

Formoterol for the Treatment of Chronic Obstructive Pulmonary Disease

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Donald P Tashkin

Department of Medicine, David Geffen
School of Medicine at UCLA, Los Angeles,
CA, USA

Abstract: Bronchodilators, including long-acting β_2 -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 β_2 -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 β_2 -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

Correspondence: Donald P Tashkin
David Geffen School of Medicine at UCLA,
10388 Le Conte Avenue, Los Angeles, CA
90095, USA
Tel +1 310 825 3163
Fax +1 310 206 5088
Email dtashkin@mednet.ucla.edu

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 (FEV₁), 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 μ g) 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_{2 α} , 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 - adrenoceptors, formoterol exhibits greater β_2 -adrenoceptor 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 FEV₁ 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	Olodaterol	Vilanterol	Salmeterol
B2 agonism	Full agonist	Partial agonist	Nearly full agonist	Partial agonist	Partial agonist
Selectivity	$\beta_2 > \beta_3 > \beta_1$	$\beta_2 > \beta_3 > \beta_1$	$\beta_2 \gg \beta_1 > \beta_3$	$\beta_2 \gg \beta_3 > \beta_1$	$\beta_2 \gg \beta_1 > \beta_3$
Potency	++	+	++	++	+
Lipophilicity	++	+++	++	+++	+++
Elimination half-life	~10 hours	40–56 hours	7.5 hours	21 hours	5.5 hours
Onset of action in COPD	Within 5 minutes	Within 5 minutes	Within 5 minutes	Within 5 minutes	~10 minutes
Duration of action	12 hours	24 hours	≥24 hours	22 hours	12 hours

Note: Data from these studies.^{1,3–7,53–59}

Abbreviations: COPD, chronic obstructive pulmonary disease; LABA, long-acting β_2 -agonist.

was 80% of the maximal effect of the drug.⁸ Formoterol exhibited faster onset of bronchodilator action within the first 2 hours of administration compared with tiotropium in patients with COPD.⁹ Fluticasone/formoterol had a faster onset of bronchodilator action compared with fluticasone/salmeterol in patients with asthma; similarly, glycopyrronium/formoterol also had a faster onset of bronchodilator action compared with umeclidinium/vilanterol.^{10,11} The rapid onset of formoterol in combination with budesonide was confirmed in a study comparing the Turbuhaler[®] and Spiromax[®] devices in patients with COPD;¹² these results are consistent with studies in patients with asthma.^{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.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.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[®] 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 acclidinium 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.¹⁶

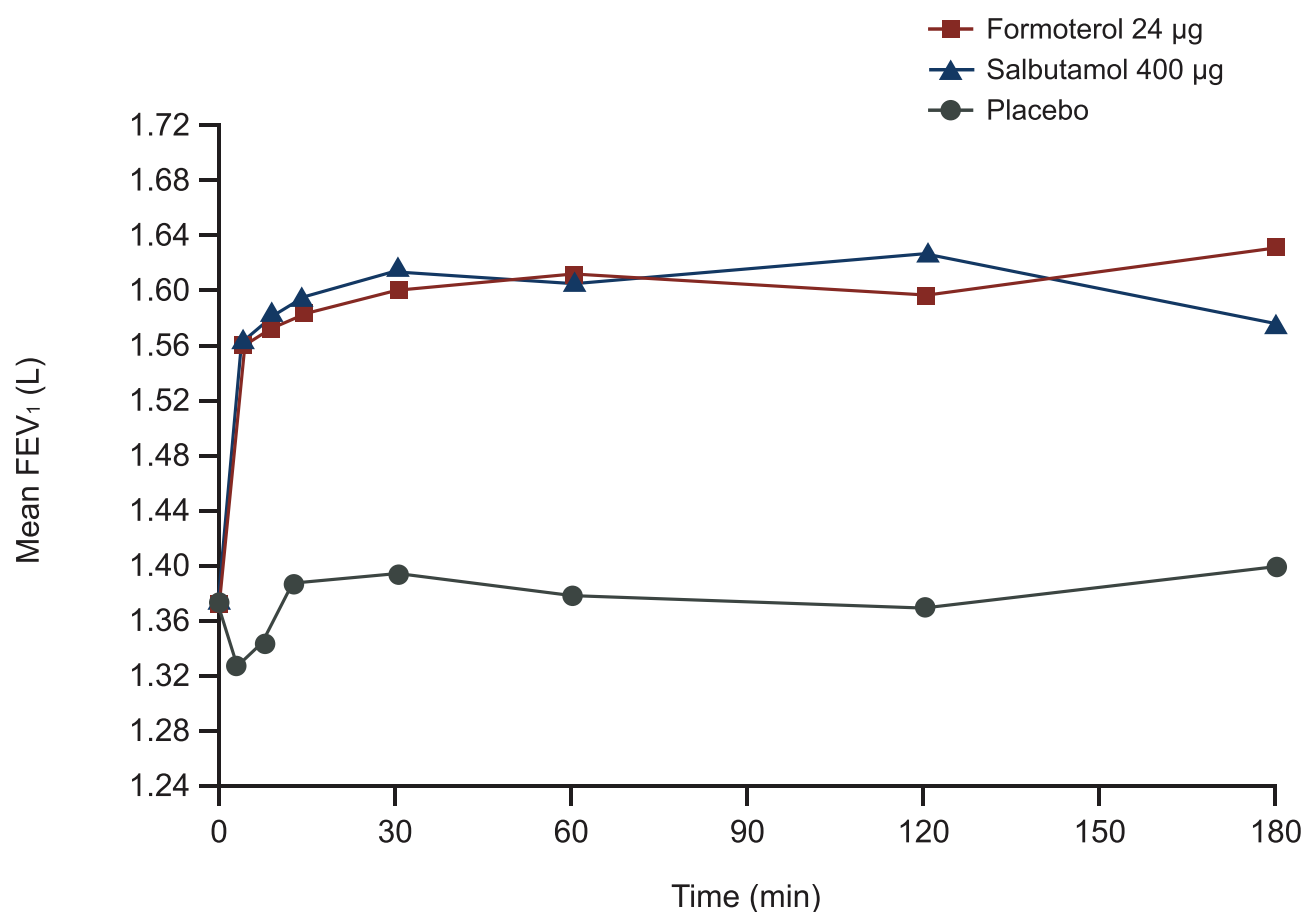


Figure 1 The bronchodilator effect of formoterol occurs rapidly. A single inhalation of medication was administered to 24 patients with stable COPD in a randomized, three-way, crossover study. Reprinted from *Respiratory Medicine*, Vol 95 (10), Benhamou et al, Rapid onset of bronchodilation in COPD: a placebo-controlled study comparing formoterol (Foradil Aerolizer) with salbutamol (Ventodisk), pages 817–821, Copyright 2001, with permission from Elsevier.⁸

Abbreviations: COPD, chronic obstructive pulmonary disease; FEV₁, forced expiratory volume in 1 second.

Table 2 Available Formoterol Products

Formoterol Products	Brand Name	Delivery Method	Approvals	Dosage
Monotherapy products				
Formoterol	Atimos Modulite®	pMDI	EU	12 µg BID; up to 4 inhalations daily for severe COPD
Formoterol inhalation powder ^a	Foradil Aerolizer®	Capsule used with Aerolizer inhaler	US 2001 EU	12 µg every 12 hours
Formoterol inhalation solution	Perforomist®	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		100/6 µg per inhalation; 2 inhalations BID 100/6 µg per inhalation (dosing frequency not specified)
Budesonide-formoterol	Symbicort® Symbicort Turbuhaler® Fobumix Easyhaler®	pMDI DPI DPI	US 2006 EU 2014 EU 2016	160/4.5 µg per inhalation; 2 inhalations BID 200/6 µg per inhalation; 2 inhalations BID 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
Acclidinium-formoterol	Duaklir Pressair® Duaklir Genuair®	DPI DPI	US 2019 EU 2014	400/12 µg per inhalation; 1 inhalation BID 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
Beclomethasone-formoterol-glycopyrronium	Trimbow®	pMDI	EU 2017	100/6/10 µg per inhalation; 2 inhalations BID

Note: ^aNo longer available.

