



# Fixed-Dose Combinations of Long-Acting Bronchodilators for the Management of COPD: Global and Asian Perspectives

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## ABSTRACT

Maintenance bronchodilator therapy with long-acting  $\beta$ -agonists (LABAs) and long-acting muscarinic antagonists (LAMAs) is the cornerstone treatment for patients with stable chronic obstructive pulmonary disease (COPD). Fixed-dose combinations (FDCs) of LABA/LAMA are recommended for the majority of symptomatic COPD patients by global guidelines; regional guidelines such as the Japanese and Korean

guidelines also provide similar recommendations for the use of LABA/LAMA FDCs. This review comprehensively describes the latest clinical evidence from key studies on the efficacy and safety of four approved LABA/LAMA fixed-dose combinations: indacaterol/glycopyrronium, vilanterol/umeclidinium, formoterol/aclidinium, and olodaterol/tiotropium. Additionally, in this review we describe the rationale behind the use of LABA/LAMA FDC therapy, key findings from the preclinical and clinical trial evaluation of respective LABA and LAMA monocomponents, and the efficacy and safety of LABA/LAMA FDCs. Special emphasis is placed on the clinical evidence for the monocomponents and LABA/LAMA FDCs from the Asian population. This detailed overview of the efficacy and safety of LABA/LAMA FDCs in global and Asian COPD patients is envisaged to provide a better understanding of the benefits of these therapies and to inform healthcare providers and patients on their appropriate use.

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## INTRODUCTION

### Burden of Chronic Obstructive Pulmonary Disease

Chronic obstructive pulmonary disease (COPD) is a chronic inflammatory disease of the airways characterized by persistent symptoms, progressive breathlessness, and poorly reversible airflow obstruction, which ultimately lead to impaired quality of life in these patients [1, 2]. Moreover, COPD exacerbations (acute worsening of the usual symptoms beyond normal day-to-day variation) impose a significant burden on patients due to increased morbidity and associated healthcare costs [3, 4]. COPD is currently the fourth leading cause of death worldwide; the global burden of COPD is indicated by a prevalence of 251 million cases of this disease [5]. In Asia, the estimated COPD prevalence was 6.2%, with 19.1% of patients having severe COPD [6]. The prevalence of COPD in Japan was reported to be 8.6% in a large epidemiological study [7]. In Korea, the prevalence of COPD was found to be 13.4% in a survey population aged 40 years or more [8]. Differences in COPD prevalence and clinical management exist between Asian and global populations: smoke from biomass fuels and industrial toxins are major risk factors, apart from tobacco smoke; rates of COPD-associated mortality and morbidity are higher in Asia; differences in overall healthcare management structure and cultural differences [6, 9].

### Management of Stable COPD

The Global Initiative for Chronic Obstructive Lung Disease (GOLD) strategy provides recommendations for COPD maintenance therapy based on COPD severity, symptoms assessment, and exacerbation history [1]. Long-acting bronchodilators (with a duration of action up to 24 h), such as long-acting muscarinic antagonists (LAMAs) and long-acting  $\beta_2$ -agonists (LABAs), are the cornerstone of maintenance therapy for patients with moderate-to-very-severe COPD [1, 10]. Addition of an inhaled corticosteroid (ICS) to long-acting bronchodilators is

considered for patients with frequent exacerbations and high blood eosinophil levels [1]. Several devices with distinct characteristics are available to deliver inhaled treatments to COPD patients: pressurized metered dose inhalers (pMDIs), dry powder inhalers (DPIs), soft mist inhalers (SMIs), and nebulizers [11].

### Place of Bronchodilators in Guideline-Recommended Pharmacological Treatment of COPD

Based on strong clinical evidence, the GOLD 2019 strategy recommends treatment with a LABA/LAMA combination for patients with stable COPD considering its superiority versus monotherapy or LABA/ICS, and its lower risk of pneumonia versus ICS-containing therapy [1]. Moreover, combination inhaler therapy is recommended as the first-line therapy for symptomatic patients with at least two COPD exacerbations or one exacerbation requiring hospitalization in the past year (GOLD group D) [1]. Patients without a significant exacerbation history but with persistent symptoms on monotherapy (LAMA or LABA alone) are also eligible for LABA/LAMA combination therapy (GOLD group B). Therefore, patients in groups B and D have potential for receiving LABA/LAMA combination therapy.

It is noteworthy that the global treatment guidelines for COPD do not recommend region-specific treatment options; thus, regional guidelines such as those in Japan and Korea draw substantially from the global guidelines for treatment recommendations [12, 13]. This review article provides an objective overview of the available inhaled LABA/LAMA fixed-dose combinations (FDCs) for the treatment of COPD with emphasis on the efficacy and safety of their monocomponents, particularly in the context of management of COPD patients from the Asian region. We envisage providing a foundation for informed decision-making by respiratory physicians that would allow appropriate selection of the optimal bronchodilation therapy with LABA/LAMA FDCs for COPD patients.

## Compliance with Ethics Guidelines

This article is based on previously conducted studies and does not contain any studies with human participants or animals performed by any of the authors.

## FIXED-DOSE COMBINATIONS OF LONG-ACTING BRONCHODILATORS FOR COPD

### Rationale for Use of LABA/LAMA FDC

LAMAs inhibit the action of acetylcholine at muscarinic receptors, while LABAs enhance cyclic adenosine monophosphate (cAMP) signaling through stimulation of  $\beta_2$ -adrenergic receptors [14]. Even though a LAMA or a LABA may have an excellent therapeutic profile, monotherapy is not always satisfactory for patients with more severe COPD [15]. Combination therapy has the potential for enhancing and prolonging the effects of monocomponents. Combining LABAs and LAMAs with different mechanisms may increase the degree of bronchodilation with little increase in the risk of side effects compared to increasing the dose of a single bronchodilator [1]. These drugs improve symptoms and quality of life by improving airflow and hence gaseous exchange, and by reversing air trapping and dynamic lung hyperinflation through dilatation of both

medium and small airways [16]. Furthermore, FDCs might improve adherence by decreasing the number of medications and/or the number of daily doses required with monotherapy, as well as by offering the opportunity to use a single inhaler [17]. Notably, because of the differences in mechanism of action, administering two bronchodilators may overcome patient-specific differences in treatment responses [1]. The combination of a LABA and a LAMA may compensate for differences in the sympathetic and parasympathetic activity throughout the day [18]. LABA/LAMA FDC may also provide enhanced bronchodilation over monocomponents by allowing for the differences in receptor distribution in the lungs; the  $M_3$  receptors are distributed primarily in the bronchus and are not present in the lung parenchyma, while the  $\beta_2$ -receptors are predominantly in the sub-segmental bronchus and lung parenchyma [19]. Moreover, safety of LABA/LAMA FDC and monotherapies is comparable [20]. LABA/LAMA FDCs currently approved as maintenance bronchodilator treatment of patients with COPD in Asia are listed in Table 1.

