New developments in the combination treatment of COPD: focus on umeclidinium/vilanterol

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Abstract: An increasing body of evidence suggests that the long-acting muscarinic antagonist (LAMA)/long-acting β2-agonist (LABA) combination appears to play an important role in maximizing bronchodilation, with studies to date indicating that combining different classes of bronchodilators may result in significantly greater improvements in lung function compared to the use of a single drug, and that these combinations are well tolerated in patients with moderate-to-severe chronic obstructive pulmonary disease (COPD). An inhaled, fixed-dose combination of two 24-hour bronchodilators, the LAMA umeclidinium and the LABA vilanterol, is under development as a once-daily treatment for COPD. The efficacy of both mono-components has already been demonstrated. The information currently available suggests that umeclidinium/vilanterol is an effective once-daily dual bronchodilator fixed-dose combination in the treatment of COPD. However, it remains to be seen if it compares favorably with current therapies. Moreover, the question remains whether umeclidinium/vilanterol fixed-dose combination, which significantly improves FEV1, is also associated with improvements in other outcome measures that are important to COPD patients.

Keywords: muscarinic antagonist, dual bronchodilation, COPD

Introduction

Long-acting inhaled bronchodilators feature prominently in the recommended management strategy for chronic obstructive pulmonary disease (COPD).1,2 Two classes of long-acting inhaled bronchodilators are available – long-acting β2-agonists (LABAs) and long-acting muscarinic antagonists (LAMAs). LABAs directly induce bronchodilation by relaxing airway smooth muscle through stimulation of β2-adrenoceptors, whereas LAMAs prevent acetylcholine-induced bronchoconstriction by acting as competitive antagonists on muscarinic receptors.3

Symptomatic treatment with bronchodilators is recommended as the first stage of therapy for COPD.1,2 However, experts agree that, in patients not fully controlled with one long-acting bronchodilator, maximizing bronchodilation (ie, adding another bronchodilator with a different mechanism of action) is the preferable option.4 In effect, guidelines recommend combination therapy involving two long-acting bronchodilators with differing mechanisms of action in patients whose COPD is not sufficiently controlled with monotherapy.2 In particular, the Global initiative for chronic Obstructive Lung Disease (GOLD) report suggests use of LAMA/LABA dual therapy as a treatment alternative for patients in groups B (high symptoms/low risk), C (low symptoms/high risk), and D (high symptoms/high risk).2
Clinical evidence supporting dual bronchodilation

An increasing body of evidence suggests that the LAMA/LABA combination appears to play an important role in maximizing bronchodilation, with studies to date indicating that combining different classes of bronchodilators may result in significantly greater improvements in lung function compared to the use of a single drug, and that these combinations are well tolerated in patients with moderate-to-severe COPD. However, forced expiratory volume in 1 second (FEV₁) alone may not adequately reflect the overall health status of the patient. Published evidence suggests that LAMA/LABA combination therapies demonstrate greater improvements in patient-centered outcomes such as dyspnea, symptoms, rescue medication use, and quality of life than individual drugs used alone. Moreover, the LAMA/LABA combination seems to be superior in preventing COPD exacerbations compared with LAMA alone.

Moreover, although management of COPD can be achieved with a high dose of a single agent, combining two or more classes of molecules allows the use of lower doses that demonstrate the same efficacy while decreasing adverse effects.

Pharmacological rationale for dual bronchodilation

Airway tone is regulated by both the parasympathetic and sympathetic nervous systems. The complete nature of interactions between the two physiological systems is not yet fully understood, but there is enough evidence to suggest that combining β₂-agonists and muscarinic antagonists is pharmacologically reasonable for several reasons that have been reviewed in detail recently.

β₂-agonists can amplify the bronchial smooth muscle relaxation directly induced by the muscarinic antagonist by decreasing the release of acetylcholine via a modulation of cholinergic neurotransmission that involves calcium-activated potassium (KCa) channels rather than adenylyl cyclase and cyclic adenosine monophosphate. Activation of KCa channels is thought to hyperpolarize the cell membrane, thus causing reductions in the concentration of intracellular Ca²⁺ and acetylcholine release in prejunctional cholinergic nerves. Therefore, we could assume that the addition of a muscarinic antagonist can reduce bronchoconstriction effects of acetylcholine, the release of which will have been modified by the β₂-agonist, and thereby amplify the bronchodilation elicited by the same β₂-agonist through the direct stimulation of smooth muscle β₂-adrenoceptors.