Abbreviations: BID, twice daily; COPD, chronic obstructive pulmonary disease; DPI, dry powder inhaler; EU, European Union; ICS, inhaled corticosteroid; LABA, long-acting β_2 -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.¹ 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.¹⁷ 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;

$p=0.0092$).¹⁷ The mean difference in trough FEV₁ versus placebo across studies was 45 mL with formoterol 12 µg BID.¹⁷ In a 12-week, randomized, double-blind trial, formoterol via inhalation solution (20 µg/2 mL) and via DPI (12 µg) demonstrated similar efficacy.¹⁸

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.¹ Triple therapy represents another treatment option, particularly for

Table 3 Efficacy of Formoterol in Combination with ICS

Clinical Trial	Patient Population	Treatments and Duration ^a	Key Findings
SHINE¹⁹ US, EU, South Africa	- Current or ex-smokers (≥10 pack-years) - Age ≥40 years - COPD dx and symptoms >2 years ≥1 COPD exacerbation within 1 year of study - Use of SABA as rescue medication - Prebronchodilator FEV₁ ≤50% - FEV₁/FVC <70% - mMRC dyspnea ≥2	BUD/FF HFA pMDI 2 doses: 320/9 µg BID (n=277) 160/9 µg BID (n=281) vs Monocomponents (BUD [n=275] or FF [n=284] alone or in combination via separate inhalers) BUD + FF [n=287] vs Placebo (n=300) x 26 weeks	- BUD/FF 320/9 µg significantly improved predose FEV₁ (p≤0.026) and 1-hour post-dose FEV₁ (p≤0.039) vs BUD, FF, placebo - BUD/FF 160/9 µg significantly improved predose FEV₁ (p≤0.002) and 1-hour post-dose FEV₁ (p<0.001) vs BUD, placebo - FF alone significantly improved predose FEV₁ (p=0.039) and 1-hour postdose FEV₁ vs placebo (p<0.001) - Both BUD/FF doses significantly improved COPD-related symptoms and decreased daily rescue medication use vs placebo - Most common AEs: COPD (highest in FF group), nasopharyngitis, oral candidiasis, bronchitis, sinusitis, and diarrhea; no difference in pneumonia between treatment groups
SUN²⁰ US, EU, Mexico	- Current or ex-smokers (≥10 pack-years) - Age ≥40 years - COPD dx and symptoms >2 years ≥1 COPD exacerbation within 1 year of study - Use of SABA as rescue medication - Prebronchodilator FEV₁ ≤50% - FEV₁/FVC <70% - mMRC dyspnea ≥2	BUD/FF HFA pMDI 2 doses: 320/9 µg BID (n=494) 160/9 µg BID (n=494) vs FF DPI 9 µg BID (n=495) vs Placebo (n=481) x 52 weeks	- BUD/FF 320/9 µg significantly improved predose FEV₁ and 1-hour postdose FEV₁ vs FF (p≤0.023) and placebo (p<0.001) - BUD/FF 160/9 µg significantly improved predose FEV₁ and 1-hour postdose FEV₁ vs placebo (p<0.001) - 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) - Most common AEs: oral candidiasis, COPD, dysphonia; incidence of pneumonia-related AEs similar between treatment groups
RISE²¹ US, Mexico, South America, EU, South Africa	- Current or ex-smokers (≥10 pack-years) - Age ≥40 years - COPD dx and symptoms >1 year ≥1 moderate/severe COPD exacerbation within 1 year of study - Use of SABA as rescue medication - Postbronchodilator FEV₁ ≤70% - FEV₁/FVC <70% - mMRC dyspnea ≥2	BUD/FF pMDI 320/9 µg BID (n=606) vs FF DPI 9 µg BID (n=613) x 26 weeks	- 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) - Time to first exacerbation was significantly reduced by 22% with BUD/FF vs FF (p=0.0164) - BUD/FF also significantly reduced nighttime awakenings and rescue medication use - Incidence of AEs was similar between treatment groups; most common AEs were COPD, nasopharyngitis

(Continued)

Table 3 (Continued).

Clinical Trial	Patient Population	Treatments and Duration ^a	Key Findings
TELOS²² US, Canada, EU	- Current or ex-smokers (≥10 pack-years) - Age 40–80 years - Symptomatic COPD (CAT score ≥10) despite treatment with ≥1 bronchodilator for ≥6 weeks - Postbronchodilator FEV₁ ≥30% but <80% - FEV₁/FVC <70%	BUD/FF MDI (co-suspension delivery) 320/10 µg BID (n=655) vs BUD/FF MDI (co-suspension delivery) 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) x 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 - Differences in predose FEV₁ were greater for patients with eosinophils ≥150 cells/mm³ between BUD/FF 320/10 and 160/10 µg vs FF MDI - BUD/FF 320/9 µg and BUD/FF 160/9 µg significantly improved FEV₁ AUC_{0–4h} vs BUD (p<0.0001) - 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) - AEs were similar across treatment groups, with a low incidence of pneumonia in all groups
Calverley et al²³ EU	- Current or ex-smokers (≥20 pack-years) - Age ≥40 years - COPD dx and symptoms >2 years ≥1 COPD exacerbation within 1 year of study - Postbronchodilator FEV₁ 30% to 50% - 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) x 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) - 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 - Rates of hospitalization due to exacerbation were significantly higher with BDP/FF vs BUD/FF and FF: 0.074, 0.033, and 0.040 (p≤0.008) - AEs were similar between treatment groups; most common AE: COPD exacerbation/worsening
FORWARD¹⁶ EU	- Current or ex-smokers (≥10 pack-years) - Age ≥40 years - Severe COPD dx ≥1 COPD exacerbation within 1 year of study - Postbronchodilator FEV₁ 30% to 50% - FEV₁/FVC <70%	Extrafine BDP/FF pMDI 200/12 µg BID (n=595) vs FF pMDI 12 µg BID (n=591) x 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) - Time to first exacerbation was significantly reduced by 20% - BDP/FF significantly improved predose morning FEV₁ at week 12 vs FF (81 mL vs 12 mL; mean difference, 69 mL; p<0.001) - 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

Tashkin et al²⁴ Two studies of identical design were pooled North, Central, and South America; EU; Africa; Asia	• Current or ex-smokers pack-years • Age ≥ 40 years • COPD dx and symptoms > 2 years • Prebronchodilator FEV₁/FVC $\leq 70\%$ • Postbronchodilator FEV₁ 25% to 60%	MF/FF 400/10 μg BID (n=442) vs MF/FF 200/10 μg BID (n=446) vs MF 400 μg BID (n=463) vs FF 10 μg BID (n=452) vs Placebo (n=448) x 52 weeks	• MF/FF 400/10 μg and 200/10 μg significantly improved FEV₁, AUC_{0-12h} vs MF 400 μg and placebo at week 13 (both $p < 0.001$) and all endpoints; FF 10 μg was also superior to placebo • MF/FF 400/10 μg significantly improved predose morning FEV₁ vs FF ($p \leq 0.008$) and placebo ($p < 0.001$); MF/FF 200/10 was significantly superior to placebo • Exacerbation rates (per patient-year) were lower in MF/FF and MF groups: MF/FF 400/10, 0.33; MF/FF 200/10, 0.34; MF 400, 0.35; FF 10, 0.42 • Most common AEs: headache, COPD, nasopharyngitis, upper respiratory tract infection, and hypertension; pneumonia was infrequently reported: MF/FF 400/10, 2.0%; MF/FF 200/10, 1.1%; MF 400, 1.1%; FF 10, 1.3%; placebo, 0.7%
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Abbreviations: AE, adverse event; AUC_{0-4h}, area under the curve from 0 to 4 hours; AUC_{0-12h}, area under the curve from 0 to 12 hours; BDP, beclomethasone dipropionate; BID, twice daily; BUD, budesonide; CAT, COPD Assessment Test; COPD, chronic obstructive pulmonary disease; DPI, dry powder inhaler; dx, diagnosis; EU, European Union; FEV₁, forced expiratory volume in 1 second; FF, formoterol fumarate; FVC, forced vital capacity; HFA, hydrofluoroalkane; LSM, least squares mean; MDI, metered-dose inhaler; MF, mometasone furoate; mMRC, modified Medical Research Council dyspnea scale; pMDI, pressurized metered-dose inhaler; SABA, short-acting β_2 -agonist; US, United States.

