

# Efficacy of tiotropium–olodaterol fixed-dose combination in COPD

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**Abstract:** Tiotropium–olodaterol, formulated in the Respimat soft-mist inhaler, is an inhaled fixed-dose combination (FDC) of a long-acting muscarinic antagonist (LAMA) and a long-acting  $\beta_2$ -agonist (LABA), commercialized under the name of Spiolto or Stiolto. The efficacy of tiotropium–olodaterol 5–5  $\mu\text{g}$  once daily in adult patients with COPD was documented in eleven large, multicenter trials of up to 52 weeks duration. Tiotropium–olodaterol 5–5  $\mu\text{g}$  not only improved spirometric values to a significantly greater extent than placebo but also resulted in statistically significant beneficial effects on dyspnea, markers of hyperinflation, use of rescue medication, health-related quality of life, and exercise endurance. Improvements exceeded the minimal clinically important difference (MCID) for forced expiratory volume in 1 second ( $\text{FEV}_1$ ), dyspnea, and quality of life. Differences between tiotropium–olodaterol 5–5  $\mu\text{g}$  and the respective monocomponents were statistically significant for  $\text{FEV}_1$ , dyspnea, markers of hyperinflation, use of rescue medication, and health-related quality of life, but did not reach the MCID. However, dual bronchodilatation significantly increased the number of patients who exceeded the MCID for dyspnea and quality of life. Moreover, tiotropium–olodaterol 5–5  $\mu\text{g}$  was significantly more effective than salmeterol–fluticasone (FDC) twice daily at improving pulmonary function. Differences between tiotropium–olodaterol and other LAMA/LABA FDCs were not observed for  $\text{FEV}_1$  or other efficacy markers. Therefore, tiotropium–olodaterol is a valuable option in the treatment of COPD patients who remain symptomatic under monotherapy.

**Keywords:** COPD, bronchodilatation, dyspnea, exacerbation, exercise tolerance, LABA, LAMA, spirometry

## Introduction

COPD is a preventable and treatable disease characterized by persistent airflow limitation caused by smoking and/or exposure to noxious gases. This disease is characterized by chronic and progressive breathlessness, cough, sputum production, and reduced exercise tolerance, punctuated by episodes of acute worsening of symptoms needing additional treatment and possibly emergency or hospital care. This all eventually leads to reduced activities of daily living and poor quality of life. COPD is not curable, and represents a major cause of morbidity and mortality with a considerable economic and social impact.<sup>1</sup>

COPD results from persistent pathologic abnormalities in the small airways, most often associated with parenchymal destruction, which are both progressive in nature and lead to an annual decline in forced expiratory volume in 1 second ( $\text{FEV}_1$ ) that is faster than normal.<sup>2–6</sup> Small-airway disease (obstructive bronchiolitis) leads to airflow limitation and spirometric abnormalities. Parenchymal destruction and loss of alveoli (emphysema) further enhance that airflow limitation and are also responsible for an abnormal increase in static lung volumes and a decrease in forced

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vital capacity (FVC). For many years, the Global Initiative for Chronic Obstructive Lung Disease (GOLD) has used an  $FEV_1:FVC$  ratio of  $<0.7$  to define airway obstruction in COPD patients and classified them into four stages depending on their postbronchodilator  $FEV_1$  value. The new GOLD COPD classification distinguishes four different patient categories, A–D, according to symptoms, degree of airflow limitation, and exacerbation history.<sup>1</sup> The management of COPD consists essentially of smoking cessation, reduction of occupational risk factors, influenza vaccination, promotion of physical activity, pulmonary rehabilitation, and treatment with bronchodilating and anti-inflammatory medicines.<sup>1</sup>

## Scientific and clinical rationale for dual long-acting bronchodilatation in COPD

In COPD, airway obstruction is partially reversible, being regulated by the parasympathetic and sympathetic pathways. Although the major part of this reversible component is believed to be cholinergic in nature, the activation of  $\beta_2$ -adrenoceptors, which are abundantly present on human airway smooth-muscle cells, will stimulate adenylyl cyclase activity and contribute to smooth-muscle relaxation. Consequently, combining  $\beta_2$ -agonists and muscarinic antagonists is a logical option, not only because a muscarinic antagonist can reduce the bronchoconstrictive effect of acetylcholine but also because  $\beta_2$ -agonists reduce the release of acetylcholine, and amplify in that way the bronchodilatation elicited by direct stimulation of the  $\beta_2$ -adrenoceptors on the smooth-muscle cells.<sup>7–9</sup>

Inhaled short-acting bronchodilators are widely used for symptomatic relief in COPD patients at any stage of disease severity.<sup>1</sup> Their acute effect on  $FEV_1$  is variable,<sup>10</sup> and the relationship between spirometric changes and symptoms is rather poor.<sup>11</sup> Physiological studies have shown, however, that better lung emptying, resetting of functional residual capacity (FRC) at a lower lung volume, and hence a reduction in lung hyperinflation are the main mechanisms by which COPD patients derive symptomatic benefits from inhaled short-acting bronchodilators.<sup>12–14</sup> Although maximal bronchodilatation can be achieved with a high dose of one single agent, combining two different classes of short-acting bronchodilators allows the use of lower doses, with the same efficacy results and fewer adverse effects.<sup>15</sup>

Tiotropium (TIO) was the first 24-hour long-acting muscarinic antagonist (LAMA) specifically developed for the treatment of COPD. It not only improves spirometric variables, dyspnea, and exercise tolerance<sup>13,16</sup> but also results

in significant enhancements in quality of life, improved responses to pulmonary rehabilitation, and significant reductions in exacerbation rate.<sup>17,18</sup> Likewise, long-acting  $\beta_2$ -agonists (LABAs) yield beneficial effects on dyspnea, exercise tolerance, and quality of life to an extent that is largely comparable in magnitude with those of TIO.<sup>19</sup> However, TIO provides better protection against exacerbations compared to LABAs, such as salmeterol (SALM) and indacaterol (IND).<sup>19–21</sup> The GOLD strategy currently recommends the addition of a second long-acting bronchodilator for patients in GOLD COPD classes B–D to optimize symptom relief and produce greater and more sustained bronchodilatation in cases where the patient's symptoms have not improved with single agents.<sup>1</sup>

In the last few years, the number of LABAs and LAMAs has expanded, adding several agents to the first-generation long-acting bronchodilators: SALM and formoterol (FORM) as LABAs and TIO as a LAMA. These include IND, olodaterol (OLO), and vilanterol (VIL) as LABAs, and glycopyrronium (GLY), aclidinium (ACL), and umeclidinium (UMEC) as LAMAs.<sup>7,8</sup> In the light of the GOLD recommendations, pharmaceutical companies have combined LAMAs and LABAs in one inhaler.

Four LAMA/LABA fixed-dose combinations (FDCs) are currently approved by the European Medicines Agency for the treatment of COPD: UMEC/VIL, TIO/OLO, and GLY/IND as once-daily FDCs, and ACL/FORM as a twice-daily FDC. Conversely, the US Food and Drug Administration has approved only UMEC/VIL and TIO/OLO as once-daily FDCs and ACL/FORM and GLY/IND as twice-daily FDCs, the latter at a reduced dose.<sup>22</sup> A fifth FDC, GLY/FORM, is still under clinical development.

The purpose of this review is to assess the clinical effects of TIO/OLO FDCs at the recommended daily dose of TIO 5  $\mu$ g and OLO 5  $\mu$ g (TIO/OLO 5/5  $\mu$ g, ie, two inhalations of TIO/OLO 2.5/2.5  $\mu$ g once daily). The first part of this review focuses on differences between TIO/OLO 5/5  $\mu$ g and placebo, between TIO/OLO 5/5  $\mu$ g and their respective monocomponents TIO and OLO, and between TIO/OLO 5/5  $\mu$ g and the LABA–inhaled corticosteroid (ICS) FDC SALM–fluticasone (FLU). The second part concentrates on comparisons between TIO/OLO 5/5  $\mu$ g and other LAMA/LABA FDCs, whereas the potential clinical benefits of adding a LABA to a LAMA in the treatment of COPD are reviewed in the last part of the paper. The pharmacological properties of TIO/OLO 5/5  $\mu$ g FDC will not be considered in this paper, as they have recently been reviewed in detail elsewhere.<sup>23–25</sup> Safety issues are however briefly summarized.

