

Umeclidinium bromide/vilanterol combination in the treatment of chronic obstructive pulmonary disease: a review

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Abstract: Chronic obstructive pulmonary disease (COPD) is a common disease among the elderly that could be prevented by smoking cessation. As it is characterized by airflow limitation that is not fully reversible, bronchodilator therapy is the first choice of treatment. Symptomatic COPD patients with or without risk for future exacerbations have a strong indication for the permanent use of long- and ultralong-acting β_2 -agonists and/or long-acting muscarinic antagonists. Combining bronchodilators is an effective approach, as they demonstrate synergic action at a cellular level and have additive clinical benefits and fewer adverse events compared with increased doses of the monocomponents. Novel fixed-dose combinations of long-acting β_2 -agonists/long-acting muscarinic antagonists in one inhaler have been approved for clinical use by the US Food and Drug Administration and the European Medicines Agency. This review focuses on published clinical trials about the fixed-dose combination of umeclidinium/vilanterol trifenatate in patients with COPD. Results from six studies (five of them of 12 weeks' duration and one that lasted 1 year, including more than 6,000 patients in total) showed that umeclidinium/vilanterol trifenatate improved lung function, dyspnea, and health-related quality of life and decreased the exacerbation rate with no serious adverse events. More longstanding trials are needed to evaluate the effect of the drug on disease progression and compare it directly with other fixed-dose combinations.

Keywords: COPD treatment, bronchodilators, lung function, long-acting β_2 -agonists, long-acting muscarinic receptor antagonist combination, umeclidinium/vilanterol

Introduction

Chronic obstructive pulmonary disease (COPD) is a common, preventable, and treatable disease characterized by airflow limitation that is not fully reversible and is usually progressive during follow-up.^{1,2} It is estimated that the prevalence of the disease that is clinically significant is 10.1% in adults aged 40 years and older,³ and males, current or former smokers, and the elderly are more commonly affected.⁴ By 2030, COPD is expected to become the fourth leading cause of death worldwide and the third leading cause in middle-income countries.⁵

Patients usually present with dyspnea,⁶ reduced physical activity,⁷ worsening of health-related quality of life, and exacerbations of the disease. The latter contribute to COPD severity, as they are related to more rapid decline in lung function⁸ and worse prognosis.⁹ In addition, the systemic manifestations of the disease and comorbidities have been proven to act as prognostic factors.^{10,11}

Although COPD is a chronic, incurable disease, its treatment can be divided into three different components: prevention (smoking cessation, avoidance of occupational and environmental exposure, vaccinations), pharmacotherapy (bronchodilators, inhaled

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corticosteroids [ICS], roflumilast), and nonpharmacological strategies (pulmonary rehabilitation, long-term oxygen therapy, lung volume reduction surgery).¹

Maintenance treatment with long-term bronchodilators (long-acting muscarinic antagonists [LAMAs] and long-acting β_2 -agonists [LABAs]) are considered the basis of pharmacotherapy for COPD, as they improve lung function, reduce dyspnea, increase exercise capacity, and prevent future exacerbations.^{12,13} Moreover, a subgroup analysis of the Understanding Potential Long-Term Impacts on Function with Tiotropium (UPLIFT) study showed that tiotropium reduced the rate of decline of lung function in the early stage of COPD.¹⁴

Using LAMAs and LABAs in a fixed-dose combination inhalation device is a new treatment option for COPD patients and is recommended by the Global Initiative for Chronic Obstructive Lung Disease (GOLD) as the first or alternative choice for groups B–D.¹ Combining bronchodilators of different classes leads to an improvement in efficacy with fewer adverse events in comparison with increased doses of the monocomponents.¹⁵

In this review, we mainly evaluate clinical trials of the fixed-dose combination umeclidinium/vilanterol trifenatate (UMEC/VI) in COPD patients. This combination of UMEC/VI at a dose of 62.5/25 μ g, delivered by the dry powder device Ellipta® has been licensed (1 year ago in the United States and 6 months ago in the European Union)^{16,17} for once-daily maintenance treatment in COPD patients.