Note: ^aBold font indicates trial duration.

patients with a high risk of exacerbations and elevated eosinophil levels, as discussed below.¹ 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).^{19,20} 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 $\leq 50\%$ 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.¹⁹ 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.²⁰ 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]).²¹ 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.²² 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 .²² Enrolled patients had symptomatic, moderate to very severe COPD, with no requirement for a history of

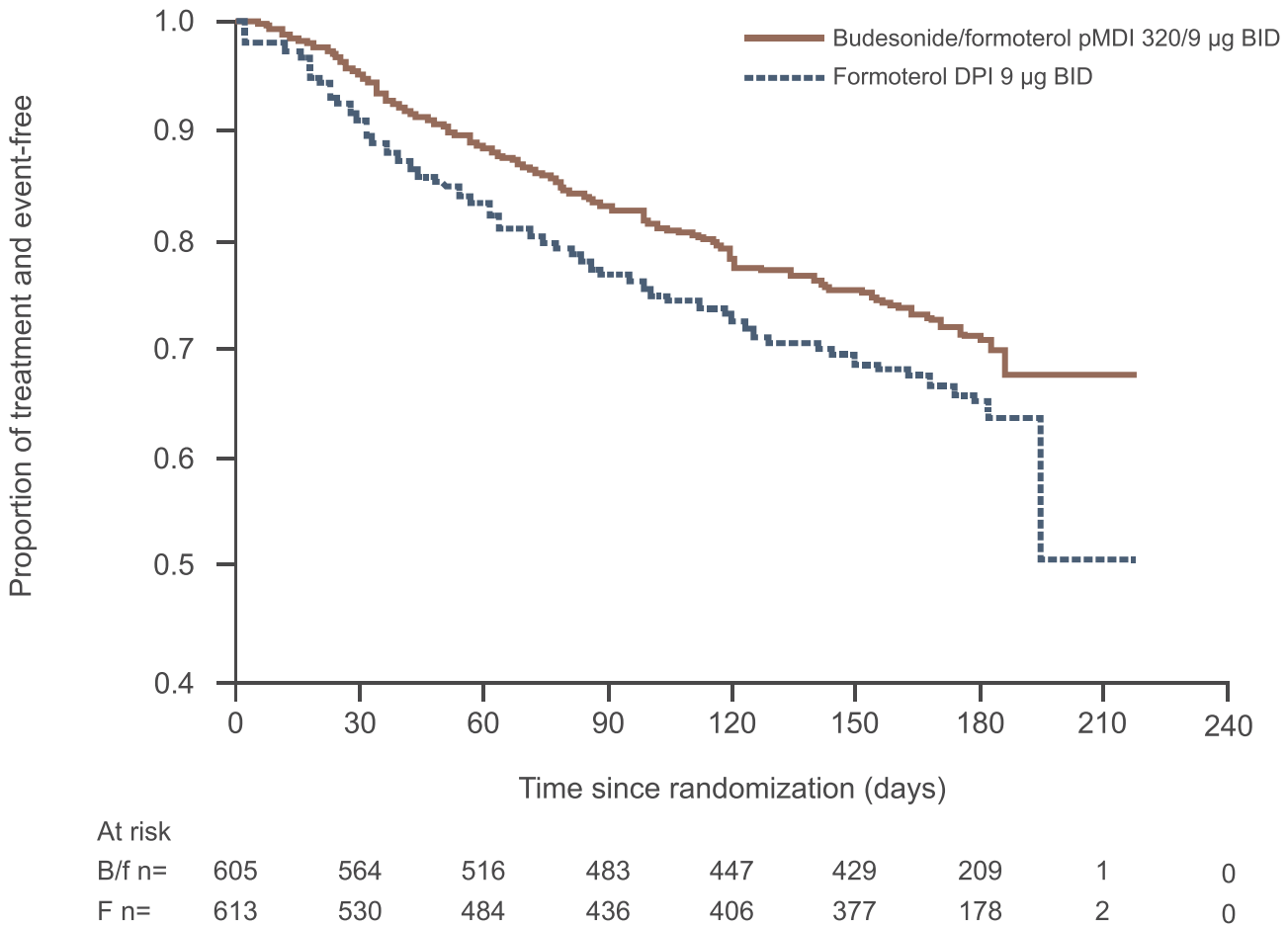


Figure 2 Time to first moderate or severe exacerbation^a in the RISE study.
Notes: ^aBetween-treatment difference in time to first moderate or severe exacerbation, $p < 0.016$; Cox regression model. Reprinted from *Respiratory Medicine*, Vol 132, Ferguson et al, Effect of budesonide/formoterol pressurized 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.²¹
Abbreviations: B/f, budesonide/formoterol; BID, twice daily; DPI, dry powder inhaler; f, formoterol; pMDI, pressurized metered-dose inhaler.

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.²³ 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.¹⁶ 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.²⁴ MF plus formoterol demonstrated dose-dependent improvements in lung function; both doses reduced exacerbations and improved respiratory health status compared with placebo.²⁴ However, the fixed-dose combination of MF/formoterol is not approved for the treatment of COPD.

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.¹ The Phase III PINNACLE studies compared the combination of glycopyrrolate and formoterol (GFF) formulated for the AEROSPHERE™ inhaler using co-suspension delivery in

Table 4 Efficacy of Formoterol in Combination with LAMAs

Clinical Trial	Patient Population	Treatments and Duration ^a	Key Findings
PINNACLE-1 ³⁰ US, Australia, New Zealand	- Current or ex-smokers (≥ 10 pack-years) - Age 40–80 years - Moderate to very severe COPD - Postbronchodilator FEV₁ <80% - FEV₁/FVC <70%	GFF pMDI 18/9.6 μ g BID (n=526) vs GP pMDI 18 μ g BID (n=451) vs FF pMDI 9.6 μ g BID (n=449) vs OL tiotropium 18 μ g QD (n=451) vs Placebo BID (n=219) x 24 weeks	- GFF, GP, and FF pMDI significantly improved predose morning trough FEV₁ 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 FEV₁ 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 ³⁰ US	Same as above	GFF pMDI 18/9.6 μ g BID (n=510) vs GP pMDI 18 μ g BID (n=439) vs FF pMDI 9.6 μ g BID (n=437) vs Placebo BID (n=223) x 24 weeks	- GFF, GP, and FF pMDI significantly improved predose morning trough FEV₁ 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 FEV₁ at week 24 vs monocomponents (all p<0.0001)
PINNACLE-3 ³¹ US, Australia, New Zealand	- 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 μ g BID (n=1035) vs GP pMDI 18 μ g BID (n=888) vs FF pMDI 9.6 μ g BID (n=884) vs OL tiotropium 18 μ g QD (n=450) x 28 weeks	- GFF pMDI significantly improved predose morning trough FEV₁ over 52 weeks vs GP, FF, and tiotropium (p<0.0001 vs GP, FF, and p=0.0117 vs tiotropium) - GFF also significantly improved 2-hour postdose FEV₁ 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 ³² Asia, EU, US	Same as PINNACLE-1 and -2	GFF pMDI 18/9.6 μ g BID (n=555) vs GP pMDI 18 μ g BID (n=480) vs FF pMDI 9.6 μ g BID (n=483) vs Placebo BID (n=238) x 24 weeks	- GFF pMDI significantly improved predose morning trough FEV₁ at week 24 vs GP, FF, and placebo (all p<0.0001) - GFF significantly improved 2-hour postdose change from baseline FEV₁ 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)

(Continued)

Table 4 (Continued).

