Introduction

Chronic obstructive pulmonary disease (COPD) is a common, preventable and treatable disease, characterized by persistent airflow limitation and respiratory symptoms, resulting in breathlessness and poor quality of life. In addition to significantly limiting quality of life, it has been associated with increased mortality and contributes to a significant economic and social burden on patients. It is the fourth leading cause of death worldwide, and is projected to become the third by 2030. With increasing prevalence of smoking in developing countries, and aging populations in high-income countries, the burden of COPD is expected to increase considerably over the next 30 years.

In Asia, the prevalence of COPD is high (6.2% as of 2012), indicating a substantial socioeconomic burden. Exposure to smoke from biomass fuel is a risk factor for COPD in the Asia-Pacific region; in particular, the prevalence of COPD among...
Optimal bronchodilation for COPD

women exposed to biomass smoke is very high. Differences exist between Asian and other populations in disease prevalence and clinical practices for COPD, including higher rates of COPD-associated mortality and morbidity, differences in healthcare management structure and cultural practices.

Exacerbations are a hallmark of COPD; these acute events negatively impact health status, disease progression, and frequency of hospitalization, and contribute majorly to the total COPD burden on healthcare systems. The primary treatment goals of COPD are reduction in symptoms and future risk of exacerbations. Bronchodilators provide improvements in lung function and reduce symptoms and exacerbations, and are therefore the cornerstone of pharmacological management of COPD. For patients with relatively few COPD symptoms and low risk of exacerbations, short-acting bronchodilators are a treatment option; these are also used as rescue medications on an "as needed" basis to improve breathlessness and exercise limitation. However, the majority of patients with significant breathlessness may require a more intensive treatment than short-acting bronchodilators alone, and long-acting bronchodilators are preferred. For patients uncontrolled on monotherapy, combining different classes of bronchodilators can help achieve better treatment outcomes.

The Global Initiative for Chronic Obstructive Lung Disease (GOLD) 2018 does not recommend a singular long-acting β2-agonist/long-acting muscarinic antagonists (LABA/LAMA) fixed-dose combination (FDC) as the preferred choice for COPD management. Head-to-head studies among LABA/LAMA FDCs, along with previous network meta-analyses suggested that effects of all LABA/LAMA FDCs may not always be similar and that an efficacy gradient exist, which potentially indicates that optimal bronchodilation with LABA/LAMA may not be a mere drug-class effect. Here, we review and compare the efficacy and safety of available inhaled LABA/LAMA FDCs for the management of COPD, with the aim of providing physicians with a framework for selection of optimal bronchodilation therapy with LABA/LAMA FDCs.

Positioning of LABA/LAMA in COPD Treatment Guidelines

GOLD 2018 recommends the use of LABA/LAMA as the first-line treatment option in the majority of symptomatic patients with COPD, and as a preferred treatment option in all patients for whom maintenance therapy is recommended. Other guidelines such as the Spanish COPD Guidelines (GesEPoC) 2017 recommend LABA/LAMA as first-line treatment in high-risk patients, irrespective of their clinical phenotype. High-risk COPD patients were defined as those with severe airflow limitation or high grade dyspnea or at least two moderate exacerbations or one hospital admission in the previous year, or a combination of these factors. Moreover, a recently reported two-step treatment algorithm suggests that patients with either a modified Medical Research Council (mMRC) score >1 or with more than one exacerbation in the previous year should initiate treatment with LABA/LAMA.

Specific to Korea, the Korean clinical practice guideline for COPD provides recommendations on diagnosis, assessment, monitoring, management, exacerbation, and comorbidities of COPD. Patients are classified into three groups based on the severity of airflow limitation, symptoms and exacerbation frequency: G (forced expiratory volume in 1 second (FEV1) ≥60%, mMRC 0–1 or COPD assessment test (CAT) <10, exacerbation ≤1/yr), N (FEV1 ≥60%, mMRC ≥2 or CAT ≥10, exacerbation ≥1/yr), and D (FEV1 <60%, exacerbation ≥2/yr or one hospitalization due to exacerbation, irrespective of symptom scores). LABA/LAMA is recommended for patients in group N, who have severe breathlessness or show no improvement in symptoms with monotherapy or experience exacerbations. In group D patients, LABA/LAMA can be administered as a first-line therapy along with a LAMA or ultra-LABA or LABA/inhaled corticosteroid (ICS).

Treatment with LABA/LAMA is recommended based on its superior results versus monocomponents and LABA/ICS, and lower risk of development of pneumonia versus ICS. A switch to ICS-containing therapy is suggested only for those patients who develop further exacerbations on LABA/LAMA therapy, and have an inflammatory profile susceptible to respond to the treatment with ICS.

Overview of Key Trials of LABA/LAMA FDCs

Five LABA/LAMA FDCs have been approved to date (Table 1), either as once- or twice-daily inhalations. Efficacy and safety of these LABA/LAMA FDCs have been evaluated in various placebo- and active-controlled clinical trials (Table 2). Active comparators mainly included the respective monocomponents, tiotropium (TIO) or salmeterol/fluticasone (SFC). Feldman et al. reported a head-to-head comparison of vilanterol/umeclidinium 25/62.5 μg once daily (VI/UMEC) and olodaterol/tiotropium 5/5 μg once daily (OLO/TIO) in symptomatic COPD patients. Another trial evaluating the efficacy and safety of formoterol fumarate/indacaterol 18/7.5 μg twice daily (FF/IND) versus FF/GP 25/5 μg once daily is underway in patients with moderate-to-very-severe COPD (AERISTO; NCT03162055). A head-to-head study comparing the efficacy and safety of indacaterol/glycopyrrolate 27.5/15.6 μg twice daily with VI/UMEC 25/62.5 μg once daily has also been reported.

Patient population, study duration and endpoints are important considerations when comparing each of these studies (Table 2). The majority of the studies included patients with moderate COPD and without exacerbation history, and evaluated change in lung function as the primary endpoint.
Apart from three indacaterol/glycopyrronium (IND/GLY) studies (SPARK, LANTERN, and FLAME)\textsuperscript{26-28} and one OLO/TIO trial (DYNAGITO)\textsuperscript{29}, patients with recent history of COPD exacerbation were excluded from participation in the trial. The SPARK study was the first to evaluate the effect of LABA/LAMA (IND/GLY) versus LAMA (GLY and open-label TIO) on the rate of moderate or severe COPD exacerbations as a primary endpoint in patients with severe-to-very severe COPD\textsuperscript{26}, followed by the FLAME study, which evaluated the annualized rate of exacerbations with IND/GLY 110/50 μg once daily versus SFC 50/500 μg twice daily (LABA/ICS) as a primary endpoint\textsuperscript{29}. Recently, the 52-week DYNAGITO trial, evaluated the annualized rate of moderate-to-severe exacerbations with OLO/TIO 5/5 μg once daily versus TIO 5 μg once daily in patients with severe-to-very severe COPD\textsuperscript{29}. The majority of the studies were of 24-week duration or less, with the exception of few with study duration of 52 weeks or more\textsuperscript{26,28-14}.