## Therapeutic efficacy

Data presented in this section are based on several Phase III, multicenter, randomized, double-blind, controlled studies on the effects of TIO/OLO 5/5 µg in patients with COPD (Table 1). In these studies, over 10,000 patients have been involved. Ten of these studies (eight of which were replicate studies) have been published as full papers in peer reviewed journals,<sup>26–31</sup> one being available only as a European Respiratory Society abstract.<sup>32</sup> Four studies used a crossover design,<sup>26,29,31,32</sup> six studies were placebo controlled,<sup>26,28,31,32</sup> and four studies compared TIO/OLO with TIO and/or OLO as monotherapy.<sup>27,30</sup> In one trial, TIO/OLO was compared with the LABA/ICS SALM/FLU FDC.<sup>29</sup> Based on findings from earlier dose-ranging studies,<sup>33</sup> two once-daily dosages of TIO/OLO, 2.5/5 and 5/5 µg were assessed in these trials. This section focuses only on the data of the currently recommended dosage of once-daily TIO/OLO 5/5 µg, which generally

provides greater benefits than the once-daily 2.5/5 µg dosage in terms of pulmonary function, health-related quality of life (HR-QoL) and most other COPD outcomes. In almost all studies, TIO/OLO FDC was formulated in the Respimat® soft-mist inhaler. In the first two replicate studies,<sup>30</sup> however, TIO and OLO were inhaled separately via HandiHaler® and Respimat, respectively. In these two studies, TIO was provided at the equivalent dose of 18 µg per inhalation.

In all these randomized controlled trials (RCTs), patients were aged ≥40 years and were current or former cigarette smokers, with a smoking history of >10 pack-years. Importantly, patients with a current diagnosis of asthma or other known respiratory disorders were excluded. Patients participating in these studies exhibited postbronchodilator FEV<sub>1</sub>:FVC ratio <0.7 and postbronchodilator FEV<sub>1</sub> <80%<sup>26,27</sup> or 30%–80% of the predicted value.<sup>28–32</sup> An overview of the key characteristics of the TIO/OLO

**Table 1** Completed Phase III studies comparing clinical effects of tiotropium–olodaterol fixed-dose combinations with mono-components and/or placebo in patients with COPD

Title	Study	Daily treatments (patients randomized)	Primary end point	Key secondary end points
ANHELTO I+2	ZuWallack et al <sup>30</sup>	OLO 5 µg + TIO 18 µg (567/566) <sup>a</sup> TIO 18 µg (565/566)	FEV <sub>1</sub> AUC <sub>0–3</sub> at week 12 Trough FEV <sub>1</sub> at week 12	SGRQ total score at week 12
TONADO I+2	Buhl et al <sup>27</sup>	TIO/OLO 5/5 µg (522/507) TIO/OLO 2.5/5 µg (522/508) OLO 5 µg (528/510) TIO 5 µg (527/506) TIO 2.5 (525/507)	FEV <sub>1</sub> AUC <sub>0–3</sub> at week 24 Trough FEV <sub>1</sub> at week 24 SGRQ at week 24	TDI at week 24
VIVACITO	Beeh et al <sup>26</sup>	TIO/OLO 5/5 µg (139) TIO/OLO 2.5/5 µg (136) OLO 5 µg (138) TIO 5 µg (138) TIO 2.5 (137) PLA (138)	FEV <sub>1</sub> AUC <sub>0–24</sub> at week 6	FEV <sub>1</sub> AUC <sub>0–12</sub> at week 6 FEV <sub>1</sub> AUC <sub>12–24</sub> at week 6 Peak FEV <sub>1</sub> AUC <sub>0–3</sub> at week 6 Trough FEV <sub>1</sub> at week 6 ΔRV and ΔFRC at week 6
OTEMTO I+2	Singh et al <sup>28</sup>	TIO/OLO 5/5 µg (204/202) TIO/OLO 2.5/5 µg (202/202) TIO 5 µg (204/203) PLA (204/202)	SGRQ at week 12 FEV <sub>1</sub> AUC <sub>0–3</sub> at week 12 Trough FEV <sub>1</sub> at week 12	TDI at week 12
ENERGITO	Beeh et al <sup>29</sup>	TIO/OLO 5/5 µg (221) TIO/OLO 2.5/5 µg (215) SALM/FLU 50/500 µg BID (215) SALM/FLU 50/250 µg BID (212)	FEV <sub>1</sub> AUC <sub>0–12</sub> at week 6	FEV <sub>1</sub> AUC <sub>0–24</sub> FEV <sub>1</sub> AUC <sub>12–24</sub> at week 6 Peak FEV <sub>1</sub> AUC <sub>0–3</sub> at week 6 Trough FEV <sub>1</sub> at week 6
TORRACTO	Maltais et al <sup>32b</sup>	TIO/OLO 5/5 µg (139) TIO/OLO 2.5/5 µg (133) PLA (132)	Endurance time during constant work rate cycle ergometry at week 12	Endurance time during shuttle walking test at week 12 Pre-exercise IC at week 12
MORACTO I+2	O'Donnell et al <sup>31</sup>	TIO/OLO 5/5 µg (226/224) TIO/OLO 2.5/5 µg (223/219) TIO 5 µg (227/218) OLO 5 µg (217/219) PLA (222/216)	Pre-exercise IC at week 6 Endurance time during constant work-rate cycle ergometry at week 6	

**Notes:** <sup>a</sup>Treatments were inhaled separately via OLO Respimat and TIO HandiHaler; <sup>b</sup>available only as abstract. I+2, replicate studies.

**Abbreviations:** AUC, area under the curve; BID, bis in die (twice daily); FEV<sub>1</sub>, forced expiratory volume in 1 second; IC, inspiratory capacity; PLA, placebo; SALM/FLU, salmeterol/fluticasone; SGRQ, St George's Respiratory Questionnaire (score); TDI, Transition Dyspnea Index; TIO/OLO, tiotropium–olodaterol fixed-dose combination; ΔRV, change in RV after treatment versus placebo; ΔFRC, change in FRC after treatment versus placebo.

RCTs is provided in Table 1. The majority of patients in the ANHELTO, VIVACITO, OTEMTO, TONADO, and ENERGITO studies belonged to GOLD stage II (50%–72%) or stage III (27%–40%).<sup>26–30</sup> COPD stage IV patients were absent in the ENERGITO, MORACTO, and TORRACTO studies,<sup>29,31,32</sup> whereas for the ANHELTO, OTEMTO, VIVACITO, and TONADO studies only 0.2%, 0.5%–1.5%, 2%, and 10%–12%, respectively, were classified as GOLD stage IV.<sup>26–28,30</sup> The distribution of COPD patients according to the new GOLD subgroups was available for two studies: in OTEMTO, 30% of the patients belonged to GOLD subgroup A, 30% to subgroup B, 15.3% to subgroup C, and 24.7% to subgroup D, whereas in TONADO 41.3% were classified as GOLD subgroups A and B and 58.7% as GOLD subgroups C and D.<sup>34,35</sup>

The percentage of patients on ICS varied between 9.6% for ENERGITO and 34.8%–41.9% for OTEMTO, 35.8%–37.8% for ANHELTO, 41.1% for VIVACITO, and 45.1%–49.2% for TONADO.<sup>26,28–30</sup> Between 0.2% and 11% of patients were on xanthines.<sup>26,27,29,36</sup> Inhaled salbutamol was provided as rescue medication for use throughout these studies.

## Comparison between TIO/OLO 5/5 µg and placebo

FDC TIO/OLO 5/5 µg was associated with clinically and statistically significant benefits over placebo for several measures of efficacy and HR-QoL (Tables 2 and 3).