The role of LAMA/LABA combinations in COPD treatment

Short-acting β_2 -agonists and muscarinic antagonists are recommended as a first choice for COPD patients in GOLD group A (few symptoms, forced expiratory volume in 1 second [FEV_1] >50% predicted, and 0–1 moderate exacerbations in the previous year). These drugs could be used as relievers of symptoms or on a regular basis, but they are less convenient (low adherence) than long-term bronchodilators.¹ In addition, their short action leads to lower trough FEV_1 compared with LAMAs and LABAs.¹⁸

In group B (more symptoms, FEV_1 >50% predicted, and 0–1 moderate exacerbations in the previous year), the recommendation of GOLD is LAMA or LABA, and their combination is an alternative choice.¹ Patients in group C (fewer symptoms, FEV_1 <50% predicted, or 2 moderate/1 severe exacerbation in the previous year) are generally suggested to use two drugs (LAMA/LABA combination and LAMA or LABA plus ICS or phosphodiesterase 4 inhibitor) or LAMA monotherapy.¹ In group D (more symptoms, FEV_1 <50%

predicted, or 2 moderate/1 severe exacerbation in the previous year), the recommendation is for the use of two or three drugs with all regimens including LAMA and/or LABA.¹

Studies that used the GOLD 2011 classification for major COPD cohorts concluded that the majority of patients (63%–79%) in groups C and D were categorized there because of lung function (FEV_1 <50% predicted, groups C₁ and D₁) and history of frequent or severe exacerbations.^{19,20} All these patients should be probably treated with a LAMA/LABA combination.

ICS are recommended for patients in group C or D, with frequent exacerbations that do not respond to treatment with long-term bronchodilators. The stable finding of increased risk for pneumonia among studies^{21–23} should be possibly taken into account in patients with a history of severe lower respiratory infections. However, in everyday clinical practice, there is overtreatment of COPD with ICS,²⁴ and recent studies showed that discontinuation of ICS in patients who were not frequent exacerbators did not increase exacerbation rate.^{25,26} Roflumilast (a phosphodiesterase 4 inhibitor) is recommended for patients with severe obstruction, clinical phenotype of chronic bronchitis, and frequent exacerbations. All studies used roflumilast as add-on therapy with long-acting bronchodilators.^{27,28}

Combining LAMAs with LABAs is currently proposed by GOLD as a separate treatment option, even though their clinical effectiveness over monocomponents was proved almost 10 years ago.^{1,29} There are several proposed mechanisms that justify the combination therapy: they demonstrate different ways of action (LAMAs inhibit the action of acetylcholine at M_1 and M_3 receptors; LABAs promote stimulation of β_2 -adrenoreceptor, leading to an increase in cyclic adenosine monophosphate) that both result in smooth muscle relaxation and possibly interact at intracellular level;^{30,31} sympathetic activity is increased during the day, whereas the parasympathetic system is more active at night, so an intervention for both systems might produce additive effects;^{30,32} there are some data about the anti-inflammatory properties of long-acting bronchodilators,^{33,34} as well as an cooperative in vitro effect;³⁵ and adverse events related to a LAMA/LABA combination are less than giving monocomponents in increased doses,¹ whereas fixed-dose combinations possibly increase adherence to treatment as a result of less-complicated dosing schemes.³⁶

The fixed-dose combination of UMEC/VI

UMEC is a novel LAMA with strong M_3 affinity. It has fast onset of action (time to maximal plasma concentration

[T_{max}], 5–15 minutes) and slow functional reversibility at the M₃ receptor, whereas in short-term administration, there were no adverse events related to electrocardiogram, blood pressure, and clinical laboratory tests.³⁷ In addition, in a 12-week clinical study among COPD patients with moderate to very severe disease, UMEC in doses of 62.5 and 125 µg showed improvement from baseline in trough FEV₁ at the end of the study (127 and 152 mL, respectively, compared with placebo; $P < 0.001$).³⁸ There was also clinically significant improvement both in dyspnea score and health status, as evaluated by the St George's Respiratory Questionnaire. In a 24-week clinical study of UMEC/VI in two different doses, the subgroup of patients who received the mono-component UMEC at 125 µg had a numerical difference in trough FEV₁ (186 vs 149 mL), 0–6 hours weighted mean FEV₁ (206 vs 180 mL), and peak FEV₁ (282 vs 256 mL) from baseline on day 169 compared with those who were treated with tiotropium 18 µg.³⁹

VI is a selective (greater selectivity for β₂-adrenoreceptor than formoterol, indacaterol, and albuterol)⁴⁰ ultra-LABA with rapid onset (5 minutes) and prolonged action that is administered once daily.⁴¹ In a dose–response study of VI administered to 602 patients with moderate-severe COPD over the course of a 4-week period, the doses of 25 and 50 µg showed an increase in trough FEV₁ of 137 and 165 mL, respectively, over placebo (both $P < 0.001$).⁴² There were no adverse events with regard to blood pressure, electrocardiogram, and blood glucose and potassium levels.