### Contribution of Individual Components of LABA/LAMA FDCs to Treatment Efficacy

#### LABAs

Inhaled LABAs stimulate the  $\beta$ -adrenergic receptors in the airway smooth muscle cells to

**Table 1** Approved fixed-dose combinations of LABAs and LAMAs for COPD treatment

LABA/LAMA	Device	Approved dose	Frequency of administration
Indacaterol/glycopyrronium	Breezhaler <sup>®</sup>	110/50 $\mu\text{g}^{\text{a}}$	Once daily
	Neohaler <sup>®</sup>	27.5/15.6 $\mu\text{g}^{\text{b}}$	Twice daily
Vilanterol/umeclidinium	Ellipta <sup>®</sup>	22/55 $\mu\text{g}^{\text{a}}$	Once daily
		25/62.5 $\mu\text{g}^{\text{c}}$	Once daily
Formoterol/acclidinium	Genuair <sup>®</sup>	12/340 $\mu\text{g}$	Twice daily
Olodaterol/tiotropium	Respimat <sup>®</sup>	2.5/2.5 $\mu\text{g}^{\text{d}}$	Once daily

<sup>a</sup> Approved dose in Europe and Asia

<sup>b</sup> Approved dose in the USA

<sup>c</sup> Approved dose in USA and Japan

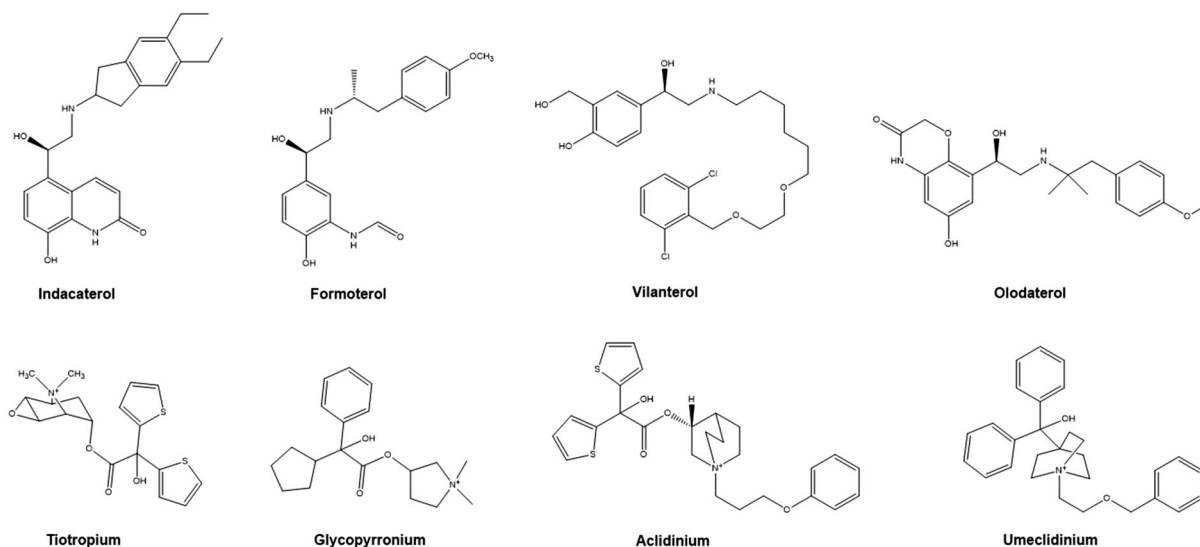
<sup>d</sup> Two puffs once daily

elicit bronchodilation; the method of inhaled delivery reduces side effects when compared to oral or intravenous treatment with  $\beta$ -agonists [21]. LABAs, like LAMAs, are recommended as first-line maintenance bronchodilator therapy in patients without history of exacerbation but with significant symptoms (GOLD group B) [1]. In general, LABAs have an acceptable safety profile, although there is still a debate on their cardiovascular safety [22, 23]. Key LABAs used for the treatment of COPD include formoterol, indacaterol, and olodaterol (Fig. 1). Pivotal global clinical studies on these LABAs and their key outcomes are listed in Table S1 (see supplementary material).

**Formoterol** Formoterol is a twice-daily LABA that produces a bronchodilator effect for up to 12 h with an onset of action of approximately 7 min upon inhalation. Formoterol exhibits a rapid onset of bronchodilation similar to that observed with salbutamol, yet its long bronchodilation duration is comparable to salmeterol. The approved dose range is between 12 and 24  $\mu\text{g}$  twice daily [24, 25]. Pharmacological characterization of formoterol demonstrated that clear effects were maintained for 12 h after inhalation; formoterol showed higher intrinsic

activity than salmeterol, which meant that it was a full  $\beta_2$ -agonist [26]. Formoterol has been shown to better reduce dynamic hyperinflation, which is responsible for exercise intolerance and dyspnea in COPD patients, compared with other bronchodilators, e.g., salmeterol and ipratropium [25]. Formoterol reduced exacerbations, increased days free of rescue medication use, and improved patients' quality of life and disease symptoms [25, 27]. Formoterol is generally considered to be well tolerated, and a low incidence of adverse events has been reported versus placebo across clinical studies [25].

**Indacaterol** Indacaterol is a once-daily LABA that has a fast onset of action (approximately 5 min) due to its rapid absorption. It was approved by the European Medicines Agency (EMA) in 2009 and by the US Food and Drug Administration (FDA) in 2011 for maintenance treatment of patients with COPD. Indacaterol is approved at once-daily doses of 150 and 300  $\mu\text{g}$  in Europe and in Korea, at 75  $\mu\text{g}$  once daily in the USA, and at 150  $\mu\text{g}$  once daily in Japan [28, 29]. In vitro and in vivo assessments showed that indacaterol had a superior duration of action compatible with once-daily dosing in



**Fig. 1** Major inhaled LABAs and LAMAs used in FDCs. FDC fixed-dose combination, LABAs long-acting  $\beta_2$ -agonists, LAMAs long-acting muscarinic antagonists

humans, together with a fast onset of action and an improved cardiovascular safety profile over other LABAs [30]. In phase III studies, indacaterol showed sustained 24-h bronchodilation and significantly greater efficacy in terms of lung function, symptom control, and quality of life compared with placebo, and comparable or superior efficacy compared with twice-daily LABAs and/or tiotropium with good safety profile [31–35]. In a network meta-analysis, indacaterol 300 µg, followed by 150 and 75 µg, was the most effective LABA monotherapy for moderate-to-severe COPD [36].

**Vilanterol** Vilanterol is not available as a single agent and is approved for use in COPD only in an FDC with umeclidinium.

**Olodaterol** Olodaterol is a LABA with bronchodilator effect up to 24 h. The approved dose is 5 µg once daily (EU and USA; not approved in Korea and Japan) [37]. In vitro pharmacological characterization showed that olodaterol had a potent, nearly full agonistic response for  $\beta_2$ -receptors; in vivo, olodaterol provided bronchoprotection over 24 h; further, olodaterol showed a rapid onset of action comparable with that of formoterol [38]. In similar randomized clinical trial conditions, olodaterol and indacaterol have been shown to have similar efficacy in COPD patients [39]. Long-term safety data in patients with moderate-to-severe COPD showed that olodaterol had a good safety profile, comparable with formoterol [40].

