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Efficacy and safety of once-daily umeclidinium/vilanterol 62.5/25 mcg in COPD

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Randomised

Summary
Study objective: To examine the efficacy and safety of the once-daily, inhaled, long-acting muscarinic antagonist/β_2-agonist combination umeclidinium/vilanterol (UMEC/VI) compared with UMEC and VI monotherapies in patients with chronic obstructive pulmonary disease (COPD).
Methods: In this 24-week, double-blind, placebo-controlled, parallel-group study (ClinicalTrials.gov: NCT01313650) eligible patients were randomised 3:3:3:2 to treatment with UMEC/VI 62.5/25 mcg, UMEC 62.5 mcg, VI 25 mcg or placebo administered once daily via dry powder inhaler ($N = 1532$; intent-to-treat population). Primary endpoint was trough forced expiratory volume in one second (FEV_1) on Day 169 (23–24 h post-dose). Additional lung-function, symptomatic, and health-related quality-of-life endpoints were assessed, including 0–6 h weighted-mean FEV_1, rescue salbutamol use, Transition Dyspnoea Index (TDI), Shortness Of Breath With Daily Activity (SOBDA) and St. George's Respiratory Questionnaire (SGRQ) scores. Safety evaluations included adverse events (AEs), vital signs, 12-lead/24-h Holter electrocardiography parameters and clinical laboratory/haematology measurements.
Results: All active treatments produced statistically significant improvements in trough FEV_1 compared with placebo on Day 169 (0.072–0.167 L, all $p < 0.001$); increases with UMEC/VI 62.5/25 mcg were significantly greater than monotherapies (0.052–0.095 L, $p \leq 0.004$). Improvements were observed for UMEC/VI 62.5/25 mcg vs placebo for weighted-mean FEV_1

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on Day 168 (0.242 L, $p < 0.001$), rescue salbutamol use during Weeks 1–24 (−0.8 puffs/day, $p = 0.001$), TDI (1.2 units, $p < 0.001$), SOBDA (−0.17 units, $p < 0.001$) and SGRQ (−5.51 units, $p < 0.001$) scores. No clinically-significant changes in vital signs, electrocardiography, or laboratory parameters were observed.

Conclusion: Once-daily UMEC/VI 62.5/25 mcg was well tolerated and provided clinically-significant improvements in lung function and symptoms in patients with COPD.

Introduction

Chronic obstructive pulmonary disease (COPD) is a preventable and treatable disease characterised by persistent airflow limitation [1,2]. Bronchodilators are central to the pharmacological management of COPD and include muscarinic antagonists and β_2-agonists [2]. Muscarinic antagonists act by binding to the M_3 receptor subtype localised in airway smooth muscle, thereby blocking the bronchoconstrictive response to cholinergic nervous stimulation and facilitating airway smooth muscle relaxation [3,4]. β_2-agonists stimulate β_2-adrenergic receptors, increasing cyclic adenosine monophosphate and facilitating smooth muscle relaxation [4]. These two distinct and complementary mechanisms of inducing bronchodilation provide opportunities for combination long-acting bronchodilator therapies that may improve treatment efficacy. Long-acting agents may also improve compliance due to the convenience of once-daily maintenance treatment. Clinical studies support this rationale, with the co-administration of long-acting muscarinic antagonists (LAMA) and long-acting β_2-agonists (LABA) demonstrating significantly greater improvements in lung function compared with individual treatments in patients with COPD [4–11]. Further, a LAMA/LABA combination may be associated with a lower risk of side effects compared with increasing the dose of a single agent [2].

A fixed-dose combination of the orally inhaled LAMA, umeclidinium bromide (UMEC) and the orally inhaled LABA, vilanterol (VI), is currently in development as a maintenance treatment for patients with COPD. Initial dose-ranging studies showed that both agents were well tolerated and significantly improved lung function compared with placebo over 24 h in patients with COPD [12,13].

Here we present the results of a large, placebo-controlled study that examined the efficacy and safety of once-daily UMEC/VI 62.5/25 mcg compared with UMEC 62.5 mcg, VI 25 mcg and placebo.

Methods

Study design and treatments

This 24-week, randomised, double-blind, placebo-controlled, multicentre, parallel-group study was conducted in a total of 163 centres in 13 countries from 30 March 2011 to 5 April 2012 (ClinicalTrials.gov identifier: NCT01313650; GSK study number: DB2113373). Further details are provided in Online Supplementary Materials. Eligible patients with COPD were randomly assigned 3:3:3:2 to receive one of three active treatments: UMEC/VI 62.5/25 mcg (delivering 55/22 mcg), UMEC 62.5 mcg (delivering 55 mcg), VI 25 mcg (delivering 22 mcg) or placebo. The randomisation ratio allowed for additional exposure to the active treatments compared with placebo, for the evaluation of safety. All treatments were administered once daily as a single inhalation in the morning, delivered via a dry powder inhaler (DPI).

