

# Efficacy and safety of once-daily inhaled umeclidinium/vilanterol in Asian patients with COPD: results from a randomized, placebo-controlled study

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**Background:** Combination of the inhaled long-acting muscarinic antagonist umeclidinium (UMEC; GSK573719) with the long-acting  $\beta_2$ -agonist vilanterol (VI) is an approved maintenance treatment for COPD in the US and EU. We compared the efficacy and safety of UMEC/VI with placebo in patients with COPD of Asian ancestry.

**Patients and methods:** In this 24-week, Phase III, multicenter, randomized, double-blind, placebo-controlled, parallel-group study, patients were randomized 1:1:1 to UMEC/VI 125/25  $\mu\text{g}$ , UMEC/VI 62.5/25  $\mu\text{g}$ , or placebo. The primary efficacy end point was trough forced expiratory volume in 1 second ( $\text{FEV}_1$ ) on day 169; secondary end points were Transition Dyspnea Index (TDI) focal score at week 24 and weighted mean (WM)  $\text{FEV}_1$  over 0–6 hours postdose on day 1. Additional end points and safety were also assessed.

**Results:** Both UMEC/VI 125/25  $\mu\text{g}$  and UMEC/VI 62.5/25  $\mu\text{g}$  statistically significantly improved trough  $\text{FEV}_1$  at day 169 versus placebo (UMEC/VI 125/25  $\mu\text{g}$ , 0.216 L, [95% confidence interval [CI] 0.175–0.257]; UMEC/VI 62.5/25  $\mu\text{g}$ , 0.151 L, 95% CI 0.110–0.191; both  $P < 0.001$ ). Statistically significant improvements in TDI score were observed for both UMEC/VI groups versus placebo (UMEC/VI 125/25  $\mu\text{g}$ , 0.9, 95% CI 0.3–1.4,  $P = 0.002$ ; UMEC/VI 62.5/25  $\mu\text{g}$ , 0.7, 95% CI 0.1–1.2,  $P = 0.016$ ). On day 1, both UMEC/VI groups improved 0–6-hour WM  $\text{FEV}_1$  versus placebo (UMEC/VI 125/25  $\mu\text{g}$ , 0.182 L, 95% CI 0.161–0.203; UMEC/VI 62.5/25  $\mu\text{g}$ , 0.160 L, 95% CI 0.139–0.181; both  $P < 0.001$ ). Statistically significant improvements for UMEC/VI groups versus placebo were observed for rescue albuterol use at weeks 1–24 (puffs/day, both  $P < 0.001$ ). The incidence of adverse events was similar across groups.

**Conclusion:** In Asian patients with COPD, once-daily UMEC/VI 125/25  $\mu\text{g}$  and UMEC 62.5/25  $\mu\text{g}$  resulted in clinically meaningful and statistically significant improvements in lung-function end points versus placebo. Symptomatic and quality of life measures also improved. The safety profile of UMEC/VI was consistent with previous studies.

**Keywords:** chronic obstructive pulmonary disease, umeclidinium, vilanterol, Asian

## Introduction

### What is known?

Previous studies have shown that combination treatment with umeclidinium (UMEC)/vilanterol (VI) improves lung function compared with monotherapies, and the tolerability and safety of UMEC/VI has also been studied. However, few patients in these studies were Asian, and specific subanalyses of these populations were not carried out.

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## What is new?

This is the first study to comprehensively investigate long-acting muscarinic antagonist (LAMA)/long-acting  $\beta_2$ -agonist (LABA) combination dual-bronchodilator therapy in Asian patients with COPD. In this population, once-daily UMEC/VI 125/25  $\mu\text{g}$  and UMEC 62.5/25  $\mu\text{g}$  resulted in clinically meaningful and statistically significant improvements in lung-function end points compared with placebo, which is consistent with previous studies.

COPD is characterized by persistent airflow obstruction, and is a major health burden worldwide.<sup>1</sup> It has been estimated that 65 million people worldwide have moderate–severe COPD.<sup>2</sup> The prevalence of COPD in Asian countries has been reported to be between 5.4% and 13.4%, with figures expected to rise.<sup>3–5</sup> Pharmacological management of stable COPD is predominantly focused on improvement of lung function, symptom reduction, decreasing COPD exacerbations, and improving quality of life (QoL) and exercise tolerance. Inhaled bronchodilators, such as LABAs and LAMAs, are central to the pharmacological management of COPD.<sup>6</sup> LABAs exert their bronchodilatory effect through stimulation of  $\beta_2$ -adrenergic receptors, subsequently increasing cyclic adenosine monophosphate and causing relaxation of airway smooth muscle.<sup>1</sup> LAMAs inhibit muscarinic receptors in the airways and block cholinergic bronchoconstriction, thereby decreasing airway smooth-muscle contraction.<sup>6</sup> The complementary mechanisms of bronchodilatory action of coadministered LAMAs and LABAs leads to improvements in lung function in patients with COPD compared with LAMA or LABA monotherapy.<sup>6–9</sup> LAMA/LABA combination therapy may also decrease the risk of side effects when compared with dose escalation of LAMA and LABA monotherapies,<sup>1</sup> and has the potential to offer improved convenience over monotherapies and subsequently improve treatment compliance.

The combination of the inhaled LAMA UMEC with the LABA VI is an approved maintenance treatment for COPD in the US and EU.<sup>9</sup> Previous studies in predominantly Western populations have provided evidence for the efficacy of UMEC/VI 125/25  $\mu\text{g}$  and 62.5/25  $\mu\text{g}$  as maintenance therapy in the treatment of moderate–very severe COPD.<sup>6,9,10</sup> As interethnic differences are known to exist for some drug classes, the characterization of the efficacy and safety profile of inhaled UMEC/VI in patients with COPD of Asian ancestry is warranted. This study evaluated the efficacy and safety of UMEC/VI 125/25  $\mu\text{g}$  and 62.5/25  $\mu\text{g}$  administered once daily over 24 weeks in patients of Asian ancestry with COPD.

## Patients and methods

### Study design

This was a 24-week, Phase III, multicenter, randomized, double-blind, placebo-controlled, parallel-group study (ClinicalTrials.gov identifier NCT01636713, GSK study DB2114634) of once-daily UMEC/VI 125/25  $\mu\text{g}$  and 62.5/25  $\mu\text{g}$  conducted in mainland People's Republic of China, Philippines, South Korea, Taiwan, and Thailand.

