

# Umeclidinium/Vilanterol Versus Tiotropium/Olodaterol in Maintenance-Naïve Patients with Moderate Symptomatic Chronic Obstructive Pulmonary Disease: A Post Hoc Analysis

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## ABSTRACT

**Introduction:** Appropriate timing for dual bronchodilator therapy initiation in chronic obstructive pulmonary disease (COPD) management is uncertain. Combination therapy is recommended as step-up from monotherapy or first-line treatment in patients with persistent symptoms. In this setting, umeclidinium/

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vilanterol (UMEC/VI) demonstrated improved lung function and reduced rescue medication use over tiotropium/olodaterol (TIO/OLO). This subgroup analysis explored efficacy differences between these combinations in patients naïve to COPD maintenance therapy before study entry.

**Methods:** Post hoc analysis of an 8-week, randomized, open-label, assessor-blind, two-period crossover study (204990; NCT02799784) comparing UMEC/VI 62.5/25 mcg and TIO/OLO 5/5 mcg, focused on maintenance-naïve (MN) patients with moderate COPD and persistent symptoms (modified Medical Research Council dyspnea score  $\geq 2$ ). Change from baseline (CFB) in trough forced expiratory volume in 1 s (FEV<sub>1</sub>), percentage of FEV<sub>1</sub> responders (CFB  $\geq 100$  ml), rescue medication use and safety were evaluated.

**Results:** The MN population comprised 63% of the intent-to-treat (ITT) population (148/236 patients) and had similar baseline demographics. At week 8, adjusted mean (standard error) improvements in trough FEV<sub>1</sub> from baseline were clinically meaningful for both combinations (UMEC/VI: 167 [17] ml; TIO/OLO 110 [18] ml; adjusted mean difference [95% confidence interval (CI)]: 57 [23–92] ml;  $p = 0.001$ ; %CFB: 11 vs. 8%). Proportion of FEV<sub>1</sub> responders was greater with UMEC/VI versus TIO/OLO at week 8 (60 vs. 42%; odds ratio [95% CI] 1.90 [1.12–3.22];  $p = 0.018$ ). Reduction in rescue medication use was 0.20 (95% CI 0.07–0.34)

puffs/day greater with UMEC/VI versus TIO/OLO over weeks 1–8 ( $p = 0.003$ ). Adverse events incidence was similar (UMEC/VI: 24%; TIO/OLO: 29%).

**Conclusions:** These results highlight that the efficacy difference between UMEC/VI and TIO/OLO demonstrated in the ITT population is maintained in MN patients. Greater lung function improvements with UMEC/VI versus TIO/OLO were accompanied by symptom improvements, as reflected in a significantly lower need for supplemental rescue medication.

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**Keywords:** COPD; LABA; LAMA; Long-acting muscarinic antagonist; Long-acting  $\beta_2$ -agonist; Maintenance-naïve; Olodaterol; Tiotropium; Umeclidinium; Vilanterol

## INTRODUCTION

Inhaled long-acting bronchodilators form the foundation of chronic obstructive pulmonary disease (COPD) therapy, with treatment strategies including long-acting muscarinic antagonist (LAMA) or long-acting  $\beta_2$ -agonist (LABA) monotherapy, or a LAMA/LABA combination, depending on symptom burden and risk of exacerbations [1–4]. The precise timing of when to initiate LAMA/LABA combination therapy is the subject of ongoing scientific debate.

Pharmacological treatment of COPD is usually started late in the course of the disease, often in patients who are already experiencing a significant burden associated with disease symptoms and severe lung function impairment [5]. A majority of patients who receive LAMA or LABA monotherapy continue to experience ongoing moderate-to-severe dyspnea, regardless of the level of lung function impairment [6], and this symptom persistence can be associated with poor health status, as well as a higher risk for moderate and severe exacerbations and augmented disease management costs [7, 8]. There is now a large body of evidence to show that LAMA/LABA combinations consistently improve lung function, breathlessness and health status with no

increased incidence of adverse events (AEs), compared with either LABA or LAMA alone [4, 9–15]. As such, LAMA/LABA combination therapy is recommended as initial therapy in most patients with persistent COPD symptoms [1]. However, LAMA/LABA bronchodilation appear to be similarly beneficial compared with LAMA monotherapy in symptomatic patients who have or have not previously received a COPD maintenance treatment, which questions the rationale for a delayed stepwise approach in managing persistent symptoms [16, 17]. There is also evidence that early use of LAMA/LABA combinations may improve disease stability compared with LAMA monotherapy by protecting symptomatic patients, including maintenance-naïve (MN) patients, from further disease deterioration [16, 18–20]. Dual therapy could therefore provide the opportunity for maximal bronchodilation, with a view to minimizing daily symptoms, improving quality of life (QoL), and preventing further disease deterioration.