### Pulmonary function

TIO/OLO 5/5 µg once daily was effective in improving pulmonary function in patients with COPD in one 6-week

and two 12-week trials.<sup>26,28</sup> Compared with placebo, dual bronchodilatation significantly improved the 0- to 24-hour weighted mean FEV<sub>1</sub> by 280 mL and trough FEV<sub>1</sub> by 160 mL, as well as the FEV<sub>1</sub> area under the curve (AUC) from 0 to 12 hours (FEV<sub>1</sub> AUC<sub>0–12</sub>), FEV<sub>1</sub> AUC<sub>12–24</sub>, and FEV<sub>1</sub> AUC<sub>0–3</sub> after 6 weeks.<sup>26</sup> Similar observations were made for trough FEV<sub>1</sub> (160 mL) and FEV<sub>1</sub> AUC<sub>0–3</sub> after 12 weeks of treatment in another study.<sup>28</sup> All improvements exceeded the threshold of clinical significance, estimated to be 100–140 mL.<sup>37,38</sup>

### Symptoms

TIO/OLO 5/5 µg once daily was associated with statistically and clinically significant benefits in dyspnea relative to placebo. In OTEMTO 1 and 2, TIO/OLO 5/5 µg significantly improved Mahler Transition Dyspnea Index (TDI) focal scores at 12 weeks compared with placebo by 2.05 and 1.2 units, respectively,<sup>28</sup> exceeding the minimal clinically important difference (MCID) of ≥1 unit defined for that variable.<sup>37,38</sup> The overall number of responders was 53.9% after TIO/OLO 5/5 µg and 26.2% after placebo. Consistent with these findings, significantly more patients on TIO/OLO 5/5 µg than placebo recipients also reduced the use of rescue medication from three puffs/day to 1.8 puffs/day.<sup>39</sup>

### Health-related quality of life

Clinically and statistically significant differences were observed between once-daily TIO/OLO 5/5 µg and placebo for HR-QoL. St George's Respiratory Questionnaire (SGRQ) scores decreased by 4.89 units and 4.56 units compared with placebo in OTEMTO 1 and 2, respectively.<sup>28</sup> The percentage of patients classified as SGRQ responders (defined as an improvement from baseline exceeding 4 units)<sup>37,38</sup>

**Table 2** Differences in TIO/OLO 5/5 µg, TIO monotherapy, OLO monotherapy, and PLA for different spirometric end points derived from key clinical studies

Study	AUC <sub>0–24</sub> FEV <sub>1</sub> (mL)	Peak <sub>0–3</sub> FEV <sub>1</sub> (mL)	AUC <sub>0–3</sub> FEV <sub>1</sub> (mL)	Trough FEV <sub>1</sub> (mL)
<b>TIO/OLO 5/5 µg vs PLA</b>				
Beeh et al <sup>26</sup>	Δ=280	411 vs 72		201 vs -6
Singh et al <sup>28</sup>			Δ=331 and Δ=299	Δ=162 and Δ=166
<b>TIO/OLO 5/5 µg vs TIO 5 µg</b>				
Beeh et al <sup>26</sup>	Δ=110	411 vs 300		201 vs 122
Singh et al <sup>28</sup>			Δ=111 and Δ=105	Δ=28 and Δ=39
Buhl et al <sup>27</sup>			Δ=117 and Δ=103	Δ=71 and Δ=50
<b>TIO 18 µg + OLO 5 µg<sup>a</sup> vs TIO 18 µg</b>				
ZuWallack et al <sup>30</sup>			Δ=117 and Δ=106	Δ=60 and Δ=40
<b>TIO/OLO 5/5 µg vs OLO 5 µg</b>				
Beeh et al <sup>26</sup>	Δ=115	411 vs 291		201 vs 109
Buhl et al <sup>27</sup>			Δ=123 and Δ=132	Δ=82 and Δ=88

**Note:** <sup>a</sup>Treatments inhaled separately via OLO Respimat and TIO HandiHaler.

**Abbreviations:** AUC, area under the curve; FEV<sub>1</sub>, forced expiratory volume in 1 second; PLA, placebo; TIO/OLO, tiotropium–olodaterol fixed-dose combination.

**Table 3** Differences in TIO/OLO 5/5 µg, TIO monotherapy, OLO monotherapy, and PLA in key clinical studies, highlighting number of responders and number needed to treat

Study	TDI	TDI responders (%)	NNT (95% CI)	SGRQ	SGRQ responders (%)	NNT (95% CI)
<b>TIO/OLO 5/5 µg vs PLA</b>						
Singh et al <sup>28</sup>	2.1 and 1.2	53.9 vs 26.2	4 (3.1–4.2)	–4.89 and –4.59	53.1 vs 31.2 and 51.8 vs 32.6	5 (3.8–5.7) and 6 (4.2–6.6)
<b>TIO/OLO 5/5 µg vs TIO 5 µg</b>						
Singh et al <sup>28</sup>	0.6 and 0.6	53.9 vs 41	8 (5.8–11.7)	–2.49 and –1.72	53.1 vs 41.7 and 51.8 vs 41.1	9 (6.3–14.2) and 10 (6.6–15.7)
Buhl et al <sup>27</sup>	0.4	54.9 vs 50.6 (NS)	24 (NS)	–1.23	57.5 vs 48.7	12 (7.6–22.5)
<b>TIO 18 µg + OLO 5 µg vs TIO 18 µg</b>						
ZuWallack et al <sup>30</sup>				–1.85	49.3 vs 42.5	15 (9–40)
<b>TIO/OLO 5/5 µg vs OLO 5 µg</b>						
Buhl et al <sup>27</sup>	0.4	54.9 vs 48.2	15 (9–42.9)	–1.69	57.5 vs 44.8	8 (5.9–12)

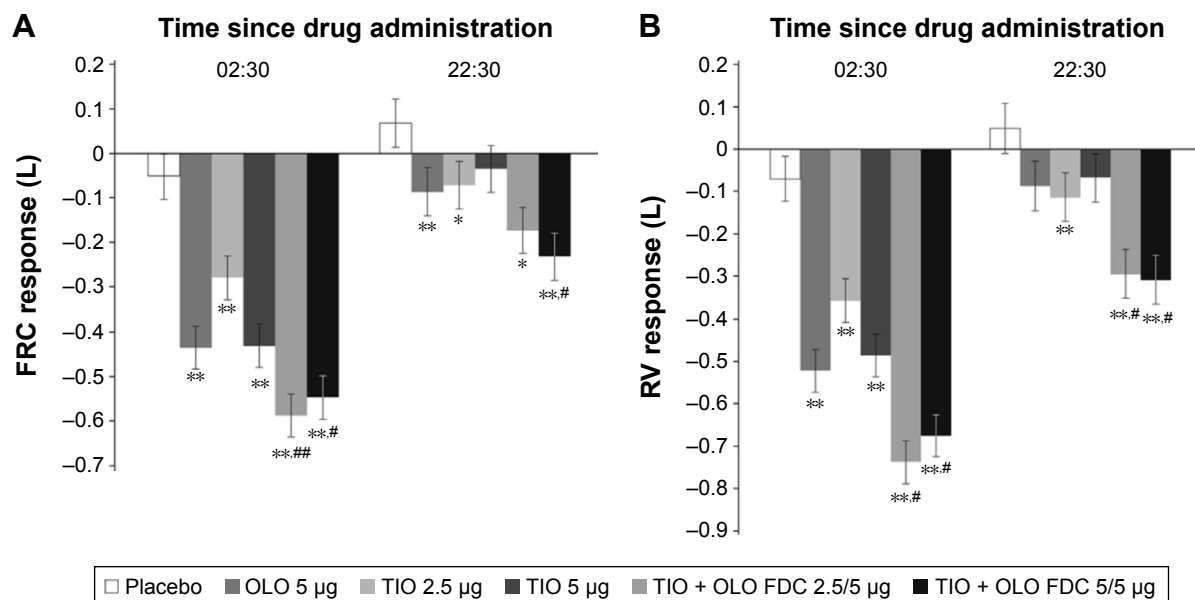
**Abbreviations:** NNT, number needed to treat; CI, confidence interval; NS, not significant; PLA, placebo; SGRQ, St George's Respiratory Questionnaire (score); TDI, Transition Dyspnea Index; TIO/OLO, tiotropium–olodaterol fixed-dose combination.

at 12 weeks increased from 31.9% in the placebo arm to 52.4% (full analysis) with TIO/OLO 5/5 µg (Table 2), with an odds ratio of being a responder for TIO/OLO 5/5 µg versus placebo of approximately 2.5 (95% confidence interval [CI] 1.6–3.8).<sup>28</sup>

#### Markers of hyperinflation and exercise tolerance

TIO/OLO 5/5 µg was associated with reductions in FRC and residual volume (RV) at 2 hours 30 minutes and 22 hours 30 minutes postdose relative to placebo (Figure 1). Changes from baseline for FRC were –547 mL after TIO/OLO 5/5 and –52 mL after placebo at 2.5 hours postdose. Even at

22.5 hours postdose, the difference between TIO/OLO 5/5 µg and placebo exceeded 300 mL. These improvements in FRC and RV were mirrored by changes in inspiratory capacity (IC): 351 mL after TIO/OLO 5/5 µg and 16 mL after placebo compared with baseline values 2.5 hours postdose.<sup>26</sup> Differences between treatments still averaged 200 mL 22.5 hours postdose and reached statistical significance. These beneficial effects of TIO/OLO 5/5 µg on hyperinflation at rest were confirmed in three other placebo-controlled crossover studies. The MORACTO studies demonstrated that TIO/OLO 5/5 µg once daily improved IC by 244 and 265 mL after 6 weeks, whereas TORRACTO showed an IC increase of 234 mL



**Figure 1** Adjusted mean FRC (A) and RV (B) responses at 6 weeks ± SE, measured by body plethysmography at 2 hours 30 minutes (02:30) and 22 hours 30 minutes postdose.