It should also be noted that most of these studies evaluated predominantly the Western population. A few studies/subgroup analyses have been conducted in the Asian population to address inter-ethnic differences\textsuperscript{37-61}. Furthermore, IND/GLY 110/50 μg once daily is being evaluated in mild-to-moderate COPD patients who remain symptomatic on TIO 18 μg once daily monotherapy in Korea. The primary objective of this 12-week randomized trial is to demonstrate superiority of IND/GLY over TIO in improving trough FEV\textsubscript{1}\textsuperscript{37}. The efficacy and safety of the U.S. approved dose of indacaterol/glycopyrronium 27.5/15.6 μg twice daily versus monocomponents and placebo has been well established in symptomatic patients with moderate-to-severe COPD, as seen in the FLIGHT studies from the EXPEDITION trial program\textsuperscript{62,63}; however, this review discusses only the once-daily dosage of IND/GLY.

In terms of pragmatic/real-world evidence on LABA/LAMA effectiveness, the CRYSTAL study, a 12-week, open-label pragmatic trial, was the first to evaluate the efficacy and safety of a direct switch from previous treatments to IND/GLY 110/50 μg once daily on lung function and dyspnea in patients with moderate COPD and a history of up to one exacerbation in the previous year\textsuperscript{64}. A 12-month pragmatic study comparing the time to first moderate or severe COPD exacerbation with OLO/TIO and ICS-based triple therapy is ongoing (ARWISE, NCT03265145). FLASH was a 12-week, multi-center, double-blind trial that investigated the efficacy and safety of a direct switch, without a wash-out period, from SFC 50/500 μg twice daily to IND/GLY 110/50 μg once daily in symptomatic COPD patients\textsuperscript{65}. To further explore the positioning of ICS containing triple therapy in COPD management, the 26-week, double-blind, randomized, multi-center SUNSET trial has evaluated the efficacy and safety of the switch from long-term triple therapy to IND/GLY in patients with moderate-to-severe COPD with not more than one exacerbation in the previous year (NCT02603393).