However, this mechanism seems unlikely, there is documentation clearly indicating that β₂-agonists facilitate rather than inhibit parasympathetic acetylcholine release in the airways. Therefore, it has been suggested that crosstalk between muscarinic receptors and β₂-adrenoceptors, causing functional antagonism at the level of the airway smooth muscle itself, seems more likely to be of importance. In effect, crosstalk between Gq-coupled M₁ receptors and Gq-coupled β₂-adrenoceptors may have a major influence on β-agonist-induced relaxation, presumably by activation of protein kinase C (PKC) and subsequent phosphorylation of the β₂-adrenoceptor and/or Gq protein. Interestingly, PKC activation also enhances β-agonist-induced relaxation, presumably by activation of G-protein receptor kinase 2. Both mechanisms could contribute to the beneficial bronchodilatory effects of dual bronchodilator therapy.

Another possibility is the fact that the antimuscarinic agent and not the β₂-adrenoceptor agonist can suppress mucus/liquid secretions; hence, surface tension changes that would collapse the airways do not occur.

Recent findings showed that β₂-adrenoceptors and muscarinic receptors mediate opposing effects on endothelin-1 expression in human lung fibroblasts. Since muscarinic upregulation of endothelin-1 contributes to profibrotic effects of muscarinic stimuli, inhibition of endothelin-1 expression could contribute to long-term beneficial effects of long-acting β₂-adrenoceptor agonists and long-acting muscarinic antagonists. Moreover, β₂-agonists and antimuscarinic drugs additively control transforming growth factor (TGF)-β1-mediated neutrophilic inflammation in COPD.

Development of fixed-dose combinations of LAMAs and LABAs

Fixed-dose combinations of LAMAs and LABAs offer the potential of improved convenience and compliance over use of separate inhalers, and, during their development, the dose of each agent to be used in combination can be optimized. Therefore, there is a strong interest in developing a LABA/LAMA fixed-dose combination therapy.

Glycopyrronium/indacaterol, tiotropium/olodaterol, and umeclidinium/vilanterol are in advanced development for the treatment of COPD and demonstrate significant bronchodilatory effects. Acidinium or glycopyrronium are combined
with formoterol, but these combinations have a 12-hour duration of action.17–19

Development of umeclidinium/vilanterol fixed-dose combination

GlaxoSmithKline (London, UK) and Theravance (South San Francisco, CA, USA) are developing an inhaled fixed-dose combination of two 24-hour bronchodilators, the LAMA umeclidinium and the LABA vilanterol, as a once-daily treatment for COPD. The efficacy of both mono-components will be discussed, although it should be noted that the results of several Phase III clinical trials are not yet available.

Umeclidinium

Umeclidinium bromide (GSK573719) is a novel quinclidine-based quaternary ammonium inhaled long-acting muscarinic antagonist. Its preclinical pharmacology has been well characterized.20 In vitro, umeclidinium displayed subnanomolar affinity for all the cloned human M1–M5 muscarinic receptors, which ranged from 0.05 to 0.16 nM. Umeclidinium showed kinetic selectivity for M2 receptors over M3 and dissociation from the M3 muscarinic receptors, which was slower than that for the M2 muscarinic receptors (half-life \( t_{1/2} \) values: 82 and 9 minutes, respectively). In isolated human bronchial strips, umeclidinium was potent and showed competitive antagonism (\(-\log pA_2 = 316 \) pM) versus carbachol, and was slowly reversible in a concentration-dependent manner (1–100 nM). The time to 50% restoration of contraction at 10 nM was about 381 minutes (versus 413 minutes for tiotropium bromide). In conscious guinea pigs, intratracheal administration of GSK573719 dose-dependently blocked acetylcholine (ACh)-induced bronchoconstriction with long duration of action, and was comparable to tiotropium; 2.5 \( \mu \)g elicited 50% bronchoprotection for >24 hours.20

A pharmacokinetic study in patients with COPD demonstrated that maximum observed plasma umeclidinium concentration \( (C_{max}) \) was reached rapidly (time to reach the maximum plasma concentration \( [t_{max}] \): after single dose, \(~5–15\) minutes; and repeat doses, \(5–7\) minutes).21 Following repeat dosing, the geometric mean plasma elimination \( t_{1/2} \) was approximately 27 hours, and statistically significant accumulation was observed for the area under the plasma concentration–time curve, maximum plasma concentration, and cumulative amount of unchanged drug excreted into the urine at 24 hours (range 1.5- to 4.5-fold).21,22