A central randomisation schedule was generated using a validated computerised system (RandAll). Patients were randomised using an automated, interactive telephone-based system that registered and randomised medication assignment. Ten study outpatient visits were conducted throughout the study (see Supplementary Materials).

Patients

Eligible patients were current or former cigarette smokers aged $\geq$40 years with a clinically established history of COPD characterised by airflow limitation that is not fully reversible [1] and documented based on a smoking history of $\geq$10 pack-years, had a post-salbutamol forced expiratory volume in one second (FEV_1)/forced vital capacity (FVC) ratio of $<$0.70 and a post-salbutamol FEV_1 of $\leq$70% of predicted normal values (calculated using the National Health and Nutrition Examination Survey III) [14, 15] and had a score of $\geq$2 on the modified Medical Research Council Dyspnoea Scale [16]. Patients were excluded if they had a current diagnosis of asthma or other known respiratory disorders, including α-1 antitrypsin deficiency, active tuberculosis, bronchiectasis, sarcoidosis, lung fibrosis, pulmonary hypertension, interstitial lung disease, any clinically significant uncontrolled disease (including cardiovascular-related disease) as determined by the study investigators, an abnormal and clinically significant electrocardiogram (ECG) or 24-h Holter ECG (if conducted), or significantly abnormal clinical laboratory finding. Concomitant use of inhaled salbutamol (albuterol) as rescue medication was allowed. Inhaled corticosteroids (ICS) were allowed at a stable dose of $\leq$1000 mcg/day of fluticasone propionate or equivalent from 30 days prior to screening onward. Other permitted and prohibited medications are provided in the Online Supplement.

All patients provided written informed consent prior to study participation. The study was approved by local ethics review committees and was conducted in accordance with the Declaration of Helsinki and Good Clinical Practice guidelines (WMA Declaration of Helsinki, 2008).

Outcomes and assessments

Lung function

The primary efficacy endpoint was pre-dose trough FEV_1 on treatment Day 169, defined as the mean of FEV_1 values obtained 23 h and 24 h after dosing on Day 168 (Week 24 visit). Secondary and additional lung function endpoints were: weighted mean FEV_1 over 0—6 h post-dose on Day 168; trough and 0—6 h weighted mean FEV_1 at other visits, serial FEV_1 assessments, time to onset during 0—6 h post-dose on Day 1, proportion of patients achieving an increase in FEV_1 of $\geq$12% and $\geq$0.2 L above baseline at any time during 0—6 h post-dose on Day 1, proportion of patients achieving an increase of $\geq$0.1 L above baseline in trough FEV_1, peak FEV_1 and serial and trough FVC. Serial FEV_1 over 0—24 h post-dose was obtained in a subset of patients to characterise changes in lung function over the dosing interval.

FEV_1 and FVC were obtained using standard spirometry equipment that met or exceeded the minimal ATS performance recommendations [17] and reported as least squares means (LS) change from baseline. At screening, responsiveness to salbutamol (4 puffs, approximately 360 mcg) was obtained. To further characterise bronchodilator responsiveness, post-ipratropium (4 puffs, approximately 72 mcg) testing was conducted following completion of post-salbutamol spirometry.

Other outcomes

Other outcomes included: mean Transition Dyspnoea Index (TDI) focal score [18]; mean Shortness Of Breath With Daily Activity (SOBDA) score [19]; rescue salbutamol use, time to first COPD exacerbation and the St. George's Respiratory Questionnaire (SGRQ) score to assess impact on the health-related quality of life [20]. An exacerbation was defined as an acute worsening of symptoms of COPD requiring emergency treatment, hospitalisation or the use of additional pharmacotherapy beyond the study drug or rescue salbutamol (e.g. oral steroids and antibiotics). Plasma pharmacokinetic (PK) samples were collected at multiple visits for population PK analysis, to be reported elsewhere.

Safety

Safety evaluations included the incidence of adverse events (AEs), vital signs (systolic and diastolic blood pressure, and pulse rate), 12-lead ECG in all patients and 24-h Holter ECG monitoring obtained in a subset of patients, clinical chemistry and haematology.

Statistical analyses

Sample size was calculated to provide sufficient power for the primary endpoint, as well as the TDI as a symptomatic endpoint, and assumed a two-sided 5% significance level. Further details are provided in the Online Supplementary Materials. The primary analyses were performed on the intent-to-treat (ITT) population, defined as all randomised patients who had received at least one dose of the double-blind study medication. The primary analyses of the primary and secondary endpoints were performed using mixed-models repeated-measures (MMRM) with covariates of: baseline FEV_1, smoking status, day, centre grouping, treatment, day-by-baseline interaction and day-by-treatment interaction, where day was nominal. The analysis of TDI as a symptomatic endpoint used Baseline Dyspnoea Index score in place of baseline FEV_1. To account for multiplicity across treatment comparisons and endpoints, a step-down closed testing procedure was used.