The fixed-dose combination of UMEC/VI is delivered once daily via the Ellipta® multidose dry powder inhaler and has been recently approved for clinical use in the United States and European Union. Many studies concerning safety, dose response, and bronchodilatory and clinical effects (improvement in dyspnea, quality of life, and exercise capacity) of the drug proved its usefulness in COPD patients.

A safety, randomized, placebo- and moxifloxacin-controlled, 10-day study among 103 healthy subjects⁴³ concluded there were no clinically significant changes from baseline in QT interval corrected using Fridericia's correction with UMEC 500 µg and UMEC/VI 125/25 µg. On day 10, the mean change from baseline in heart rate was +8.4 beats per minute with UMEC/VI 125/25 µg and +20.3 beats per minute with UMEC 500/100 µg compared with placebo at 10 minutes postdose, whereas after this point, heart rate rapidly returned to normal levels. Another safety, placebo-controlled study of 4 weeks among 42 patients with moderate to very severe COPD showed that a supratherapeutic dose of UMEC/VI (500/25 µg) was well

tolerated.⁴⁴ There was no difference in weighted mean pulse rate over 0–6 hours at the end of the study, as well as in blood pressure, minimum/maximum pulse rate, and QT interval corrected using Fridericia's correction assessments. Both agents showed rapid absorption (median T_{max} ~6 minutes for both drugs) with no evidence of accumulation (area under the curve or C_{max} on day 28).

The largest and most recent study about safety and tolerability included 562 patients (342 completed the study) over the course of a 1-year period who were randomized to receive UMEC/VI (125/25 µg), UMEC (125 µg), and placebo.⁴⁵ Any serious on-treatment adverse events, adverse events that lead to withdrawal from the study, cardiovascular adverse events, and abnormal, clinically significant Holter electrocardiogram interpretations were similar across all treatment groups.

In Table 1, we present five published clinical trials^{39,46–48} of 24 weeks' duration that evaluated the effect of the fixed-dose combination UMEC/VI (62.5/25 and 125/25 µg) compared with its monocomponents, tiotropium and placebo, on trough FEV₁ as the primary endpoint. Another trial with a longer duration (52 weeks) was a safety and tolerability study that evaluated trough FEV₁ as a secondary endpoint. In the only study that used both doses of UMEC/VI (62.5/25 and 125/25 µg),³⁹ there was no difference between the doses in lung function as well as symptomatic improvement. For UMEC/VI (62.5/25 µg, which is the approved dose for clinical use), the differences in trough FEV₁ were 167, 52, 22, 90–95, and 60–112 mL compared with placebo, UMEC 62.5 µg, UMEC 125 µg, VI 25 µg, and tiotropium 18 µg, respectively. All these differences were statistically significant with the exception of UMEC 125 µg. The percentage of patients who achieved clinical significant bronchodilation (increase in FEV₁ ≥ 12% and 200 mL) during the initial 6 hours on the 1st day after drug administration was 61%–69%.^{39,46,48}

There were also significant effects on patient-centered outcomes of UMEC/VI (62.5/25 µg). The percentage of patients who achieved the minimally clinical important improvement in TDI (≥ 1 unit) was 58%,⁴⁶ in St George's Respiratory Questionnaire (≥ 4 units achieved) it was 49%–53%,^{46,48} and the mean reduction in rescue medication (puffs of albuterol/day) was 1.3–2.7.^{39,46} In the 52-week study,⁴⁵ fewer patients experienced COPD exacerbations with UMEC/VI 125/25 µg (13%) compared with placebo (24%). COPD exacerbations that led to hospital admission were also fewer with UMEC/VI 125/25 µg compared with placebo (6% vs 12%).

In two identical 12-week, crossover studies that included 655 patients in total, exercise time as measured