In a separate Phase I study in ipratropium bromide-responsive healthy volunteers, umeclidinium (10–350 \( \mu \)g) at doses of 100 \( \mu \)g and above, and tiotropium bromide 18 \( \mu \)g demonstrated statistically significant bronchodilatory effects relative to placebo at 12 hours post-dosing, which lasted up to 24 hours for umeclidinium 350 \( \mu \)g and for tiotropium bromide.22 Relative to placebo, these increases in specific airway conductance were 24%–34% at 12 hours post-dose and 13% at 24 hours post-dose. Increases in FEV\(_1\) achieved statistical significance at 12 and 24 hours for umeclidinium 100 \( \mu \)g and 350 \( \mu \)g compared with placebo.22

Compared with placebo, umeclidinium (125, 250, and 500 \( \mu \)g), once daily, provided statistically significant improvements in trough FEV\(_1\) (from 150–168 mL; \( P < 0.001 \)), 0–6 hour weighted mean FEV\(_1\) (from 113–211 mL; \( P < 0.001 \)), and serial FEV\(_1\) at each point in time over 24 hours after 28 days in a randomized, double-blind, placebo-controlled Phase II study.23 In a second randomized, double blind, placebo-controlled Phase II study, umeclidinium once daily (62.5–1,000 \( \mu \)g) significantly improved trough FEV\(_1\) compared with placebo after 14 days of treatment (\( P < 0.01 \)).24 Improvements in lung function with umeclidinium once daily were comparable to those seen with umeclidinium twice daily (62.5–250 \( \mu \)g) and tiotropium bromide. Umeclidinium once daily also significantly reduced the need for rescue medication compared with placebo.

Umeclidinium is well tolerated; however, the incidence of drug-related adverse events was shown to be dose-related in a randomized, double-blind, Phase II study in patients with COPD.21 Umeclidinium 1,000 \( \mu \)g once daily produced larger increases in heart rate in the 4 hours post-dose compared with umeclidinium 250 \( \mu \)g once daily or placebo; there was no dose effect on heart rate when assessed over 24 hours.

Vilanterol

Vilanterol trifenate (GW642444) is a novel LABA with inherent 24-hour activity. It is a highly lipophilic molecule partitioning into cell membrane and forming deposits of drug, but it is not possible to rule out that vilanterol binds directly to an anchored binding site within the \( \beta_2 \)-adrenoceptor.25 Vilanterol displays a subnanomolar affinity for the \( \beta_2 \)-adrenoceptor (AR) that is comparable with that of salmeterol but higher than that of olodaterol, formoterol, and indacaterol, and it is highly selective for the \( \beta_2 \)-adrenoceptor, with at least 1,000-fold selectivity over both \( \beta_3 \) and \( \beta_5 \)-adrenoceptor subtypes.25 Vilanterol demonstrates similar selectivity as salmeterol for \( \beta_2 \)- over \( \beta_3 \)-adrenoceptor and \( \beta_5 \)- over \( \beta_5 \)-adrenoceptor, and is significantly more selective than formoterol, indacaterol, and isoprenaline for \( \beta_2 \)- over
β₁-adrenoceptor and β₂ over β₂-adrenoceptor. It also shows a level of intrinsic efficacy that is comparable to indacaterol but significantly greater than that of salmeterol and significantly lower than formoterol and isoprenaline. In addition, vilanterol has been shown in isolated human small airways to have a significantly faster onset of action than salmeterol (t₁/₂ = 3.1 ± 0.3 minutes vs t₁/₂ = 8.3 ± 0.8 minutes, respectively), but only vilanterol was shown to be significantly different from vehicle-treated airways at 22 hours and no significant duration was observed at 28 hours for vilanterol or salmeterol.

Oral vilanterol is well absorbed in humans and is subject to extensive first-pass metabolism to metabolites, with negligible β-agonist pharmacologic activity. The metabolism of vilanterol is mainly by O-dealkylation, and metabolites are excreted via both feces and urine. To a large extent, the low dose levels often associated with inhalation molecules mitigate any metabolite or metabolism safety concerns.

In Phase I studies, vilanterol (25–100 µg) was rapidly absorbed into the plasma of healthy subjects (median t_max at 5–10 minutes), with approximate dose-proportional increases in C_max across the dose range. In subjects with COPD, median t_max was achieved 10 minutes post-dose following the 25 and 50 µg doses. When administered as a single dose (25–100 µg), vilanterol was well tolerated in subjects with COPD. It produced increases in FEV₁ from as early as 5 minutes after dosing. There were statistically significant increases in FEV₁ at all time points, from 5 minutes to 25 hours post-dose, for all doses of vilanterol (25, 50, and 100 µg, compared with placebo). Mean FEV₁ (difference from baseline) 23–24 hours after dosing was at least 200 mL greater than placebo for all doses, indicating 24-hour duration of action after a single dose.