### Patients

Eligible patients were male or female,  $\geq 40$  years of age at screening, with an established clinical history of COPD, as defined by the American Thoracic Society/European Respiratory Society criteria.<sup>11</sup> Patients were also current or former smokers with a smoking history  $\geq 10$  pack-years; had a postalbuterol forced expiratory volume in 1 second ( $\text{FEV}_{1\text{p}}$ )/forced vital capacity (FVC) ratio of  $< 0.70$  and a postalbuterol  $\text{FEV}_1 \leq 70\%$  of predicted normal values (based on National Health and Nutrition Examination Survey III reference equations at visit 1),<sup>12,13</sup> and a dyspnea score of  $\geq 2$  on the modified Medical Research Council Dyspnea Scale at screening. Patients were excluded if they had a current diagnosis of asthma or any other known respiratory disorder, including  $\alpha_1$ -antitrypsin deficiency or active lung infection, eg, tuberculosis, lung cancer, clinically significant bronchiectasis, pulmonary hypertension, sarcoidosis, or interstitial lung disease. Patients with a previous history or current evidence of clinically significant or uncontrolled cardiovascular, neurological, psychiatric, renal, hepatic, immunological, endocrine, or hematological abnormalities were also excluded. A full list of inclusion and exclusion criteria is detailed in the Supplementary materials.

Written informed consent was obtained from each patient prior to the performance of any study-specific procedure. This study was conducted in accordance with International Conference on Harmonisation Good Clinical Practice and all applicable subject privacy requirements, and the ethical principles that are outlined in the Declaration of Helsinki 2008. This study was approved by the Ethics Committee of the First Affiliated Hospital of Guangzhou Medical University and other local ethics committees.

### Treatments

Eligible patients were randomized to UMEC/VI 125/25  $\mu\text{g}$  (delivering 113  $\mu\text{g}$  UMEC and 22  $\mu\text{g}$  VI), UMEC/VI 62.5/25  $\mu\text{g}$  (delivering 55  $\mu\text{g}$  UMEC and 22  $\mu\text{g}$  VI), and placebo treatment groups in a 1:1:1 ratio in accordance with the randomization schedule, following a 7- to 14-day run-in period. The randomization schedule was generated by

GlaxoSmithKline using the validated computerized system RandAll version 2.5. All randomized study medication was delivered via dry-powder inhalers each morning.

All patients received supplemental albuterol (metered-dose inhaler and/or nebulas) to be used as rescue medication throughout the study. The use of inhaled corticosteroid was permitted provided the dose did not exceed 1,000  $\mu\text{g}$  of fluticasone propionate or equivalent per day, and the inhaled corticosteroid was not initiated or discontinued within 30 days prior to study entry.

Investigational product taken during the 24-week treatment period was administered in a double-blind fashion. Neither the subject nor the study physician knew which study medication the subject was receiving.

## Study outcomes

### Lung-function end points

The primary efficacy end point was trough  $\text{FEV}_1$  on day 169 (defined as the mean of the  $\text{FEV}_1$  values obtained at 23 and 24 hours after the dose administered on day 168). The secondary lung-function end point was weighted mean (WM)  $\text{FEV}_1$  over 0–6 hours after dosing on day 1. Other lung-function end points included trough  $\text{FEV}_1$  at other time points; serial  $\text{FEV}_1$  over 0–6 hours postdose at day 1; the proportion of patients achieving an increase in  $\text{FEV}_1$  of  $\geq 12\%$  and  $\geq 0.200$  L above baseline at any time 0–6 hours postdose on day 1; the proportion of patients achieving an increase of  $\geq 0.100$  L above baseline in trough  $\text{FEV}_1$ ; and trough and serial FVC and time to onset (defined as an increase of 0.100 L in  $\text{FEV}_1$  above baseline) 0–6 hours postdose at day 1.

### Symptomatic end points

Symptomatic end points included Transition Dyspnea Index (TDI) focal score at week 24 (which was a secondary end point in this study), TDI focal score recorded at other time points, and proportion of TDI responders (a responder to TDI was defined as a patient who reported a TDI score of  $\geq 1$  unit). Additional symptomatic end points were rescue-albuterol use (percentage of rescue-free days and puffs/day) and time to first COPD exacerbation (defined as an acute worsening of symptoms of COPD requiring the use of rescue albuterol or any treatment beyond study medication).

### Health-related QoL assessments

Health-related QoL (HRQoL) was measured by the St George's Respiratory Questionnaire (SGRQ), COPD assessment test (CAT), and a COPD-related health care resource-utilization assessment. Further information on HRQoL assessments is detailed in the Supplementary materials.

## Safety assessments

Safety assessments included the incidence of adverse events (AEs) and serious AEs (SAEs), vital signs (including pulse rate and systolic and diastolic blood pressure), 12-lead electrocardiogram (ECG) parameters, and clinical chemistry and hematology parameters (including routine urinalysis). AEs and SAEs were recorded from visit 2 (study-treatment start) until visit 9 (follow-up). Any SAEs assessed as related to study participation (eg, study treatment, protocol-mandated procedures, invasive tests, or change in existing therapy) or related to a GlaxoSmithKline concomitant medication, were recorded from the time informed consent was given up to and including any follow-up contact.

## Statistical analysis

Sample size was calculated based on the primary end point of trough  $\text{FEV}_1$  on day 169 and assumed 90% power, and a two-sided 5% significance level. Furthermore, an estimate of residual standard deviation (SD) of 0.240 L was calculated, in addition to a treatment difference from any UMEC/VI group and placebo of 0.100 L. Based upon these assumptions, 123 evaluable subjects were required for each treatment arm. However, this was increased to 191 evaluable subjects per arm, in order to meet individual country and regional requirements and account for an estimated 21% withdrawal rate over the 24-week study period. Primary analyses were performed on the intent-to-treat (ITT) population, defined as all patients randomized to treatment who had received at least one dose of randomized study medication during the treatment period. For the primary end point of trough  $\text{FEV}_1$  on day 169, mixed model for repeated measures (MMRM) analysis was performed with all available postbaseline assessments for subjects in the ITT population, including the following covariates: baseline  $\text{FEV}_1$  (mean of the two assessments made 30 and 5 minutes predose on day 1), smoking status, day, country/region, treatment, day-by-baseline interaction and day-by-treatment interaction, where "day" was nominal. Analysis of mean TDI focal score on days 28, 84, and 168 used MMRM analysis with Baseline Dyspnea Index score in place of the baseline  $\text{FEV}_1$ . WM clinic visit  $\text{FEV}_1$  over 0–6 hours postdose was analyzed using analysis of covariance with baseline  $\text{FEV}_1$  (mean of the two assessments made 30 and 5 minutes predose on day 1), treatment, smoking status, and country/region as covariates. Time to onset of bronchodilation and time to first COPD exacerbation were analyzed using Cox's proportional hazard model with covariates of treatment, smoking status, and country/region.

A step-down testing procedure was employed to adjust for multiplicity on the primary efficacy end point, whereby interpretation of the comparisons between UMEC/VI 62.5/25 µg versus placebo were only carried out if the UMEC/VI 125/25 µg versus placebo comparison was shown to be statistically significant.