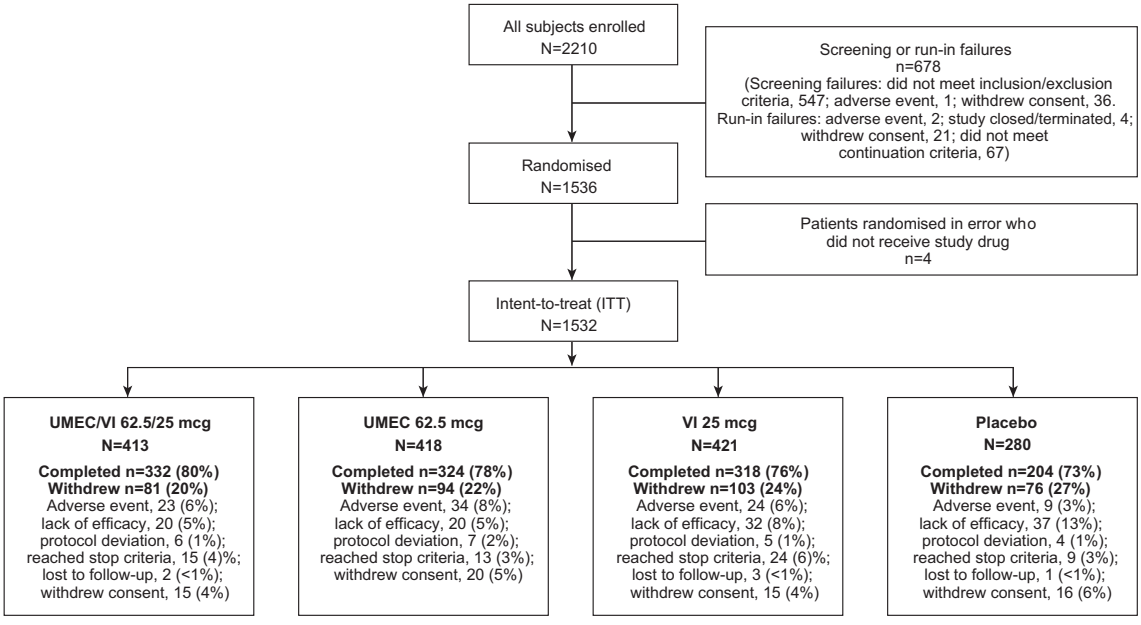

Figure 1 Patient disposition and flow diagram. Note: Some patients were classed by the reporting investigator as completers but did not have a Day 169 Visit or did not complete Day 169; others attended a Day 169 Visit or completed Day 169 assessments but were not classed as completers by the reporting investigator. Patients were considered to have completed if they completed the last clinic visit excluding follow-up (Visit 9) and did not withdraw at that visit.

The sample size (approximately 198 planned patients) for the 24-h Holter analysis subset was selected to provide a descriptive evaluation of the 24-h serial FEV_1 profiles and to allow for additional assessment of cardiovascular safety using 24-h Holter monitoring.

Results

Patients

Of 2210 patients screened, 1532 patients were included in the ITT population. In total, 1178 patients completed the study and 197 patients were included in the 24-h Holter/24-h serial FEV_1 subset; patient disposition and reasons for discontinuation are shown in Fig. 1. Across the groups, 58–64% of patients reported having a cardiovascular related current medical condition and 49–52% of patients used ICS.

Patient demographics and baseline characteristics are shown in Table 1 and were similar across treatment groups and consistent with moderate-to-severe COPD.

Efficacy outcomes

Lung function

Lung function outcomes are summarised in Supplementary Table 1. Statistically significant improvements in trough FEV_1 at Day 169 were observed for UMEC/VI 62.5/25 mcg, UMEC 62.5 mcg and VI 25 mcg compared with placebo ([difference; *p*-value] 0.167 L, 0.115 L, and 0.072 L; all $p < 0.001$) (Fig. 2a, Supplementary Table 1). Statistically significant improvements were also demonstrated for UMEC/VI 62.5/25 mcg compared with UMEC 62.5 mcg (0.052 L; $p = 0.004$) and VI 25 mcg at Day 168 (0.095 L; $p < 0.001$).

Greater increases from baseline in 0–6 h weighted mean FEV_1 at Day 168 were also observed with UMEC/VI 62.5/25 mcg, UMEC 62.5 mcg and VI 25 mcg compared with placebo (0.242 L, 0.150 L and 0.122 L; all $p < 0.001$) (Fig. 2b). Similarly, greater increases were observed for UMEC/VI 62.5/25 mcg compared with UMEC 62.5 mcg (0.092 L; $p < 0.001$) and VI 25 mcg (0.120 L; $p < 0.001$) at Day 168.

In the subset of patients with serial spirometry over 24 h, improvements in serial FEV_1 values were obtained with

Table 1 Patient demographics and baseline characteristics (intent-to-treat population).