In a subsequent Phase IIb study, once-daily administration of vilanterol in patients with moderate-to-severe COPD provided clinically relevant 24-hour improvement in lung function with a rapid onset of effect and a safety and tolerability profile comparable with placebo at the end of the 28-day treatment period. The 25 µg and 50 µg doses of vilanterol appear to offer the greatest clinical benefit without any safety concerns. At the 25 µg dose level, the likelihood of pharmacologically inactive metabolites causing unexpected toxicity is negligible.

**Umeclidinium/vilanterol**
A Phase I trial has evaluated the safety and tolerability, pharmacodynamics, and pharmacokinetics of umecclidinium and vilanterol as inhaled therapies and administered concurrently from separate novel dry-powder inhaler devices in 16 healthy Japanese males. Pharmacokinetic assessments showed rapid absorption for both drugs (T_max = 5 minutes for both umecclidinium and vilanterol) followed by rapid elimination with median time to the last measurable concentration (t(last) of 4–5 hours for umecclidinium and median t(last) of 1.5–2.0 hours for vilanterol. The concurrent administration of umecclidinium and vilanterol resulted in a 30% higher umecclidinium C_max than with umecclidinium alone, although the treatment ratio for area under the curve (AUC) parameters, with the exception of AUC_0-24, showed no difference. There was no difference in vilanterol C_max when delivered concurrently with umecclidinium or when administered alone. However, AUC parameters indicated that the concurrent administration of umecclidinium and vilanterol resulted in an up to 39% higher systemic exposure to vilanterol when compared to vilanterol alone. Nonetheless, single inhaled doses of umecclidinium 500 µg, vilanterol 50 µg, and the combination were safe and well tolerated, and no trends between individual maximum heart rate and umecclidinium C_max or vilanterol C_max when administered as umecclidinium/vilanterol combination or as umecclidinium or vilanterol monotherapy were noted.

Another Phase I study estimated the effect of 10 days of inhaled umecclidinium bromide/vilanterol combination and umecclidinium bromide monotherapy on the QT interval using Fridericia’s correction (QTcF) in at least 103 healthy subjects compared with placebo, with moxifloxacin as a positive control. Moxifloxacin demonstrated a clinically significant increase in QTcF, whereas no difference in QTcF was observed between umecclidinium/vilanterol 125/25 µg or umecclidinium 500 µg and placebo. Umecclidinium/vilanterol 500/100 µg increased QTcF, on average, by 8.2 milliseconds (90% confidence interval [CI]: 6.2, 10.2) at 30 minutes only. Both umecclidinium/vilanterol dosages increased heart rate compared with placebo, with the maximum increase occurring 10 minutes post-dose (umecclidinium/vilanterol 125/25 µg: 8.4 bpm [90% CI: 7.0, 9.8]; umecclidinium/vilanterol 500/100 µg: 20.3 bpm [90% CI: 18.9, 21.7]), followed by a rapid decline. Umecclidinium systemic exposure following umecclidinium 500 µg was higher than exposure following umecclidinium/vilanterol 500/100 µg; umecclidinium and vilanterol exposure following umecclidinium/vilanterol 500/100 µg was ~4-fold higher than exposure following umecclidinium/vilanterol 125/25 µg. Exploratory analysis suggested a relationship between vilanterol plasma C_max concentrations and heart rate for umecclidinium/
vilanterol 500/100 µg. Twenty percent of subjects under the supratherapeutic dose, umecclidinium/vilanterol 500/100 µg, reported mild palpitations with no electrocardiograph (ECG) abnormalities.