Table 1 Randomized controlled studies for UMEC/VI in COPD patients

Reference	Duration and study groups	1. Primary endpoint 2. Additional outcomes	Results for primary endpoint	Results for the additional outcomes
Donohue et al; ⁴⁶ study NCT01313650	24 weeks; UMEC/VI 62.5/25 µg (N=413), VI 25 µg (N=421), UMEC 62.5 µg (N=418), placebo (N=280)	1. Trough FEV ₁ (day 169) 2a. Mean FEV ₁ 0–6 hours postdose (day 168) 2b. TDI 2c. Time to first exacerbation 2d. SGRQ 2e. Safety	1. 167, 72, and 115 mL compared with placebo (all $P<0.001$)	2a. 242, 122, and 150 mL compared with placebo (all $P<0.001$) 2b. 58%, 51%, 53%, and 41% response for TDI 2c. HR: 0.5 * 0.7, 0.6† vs placebo 2d. 49%, 48%, 44%, and 34% response for SGRQ 2e. 5%, 6%, 6%, and 3% SAEs
Celli et al; ⁴⁷ study NCT01313637	24 weeks; UMEC/VI 125/25 µg (N=403), VI 25 µg (N=404), UMEC 125 µg (N=407), placebo (N=275)	1. Trough FEV ₁ (day 169) 2a. Mean FEV ₁ 0–6 hours postdose (day 168) 2b. TDI 2c. Time to first exacerbation 2d. SGRQ 2e. Safety	1. 238, 124, and 160 mL compared with placebo (all $P<0.001$)	2a. 287, 145, and 178 mL compared with placebo (all $P<0.001$) 2b. 49%, 38%, 41%, and 30% response for TDI 2c. HR: 0.4, 0.5, 0.5 vs placebo (all $P<0.001$) 2d. 49%, 41%, 40%, and 37% response for SGRQ 2e. 6%, 5%, 5%, and 6% SAEs
Decramer et al; ³⁹ study NCT01316900	24 weeks; UMEC/VI 125/25 µg (N=214), UMEC/VI 62.5/25 µg (N=212), VI 25 µg (N=209), TIO 18 µg (N=208)	2e. Safety 1. Trough FEV ₁ (day 169) 2a. Mean FEV ₁ 0–6 hours postdose (day 168) 2b. TDI 2c. Time to first exacerbation 2d. SGRQ	1a. 88 and 90 mL compared with TIO ($P\leq 0.001$) b. 88 and 90 mL compared with VI ($P\leq 0.001$)	2a. 83 and 74 mL compared with TIO ($P<0.01$); 86 and 77 mL compared with VI ($P<0.01$) 2b. NS compared with TIO, 0.8 units (125/25) compared to VI ($P=0.0126$) 2c. NS compared with TIO and VI 2d. NS compared with TIO and VI 2e. SAE: 3% vs 6% and 7% (62.5/25), TIO and VI 2a. 101 and 96 mL compared with UMEC ($P<0.0001$) 76 and 70 mL compared with UMEC ($P<0.01$) 2b. NS compared with TIO and UMEC 2c. NS compared with TIO and UMEC 2d. NS compared with TIO and UMEC 2e. SAE: 10% vs 4% and 7% (62.5/25), TIO and UMEC
Decramer et al; ³⁹ study NCT01316913	24 weeks; UMEC/VI 125/25 µg (N=215), UMEC/VI 62.5/25 µg (N=217), UMEC 125 µg (N=222), TIO 18 µg (N=215)	2e. Safety 1. Trough FEV ₁ (day 169) 2a. Mean FEV ₁ 0–6 hours postdose (day 168) 2b. TDI 2c. Time to first exacerbation 2d. SGRQ	1a. 74 and 60 mL compared with TIO b. No significant difference compared with UMEC	2a. 101 and 96 mL compared with UMEC ($P<0.0001$) 76 and 70 mL compared with UMEC ($P<0.01$) 2b. NS compared with TIO and UMEC 2c. NS compared with TIO and UMEC 2d. NS compared with TIO and UMEC 2e. SAE: 10% vs 4% and 7% (62.5/25), TIO and UMEC
Maleki-Yazdi et al; ⁴⁸ study NCT01777334	24 weeks; UMEC/VI 62.5/25 µg (N=454), TIO 18 µg (N=451)	2e. Safety 1. Trough FEV ₁ (day 169) 2a. Mean FEV ₁ 0–6 hours postdose (day 168) 2b. SGRQ 2c. Safety	1. 112 mL compared with TIO ($P<0.001$)	2a. 105 mL compared with TIO ($P<0.001$) 2b. 53% vs 46% response for SGRQ 2c. 4% vs 4% SAEs, 4% vs 3% AEs
Donohue et al; ⁴⁵ study NCT01316887	52 weeks; UMEC/VI 125/25 µg (N=226), UMEC 125 µg (N=227), placebo (N=109)	1. Safety assessments 2a. Trough FEV ₁ at 12 months 2b. COPD exacerbations 2c. Time to first exacerbation	1a. 6%, 7%, and 6% SAEs; 8%, 9%, and 12% AEs; 15%, 22%, and 23% CV AEs b. Postbaseline electrocardiogram abnormalities were higher than placebo	2a. 231 and 178 mL compared with placebo 2b. 13%, 15%, and 24% 2c. HR: 0.6, 0.4 vs placebo

Notes: Data in the results columns are presented according to the order of the study groups in the second column. * $P\leq 0.01$, † $P<0.005$, trough forced expiratory volume in 1 second (FEV₁) was defined as the mean of the values obtained 23 and 24 hours after the previous day's dosing.