Clinical Trial	Patient Population	Treatments and Duration ^a	Key Findings
AUGMENT³⁴ North America, Australia, New Zealand	- Current or ex-smokers (≥ 10 pack-years) - Age ≥ 40 years - Postbronchodilator FEV₁ $\geq 30\%$ to $<80\%$ - FEV₁/FVC $<70\%$	ACU/FF DPI 400/12 μg BID (n=335) vs ACU/FF DPI 400/6 μg BID (n=333) vs ACL DPI 400 μg BID (n=337) vs FF DPI 12 μg BID (n=332) vs Placebo DPI (n=331) x 24 weeks	- Both doses of ACU/FF significantly improved 1-hour postdose FEV₁ change from baseline to week 24 vs ACL (LSM difference, 108 mL and 87 mL, respectively $p<0.0001$) - ACU/FF 400/12 μg significantly improved predose morning trough FEV₁ from baseline to week 24 vs FF (LSM difference, 45 mL; $p=0.01$) - Numerically greater improvements in FEV₁ measurements were observed for the higher dose of ACU/FF vs the lower dose - TDI focal scores were significantly improved with ACU/FF vs ACL, FF ($p\leq 0.01$), and placebo ($p<0.0001$) - SGRQ total scores were significantly improved at week 24 for ACU/FF and monocomponents vs placebo ($p<0.05$) - Most common AEs were cough and nasopharyngitis
ACLIFORM-COPD³⁵ EU, South Africa, South Korea	- Current or ex-smokers (≥ 10 pack-years) - Age ≥ 40 years - Postbronchodilator FEV₁ $\geq 30\%$ to $<80\%$ - FEV₁/FVC $<70\%$	ACU/FF DPI 400/12 μg BID (n=385) vs ACU/FF DPI 400/6 μg BID (n=381) vs ACL DPI 400 μg BID (n=385) vs FF DPI 12 μg BID (n=384) vs Placebo DPI (n=194) x 24 weeks	- Both doses of ACU/FF significantly improved 1-hour postdose FEV₁ change 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 ACU/FF (1.29 and 1.16) - Incidences of AEs were similar across combination, monotherapy, and placebo arms
AFFIRM-COPD²⁵ EU, Canada, South Africa	- Current or ex-smokers (≥ 10 pack-years) - Age ≥ 40 years - Postbronchodilator FEV₁ $<80\%$ - FEV₁/FVC $<70\%$ - CAT score ≥ 10	ACU/FF DPI 400/12 μg BID (n=468) vs Salmeterol/fluticasone DPI 50/500 μg BID (n=463) x 24 weeks	- Peak FEV₁ was significantly greater with ACU/FF vs salmeterol/fluticasone at week 24, with significant differences observed after first dose ($p<0.0001$) - Mean increase in peak FEV₁ at week 24 was 93 mL greater with ACU/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
AMPLIFY³⁹ EU, Israel, US	- Current or ex-smokers (≥ 10 pack-years) - Age ≥ 40 years - Postbronchodilator FEV₁ $<80\%$ - FEV₁/FVC $<70\%$ - CAT score ≥ 10	ACU/FF DPI 400/12 μg BID (n=314) vs ACL DPI 400 μg BID (n=475) vs FF DPI 12 μg BID (n=319) vs Tiotropium DPI 18 μg QD (n=475) x 24 weeks	- ACU/FF significantly improved 1-hour postdose FEV₁ from baseline at week 24 vs ACL, FF, and tiotropium (all $p<0.0001$) - ACU/FF significantly improved predose morning trough FEV₁ vs FF ($p<0.001$) - SGRQ total score improved vs baseline $>$MCID for ACU/FF (4.68), ACL (4.95), and tiotropium (5.58); improvement for FF was 3.96 - Early morning symptom severity was significantly improved with ACU/FF vs tiotropium ($p<0.05$) - Most common AEs: COPD exacerbation, nasopharyngitis, and headache

Abbreviations: ACL, acclidinium; AE, adverse event; BID, twice daily; CAT, COPD Assessment Test; DPI, dry powder inhaler; EU, European Union; FEV₁, forced expiratory volume in 1 second; FF, formoterol fumarate; FVC, forced vital capacity; GF, 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).²⁵ The fixed-dose GFF pMDI formulation demonstrated lasting stability, dose uniformity, and pharmacokinetics that fell within bioequivalence bounds for the monocomponents (Figure 3).²⁶ 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.^{27–29}

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.³⁰ 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 -2.³¹ 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.³² 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).³³ 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

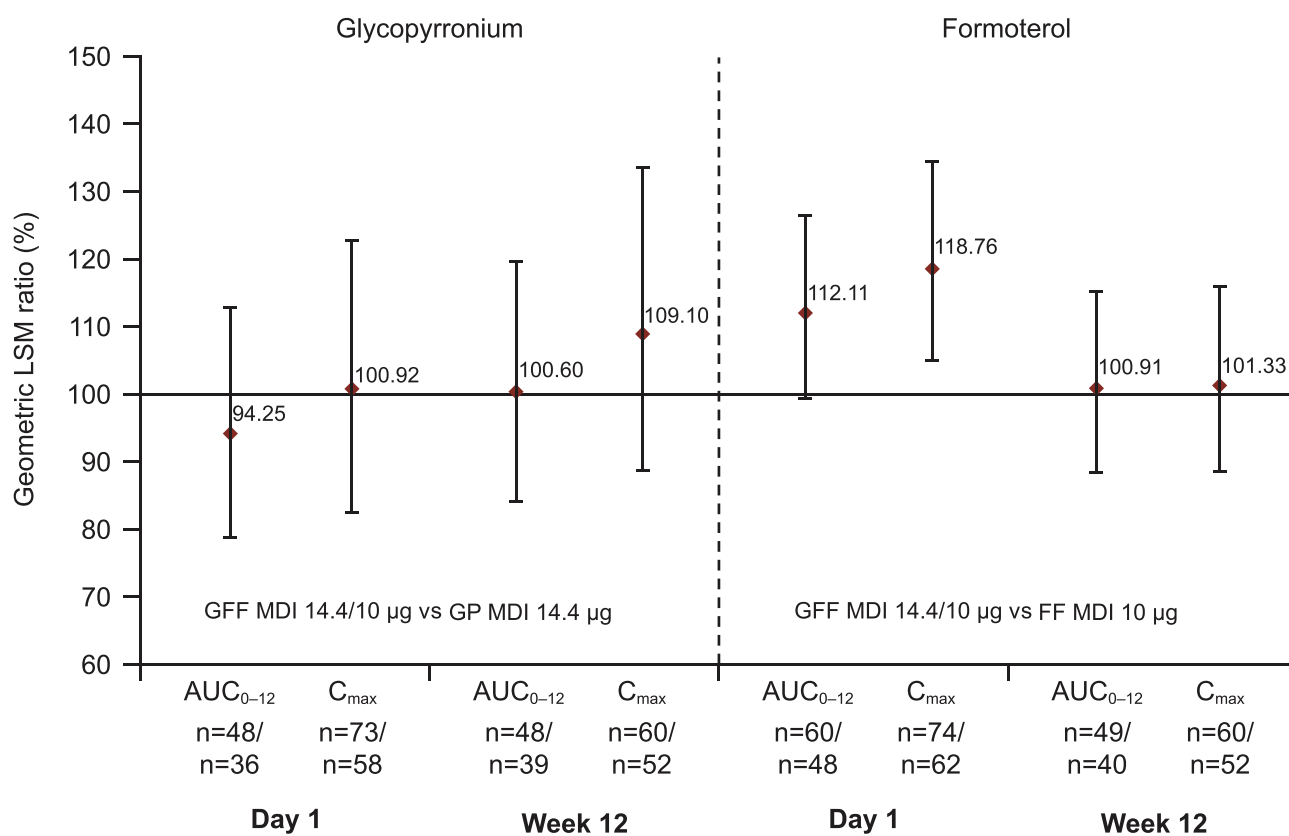


Figure 3 Relative bioavailability for glycopyrronium/formoterol combination versus glycopyrronium or formoterol monotherapy. Reprinted from *International Journal of Chronic Obstructive Pulmonary Disease*, Vol 13, Ferguson et al, Pharmacokinetics of glycopyrronium/formoterol fumarate dihydrate delivered via metered-dose inhaler using co-suspension delivery technology in patients with moderate-to-very severe COPD, pages 945–993, Copyright 2018, with permission from Dove Medical Press.²⁶

Abbreviations: AUC₀₋₁₂, area under the curve from 0 to 12 hours; C_{max}, maximum concentration achieved; FF, formoterol fumarate; GFF, glycopyrronium/formoterol fumarate; GP, glycopyrronium; LSM, least squares mean; MDI, metered-dose inhaler.