### Clinical Trial Evidence: Efficacy of LABA/LAMA

Efficacy of LABA/LAMA FDCs has been assessed in terms of improvement in key clinical outcomes such as lung function, dyspnea, health-related quality of life, rescue medication use, and exacerbations. These outcomes were also assessed in patients of Asian origin; results of subgroup analyses and studies in the Asian sub-populations were generally in line with those of the overall population. With very limited direct...
| Study                        | Duration (wk) | Treatment arms | Patient population                                                                 | Primary endpoint |
|------------------------------|---------------|----------------|------------------------------------------------------------------------------------|------------------|
| Lung function                |               |                |                                                                                   |                  |
| Bateman et al.\(^6\) NCT01202188 (SHINE) | 26            | IND/GLY 110/50 μg q.d. IND 150 μg q.d. GLY 50 μg q.d. OLTIO 18 μg q.d. Placebo | Moderate-to-severe COPD and symptomatic | Trough FEV\(_1\) at week 26 vs. monocomponents |
| Vogelmeier et al.\(^7\) NCT01315249 (ILLUMINATE) | 26            | IND/GLY 110/50 μg q.d. SFC 50/500 μg b.i.d. | Moderate-to-severe COPD and symptomatic no COPD exacerbation requiring treatment with antibiotics, systemic corticosteroids and/or hospitalization in the previous year | FEV\(_1\) AUC\(_{0-1.5h}\) at week 26 vs. SFC |
| Dahl et al.\(^7\) NCT01529632 (BEACON) | 4             | IND/GLY 110/50 μg q.d. IND 150 μg q.d. and GLY 50 μg q.d. (free combination) | Moderate-to-severe COPD and symptomatic | Trough FEV\(_1\) at week 4 (non-inferiority of IND/GLY to IND+GLY [free combination]) |
| Zhong et al.\(^7\) NCT01709903 (LANTERN) | 26            | IND/GLY 110/50 μg q.d. SFC 50/500 μg b.i.d. | Moderate-to-severe COPD with ≤1 COPD exacerbation in the previous year; mMRC grade≥2 | Trough FEV\(_1\) at week 26 (non-inferiority of IND/GLY to SFC) |
| Feldman et al.\(^8\) NCT02799784 | 8             | VU/UMEC 25/62.5 μg q.d. OLO/TIO 5/5 μg q.d. | Post-bronchodilator FEV\(_1\) ≤70% predicted and mMRC grade≥2 | Trough FEV\(_1\) (week 8) |
| Donohue et al.\(^9\) NCT01313630 | 24            | VU/UMEC 25/62.5 μg UMEC 62.5 μg V125 μg Placebo | Post-bronchodilator FEV\(_1\) ≤70% predicted and mMRC grade≥2 | Trough FEV\(_1\) (day 169) |
| Celli et al.\(^9\) NCT01313637 | 24            | VU/UMEC 25/125 μg q.d. UMEC 125 μg q.d. V125 μg q.d. Placebo | Post-bronchodilator FEV\(_1\) ≤70% predicted and mMRC grade≥2 | Trough FEV\(_1\) (day 169) |
| Decramer et al.\(^9\) NCT01316900 | 24            | VU/UMEC 25/125 μg q.d. V1/UMEC 25/62.5 μg q.d. V125 μg q.d. TIO 18 μg q.d. | Post-bronchodilator FEV\(_1\) ≤70% predicted and mMRC grade≥2 | Trough FEV\(_1\) (day 169) |
| Maleki-Yazdi et al.\(^9\) NCT01777334 | 24            | VU/UMEC 25/62.5 μg q.d. TIO 18 μg q.d. | Post-bronchodilator FEV\(_1\) ≤70% predicted and mMRC grade≥2 | Trough FEV\(_1\) (day 169) |
| Singh et al.\(^9\) NCT01822899 | 12            | VU/UMEC 25/62.5 μg q.d. SFC 50/500 μg b.i.d. | Symptomatic patients with moderate-to-severe COPD with no exacerbations in the year prior to enrolment | FEV\(_1\) AUC\(_{0-24h}\) at week 12 |
| Study            | Duration (wk) | Treatment arms | Patient population                                                                 | Primary endpoint                                      |
|------------------|---------------|----------------|-------------------------------------------------------------------------------------|--------------------------------------------------------|
| Donohue et al.   | 12            | VI/UMEC 25/62.5 μg q.d. SFC 50/250 μg b.i.d. | Symptomatic patients with moderate-to-severe COPD with no exacerbations in the year prior to enrolment | FEV\textsubscript{1} AUC\textsubscript{0–24h} at week 12 |
| Buhl et al.      | 52            | OLO/TIO 5/5 μg q.d. OLO/TIO 5/2.5 μg q.d. OLO 5 μg q.d. TIO 5 μg q.d. TIO 2.5 μg q.d. | Moderate-to-very-severe COPD                          | FEV\textsubscript{1} AUC\textsubscript{0–24} at week 24 Trough FEV\textsubscript{1} at week 24 SGRQ at week 24 |
| Beeh et al.      | 6             | OLO/TIO 5/5 μg q.d. OLO/TIO 5/2.5 μg q.d. OLO 5 μg q.d. TIO 5 μg q.d. Placebo | Post-bronchodilator FEV\textsubscript{1} <80% predicted | FEV\textsubscript{1} AUC\textsubscript{0–24} at week 6 |
| Singh et al.     | 12            | OLO/TIO 5/5 μg q.d. OLO/TIO 5/2.5 μg q.d. TIO 5 μg q.d. Placebo | Moderate-to-very-severe COPD                          | FEV\textsubscript{1} AUC\textsubscript{0–24} at week 12 Trough FEV\textsubscript{1} at week 12 SGRQ at week 12 |
| Beeh et al.      | 6             | OLO/TIO 5/5 μg q.d. OLO/TIO 5/2.5 μg q.d. SFC 50/500 μg b.i.d. SFC 50/250 μg b.i.d. | Moderate-to-very-severe COPD                          | FEV\textsubscript{1} AUC\textsubscript{0–12} at week 6 |
| Singh et al.     | 24            | FOR/ACLI 12/400 μg b.i.d. FOR/ACLI 6/400 μg b.i.d. ACLI 400 μg b.i.d. FOR 12 μg b.i.d. Placebo | Moderate-to-severe COPD | Co-primary endpoints were change from baseline at Week 24 in 1-hour morning post-dose FEV\textsubscript{1}, versus ACLI 400 μg and morning pre-dose (trough) FEV\textsubscript{1}, versus FORM 12 μg |
| D'Urzo et al.    | 24            | FOR/ACLI 12/400 μg b.i.d. FOR/ACLI 6/400 μg b.i.d. ACLI 400 μg b.i.d. FOR 12 μg b.i.d. Placebo | Moderate-to-severe COPD | Change from baseline to week 24 in 1-hour morning post-dose FEV\textsubscript{1}, and change from baseline to week 24 in morning pre-dose (trough) FEV\textsubscript{1} |
| Vogelmeier et al.| 24            | FOR/ACLI 12/400 μg b.i.d. SFC 50/500 μg b.i.d. | Moderate-to-severe COPD | Peak FEV\textsubscript{1} at week 24 |
| Martinez et al.  | 24            | FF/GP 9.6/18 μg b.i.d. GP 18 μg b.i.d. FOR 9.6 μg b.i.d. OL TIO 18 μg q.d. Placebo | Moderate-to-very-severe COPD                          | Change from baseline in morning pre-dose trough FEV\textsubscript{1} at week 24 |
| Study | Duration (wk) | Treatment arms | Patient population | Primary endpoint |
|-------|---------------|----------------|--------------------|------------------|
| Martínez et al.\(^5\) NCT01854658 (PINNACLE-2) | 24 | FF/GP 9.6/18 μg b.i.d.  
GP 18 μg b.i.d.  
FOR 9.6 μg b.i.d.  
OL TIO 18 μg q.d.  
Placebo | Moderate-to-very-severe COPD | Change from baseline in morning pre-dose trough FEV\(_1\) at week 24 |
| Mahler et al.\(^3\) NCT01490125 (BLAZE) | 6 per period (3 period study) | IND/GLY 110/50 μg q.d.  
OL TIO 18 μg q.d. | Moderate-to-severe COPD with mMRC grade ≥2 | Patient-reported dyspnea (SAC BDI/TDI) at week 6 vs. placebo |
| Buhl et al.\(^3\) NCT01574651 (QUANTIFY) | 26 | IND/GLY 110/50 μg q.d.  
OL TIO 18 μg q.d. | Moderate-to-severe COPD | SGaQ at week 26 (non-inferiority of IND/GLY to TIO+formoterol) |
| Singh et al.\(^5\) NCT01964352  
NCT02006732 (OTEMTO 1+2) | 12 | OLO/TIO 5/5 μg q.d.  
OLO/TIO 5/2.5 μg q.d.  
TIO 5 μg q.d.  
Placebo | Moderate-to-very-severe COPD | SGaQ at week 12  
FEV\(_1\) AUC\(_{0-3}\) at week 12  
Trough FEV\(_1\) at week 12 |
| Beeh et al.\(^3\) NCT01294787 (BRIGHT) | 15 (3 per period) | IND/GLY 110/50 μg q.d.  
OL TIO 18 μg q.d. | Moderate-to-severe COPD | Exercise endurance time (SMETT) at week 3 vs placebo |
| Maltais et al.\(^3\) NCT01525615 (TORRACTO) | 12 | OLO/TIO 5/5 μg q.d.  
OLO/TIO 5/2.5 μg q.d.  
Placebo | Moderate-to-very-severe COPD | Endurance time during constant work rate cycle ergometry at week 12 |
| O'Donnell et al.\(^5\) NCT01533922  
NCT01553935 (MORACTO 1+2) | 6 | OLO/TIO 5/5 μg q.d.  
OLO/TIO 5/2.5 μg q.d.  
TIO 5 μg q.d.  
OLO 5 μg q.d. | Moderate-to-very-severe COPD | Pre-exercise IC at week 6  
Endurance time during constant work rate cycle ergometry at week 6 |
| Troosters et al.\(^5\) NCT02085161 (PHYSACTO) | 8 | OLO/TIO 5/5 μg q.d.  
OLO/TIO 5/5 μg q.d. with exercise training  
TIO 5 μg q.d.  
Placebo | Moderate-to-very severe COPD without an acute exacerbation in the month prior to study | Improvement in exercise endurance capacity |
| Wedzicha et al.\(^5\) NCT01120691 (SPARK) | 64–76 | IND/GLY 110/50 μg q.d.  
GLY 50 μg q.d.  
OL TIO 18 μg q.d. | Severe-to-very-severe COPD with ≥1 COPD exacerbation requiring treatment with systemic corticosteroids and/or antibiotics in the previous year | Rate of moderate or severe exacerbations vs GLY |
| Study                        | Duration (wk) | Treatment arms                 | Patient population                                                                 | Primary endpoint                                                                 |
|------------------------------|---------------|--------------------------------|-------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------|
| Wedzicha et al.\textsuperscript{20} NCT01782326 (FLAME) | 52            | IND/GLY 110/50 μg q.d. SFC 50/500 μg b.i.d. | Moderate-to-very-severe COPD with mMRC grade ≥2 and a documented history of ≥1 COPD exacerbation requiring treatment with systemic corticosteroids and/or antibiotics in the previous 1 year | Rate of COPD exacerbations during 52 weeks of treatment (non-inferiority of IND/GLY to SFC) |
| Calverley et al.\textsuperscript{21} NCT02296138 (DYNAGITO) | 52            | OLO/TIO 5/5 μg q.d TIO 5 μg q.d | Moderate-to-very severe COPD with ≥1 COPD exacerbation requiring treatment with systemic corticosteroids and/or antibiotics in the previous year, with or without hospitalization | Rate of moderate and severe COPD exacerbations during 52 weeks of treatment |
| Dahl et al.\textsuperscript{22} NCT01120717 (ENLIGHTEN) | 52            | IND/GLY 110/50 μg q.d. Placebo | Moderate-to-severe COPD and symptomatic | Frequency of treatment-emergent AEs vs. placebo |
| Asai et al.\textsuperscript{23} NCT01285492 (ARISE) | 52            | IND/GLY 110/50 μg q.d. OLO TIO 18 μg q.d. | Japanese patients with moderate-to-severe COPD | AEs, SAEs, or death |
| Donohue et al.\textsuperscript{24} NCT01316887 | 52            | VI/UMEC 25/125 μg q.d. UMEC 125 μg q.d. | Moderate-to-severe COPD with mMRC grade ≥2 | Safety assessments |
| Hanania et al.\textsuperscript{25} NCT01970878 (PINNACLE-3) | 52            | FF/GP 9.6/18 μg b.i.d. GP 18 μg b.i.d. FOR 9.6 μg b.i.d. OLO TIO 18 μg q.d. Placebo | Moderate-to-very-severe COPD | Long-term safety and tolerability over 52 weeks |

