherapy. Reprinted from International Journal of Chronic Obstructive Pulmonary Disease, Vol 13, Ferguson et al, Pharmacokinetics of glycopyrronium/formoterol fumarate dihydrate delivered via metered-dose inhaler using co-suspension delivery technology in patients with moderate-to-severe COPD, pages 945–593, Copyright 2018, with permission from Dove Medical Press. Abbreviations: AUC, area under the curve from 0 to 12 hours; Cmax, maximum concentration achieved; FF, formoterol fumarate; GFF, glycopyrronium/formoterol fumarate; GP, glycopyrronium; LSM, least squares mean; MDI, metered-dose inhaler.
Figure 4 Effects of fixed-dose glycopyrrolate/formoterol combination on change from baseline in (A) Predose morning trough FEV1 and (B) Peak change in FEV1 within 2 hours postdose over 52 weeks versus monocomponents and open-label tiotropium. Reprinted from Respiratory Medicine, Vol 126, Hanania et al, Long-term safety and efficacy of glycopyrrolate/formoterol metered-dose inhaler using novel Co-Suspension delivery Technology in patients with chronic obstructive pulmonary disease, pages 105–115, Copyright 2017, with permission from Elsevier.31

Abbreviations: FEV1, forced expiratory volume in 1 second; FF, formoterol fumarate; GFF, glycopyrrolate/formoterol fumarate; GP, glycopyronium; LSM, least squares mean; MDI, metered-dose inhaler; SE, standard error.
### Table 5: Efficacy of Formoterol in Triple Therapy Combinations