## Results

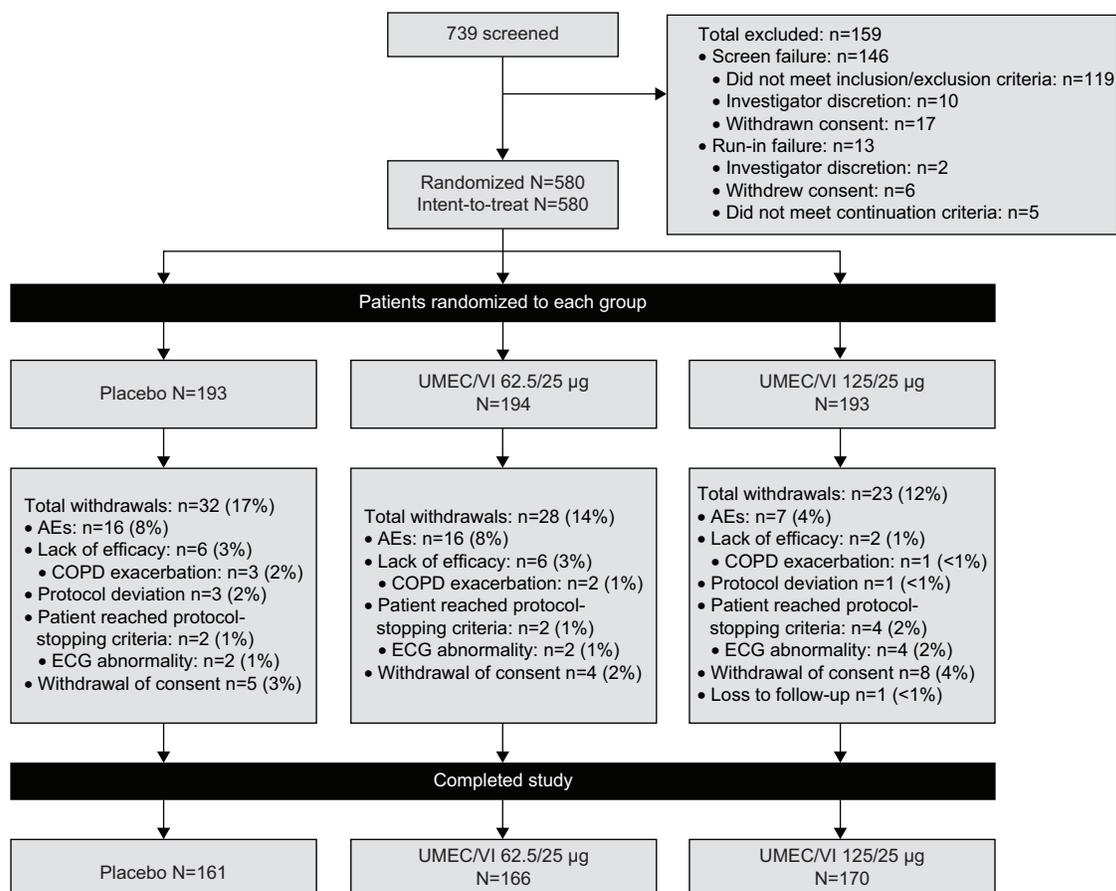
### Study population

Of the 739 patients screened, a total of 580 patients were enrolled from July 16, 2012 to October 25, 2013 and included in the ITT population. The majority of patients (n=497 [86%]) completed the study (Figure 1). Patients were enrolled across 44 centers in the People's Republic of China (n=385 [66%]), Taiwan (n=82 [14%]), South Korea (n=51 [9%]), the Philippines (n=33 [6%]), and Thailand (n=29 [5%]). Patient baseline demographics and clinical characteristics were mainly similar between treatment groups; however, there was a higher percentage of subjects in GOLD (Global

initiative for chronic Obstructive Lung Disease) stage IV in the UMEC/VI 62.5/25 µg treatment group (18%) compared with placebo (13%) and UMEC 125/25 µg treatment groups (11%). The majority of patients were male, of East Asian heritage and had moderate–severe impairment in airflow obstruction (Table 1). A total of 83 (14%) patients withdrew from the study, and withdrawal rates were similar across all treatment groups (UMEC/VI 125/25 µg, 12%; UMEC/VI 62.5/25 µg, 14%; placebo, 17%).

### Efficacy – lung function

Both UMEC/VI 125/25 µg and UMEC/VI 62.5/25 µg demonstrated a statistically significantly greater change from baseline in trough FEV<sub>1</sub> at day 169 compared with placebo (UMEC/VI 125/25 µg, 0.216 L, 95% confidence interval [CI] 0.175–0.257; UMEC/VI 62.5/25 µg, 0.151 L, 95% CI 0.110–0.191; both  $P < 0.001$ ) (Table 2). The treatment differences relative to placebo were also statistically significant versus placebo at all other time points assessed (Figure 2). On day 1,