While there is increasing evidence of an efficacy gradient within the LAMA and LAMA/LABA classes with respect to lung function [15, 21–23], the comparative efficacy of different dual bronchodilator combinations used as first-line therapy has not been studied in appropriately symptomatic patients [24]. The LAMA/LABA combinations umeclidinium/vilanterol (UMEC/VI) 62.5/25 mcg, delivered via the ELLIPTA dry powder inhaler, and tiotropium/olodaterol (TIO/OLO) 5/5 mcg, delivered via the Respimat soft mist inhaler, are the only LAMA/LABA combinations approved in the USA, Europe and other parts of the world as once-daily maintenance therapies for COPD [25–28]. The first direct comparison of these once-daily fixed-dose combinations, in an 8-week crossover study in patients with moderate COPD and persistent symptoms of dyspnea, demonstrated the superiority of UMEC/VI over TIO/OLO for the primary endpoint of trough forced expiratory volume in 1 s ( $FEV_1$ ) [21].

With the prospect of early dual bronchodilation for symptomatic patients in mind, further investigation of LAMA/LABA combinations in MN patients should provide valuable information for clinicians and prescribers to aid

decision-making. Here, we investigated the efficacy and safety of UMEC/VI and TIO/OLO in a large subgroup of patients from this head-to-head study who were initiated on a COPD maintenance therapy at randomization.

## METHODS

### Study Design

This was a post hoc analysis of an 8-week, multicenter, randomized, open-label, two-period crossover study (NCT02799784; GSK clinical study identifier 204990) conducted in centers across Germany, Spain, UK, and the USA between July 2016 and April 2017 [21]. The objective of the current analysis was to evaluate the efficacy and safety of UMEC/VI versus TIO/OLO in an unexpectedly large subgroup of patients who were initiated on a COPD maintenance therapy at randomization.

The study was conducted in accordance with the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use Good Clinical Practice guidelines and with principles of the Declaration of Helsinki. The protocol was reviewed and approved by all appropriate institutional review boards (IRBs) or independent ethics committees (Ethik-Kommission [Germany], Comité Ético de Investigación [Spain], Chesapeake IRB [US], and United Kingdom Ethics Committee). Informed consent was obtained from all patients prior to inclusion in the study.

### Patients

Eligibility criteria for enrollment in the study have been previously reported [21]. In brief, patients were  $\geq 40$  years of age with a diagnosis of COPD in accordance with the American Thoracic Society/European Respiratory Society (ATS/ERS) definition [29]; current or former smokers with a smoking history of  $\geq 10$  pack-years; had a pre- and post-bronchodilator FEV<sub>1</sub>/forced vital capacity (FVC) ratio  $< 0.70$

and a post-bronchodilator FEV<sub>1</sub>  $\leq 70\%$  and  $\geq 50\%$  of predicted normal values at enrollment (visit 1) [30]; and had a score of  $\geq 2$  on the modified Medical Research Council Dyspnea Scale (mMRC) [31].

Patients with any major respiratory disease other than COPD were excluded, as were those who had experienced a moderate/severe exacerbation or lower respiratory tract infection during the run-in period.

### Randomization

Following a 2-week run-in period, eligible patients were randomly assigned to receive one of two treatment sequences: once-daily open-label UMEC/VI (62.5/25 mcg) administered via the ELLIPTA inhaler (via one inhalation) for 8 weeks followed by once-daily open-label TIO/OLO (5/5 mcg) administered via the Respimat inhaler (via two puffs of 2.5/2.5 mcg) for 8 weeks, or vice versa. Randomization was an automated process conducted using the RAMOS system. Patients had a 3-week washout period between treatments.

As placebo Respimat inhalers were not available from Boehringer Ingelheim, treatments were administered open label. However, all technicians performing spirometry were blinded to treatment allocation throughout the study.