| Clinical Trial | Patient Population | Treatments and Duration | Key Findings |
|----------------|--------------------|-------------------------|--------------|
| **TRILOGY**[^4] EJ | ● Age ≥40 years <br> ● Postbronchodilator FEV<sub>1</sub> <50% <br> ● FEV<sub>1</sub>/FVC <70% <br> ● ≥1 moderate or severe COPD exacerbation within 1 year of study <br> ● Use of ICS/LABA, ICS/LAMA, LAMA/LABA, or LAMA monotherapy ≥2 months <br> ● CAT score ≥10 <br> ● BDI focal score ≤10 | Extrafine BDP/FF/GP pMDI 200/12/25 μg BID (n=680) × 52 weeks | ● Triple therapy was superior to BDP/FF for predose FEV<sub>1</sub> (mean difference, 81 mL; p<0.001) and 2-hour postdose FEV<sub>1</sub> (mean difference, 117 mL; p<0.001) at week 26 <br> ● TDI improved in both groups (mean difference, 0.21 units) <br> ● Moderate to severe exacerbations occurred in 31% and 35% for adjusted annual rates of 0.41 and 0.53 for BDP/FF/GP vs BDP/FF, respectively (RR, 0.77; p=0.005) <br> ● In patients with history of >1 exacerbation, BDP/FF/GP reduced rate of moderate to severe exacerbations by 33% (p=0.019) <br> ● Treatment-emergent AEs were similar between groups |
| **TRINITY**[^1] EJ, South America, Mexico | ● Current or ex-smokers <br> ● Age ≥40 years <br> ● Postbronchodilator FEV<sub>1</sub> <50% <br> ● FEV<sub>1</sub>/FVC <70% <br> ● ≥1 moderate or severe COPD exacerbation within 1 year of study <br> ● Use of ICS/LABA, ICS/LAMA, LAMA/LABA, or LAMA monotherapy ≥2 months <br> ● CAT score ≥10 | Extrafine BDP/FF/GP pMDI 200/12/25 μg BID (n=1077) <br> Extrafine BDP/FF pMDI 200/12 μg BID (n=630) × 52 weeks | Rates (per-patient-per-year) of moderate to severe COPD exacerbations were 0.46 for BDP/FF/GP, 0.57 for tiotropium, and 0.45 for BDP/FF + tiotropium <br> Fixed triple therapy was superior to tiotropium (p=0.0025) <br> Fixed and open triple therapy were similar <br> Reductions in exacerbations were greater for patients with eosinophil count ≥2% <br> BDP/FF/GP also significantly improved predose FEV<sub>1</sub> vs tiotropium (mean difference, 61 mL; p<0.001) <br> Most common AE was COPD exacerbation and pneumonia was reported in all treatment groups (BDP/FF/GP, 3%; tiotropium, 2%; BDP/FF + tiotropium, 2%) |
| **TRIBUTE**[^3] EJ | ● Current or ex-smokers <br> ● Age ≥40 years <br> ● Postbronchodilator FEV<sub>1</sub> <50% <br> ● FEV<sub>1</sub>/FVC <70% <br> ● ≥1 moderate or severe COPD exacerbation within 1 year of study <br> ● Use of ICS/LABA, ICS/LAMA, LAMA/LABA, or LAMA monotherapy ≥2 months <br> ● CAT score ≥10 | Extrafine BDP/FF/GP pMDI 200/12/20 μg BID (n=764) × 52 weeks | Rates (per-patient-per-year) of moderate to severe COPD exacerbations were 0.50 for BDP/FF/GP and 0.59 for IND/GP (RR, 0.85; p=0.043) <br> Reductions in exacerbations were greater for patients with eosinophil count ≥2% <br> BDP/FF/GP also significantly improved mean change from baseline in FEV<sub>1</sub> vs IND/GP at weeks 12 and 40 (mean difference, 32 mL; p<0.01) <br> Most common AE was COPD exacerbation; pneumonia was reported in 4% of patients in each treatment group |
| **KRONOS**[^5] Canada, China, Japan, US | ● Current or ex-smokers (≥10 pack-years) <br> ● Age 40–80 years <br> ● Postbronchodilator FEV<sub>1</sub> ≥25% to <80% <br> ● FEV<sub>1</sub>/FVC <70% <br> ● Use of ≥2 inhaled maintenance therapies for ≥26 weeks <br> ● CAT score ≥10 | BUD/GP/FF pMDI 320/18/9.6 μg BID (n=639) vs GFF pMDI 18/9.6 μg BID (n=625) × 24 weeks | Triple therapy significantly improved FEV<sub>1</sub>, AUC<sub>0–4h</sub>, vs both BUD/FF arms (LSM difference, 104 mL and 91 mL; both p<0.001) <br> BUD/GP/FF also significantly improved predose morning trough FEV<sub>1</sub> vs GFF (22 mL; p=0.139) and BUD/FF pMDI (74 mL; p<0.001) <br> Annual rates of moderate to severe COPD exacerbations were 0.46 for BUD/GP/FF vs 0.95 for GFF (p=0.001), 0.56 for BUD/GP pMDI, and 0.55 for BUD/FF DPI <br> TDI focal score was significantly improved with triple therapy vs BUD/FF DPI but not vs GFF or BUD/FF pMDI <br> Most common AEs were nasopharyngitis and upper respiratory tract infection; pneumonia occurred in 2% of all groups except OL BUD/FF DPI, where it occurred in 1% |

(Continued)
combination of these drugs in patients with COPD (Table 4). The AUGMENT and ACLIFORM-COPD studies (NCT01437397 and NCT01462942, respectively) demonstrated greater improvements in lung function for aclidinium/formoterol combination therapy compared with either component as monotherapy and with placebo.\cite{43,44} Greater improvements were observed with the higher dose of aclidinium/formoterol (400/12 μg BID vs 400/6 μg BID), but both doses provided clinically meaningful improvement (≥1 unit) in Transition Dyspnea Index (TDI) focal score versus placebo. Several analyses were conducted using pooled data from the AUGMENT and ACLIFORM-COPD studies. In a prespecified analysis of symptoms and exacerbations, aclidinium/formoterol 400/12 μg significantly improved symptom control over 24 hours compared with its monocomponents and placebo and reduced the frequency of moderate or severe exacerbations by 29% versus placebo (p<0.05).\cite{45} The fixed-dose combination of aclidinium and formoterol also provided consistent improvements in patients with more and fewer symptoms based on the Baseline Dyspnea Index and the Evaluating Respiratory Symptoms (E-RS) in COPD diary.\cite{46} Patient subgroups according to airflow obstruction severity, age, sex, and exacerbation history were also evaluated using pooled AUGMENT and ACLIFORM-COPD data.\cite{47} This analysis showed that combination therapy was more effective than placebo across all subgroups.