**Figure 1** Patient disposition.

**Abbreviations:** AEs, adverse events; ECG, electrocardiogram; UMEC, umecldinium; VI, vilanterol.

**Table 1** Baseline demographics and characteristics

Characteristics	Placebo n=193	UMEC/VI 62.5/25 µg n=194	UMEC/VI 125/25 µg n=193	Total n=580
<b>Age (years), mean (SD)</b>	64.3 (8.78)	64.0 (8.71)	63.7 (8.26)	64.0 (8.57)
<b>Male, n (%)</b>	177 (92)	183 (94)	182 (94)	542 (93)
<b>Ethnicity, n (%)</b>				
Asian	193 (100)	194 (100)	193 (100)	580 (100)
East Asian	177 (88)	173 (89)	173 (90)	516 (89)
Southeast Asian	21 (11)	21 (11)	20 (10)	62 (11)
Mixed Asian heritage	2 (1)	0	0	2 (<1)
<b>Body mass index (kg/m<sup>2</sup>), mean (SD)</b>	22.44 (3.633)	22.19 (3.611)	22.41 (3.454)	22.35 (3.562)
<b>Smoking status: current smoker, n (%)</b>	65 (34)	56 (29)	48 (25)	169 (29)
<b>Smoking pack-years,<sup>a</sup> mean (SD)</b>	37.1 (21.83)	37.6 (19.76)	38.9 (22.43)	37.9 (21.34)
<b>Duration of COPD, n (%)</b>				
< 1 year	40 (21)	45 (23)	47 (24)	132 (23)
≥ 1 to <5 years	93 (48)	82 (42)	85 (44)	260 (45)
≥ 5 to <10 years	37 (19)	39 (20)	32 (17)	108 (19)
≥ 10 to <15 years	14 (7)	20 (10)	22 (11)	56 (10)
≥ 15 to <20 years	5 (3)	3 (2)	2 (1)	10 (2)
≥ 20 to <25 years	3 (2)	3 (2)	2 (1)	8 (1)
≥ 25 years	1 (<1)	2 (1)	3 (2)	6 (1)
<b>GOLD stage, n (%)</b>				
Stage II (≥50%–<80% predicted FEV <sub>1</sub> )	89 (46)	74 (38)	88 (46)	251 (43)
Stage III (≥30%–<50% predicted FEV <sub>1</sub> )	79 (41)	84 (44)	84 (44)	247 (43)
Stage IV (<30% predicted FEV <sub>1</sub> )	25 (13)	35 (18)	21 (11)	81 (14)
<b>Reversible to albuterol and ipratropium,<sup>b</sup> n (%)</b>	n=191 <sup>d</sup> 95 (50)	n=192 <sup>d</sup> 85 (44)	n=193 91 (47)	n=573 <sup>d</sup> 271 (47)
<b>Postalbuterol FEV<sub>1</sub>, L (SD)</b>	n=193 1.168 (0.3708)	n=193 <sup>d</sup> 1.131 (0.3965)	n=193 1.195 (0.3889)	n=579 <sup>d</sup> 1.164 (0.3858)
<b>Postalbuterol FEV<sub>1</sub>/FVC, mean (SD)</b>	n=193 40.110 (9.5767)	n=193 <sup>d</sup> 38.814 (11.2420)	n=193 40.566 (10.5418)	n=579 <sup>d</sup> 39.830 (10.4840)
<b>ICS use, n (%)</b>	99 (51)	104 (54)	98 (51)	301 (52)
<b>Pretreatment concomitant COPD medications,<sup>c</sup> n (%)</b>				
Any medication	153 (79)	147 (76)	145 (75)	445 (77)
ICS	102 (53)	108 (56)	98 (51)	308 (53)
Long-acting β-agonist	93 (48)	97 (50)	84 (44)	274 (47)
Short-acting β-agonist	42 (22)	45 (23)	44 (23)	131 (23)
Xanthine	51 (26)	40 (21)	36 (19)	127 (22)
Long-acting anticholinergic	34 (18)	31 (16)	36 (19)	101 (17)
Mucolytics	23 (12)	26 (13)	23 (12)	72 (12)
Other COPD medication	21 (11)	13 (7)	21 (11)	55 (9)
Cold, cough, nasal, and/or throat medication	13 (7)	12 (6)	11 (6)	36 (6)
Short-acting anticholinergic	6 (3)	14 (7)	11 (6)	31 (5)

**Notes:** <sup>a</sup>Smoking pack-years = (number of cigarettes smoked per day/20) × number of years smoked; <sup>b</sup>reversible was an increase in FEV<sub>1</sub> of ≥12% and ≥0.200 L following administration of both albuterol and ipratropium; nonreversible was an increase in FEV<sub>1</sub> of <0.200 L or a ≥0.200 L increase that was <12% from prealbuterol FEV<sub>1</sub>; <sup>c</sup>not given for an exacerbation; <sup>d</sup>These are the number of patients available to measure these values, which is different from those shown elsewhere in the table.

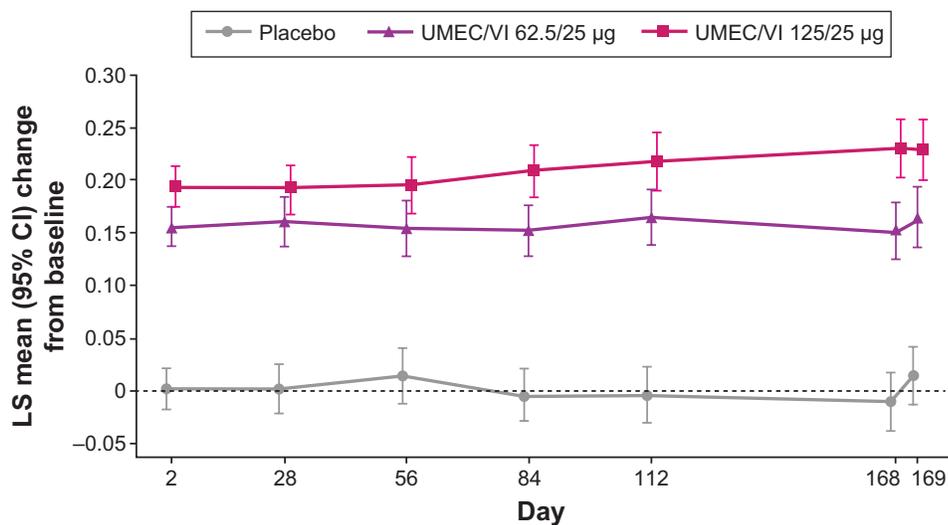
**Abbreviations:** FEV<sub>1</sub>, forced expiratory volume in 1 second; FVC, forced vital capacity; GOLD, Global initiative for chronic Obstructive Lung Disease; ICS, inhaled corticosteroid; SD, standard deviation; UMEC, umeclidinium; VI, vilanterol.