	Placebo ($N = 280$)	UMEC 62.5 ($N = 418$)	VI 25 ($N = 421$)	UMEC/VI 62.5/25 ($N = 413$)
Age (y)				
Mean (SD)	62.2 (9.04)	64.0 (9.16)	62.7 (8.52)	63.1 (8.71)
Sex				
Female *n* (%)	85 (30)	120 (29)	136 (32)	108 (26)
Male *n* (%)	195 (70)	298 (71)	285 (68)	305 (74)
Current smoker at screening[a]				
n (%)	150 (54)	207 (50)	199 (47)	203 (49)
Smoking pack-years				
Mean (SD)	47.2 (27.21)	46.8 (27.03)	44.7 (23.16)	46.5 (25.80)
ICS use at screening				
n (%)	137 (49)	219 (52)	212 (50)	212 (51)
Post-salbutamol % predicted FEV_1				
Mean (SD)	46.7 (12.71)	46.8 (13.39)	48.2 (13.27)	47.8 (13.19)
Post-salbutamol FEV_1/FVC				
Mean (SD)	47.1 (11.47)	46.8 (11.07)	47.4 (11.49)	48.0 (11.42)
GOLD stage				
n	280	417	420	412
II, *n* (%)	119 (43)	191 (46)	197 (47)	201 (49)
III, *n* (%)	133 (48)	172 (41)	179 (43)	166 (40)
IV, *n* (%)	28 (10)	54 (13)	44 (10)	45 (11)
% reversibility to salbutamol				
Mean (SD)	15.3 (15.54)	13.9 (14.92)	15.7 (15.57)	13.9 (15.06)
% reversibility to salbutamol and ipratropium[b]				
Mean (SD)	22.7 (19.61)	22.3 (18.51)	23.6 (19.42)	22.2 (18.82)
Reversible to salbutamol				
n (%)	91 (33)	121 (29)	155 (37)	129 (31)
Reversible to salbutamol and ipratropium				
n (%)	146 (54)	223 (54)	230 (56)	227 (56)

FEV_1, forced expiratory volume in one second; FVC, forced vital capacity; GOLD, Global Initiative for Chronic Obstructive Lung Disease; ICS, inhaled corticosteroid; SD, standard deviation.

[a] Reclassified: patient reclassified as current smoker if smoked within 6 months.

[b] Reversibility to salbutamol and ipratropium was defined as an increase in FEV_1 of $\geq$12% and $\geq$0.2 L following administration of both salbutamol and ipratropium.

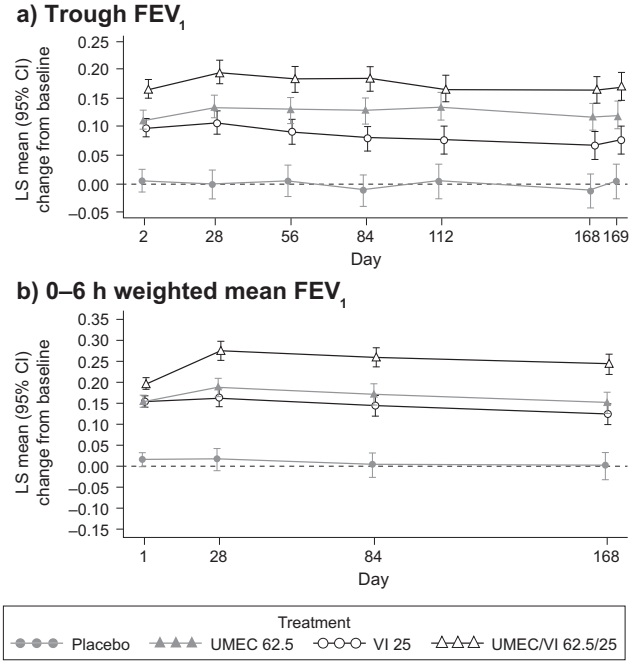

Figure 2 Measurement of lung function: least squares (LS) mean (95% confidence interval [CI]) change from baseline in (a) trough forced expiratory volume in one second (FEV_1, L) and (b) 0—6 h weighted mean FEV_1 (L, intent-to-treat population). UMEC = umeclidinium bromide; VI = vilanterol. Analysis performed using a repeated measures model with covariates of treatment, baseline, smoking status, center group, Day, day by baseline, and Day by treatment interactions.