LABA/LAMA: long-acting β2-agonist/long-acting muscarinic antagonist; FDC: fixed-dose combination; IND/GLY: indacaterol/glycopyrronium; q.d.: once daily; IND: indacaterol; GLY: glycopyrronium; OL: open label; TIO: tiotropium; COPD: chronic obstructive pulmonary disease; FEV\textsubscript{1}: forced expiratory volume in 1 second; SFC: salmeterol/fluticasone; b.i.d.: twice daily; AUC: area under the curve; mMRC: modified Medical Research Council; VI/UMEC: vilanterol/umeclidinium; OLO/TIO: olodaterol/tiotropium; UMEC: umeclidinium; VI: vilanterol; FOR/ACLI: formoterol/aclidinium; ACLI: aclidinium; FOR: formoterol; FF/GP: formoterol fumarate/glycopyrrolate; GP: glycopyrrolate; SGRQ: St. George’s Respiratory Questionnaire; BDI: baseline dyspnea index; TDI: transition dyspnea index; AEs: adverse events; SAEs: serious adverse events.
head-to-head data available, comparative efficacy of different LABA/LAMA FDCs can be evaluated only by drawing an indirect comparison between the outcomes of individual studies.

1. Lung function

Lung function outcomes for each LABA/LAMA FDC versus placebo, TIO, and SFC are presented in Table 3. In general, all FDCs improved trough FEV₁ and peak FEV₁. IND/GLY 110/50 µg once daily demonstrated a faster onset of action versus all comparators, while formoterol/aclidinium (FOR/ACLI) 12/400 µg twice daily and FF/GP 9.6/18 µg twice daily demonstrated it against placebo. Onset of action was reported for VI/UMEC 25/62.5 µg once daily versus placebo at 15 minutes. In the only head-to-head comparison, VI/UMEC 25/62.5 µg once daily demonstrated a significant improvement in trough FEV₁ versus OLO/TIO 5/5 µg once daily at week 8 (least square means [LSM] difference, 53 mL; 95% confidence interval [CI], 26–80 mL; p<0.0001)²⁵. In the CRYStal study, IND/GLY 110/50 µg once daily significantly improved lung function after direct switch from LAMA, LABA, or LABA/ICS²². A significant improvement in lung function was also observed in patients who directly switched from SFC 50/500 µg twice daily to IND/GLY 110/50 µg once daily without a washout period in the FLASH study⁶⁰.

VI/UMEC 25/62.5 µg once daily resulted in clinically meaningful and statistically significant improvements in lung function versus placebo in Asian patients with COPD⁶¹. Improvement in trough FEV₁ with OLO/TIO 5/5 µg once daily versus TIO 5 µg once daily was greater in Japanese patients (change from baseline, 108 mL; p<0.0001) compared with the overall population in the TOnado trial³². IND/GLY 110/50 µg once daily demonstrated significant improvement in pre-dose FEV₁ versus TIO 18 µg once daily in Japanese patients from SHINE and ARISE study⁶¹. In the Chinese cohort of the LANTERN study, IND/GLY 110/50 µg once daily showed superiority over SFC 50/500 µg twice daily, with a statistically significant and clinically meaningful improvement in trough FEV₁ FEV₁ area under the curve from 0 to 4 hours, and peak FEV₁⁶¹.

### Table 3. Improvement in lung function with LABA/LAMA FDCs versus placebo, TIO and SFC

| Variable                  | IND/GLY 110/50 µg q.d. | VI/UMEC 25/62.5 µg q.d. | OLO/TIO 5/5 µg q.d.* | FOR/ACLI 12/400 µg b.i.d. | FF/GP 9.6/18 µg b.i.d. |
|---------------------------|------------------------|-------------------------|----------------------|--------------------------|------------------------|
| **Trough FEV₁, mL**       |                        |                         |                      |                          |                        |
| Placebo                   | 189 to 200             | 167                     | 162 to 208           | 129 to 143               | 103 to 150             |
| TIO 18 µg q.d.            | 60 to 100              | 60 to 112               | NS to 79             | NA                       | NS to 25               |
| SFC 50/500 µg b.i.d.      | 62 to 103              | 82 to 98                | 58                   | NS                       | NA                     |
| **Peak FEV₁, mL**         |                        |                         |                      |                          |                        |
| Placebo                   | 330                    | 224                     | 323 to 339           | 285 to 334               | 267 to 291             |
| TIO 18 µg q.d.            | 130                    | 72 to 95                | 111 to 135           | NA                       | 93 to 97               |
| SFC 50/500 µg b.i.d.      | 121 to 155             | 97 to 122               | 147                  | 93                       | NA                     |
| **FEV₁, 5-min post morning dose, study end, mL** | | | | |
| Placebo                   | 290                    | 112⁷                     | NA                   | 108 to 128               | 186* to 187*            |
| TIO 18 µg q.d.            | 94 to 120              | NA                       | NA                   | NA                       | NA                     |
| SFC 50/500 µg b.i.d.      | 150                    | NA                       | NA                   | NA                       | NA                     |
| **FEV₁, AUC₀−₁h**         |                        |                         |                      |                          |                        |
| Placebo                   | 320⁴ to 330⁴           | 242³                   | 280⁴ to 331**        | 221††                    | NA                     |
| TIO 18 µg q.d.            | 110⁴                   | 74¹ to 105⁷             | 103** to 117**       | NA                       | NA                     |
| SFC 50/500 µg b.i.d.      | 110** to 138**         | 74 to 101¹             | 86                   | 90                       | NA                     |

Values are presented as minimum and maximum mean LSM treatment difference value from all trials analyzed.

* For OLO/TIO 5/5 µg q.d. studies, TIO 5 µg q.d. used as comparator. †FEV₁, 15-min post morning dose on day 1. ‡FEV₁, 5-min post morning dose, day 1. §FEV₁, AUC₀−₁h. §§FEV₁, AUC₀−₁h. "FEV₁, AUC₀−₁h. ""FEV₁, AUC₀−₁h. """"FEV₁, AUC₀−₁h. Lab/LAMA: long-acting β₂-agonist/long-acting muscarinic antagonist; FDC: fixed-dose combination; TIO: tiotropium; SFC: salmeterol/fluticasone; IND/GLY: indacaterol/glycopyrronium; q.d.: once daily; VI/UMEC: vilanterol/umeclidinium; OLO/TIO: olodaterol/tiotropium; FF/GP: formoterol fumarate/glycopyrrolate; FEV₁: forced expiratory volume in 1 second; NS: non-significant; NA: not available (no outcomes in any of the trials evaluated); AUC: area under the curve.
Table 4. Improvement in dyspnea with LABA/LAMA FDCs versus placebo, TIO and SFC

| Variable                        | IND/GLY 110/50 μg q.d. | VI/UMEC 25/62.5 μg q.d. | OLO/TIO 5/5 μg q.d.* | FOR/ACLI 12/400 μg b.i.d. | FF/GP 9.6/18 μg b.i.d. |
|--------------------------------|------------------------|------------------------|----------------------|---------------------------|------------------------|
| TDI total score                |                        |                        |                      |                           |                        |
| Placebo                        | 1.09 to 1.37           | 1.20                   | 1.20 to 2.05         | 1.29 to 1.44              | NA                     |
| TIO 18 μg q.d.                 | 0.49 to 0.51           | NS                     | 0.35 to 0.61         | NA                        | NS                     |
| SFC 50/500 μg b.i.d.           | NS to 0.76             | NS                     | NA                   | NS                        | NA                     |
| Proportion of patients achieving MCID (odds ratio) |                        |                        |                      |                           |                        |
| Placebo                        | 1.86 to 2.78           | 2.0                    | NA                   | 2.54 to 2.80              | NA                     |
| TIO 18 μg q.d.                 | 1.78                   | NS                     | NA                   | NA                        | NS                     |
| SFC 50/500 μg b.i.d.           | 1.56                   | NA                     | NA                   | NA                        | NA                     |