**Notes:** \* $P < 0.05$  versus placebo; \*\* $P < 0.0001$  versus placebo; # $P < 0.05$  versus all monotherapies; ### $P < 0.01$  versus all monotherapies. Reproduced from Beeh KM, Westerman J, Kirsten AM, et al. The 24-h lung-function profile of once-daily tiotropium and olodaterol fixed-dose combination in chronic obstructive pulmonary disease. *Pulm Pharmacol Ther.* 2015;32:53–59.<sup>26</sup>

**Abbreviations:** FRC, functional residual capacity; RV, residual volume; SE, standard error; OLO, olodaterol; TIO, tiotropium; FDC, fixed-dose combination.

after a 12-week treatment with TIO/OLO 5/5  $\mu\text{g}$ .<sup>23,40,41</sup> These gains in IC persisted during exercise and contributed to significantly improved exercise endurance upon treatment with TIO/OLO 5/5  $\mu\text{g}$ . Compared with placebo, endurance time during constant work-rate cycle ergometry increased by 79 and 54 seconds in MORACTO<sup>31</sup> and 64 seconds in TORRACTO.<sup>32</sup> Breathing discomfort at isotime was reduced in patients treated with TIO/OLO 5/5  $\mu\text{g}$ , with mean Borg scale values of 4.44 with TIO/OLO 5/5  $\mu\text{g}$  and 5.14 with placebo.<sup>31</sup> In that study, the endurance shuttle-walk test also increased by 21% with TIO/OLO 5/5  $\mu\text{g}$  at week 12 compared with placebo.

## Comparison between TIO/OLO 5/5 $\mu\text{g}$ and TIO 5 $\mu\text{g}$ monotherapy

For a variety of clinical endpoints, differences between TIO/OLO 5/5  $\mu\text{g}$  FDC and TIO 5  $\mu\text{g}$  monotherapy – both administered via the Respimat soft-mist inhaler – generally reached statistical significance in favor of dual bronchodilatation, without however reaching the threshold of clinical significance (Tables 2 and 3). However, we need to take into account the fact that thresholds of MCIDs have been established in the past by comparing a single active treatment with placebo. Whether the same thresholds of MCIDs should be applied when comparing dual combinations with their active monocomponents is still a matter of debate.<sup>38</sup>

### Pulmonary function

Data from the VIVACITO trial showed that once-daily TIO/OLO 5/5  $\mu\text{g}$  produced significant improvements in FEV<sub>1</sub>, AUC<sub>0–24</sub>, FEV<sub>1</sub> AUC<sub>0–12</sub>, and FEV<sub>1</sub> AUC<sub>12–24</sub> compared with once-daily TIO 5  $\mu\text{g}$  monotherapy (Table 2).<sup>26</sup> Moreover, TIO/OLO 5/5  $\mu\text{g}$  also significantly improved AUC<sub>0–3</sub>, FEV<sub>1</sub> and trough FEV<sub>1</sub> at the end of the study period compared with TIO 5  $\mu\text{g}$ . Likewise, ANHELTO 1 and 2 showed that dual bronchodilatation also improved pulmonary function significantly more than once-daily monotherapy with TIO.<sup>30</sup> In these two replicate studies, OLO 5  $\mu\text{g}$  was inhaled via the Respimat, while TIO 18  $\mu\text{g}$  (equivalent to TIO 5  $\mu\text{g}$  via Respimat) was administered via HandiHaler. In the OTEMTO 1 and 2 studies, statistically significant differences in favor of TIO/OLO 5  $\mu\text{g}$  were seen at the end of the study periods compared with TIO 5  $\mu\text{g}$  monotherapy. Differences ranged between 105 and 111 mL for peak AUC<sub>0–3</sub>, FEV<sub>1</sub> and between 28 and 39 mL for trough FEV<sub>1</sub>.<sup>28</sup> Similar findings were observed in TONADO, in which more than 5,000 patients were involved:<sup>27</sup> statistically significant improvements were noted for both AUC<sub>0–3</sub>, FEV<sub>1</sub> and trough

FEV<sub>1</sub> with TIO/OLO 5  $\mu\text{g}$  compared with TIO 5  $\mu\text{g}$  after 24 weeks (Table 2). These improvements in FEV<sub>1</sub> persisted for 52 weeks. Responses in trough FVC and AUC<sub>0–3</sub> FVC to once-daily TIO/OLO 5/5  $\mu\text{g}$  and TIO 5  $\mu\text{g}$  were similar to those reported in other trials.<sup>28</sup>

### Symptoms and use of rescue medication

As summarized in Table 3, TIO/OLO 5/5  $\mu\text{g}$  differed significantly from TIO 5  $\mu\text{g}$  monotherapy in terms of alleviating symptoms of dyspnea, as measured by TDI at week 12, the mean difference equaling approximately 0.6 units in both OTEMTO studies.<sup>28</sup> The overall number of responders on the TDI was 53.9% after TIO/OLO 5  $\mu\text{g}$  and 41% after TIO 5  $\mu\text{g}$ , corresponding with a number needed to treat (NNT) of eight.<sup>39</sup> TIO/OLO 5/5  $\mu\text{g}$  also significantly lowered the use of rescue salbutamol more than TIO 5  $\mu\text{g}$ : 1.8 puffs/day for dual bronchodilatation versus 2.4 puffs/day for once-daily TIO 5  $\mu\text{g}$ .<sup>39</sup> TONADO showed comparable statistically significant differences between TIO/OLO 5/5  $\mu\text{g}$  and TIO 5  $\mu\text{g}$ , with a difference in TDI of 0.36 units in favor of double bronchodilatation. In this study, daytime use of rescue salbutamol was 0.97 puffs/day with TIO 5  $\mu\text{g}$  and 0.76 puffs/day with TIO/OLO 5/5  $\mu\text{g}$ , whereas the nighttime use of salbutamol was 1.69 and 1.24 puffs/day, respectively.<sup>27,40,41</sup> ANHELTO had already previously demonstrated that the number of rescue-medication-free days increased by about 8% with the combination treatment compared with TIO monotherapy.<sup>30</sup>

### Health-related quality of life

OTEMTO 1 and 2 demonstrated that overall improvements in SGRQ with TIO 5  $\mu\text{g}$  were small compared to placebo (–2.4 [ $P < 0.05$ ] and –2.85 units [not significant]) and did not reach the MCID.<sup>28</sup> This contrasts with improvements of more than 4 units with TIO/OLO 5/5  $\mu\text{g}$  compared with placebo. The likelihood of becoming a responder for the SGRQ compared with baseline was 41.4% with TIO 5  $\mu\text{g}$  and 52.4% with TIO/OLO 5/5  $\mu\text{g}$ , with an odds ratio of approximately 1.5, corresponding with an NNT of nine to ten (Table 3). Similar observations were made in ANHELTO (Table 3).<sup>30</sup> More pronounced clinically meaningful improvements in SGRQ total scores were reached in TONADO with TIO/OLO 5/5  $\mu\text{g}$  (–6.8 units) and TIO 5  $\mu\text{g}$  (–5.6 units) compared to baseline.<sup>27</sup> The difference between TIO/OLO 5/5  $\mu\text{g}$  and TIO 5  $\mu\text{g}$  (1.2 units) reached statistical significance but failed to reach the threshold of MCID. In that study, the number of participants exhibiting an MCID in HR-QoL increased compared with baseline from 48.7% with TIO 5  $\mu\text{g}$  to 57.5% with TIO/OLO 5/5, corresponding to an NNT of 12.