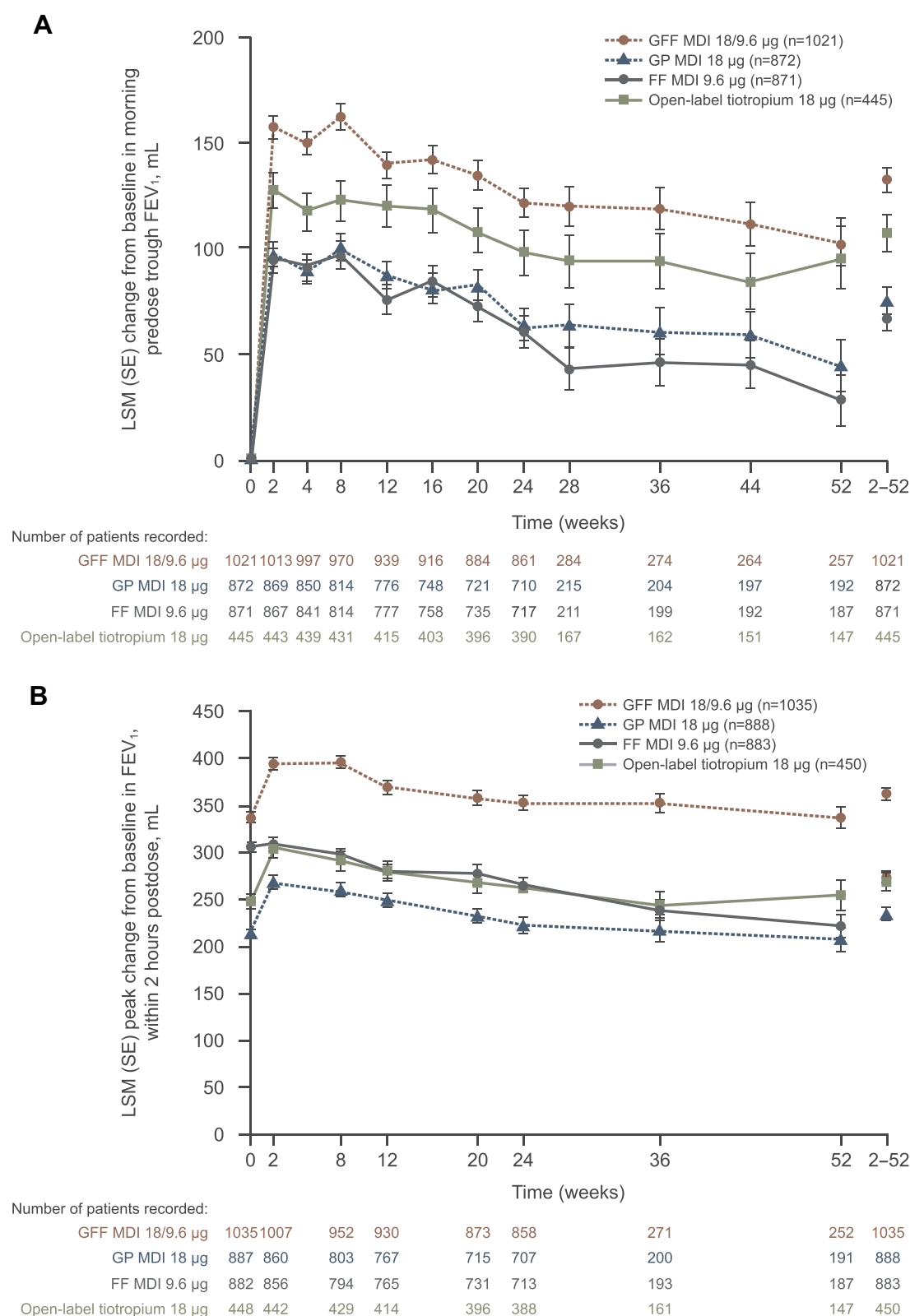


Figure 4 Effects of fixed-dose glycopyrrolate/formoterol combination on change from baseline in (A) Predose morning trough FEV₁ and (B) Peak change in FEV₁ within 2 hours postdose over 52 weeks versus monocomponents and open-label tiotropium. Reprinted from *Respiratory Medicine*, Vol 126, Hanania et 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, glycopyrronium; 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 ^a	Key Findings
TRILOGY⁴⁰ EU	● Age ≥40 years ● Postbronchodilator FEV₁ <50% ● FEV₁/FVC <70% ● ≥1 moderate or severe COPD exacerbation within 1 year of study ● Use of ICS/LABA, ICS/LAMA, LAMA/LABA, or LAMA monotherapy ≥2 months ● CAT score ≥10 ● BDI focal score ≤10	Extrafine BDP/FF/GP pMDI 200/1/2/25 µg BID (n=687) vs Extrafine BDP/FF pMDI 200/12 µg BID (n=680) x 52 weeks	● Triple therapy was superior to BDP/FF for predose FEV₁ (mean difference, 81 mL; p<0.001) and 2-hour postdose FEV₁ (mean difference, 117 mL; p<0.001) at week 26 ● TDI improved in both groups (mean difference, 0.21 units) ● 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) ● In patients with history of >1 exacerbation, BDP/FF/GP reduced rate of moderate to severe exacerbations by 33% (p=0.019) ● Treatment-emergent AEs were similar between groups
TRINITY⁴¹ EU, South America, Mexico	● Current or ex-smokers ● Age ≥40 years ● Postbronchodilator FEV₁ <50% ● FEV₁/FVC <70% ● ≥1 moderate or severe COPD exacerbation within 1 year of study ● Use of ICS/LABA, ICS/LAMA, LAMA/LABA, or LAMA monotherapy ≥2 months ● CAT score ≥10	Extrafine BDP/FF/GP pMDI 200/1/2/25 µg BID (n=1077) vs Tiotropium DPI 18 µg QD (n=1076) vs Extrafine BDP/FF pMDI 200/12 µg BID plus tiotropium DPI 18 µg QD (n=537) x 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 ● Fixed triple therapy was superior to tiotropium (p=0.0025) ● Fixed and open triple therapy were similar ● Reductions in exacerbations were greater for patients with eosinophil count ≥2% ● BDP/FF/GP also significantly improved predose FEV₁ vs tiotropium (mean difference, 61 mL; p<0.0001) ● Most common AE was COPD exacerbation and pneumonia was reported in all treatment groups (BDP/FF/GP, 3%; tiotropium, 2%; BDP/FF + tiotropium, 2%)
TRIBUTE⁴² EU	● Current or ex-smokers ● Age ≥40 years ● Postbronchodilator FEV₁ <50% ● FEV₁/FVC <70% ● ≥1 moderate or severe COPD exacerbation within 1 year of study ● Use of ICS/LABA, ICS/LAMA, LAMA/LABA, or LAMA monotherapy ≥2 months ● CAT score ≥10	Extrafine BDP/FF/GP pMDI 200/1/2/20 µg BID (n=764) vs IND/GP DPI 85/43 µg QD (n=768) x 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) ● Reductions in exacerbations were greater for patients with eosinophil count ≥2% ● BDP/FF/GP also significantly improved mean change from baseline in FEV₁ vs IND/GP at weeks 12 and 40 (mean difference, 32 mL; p<0.01) ● Most common AE was COPD exacerbation; pneumonia was reported in 4% of patients in each treatment group
KRONOS⁵¹ Canada, China, Japan, US	● Current or ex-smokers (≥10 pack-years) ● Age 40–80 years ● Postbronchodilator FEV₁ ≥25% to <80% ● FEV₁/FVC <70% ● Use of ≥2 inhaled maintenance therapies for ≥6 weeks ● 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) vs BUD/FF pMDI 320/9.6 µg BID (n=314) vs OL BUD/FF DPI 400/12 µg BID (n=318) x 24 weeks	● Triple therapy significantly improved FEV₁ AUC_{0-4h} vs both BUD/FF arms (LSM difference, 104 mL and 91 mL; both p<0.0001) ● BUD/GP/FF also significantly improved predose morning trough FEV₁ vs GFF (22 mL; p=0.139) and BUD/FF pMDI (74 mL; p<0.0001) ● Annual rates of moderate to severe COPD exacerbations were 0.46 for BUD/FF/GP vs 0.95 for GFF (p<0.0001), 0.56 for BUD/FF pMDI, and 0.55 for BUD/FF DPI ● TDI focal score was significantly improved with triple therapy vs BUD/FF DPI but not vs GFF or BUD/FF pMDI ● 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)