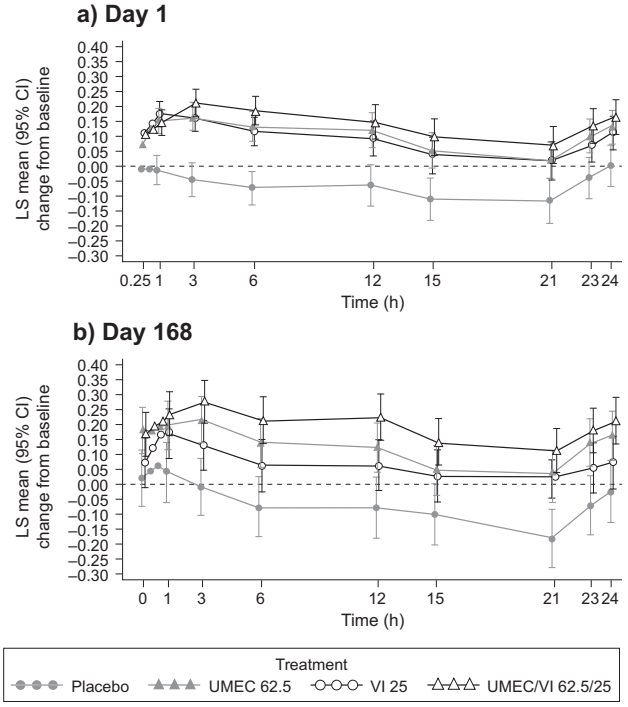

Figure 3 Serial trough forced expiratory volume in one second (FEV_1, L): least squares (LS) mean (95% confidence interval [CI]) change from baseline in FEV_1 over time on Day 1, 84 and 168 (L, 24-h population). UMEC = umeclidinium bromide; VI = vilanterol. Analysis performed using a repeated measures model with covariates of treatment, baseline (mean of the two FEV_1 assessments made 30 and 5 min pre-dose on Day 1), smoking status, center group, Day, Day by baseline, and Day by treatment interactions.

UMEC/VI 62.5/25 mcg compared with UMEC 62.5 mcg, VI 25 mcg, and placebo for most timepoints (Fig. 3). In the ITT population, on Day 1 UMEC/VI 62.5/25 mcg treatment resulted in improvements in FEV_1 after 15 min (first assessment) compared with placebo (0.112 L; $p < 0.001$). The median time to onset, defined as a post-dose $FEV_1 \geq 0.1$ L above baseline, during 0—6 h post-dose Day 1 was shorter with UMEC/VI 62.5/25 mcg and VI 25 mcg (27 min and 31 min, respectively) compared with UMEC 62.5 mcg (56 min).

Peak FEV_1 increases for UMEC/VI 62.5/25 mcg relative to baseline over 6 h on Day 1 and Day 168 were 0.273 L and 0.320 L, respectively. UMEC/VI 62.5/25 mcg also provided improvements in peak FEV_1 compared with placebo, UMEC 62.5 mcg and VI 25 mcg at Day 168 (0.094—0.224 L; all $p < 0.001$).

Improvements in trough FVC change from baseline were observed at Day 169 for UMEC/VI 62.5/25 mcg, UMEC 62.5 mcg and VI 25 mcg compared with placebo (0.248 L, 0.175 L, and 0.105 L; all $p \leq 0.002$). Improvements were also demonstrated for UMEC/VI 62.5/25 mcg compared with UMEC 62.5 mcg and VI 25 mcg (0.074 L and 0.143 L; $p = 0.012$ and $p < 0.001$, respectively) (Supplementary Table 1).

Other efficacy outcomes

All active treatment groups increased TDI focal score at Day 168 and throughout the study compared with placebo (Table 2, Fig. 4). At Days 28, 84 and 168, the odds of being a responder according to TDI focal score (defined as those with an improvement of $\geq$1 unit [21]) was higher for UMEC/VI 62.5/25 mcg compared with VI 25 mcg (odds ratio [OR] at all timepoints: 1.4; all $p \leq 0.038$) and for all active treatments compared with placebo (OR: 1.5—3.1; all $p \leq 0.013$).

At Week 24, UMEC/VI 62.5/25 mcg, UMEC 62.5 mcg and VI 25 mcg were associated with improvements in SOBDA score compared with placebo (Table 2).

Over the 24-week study period, all active treatments resulted in less rescue salbutamol use compared with placebo (Table 2).

Health-related quality of life

All active treatments resulted in an improvement (i.e. a reduction) in SGRQ score at Day 168 and a greater proportion of patients demonstrated a clinically meaningful response in SGRQ score compared with placebo. Improvements were similar across active treatment groups (Table 2).

COPD exacerbations

On-treatment COPD exacerbations were reported in 13% of patients in the placebo group and 7—9% in active treatment groups. The analysis of time to first COPD exacerbation indicated that UMEC/VI 62.5/25 mcg and UMEC 62.5 mcg resulted in a lower risk of COPD exacerbation compared with placebo (Table 2).

Table 2 Summary of additional efficacy measures.