Values are presented as LSM treatment difference, unless otherwise specified. Data expressed as minimum and maximum mean value from all trials analyzed.

*For OLO/TIO 5/5 μg q.d. studies, TIO 5 μg q.d. used as comparator.

LABA/LAMA: long-acting β2-agonist/long-acting muscarinic antagonist; FDC: fixed-dose combination; TIO: tiotropium; SFC: salmeterol/fluticasone; IND/GLY: indacaterol/glycopyrrolate; q.d.: once daily; VI/UMEC: vilanterol/umeclidinium; OLO/TIO: olodaterol/tiotropium; FOR/ACLI: formoterol/aclidinium; b.i.d.: twice daily; FF/GP: formoterol fumarate/glycopyrrolate; TDI: transition dyspnea index; NA: not available (no outcomes in any of the trials evaluated); TIO: tiotropium; NS: non-significant; SFC: salmeterol/fluticasone; MCID: minimum clinically important difference.

2. Dyspnea

Improvement in dyspnea with LABA/LAMA FDCs was ≥1 unit on the transition dyspnea index (TDI) scale (minimal clinically important difference [MCID]) versus placebo in the majority of studies, with a greater number of patients on LABA/LAMA FDCs reaching MCID versus placebo (Table 4). IND/GLY 110/50 μg once daily significantly reduced dyspnea versus TIO 18 μg once daily and SFC 50/500 μg twice daily; OLO/TIO 5/5 μg once daily also demonstrated a significant reduction in dyspnea versus TIO 5 μg once daily. Reduction in dyspnea with other LABA/LAMA FDCs versus TIO 18 μg once daily and SFC 50/500 μg twice daily was either non-significant or not evaluated. In the FLASH study, patients who directly switched to IND/GLY 110/50 μg once daily from SFC 50/500 μg twice daily without a washout period showed numerical improvements in TDI total score and a greater proportion of those patients achieved MCID.

Significant improvements in TDI total score were observed with VI/UMEC 25/62.5 μg once daily and VI/UMEC 25/125 μg once daily versus placebo (LSM treatment difference, 0.7 and 0.9, respectively) in COPD patients of Asian ancestry. Improvement in TDI focal score was comparable between patients on IND/GLY 110/50 μg once daily and SFC 50/500 μg twice daily at week 26 (LSM treatment difference, 0.11) in the Chinese cohort of the LANTERN study. In the Japanese cohort of the TOnado trial, OLO/TIO 5/5 μg once daily improved TDI focal score by 0.71 (p=0.05) versus TIO 5 μg once daily, which was greater than the improvement in the overall population.

3. Health-related quality of life and rescue medication use

All LABA/LAMA FDCs improved St. George's Respiratory Questionnaire (SGRQ) scores and significantly increased the number of patients reaching MCID of ≥4 units versus placebo; the proportion of patients achieving MCID was not significantly greater with IND/GLY 110/50 μg once daily versus placebo. In the Japanese cohort of the LANTERN study, OLO/TIO 5/5 μg once daily significantly reduced rescue medication use versus TIO 18 μg once daily and FOR/ACLI 12/400 μg twice daily reduced the use versus placebo. Improvements in SGRQ total score versus SFC 50/500 μg twice daily were either non-significant or not available for LABA/LAMA FDCs, except IND/GLY 110/50 μg once daily. While improvements in SGRQ total score with IND/GLY 110/50 μg once daily were similar to those with SFC 50/500 μg twice daily in the ILLUMINATE and LANTERN studies, IND/GLY 110/50 μg once daily significantly improved SGRQ total score and the proportion of patients achieving MCID compared with SFC 50/500 μg twice daily in the FLAME study.

VI/UMEC 25/62.5 μg once daily and FF/GP 9.6/18 μg twice daily significantly reduced daily rescue medication use compared with TIO 18 μg once daily and placebo; furthermore, OLO/TIO 5/5 μg once daily significantly reduced rescue medication use versus TIO 5 μg once daily and FOR/ACLI 12/400 μg twice daily reduced the use versus placebo. There was a significant reduction in the use of daily rescue medication with IND/GLY 110/50 μg once daily (LSM treatment difference, −0.25; p<0.001) and VI/UMEC 25/62.5 μg once daily (LSM treatment difference, −0.3; p=0.006) versus SFC 50/500 μg twice daily. Daily rescue medication use was significantly less in patients receiving VI/UMEC 25/62.5 μg once daily versus OLO/TIO 5/5 μg once daily (LSM treatment difference, −0.3; p=0.003).
Optimal bronchodilation for COPD

Table 5. Improvement in health-related quality of life and reduction in rescue medication use with LABA/LAMA FDCs versus placebo, TIO and SFC

| Variable                     | IND/GLY 110/50 µg q.d. | VI/UMEC 25/62.5 µg q.d. | OLO/TIO 5/5 µg q.d.* | FOR/ACLI 12/400 µg b.i.d. | FF/GP 9.6/18 µg b.i.d. |
|------------------------------|-------------------------|-------------------------|----------------------|---------------------------|------------------------|
| SGRQ total score             |                         |                         |                      |                           |                        |
| Placebo                      | −3.01                   | −5.51                   | −4.56 to −4.89       | NS to −4.36               | NS to −2.52            |
| TIO 18 µg q.d.               | −1.7 to −3.1            | NS to −2.1              | −1.23 to −2.49       | NA                        | NA                     |
| SFC 50/500 µg b.i.d.         | NS to −1.3              | NS                      | NA                   | NS                        | NA                     |

Proportion of patients achieving MCID for SGRQ total score (odds ratio)

| Placebo                      | NS                      | 2                       | 2.2–2.5              | 2.3                       | NS to 1.49             |
| TIO 18 µg q.d.               | NS to 1.48†             | NS to 1.4               | 1.43 to 1.58         | NA                        | NS                     |
| SFC 50/500 µg b.i.d.         | NS to 1.30              | NA                      | NA                   | NR†                       | NA                     |

Rescue medication use (puffs/day)

| Placebo                      | −0.73 to −1.43          | −0.8                    | NA                   | −0.66; NR†                | −1.04 to −1.08         |
| TIO 18 µg q.d.               | −0.45 to −1.08          | −0.5 to −0.7            | −0.55§               | NA                        | −0.34 to −0.51         |
| SFC 50/500 µg b.i.d.         | NS to −0.39             | NS to −0.3              | NA                   | NA                        | NA                     |

Data expressed as minimum and maximum mean value from all trials analyzed.