Table 5 (Continued).

Clinical Trial	Patient Population	Treatments and Duration ^a	Key Findings
ETHOS^{44,45} EU, China, US	• Current or ex-smokers (≥10 pack-years) • Age 40–80 years • Postbronchodilator FEV₁ <65% • FEV₁/FVC <70% • Moderate or severe exacerbation history within 1 year of study: ◦ ≥1, if postbronchodilator FEV₁ <50% ◦ ≥2 moderate or ≥1 severe, if postbronchodilator FEV₁ ≥50% • Use of ≥2 inhaled maintenance therapies for ≥6 weeks • CAT score ≥10	BUD/GP/FF pMDI 320/18/9.6 µg BID vs BUD/GP/FF pMDI 160/18/9.6 µg BID vs BUD/FF pMDI 320/9.6 µg BID vs GFF pMDI 18/9.6 µg BID All products formulated using co-suspension technology x 52 weeks	• Both doses of BUD/GP/FF significantly reduced moderate or severe exacerbations vs dual therapies, GFF, and BUD/FF

Abbreviations: AE, adverse event; AUC_{0-4h}, area under the curve from 0 to 4 hours; BDI, baseline dyspnea index; BDP, beclomethasone dipropionate; BID, twice daily; BUD, budesonide; CAT, COPD Assessment Test; COPD, chronic obstructive pulmonary disease; DPI, dry powder inhaler; EU, European Union; FEV₁, forced expiratory volume in 1 second; FF, formoterol fumarate; GFF, glycopyrronium/formoterol fumarate; GP, glycopyrronium bromide; ICS, inhaled corticosteroid; IND, indacaterol; LABA, long-acting β₂-agonist; LAMA, long-acting muscarinic antagonist; LSM, least squares mean; OL, open-label; pMDI, pressurized metered-dose inhaler; QD, once daily; RR, rate ratio; TDI, Transition Dyspnea Index; US, United States.

Note: ^aBold font indicates trial duration.

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.^{34,35} 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).³⁶ 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.³⁷ Patient subgroups according to airflow obstruction severity, age, sex, and exacerbation history were also evaluated using pooled AUGMENT and ACLIFORM-COPD data.³⁸ 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 FEV₁ but similar results for dyspnea, health status, and exacerbation risk.²⁵ The AMPLIFY study (NCT02796677) demonstrated that twice daily aclidinium/formoterol significantly improved 1-hour postdose FEV₁ compared with the monocomponents and tiotropium, and combination therapy also improved early morning symptom control compared with tiotropium.³⁹

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.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 FEV₁ <50% and ≥ 1 moderate to severe COPD exacerbation in the previous year.⁴⁰ Triple therapy demonstrated significant improvements in FEV₁ but not dyspnea at week 26.⁴⁰ 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.⁴¹ The fixed-dose triple therapy was superior to tiotropium for exacerbations and predose FEV₁ 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.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/glycopyrrolate/formoterol fumarate (BUD/GP/FF) pMDI with several dual therapies and found a significant improvement in FEV₁ area under the curve from 0 to 4 hours with triple therapy compared with budesonide-based dual therapies.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 glycopyrrolate plus formoterol.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 glycopyrrolate and formoterol compared with dual therapy.^{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.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.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.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.⁴⁶ Two studies found no effects of therapeutic and suprathreshold dosages of glycopyrrolate/formoterol pMDI using co-suspension delivery technology on cardiovascular parameters.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 μ g BID compared with those receiving placebo.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.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.⁴⁹ The incidence of pneumonia varies for several reasons, including severity of COPD, exacerbation history, and specific ICS used.⁴⁹ The PATHOS study (NCT01146392) showed an approximately 75% greater risk of pneumonia with fluticasone/salmeterol compared with budesonide/formoterol.⁵⁰ Pneumonia occurred at similar rates among patients receiving

budesonide/formoterol, formoterol monotherapy, and placebo in the SUN and SHINE studies,^{19,20} as well as with triple therapy compared with LAMA/LABA therapy in the KRONOS study.⁵¹

Objective measurements of lenticular opacity, intraocular pressure, and bone mineral density have failed to reveal significant changes between LABA monotherapy and ICS/LABA combination therapy.⁴⁹ 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.⁵²

Conclusions

Formoterol is a highly selective and potent β_2 -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/Innoviva and as a speaker for AstraZeneca, Boehringer Ingelheim, and Sunovion. The author reports no other conflicts of interest in this work.