	Placebo ($N = 280$)	UMEC 62.5 ($N = 418$)	VI 25 ($N = 421$)	UMEC/VI 62.5/25 ($N = 413$)
TDI focal score, Day 168				
LS mean (SE)	1.2 (0.20)	2.2 (0.16)	2.1 (0.16)	2.4 (0.16)
Difference vs placebo, (95% CI)	—	1.0* (0.5, 1.5)	0.9* (0.4, 1.4)	1.2* (0.7, 1.7)
UMEC/VI vs individual components, (95% CI)	—	0.3 (−0.2, 0.7)	0.4 (−1.0, 0.8)	—
Proportion of responders according to TDI focal score, Day 168				
Responder *n* (%)	106 (41)	207 (53)	197 (51)	226 (58)
OR vs placebo, (95% CI)	—	1.6† (1.2, 2.3)	1.5‡ (1.1, 2.1)	2.0* (1.5, 2.8)
SOBDA score, Week 24				
LS mean change from baseline (SE)	−0.06 (0.037)	−0.16 (0.029)	−0.21 (0.030)	−0.23 (0.029)
Difference vs placebo, (95% CI)	—	−0.10‡ (−0.19, 0.00)	−0.14† (−0.24, −0.05)	−0.17* (−0.26, −0.08)
UMEC/VI vs individual Components, (95% CI)	—	−0.08 (−0.16, 0.01)	−0.03 (−0.11, 0.05)	—
Proportion of responders[a] according to SOBDA score, Week 24 (threshold = −0.1)				
Responder *n* (%)	52 (21)	112 (30)	109 (29)	121 (32)
OR vs placebo, (95% CI)	—	1.7† (1.2, 2.5)	1.6‡ (1,1, 2.3)	1.8† (1.2, 2.6)
SGRQ score, Day 168				
Change from baseline (SE)	−2.56 (0.950)	−7.25 (0.753)	−7.75 (0.760)	−8.07 (0.749)
Difference vs placebo, (95% CI)	—	−4.69* (−7.07, −2.31)	−5.19* (−7.58, −2.80)	−5.51* (−7.88, −3.13)
UMEC/VI vs individual Components, (95% CI)	—	−0.82 (−2.90, 1.27)	−0.32 (−2.41, 1.78)	—
Proportion of responders[b] according to SGRQ total score, Week 24				
Responder *n* (%)	86 (34)	172 (44)	181 (48)	188 (49)
OR vs placebo, (95% CI)	—	1.6† (1.2, 2.3)	1.9* (1.3, 2.6)	2.0* (1.4, 2.8)
Salbutamol use (puffs/day, weeks 1−24)				
LS mean change from baseline (SE)	−1.4 (0.2)	−1.7 (0.16)	−2.4 (0.16)	−2.3 (0.16)
Difference vs placebo, (95% CI)	—	−0.3 (−0.8, 0.2)	−0.9* (−1.4, −0.4)	−0.8* (−1.3, −0.3)
UMEC/VI vs individual components, (95% CI)	—	−0.6‡ (−1.0, −0.1)	0.1 (−0.3, 0.5)	—
Time to first COPD exacerbation				
HR vs placebo (95% CI)	—	0.6‡ (0.4, 1.0)	0.7 (0.4, 1.1)	0.5† (0.3, 0.8)

*$p \leq 0.001$; †$p \leq 0.01$; ‡$p < 0.05$.

TDI, transition dyspnoea index; LS, Least squares; SE, standard error; CI, confidence interval; SOBDA, shortness of breath with daily activities; OR, odds ratio; SGRQ, St. George's respiratory questionnaire; COPD, chronic obstructive pulmonary disease; HR, hazard ratio; UMEC/VI, umeclidinium/vilanterol.

[a] Response is defined as a difference between mean post-treatment SOBDA score and baseline SOBDA score of ≤−0.1.

[b] Response is defined as an SGRQ total score of 4 units below baseline (score on Day 1) or lower.

Pharmacokinetics

Population PK analyses indicated no difference in the systemic exposure of UMEC 62.5 mcg or VI 25 mcg when administered as monotherapy compared with UMEC/VI 62.5/25 mcg.

Safety

The incidence of treatment-emergent AEs (TEAEs) was similar across treatment groups (Table 3). The most frequent TEAEs were: headache, nasopharyngitis, upper respiratory tract infection and cough; incidences were similar across treatment groups (Table 3). AEs that led to study withdrawal were infrequent (active treatment groups: 6−8%; placebo: 3%), as were serious AEs (SAEs; active treatment groups: 5−6%; placebo: 3%) (Table 3). The only SAE or AE leading to study withdrawal in ≥1% of patients in any treatment group was related to worsening COPD. Fatal AEs occurred in 9 patients: 3 in the VI 25 mcg group (sudden death, COPD exacerbation, COPD exacerbation/renal failure), 3 in the UMEC/VI 62.5/25 mcg group (COPD exacerbation/respiratory failure, myocardial infarction, unknown cause) and 3 in the UMEC 62.5 mcg group (COPD/acute respiratory failure, sudden death, cholecystitis and peritonitis).

No clinically meaningful changes were observed in vital signs, 12-lead ECG and 24-h Holter ECG parameters, or clinical laboratory tests for UMEC/VI 62.5/25 mcg, UMEC 62.5 mcg and VI 25 mcg, compared with placebo. The overall incidence of patients with one or more abnormal, clinically significant, post-baseline 12-lead ECG result was similar across active treatment groups (18−22%) and placebo (22%).