### LAMAs

LAMAs cause relaxation of airway smooth muscles by blocking acetylcholine activity at the receptor in the large and small airways, glandular and epithelial cells, as well as various other cells of the lung [16, 41]. LAMAs are recommended as first-line maintenance bronchodilator therapy in patients with stable COPD without significant symptoms but who have a high risk of exacerbations (GOLD group C) and those without a history of exacerbation but with significant symptoms (GOLD group B) [1]. Four LAMAs are approved for use in the treatment of COPD: tiotropium bromide, aclidinium bromide, glycopyrronium bromide, and

umeclidinium bromide (Fig. 1). Pivotal clinical studies on these LAMAs and their key outcomes are listed in Table S2 (see supplementary material).

**Tiotropium** Tiotropium was the first once-daily LAMA approved for COPD [42]. Preclinical evaluation of tiotropium compared with other LAMAs showed that tiotropium had high affinity and potency toward the human muscarinic  $M_3$  receptor, comparable with glycopyrronium and aclidinium, but a significantly longer dissociation half-life [43]. Tiotropium inhibited remodeling of the airways as well as pulmonary inflammation in a guinea pig model of COPD [44]. Also in a guinea pig model, treatment with inhaled tiotropium considerably inhibited the increase in airway smooth muscle mass, myosin expression, and contractility [45]. Tiotropium was significantly more effective than short-acting muscarinic antagonist ipratropium 40 µg four-times daily in improving FEV<sub>1</sub>, and generally improved lung function to a significantly greater extent than salmeterol in patients with COPD [46, 47]. The long-term efficacy (improvements in lung function, quality of life, and exacerbations) and safety of tiotropium have been demonstrated in the Understanding Potential Long-Term Impacts on Function with Tiotropium (UPLIFT) study and a subsequent subgroup analysis of this study [48–50]. The 1-year Prevention of Exacerbations with Tiotropium in COPD (POET-COPD) study showed that tiotropium was more effective than salmeterol in preventing exacerbations in patients with moderate-to-very-severe COPD [51]. In the indacaterol: providing opportunity to re-engage patients with life (INVIGORATE) study in exacerbating patients with severe COPD, indacaterol and tiotropium provided clinically relevant improvements in lung function with comparable safety profiles, while tiotropium afforded greater protection from exacerbations compared to indacaterol [52]. In the TIOtiotropium Safety and Performance In Respimat<sup>®</sup> (TIOSPIR) study, assessment of tiotropium delivered via two different devices (HandiHaler<sup>®</sup> and Respimat<sup>®</sup>) showed that tiotropium Respimat<sup>®</sup> 5 µg or 2.5 µg had a safety profile and exacerbation efficacy similar to that

of tiotropium HandiHaler® 18 µg in patients with COPD [53]. In comparing the relative clinical effects of tiotropium alone versus LABAs (salmeterol, formoterol, and indacaterol) alone, in randomized studies, it was shown that fewer patients with COPD experienced one or more exacerbations with tiotropium than with LABAs, with no statistical difference in mortality observed between the treatment groups. There was no statistically significant difference in FEV<sub>1</sub> or symptom score between tiotropium and LABAs, but there was a lower rate of non-fatal serious adverse events recorded with tiotropium compared with LABAs and a lower rate of study withdrawals [54].

**Acclidinium** Acclidinium bromide is a twice-daily LAMA approved for use in the treatment of COPD in Europe, the USA, and Japan, at 400 µg twice daily [55]. A pharmacological assessment of the onset of action of acclidinium versus tiotropium in patients with COPD and human isolated bronchi showed that bronchodilation induced by acclidinium was faster than that induced by tiotropium [56]; other in vivo and in vitro analyses showed that acclidinium and glycopyrronium were both potent antagonists at muscarinic receptors with similar kinetic selectivity for M<sub>3</sub> receptors versus M<sub>2</sub> [57]. Four phase III clinical trials demonstrated benefits of acclidinium on the overall lung function and health status of patients with COPD, with a tolerability profile comparable with placebo [58]. Acclidinium showed similar effect on reducing exacerbations compared with tiotropium [59].

**Glycopyrronium** Glycopyrronium bromide has a rapid onset (5 min) and 24-h duration of action. The recommended dose is 50 µg once daily; in the USA, the approved dose is 12.5 µg twice daily [60]. Pharmacological characterization of glycopyrronium showed that it had a more rapid onset of action (3–4.8 times) versus tiotropium; glycopyrronium also had greater equilibrium binding and kinetic selectivity for M<sub>3</sub> versus M<sub>2</sub> receptors [61]. In assessment of lung muscarinic receptor binding, the effect of glycopyrronium lasted for 24 h, with little influence on the muscarinic receptors in the

bladder and submaxillary gland [62]. The Symptoms and Pulmonary function in the moRnING (SPRING) study, which assessed the rapid onset bronchodilator profiles of LAMAs, demonstrated superiority of glycopyrronium versus tiotropium in terms of superior bronchodilation in the first 4 h after administration [63]. The FAST study characterized the earlier onset of action associated with glycopyrronium; it was superior to tiotropium in terms of early bronchodilation. Both glycopyrronium and tiotropium showed similar improvements in static lung volume parameters; glycopyrronium reduced specific airway resistance faster than tiotropium [64]. In clinical studies of 6–12 months' duration in patients with moderate-to-severe COPD, glycopyrronium improved lung function, reduced breathlessness, improved symptoms, and reduced moderate-to-severe exacerbations to a similar extent as tiotropium [65]. Glycopyrronium also produced immediate and significant improvement in exercise tolerance and had a similar safety profile to tiotropium [66]. Pooled data from clinical studies in over 4000 patients with COPD showed that the overall safety profile of glycopyrronium was similar to placebo and tiotropium [67].

**Umeclidinium** Umeclidinium bromide is delivered once daily; the FDA and EMA approved dose is 62.5 µg [68]. Pharmacological assessment of umeclidinium showed competitive antagonism of muscarinic cholinergic receptors. Umeclidinium dose-dependently blocked acetylcholine-induced bronchoconstriction with a long duration of action, and was comparable to tiotropium; umeclidinium 2.5 µg offered 50% bronchoprotection for more than 24 h. This pharmacological profile translated into 24-h duration of bronchodilation in vivo [69]. There is a clinically meaningful increase in FEV<sub>1</sub> at the current approved dose of umeclidinium. Results generated by pivotal trials indicate comparable effectiveness between umeclidinium and tiotropium [70, 71]. Umeclidinium 62.5 µg demonstrated superior efficacy to tiotropium 18 µg for improvement in trough FEV<sub>1</sub> after 12 weeks with a similar safety profile [72]. A pooled meta-analysis of phase III

studies showed that umeclidinium had safety similar to placebo; there were no significant differences between umeclidinium and tiotropium [73].