**Table 2** Summary of lung-function, symptomatic, and health-related quality of life measures (ITT population)

Outcomes	Placebo n=193	UMEC/VI 62.5/25 µg n=194	UMEC/VI 125/25 µg n=193
<b>Trough FEV<sub>1</sub> on day 169, L</b>	n=162	n=165	n=168
LS mean (SE)	1.040 (0.0147)	1.191 (0.0146)	1.256 (0.0146)
LS mean change (SE)	0.013 (0.0147)	0.164 (0.0146)	0.229 (0.0146)
Column versus placebo difference (95% CI)	–	0.151 (0.110–0.191)***	0.216 (0.175–0.257)***
<b>WM FEV<sub>1</sub> 0–6 hours postdose on day 1</b>	n=190	n=192	n=192
LS mean (SE)	1.038 (0.0075)	1.197 (0.0075)	1.220 (0.0075)
LS mean change (SE)	0.015 (0.0075)	0.174 (0.0075)	0.197 (0.0075)
Column versus placebo difference (95% CI)	–	0.160 (0.139–0.181)***	0.182 (0.161–0.203)***
<b>Serial FEV<sub>1</sub> at 15 minutes postdose at day 1</b>	n=191	n=193	n=191
LS mean (SE)	1.028 (0.0063)	1.133 (0.0063)	1.144 (0.0063)
LS mean change (SE)	0.001 (0.0063)	0.106 (0.0063)	0.117 (0.0063)
Column versus placebo difference (95% CI)	–	0.105 (0.087–0.122)***	0.116 (0.098–0.134)***
<b>Patients achieving an increase in FEV<sub>1</sub> of ≥12% and ≥0.200 L above baseline at any time 0–6 hours postdose on day 1</b>			
Increase, n (%)	10 (5)	98 (51)	112 (58)
Column versus placebo odds ratio (95% CI)	–	20.5 (10.1–41.6)***	27.8 (13.7–56.6)***
<b>Patients achieving an increase of ≥0.100 L above baseline in trough FEV<sub>1</sub> at day 169</b>			
Increase, n (%)	42 (22)	112 (58)	118 (61)
Column versus placebo odds ratio (95% CI)	–	5.3 (3.4–8.4)***	6.1 (3.8–9.7)***
<b>Trough FVC at day 169</b>	n=162	n=165	n=168
LS mean (SE)	2.678 (0.0282)	2.938 (0.0280)	3.005 (0.0279)
LS mean change (SE)	0.030 (0.0282)	0.290 (0.0280)	0.358 (0.0279)
Column versus placebo difference (95% CI)	–	0.260 (0.182, 0.338)***	0.328 (0.250, 0.405)***
<b>Serial trough FVC 15 minutes postdose at day 1</b>	n=191	n=193	n=191
LS mean (SE)	2.662 (0.0172)	2.902 (0.0171)	2.899 (0.0172)
LS mean change (SE)	0.015 (0.0172)	0.255 (0.0171)	0.251 (0.0172)
Column versus placebo difference (95% CI)	–	0.240 (0.192–0.288)***	0.236 (0.188–0.284)***
<b>Time to onset, minutes<sup>a</sup></b>	–	28	21
Column versus placebo hazard ratio (95% CI)	–	7.84 (5.69–10.82)***	8.65 (6.27–11.94)***
<b>TDI focal score on day 168</b>	n=162	n=162	n=168
LS mean (SE)	2.0 (0.20)	2.7 (0.20)	2.9 (0.20)
Column versus placebo difference (95% CI)	–	0.7 (0.1–1.2)*	0.9 (0.3–1.4)**
<b>TDI responders at day 168 (≥1-unit change)</b>	n=186	n=184	n=186
Responder, n (%)	105 (56)	118 (64)	128 (69)
Column versus placebo odds ratio (95% CI)	–	1.3 (0.9–2.1)	1.6 (1.1–2.5)*
<b>Rescue-medication use (puffs/day) (weeks 1–24)</b>	n=169	n=172	n=173
LS mean (SE)	1.5 (0.09)	0.8 (0.09)	0.8 (0.09)
LS mean change (SE)	–0.2 (0.09)	–0.8 (0.09)	–0.8 (0.09)
Column versus placebo difference (95% CI)	–	–0.6 (–0.9 to –0.4)***	–0.7 (–0.9 to –0.4)***
<b>Time to first on-treatment COPD exacerbations</b>			
Patients with a COPD exacerbation, n (%)	32 (17)	20 (10)	13 (7)
Probability of having event, % (95% CI)	17.2 (12.4–23.4)	10.9 (7.2–16.4)	7.0 (4.1–11.7)
Column versus placebo hazard ratio (95% CI)	–	0.6 (0.3–1.0)	0.4 (0.2–0.7)**
<b>SGRQ total score at day 168</b>	n=158	n=157	n=163
LS mean (SE)	35.11 (1.035)	33.09 (1.035)	31.35 (1.022)
LS mean change (SE)	–6.30 (1.035)	–8.32 (1.035)	–10.06 (1.022)
Column versus placebo difference (95% CI)	–	–2.02 (–4.90 to 0.86)	–3.76 (–6.62 to –0.90)**
<b>SGRQ responders (&gt;4-unit decrease from baseline) at day 168</b>			
Responders, n (%)	84 (46)	102 (56)	107 (58)
Column versus placebo odds ratio (95% CI)	–	1.5 (1.0–2.4)*	1.8 (1.1–2.7)**
<b>COPD assessment test at day 168</b>	n=164	n=166	n=170
Change from baseline, mean (SD)	–2.26 (6.695)	–3.24 (6.488)	–3.54 (6.386)
<b>Health care-resource utilization, n (%)</b>			
Patients requiring unscheduled health care	2 (1)	3 (2)	4 (2)
Patients making an office/practice visit	0	1 (<1)	3 (2)
Patients making urgent care/outpatient visit	0	2 (1)	1 (<1)
Patients making an emergency room visit	2 (1)	1 (<1)	0
Patients spending time in intensive care	0	0	0

**Notes:** \* $P \leq 0.05$ ; \*\* $P \leq 0.01$ ; \*\*\* $P < 0.001$ ; <sup>a</sup>the first time during the 0- to 6-hour postdose period at which a scheduled postdose FEV<sub>1</sub> was  $\geq 0.100$  L above baseline.

**Abbreviations:** CI, confidence interval; FEV<sub>1</sub>, forced expiratory volume in 1 second; FVC, forced vital capacity; ITT, intent-to-treat; LS, least squares; SE, standard error; SGRQ, St George's Respiratory Questionnaire; TDI, Transition Dyspnea Index; UMEC, umeclidinium; VI, vilanterol; WM, weighted mean.



**Figure 2** LS mean change from baseline in trough FEV<sub>1</sub> up to day 169 (ITT population).

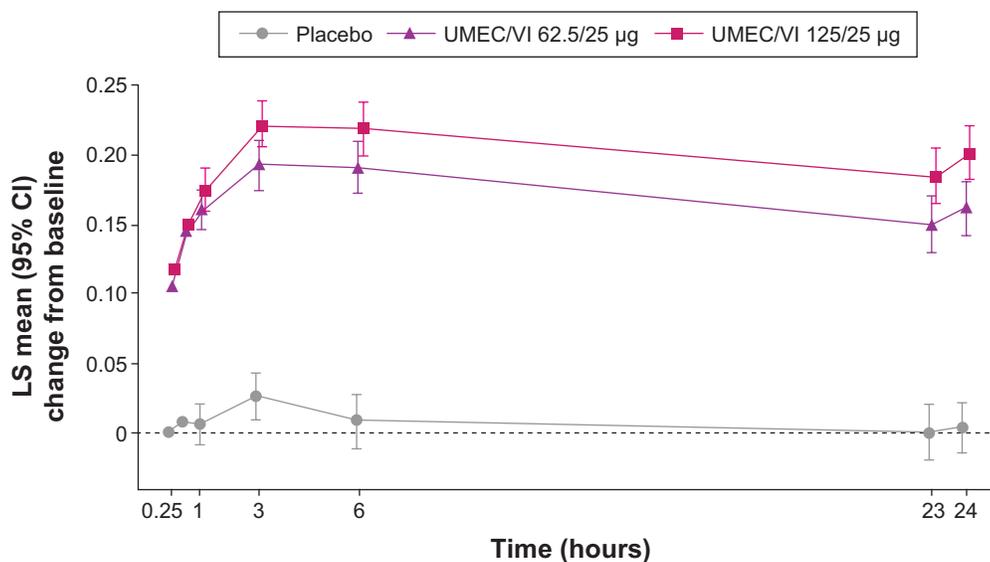
**Abbreviations:** CI, confidence interval; FEV<sub>1</sub>, forced expiratory volume in 1 second; ITT, intent-to-treat; LS, least squares; UMEC, umeclidinium; VI, vilanterol.

statistically significantly greater changes from baseline in 0- to 6-hour WM FEV<sub>1</sub> were observed for both the UMEC/VI 125/25 µg and UMEC/VI 62.5/25 µg treatment groups compared with placebo (UMEC/VI 125/25 µg, 0.182 L, 95% CI 0.161–0.203; UMEC/VI 62.5/25 µg, 0.160 L, 95% CI 0.139–0.181; both  $P < 0.001$ ) (Table 2).