In the AFFIRM-COPD study (NCT01908140), aclidinium/formoterol was compared with salmeterol/fluticasone, and the LAMA/LABA combination demonstrated superiority for peak FEV\textsubscript{1} but similar results for dyspnea, health status, and exacerbation risk.\cite{48} The AMPLIFY study (NCT02796677) demonstrated that twice daily aclidinium/formoterol significantly improved 1-hour postdose FEV\textsubscript{1} compared with the monocomponents and tiotropium, and combination therapy also improved early morning symptom control compared with tiotropium.\cite{49}

### Triple Therapy Regimens Containing Formoterol

Patients who have persistent breathlessness or exercise limitation or who are at risk for an exacerbation on ICS/LABA or LAMA/LABA treatment can step up to triple therapy that combines medicines from all three pharmacological categories.\cite{1} Several clinical trials have evaluated triple therapy combinations including formoterol with various other components (Table 5).

The TRILOGY study (NCT01917331) compared a single-inhaler combination of extrafine beclomethasone
dipropionate, formoterol fumarate, and glycopyrronium bromide (BDP/FF/GB) with beclomethasone dipropionate and formoterol fumarate (BDP/FF) in patients with post-bronchodilator FEV$_1$ <50% and ≥1 moderate to severe COPD exacerbation in the previous year.\textsuperscript{40} Triple therapy demonstrated significant improvements in FEV$_1$ but not dyspnea at week 26.\textsuperscript{40,41} The annual exacerbation rate was reduced by 23% with triple therapy. The TRINITY study (NCT01911364) compared extrafine BDP/FF/GB (fixed triple), tiotropium, and BDP/FF plus tiotropium (open triple) and found exacerbation rates of 0.46, 0.57, and 0.45, respectively.\textsuperscript{41} The fixed-dose triple therapy was superior to tiotropium for exacerbations and predose FEV$_1$ and noninferior to open triple therapy. In the TRIBUTE study (NCT02579850), the effects of BDP/FF/GB in a single inhaler were compared with those of dual bronchodilators using indacaterol and glycopyrrolate.\textsuperscript{42} The rate of moderate to severe COPD exacerbations over 52 weeks was reduced by 15% with triple therapy (p=0.043), with a greater relative effect in patients with blood eosinophils >2%.

The KRONOS study (NCT01349803) compared budesonide/glycopyrrolat/formoterol fumarate (BUD/GP/FF) pMDI with several dual therapies and found a significant improvement in FEV$_1$ area under the curve from 0 to 4 hours with triple therapy compared with budesonide-based dual therapies.\textsuperscript{43} Unlike other studies of triple therapy, KRONOS did not restrict the population based on history of exacerbations. In this population, the triple therapy regimen significantly reduced exacerbation rates versus dual therapy with glycopyrrolate and formoterol pMDI, thus supporting the use of triple therapy for patients with lower exacerbation risk. In the ETHOS study (NCT02465567), two different doses of budesonide were used in triple therapy regimens and compared with two dual therapy regimens, budesonide plus formoterol and glycopyrrolat plus formoterol.\textsuperscript{44} The recently published study indicates a significant reduction in the rate of moderate to severe exacerbations with triple therapy using high- and low-dosage budesonide plus glycopyrrolat and formoterol compared with dual therapy.\textsuperscript{44,45}