Maintenance medications for COPD (other than the study medications) were not permitted during any study periods. As-needed use of supplemental albuterol was permitted in the run-in, treatment and washout periods to treat symptoms and provide additional symptomatic relief in the event of breakthrough symptoms on study treatment. Spirometry testing at clinic visits was performed in accordance with ATS/ERS guidelines and following an appropriate 4-h washout of as-needed albuterol therapy [32].

### Endpoints

The study endpoints have been described previously [21]. The endpoints evaluated in this post hoc analysis were change from baseline

(CFB) in trough FEV<sub>1</sub> (ml and ratio to baseline) at weeks 4 and 8, the proportion of responders at weeks 4 and 8 (defined as FEV<sub>1</sub> CFB  $\geq$  100 ml), CFB in trough FVC and inspiratory capacity (IC) at weeks 4 and 8 (derived using spirometry), use of rescue albuterol over weeks 1–8 (puffs per day) captured using an eDiary, change from baseline in COPD Assessment Test (CAT) score and CAT response rate ( $\geq$  2 units decrease in CAT score from baseline) [33] at weeks 4 and 8, and CFB in daily respiratory symptoms using the Evaluating Respiratory Symptoms—COPD (E-RS<sub>COPD</sub>) scale (weeks 1–8) [34, 35].

Safety endpoints included the incidence of AEs and serious AEs (SAEs). Moderate and severe exacerbations, defined as worsening of symptoms requiring the use of antibiotics or systemic corticosteroids or a worsening of symptoms requiring hospitalization or an emergency department visit lasting > 24 h, respectively, were also reported descriptively as safety endpoints.

### Study Populations

All randomized patients who received  $\geq$  1 dose of study medication were included in the intent-to-treat (ITT) population. The MN population, used for the current post hoc analysis, included all patients who had not received a maintenance treatment (LAMA, LABA alone or in combination  $\pm$  ICS) for COPD in the 30 days that records were kept prior to screening, i.e., at least 6 weeks prior to randomization. Permitted treatment included short-acting bronchodilators, anti-infectives (antibiotics, antifungals, antivirals, antiseptics), acute exacerbation treatment, and oxygen therapy. These criteria have been used previously to define MN populations in studies comparing UMEC/VI with TIO in patients with COPD [16, 17].

### Statistical Analysis

Treatment differences are presented as adjusted [least squares (LS)] means or odds ratios (ORs) with 95% confidence intervals (CI) and *p* values. Lung function, CAT endpoints, E-RS<sub>COPD</sub> total

score, and rescue medication use were assessed using mixed model repeated measures (MMRM) analysis. Trough FEV<sub>1</sub> and CAT responder analyses were performed using a generalized linear mixed model. Covariates have been described previously [21]. Baseline FEV<sub>1</sub>, FVC or IC was the mean of the two assessments taken 30 and 5 min pre-dose on day 1. Baseline CAT score was the score recorded prior to dosing on day 1, baseline E-RS<sub>COPD</sub> score and rescue medication use were the means during the week prior to day 1.

## RESULTS

### Patient Disposition and Demographics

The ITT population, described previously [21], comprised 236 patients, of whom 148 (63%) were included in the MN population. Baseline characteristics were generally similar between the MN and ITT populations (Table 1); however, the MN population included a greater proportion of current smokers (MN: 62%; ITT: 53%) and a greater proportion of females (MN: 47%; ITT: 40%). The MN population also had a higher burden of symptoms, with 44% of the patients experiencing severe/very severe dyspnea (mMRC score  $\geq$  3) at baseline compared with 34% of the ITT population (Table 1).

### Lung Function

At week 8, the change from baseline in trough FEV<sub>1</sub> was significantly greater in MN patients during UMEC/VI treatment than TIO/OLO treatment, with LS mean (standard error [SE]) changes of 167 (17) and 110 (18) ml, respectively (adjusted difference 57 ml [95% CI 23, 92]; *p* = 0.001) (Table 2 and Fig. 1). A similar magnitude of improvement in trough FEV<sub>1</sub> was also observed with UMEC/VI and TIO/OLO at the week 4 visit, with LS mean (SE) changes from baseline of 171 (17) and 117 (17) ml, respectively (adjusted difference 54 ml [95% CI 23, 86]; *p* < 0.001), highlighting an early plateau in bronchodilation on both treatments (Table 2 and Fig. 1). The percent CFB in trough