On day 1, serial FEV<sub>1</sub> for both UMEC/VI 125/25 µg and UMEC/VI 62.5/25 µg demonstrated statistically significantly greater changes compared with placebo at 15 minutes post-dose (UMEC/VI 125/25 µg, 0.116 L, 95% CI 0.098–0.134; UMEC/VI 62.5/25 µg, 0.105 L, 95% CI 0.087–0.122; both  $P < 0.001$ ), which were sustained at each time point up to

24 hours postdose (Figure 3). Furthermore, patients had statistically significantly higher odds of achieving an increase in FEV<sub>1</sub> of  $\geq 12\%$  and  $\geq 0.200$  L above baseline at day 1 compared with placebo (UMEC/VI 125/25 µg, odds ratio [OR] 27.8, 95% CI 13.7–56.6; UMEC/VI 62.5/25 µg, OR 20.5, 95% CI 10.1–41.6; both  $P < 0.001$ ) and also a statistically significantly higher OR of achieving an increase in trough FEV<sub>1</sub> of  $\geq 0.100$  L above baseline at day 169 compared with placebo (UMEC/VI 125/25 µg, OR 6.1, 95% CI 3.8–9.7; UMEC/VI 62.5/25 µg, OR 5.3, 95% CI 3.4–8.4; both  $P < 0.001$ ).

Treatment differences for trough FVC were statistically significantly greater for patients receiving UMEC/VI



**Figure 3** LS mean change from baseline in serial FEV<sub>1</sub> on day 1 (ITT population).

**Abbreviations:** CI, confidence interval; FEV<sub>1</sub>, forced expiratory volume in 1 second; ITT, intent-to-treat; LS, least squares; UMEC, umeclidinium; VI, vilanterol.

compared with patients receiving placebo at day 169 and all other time points assessed (day 169: UMEC/VI 125/25  $\mu\text{g}$ , 0.328, 95% CI 0.250–0.405; UMEC/VI 62.5/25  $\mu\text{g}$ , 0.260, 95% CI 0.182–0.338; both  $P < 0.001$ ). Serial trough FVC measurements for both UMEC/VI treatment groups demonstrated improvements in least-squares mean change from baseline at 15 minutes postdose compared with placebo (UMEC/VI 125/25  $\mu\text{g}$ , 0.236, 95% CI 0.188–0.284; UMEC/VI 62.5/25  $\mu\text{g}$ , 0.240, 95% CI 0.192–0.288; both  $P < 0.001$ ), which were sustained up to 24 hours postdose on day 1.

## Efficacy – symptoms

Clinically meaningful improvements in TDI score (defined as a TDI score of  $\geq 1$  unit) were observed for both UMEC/VI doses at day 168 and both other days assessed (day 28 and day 84). Furthermore, TDI scores for the UMEC/VI treatment groups were statistically significantly greater compared with placebo at day 168 (UMEC/VI 125/25  $\mu\text{g}$ , 0.9, 95% CI 0.3–1.4,  $P = 0.002$ ; UMEC/VI 62.5/25  $\mu\text{g}$ , 0.7, 95% CI 0.1–1.2,  $P = 0.016$ ) (Table 2). The treatment differences for both UMEC/VI 62.5/25 and 125/25  $\mu\text{g}$  versus placebo were also statistically significant at days 28 and 84 ( $P < 0.001$  for both treatments) (Figure 4).

Patients receiving UMEC/VI also had statistically significantly higher odds of being a TDI responder compared with placebo at all time points assessed, except for day 168 with UMEC/VI 62.5/25  $\mu\text{g}$  (day 168: OR UMEC/VI 125/25  $\mu\text{g}$ , 1.6, 95% CI 1.1–2.5,  $P = 0.022$ ; UMEC/VI 62.5/25  $\mu\text{g}$ , 1.3, 95% CI 0.9–2.1,  $P = 0.163$ ) (Table 2). Rescue-medication use (puffs/day) was statistically

significantly reduced with UMEC/VI compared with placebo (UMEC/VI 125/25  $\mu\text{g}$ ,  $-0.7$ , 95% CI  $-0.9$  to  $-0.4$ ; UMEC/VI 62.5/25  $\mu\text{g}$ ,  $-0.6$ , 95% CI  $-0.9$  to  $-0.4$ ;  $P < 0.001$  for both), while the percentage of rescue-free days over weeks 1–24 was greater for UMEC 125/25  $\mu\text{g}$  (67.8%) and UMEC 62.5/25  $\mu\text{g}$  (64.0%) compared with placebo (48.6%).

On-treatment COPD exacerbations were reported by more patients receiving placebo (17%) compared with UMEC/VI 125/25  $\mu\text{g}$  and 62.5/25  $\mu\text{g}$  (7% and 10%, respectively). Analysis of time to first COPD exacerbation found that UMEC/VI 125/25  $\mu\text{g}$  also reduced the risk of COPD exacerbation compared with placebo, but not for UMEC/VI 62.5/25  $\mu\text{g}$  (UMEC/VI 125/25  $\mu\text{g}$ , hazard ratio 0.4, 95% CI 0.2–0.7],  $P = 0.004$ ; UMEC/VI 62.5/25  $\mu\text{g}$ , hazard ratio 0.6, 95% CI 0.3–1.0,  $P = 0.069$ ).

## Health-related QoL

UMEC/VI was associated with statistically significant reductions in SGRQ total score that were approximate to the minimal clinically important reduction of 4 units<sup>14</sup> at all time points for UMEC/VI 125/25  $\mu\text{g}$  and at day 84 for UMEC/VI 62.5/25  $\mu\text{g}$  compared with placebo (see Table S2 for data). Furthermore, patients treated with UMEC/VI had higher odds of being an SGRQ responder (defined as a  $>4$ -unit decrease from baseline) at day 168 relative to placebo (UMEC/VI 125/25  $\mu\text{g}$ , OR 1.8, 95% CI 1.1–2.7,  $P = 0.010$ ; UMEC/VI 62.5/25  $\mu\text{g}$ , OR 1.5, 95% CI 1.0–2.4,  $P = 0.045$ ) (Table 2). Clinically meaningful improvements from baseline in mean CAT scores were observed for both UMEC/VI treatment groups at day 168 (UMEC/VI 125/25  $\mu\text{g}$ ,  $-3.54$ ,