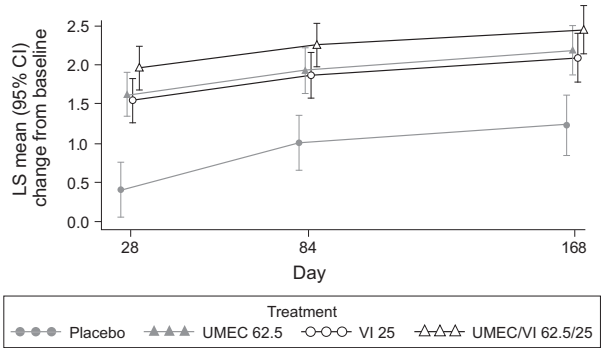

Figure 4 Least squares (LS) mean transition dyspnoea index focal score (intent-to-treat population). CI = confidence interval; UMEC = umeclidinium bromide; VI = vilanterol. Analysis performed using a repeated measures model with covariates of treatment, baseline dysnpoea index focal score, smoking status, center group, Day, Day by baseline dysnpoea index focal score, and Day by treatment interactions.

Discussion

This clinical trial was the first to evaluate the efficacy and safety of the long-acting bronchodilator combination UMEC/VI 62.5/25 mcg when administered once-daily for 24 weeks in patients with COPD. Compared with UMEC 62.5 mcg and VI 25 mcg monotherapies, UMEC/VI 62.5/25 mcg was shown to provide significant improvements in pre-dose trough FEV_1, as well as improvements in 0—6 h weighted-mean FEV_1. These benefits were substantial, with a peak FEV_1 increase from baseline of 0.273 L following the first dose of UMEC/VI 62.5/25 mcg. These benefits were also maintained for the duration of the study with no evidence of tolerance. Treatment improvements with UMEC/VI 62.5/25 mcg compared with UMEC 62.5 mcg and VI 25 mcg monotherapies at Day 169 (0.052 L and 0.095 L for trough FEV_1; 0.092 L and 0.120 L for 0—6 h weighted-mean FEV_1) at study conclusion were of a magnitude considered clinically meaningful in COPD [22]. Overall, the lung function findings demonstrate that both UMEC 62.5 mcg and VI 25 mcg are efficacious compared with placebo and that both contribute to the bronchodilator efficacy of UMEC/VI 62.5/25 mcg over the entire 24-h dosing interval, showing that both are effective bronchodilators suitable for once-daily dosing.

The findings for the symptom and health-related quality of life (HRQoL) measures indicate that the benefits of UMEC/VI 62.5/25 mcg on lung function translated into subjective symptomatic improvements that were noticeable to the study participants. Throughout the study, UMEC/VI 62.5/25 mcg improved dyspnoea compared with placebo, as demonstrated by treatment differences in TDI score that exceeded 1.0 unit (considered the minimal clinically-important difference [MCID] for this measure) [21]. These findings were consistent with improvements in dyspnoea associated with activities of daily living, as assessed by the SOBDA questionnaire; SOBDA is a daily, patient-reported outcome measure that evaluates changes in the ability to carry out daily activities [19]. Additionally, reductions in rescue use further support that UMEC/VI treatment results in noticeable improvements in patients with COPD. Improvements in HRQoL with UMEC/VI 62.5/25 mcg treatment were indicated by improvements in SGRQ score that exceed the MCID of 4 units compared with placebo [20]. Overall, treatment differences between UMEC/VI 62.5/25 mcg and both UMEC 62.5 mcg and VI 25 mcg monotherapies were not as clearly defined for health outcomes measures as they were for lung function assessments. Nevertheless, numerically larger

Table 3 Adverse events; *n* (%).

	Placebo (N = 280)	UMEC 62.5 (N = 418)	VI 25 (N = 421)	UMEC/VI 62.5/25 (N = 413)
On-treatment AEs	130 (46%)	216 (52%)	204 (48%)	212 (51%)
Post-treatment AEs	5 (2%)	15 (4%)	19 (5%)	10 (2%)
On-treatment SAEs	9 (3%)	27 (6%)	24 (6%)	21 (5%)
Post-treatment SAEs	0	5 (1%)	4 (<1%)	2 (<1%)
AEs leading to withdraw/discontinuation of study medication[a]	9 (3%)	34 (8%)	24 (6%)	23 (6%)
Fatal SAEs	0	3 (<1%)	3 (<1%)	3 (<1%)
AEs occurring in ≥3% of patients in any treatment group				
Headache	26 (9%)	32 (8%)	25 (6%)	35 (8%)
Nasopharyngitis	16 (6%)	29 (7%)	26 (6%)	39 (9%)
Upper respiratory tract infection	14 (5%)	21 (5%)	18 (4%)	13 (3%)
Cough	7 (3%)	16 (4%)	15 (4%)	6 (1%)
Oropharyngeal pain	4 (1%)	6 (1%)	14 (3%)	13 (3%)
Back pain	7 (3%)	8 (2%)	7 (2%)	13 (3%)
Chronic obstructive pulmonary disease	3 (1%)	12 (3%)	8 (2%)	7 (2%)
Arthralgia	3 (1%)	12 (3%)	2 (<1%)	4 (<1%)

On-treatment AEs were defined as those occurring with an onset on or after the date of the first dose of study drug, and up to 1 day after the date of the last recorded dose of study drug. Post-treatment AEs were defined as those with an onset starting 2 days or more after the date of the last recorded dose of study drug.