References

- Global Initiative for Chronic Obstructive Lung Disease (GOLD). *Global Strategy for the Diagnosis, Management, and Prevention of Chronic Obstructive Pulmonary Disease (2020 Report)*. 2020.
- Anderson GP. Formoterol: pharmacology, molecular basis of agonism, and mechanism of long duration of a highly potent and selective beta 2-adrenoceptor agonist bronchodilator. *Life Sci*. 1993;52(26):2145–2160. doi:10.1016/0024-3205(93)90729-M
- Cazzola M, Page CP, Calzetta L, Matera MG. Pharmacology and therapeutics of bronchodilators. *Pharmacol Rev*. 2012;64(3):450–504. doi:10.1124/pr.111.004580
- Lecaillon JB, Kaiser G, Palmisano M, Morgan J, Della Cioppa G. Pharmacokinetics and tolerability of formoterol in healthy volunteers after a single high dose of Foradil dry powder inhalation via Aerolizer. *Eur J Clin Pharmacol*. 1999;55(2):131–138. doi:10.1007/s002280050607
- Nials AT, Ball DI, Butchers PR, et al. Formoterol on airway smooth muscle and human lung mast cells: a comparison with salbutamol and salmeterol. *Eur J Pharmacol*. 1994;251(2–3):127–135. doi:10.1016/0014-2999(94)90392-1
- Bouyssou T, Casarosa P, Naline E, et al. Pharmacological characterization of olodaterol, a novel inhaled beta2-adrenoceptor agonist exerting a 24-hour-long duration of action in preclinical models. *J Pharmacol Exp Ther*. 2010;334(1):53–62. doi:10.1124/jpet.110.167007
- Slack RJ, Barrett VJ, Morrison VS, et al. In vitro pharmacological characterization of vilanterol, a novel long-acting beta2-adrenoceptor agonist with 24-hour duration of action. *J Pharmacol Exp Ther*. 2013;344(1):218–230. doi:10.1124/jpet.112.198481
- Benhamou D, Cuvelier A, Muir JF, et al. Rapid onset of bronchodilation in COPD: a placebo-controlled study comparing formoterol (Foradil Aerolizer) with salbutamol (Ventodisk). *Respir Med*. 2001;95(10):817–821. doi:10.1053/rmed.2001.1161
- Richter K, Stenglein S, Mucke M, et al. Onset and duration of action of formoterol and tiotropium in patients with moderate to severe COPD. *Respiration*. 2006;73(4):414–419. doi:10.1159/000091996
- Bodzent-Lukaszuk A, Dymek A, McAulay K, Mansikka H. Fluticasone/formoterol combination therapy is as effective as fluticasone/salmeterol in the treatment of asthma, but has a more rapid onset of action: an open-label, randomized study. *BMC Pulm Med*. 2011;11:28. doi:10.1186/1471-2466-11-28
- Maltais F, Ferguson GT, Feldman GJ, et al. A randomized, double-blind, double-dummy study of glycopyrrolate/formoterol fumarate metered dose inhaler relative to umeclidinium/vilanterol dry powder inhaler in COPD. *Adv Ther*. 2019;36(9):2434–2449. doi:10.1007/s12325-019-01015-3
- Cazzola M, Ora J, Di Paolo A, Puxeddu E, Calzetta L, Rogliani P. Onset of action of budesonide/formoterol Spiromax[®] compared with budesonide/formoterol Turbuhaler[®] in patients with COPD. *Pulm Pharmacol Ther*. 2016;39:48–53. doi:10.1016/j.pupt.2016.06.006
- Palmqvist M, Persson G, Lazer L, Rosenborg J, Larsson P, Lotvall J. Inhaled dry-powder formoterol and salmeterol in asthmatic patients: onset of action, duration of effect and potency. *Eur Respir J*. 1997;10(11):2484–2489. doi:10.1183/09031936.97.10112489
- Richter K, Janicki S, Jorres RA, Magnussen H. Acute protection against exercise-induced bronchoconstriction by formoterol, salmeterol and terbutaline. *Eur Respir J*. 2002;19(5):865–871. doi:10.1183/09031936.02.00228502
- Cazzola M, Paggiaro P, Palange P, et al. Onset of action of formoterol versus salmeterol via dry powder inhalers in moderate chronic obstructive pulmonary disease: a randomized, placebo-controlled, double-blind, crossover study. *Clin Drug Investig*. 2012;32(3):147–155. doi:10.2165/11630880-000000000-00000
- Wedzicha JA, Singh D, Vestbo J, et al. Extrafine beclomethasone/formoterol in severe COPD patients with history of exacerbations. *Respir Med*. 2014;108(8):1153–1162. doi:10.1016/j.rmed.2014.05.013
- Kew KM, Mavergames C, Walters JA. Long-acting beta2-agonists for chronic obstructive pulmonary disease. *Cochrane Database Syst Rev*. 2013;(10):CD010177. doi:10.1002/14651858.CD010177.pub2
- Gross NJ, Donohue JF. Nebulized formoterol: a review of clinical efficacy and safety in COPD. *Int J Chron Obstruct Pulmon Dis*. 2010;5:223–232. doi:10.2147/COPD.S11006
- Tashkin DP, Rennard SI, Martin P, et al. Efficacy and safety of budesonide and formoterol in one pressurized metered-dose inhaler in patients with moderate to very severe chronic obstructive pulmonary disease: results of a 6-month randomized clinical trial. *Drugs*. 2008;68(14):1975–2000. doi:10.2165/00003495-200868140-00004