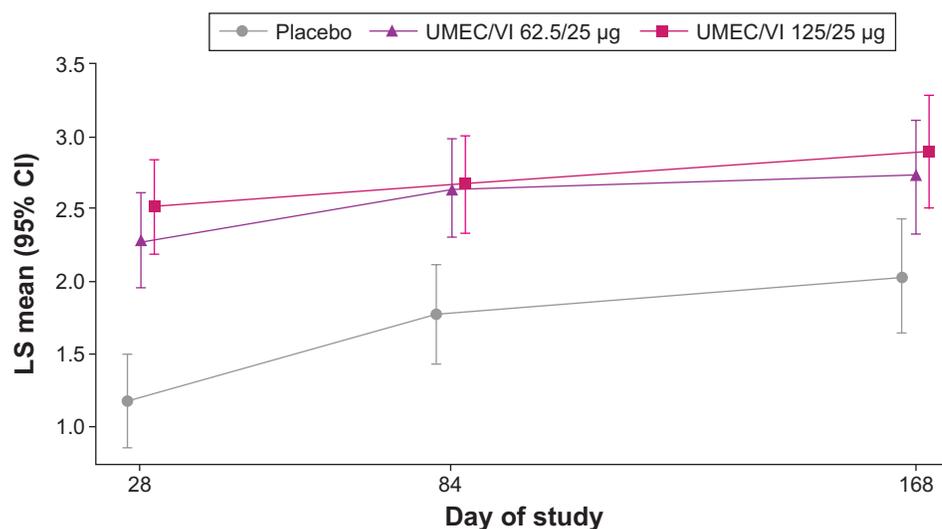


Figure 4 LS mean TDI focal score (ITT population).

Abbreviations: CI, confidence interval; ITT, intent-to-treat; LS, least squares; TDI, Transition Dyspnea Index; UMEC, umeclidinium; VI, vilanterol.

minimum–maximum  $-27.0$  to  $17.0$ ,  $SD = 6.386$ ; UMEC/VI  $62.5/25 \mu\text{g}$ ,  $-3.24$ , minimum–maximum  $-21.0$  to  $16.0$ ,  $SD = 6.488$ ). The proportion of patients who reported unscheduled health care utilization was low (1%–2% across treatment groups).

## Safety

The incidence of AEs was similar across treatment groups (placebo, 39%; UMEC/VI  $125/25 \mu\text{g}$ , 34%; UMEC/VI  $62.5/25 \mu\text{g}$ , 34%); nasopharyngitis and upper respiratory tract infection were the most common AEs across the treatment groups (Table 3). AEs associated with antimuscarinic effects, such as dry mouth and urinary retention, were low and similar across UMEC/VI treatment groups and placebo. Overall, the incidence of drug-related AEs was low across both UMEC/VI treatment groups (UMEC/VI  $125/25 \mu\text{g}$ , 5%; UMEC/VI  $62.5/25 \mu\text{g}$ , 4%) and similar to placebo (5%). There was a low incidence of cardiovascular AEs of special interest (2%–6%) and pneumonia and lower respiratory tract infections (as an AE of special interest, 2%–3%) across treatment groups.

On-treatment nonfatal SAEs reported by  $>1\%$  of patients in any treatment group were COPD (placebo, 5%; UMEC/VI

$125/25 \mu\text{g}$ , 1%; UMEC/VI  $62.5/25 \mu\text{g}$ , 5%) and pneumonia (placebo, 1%; UMEC/VI  $125/25 \mu\text{g}$ ,  $<1\%$ ; UMEC/VI  $62.5/25 \mu\text{g}$ , 1%). Two deaths occurred during the study. One patient in the UMEC/VI  $125/25 \mu\text{g}$  group had acute respiratory failure, COPD, pneumonia, and septic shock, which was considered to be treatment-related by the study investigator. One patient in the UMEC/VI  $62.5/25 \mu\text{g}$  group died of drowning, which was not considered to be treatment-related. There were no clinically-meaningful effects on vital signs, ECGs, or clinical chemistry and hematology parameters.

## Discussion

This study aimed to examine the efficacy and safety of once-daily inhaled UMEC/VI  $125/25 \mu\text{g}$  and  $62.5/25 \mu\text{g}$  in patients of Asian ancestry with COPD over a 24-week period. In this previously unstudied population, treatment with once-daily UMEC/VI  $125/25 \mu\text{g}$  and UMEC/VI  $62.5/25 \mu\text{g}$  resulted in clinically meaningful improvements in lung-function measurements compared with placebo over a 24-week period.

In addition to improvements in lung function, there was evidence of symptomatic improvement with both UMEC/VI treatment doses, with statistically significant improvements in focal TDI score and a suggested benefit on the frequency of

**Table 3** Overall summary of AEs (ITT population)

	Placebo n=193	UMEC/VI 62.5/25 $\mu\text{g}$ n=194	UMEC/VI 125/25 $\mu\text{g}$ n=193
<b>All AEs, n (%)</b>			
Any on-treatment AE	76 (39)	65 (34)	66 (34)
Any posttreatment AE	2 (1)	1 ( $<1$ )	4 (2)
Any on-treatment drug-related AE	10 (5)	7 (4)	9 (5)
Any AE leading to permanent discontinuation of study drug or withdrawal from study <sup>a</sup>	17 (9)	16 (8)	7 (4)
Any on-treatment nonfatal SAE	17 (9)	14 (7)	5 (3)
Any posttreatment nonfatal SAE	1 ( $<1$ )	0	0
Any on-treatment drug-related nonfatal SAE	1 ( $<1$ )	1 ( $<1$ )	0
Any drug-related fatal SAE	0	0	1 ( $<1$ )
Any fatal SAE	0	1 ( $<1$ )	1 ( $<1$ )
<b>AE reported by <math>\geq 3\%</math> of patients in any treatment group, n (%)</b>			
Nasopharyngitis	18 (9)	17 (9)	18 (9)
Upper respiratory tract infection	11 (6)	19 (10)	13 (7)
Chronic obstructive pulmonary disease	9 (5)	9 (5)	3 (2)
Cough	4 (2)	6 (3)	4 (2)
<b>On-treatment AEs of special interest,<sup>b</sup> n (%)</b>			
Any cardiovascular event	6 (3)	3 (2)	11 (6)
<b>Anticholinergic events, n (%)</b>			
Dry mouth	3 (2)	1 ( $<1$ )	4 (2)
Urinary retention	0	0	1 ( $<1$ )

**Notes:** <sup>a</sup>Includes both on-treatment and posttreatment AEs; <sup>b</sup>incidence of AEs of special interest comprised of events in selected Standardised MedDRA Queries (SMQs) and/or individual preferred terms (PTs). Cardiovascular AEs of special interest comprised SMQs for cardiac arrhythmias, cardiac failure, cardiac ischemia (myocardial infarction, other ischemic heart disease), and stroke (central nervous system hemorrhages and cerebrovascular conditions). Anticholinergic AEs of special interest comprised terms in the anticholinergic syndrome SMQs. Urinary retention comprised PTs of urinary retention, urinary hesitation, decreased micturition frequency, decreased urine flow, and Fowler's syndrome.

**Abbreviations:** AE, adverse event; ITT, intent-to-treat; SAE, serious AE; UMEC, umeclidinium; VI, vilanterol.

COPD exacerbations. The improvements in lung function and COPD symptoms had additional benefits on QoL parameters, with improvements observed in SGRQ and CAT scores.