**Table 1** Baseline patient demographics and clinical characteristics (overall ITT and MN populations)

	Overall ITT ( <i>N</i> = 236)	MN subgroup ( <i>N</i> = 148)
Mean age, years (SD)	64.4 (8.5)	62.9 (7.9)
Male sex, <i>n</i> (%)	142 (60)	78 (53)
Current smoker at screening, <i>n</i> (%)	125 (53)	92 (62)
Exacerbation history in the 12 months prior to screening, <i>n</i> (%)		
≥ 1 requiring OCS/antibiotics	33 (14)	19 (13)
2 requiring OCS/antibiotics	4 (2)	3 (2)
Requiring hospitalization	6 (3)	3 (2)
Mean post-bronchodilator FEV <sub>1</sub>		
ml (SD)	1734 (406)	1722 (411)
% predicted (SD)	59.6 (5.6)	59.6 (5.5)
Reversible to albuterol <sup>a</sup> , <i>n</i> (%)	86 (36)	52 (35)
GOLD 2017 mMRC/exacerbation category [43], <i>n</i> (%)		
Group B	224 (95)	140 (95)
Group D	12 (5)	8 (5)
mMRC score, <i>n</i> (%)		
2 (moderate)	156 (66)	83 (56)
3 (severe)	71 (30)	59 (40)
4 (very severe)	9 (4)	6 (4)

FEV<sub>1</sub> forced expiratory volume in 1 s, GOLD Global Initiative for Chronic Obstructive Lung Disease, ITT intent-to-treat, mMRC modified Medical Research Council, MN maintenance-naïve, OCS oral corticosteroids, SD standard deviation

<sup>a</sup> Reversibility defined as an increase in FEV<sub>1</sub> of ≥ 12% and ≥ 200 ml following administration of bronchodilator

FEV<sub>1</sub> (ratio of on-treatment:baseline value) showed an increase in magnitude of response of 11% on UMEC/VI compared with 8% on TIO/OLO at week 8 (between-treatment difference: 3% [95% CI 1, 5]; *p* = 0.004; Table 2).

A greater proportion of patients achieved a clinically meaningful increase in trough FEV<sub>1</sub> (≥ 100 ml CFB) with UMEC/VI than with TIO/OLO at week 4 (62 vs. 46%; OR 1.79 [95% CI 1.10, 2.92]; *p* = 0.020) and at week 8 (60 vs. 42%; OR 1.90 [95% CI 1.12, 3.22]; *p* = 0.018).

Within-patient differences between UMEC/VI and TIO/OLO in trough FEV<sub>1</sub> response at week 8 are presented descriptively in Fig. 2. Overall, 56% of individuals achieved a clinically meaningful within-patient increase (≥ 100 ml)

in trough FEV<sub>1</sub> response with UMEC/VI compared with TIO/OLO and 18% of individuals achieved a clinically meaningful increased response favoring TIO/OLO compared with UMEC/VI, whereas 26% of patients showed no clinically meaningful benefits in favor of either treatment.

Both FVC and IC improvements were greater with UMEC/VI versus TIO/OLO (adjusted difference: 42 and 71 ml for FVC, 66 and 55 ml for IC, at weeks 4 and 8, respectively) but at week 4 the treatment difference in favor of UMEC/VI failed to achieve statistical significance for the FVC endpoint (Table 2).



**Table 2** Summary of adjusted on-treatment LS means and change from baseline in lung function in MN patients

	UMEC/VI ( <i>N</i> = 147)	TIO/OLO ( <i>N</i> = 145)	Difference (95% CI) UMEC/VI vs. TIO/OLO; <i>p</i> value
Trough FEV <sub>1</sub>			
Week 4, LS mean (SE), ml	1753 (17)	1699 (17)	
LS mean CFB (SE), ml	171 (17)	117 (17)	54 (23, 86); <i>p</i> < 0.001
LS mean ratio to BL (Logs SE)	1.11 (0.01)	1.08 (0.01)	1.03 (1.01, 1.05); <i>p</i> = 0.003
Week 8, LS mean (SE), ml	1749 (17)	1692 (18)	
LS mean CFB (SE), ml	167 (17)	110 (18)	57 (23, 92); <i>p</i> = 0.001
LS mean ratio to BL (Logs SE)	1.11 (0.01)	1.08 (0.01)	1.03 (1.01, 1.05); <i>p</i> = 0.004
FVC, ml			
Week 4, LS mean (SE), ml	3037 (24)	2994 (24)	
LS mean CFB (SE), ml	199 (24)	157 (24)	42 (− 4, 89); <i>p</i> = 0.072
Week 8, LS mean (SE), ml	3031 (24)	2959 (24)	
LS mean CFB (SE), ml	193 (24)	122 (24)	71 (27, 116); <i>p</i> = 0.002
IC, ml			
Week 4, LS mean (SE), ml	2536 (21)	2471 (22)	
LS mean CFB (SE), ml	161 (21)	95 (22)	66 (19, 113); <i>p</i> = 0.006
Week 8, LS mean (SE), ml	2526 (21)	2471 (21)	
LS mean CFB (SE), ml	151 (21)	96 (21)	55 (9, 102); <i>p</i> = 0.02