### **Efficacy and Safety of LABA/LAMA FDC Bronchodilators in COPD**

Once-daily LABA/LAMA combinations (indacaterol plus glycopyrronium, vilanterol plus umeclidinium bromide, and olodaterol plus tiotropium bromide) and a twice-daily combination (aclidinium plus formoterol) have been developed or are in clinical development. A systematic review of the efficacy and safety of LABA/LAMA FDCs identified randomized placebo-controlled studies of at least 3 months; all LABA/LAMA combinations improved lung function, transition dyspnea index (TDI), and St. George's Respiratory Questionnaire (SGRQ) scores compared with monocomponents [74]. Indirect comparisons found no significant differences between LABA/LAMA combinations in terms of greater efficacy for trough FEV<sub>1</sub>, TDI, and SGRQ scores versus a LAMA or LABA/ICS [74]. The major clinical studies on the LABA/LAMA FDCs are listed in Table 2.

#### ***Indacaterol/Glycopyrronium***

Indacaterol/glycopyrronium contains indacaterol 110 µg and glycopyrronium 50 µg taken once daily via a DPI device, Breezhaler® or twice-daily (27.5/15.6 µg) via the Neohaler® (USA) [75]. The efficacy of indacaterol/glycopyrronium has been reported in a series of phase III clinical trials under the large IGNITE (indacaterol and glycopyrronium bromide clinical studies) program [76]. Once-daily indacaterol/glycopyrronium demonstrated superior and clinically meaningful efficacy outcomes versus placebo and superiority versus treatment with a single bronchodilator (indacaterol, glycopyrronium, or open-label tiotropium), with a safety and tolerability profile similar to placebo [77]. Indacaterol/glycopyrronium was superior in preventing moderate-to-severe COPD exacerbations compared with glycopyrronium [78]. Indacaterol/glycopyrronium provided superior improvements in patient-reported dyspnea and

lung function versus placebo and tiotropium [79]. In patients with moderate-to-severe COPD, indacaterol/glycopyrronium improved exercise endurance time versus placebo but did not show numerical and statistically significant difference versus blinded tiotropium, while indacaterol/glycopyrronium significantly improved lung hyperinflation versus both placebo and tiotropium [80]. The EXPEDITION program showed that indacaterol/glycopyrronium 27.5/12.5 µg twice daily elicited a significant improvement in lung function and patient-reported outcomes, COPD exacerbations, and quality of life when compared with monocomponents and placebo [81]. Once-daily indacaterol/glycopyrronium provided significant, sustained, and clinically meaningful improvements in lung function and dyspnea versus twice-daily salmeterol/fluticasone on non-exacerbating COPD patients [82]. The landmark effect of indacaterol glycopyrronium vs. fluticasone salmeterol on COPD exacerbations (FLAME) study demonstrated the superiority of once-daily indacaterol/glycopyrronium 110/50 µg over twice-daily salmeterol/fluticasone 50/500 µg (a LABA/ICS) in reducing the rate of COPD exacerbations with reduced risk of pneumonia in exacerbating patients with moderate-to-very-severe COPD [83]. In a prospective analysis of the FLAME study, indacaterol/glycopyrronium provided superior or similar benefits over salmeterol/fluticasone independent of blood eosinophil levels [84]. It should be noted that FLAME excluded patients with a high blood eosinophil count (greater than 600 cells/µL) and any history of asthma [83]. A systematic review reported that indacaterol/glycopyrronium had clinically significant effects on symptoms, including dyspnea and health status, lung function, and rate of moderate or severe exacerbations compared to monotherapies in patients with moderate-to-very-severe COPD [85]. Indacaterol/glycopyrronium has been shown to be well tolerated generally, with most adverse events being of mild-to-moderate severity [86].

#### ***Vilanterol/Umeclidinium***

Vilanterol/umeclidinium was the first fixed LABA/LAMA combination to get approval by

**Table 2** Key studies on major LABA/LAMA fixed-dose combinations in patients with COPD

Study	Comparators	Key objectives/endpoints	Key efficacy outcomes
Indacaterol/glycopyrronium			
Bateman et al. (SHINE) [77]	Indacaterol 150 µg, glycopyrronium 50 µg, OL-tiotropium 18 µg or placebo	Trough FEV <sub>1</sub> at week 26	IND/GLY demonstrated superior and clinically meaningful outcomes versus placebo and superiority versus mono-bronchodilators
Wedzicha et al. (SPARK) [78]	Glycopyrronium 50 µg, or OL-tiotropium 18 µg	Rate of moderate-to-severe COPD exacerbations	IND/GLY significantly reduced the rate of moderate-to-severe exacerbations versus glycopyrronium; this effect was not statistically significant versus tiotropium
Mahler et al. (BLAZE) [79]	Placebo or tiotropium 18 µg	Improvement in dyspnea	IND/GLY provided superior improvements in patient-reported dyspnea and lung function versus placebo and tiotropium
Beeh et al. (BRIGHT) [80]	Placebo or tiotropium 18 µg	Exercise endurance time at day 21	IND/GLY significantly improved exercise endurance time compared with placebo
Mahler et al. (FLIGHT1 and FLIGHT2) [81]	Indacaterol 27.5 µg bid glycopyrrolate 15.6 µg bid or placebo	Standardized AUC from 0–12 h for FEV <sub>1</sub> at week 12	IND/GLY was statistically superior in terms of FEV <sub>1</sub> AUC <sub>0–12h</sub> compared with its monocomponents
Vogelmeier et al. (ILLUMINATE) [82]	SFC 50/500 µg bid	FEV <sub>1</sub> AUC <sub>0–12h</sub> after 26 weeks	IND/GLY provided significant, sustained, and clinically meaningful improvements in lung function versus twice-daily SFC
Wedzicha et al. (FLAME) [83]	SFC 50/500 µg bid	Annual rate of all COPD exacerbations	IND/GLY was more effective than SFC in preventing COPD exacerbations in patients with a history of 1 or more exacerbations during the previous year
Vilanterol/umeclidinium			
Donohue et al. [88]	Umeclidinium 62.5 µg, vilanterol 25 µg, or placebo	Trough FEV <sub>1</sub> on day 169	Vilanterol/umeclidinium 25/62.5 µg provided numerical improvements in lung function and symptoms in patients with COPD compared with monocomponents