*For OLO/TIO 5/5 µg q.d. studies, TIO 5 µg q.d. used as comparator. Differences were statistically significant at all time points up to Week 52 (at week 64, p=0.051). 52.6% patients in FOR/ACLI arm and 55.8% in SFC arm achieved MCID for SGRQ total score. Significant reductions in the use of rescue medication versus placebo were also observed in the AUGMENT study (puffs/day not reported).

For OLO/TIO 5/5 µg q.d. studies, TIO 5 µg q.d. used as comparator. Differences were statistically significant at all time points up to Week 52 (at week 64, p=0.051). 52.6% patients in FOR/ACLI arm and 55.8% in SFC arm achieved MCID for SGRQ total score.

Approximate value.

LABA/LAMA: long-acting β2-agonist/long-acting muscarinic antagonist; FDC: fixed-dose combination; TIO: tiotropium; SFC: salmeterol/fluticasone; IND/GLY: indacaterol/glycopyrronium; q.d.: once daily; VI/UMEC: vilanterol/umeclidinium; OLO/TIO: olodaterol/tiotropium; FOR/ACLI: formoterol/acidinium; b.i.d.: twice daily; FF/GP: formoterol fumarate/glycopyrrolate; SGRQ: St. George’s Respiratory Questionnaire; NS: not significant; NA: not available (no outcomes in any of the trials evaluated); MCID: minimum clinically important difference; NR: not reported (outcomes not reported in required units).

-0.25; p<0.001)19. The rescue medication use was comparable between IND/GLY 110/50 µg once daily and SFC 50/500 µg twice daily after 12 weeks of treatment in the FLASH study26.

Improvement in SGRQ total score was greater with OLO/TIO 5/5 µg once daily versus TIO 5 µg once daily (adjusted mean treatment difference, −3.60; p<0.05) in the Japanese subpopulation of patients from the TOnado study59. VI/UMEC 25/125 µg once daily and VI/UMEC 25/62.5 µg once daily reduced the SGRQ total score (treatment difference, −3.76 and −2.02, respectively), compared with placebo in Asian patients with COPD; the reduction was significant with VI/UMEC 25/125 µg once daily26. IND/GLY 110/50 µg once daily significantly improved SGRQ total score, compared with TIO 18 µg once daily (LSM treatment difference, −3.59; p=0.015) in the Japanese patients, with a higher proportion of patients in IND/GLY group achieving MCID61. In the Chinese cohort of the LANTERN study, a similar improvement in SGRQ total score was observed with IND/GLY 110/50 µg once daily and SFC 50/500 µg twice daily at week 26 (LSM treatment difference, −1.47; p=0.117)60.

Rescue medication use was significantly reduced with VI/UMEC 25/62.5 µg once daily (−0.6, p<0.001), while the percentage of rescue medication-free days over weeks 1–24 was greater with VI/UMEC 25/62.5 µg once daily (64.0%) compared with placebo (48.6%) in the Asian population58. In Japanese patients from SHINE and ARISE studies, IND/GLY 110/50 µg once daily significantly reduced the use of daily rescue medication versus TIO 18 µg once daily (LSM treatment difference, −0.41; p=0.013)61. Reductions in the mean daily number of puffs of rescue medication from baseline (IND/GLY 110/50 µg once daily, −1.75; SFC 50/500 µg twice daily, −1.76) and increase in the percentage of days with no rescue medication use (IND/GLY 110/50 µg once daily, 71.13%; SFC 50/500 µg twice daily, 70.16%) during the treatment period were comparable between the IND/GLY and SFC treatment groups in the Chinese cohort of the LANTERN study60.

4. COPD exacerbations

1) LABA/LAMA versus placebo or TIO

VI/UMEC 25/62.5 µg showed a decrease in the time to the first exacerbation versus placebo (Table 6). Reduction in
the rate of exacerbation, though not significant, was also observed with FOR/ACLI 12/400 μg twice daily versus placebo. VI/UMEC 25/62.5 μg q.d. once daily reduced the risk of COPD exacerbation compared with placebo (hazard ratio [HR], 0.6; p=0.004) in Asian patients with COPD. In patients with severe-to-very-severe airflow limitation and ≥1 exacerbation the previous year, IND/GLY 110/50 μg once daily reduced the rate of moderate or severe exacerbation by 10% versus open-label TIO 18 μg q.d. (p=0.096). In the 52-week DYNAGITO trial, there was a numerical reduction of 7% in the rate of moderate and severe exacerbation with OLO/TIO 5/5 μg once daily versus TIO 5 μg once daily (HR, 0.95; p=0.12); the reduction in rate and risk of exacerbation with OLO/TIO 5/5 μg once daily was non-significant. In the 52-week PINNACLE 3 trial, 23% of patients in the FF/GP 9.6/18 μg once-daily group experienced exacerbation of any severity versus 25.1% patients in the open-label TIO 18 μg once-daily group; the time to first moderate or severe exacerbation was similar between both the groups.

2) LABA/LAMA versus LABA/ICS

IND/GLY is the only LABA/LAMA FDC that significantly reduced the rate of COPD exacerbations compared with LAMA (GLY) and LABA/ICS (SFC) (Table 6). In the FLAME study, IND/GLY 110/50 μg once daily significantly reduced the rate of all (11%) and moderate or severe exacerbations (17%), compared with SFC 50/500 μg twice daily. IND/GLY 110/50 μg once daily significantly prolonged the time to first exacerbation, first moderate or severe exacerbation and first severe exacerbation relative to SFC 50/500 μg twice daily, with respective risk reductions of 16%, 22%, and 19%.

In the FLASH study, the proportion of patients experiencing exacerbations was lower with IND/GLY 110/50 μg once daily versus SFC 50/500 μg twice daily. No significant difference in the incidence of exacerbations was observed with FOR/ACLI 12/400 μg twice daily versus SFC 50/500 μg twice daily in the AFFIRM COPD trial. COPD exacerbations (worsening), captured as safety events, occurred at a similar rate for VI/UMEC and IND/GLY once daily.
25/62.5 μg once daily\textsuperscript{43} and OLO/TIO 5/5 μg once daily\textsuperscript{46} versus SFC 50/500 μg twice daily. In the Chinese cohort of the LANTERN study, the annualized rate of moderate or severe COPD exacerbations was significantly lower (43%) with IND/GLY 110/50 μg once daily compared with SFC 50/500 μg twice daily (rate ratio [RR], 0.57; p=0.015)\textsuperscript{46}. However, with the exception of FLAME study, the remaining studies were not powered to detect an effect of treatment on exacerbation rates. No exacerbation data for FF/GP 12/400 μg twice daily versus LABA/ICS have been reported to date.