AEs, adverse events; SAEs, serious adverse events; UMEC/VI, umeclidinium/vilanterol.

[a] Includes both on- and post-treatment AEs.

improvements were indicative of additional benefit with UMEC/VI 62.5/25 mcg.

Although consistent with previous studies showing reductions in exacerbations with long-acting bronchodilator treatment [23,24], this study was not designed to examine treatment effects on COPD exacerbations. Yet, time to first exacerbation (an important measure of potential effectiveness in COPD patients) showed that the risk of a COPD exacerbation was lower with UMEC/VI 62.5/25 mcg, UMEC 62.5 mcg and VI 25 mcg vs placebo, suggesting a potential benefit for each active treatment. Additional studies are required to fully evaluate the effect of UMEC/VI 62.5/25 mcg on the annual rate of exacerbations (particularly in patients most at risk) relative to long-acting bronchodilator monotherapy.

Class-effects such as, tremor, blood pressure changes, tachycardia, arrhythmias, and palpitations associated with high doses of LABAs [25,26] were not observed at higher incidences with UMEC/VI 62.5/25 mcg or VI 25 mcg compared with placebo. Additionally, the incidence of AEs consistent with anticholinergic effects, such as dry mouth, gastrointestinal events (e.g. constipation), ocular events (e.g. blurred vision, glaucoma), tachycardia and urinary retention [27] were low ($<3\%$) and similar with UMEC/VI 62.5/25 mcg, UMEC 62.5 mcg and placebo. These findings are consistent with an evaluation of a higher dose of UMEC/VI (500/25 mcg), which showed a low incidence of anticholinergic-related AEs ($\leq 2\%$) and no evidence of clinically relevant treatment effects on ECG, vital signs, or laboratory assessments compared with placebo over 4 weeks [28]. In previous dose-ranging studies of UMEC, an increased incidence of potentially drug-related effects such as dry mouth and cough were observed at doses of 250 mcg and higher [12,29] and dose-ranging evaluations of VI (up to 50 mcg) in COPD and asthma have shown VI to have a safety and tolerability profile similar to placebo [13,30]. The results presented here confirm and extend these findings over a longer treatment duration, with a low incidence of anticholinergic- or β-agonist-associated AEs reported for UMEC/VI 62.5/25 mcg treatment. Further, no clinically significant treatment-related changes were reported for blood pressure, heart rate or QT interval and no apparent treatment differences for abnormal 12-lead ECG findings were observed for any of the active treatments.

There are limitations to the interpretation of data from this study. There was no head-to-head comparison with an approved LAMA or LABA monotherapy. There are also no approved LAMA/LABA combination products available for comparison. Concomitant inhaled corticosteroid or bronchodilator therapies (e.g. rescue salbutamol) were permitted during the study, representing real-world treatment scenarios. However, these concomitant treatments are unlikely to have influenced clinical outcomes when used in these doses or regimens (e.g. lower salbutamol use than indicated for bronchospasm [31]), particularly as their administration was similarly distributed between all study groups, including placebo.

The results of this study demonstrate that UMEC/VI 62.5/25 mcg provides more effective treatment than UMEC 62.5 mcg or VI 25 mcg monotherapies over 24 weeks in patients with COPD, with a similar tolerability and safety profile. Both UMEC 62.5 mcg and VI 25 mcg were shown to be efficacious compared with placebo. The study findings confirm the rationale for the development of a combination long-acting bronchodilator therapy utilising medications with distinct and complementary mechanisms of action, and the convenience of a once-daily dosing regimen further supports UMEC/VI 62.5/25 mcg as a maintenance treatment for COPD.

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Author contribution and role of funding source

Author roles: J.F.D. contributed as a member of the Steering Committee in the design, review and analysis of data, discussion and writing of manuscript. M.R.M.-Y. conducted the actual research and data analysis and participated in manuscript writing and review. All authors were involved in critical review and writing of the manuscript.

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Conflict of interest statement

J.F.D. has served as consultant to Almirall, AstraZeneca, Boehringer Ingelheim, Dey, Elevation Pharmaceuticals, Forest Laboratories, GlaxoSmithKline, Novartis, Pearl Pharmaceuticals, Pfizer and Sunovion; and has received research grants from Boehringer Ingelheim, GlaxoSmithKline and Novartis. M.R.M.-Y. has been a consultant to and received research grants from Almirall, AstraZeneca, Boehringer Ingelheim, Forest Laboratories, GlaxoSmithKline, Novartis, Merck, Ono Pharmaceuticals and Pfizer.

S.K., R.M., C.K. and A.C. are employees of GlaxoSmithKline. S.K., C.K. and A.C. hold stocks/shares in GlaxoSmithKline.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.rmed.2013.06.001.

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