**Table 2** continued

Study	Comparators	Key objectives/endpoints	Key efficacy outcomes
Donohue et al. [89]	Umeclidinium 125 µg or placebo	Adverse events, clinical chemistry and hematology parameters, vital signs, 12-lead, and 24-h Holter electrocardiograms	Vilanterol/umeclidinium 25/125 µg and umeclidinium 125 µg were well tolerated over 12 months
Formoterol/acclidinium			
Singh et al. (ACLIFORM) [94]	Acclidinium 400 µg, formoterol 12 µg, or placebo	1-h post-dose FEV <sub>1</sub> and trough FEV <sub>1</sub> at week 24	Formoterol/acclidinium 12/400 µg and 6/400 µg significantly improved 1-h post-dose FEV <sub>1</sub> versus placebo and monotherapy. Improvements in trough FEV <sub>1</sub> were significantly greater against formoterol and numerically greater versus acclidinium
D'Urzo et al. (AUGMENT) [95]	Acclidinium 400 µg, formoterol 12 µg, or placebo	1-h morning post-dose FEV <sub>1</sub> and morning pre-dose (trough) FEV <sub>1</sub> at week 24	Formoterol/acclidinium significantly improved 1-h post-dose FEV <sub>1</sub> versus acclidinium. Improvements in trough FEV <sub>1</sub> were significantly greater against formoterol and numerically greater versus acclidinium
Olodaterol/tiotropium			
Buhl et al. (TONADO 1 and TONADO 2) [99]	Tiotropium 2.5 µg or 5 µg, or olodaterol 5 µg	FEV <sub>1</sub> AUC <sub>0–3</sub> response, trough FEV <sub>1</sub> response, and SGRQ total score at 24 weeks	Significant improvements in lung function and health-related quality of life with once-daily olodaterol/tiotropium versus monocomponents over 1 year
O'Donnell et al. (MORACTO 1 and MORACTO 2) [101]	Tiotropium 5 µg or olodaterol 5 µg, or placebo	Inspiratory capacity prior to exercise and exercise endurance time during constant work-rate cycle ergometry to symptom limitation at 75% of peak incremental work rate after 6 weeks (2 h post-dose)	Significant improvements in inspiratory capacity versus placebo and monotherapies, and significant improvements in exercise endurance time versus placebo
Buhl et al. (TONADO 1 and TONADO 2) [102]	Tiotropium 2.5 µg or 5 µg, or olodaterol 5 µg	Adverse events, electrocardiogram, and laboratory data	Olodaterol/tiotropium 5/5 and 5/2.5 µg were well tolerated

**Table 2** continued

Study	Comparators	Key objectives/endpoints	Key efficacy outcomes
Calverley et al. (DYNAGITO) [103]	Tiotropium 5 µg	Rate of moderate and severe COPD exacerbations	Rate of moderate and severe exacerbations was lower but not statistically significant with olodaterol/tiotropium than tiotropium

*AUC* area under the curve, *bid* twice daily, *COPD* chronic obstructive pulmonary disease, *FEV<sub>1</sub>* forced expiratory volume in 1 s, *FLAME* Effect of Indacaterol Glycopyrronium vs. Fluticasone Salmeterol on COPD Exacerbations, *FVC* forced vital capacity, *HR* heart rate, *IND/GLY* indacaterol/glycopyrronium, *LABA* long-acting β<sub>2</sub>-agonist, *LAMA* long-acting muscarinic antagonist, *OL* open label, *SFC* salmeterol/fluticasone, *SGRQ* St. George's Respiratory Questionnaire *TDI* transition dyspnea index

the FDA. It is approved in Europe at 22/55 µg once daily, in the USA and Japan at 25/62.5 µg once daily, administered via the DPI Ellipta<sup>®</sup> [87]. When compared with monocomponents, vilanterol/umeclidinium 25/62.5 µg provided greater improvements in FEV<sub>1</sub> and FVC but improvements in dyspnea and quality of life were similar in all active treatment groups [88]. Treatment with vilanterol/umeclidinium resulted in a lower risk of COPD exacerbations versus placebo [89]. A systematic review, which included studies of 12- to 52-week duration, compared vilanterol/umeclidinium with monocomponents or salmeterol/fluticasone in patients with moderate-to-severe COPD. Statistically significant differences were found in trough FEV<sub>1</sub> compared with the comparators. Compared with umeclidinium or vilanterol, there were a greater likelihood of patients experiencing a minimal clinically important difference (MCID) in TDI and statistically significant reductions in the risk of COPD exacerbations [90]. Vilanterol/umeclidinium generally showed favorable effects on lung function, quality of life, dyspnea, rescue medication use, and exercise capacity, with no clinically meaningful treatment-related changes in vital signs or clinical laboratory parameters when compared with either placebo or monocomponents [91]. In a 12-week study, vilanterol/umeclidinium 25/62.5 µg showed significantly greater improvements in lung function versus salmeterol/fluticasone 50/500 µg. Both treatments

produced clinically meaningful improvements in TDI and SGRQ scores, but there was no statistical difference between the two treatment arms [92].

#### **Formoterol/Aclidinium**

This twice-daily FDC is administered using Genuair<sup>®</sup>, a multiple-dose DPI [93]. Most published data on formoterol/aclidinium is from two 24-week randomized, placebo-controlled studies, AUGMENT and ACLIFORM. Formoterol/aclidinium at doses of 12/400 µg and 6/400 µg was compared with its monocomponents and placebo [94, 95]. The 1-h post-dose FEV<sub>1</sub>, but not trough FEV<sub>1</sub>, was significantly higher with both FDC doses compared with acclidinium in both studies. In AUGMENT, the higher FDC dose significantly improved trough FEV<sub>1</sub> compared with formoterol but there was no significant difference for the lower dose. A greater effect for the higher FDC on trough FEV<sub>1</sub> was also observed in ACLIFORM, indicating that the higher FDC is superior to the monocomponents and the lower FDC dose [94, 95]. The above studies showed a decrease in symptoms and exacerbations versus placebo in the groups treated with formoterol/aclidinium and its good safety profile [96]. In a 24-week study in patients with moderate-to-severe COPD, formoterol/aclidinium produced statistically significant increases in peak FEV<sub>1</sub> compared with salmeterol/fluticasone and similar changes in symptom control and risk of exacerbations; however,

**Table 3** Key clinical studies on major LABAs, LAMAs, and LABA/LAMA fixed-dose combinations in Asian patients with COPD

Study	Comparators	Key objectives/endpoints	Key efficacy outcomes
LABAs			
Formoterol			
Bogdan et al. [104]	Placebo	Change (ratio) from baseline to treatment period in FEV <sub>1</sub> 60 min post-dose	Formoterol 4.5 µg and 9 µg bid was effective and well tolerated in patients with COPD; there was no difference between formoterol doses for the primary endpoint in Japanese and European COPD patients
Minakata et al. [105]	Placebo	1-h post-dose FEV <sub>1</sub> on the last day of the 1-week treatment period	Treatment with formoterol 4.5, 9, and 18 µg bid showed significantly superior effects to placebo on FEV <sub>1</sub> in Japanese patients COPD patients
Indacaterol			
Hosoe et al. [106]	Placebo	24-h post-dose (trough) FEV <sub>1</sub> , pharmacokinetics, and safety	Indacaterol provided 24-h bronchodilation with a fast onset of action and similar pharmacokinetic and safety profiles in Caucasian and Japanese patients
Kato et al. [107]	Placebo	Standardized FEV <sub>1</sub> AUC <sub>(22–24h)</sub>	In the Japanese COPD patients, single doses of indacaterol (150, 300, and 600 µg) provided sustained 24-h bronchodilation, with onset of action within 5 min post-dose
Kinoshita et al. [109]	Placebo	Trough FEV <sub>1</sub> , health status (SGRQ), and TDI at week 12	Indacaterol 150 µg and 300 µg provided clinically meaningful and significant bronchodilation and improvements in dyspnea and health status versus placebo in Asian COPD patients