Abbreviations: COPD, chronic obstructive pulmonary disease; UMEC, umecidinium; VI, vilanterol; TIO, tiotropium; TDI, transition dyspnea index; SGRQ, St George's respiratory questionnaire; response, reduction from baseline in SGRQ total score of ≥ 4 units and ≥ 1 unit for TDI; NS, not significant; SAEs, serious adverse events on treatment; AEs, adverse events leading to permanent discontinuation or withdrawal; CV AEs, cardiovascular adverse events; FEV₁, forced expiratory volume in one second; HR, hazard ratio.

by the endurance shuttle walking test 3 hours after drug administration was the primary endpoint.⁴⁹ One study showed significant increase in exercise time compared with placebo (+69.5 seconds for UMEC/VI 62.5/25 µg; $P=0.003$), as well as the post hoc integrated analysis (+43.7 seconds for UMEC/VI 62.5/25 µg; $P=0.001$). Improvements in exercise endurance and trough FEV₁ were similar for both doses of UMEC/VI.

In a more recent IIIb, randomized, 12-week clinical trial among 716 moderate/severe COPD patients, with no moderate/severe exacerbations during the last year, UMEC/VI (62.5/25 µg) was compared with fluticasone propionate/salmeterol (500/50 µg twice a day).⁵⁰ All lung function indices were improved significantly with UMEC/VI, and there was no difference in dyspnea score or health-related quality of life.

In Table 2, we present the main fixed-dose combinations of LAMA/LABA that either have been approved for clinical use, such as indacaterol/glycopyrronium, which is delivered via the Breezhaler® dry powder device, or are in the development phase (eg, tiotropium/olodaterol via the Respimat® device, aclidinium bromide/formoterol via the Genuair®, and glycopyrrolate/formoterol via metered dosed inhaler). All combinations seem promising, as they fulfill important characteristics of an ideal bronchodilator: early onset of action, significant effect during the initial 4–6 hours, long-standing action, and favorable safety profile in a disease that is mainly characterized by irreversible airway obstruction.

Conclusion

The UMEC/VI combination is an effective and safe bronchodilator delivered via an innovative and easy-to-use device that significantly improved clinical status compared with placebo. More longstanding studies are needed to investigate its role on exacerbations, hospitalizations, disease progression (annual FEV₁ decline), and mortality, as well as head-to-head comparisons with other fixed-dose combinations. Patients in group B and those with diminished lung function (FEV₁<50% predicted) and infrequent exacerbations (groups C₁ and D₁) should be the target population for these combinations, and ICS could be the next step, based on a personalized medical approach.

Disclosure

DS has received honoraria for speaking from Astra Zeneca, Menarini, Chiesi, Novartis, and Boehringer-Ingelheim and financial support to attend advisory board meetings and congresses from Novartis, Boehringer-Ingelheim, and Menarini. LS has received honoraria for speaking from Astra Zeneca,

Table 2 Comparison of various long-acting muscarinic antagonists/long-acting β₂-agonists fixed-dose combinations on lung function parameters

	Umeclidinium/vilanterol (62.5/25 µg once a day) ⁴⁶	Indacaterol/glycopyrronium (110/50 µg once a day) ⁵¹	Tiotropium/olodaterol (5/10 µg once a day) ⁵²	Aclidinium/formoterol (400/12 µg twice a day) ⁵³	Glycopyrrolate/formoterol (72/9.6 µg twice a day) ⁵⁴
Trough forced expiratory volume in 1 second vs placebo, mL	167	200	57 (vs tiotropium)	143	234
Time to onset of action, (minutes)	15	5		5	5
Forced expiratory volume in 1 second area under the curve	242 (0–6 hours)	340 (0–4 hours)		221 (0–12 hours)	298 (0–12 hours)
Peak forced expiratory volume in 1 second vs placebo, mL	224	330	144 (vs tiotropium)	299	328
Trough forced vital capacity vs placebo, mL	248	–	117 (vs tiotropium)	–	–

Menarini, and Chiesi and financial support to attend advisory board meetings and congresses from Novartis, Boehringer-Ingelheim, and Menarini.

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