A Phase II study that has assessed the safety, tolerability, pharmacokinetics, and pharmacodynamics of the inhaled combination of umecclidinium bromide 500 µg and vilanterol 25 µg administered once daily via a novel dry powder inhaler over 28 days compared to placebo in subjects with COPD has been completed.31 Umecclidinium bromide/vilanterol was shown to be non-inferior to placebo for the primary end point, which was the mean change from baseline in 0–6 hours post-dose weighted mean pulse rate after 28 days of treatment (difference of −0.5 bpm; 95% CI: −5.5, 4.5). No clinically significant differences were noted for evaluations of blood pressure, minimum and maximum heart rate, and QTcF. There was no apparent difference between treatments for abnormal ECG findings or ventricular and supraventricular ectopic beats during Holter monitoring. A total of eleven (26%) umecclidinium/vilanterol-treated patients reported adverse events with no single adverse event reported for more than one patient; none of the adverse events were serious. Raw mean change from baseline in trough FEV\textsubscript{1}, on day 29 with umecclidinium/vilanterol was 163 mL, and with placebo, 9 mL. Pharmacokinetic results suggested rapid absorption (median t\textsubscript{max} ∼6 minutes for both drugs). The rapid absorption of umecclidinium/vilanterol was followed by a rapid decline in plasma concentrations, indicating rapid distribution and elimination of both drugs, with no evidence of accumulation on day 28 versus day 1.

In a randomized, double-blind, placebo-controlled, parallel-group study that evaluated efficacy and safety of 24-week treatment with once-daily umecclidinium/vilanterol 62.5/25 µg in 1,532 patients with moderate-to-severe COPD, the combination was well tolerated and resulted in improvements in lung function, dyspnea, and health-related quality of life, compared with placebo.32 It also provided improvements in lung function when comparing umecclidinium/vilanterol versus umecclidinium alone and vilanterol alone (improvements in trough FEV\textsubscript{1} vs umecclidinium 62.5 µg and vilanterol 25 µg: 52–95 mL; all P ≤ 0.004). Interestingly, the active therapies were not associated with treatment-related changes in Holter assessments.

In another 24-week study, once-daily umecclidinium/vilanterol 125/25 µg was compared with umecclidinium 125 µg and vilanterol 25 µg in 1,489 patients suffering from moderate-to-severe COPD.33 All active treatments produced statistically significant improvements in trough FEV\textsubscript{1} versus placebo (124–238 mL; all P < 0.001), and improvements with umecclidinium/vilanterol 125/25 µg were statistically significantly greater than umecclidinium 125 µg or vilanterol 25 µg (79–114 mL; all P < 0.001). Clinical benefits with umecclidinium/vilanterol 125/25 µg versus placebo, umecclidinium 125 µg, and vilanterol 25 µg were also observed for salbutamol rescue use and measures of health-related quality of life (P ≥ 0.004). Active treatments were not associated with any treatment-related changes in vital signs, ECG assessments, or clinical laboratory parameters.

Umecclidinium/vilanterol 62.5/25 µg and umecclidinium/vilanterol 125/25 µg were also compared with tiotropium 18 µg or vilanterol 25 µg over 24 weeks in subjects with COPD.34 The intent-to-treat population comprised 843 patients. Least squares mean change from baseline trough FEV\textsubscript{1} and 0–6-hour weighted mean FEV\textsubscript{1} showed statistically significant improvements with both umecclidinium/vilanterol dosages compared with tiotropium 18 µg or vilanterol 25 µg alone (P ≤ 0.005).

The positioning of umecclidinium/vilanterol in the treatment of COPD

We are convinced that monotherapy should be the first choice for maintenance treatment in patients with stable COPD, whereas LAMA/LABA combination therapy should be recommended in patients with COPD who remain breathless or have exacerbations despite treatment with a LAMA or LABA or for whom treatment with an inhaled corticosteroid is not possible. The great interest within the pharmaceutical industry in the discovery of novel bronchodilators that can be used as single agents and also as a part of a combination therapy for the therapy of COPD is not surprising.

Discussion

The currently available information suggests that umecclidinium/vilanterol is an effective once-daily dual bronchodilator fixed-dose combination in the treatment of COPD. However, it remains to be known if it compares favorably with current therapies, and more information on its safety profile is needed before we can surmise its real benefit in the treatment of COPD. The results of several clinical trials that are ongoing, or finished but not yet communicated to the scientific community, can be expected to be of great help. In the meantime, we must point out that the information on umecclidinium and vilanterol as monotherapies also remains relatively scarce.
We consider it critical to know whether and how umeclidinium differs not only from tiotropium bromide but also, and above all, from aclidinium bromide and glycopyrronium bromide. These novel LAMAs achieve maximal bronchodilation on the first day of dosing or have a faster onset of action than tiotropium bromide, which may offer advantages in terms of improving symptom control. A comparison of umeclidinium with these two LAMAs is, therefore, imperative.