**Table 3** continued

Study	Comparators	Key objectives/endpoints	Key efficacy outcomes
Kim et al. [111]	Placebo	Trough FEV <sub>1</sub> at week 8	Indacaterol 150 µg showed significantly superior bronchodilation, significant improvement in breathlessness, and improved health status with comparable safety versus placebo in Korean COPD patients with destroyed lung by tuberculosis and moderate-to-severe airflow limitation
To et al. [112]	Placebo	Trough FEV <sub>1</sub> (average of 23 h 10 min and 23 h 45 min post-dose values) at week 12	Indacaterol demonstrated clinically relevant improvements versus placebo in lung function, dyspnea, and health status in Asian COPD patients irrespective of disease severity
Olodaterol			
Ichinose et al. [113]	Placebo	Trough FEV <sub>1</sub> after 4 weeks	Olodaterol 2 µg, 5 µg, and 10 µg showed statistically significant improvements in trough FEV <sub>1</sub> versus placebo
LAMAs			
Tiotropium			
Ichinose et al. [115]	Placebo	Peak, trough, and average FEV <sub>1</sub>	In Japanese patients with COPD, tiotropium Respimat 5 µg and tiotropium HandiHaler® 18 µg showed a similar profile of efficacy, safety, and pharmacokinetics
Zhong et al. (TIOSPIR®) [116]	Placebo	Time to death and time to first COPD exacerbation	Tiotropium Respimat 5 µg and HandiHaler® 18 µg showed similar safety and exacerbation efficacy profiles in patients with COPD from Asia. Asian patients had lower risk of, and fewer, exacerbations overall, but a higher proportion of severe exacerbations than those in the rest of the world

**Table 3** continued

Study	Comparators	Key objectives/endpoints	Key efficacy outcomes
Tang et al. [117]	Placebo	Trough FEV <sub>1</sub> and the time to first exacerbation	Tiotropium significantly improved lung function and quality of life, delayed the time to first exacerbation, and reduced the number of exacerbations in Chinese patients with COPD
Zhou et al. [118]	Placebo	Between-group difference in the change from baseline in FEV <sub>1</sub> before bronchodilator use at week 24	Tiotropium 18 µg provided higher FEV <sub>1</sub> than placebo at 24 months and mitigated the annual decline in the FEV <sub>1</sub> after bronchodilator use in COPD patients of GOLD stage 1 or 2
Aclidinium			
Lee et al. [119]	Placebo	Change in trough FEV <sub>1</sub> at 12 weeks	In Korean patients with COPD, significant improvement in trough FEV <sub>1</sub> from baseline was shown with aclidinium versus placebo
Glycopyrronium			
Sekiya et al. (GLOW4) [120]	OL-tiotropium 18 µg	Safety and tolerability	Similar overall incidence of adverse events between glycopyrronium and tiotropium
Fukushima et al. [121]	Placebo	Change from baseline in morning pre-dose trough FEV <sub>1</sub>	Glycopyrronium 14.4 µg was the most appropriate dose for use in phase III studies in Japanese patients with moderate-to-severe COPD
Wang et al. (GLOW7) [122]	Placebo	Trough FEV <sub>1</sub> at week 12	Glycopyrronium 50 µg significantly improved lung function, dyspnea, and health status compared with placebo
Umeclidinium			
Yamagata et al. [123]	NA (single-arm study)	Incidence and severity of all AEs throughout the 52-week treatment period	Umeclidinium 125 µg was well tolerated over 52 weeks of treatment in Japanese patients with COPD

**Table 3** continued

Study	Comparators	Key objectives/endpoints	Key efficacy outcomes
LABA/LAMA FDCs			
Indacaterol/glycopyrronium			
Zhong et al. (LANTERN) [124]	SFC 50/500 µg bid	Non-inferiority of IND/GLY versus SFC for trough FEV <sub>1</sub> at week 26	Statistically significant superiority of IND/GLY to SFC for trough FEV <sub>1</sub> and FEV <sub>1</sub> AUC <sub>0–4h</sub> at week 26
Zhong et al. [125]	SFC 50/500 µg bid	Non-inferiority of IND/GLY versus SFC in terms of trough FEV <sub>1</sub> at week 26	IND/GLY showed superiority over SFC with a statistically significant and clinically meaningful improvement in trough FEV <sub>1</sub> in Chinese patients with COPD
Hashimoto et al. [126]	Glycopyrronium 50 µg, indacaterol 150 µg, OL-tiotropium 18 µg od, or placebo	Trough FEV <sub>1</sub> at week 26	IND/GLY demonstrated superior efficacy and comparable safety compared with its monocomponents, open-label tiotropium, and placebo
Asai et al. (SHINE and ARISE pooled) [127]	Tiotropium 18 µg od	Pre-dose FEV <sub>1</sub> at week 12 and week 24/26 (ARISE/SHINE) and FEV <sub>1</sub> at 30 min and 60 min post-dose at day 1, week 12, and week 24/26	Compared to tiotropium, IND/GLY provided significant improvements in lung function, health status, and rescue medication use, while having a good safety profile in Japanese patients with moderate-to-severe COPD
Wedzicha et al. (FLAME subgroup) [130]	SFC 50/500 µg bid	Annualized rate of COPD exacerbations	IND/GLY significantly reduced the rate of moderate/severe exacerbations and prolonged time to first moderate/severe exacerbation versus SFC
Vilanterol/umeclidinium			
Zheng et al. [131]	Placebo	Trough FEV <sub>1</sub> on day 169	In Asian patients with COPD, once-daily VI/UMEC 25/125 µg and VI/UMEC 25/62.5 µg resulted in clinically meaningful and statistically significant improvements in lung function versus placebo

**Table 3** continued

Study	Comparators	Key objectives/endpoints	Key efficacy outcomes
Olodaterol/tiotropium			
Ichinose et al. [132]	Olodaterol 5 µg od	Long-term safety over 1 year	No safety concerns for long-term OLO/TIO 5/5 and 2.5/5 µg were identified in Japanese patients with COPD
Ichinose et al. (TONADO®) [133]	Tiotropium 2.5 or 5 µg od, or olodaterol 5 µg od	Trough FEV <sub>1</sub> at week 24	OLO/TIO 5/5 µg was superior to each monotherapy for lung function and SGRQ in the Japanese subpopulation of patients with COPD
Bai et al. [134]	Tiotropium 2.5 or 5 µg od, or olodaterol 5 µg od	Trough FEV <sub>1</sub> at week 24 (in East Asian and global populations from the TONADO® trials)	The East Asian population showed slightly greater trough FEV <sub>1</sub> treatment differences between OLO/TIO 5/5 µg and tiotropium compared to the overall population
Ichinose et al. (VESUTO®) [135]	Tiotropium 5 µg od	IC at rest measured at 60 min post-dose after 6 weeks of treatment	OLO/TIO significantly increased IC compared with tiotropium after 6 weeks of treatment
Ichinose et al. (DYNAGITO®) [136]	Tiotropium 5 µg od	Rate of moderate and severe COPD exacerbations	Rate of moderate and severe exacerbations was lower with olodaterol/tiotropium than tiotropium