Safety of LABA/LAMA FDCs

1. Indacaterol/glycopyrronium

IND/GLY 110/50 μg once-daily demonstrated an acceptable safety profile, with adverse events (AEs) and serious AEs (SAEs) occurrence similar to placebo, TIO or SFC\textsuperscript{26-28,33,35,36}. In a pooled safety analysis, the hazard ratio for IND/GLY versus placebo indicated no significant increase in the overall risk for death (HR, 0.93; 95% CI, 0.34–2.54); cerebro-/cardiovascular event (HR, 0.60; 95% CI, 0.29–1.24); major adverse cardiac event (MACE) (HR, 1.04; 95% CI, 0.45–2.42); pneumonia (HR, 1.10; 95% CI, 0.54–2.25); COPD exacerbations (HR, 0.60; 95% CI, 0.40–0.91); and atrial flutter/fibrillation (HR, 1.03; 95% CI, 0.49–2.18). No significant increase in risk was observed for IND/GLY versus placebo for any of the analyzed cardiovascular (CV) safety endpoints\textsuperscript{46}. The incidence of pneumonia was 3.2% in the IND/GLY group versus 4.8% in the SFC group (p=0.02) in the FLAME study\textsuperscript{28}, and 0.8% versus 2.7% between these treatment groups in the LANTERN study\textsuperscript{27}.

2. Vilanterol/umeclidinium

VI/UMEC 25/62.5 μg was generally well tolerated for up to 24 weeks\textsuperscript{38-41}. The safety profile of VI/UMEC was generally similar to that of the placebo and comparable with that of TIO, OLO/TIO, or SFC. The most commonly reported AEs were headache (7%–10% for VI/UMEC vs. 4%–10% for all comparators) and nasopharyngitis (3%–10% for VI/UMEC vs. 2%–8% for all comparators)\textsuperscript{47}. A pooled analysis of data from eight trials showed that VI/UMEC 25/62.5 μg was not associated with a clinically relevant increase in CV events. Rates of CV death, myocardial infarction, non-fatal stroke and nonfatal cardiac ischemia were ≤1% with VI/UMEC 25/62.5 μg. The trials included in this pooled analysis were not powered to detect differences in MACE outcomes\textsuperscript{48}. In a head-to-head trial that evaluated VI/UMEC versus OLO/TIO, AEs were reported by 25% and 31% of patients, respectively, while 1% or fewer patients in both treatment groups reported on-treatment SAEs. No deaths were reported during the study\textsuperscript{49}.

3. Olodaterol/tiotropium

The safety profile of OLO/TIO 5/5 μg was comparable with that of TIO 5 μg once daily. Treatment-emergent AEs were reported in 74.0% and 73.3% of patients receiving OLO/TIO and TIO respectively in the combined analysis of the TOnado 1 and 2 studies. Most commonly reported AE was COPD exacerbation (32.3% in OLO/TIO and 32.9% in TIO groups)\textsuperscript{31}. CV SAEs and cerebrovascular SAEs occurred at a similar rate in the OLO/TIO and TIO groups, the respective rates were 1.8% and 0.5% in both the groups\textsuperscript{46}. The tolerability profile of OLO/TIO in other phase III trials was generally similar to that in the TOnado trials, with no new safety concerns identified. There were no significant differences in the occurrence of AEs when comparing OLO/TIO with the monocomponents (RR, 0.99; 95% CI, 0.96–1.02) or with SFC (RR, 1.02; 95% CI, 0.85–1.23)\textsuperscript{36,71}. The incidence of SAEs was similar between participants receiving OLO/TIO versus monocomponents or placebo (RR, 0.99; 95% CI, 0.88–1.11)\textsuperscript{34} and versus SFC (RR, 0.80; 95% CI, 0.39–1.65)\textsuperscript{48}.

4. Formoterol/aclidinium

In the ACLIFORM-COPD trial, the incidence of treatment-emergent AEs was comparable across the FOR/ACLI 12/400 μg (50.4%) and placebo (53.1%) groups; the occurrence of SAEs was low and comparable between the FOR/ACLI 12/400 μg (6.0%) and placebo (6.2%) groups\textsuperscript{47}. The incidence of treatment-emergent AEs was 64.2% in the FOR/ACLI 12/400 μg group and 54.5% in the placebo group in the AUGMENT trial\textsuperscript{48}. The most commonly reported AE was COPD exacerbation (9.4% in FOR/ACLI and 13.9% in placebo) in the ACLIFORM-COPD trial\textsuperscript{47} and cough (5.1% in FOR/ACLI and 3.6% in placebo) in the AUGMENT trial\textsuperscript{48}. The incidence of MACE was low and comparable across both treatment arms in both studies. In the AUGMENT study, MACE based on adjudicated SAEs was reported in two patients (0.6%) in the FOR/ACLI 12/400 μg group and two patients (0.6%) in placebo group. One death was reported in the FOR/ACLI 12/400 μg group in the AUGMENT study\textsuperscript{48}.

5. Formoterol fumarate/glycopyrrolate

In the 52-week PINNACLE 3 trial, the incidence of treatment-related AEs was comparable across the FF/GP 9.6/18 μg (12.5%) and TIO 18 μg (12.0%) groups; SAEs occurred in 11.0% and 10.9% of patients in the FF/GP and TIO groups, respectively. Pneumonia was reported more frequently in the FF/GP (2.5%) group, compared with the TIO group (1.3%). The incidence of MACE was low and similar across the treatment groups. Four deaths were reported in the FF/GP treatment group and five deaths were reported in the TIO group\textsuperscript{32}.  

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Discussion

LABA/LAMA FDCs provides an effective treatment option in the management of COPD, and is recommended as the first-line treatment option in the majority of symptomatic patients with COPD. However, evidence of comparative efficacy and safety of LABA/LAMA FDCs is limited owing to scarce head-to-head comparison data among LABA/LAMA FDCs; this review tries to bridge this gap by discussing the key data on various clinical endpoints related to efficacy and safety. TIO and SFC are considered as standards of care for COPD patients, and are commonly used active comparators in LABA/LAMA trials. LABA/LAMA FDCs provided benefits greater than placebo and greater than or similar to TIO in improving lung function, dyspnea, health-related quality of life, reducing rescue medication use and preventing exacerbations. Improvements in clinical endpoints were also noted versus SFC.

While this review provides an indirect comparison between the available LABA/LAMA FDCs, some considerations should be taken into account while interpreting the results. Variability in study methodology e.g., trial duration, patient population, and endpoints, was evident. The GOLD 2018 strategy recommends the use of LABA/LAMA FDCs as an initial therapy for group D patients; however, this patient population was frequently excluded from the studies included in this review. All the studies, with the exception of the SPARK, FLAME, and DYNAGITO studies, did not recruit patients with very severe COPD (GOLD group D patients). Moreover, the majority of the evaluated study population excluded patients with a history of exacerbation, with the exception of three IND/GLY studies (SPARK, LANTERN, and FLAME studies) and one OLO/TIO (DYNAGITO) study. This review also discusses the evaluation of LABA/LAMA FDCs in Asian population to address the interethnic differences in treatment effectiveness. The efficacy of LABA/LAMA FDCs (IND/GLY, VI/UMEC, and OLO/TIO) in Asian population was found to be comparable with that of the overall population. In the Japanese cohort of the TOnado study, OLO/TIO showed greater improvements in lung function, dyspnea and health status, compared with the overall study population. In Korea, IND/GLY is being evaluated in a 12-week trial in mild-to-moderate COPD patients symptomatic on TIO monotherapy.