All LS means are adjusted for baseline values

BL baseline, CFB change from baseline, CI confidence interval, FEV<sub>1</sub> forced expiratory volume in 1 s, FVC forced vital capacity, IC inspiratory capacity, LS least squares, MN maintenance-naïve, SE standard error, TIO/OLO tiotropium/olodaterol, UMEC/VI umeclidinium/vilanterol

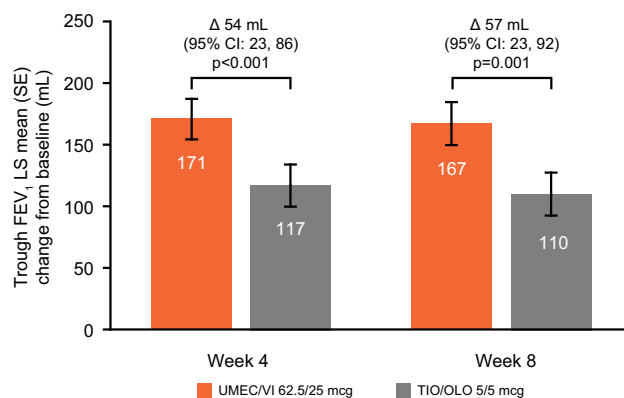
### Patient-Reported Outcomes

The LS mean (SE) reduction from baseline in rescue medication use averaged across all study weeks was greater in patients receiving UMEC/VI (0.80 [0.10] puffs/day) compared with TIO/OLO (0.59 [0.10] puffs/day) (difference: 0.20 [95% CI 0.07, 0.34] puffs/day in favor of UMEC/VI; *p* = 0.003) (Table 3).

There were no statistically significant differences between UMEC/VI and TIO/OLO in LS mean change from baseline in CAT score or in the proportion of CAT responders ( $\geq 2$  units

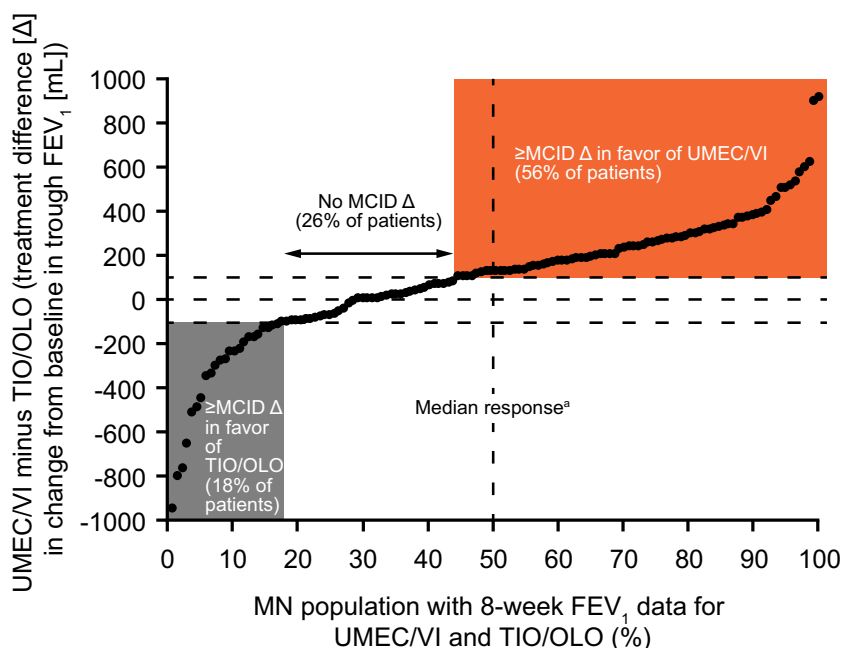
decrease in CAT score from baseline) in the MN population at either week 4 or week 8 (Table 3).