*AUC* area under the curve, *bid* twice daily, *COPD* chronic obstructive pulmonary disease, *FEV<sub>1</sub>* forced expiratory volume in 1 s, *IC* inspiratory capacity, *IND/GLY* indacaterol/glycopyrronium, *NA* not applicable, *od* once daily, *OL* open label, *OLO/TIO* olodaterol/tiotropium, *SFC* salmeterol/fluticasone, *SGRQ* St. George's respiratory questionnaire, *TDI* transition dyspnea index, *VI/UMEC* vilanterol/umeclidinium

there were no significant differences in trough FEV<sub>1</sub> between the formoterol/acclidinium and salmeterol/fluticasone [97].

### **Olodaterol/Tiotropium**

Olodaterol/tiotropium is the most recently approved LABA/LAMA. It is delivered once daily via the RespiMat® SMI [98]. In a combined analysis of two 52-week replicate studies (TONADO 1 and 2), two doses of olodaterol/tiotropium (5/5 µg or 5/2.5 µg) were compared with its monocomponents in patients with moderate-to-

very-severe COPD. Both doses significantly improved lung function, dyspnea, reduced the risk of moderate-to-severe exacerbations, and improved quality of life over monocomponents [99]. A Cochrane review of olodaterol/tiotropium compared with monotherapy found that the FDC resulted in a small improvement in SGRQ score compared with tiotropium monotherapy. Statistically significant effects were also seen on FEV<sub>1</sub> but not on hospital admissions or mortality [100]. In two replicate 6-week, incomplete-crossover studies in patients

with moderate-to-severe COPD (MORACTO 1 and 2), olodaterol/tiotropium improved dyspnea and exercise tolerance versus placebo but not consistently versus monotherapies [101]. Olodaterol/tiotropium has been shown to have similar safety compared to monocomponents [102]. In the recently completed DYNAGITO study, a reduction in rate of moderate to severe exacerbations was observed with olodaterol/tiotropium 5/5  $\mu\text{g}$  versus tiotropium, but this did not meet the targeted level of statistical significance [103].

### **Efficacy of LABAs, LAMAs, and LABA/LAMA FDCs in Asian Patients with COPD**

Several de novo clinical studies as well as post hoc and subgroup analyses of key clinical studies have explored the efficacy of long-acting bronchodilators in Asian populations (Table 3).

#### **LABAs**

Formoterol 4.5  $\mu\text{g}$  and 9  $\mu\text{g}$  twice daily were effective and well tolerated in patients with COPD; both formoterol doses similarly improved lung function in Japanese and European COPD patients [104]. In Japanese patients with COPD, twice-daily formoterol 4.5  $\mu\text{g}$ , 9  $\mu\text{g}$ , and 18  $\mu\text{g}$  showed significantly superior effects to placebo on FEV<sub>1</sub> [105]. Indacaterol provided 24-h bronchodilation with a fast onset of action and similar pharmacokinetic and safety profiles in Caucasian and Japanese COPD patients [106]; similar findings were observed in another study in exclusively Japanese patients [107]. In a predominantly Chinese population, indacaterol provided significant improvements in breathlessness and health status [108]; additionally, indacaterol provided clinically significant bronchodilation and improvements in dyspnea and health status in Asian COPD patients, including Japanese patients [109]. In a large real-life observational study in South Korea, indacaterol was shown to be well tolerated in COPD patients [110]. In a phase III study, indacaterol provided significantly superior bronchodilation, significant improvement in breathlessness, and improved health status versus placebo in Korean COPD patients with

destroyed lung by tuberculosis [111]. Indacaterol demonstrated clinically relevant improvements versus placebo in lung function, dyspnea, and health status in Asian COPD patients irrespective of disease severity [112]. Once-daily olodaterol showed statistically significant increase in trough FEV<sub>1</sub> compared to placebo, demonstrated 24-h bronchodilator efficacy, and was well tolerated in Japanese patients with COPD [113].

#### **LAMAs**

In the subgroup analysis of COPD patients from Asia included in the UPLIFT study, tiotropium improved lung function, improved health-related quality of life, and reduced exacerbations over 4 years of treatment [114]. In Japanese patients with COPD, tiotropium Respimat<sup>®</sup> 5  $\mu\text{g}$  and tiotropium HandiHaler<sup>®</sup> 18  $\mu\text{g}$  showed a similar profile of efficacy, safety, and pharmacokinetics [115]. In the analysis of an Asian cohort from the TIOSPIR study, both doses of tiotropium showed similar safety and exacerbation efficacy profiles [116]. In Chinese patients with COPD, tiotropium significantly improved lung function and quality of life, and reduced the number of exacerbations [117]. Tiotropium also improved FEV<sub>1</sub> more than placebo at 24 months and ameliorated the annual decrease in FEV<sub>1</sub> after bronchodilator use in COPD patients of GOLD stages 1 or 2 from China [118]. Acclidinium 400  $\mu\text{g}$  was shown to be safe and efficacious in Korean patients with moderate-to-severe COPD [119]. Additionally, significant improvement in trough FEV<sub>1</sub> was shown with acclidinium compared with the placebo in Korean patients with COPD [119]. In the recently conducted phase II study enrolling Japanese patients with moderate-to-severe COPD, twice-daily glycopyrronium 14.4  $\mu\text{g}$  by the new co-suspension delivery technology was found to be the most appropriate dose for use in phase III studies [121], while the currently available glycopyrronium for COPD in Japan is the DPI form of 50  $\mu\text{g}$  once daily. In the glycopyrronium bromide in COPD airways7 (GLOW7) study in which the majority of enrolled patients were Chinese, glycopyrronium 50  $\mu\text{g}$  significantly improved lung function, dyspnea, and health status versus placebo



[122]. In a 52-week study, umeclidinium 125 µg was well tolerated in Japanese patients with COPD [123].