20. Rennard SI, Tashkin DP, McElhatten J, et al. Efficacy and tolerability of budesonide/formoterol in one hydrofluoroalkane pressurized metered-dose inhaler in patients with chronic obstructive pulmonary disease: results from a 1-year randomized controlled clinical trial. *Drugs*. 2009;69(5):549–565. doi:10.2165/00003495-200969050-00004
21. Ferguson GT, Tashkin DP, Skärby T, 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. *Respir Med*. 2017;132:31–41. doi:10.1016/j.rmed.2017.09.002
22. Ferguson GT, Papi A, Anzueto A, et al. Budesonide/formoterol MDI with co-suspension delivery technology in COPD: the TELOS study. *Eur Respir J*. 2018;52(3):1801334. doi:10.1183/13993003.01334-2018
23. Calverley PM, Kuna P, Monso E, et al. Beclomethasone/formoterol in the management of COPD: a randomised controlled trial. *Respir Med*. 2010;104(12):1858–1868. doi:10.1016/j.rmed.2010.09.008
24. Tashkin DP, Doherty DE, Kerwin E, et al. Efficacy and safety characteristics of mometasone furoate/formoterol fumarate fixed-dose combination in subjects with moderate to very severe COPD: findings from pooled analysis of two randomized, 52-week placebo-controlled trials. *Int J Chron Obstruct Pulmon Dis*. 2012;7:73–86. doi:10.2147/COPD.S29444
25. Vogelmeier C, Paggiaro PL, Dorca J, et al. Efficacy and safety of aclidinium/formoterol versus salmeterol/fluticasone: a Phase 3 COPD study. *Eur Respir J*. 2016;48(4):1030–1039. doi:10.1183/13993003.00216-2016
26. Ferguson GT, Rodriguez-Roisin R, Reisner C, Maes A, Siddiqui S, Martin UJ. Pharmacokinetics of glycopyrronium/formoterol fumarate dihydrate delivered via metered dose inhaler using co-suspension delivery technology in patients with moderate-to-very severe COPD. *Int J Chron Obstruct Pulmon Dis*. 2018;13:945–953. doi:10.2147/COPD.S154988
27. Reisner C, Fabbri LM, Kerwin EM, et al. A randomized, seven-day study to assess the efficacy and safety of a glycopyrrolate/formoterol fumarate fixed-dose combination metered dose inhaler using novel co-suspension delivery technology in patients with moderate-to-very severe chronic obstructive pulmonary disease. *Respir Res*. 2017;18(1):8. doi:10.1186/s12931-016-0491-8
28. Tashkin DP, Martinez FJ, Rodriguez-Roisin R, et al. A multicenter, randomized, double-blind dose-ranging study of glycopyrrolate/formoterol fumarate fixed-dose combination metered dose inhaler compared to the monocomponents and open-label tiotropium dry powder inhaler in patients with moderate-to-severe COPD. *Respir Med*. 2016;120:16–24. doi:10.1016/j.rmed.2016.09.012
29. Reisner C, Pearle J, Kerwin EM, Rose ES, Darken P. Efficacy and safety of four doses of glycopyrrolate/formoterol fumarate delivered via a metered dose inhaler compared with the monocomponents in patients with moderate-to-severe COPD. *Int J Chron Obstruct Pulmon Dis*. 2018;13:1965–1977. doi:10.2147/COPD.S166455
30. Martinez FJ, Rabe KF, Ferguson GT, et al. Efficacy and safety of glycopyrrolate/formoterol metered dose inhaler formulated using co-suspension delivery technology in patients with COPD. *Chest*. 2017;151(2):340–357. doi:10.1016/j.chest.2016.11.028
31. Hanania NA, Tashkin DP, Kerwin EM, 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. *Respir Med*. 2017;126:105–115. doi:10.1016/j.rmed.2017.03.015
32. Lipworth BJ, Collier DJ, Gon Y, et al. Improved lung function and patient-reported outcomes with co-suspension delivery technology glycopyrrolate/formoterol fumarate metered dose inhaler in COPD: a randomized phase III study conducted in Asia, Europe, and the USA. *Int J Chron Obstruct Pulmon Dis*. 2018;13:2969–2984. doi:10.2147/COPD.S171835
33. Martinez FJ, Rabe KF, Lipworth BJ, et al. Glycopyrrolate/formoterol fumarate metered dose inhaler improves lung function versus monotherapies in GOLD category a patients with COPD: pooled data from the phase III PINNACLE studies. *Int J Chron Obstruct Pulmon Dis*. 2020;15:99–106. doi:10.2147/COPD.S229794
34. D'Urzo AD, Rennard SI, Kerwin EM, et al. Efficacy and safety of fixed-dose combinations of aclidinium bromide/formoterol fumarate: the 24-week, randomized, placebo-controlled AUGMENT COPD study. *Respir Res*. 2014;15(1):123. doi:10.1186/s12931-014-0123-0
35. Singh D, Jones PW, Bateman ED, et al. Efficacy and safety of aclidinium bromide/formoterol fumarate fixed-dose combinations compared with individual components and placebo in patients with COPD (ACLIFORM-COPD): a multicentre, randomised study. *BMC Pulm Med*. 2014;14:178. doi:10.1186/1471-2466-14-178
36. Bateman ED, Chapman KR, Singh D, et al. Aclidinium bromide and formoterol fumarate as a fixed-dose combination in COPD: pooled analysis of symptoms and exacerbations from two six-month, multicentre, randomised studies (ACLIFORM and AUGMENT). *Respir Res*. 2015;16(1):92. doi:10.1186/s12931-015-0250-2
37. Miravittles M, Chapman KR, Chuecos F, Ribera A, Gil EG. The efficacy of aclidinium/formoterol on lung function and symptoms in patients with COPD categorized by symptom status: a pooled analysis. *Int J Chron Obstruct Pulmon Dis*. 2016;11:2041–2053. doi:10.2147/COPD.S114566
38. D'Urzo AD, Singh D, Donohue JF, et al. Efficacy of aclidinium/formoterol 400/12 µg, analyzed by airflow obstruction severity, age, sex, and exacerbation history: pooled analysis of ACLIFORM and AUGMENT. *Int J Chron Obstruct Pulmon Dis*. 2019;14:479–491. doi:10.2147/COPD.S185502
39. Sethi S, Kerwin E, Watz H, et al. AMPLIFY: a randomized, phase III study evaluating the efficacy and safety of aclidinium/formoterol vs monocomponents and tiotropium in patients with moderate-to-very severe symptomatic COPD. *Int J Chron Obstruct Pulmon Dis*. 2019;14:667–682. doi:10.2147/COPD.S189138
40. Singh D, Papi A, Corradi M, et al. Single inhaler triple therapy versus inhaled corticosteroid plus long-acting beta2-agonist therapy for chronic obstructive pulmonary disease (TRILOGY): a double-blind, parallel group, randomised controlled trial. *Lancet*. 2016;388(10048):963–973. doi:10.1016/S0140-6736(16)31354-X
41. Vestbo J, Papi A, Corradi M, et al. Single inhaler extrafine triple therapy versus long-acting muscarinic antagonist therapy for chronic obstructive pulmonary disease (TRINITY): a double-blind, parallel group, randomised controlled trial. *Lancet*. 2017;389(10082):1919–1929. doi:10.1016/S0140-6736(17)30188-5
42. Papi A, Vestbo J, Fabbri L, et al. Extrafine inhaled triple therapy versus dual bronchodilator therapy in chronic obstructive pulmonary disease (TRIBUTE): a double-blind, parallel group, randomised controlled trial. *Lancet*. 2018;391(10125):1076–1084. doi:10.1016/S0140-6736(18)30206-X
43. Ferguson GT, Reisner C, Pearle J, DePetrillo P, Maes A, Martin UJ. Cardiovascular safety profile of a fixed-dose combination of glycopyrrolate and formoterol fumarate delivered via metered dose inhaler using co-suspension delivery technology. *Pulm Pharmacol Ther*. 2018;49:67–74. doi:10.1016/j.pupt.2018.01.007
44. Rabe KF, Martinez FJ, Ferguson GT, et al. A phase III study of triple therapy with budesonide/glycopyrrolate/formoterol fumarate metered dose inhaler 320/18/9.6 µg and 160/18/9.6 µg using co-suspension delivery technology in moderate-to-very severe COPD: the ETHOS study protocol. *Respir Med*. 2019;158:59–66. doi:10.1016/j.rmed.2019.08.010
45. Rabe KF, Martinez FJ, Ferguson GT, et al. Triple inhaled therapy at two glucocorticoid doses in moderate-to-very-severe COPD. *N Engl J Med*. 2020;383(1):35–48. doi:10.1056/NEJMoa1916046

46. Andreas S, Bothner U, Trampisch M, Haensel M, Buhl R, Alter P. Effect of long-acting beta2-agonists olodaterol and formoterol on heart rate and blood pressure in chronic obstructive pulmonary disease patients. *Pulm Pharmacol Ther.* 2018;52:1–6. doi:10.1016/j.pupt.2018.08.002
47. Mann M, Chowdhury B, Sullivan E, Nicklas R, Anthracite R, Meyer RJ. Serious asthma exacerbations in asthmatics treated with high-dose formoterol. *Chest.* 2003;124(1):70–74. doi:10.1378/chest.124.1.70
48. SYMBICORT® (budesonide and formoterol fumarate dihydrate) [package insert]. Dunkerque, France: AstraZeneca Dunkerque Production; December 2017.
49. Tashkin DP, Strange C. Inhaled corticosteroids for chronic obstructive pulmonary disease: what is their role in therapy? *Int J Chron Obstruct Pulmon Dis.* 2018;13:2587–2601. doi:10.2147/COPD.S172240
50. Janson C, Larsson K, Lisspers KH, et al. Pneumonia and pneumonia related mortality in patients with COPD treated with fixed combinations of inhaled corticosteroid and long acting beta2 agonist: observational matched cohort study (PATHOS). *BMJ.* 2013;346:f3306. doi:10.1136/bmj.f3306
51. Ferguson GT, Rabe KF, Martinez FJ, et al. Triple therapy with budesonide/glycopyrrolate/formoterol fumarate with co-suspension delivery technology versus dual therapies in chronic obstructive pulmonary disease (KRONOS): a double-blind, parallel-group, multicentre, phase 3 randomised controlled trial. *Lancet Respir Med.* 2018;6(10):747–758. doi:10.1016/S2213-2600(18)30327-8
52. Kerwin EM, Ferguson GT, Mo M, DeAngelis K, Dorinsky P. Bone and ocular safety of budesonide/glycopyrrolate/formoterol fumarate metered dose inhaler in COPD: a 52-week randomized study. *Respir Res.* 2019;20(1):167. doi:10.1186/s12931-019-1126-7
53. Lotvall J. Pharmacology of bronchodilators used in the treatment of COPD. *Respir Med.* 2000;94(suppl E):S6–10. doi:10.1016/S0954-6111(00)90155-0
54. Zafar MA, Droege C, Foertsch M, Panos RJ. Update on ultra-long-acting beta agonists in chronic obstructive pulmonary disease. *Expert Opin Investig Drugs.* 2014;23(12):1687–1701. doi:10.1517/13543784.2014.942730
55. FORADIL AEROLIZER® (formoterol fumarate inhalation powder) [package insert]. Basle, Switzerland: Novartis Pharma AG; September 2012.
56. UTIBRON™ NEOHALER® (indacaterol and glycopyrrolate) [package insert]. Stein, Switzerland: Novartis Pharma Stein AG; October 2015.
57. STIOLTO® RESPIMAT® (tiotropium bromide and olodaterol inhalation spray) [package insert]. Ridgefield, CT: Boehringer Ingelheim Pharmaceuticals; August 2020.
58. SEREVENT DISKUS (salmeterol xinafoate inhalation powder) [package insert]. Research Triangle Park, NC: GlaxoSmithKline; January 2020.
59. BREO ELLIPTA (fluticasone furoate and vilanterol inhalation powder) [package insert]. Research Triangle Park, NC: GlaxoSmithKline; January 2019.

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