LS mean change from baseline in weekly E-RS<sub>COPD</sub> total score ranged from − 1.42 to − 1.75 for UMEC/VI and from − 1.15 to − 1.66 for TIO/OLO over weeks 1–8; between-treatment differences were not statistically significant except at week 5, when a statistically significant difference in favor of UMEC/VI was observed (difference − 0.58 [95% CI − 1.13 − 0.03]; *p* = 0.039).



**Fig. 1** Improvement in trough FEV<sub>1</sub> at weeks 4 and 8 in MN patients. *CI* confidence interval, *FEV<sub>1</sub>* forced expiratory volume in 1 s, *ITT* intent-to-treat, *LS* least squares,

*MN* maintenance-naïve, *SE* standard error, *TIO/OLO* tiotropium/olodaterol; *UMEC/VI* umeclidinium/vilanterol



**Fig. 2** Distribution of the within-patient treatment differences on trough FEV<sub>1</sub> at week 8 for UMEC/VI versus TIO/OLO observed in all individual MN patients. <sup>a</sup>Median treatment difference of 130 ml in favor of UMEC/VI. Δ, treatment difference in individual patients (UMEC/VI minus TIO/OLO), *FEV<sub>1</sub>* forced expiratory

volume in 1 s, *ITT* intent-to-treat, *MCID* minimal clinically important difference in trough FEV<sub>1</sub> (100 ml), *MN* maintenance-naïve, *TIO/OLO* tiotropium/olodaterol, *UMEC/VI* umeclidinium/vilanterol. *Values* plotted on the graph represent the net baseline-adjusted treatment differences

**Safety**

The AE profiles in the MN population were similar to those previously reported in the ITT population, with 35 (24%) patients on UMEC/VI and 42 (29%) patients on TIO/OLO experiencing at least one AE. The most frequently

reported AEs (reported in ≥ 3% patients on either treatment) for UMEC/VI and TIO/OLO were upper respiratory tract infection (6 [4%] vs. 6 [4%] patients), viral upper respiratory tract infection (5 [3%] vs. 3 [2%] patients), and sinusitis (1 [ $<$  1%] vs. 4 [3%] patients).

**Table 3** Summary of adjusted on-treatment LS means and change from baseline in patient-reported outcomes in MN patients

	UMEC/VI (N = 147)	TIO/OLO (N = 145)	Difference (95% CI) UMEC/VI vs. TIO/OLO; <i>p</i> value
Rescue medication use (puffs/day)			
Weeks 1–8, LS mean (SE)	1.59 (0.10)	1.79 (0.10)	
LS mean CFB (SE)	– 0.80 (0.10)	– 0.59 (0.10)	– 0.20 (– 0.34, – 0.07); <i>p</i> = 0.003
CAT score <sup>a</sup>			
Week 4, LS mean (SE)	17.44 (0.36)	18.04 (0.37)	
LS mean CFB (SE)	– 1.49 (0.36)	– 0.89 (0.37)	– 0.60 (– 1.35, 0.16); <i>p</i> = 0.119
Week 8, LS mean (SE)	17.46 (0.37)	17.87 (0.37)	
LS mean CFB (SE)	– 1.46 (0.37)	– 1.06 (0.37)	– 0.40 (– 1.16, 0.36); <i>p</i> = 0.296
CAT responders <sup>b</sup>			
Week 4, <i>n/N</i> (%)	67/145 (46)	53/140 (38)	OR (95% CI): 1.27 (0.77, 2.10); <i>p</i> = 0.354
Week 8, <i>n/N</i> (%)	68/145 (47)	54/142 (38)	OR (95% CI): 1.32 (0.80, 2.16); <i>p</i> = 0.278

All LS means are adjusted for baseline values

CAT COPD Assessment Test, CFB change from baseline, CI confidence interval, LS least squares, MN maintenance-naïve, *n* number of responders, *N* number of patients with available data, SE standard error, TIO/OLO tiotropium/olodaterol, UMEC/VI umeclidinium/vilanterol

<sup>a</sup> Negative CAT scores indicate clinical improvement

<sup>b</sup> CAT responder defined as  $\geq 2$  unit decrease from baseline in CAT score

On-treatment SAEs occurred in one patient on each treatment, an instance of rib fracture during treatment with UMEC/VI, and an instance of hyperglycemia during treatment with TIO/OLO. No SAEs were considered related to treatment by study investigators. No deaths were reported during the study.