### Markers of hyperinflation and exercise tolerance

Reductions in FRC and RV measured 2.5 and 22.5 hours after inhalation of TIO 5 µg were smaller (431 mL) than those obtained with TIO/OLO 5/5 µg (547 mL). This difference corresponded to a 100 mL difference in increase in IC between TIO/OLO 5/5 µg and TIO 5 µg.<sup>26</sup> Similar differences (114 and 88 mL) in improvement in IC were observed between TIO/OLO 5/5 and TIO 5 in two other 6-week studies, and these differences persisted during exercise.<sup>31</sup> In the exercise studies, no differences were observed for endurance time or Borg score for dyspnea during constant work-rate cycle ergometry after 6 weeks between TIO 5 µg and TIO/OLO 5/5. However, in a subgroup of severely hyperinflated COPD patients, statistically significant differences in endurance time during constant work rate were observed between TIO 5 µg and TIO/OLO 5/5 µg in favor of dual bronchodilatation.<sup>31</sup>

### Exacerbations

Only correctly powered studies enrolling large number of COPD patients at high risk of exacerbations (based upon prior exacerbation history and severity of airflow obstruction) will elucidate the question of whether dual bronchodilatation is superior to TIO monotherapy for prevention of exacerbations. Such a study, DYNAGITO, comparing the effects of TIO/OLO 5/5 µg and TIO 5 µg and investigating as primary outcome the annualized rate of moderate-to-severe COPD exacerbations over 1 year, is ongoing and registered as NCT02296138 at [ClinicalTrials.gov](http://ClinicalTrials.gov). Although the TONADO studies were not designed to assess this important issue, their 52-week duration was sufficient to explore the potential effects of the interventions on the occurrence of exacerbations.<sup>27</sup> In TONADO, a moderate exacerbation was defined by the need for systemic steroids or antibiotics, whereas a severe exacerbation required hospitalization. In the combined data set, the percentage of patients with at least one moderate-to-severe COPD exacerbation was 27.7% for the TIO/OLO 5/5 µg FDC and 28.8% with TIO 5 µg. Unexpectedly, the percentage of patients with at least one severe COPD exacerbation was 5.9% (n=61) for TIO/OLO 5/5 µg and 4.5% (n=47) for TIO 5 µg. These differences did not reach statistical significance.<sup>27,42</sup>

### Comparison between TIO/OLO 5/5 µg and OLO 5 µg monotherapy

As in the comparison between once-daily TIO/OLO 5/5 µg FDC and once-daily TIO 5 µg, differences between TIO/OLO 5/5 µg FDC once-daily and OLO 5 µg once-daily, both

administered via the Respimat soft-mist inhaler, were generally statistically but not clinically significant in favor of dual bronchodilatation (Tables 2 and 3).

### Pulmonary function

FEV<sub>1</sub> AUC<sub>0-24</sub>, FEV<sub>1</sub> AUC<sub>0-12</sub>, FEV<sub>1</sub> AUC<sub>12-24</sub>, FEV<sub>1</sub> AUC<sub>0-3</sub>, and trough FEV<sub>1</sub> increased significantly after a 6-week treatment with once-daily TIO/OLO 5/5 µg compared with once-daily OLO 5 µg monotherapy in VIVACITO<sup>26</sup> (Table 1). Similar findings were observed in TONADO, which demonstrated statistically significant improvements in FEV<sub>1</sub> AUC<sub>0-3</sub> and trough FEV<sub>1</sub> for TIO/OLO 5 µg in comparison with OLO 5 µg, persisting for 52 weeks. Similar responses in trough FVC and FVC AUC<sub>0-3</sub> were also observed in that study.<sup>27</sup>

### Symptoms and use of rescue medication

Statistically significant differences between TIO/OLO 5/5 µg and OLO 5 µg were observed in TONADO, reaching 0.42 units for the TDI in favor of double bronchodilatation ( $P < 0.005$ ). Moreover, daytime use of rescue salbutamol was 0.87 puffs/day with OLO 5 µg and 0.76 puffs/day with TIO/OLO 5/5 µg, whereas nighttime use of salbutamol was 1.52 and 1.24 puffs/day, respectively.<sup>27,40,41</sup>

### Health-related quality of life

In TONADO, changes in SGRQ total scores compared with baseline with OLO 5 µg reached -5.1 units (compared with -6.8 units after double bronchodilatation). The difference between TIO/OLO 5/5 µg and OLO 5 µg was thus 1.7 units, which did not reach the threshold of minimal clinical significance.<sup>27</sup> In that study, the number of responders on the SGRQ compared with baseline increased from 44.8% with OLO 5 µg to 57.5% with TIO/OLO 5/5 µg, corresponding to an NNT of eight.<sup>27</sup>

### Markers of hyperinflation and exercise tolerance

Reductions in FRC and RV versus baseline measured 2.5 hours after inhalation of OLO 5 µg were smaller (435 mL) than those with TIO/OLO 5/5 µg (547 mL). Reciprocal increases in IC were 242 mL with OLO 5 µg and 351 mL with TIO/OLO 5/5 µg 2.5 hours after inhalation.<sup>26</sup> Differences in IC between TIO/OLO 5/5 µg and OLO 5 µg were similar in magnitude in two other 6-week studies (119 and 80 mL) and these differences persisted during exercise.<sup>31,40,41</sup> Endurance time during constant work-rate cycle ergometry after TIO/OLO 5/5 µg increased by 47 seconds in MORACTO 2, whereas no such increase was seen in MORACTO 1.<sup>31</sup>

## Exacerbations

In the combined data set of TONADO, the percentage of patients with at least one moderate-to-severe COPD exacerbation was 27.7% for the TIO/OLO 5/5 µg FDC and 31.9% with OLO 5 µg. As assessed by Kaplan–Meier estimates, the risk of a moderate-to-severe exacerbation was significantly lower with TIO/OLO 5/5 µg than with OLO 5 µg, with a risk ratio of 0.83 (95% CI 0.71–0.99). Indices for severe exacerbations were comparable between TIO/OLO 5/5 µg FDC and OLO 5 µg, since the percentage of patients with at least one severe COPD exacerbation was 5.9% (n=61) for TIO/OLO 5/5 µg and 5.4% (n=56) for OLO 5 µg.<sup>27,42</sup>

## Comparison between TIO/OLO 5/5 µg and salmeterol–fluticasone propionate

In a 6-week trial that enrolled more than 200 patients with COPD, the effects of dual bronchodilatation and two strengths of SALM/FLU twice daily were compared with regard to the FEV<sub>1</sub> AUC<sub>0–12</sub> (primary end point), FEV<sub>1</sub> AUC<sub>12–24</sub>, FEV<sub>1</sub> AUC<sub>0–24</sub>, FEV<sub>1</sub> peak<sub>0–3</sub>, and trough FEV<sub>1</sub>. Treatment with TIO/OLO 5/5 µg once daily produced significantly greater improvements in pulmonary function than SALM/FLU 50/500 µg and 50/250 µg twice daily after 6 weeks.<sup>29</sup> Greater improvements in FEV<sub>1</sub> AUC<sub>0–12</sub> of approximately 125 mL were observed with TIO/OLO 5/5 µg compared with either dose of SALM/FLU. Treatment with TIO/OLO 5/5 µg once daily improved FEV<sub>1</sub> values with approximately 85 mL over the full 24-hour dosing interval compared with SALM/FLU.