Spirometry outcomes, health-related quality of life and rescue medication use were the main endpoints studied for most of the evaluated LABA/LAMA FDCs versus placebo. Data on other clinical endpoints were sparse, and not consistently reported. Improvement in lung function was consistent with all the evaluated LABA/LAMA FDCs versus placebo, LAMA and LABA/ICS. However, improvements in lung function did not always translate to similar clinical improvements in symptoms and exacerbations. While improvement in dyspnea was observed for all evaluated LABA/LAMA FDCs versus placebo except FF/GP, differences were either non-significant or not available for most of the evaluated LABA/LAMA FDCs versus LAMA and LABA/ICS. Improvement in health status was evident for all dual bronchodilators compared with placebo and LAMA; while improvement in health status was not assessed for FOR/ACLI versus TIO, it was non-significant with FF/GP versus TIO. Furthermore, a significant reduction in the SGRQ total score was observed with IND/GLY versus SFC, with a significant proportion of patients achieving clinically meaningful improvement in the SGRQ total score; other LABA/LAMA FDCs were either not evaluated or were non-significant versus SFC in improving the health status. A significant reduction in the use of rescue medication was observed with LABA/LAMA FDCs versus placebo and TIO; data are not available for OLO/TIO versus placebo and for FOR/ACLI versus TIO.

Exacerbations were evaluated as the primary endpoint in only two trials for IND/GLY, and one trial for OLO/TIO; other studies have not either evaluated exacerbations as a primary endpoint or were underpowered. FLAME was a landmark study to show superiority of IND/GLY in reducing the rate of exacerbation and improving lung function compared with SFC in exacerbating patients with moderate-to-very-severe COPD. VI/UMEC prolonged the time-to-first exacerbation (all exacerbations) versus placebo and TIO, while IND/GLY significantly reduced the annualized rate and risk of exacerbations (all and moderate-to-severe) versus SFC. In the SPARK study, IND/GLY significantly reduced the rate of all COPD exacerbations versus TIO, while a numerical reduction was observed for the rate of moderate or severe exacerbations. Reduction in the rate of moderate-to-severe exacerbations, though not significant, was also observed with OLO/TIO versus TIO in the DYNAGITO trial. VI/UMEC showed no significant effects on the rate of exacerbations compared with TIO in the active comparator studies. Nevertheless, these results confirm the benefit of LABA/LAMA versus LAMA, and reinforce the role of LABA/LAMA FDCs in current treatment recommendations.

In a head-to-head study, VI/UMEC was found to be superior to OLO/TIO in improving trough FEV1; the study presented some limitations such as absence of a placebo arm, short study duration of 8 weeks and open-label administration of treatments. In another head-to-head trial, indacaterol/glycopyrrolate 27.5/15.6 μg once daily and VI/UMEC 25/62.5 μg once daily provided clinically meaningful and comparable bronchodilation at week 12; these results pertain to the U.S. approved dose and formulation of IND/GLY and should not be extrapolated to the formulation approved outside of the United States.

All the LABA/LAMA FDCs were found to be generally well tolerated and had similar safety profiles. No major side effects were reported with LABA/LAMA FDCs in any of the trials considered for this review. COPD worsening was the most common AE; other frequently reported AEs included cough.
headache, nasopharyngitis, and upper and lower respiratory tract infections, which occurred at a similar incidence compared with placebo. Data on CV events, a common risk associated with LABAs, were inconsistent among the evaluated trials. An increased rate of pneumonia was reported with LABA/ICS compared with LABA/LAMA.

Another key aspect to consider while comparing LABA/LAMA FDCs is the choice of inhaler device, which is as important as the drug molecule, and requires careful consideration of patient’s specific needs and inhaler techniques. The majority of the available LABA/LAMA FDCs use dry powder inhalers, while OLO/TIO is delivered using the soft-mist inhaler Respimat and FF/GP is delivered via the Aerosphere pressurized metered-dose inhaler device. Ease of use and patient satisfaction are key attributes associated with preference for a particular inhaler device. Patients and health care providers also reported breath actuation as an important device attribute, as it eliminated the need for co-ordination between actuation and inspiration for effective drug inhalation. Errors in device handling are not taken into account in clinical trials and are often underestimated in real life; on an average, more than two-thirds of patients make at least one error in device handling. A real-life study that evaluated handling of most frequently used inhaler devices reported that device handling errors, including critical errors, were very common in COPD patients, and were associated with severe COPD exacerbations, even for drugs and devices that were found to be effective in reducing exacerbations in controlled clinical trials. Overall, selection of the inhaler device for LABA/LAMA FDCs is influenced by the factors described above and by evidence from both controlled and real-life assessments.

The long-term treatment of COPD with ICS has been associated with SAEs such as pneumonia; therefore, identification of patients who will benefit the most from ICS treatment is necessary to prevent undue exposure of patients to the above risks. In this regard, the recently concluded SUNSET trial has explored the effect of a switch from long-term ICS-containing triple therapy to IND/GLY, in non-exacerbating patients with moderate-to-severe COPD. Post-hoc analyses of several studies have evaluated blood eosinophil cut-offs that could predict the efficacy of LABA/ICS in COPD patients. A recent pre-specified analysis of the FLAME study prospectively investigated the role of blood eosinophils as a predictive biomarker for the use of LABA/ICS in preventing COPD exacerbations versus a LABA/LAMA. In this analysis, IND/GLY was found to be superior to SFC in preventing exacerbations in patients with ≤2%, ≥2%, <3%, ≤3%, and <150 cells/μL blood eosinophil count. At no cut-off was SFC found to be superior to IND/GLY in preventing exacerbation. Blood eosinophil cut-offs may predict the efficacy of LABA/ICS in preventing exacerbations versus bronchodilator monotherapy, but no such evidence is available to identify patients who should receive LABA/ICS instead of LABA/LAMA FDCs.

**Conclusion**

Current evidence suggests that optimal bronchodilation with LABA/LAMA FDCs plays a vital role in COPD management including reduction of exacerbations. LABA/LAMA FDCs provide greater benefits versus placebo and active comparators in patients with COPD, although with some degree of variability. There is not an equivalent amount of evidence on efficacy outcomes for all LABA/LAMA FDCs. The large IGNITE clinical trial program has established the efficacy of IND/GLY across different outcomes in COPD patients of all severities. Additionally, the TOnado program with OLO/TIO has also provided a large amount of data about efficacy and safety of this combination in COPD. However, similar robust evidence is lacking to date for other dual bronchodilators. Therefore, care should be taken when extrapolating the findings for singular LABA/LAMA FDC to the entire drug class. Greater patient and physician education and interaction are needed to ensure the use of appropriate therapy for appropriate patients.

**Authors’ Contributions**

Conceptualization: all authors. Methodology: all authors. Data curation: all authors. Writing - original draft preparation: all authors. Writing - review and editing: all authors. Approval of final manuscript: all authors.

**Conflicts of Interest**

M.M. has received speaker fees from Boehringer Ingelheim, Chiesi, Cipla, Menarini, Rovi, Grifols and Novartis, and consulting fees from Boehringer Ingelheim, Chiesi, GlaxoSmithKline, Gebro Pharma, CSL Behring, Novartis and Grifols. S.B., V.V., and R.L. are employees of Novartis. The work was funded by Novartis Korea Ltd.

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