The incidence of COPD exacerbations in MN patients was low and similar between treatments: ten (7%) patients experienced one exacerbation during UMEC/VI treatment and 12 (8%) during TIO/OLO treatment, while two (1%) and one (< 1%) patient experienced two exacerbations on UMEC/VI and TIO/OLO, respectively.

## DISCUSSION

In this secondary subgroup analysis of the head-to-head study of two once-daily LAMA/LABA combinations [21], the focus was exclusively on

the MN subgroup to provide further information around the timing of LAMA/LABA combination therapy initiation. Treatment with UMEC/VI within this subgroup provided significantly greater improvements in trough FEV<sub>1</sub>, FVC and IC compared with TIO/OLO therapy. The magnitude of the extra treatment benefit observed with UMEC/VI compared with TIO/OLO in the MN population, which comprised 63% of the total ITT population, was broadly consistent with that observed for all lung function outcomes in the ITT population during the original study [21]. In the MN population, UMEC/VI-treated patients had nearly two-fold increased odds of achieving a clinically important lung function benefit on trough FEV<sub>1</sub> ( $\geq 100$  ml CFB) than those who received TIO/OLO (OR 1.90; *p* = 0.018); responder rates were 60% and 42% at week 8, respectively. Moreover, in the descriptive analysis of individual variability in patient responses at week 8, three-fold more MN patients had trough FEV<sub>1</sub>



increases  $\geq 100$  ml in favor of UMEC/VI over TIO/OLO than vice versa (i.e., 56 vs. 18%).

This study was designed to robustly investigate whether or not an efficacy difference existed between the once-daily LAMA/LABA combinations with regards to objectively assessed spirometry. The parent study, and to a greater extent the current post hoc MN subgroup analysis, was not powered to examine improvement in subjective patient-reported outcomes. Nonetheless, as in the parent study, a statistically significantly greater reduction in the need for supplemental rescue bronchodilator medication (a clinical endpoint indicative of treatment effect on symptoms [36]) when patients were treated with UMEC/VI versus TIO/OLO was also demonstrated in the MN subgroup. Again, the magnitude of this treatment difference was similar to that observed in the ITT population, and comparable to that reported with LAMA monotherapy versus placebo across multiple clinical trials [37, 38]. However, there were no statistically significant between-treatment differences in the questionnaire-based CAT score or E-RS<sub>COPD</sub> total score at week 8. Nevertheless, a numerical difference in the CAT responder analysis was seen at week 8, with 47% of UMEC/VI-treated patients compared with 38% of TIO/OLO-treated patients obtaining clinically relevant improvements in symptoms and health-related QoL, with a similar response rate at week 4, in line with the primary study. This magnitude of improvement in symptom burden and QoL is consistent with treatment benefit on CAT and other patient-reported outcomes seen on escalating therapy from one to two bronchodilators in patients with more advanced COPD [37, 39, 40].

As with the parent study, the benefits observed with UMEC/VI compared with TIO/OLO were not accompanied by any increased potential for AEs and SAEs, with safety profiles comparable between both bronchodilators in the MN population. Likewise, a low proportion of patients in the MN population experienced exacerbations on both treatments. These findings confirm the favorable safety profile of the LAMA/LABA class versus mono bronchodilator therapy documented in long-term efficacy studies [13].