## Efficacy according to the COPD subgroups

A post hoc analysis of TONADO shows that the bronchodilating properties of TIO/OLO 5/5 µg remained preserved in more severe stages of COPD.<sup>43</sup> Post hoc analyses have also been performed for both OTEMTO and TONADO in an attempt to differentiate effects of treatments between the GOLD COPD subgroups A–D. It should however be pointed out that these studies were designed and initiated before the 2011 GOLD update.<sup>1</sup> In OTEMTO, TIO/OLO was more effective than placebo at improving FEV<sub>1</sub> AUC<sub>0–3</sub>, trough FEV<sub>1</sub>, SGRQ total score, and TDI focal score in all GOLD A–D subgroups. When comparing TIO/OLO 5/5 µg to TIO 5 µg monotherapy, FEV<sub>1</sub> AUC<sub>0–3</sub>, trough FEV<sub>1</sub>, and TDI improved in all GOLD A–D subgroups. For FEV<sub>1</sub> AUC<sub>0–3</sub>, the level of significance was reached for all subgroups, whereas statistical significance was reached only for trough FEV<sub>1</sub> in the A, B, and D subgroups and for TDI only in the

C subgroup. Likewise, treatment effects differed between subgroups for SGRQ total score, improvements being most evident in the GOLD B subgroup.<sup>35</sup> In TONADO, numerically greater responses in both FEV<sub>1</sub> AUC<sub>0–3</sub> and trough FEV<sub>1</sub> were demonstrated in patients classified as GOLD A/B compared to patients classified as GOLD C/D, with statistically significant differences between TIO/OLO 5/5 µg and both monotherapies in each subgroup.<sup>34</sup>

## Safety issues

Overall, the TIO/OLO FDC appears to be well tolerated and devoid of important side effects. In OTEMTO, the incidence of adverse events (AEs) was higher in the placebo than in the actively treated groups, leading to more frequent discontinuation of the study in the placebo group.<sup>28</sup> In VIVACITO, however, AEs were balanced among the different treatment groups.<sup>26</sup> In the combined analysis of the 52-week TONADO, the overall incidence of AEs was 74%, 73.3%, and 76.6% for TIO/OLO, TIO, and OLO, respectively. Most of these were of mild or moderate severity, without differences between treatments. Treatment-related AEs were reported in 7.1%, 6.1%, and 6.6% of patients on TIO/OLO, TIO, and OLO, and serious AEs (SAEs) in 16.4%, 16.7%, and 17.4% of patients, respectively. The most common SAEs in TIO/OLO, TIO, and OLO recipients were of respiratory origin: COPD exacerbations (6.9%, 6.3%, and 6.5%, respectively) and pneumonias (1.7%, 0.9%, and 1.4%, respectively).<sup>27</sup> Withdrawals from the study because of AEs were noted in 7.4%, 9%, and 9.9% of patients, respectively.<sup>27</sup> The incidence of cardiovascular SAEs was 1.8%, 1.8%, and 1.4% and that of cerebrovascular SAEs 0.5%, 0.5%, and 0.6% in the respective groups, without significant differences between the treatment groups.<sup>27</sup> More detailed reports on tolerability and AEs of TIO/OLO can be found elsewhere.<sup>22–25,44,45</sup>

## Comparisons between tiotropium/olodaterol 5/5 µg fixed-dose combination and other LAMA/LABA fixed-dose combinations

Since none of the currently licensed LAMA/LABA FDCs have been compared in head-to-head RCTs, they can only be weighed against each other by indirect comparisons. Such comparisons are difficult to perform, and their conclusions should be interpreted with great caution. Indeed, important between-study differences exist on how classical outcomes, such as reversibility of airway obstruction, QoL, exercise tolerance, dyspnea, and rate of exacerbations, are assessed and expressed. Moreover, study design, distribution of COPD

severity within the study population, exacerbation history, symptoms, concomitant ICS use, age and sex, degree of hyperinflation, and reversibility, as well as baseline exercise capacity and knowledge of inhaler technique, may affect the outcome of a pharmacological intervention with bronchodilators to a certain extent. Likewise, seasonal effects and (even more) the Hawthorne effect (ie, beneficial effects observed in RCTs due to the fact that patients who are participating in an RCT change their behavior, such as improved adherence to maintenance treatment and better inhaler technique) may further complicate comparisons between studies.

In order to weigh the existing LABA/LAMA formulations among one other, data from placebo-controlled studies may be completed with a “network meta-analysis”, which allows the combination of trials involving different sets of treatments, to end up with an integrated and structured single analysis. Data are now available comparing the effects of four LABA/LAMA FDCs for such end points as trough FEV<sub>1</sub>, TDI, and QoL, using that specific technique.

### Placebo-controlled studies

Despite some limitations, placebo-controlled trials allow comparison to a certain extent of the magnitude of clinical effects of other LAMA/LABA FDCs and TIO/OLO 5/5 µg with a common comparator – placebo. However, placebo-controlled trials with LAMA/LABA FDCs other than TIO/OLO are limited in number (Table 4). Overall, it appears that the magnitude of the effect observed with currently marketed FDCs is strikingly similar to those seen with TIO/OLO for trough FEV<sub>1</sub>, TDI, and HR-QoL (Table 2).<sup>46–49</sup> Likewise, the reported differences between GLY/IND 50/110 µg and placebo for lung volumes (–520 mL for FRC and 340 mL for IC at 1 hour postdose) are strikingly

similar to the changes seen 2.5 hours postdose with TIO/OLO 5/5 µg.<sup>50</sup> In two replicate studies assessing the effects of UMEC/VIL 62.5/25 µg on lung volumes, differences from placebo were –238 and –351 mL for trough FRC, –295 and –466 mL for trough RV, and 238 and 316 mL for IC 3 hours postdose.<sup>51</sup>

### Trough FEV<sub>1</sub>

In a recently published network meta-analysis,<sup>22</sup> Calzetta et al used clinical data from more than 23,000 patients to compare the effects of four LABA/LAMA FDCs with monocomponents. They demonstrated that TIO/OLO 5/5 µg increased trough FEV<sub>1</sub> by 55 mL (95% CI 46–64) compared to monocomponents, whereas UMEC/VIL 62.5/25 µg, ACL/FORM 400/12 µg, and GLY/IND 50/110 µg increased trough FEV<sub>1</sub> by 84 mL (95% CI 66–102), 46 mL (95% CI 18–74), and 89 mL (95% CI 76–103) compared to monotherapy, respectively. For GLY/IND, efficacy did not depend on the regimen of administration (once daily, 92 mL [95% CI 73–110]; twice daily, 91 mL [95% CI: 66–115]). Surprisingly, the lower dose of UMEC/VIL 62.5/25 µg elicited a greater increase in trough FEV<sub>1</sub> when compared with UMEC/VIL 125/25 µg (95 mL [95% CI 73–117] versus 72 mL [95% CI 44–100], respectively), although the difference was not statistically significant. For none of the FDCs did differences between dual bronchodilatation and monocomponents exceed the generally accepted MCID for FEV<sub>1</sub> of 100 mL.<sup>37,38</sup> The network meta-analysis presented by Calzetta et al suggested that a gradient of effectiveness among the different drug combinations may exist, with UMEC/VIL slightly exceeding the effects of GLY/IND (–12 mL), TIO/OLO (–30 mL), and ACL/FORM (–49 mL), though statistically significant differences among the FDCs were not observed.<sup>22</sup> Moreover,

**Table 4** Differences between several LAMA/LABA fixed-dose combinations and PLA

Study	n	Trough FEV <sub>1</sub> (mL)	SGRQ	TDI	FRC/IC (mL)	ET (s)
<b>GLY/IND 110/50 µg vs PLA</b>						
Bateman et al <sup>46</sup>	2,144	Δ=200	Δ=-3	Δ=1.1		
Beeh et al <sup>50</sup>	84				Δ=-520/Δ=340	Δ=60
<b>UMEC/VIL 62.5/25 µg vs PLA</b>						
Donohue et al <sup>47</sup>	1,536	Δ=167	Δ=-5.5	Δ=1.2		
Maltais et al <sup>51</sup>	308				-/Δ≈250	Δ≈69.4
Maltais et al <sup>51</sup>	349				-/Δ≈400	Δ≈21.9
<b>ACL/FORM 400/12 µg BID vs PLA</b>						
D'Urzo et al <sup>48</sup>	1,692	-35 vs 94	-6.57 vs -2.21	2 vs 0.6		
Singh et al <sup>49</sup>	1,729	Δ=143	-8.3 vs -6.5	2.5 vs 1.2		

**Abbreviations:** ACL/FORM, aclidinium–formoterol fixed-dose combination; BID, bis in die (twice daily); ET, endurance time (during constant work-rate cycle ergometry); FEV<sub>1</sub>, forced expiratory volume in 1 second; FRC, functional residual capacity; GLY/IND, glycopyrronium–indacaterol fixed-dose combination; IC, inspiratory capacity; LABA, long-acting β<sub>2</sub>-agonist; LAMA, long-acting muscarinic antagonist; PLA, placebo; SGRQ, St George's Respiratory Questionnaire (score); TDI, Transition Dyspnea Index; UMEC/VIL, umeclidinium–vilanterol fixed-dose combination.

none of the comparative studies included in that analysis was double dummy or head to head.