Further, the substantial differences in key pharmacologic parameters, such as β₂-adrenoceptor selectivity, potency, intrinsic efficacy, and lipophilicity, among available LABAs or those under development, must be considered. These differences are fundamental in characterizing the pharmacological profile (mainly onset and duration of action, but also loss of responsiveness to chronic LABA therapy) and, consequently, the clinical effect of each LABA. The clinical implications of these differences cannot be known with certainty until the drugs are directly compared in controlled trials. For this reason, we believe that comparison of vilanterol with indacaterol and olodaterol, two once-daily LABAs approved for use in monotherapy in COPD, is also now mandatory, as is a comparison of vilanterol with formoterol.

In effect, we must understand if there are differences in LABAs that could elicit a greater response when combined with a specific antimuscarinic agent. For example, it has been documented that, in patients with moderate-to-severe COPD, treatment with the combination of formoterol and ipratropium was more effective than the combination of salbutamol and ipratropium, and it is well known that formoterol is a stronger agonist with a longer duration of action. Obviously, it could also be possible that differences in the characteristics of each LAMA could influence the broncholytic response when combined with a specific LABA. Good preclinical studies using isolated human airways will likely clarify the probable differences of the potential dual bronchodilator combinations, and will allow us to translate this information in vivo. We must design appropriate clinical trials to confirm preclinical data.

This information is fundamental because, in addition to umeclidinium/vilanterol, other once-daily LABA and LAMA fixed-dose combinations, including QVA149 (the combination of indacaterol and glycopyrronium bromide) and olodaterol plus tiotropium bromide, are in clinical development as fixed combinations. Moreover, as already mentioned, some new combinations, such as formoterol plus glycopyrronium bromide and formoterol plus aclidinium bromide, are under development, with an expected twice-daily dosing regimen.

Adherence to inhaled agents is required for the management of COPD but, unfortunately, suboptimal adherence is common among patients suffering from COPD. Adherence could be improved by using simplified treatment regimens. Incorporation of once-daily dosing is an important strategy by which to improve adherence, since it is a regimen preferred by most patients. Therefore, there is a factual interest in developing once-daily dual bronchodilator combinations in an attempt to simplify treatment. In this regard, umeclidinium/vilanterol fixed-dose combination fully meets such a requirement.

Nonetheless, it has been documented recently that, with the same total daily dose of a new LAMA, a twice-daily regimen provides higher bronchodilation at trough than the once-daily regimen. For the maximum bronchodilation, there is a small difference between the two regimens, with the once-daily regimen being slightly better than the twice-daily regimen. For the overall bronchodilation response, as quantified by the FEV₁ response 24-hour AUC, the difference between the two regimens becomes even smaller.

If the aim of the dual bronchodilation is to “maximize” bronchodilation, it is obvious that it is necessary to compare the efficacy of the combination administered once daily with that obtained when it is administered twice daily. An analysis of the dose response of umeclidinium administered once or twice daily in patients with COPD documented that all once-daily doses of umeclidinium significantly (P < 0.001) increased 0–24-hour weighted mean FEV₁ at the end of treatment by 105 to 152 mL compared with placebo and were similar to increases observed with twice-daily dosing (123–145 mL). On the other hand, in patients suffering from persistent asthma, the vilanterol 6.25 µg twice-daily dose showed the greatest change in trough FEV₁; however, similar changes in weighted mean 24-hour FEV₁ with vilanterol 12.5 µg once daily were also observed. Nonetheless, it still remains to be documented that umeclidinium/vilanterol fixed-dose combination administered once daily can induce the same bronchodilation, expressed as both peak FEV₁ and 0–24-hour weighted mean FEV₁, as the same total daily dose administered twice daily.

**Conclusion**

We have focused our entire discussion on maximizing bronchodilation, but the question remains whether umeclidinium/vilanterol fixed-dose combination, which significantly improves FEV₁, is also associated with improvements in other
outcome measures. In fact, other elements of importance to COPD patients, such as exercise capacity, hospitalizations, depression, and pain must be explored. Both the EU Clinical Trials Register and the ClinicalTrials.gov register show that these outcomes have been studied or are being evaluated in clinical trials that are ongoing. The presentation of the data generated by these clinical trials will allow us to establish the importance of umeclidinium/vilanterol fixed-dose combination in the maintenance treatment of COPD. However, we strongly believe that Phase III trials comparing umeclidinium/vilanterol fixed-dose combination with other dual bronchodilator fixed-dose combinations, and also with inhaled corticosteroid/LABA combination, are needed to assess the real advantages of umeclidinium/vilanterol over other therapies.

Disclosure
The authors report no conflicts of interest in this work.

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