Safety of Inhaled Formoterol in Patients with COPD

In formoterol monotherapy studies, the most common adverse events (AEs) were headache, nausea, diarrhea, COPD exacerbation, dizziness, and cough.\textsuperscript{18} Studies comparing various combination therapies generally found similar rates of AEs between treatment groups (Tables 4 and 5), and most events were mild or moderate in severity. As an adrenergic receptor agonist, concerns regarding cardiovascular AEs have been raised with LABA treatment, and cardiovascular disease is the most prevalent comorbidity in patients with COPD.\textsuperscript{46} Neither mode of formoterol monotherapy (DPI or inhalation solution) has been shown to have clinically meaningful effects on mean or maximum heart rate, most likely resulting from its selectivity for the β$_2$-receptor.\textsuperscript{18} Studies investigating the long-term effects of LABAs on heart rate and blood pressure over 48 weeks in >3000 patients with COPD showed small quantitative changes in heart rate compared with baseline that were numerically lower with LABA versus placebo, and blood pressure decreased with all treatments.\textsuperscript{46} Two studies found no effects of therapeutic and supratherapeutic dosages of glycopyrrolat/formoterol pMDI using co-suspension delivery technology on cardiovascular parameters.\textsuperscript{43}

The US FDA had concerns about high-dose formoterol based on a 2003 review of three studies that found more frequent serious asthma exacerbations in patients receiving formoterol 24 μg BID compared with those receiving placebo.\textsuperscript{47} The FDA concluded that this finding was consistent with previously published, placebo-controlled, randomized trials of another LABA, salmeterol. In response, the FDA required a black box warning on all LABA and ICS/LABA combination products about possible AEs of LABAs in patients with asthma. Subsequently, four large, 26-week safety trials were conducted to evaluate the risk of serious asthma-related events associated with the use of ICS/LABA combination therapy.\textsuperscript{48} These trials demonstrated noninferiority of ICS/LABA compared with ICS alone in risk of hospitalizations, intubations, and deaths related to asthma. The black box warning was removed from the ICS/LABA products in 2017; however, this language is still included in the warnings and precautions section of the label.

In patients with COPD, the use of formoterol in combination with ICS may be associated with several other specific AEs, including pneumonia, changes in bone mineral density, and ophthalmologic events.\textsuperscript{49} The incidence of pneumonia varies for several reasons, including severity of COPD, exacerbation history, and specific ICS used.\textsuperscript{49} The PATHOS study (NCT01146392) showed an approximately 75% greater risk of pneumonia with fluticasone/salmeterol compared with budesonide/formoterol.\textsuperscript{50} Pneumonia occurred at similar rates among patients receiving
budesonide/formoterol, formoterol monotherapy, and placebo in the SUN and SHINE studies, as well as with triple therapy compared with LAMA/LABA therapy in the KRONOS study.

Objective measurements of lenticular opacity, intracocular pressure, and bone mineral density have failed to reveal significant changes between LABA monotherapy and ICS/LABA combination therapy. A subset of patients from the KRONOS study of triple therapy were followed for 52 weeks; changes in bone mineral density and ophthalmologic assessments were small and noninferior to the regimen not containing ICS.

Conclusions
Formoterol is a highly selective and potent β2-agonist that has a rapid onset of bronchodilation and a prolonged duration of effect. When administered as monotherapy or in combination with other agents, formoterol effectively improves lung function and reduces the risk of exacerbations and symptoms of COPD. Clinical studies of formoterol provided consistent results across broad patient populations with varying disease severity and characteristics. Different formulations and delivery devices of formoterol products are available to provide treatment options for patients with moderate to severe COPD. Formoterol is well tolerated, with a safety profile similar to that of placebo and minimal effects on the cardiovascular system.

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Disclosure
DPT serves on advisory boards for AstraZeneca, Sunovion, Mylan, and Theravance/Innoveniva and as a speaker for AstraZeneca, Boehringer Ingelheim, and Sunovion. The author reports no other conflicts of interest in this work.

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