### Transition Dyspnea Index

For all the investigated LAMA/LABA combinations, statistically significant improvements in TDI were observed compared with monocomponents. However, the overall differences in TDI between LAMA/LABA FDC and monotherapies were small and did not exceed 0.5 units.<sup>22</sup> Compared with monotherapies, differences between TIO/OLO and other LAMA/LABA FDCs were even smaller (0.3 units). The NNT to increase the TDI focal score by  $\geq 1$  unit was (compared with a LAMA) nine to 12 for TIO/OLO 5/5  $\mu\text{g}$ ,<sup>27,28</sup> nine for GLY/IND,<sup>52</sup> and 20 for UMEC/VIL 62.5/25  $\mu\text{g}$ .<sup>53</sup>

### Health-related quality of life

Overall, the investigated LAMA/LABA combinations reduced the SGRQ score significantly compared with monocomponents, with differences ranging between 1.3 and 1.5 units compared with monotherapies for the different LAMA/LABA FDCs. In this regard, differences between TIO/OLO and other LAMA/LABA FDCs did not exceed 0.2 units. Analysis of data reported in individual studies showed that the NNT to decrease the SGRQ score by  $\geq 4$  in patients already treated with TIO 5  $\mu\text{g}$  ranged between nine and 12 for TIO/OLO 5/5 (Table 3), between eleven and 16 for GLY/IND,<sup>54,55</sup> and 14 for UMEC/VIL.<sup>56</sup> The ACL/FORM formulation did not significantly influence the ratio of responder patients.<sup>57</sup>

### Hyperinflation and exercise

Network meta-analyses have thus far not addressed the effects of LAMA/LABA combinations on other clinically relevant outcomes, such as hyperinflation or exercise tolerance. The few available studies showed that reductions in FRC and RV measured 60 minutes after inhalation of GLY/IND 62.5/25  $\mu\text{g}$  were larger (520 and 520 mL, respectively) than those obtained with TIO 18  $\mu\text{g}$  inhaled via HandiHaler (400 and 410 mL, respectively), leading to a reciprocal increase in IC of 150 mL with GLY/IND 62.5/25  $\mu\text{g}$  compared with TIO 18  $\mu\text{g}$ .<sup>50</sup> These differences are in the same order of magnitude as the differences between TIO/OLO 5/5  $\mu\text{g}$  and TIO 5  $\mu\text{g}$ . Reductions in hyperinflation, seen with GLY/IND 62.5/25  $\mu\text{g}$ , were not translated into prolongations in endurance time on the cyclo-ergometer, which were similar to those obtained with TIO 18  $\mu\text{g}$  via HandiHaler. The effects of inhaled UMEC/VIL 62.5/25  $\mu\text{g}$  and UMEC 62.5  $\mu\text{g}$  on endurance time during exercise were inconsistent:<sup>51</sup> compared with placebo, endurance time increased by 69 (95% CI 24–114) and 22 (95% CI –14 to 58)

seconds with UMEC/VIL 62.5/25  $\mu\text{g}$  and by 25 (95% CI –41 to 91) and 26.5 (95% CI –26 to 79) seconds with UMEC 62.5  $\mu\text{g}$ , respectively.

### Exacerbations

Research is ongoing to determine whether the TIO/OLO 5/5  $\mu\text{g}$  FDC is superior to TIO 5  $\mu\text{g}$  in preventing COPD exacerbations. However, a few studies comparing other existing LAMA/LABA FDCs with a LAMA have already attempted to clarify the potential place of dual bronchodilatation in this regard.

In one study, the effects of GLY/IND 50/110  $\mu\text{g}$ , TIO 18  $\mu\text{g}$  (via HandiHaler), and GLY 50  $\mu\text{g}$  on exacerbations were investigated during a 64-week trial in COPD patients who all belonged to stage III/IV (GOLD B and D, new classification).<sup>55</sup> Interestingly, inclusion in that study was restricted to patients with a history of at least one COPD exacerbation requiring treatment with antibiotics and/or systemic corticosteroids within the previous year. GLY/IND 50/110  $\mu\text{g}$  significantly reduced the rate of all (mild, moderate, and severe) exacerbations by 14% compared with TIO 18  $\mu\text{g}$  via HandiHaler and by 15% compared with GLY 50  $\mu\text{g}$ . The effect was largely driven by the reduction in mild exacerbations (about three per year), since the incidence of moderate and severe exacerbations was similar among the three groups.<sup>55</sup> In that study, the NNT was 19 to prevent one exacerbation with GLY/IND 50/110  $\mu\text{g}$  compared with TIO and 25 compared with GLY.<sup>55,58</sup>

The FLAME study, a second 52-week-long study comparing the effects of GLY/IND 50/110  $\mu\text{g}$  once daily with SALM/FLU 50/500  $\mu\text{g}$  twice daily on the rate of COPD exacerbations, showed that dual bronchodilatation was more effective in reducing not only all (mild, moderate, and severe) exacerbations but also the number of both moderate and severe COPD exacerbations,<sup>53,59</sup> with an NNT of 17 for moderate and severe exacerbations. Importantly, FLAME excluded all COPD patients with a history of asthma, concomitant allergic rhinitis, or very pronounced blood eosinophilia ( $>600$  eosinophils/ $\mu\text{L}$ ).

Studies comparing the effects of UMEC/VIL and UMEC on exacerbations<sup>47,53,60,61</sup> have not yielded conclusive results, possibly because of insufficient duration and less stringent patient selection.

## Perspective: when to add a LABA to a LAMA in COPD?

The previous sections clearly demonstrate that TIO/OLO 5/5  $\mu\text{g}$ , formulated in the Respimat soft-mist inhaler,

substantially improves trough FEV<sub>1</sub>, TDI scores, markers of dynamic hyperinflation, and HR-QoL. Differences reach or even exceed the MCID for FEV<sub>1</sub>, TDI, and HR-QoL compared with placebo. TIO/OLO 5/5 µg also statistically improves spirometric variables, TDI scores, HR-QoL, and markers of hyperinflation compared to TIO 5 µg. However, the MCID between dual bronchodilatation and monotherapy is generally not reached.

Although efforts to grade and compare the effects of all available LAMA/LABA FDCs should be interpreted with caution, placebo-controlled studies and a network meta-analysis comparing the effects of TIO/OLO 5/5 µg with other available LAMA/LABA FDCs allow us to conclude that their overall effects on pulmonary function, HR-QoL, and TDI are comparable in magnitude. Therefore, if differences were to exist between different LABA/LAMA FDCs, these differences would be small and probably not clinically relevant. Possibly, the currently assessed end points and techniques used to investigate their effects are not sensitive enough to pick up the clinical impact of undeniable differences that prevail between available LAMA/LABA FDCs in terms of pharmacological characteristics of the individual LAMA and LABA components (eg, onset and duration of action, maximum effect and potency, receptor selectivity, lipophilicity, dissociation half-life, serum half-life, and metabolism issues).<sup>7,62,63</sup> Only head-to-head comparisons can solve this issue.

The potential beneficial effects of dual bronchodilatation over monotherapies in the prevention of COPD exacerbations require further investigation, however. The limited data available on TIO/OLO 5/5 µg suggest that dual bronchodilatation was superior to OLO 5 µg but not to TIO 5 µg in preventing moderate-to-severe exacerbations, a finding that is in line with a recent network meta-analysis in which the effects of several LABA/LAMA combinations were reviewed.<sup>45</sup> Differences between TIO/OLO 5/5 µg and TIO 5 µg or OLO 5 µg do not appear to exist for severe exacerbations,<sup>27</sup> and Oba et al came to the same conclusions for all LABAs, LAMAs, and LAMA/LABA FDCs.<sup>45</sup> The apparently intriguing observation that long-acting bronchodilators prevent better against mild and moderate exacerbations than against severe exacerbations may be attributed to several factors. First, the specific actions of long-acting bronchodilators might not affect the frequency of exacerbations per se, but through reducing breathlessness may increase the threshold at which a given patient will consider his/her worsening sufficiently severe to be labeled an exacerbation.<sup>64</sup> Secondly, LAMA-containing combinations could further enhance that protective effect in reducing mucus hypersecretion, although

hard evidence is still lacking to support this contention. Thirdly, the efficacy of active treatments in preventing severe exacerbations (requiring hospitalization) is difficult to prove in classical RCTs, where COPD patients are closely monitored (encompassing regular study visits and daily monitoring of symptoms and spirometry). Due to this intensive proactive monitoring in classical RCTs, COPD patients experiencing increased symptoms of an ensuing exacerbation are treated promptly (with an increase in inhaled bronchodilators, oral corticosteroids, and/or antibiotics), preventing further clinical deterioration and thereby the need for hospital admissions. Therefore, and due to exclusion of COPD patients with significant comorbidities, the incidence of hospitalizations due to COPD exacerbations are rare events in classical RCTs.