#### **LABA/LAMA FDCs**

In the LANTERN study and in its Chinese cohort, once-daily indacaterol/glycopyrronium 110/50 µg was superior to twice-daily salmeterol/fluticasone 50/500 µg in improving lung function and in reducing the rate of moderate or severe exacerbations in COPD patients with a history of at most one exacerbation in the previous year [124, 125]. In Japanese patients from the SHINE study, indacaterol/glycopyrronium demonstrated superior improvements in trough FEV<sub>1</sub> and FEV<sub>1</sub> AUC<sub>5min–4h</sub> compared to its monocomponents, open-label tiotropium and placebo, and comparable safety [126]. In a pooled analysis of the SHINE and ARISE studies, compared to tiotropium, indacaterol/glycopyrronium provided significant improvements in lung function, health status, and rescue medication use, while having a good safety profile, in Japanese patients with moderate-to-severe COPD [127]. Japanese Respiratory Society guidelines acknowledge that indacaterol/glycopyrronium is a combination of two first-line bronchodilators [128]. In Korea, indacaterol/glycopyrronium was approved in 2015 and it is being further evaluated in symptomatic patients with mild-to-moderate COPD prescribed tiotropium monotherapy [129]. In exacerbating Asian COPD patients from the FLAME study, indacaterol/glycopyrronium was more effective than salmeterol/fluticasone, with significantly less incidence of pneumonia than salmeterol/fluticasone [130]. In Asian patients with COPD, once-daily vilanterol/umeclidinium 25/62.5 µg and 25/125 µg resulted in clinically meaningful and statistically significant improvements in lung function versus placebo. Symptoms and quality of life measures were also improved [131]. In Japanese patients with COPD, no safety concerns for long-term treatment with olodaterol/tiotropium were identified. Numerical improvement in lung function was observed with olodaterol/tiotropium compared with olodaterol in Japanese patients with moderate-to-very severe COPD [132]. Olodaterol/tiotropium 5/5 µg was

superior to each monotherapy for lung function and SGRQ in the Japanese subpopulation of patients with COPD from the TONADO study [133]. A phase III study in an East Asian population showed slightly greater trough FEV<sub>1</sub> treatment differences between olodaterol/tiotropium 5/5 µg and tiotropium compared to the overall population [134]. The VESUTO<sup>®</sup> study investigated efficacy of olodaterol/tiotropium compared with tiotropium alone on inspiratory capacity, exercise capacity, and daily physical activity in Japanese patients with COPD. Olodaterol/tiotropium significantly increased inspiratory capacity compared with tiotropium after 6 weeks of treatment (primary endpoint). Although there was no statistical difference between the two arms in 6-min walk distance in the overall population, olodaterol/tiotropium significantly increased 6-min walk distance compared to tiotropium alone in the subgroup of GOLD stages III and IV [135]. In the recently reported Japanese subpopulation analysis of the DYNAGITO study, olodaterol/tiotropium 5/5 µg resulted in a 29% lower rate of moderate-to-severe exacerbations compared with tiotropium [136].

#### **LABA/LAMA/ICS Triple Therapy Versus LABA/LAMA**

Very recently, some studies have been conducted on LABA/LAMA versus LABA/LAMA/ICS to assess the contribution of ICS in the efficacy of triple therapy in COPD patients. The IMPACT study compared the efficacy of vilanterol/umeclidinium/fluticasone on the rate of moderate and severe exacerbations versus vilanterol/umeclidinium and vilanterol/fluticasone over 52 weeks in symptomatic exacerbating COPD patients with moderate-to-very severe airflow limitation; these patients could have a history of asthma. Vilanterol/umeclidinium/fluticasone significantly reduced the rate of moderate-to-severe exacerbations by 15% compared to vilanterol/fluticasone and by 25% compared to vilanterol/umeclidinium [137]. The 52-week TRIBUTE study compared formoterol/glycopyrronium/beclomethasone versus indacaterol/glycopyrronium in terms of the rate of

moderate-to-severe COPD exacerbations in exacerbating patients with severe-to-very-severe COPD; triple therapy significantly reduced the annual rate of exacerbations compared with dual bronchodilation therapy [138]. Nevertheless, it should be noted that the effects of triple therapy on COPD exacerbations were evident in patients with chronic bronchitis or elevated circulating eosinophils but not in those with emphysema or low circulating eosinophils; thus these results cannot be generalized to the whole COPD population [139]. The 26-week SUNSET study has assessed the effects of ICS withdrawal from long-term (at least 6 months) triple therapy to indacaterol/glycopyrronium or continuation of triple therapy [tiotropium (18 µg) once daily plus combination of salmeterol (50 µg) and fluticasone propionate (500 µg) twice daily] in non-frequently exacerbating patients (up to one exacerbation in the past year) with moderate-to-severe COPD [140]. Inhaled corticosteroids withdrawal led to a reduction in trough FEV<sub>1</sub> of –26 mL confidence interval limits exceeding the non-inferiority margin of –50 mL; the annualized rate of moderate or severe COPD exacerbations did not differ between treatments. However, patients with at least 300 blood eosinophils/µL at baseline showed statistically greater loss of lung function and higher exacerbation risk in LABA/LAMA compared to triple therapy, implying that COPD patients with higher blood eosinophils benefit from triple therapy [140]. The currently ongoing ETHOS study is assessing the efficacy and safety of formoterol/glycopyrronium/budesonide versus formoterol/glycopyrronium and formoterol/budesonide on COPD exacerbations over 52 weeks [141].

## COMMENTARY AND CONCLUSIONS

Important demographic differences exist between Asian and Western populations of COPD. For example, the body mass index is lower in Asian COPD patients than Western COPD patients [129, 142]. The cause of COPD is different between populations and there are more patients with biofuel-induced COPD in

Asia [143, 144]. Although smoking is still a major risk factor for COPD, genetic, environmental, and developmental factors that exert their effects during an individual's growing years can diminish the maximally attained FEV<sub>1</sub> and accelerate FEV<sub>1</sub> decline in adult life, thus increasing the risk of COPD; this aspect has recently garnered attention but remains to be specifically evaluated in Asian populations [145]. Many COPD patients in Asia have a previous history of tuberculosis [146, 147], which can contribute to the development of COPD. Notably, different COPD phenotypes exist among Asian populations. For example, the emphysema phenotype is dominant in Japanese patients with COPD [148] whereas chronic bronchitis is more prevalent than emphysema in the Korean COPD population [149]; this may influence the clinical outcomes of therapies. Air pollution is heavier in Asian countries and this definitely affects COPD outcome [150]. Even though inhaler medication use is steadily increasing in Asia, it is still used less frequently than oral therapies, which reflects the overprescription of oral medications (e.g., theophylline) to COPD patients [6, 151, 152]. Nevertheless, currently available evidence of LABA/LAMA FDC in COPD described above is consistent between Western and Asia, and therefore, global and regional COPD treatment guidelines have supported the use of LABA/LAMA FDCs in clinical practice and their use is growing.

It should be noted that phase III clinical programs on LABA/LAMA combinations in COPD have not fully shown superior efficacy of dual bronchodilators over monotherapy for effects on exercise endurance and physical activity. Moreover, COPD patients with frequent exacerbations and blood eosinophil levels of at least 300 cells/µL may still benefit from ICS therapy. Real-world assessment could further define the place of LABA/LAMA FDCs in COPD treatment.

Overall, variable clinical efficacy and safety of individual drugs, differences in population characteristics, phenotypes, patient preferences, and adherence to treatment, and inhaler device use are crucial to the optimal use of LABA/LAMA FDCs in patients with COPD in Asia and globally.

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