With a growing body of evidence demonstrating the benefits of dual bronchodilation over monotherapy in a number of clinical settings [4, 9–12, 41], focus is now turning to the relative benefits of different bronchodilator combinations [14]. Indirect evidence from network meta-analyses indicate an efficacy gradient within the LAMA/LABA class with respect to lung function [14, 15, 23], and this study, the first head-to-head study of UMEC/VI and TIO/OLO, confirmed the results of the indirect comparisons in both an all-comer and MN population [21]. The study enrolled patients with a mMRC dyspnea score  $\geq 2$  [21], indicating they had a significant symptom burden and associated level of impairment in activity at enrollment. Results from this analysis show that initiation of dual bronchodilator therapy in a MN subgroup of this symptomatic population leads to significant lung function benefits of a similar magnitude to those obtained in the ITT population [21]. Importantly, the treatment difference between the LAMA/LABA combinations observed in this study was greater in magnitude than that reported with TIO/OLO versus TIO alone in a similar MN population in the replicate OTEMTO studies [17]. Using dual therapy as a first-line maintenance therapy has been shown to provide the opportunity for improved bronchodilation and therefore potential for optimal symptom management and greater protection against further disease deterioration [16–18]. The greater lung function improvements with UMEC/VI over TIO/OLO in this MN population suggest that there is no ceiling to bronchodilation potential in patients with moderate COPD. Furthermore, demonstration of a statistically significant treatment difference on supplemental rescue medication use, a clinical endpoint reflecting an effect on symptoms [36], shows that the potential for better symptom control with improved bronchodilation in MN patients is also a realistic goal. Currently, data on the impact of initiating maintenance therapy with dual bronchodilators in MN patients are sparse and are largely obtained using post hoc analysis of prospectively collected data [16, 17, 24]. These analyses consistently indicate no diminished patient benefit or safety concern when opting to use

dual therapy as a first-line treatment option. Nevertheless, prospective studies are still needed in this area. Our study in MN patients has similar limitations, however, as the study findings were fully in line with the a priori study results in the ITT population [21], these data do provide further supportive evidence for the efficacy gradient between LAMA/LABA combinations. Moreover, as lung function and symptom improvements were observed with both dual regimens in this MN population, these data suggest that early approaches aimed at maximizing lung function are appropriate in symptomatic patients and are supportive of the use of dual bronchodilation as a first-line treatment.

The current analysis is the first direct comparison of dual bronchodilator regimens in a MN population. This population, although small in size, is arguably ideal to assess the efficacy differences between bronchodilators in the same treatment class. For instance, assessments of efficacy are not likely to be influenced by prior medication use in a MN population, as can occur with patients switching between existing maintenance therapies, having treatment withdrawn or being re-randomized to a treatment they have had previously. In our study, the MN population had not received a COPD maintenance therapy for at least 6 weeks preceding randomization. Although it cannot be confirmed whether or not patients had received maintenance therapy at an earlier time point, this period should be sufficient to ensure our definition of a MN population is representative. Moreover, the mean predicted baseline FEV<sub>1</sub> of 60% suggests that this is likely to be representative of a general population initiating a maintenance therapy. The population was also slightly younger than the overall ITT population and had a higher proportion of current smokers, trends that were also seen in the OTEMTO analysis [17].

As with the original study, the design features must also be noted when considering the limitations of this analysis. These include the open-label administration of treatments and the potentially short 8-week study duration. In order to mitigate any potential for bias on the primary outcome, the technicians performing

spirometry were blinded to treatment allocation within each study period. Furthermore, the randomized, crossover nature of the study, and the objective measurements of primary efficacy (FEV<sub>1</sub>) and safety variables were designed to minimize any bias [42]. Moreover, the 8-week study duration was deemed to be sufficient to allow robust assessments of bronchodilator response given that a plateau in response was detected after 4 weeks in the ITT and MN population with both treatments [21]. However, the study duration may have been too short to fully assess differences in longer-term outcomes such as the rate of exacerbations and changes in QoL over time. Despite these limitations, the data demonstrate that UMEC/VI improves lung function and at least one symptom measure versus TIO/OLO in MN patients. Finally, the addition of a third monotherapy arm, which could be considered as standard of care in a MN population, could have aided the interpretation of results and would have been a valuable addition to this analysis.

## CONCLUSIONS

This post hoc analysis in a subgroup of patients naïve to COPD maintenance therapy was consistent with the primary a priori parent analysis, highlighting that an efficacy gradient exists within the LAMA/LABA class favoring once-daily UMEC/VI over TIO/OLO. Further long-term, prospective studies into the effect of initiation of dual bronchodilator versus monotherapy as a first-line maintenance therapy are now needed to build on these short-term efficacy and safety findings.

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**Compliance with Ethics Guidelines.** The 204990 study was conducted in accordance with International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use—Good Clinical Practice guidelines and the principles of the Declaration of Helsinki. The protocol was reviewed and approved by all appropriate institutional review boards (IRB) or independent ethics committees (Ethik-Kommission [Germany], Comité Etico de Investigación [Spain], Chesapeake IRB [US] and United Kingdom Ethics Committee). Informed consent was obtained from all patients prior to inclusion in the study.

**Data Availability.** The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

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