In the past, it was deemed unlikely that bronchodilating drugs would affect the acute inflammatory response to respiratory infections or exposure to airway irritants accompanying more severe exacerbations, which give rise to symptoms that eventually require treatment with anti-inflammatory drugs.<sup>64</sup> This hypothesis has however been recently challenged by the FLAME study, which concluded that GLY/IND 50/110 µg once daily provided better protection than a SALM/FLU 50/500 µg FDC twice daily against mild, moderate, and severe exacerbations in COPD GOLD stage B and D patients.<sup>47,53,60,61</sup> It is crucially important to note that all COPD patients who might potentially have experienced beneficial effects from an ICS treatment (previous asthma, asthma COPD overlap syndrome, increased blood eosinophilia, and allergic rhinitis) were completely excluded from that study, maximizing in this way the effect of dual bronchodilatation. Unfortunately, this study did not address the issue of whether dual bronchodilatation is superior to a LAMA in preventing severe exacerbations in that subgroup of COPD patients.<sup>59</sup>

TIO/OLO 5/5 µg reduced markers of hyperinflation, such as FRC, compared to monotherapies, the difference exceeding 200 mL 22 hours after inhalation. The exact meaning of a 200 mL reduction in FRC is unknown, since its MCID has not been determined so far. At that time point, the effects of the monotherapies on FRC (Figure 1) have almost completely disappeared.<sup>27,51</sup> Despite its substantial effects on dynamic hyperinflation, dual bronchodilatation does not increase endurance time during constant work exercise compared to monotherapies, a feature that TIO/OLO 5/5 µg shares with other LAMA/LABA FDCs.<sup>31,32,50,51</sup> The reasons for the additional improvement in markers of hyperinflation seen with dual bronchodilatation are not translated into additional gains in endurance time are unclear. Patient selection

may definitely play a role, since TIO/OLO 5/5 µg enhances endurance time during constant work exercise in severely hyperinflated patients<sup>31</sup> compared to monotherapies. Another possibility is that a ventilatory-limited COPD patient may become limited by peripheral muscle weakness once treated with one bronchodilator. In such a case, the addition of a second long-acting bronchodilator will not affect exercise endurance, unless the prevailing limiting factor, the peripheral muscle weakness, is treated. Studies comparing the effects of dual bronchodilatation with monotherapy on the outcome of a pulmonary rehabilitation program could answer this question. Interestingly, the impact of optimization of bronchodilatation on the outcome of pulmonary rehabilitation has been nicely demonstrated previously with TIO monotherapy.<sup>18</sup>

American, European, and Japanese regulatory authorities have licensed a number of LAMA/LABA FDCs to treat COPD patients for symptom relief and pulmonary function improvement. Currently, the question remains unanswered as to whether all patients with COPD or only some phenotypes within the COPD-patient group should be treated with a LAMA/LABA FDC. Indeed, the current GOLD guidelines recommend maintenance therapy with either a LAMA or LABA in symptomatic patients with moderate or severe COPD. When patients are not adequately controlled with a single long-acting bronchodilator, combining a LAMA with a LABA may be beneficial. An ICS/LABA combination is an option for maintenance treatment in COPD patients who are at high risk of exacerbations,<sup>1</sup> especially if these exacerbations require treatment with oral corticosteroid courses only (without antibiotics). However, ICS/LABA combinations are often prescribed to patients who do not qualify for this criterion.<sup>65,66</sup>

It is tempting to initiate a treatment with a LABA/LAMA FDC in every new symptomatic COPD patient, since dual bronchodilatation yields superior effects compared to monotherapies and will result in MCIDs in the domains of pulmonary function, dyspnea, and HR-QoL compared with placebo. However, a substantial number of patients do well with monotherapy, such that this surplus in bronchodilatation does not always lead to better QoL, improved endurance time, or fewer exacerbations in every single patient.<sup>45</sup> Indeed, differences between dual bronchodilatation and monotherapy generally remain below the currently accepted MCIDs for a number of domains. It has thus been suggested that the current thresholds used to define an MCID when comparing two active treatments be redefined.<sup>38</sup>

Another option is to perform a responder analysis in studies assessing the effects of long-acting bronchodilators. This demonstrates that certain patients already reach the

MCID with one bronchodilator, and that this proportion may be increased by selective prescription of dual bronchodilatation in patients not responding to monotherapy.<sup>38</sup> The proposed strategy combines a personalized approach of the patient with an optimal use of health care resources, and should remain the strategy of choice, at least as long as price differences between dual bronchodilatation and monotherapies remain substantial. Moreover, this is in line with a general rule in medicine, which says not to treat patients with two medicines if satisfactory results may be obtained with only one medicine. Nevertheless, responder analyses and NNT calculations reported in clinical trials with COPD should be approached with caution, since a Hawthorne effect appears to be present in many trials, minimizing the effect of the intervention.<sup>38</sup> Therefore, the currently available efficacy data from classical RCTs should be completed with effectiveness data obtained in real-life studies (ie, pragmatic trials and observational studies), which may yield more realistic data in this regard. Importantly, whereas the aforementioned classical RCTs had high internal validity thanks to randomization and double-blind design, their external validity might be limited due to a (highly) selected COPD patient population that is not representative of the full spectrum of COPD patients seen in clinical practice. This has implications for real-life effectiveness (and comparative effectiveness), as well as long-term safety in a real-world setting, since many patients COPD with comorbidities (asthma, cardiovascular disease, heart failure) and polypharmacy are excluded from classical RCTs.<sup>67</sup>

If the evidence is currently lacking to initiate dual bronchodilatation in every COPD patient at the time of diagnosis, clinical studies suggest that the threshold to prescribe dual bronchodilatation should be low in patients who remain symptomatic under monotherapy, in highly breathless or hyperinflated COPD patients, in those included in a pulmonary rehabilitation program, and in those patients in COPD GOLD subgroups B and D who comply with the stringent inclusion and exclusion criteria of the recently published FLAME study.

To support early treatment of COPD patients with dual bronchodilatation, additional studies should be conducted to demonstrate its disease-modifying effect. The protocol that should be followed to conduct such an early intervention study was proposed some years ago.<sup>68</sup> Interestingly, a prespecified analysis of the UPLIFT trial showed that TIO significantly reduced the rate of decline of postbronchodilator FEV<sub>1</sub> relative to control in patients with COPD stage II, a feature that was not present in more severe COPD stages.<sup>69</sup>

## Conclusion

In conclusion, TIO/OLO 5/5 µg is a LAMA/LABA FDC formulated in a Respimat soft-mist inhaler that has been thoroughly investigated in over 10,000 COPD patients. Its effects on a variety of relevant clinical end points, including lung function, symptoms (TDI), and QoL (SGRQ), are comparable to other LAMA/LABA FDCs. In a COPD population at relatively low risk of exacerbations, TIO/OL 5/5 µg significantly reduced the rate of exacerbations compared with OLO 5 µg monotherapy, but not compared to TIO 5 µg monotherapy. Larger long-term studies in COPD patients at high risk of exacerbations are required and ongoing to investigate whether TIO/OLO 5/5 µg is also superior to TIO 5 µg monotherapy in reducing moderate and severe COPD exacerbations. Clinical studies with TIO/OLO 5/5 µg and other LAMA/LABA FDCs support their use in COPD patients who remain symptomatic and patients who frequently exacerbate and exhibit some well-defined COPD phenotypes.

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## Disclosure

The authors report no conflicts of interest in this work.

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