These observations are generally consistent with the results of previous studies in predominantly Caucasian patients with COPD, which also reported lung-function improvements, symptom improvements, and improvements in HRQoL with once-daily UMEC/VI.<sup>6–10,15</sup> In one such study, trough FEV<sub>1</sub> (primary end point) was statistically significantly improved at day 169 for UMEC/VI 62.5/25 µg compared with placebo (difference of 0.167, 95% CI 0.128–0.207 L).<sup>6</sup> Similarly, improvements in trough FEV<sub>1</sub> from baseline of 0.205–0.211 L for UMEC/VI 62.5/25 µg<sup>8,15</sup> and 0.207–0.223 L for UMEC/VI 125/25 µg<sup>7,8</sup> have been reported. Greater improvements in 0–6 hour WM FEV<sub>1</sub> (secondary end point) at day 168 were reported for UMEC/VI 62.5/25 µg compared with placebo (difference of 0.242 L, 95% CI 0.202–0.282).<sup>6</sup> Improvements from baseline in 0–6 hour WM FEV<sub>1</sub> of 0.254–0.276 L and 0.263–0.282 L have also been reported for UMEC/VI 62.5/25 µg<sup>8,15</sup> and UMEC/VI 125/25 µg, respectively.<sup>7,8</sup> TDI score at week 24, reported in several studies, ranged from 2.3 to 2.4 for UMEC/VI 62.5/25 µg<sup>6,8</sup> and from 1.8 to 2.9 for UMEC 125/25 µg.<sup>7,8</sup> Change from baseline in rescue use (puffs/day) and SGRQ total score ranged from –1.3 to –2.7 and –7.27 to –9.95, respectively, with UMEC 62.5/25 µg,<sup>6,8,15</sup> and from –2.2 to –2.7 and –3.6 to –9.95, respectively, with UMEC 125/25 µg.<sup>7,8</sup>

The safety profile of UMEC/VI was similar to that previously reported in Caucasian patients with COPD, with headache, nasopharyngitis, extrasystoles, upper respiratory tract infection, cough, and back pain being the most commonly reported AEs.<sup>6–8,10,15</sup> Both doses of UMEC/VI appeared to be well tolerated, with no notable treatment-related changes in vital signs, ECGs, or clinical laboratory parameters, and no new safety concerns were raised.

The efficacy and safety profile of UMEC/VI in Asian patients with COPD therefore appears to be consistent with previous studies in predominantly Western COPD patient populations,<sup>6,8,10</sup> suggesting that ethnicity is not a factor of variance in response to UMEC/VI treatment.

Studies of other LABA/LAMA dual bronchodilators, such as QVA149 (indacaterol and glycopyrronium), have also reported benefits in patients with COPD; however, comparisons with such studies cannot be made, due to differences in study populations and design. In addition, these studies were also carried out in predominantly Caucasian populations (approximately 20%–30% of patients were Asian), and specific subanalyses for race were not reported.<sup>16,17</sup> Similarly,

a combination of olodaterol and tiotropium has been shown to provide additional improvements in lung function compared with tiotropium alone, but specific Asian subanalyses have not been reported.<sup>18</sup>

A limitation of the present study was that although the baseline characteristics were generally balanced across the treatment groups, there was a higher percentage of patients with GOLD stage IV COPD in patients receiving UMEC/VI 62.5/25 µg (18%) compared with placebo (13%) and UMEC/VI 125/25 µg (11%). This could explain why there were greater differences in the lung-function response observed between the two UMEC/VI doses than was observed in other studies.<sup>8</sup> A large placebo response was also observed in the TDI responder analysis. The reason for this is unknown, but a similar placebo effect has been observed in a previous placebo-controlled UMEC/VI study<sup>6</sup> and another COPD trial conducted with patients of Asian heritage.<sup>19</sup>

Findings from the present study suggested a beneficial effect on the frequency of COPD exacerbations; however, it should be noted that this study was not specifically designed to evaluate the effects of UMEC/VI on COPD exacerbations, thereby limiting the interpretation of these data. Patients in this study were not required to have a history of COPD exacerbations to enroll in the study, and thus only 24%–25% of patients had an exacerbation requiring oral/systemic steroids or antibiotics. Furthermore, patients were required to be withdrawn if they experienced a COPD exacerbation; therefore, no effect on rate of exacerbations could be determined.

## Conclusion

The results of the present study indicate that UMEC/VI 125/25 µg and UMEC/VI 62.5/25 µg are beneficial for the once-daily, maintenance bronchodilator treatment of airflow obstruction in Asian patients with moderate – very severe COPD, consistent with studies in predominantly Western populations. The safety profile for UMEC/VI was also comparable to previous studies, and no new safety concerns were identified in this patient population.

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## Author contributions

JPZ, NSZ, AN, AC, and AHG all made a substantial contribution to the conception and design (eg, protocol development and/or design advice), acquisition of data (eg, study investigation), and data analysis and interpretation. All authors contributed toward drafting and critically revising the paper, gave final approval of the version to be published, and agree to be accountable for all aspects of the work.

## Disclosure

JPZ has received lecture fees from GlaxoSmithKline. AN, AC, and AHG are employees of GlaxoSmithKline and hold stocks and shares in the company. NSZ reports no conflicts of interest in this work.

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## Supplementary materials

### Full inclusion/exclusion criteria

#### Inclusion criteria

1. Type of subject: Outpatient.
2. Informed consent: Subjects gave their signed and dated written informed consent prior to study participation.
3. Age: 40 years of age or older at Screening (Visit 1).
4. Sex: Male or female subjects. A female was eligible if she was of non-childbearing potential or was using acceptable contraceptive methods.
5. COPD history: Established clinical history of COPD in accordance with the definition by the American Thoracic Society/European Respiratory Society.<sup>1</sup>
6. Tobacco use/smoking history: Current/former cigarette smokers with a history of cigarette smoking of  $\geq 10$  pack-years (number of pack-years = [number of cigarettes per day/20] x number of years smoked [eg, 20 cigarettes per day for 10 years, or 10 cigarettes per day for 20 years both equal 10 pack-years]). Former smokers were defined as those who had stopped smoking  $\geq 6$  months prior to Visit 1. Note: Pipe and/or cigar use could not be used to calculate pack-year history.
7. Severity of disease: A post-albuterol FEV<sub>1</sub>/FVC ratio of  $< 0.70$  and a post-albuterol FEV<sub>1</sub> of  $\leq 70\%$  of predicted normal values calculated using National Health and Nutrition Examination Survey III reference equations at Visit 1.<sup>2,3</sup>
8. Dyspnea: A score of  $\geq 2$  on the Modified Medical Research Council Dyspnea Scale at Screening (Visit 2).

#### Exclusion criteria

1. Pregnancy: Women who were pregnant or lactating or are planning on becoming pregnant during the study.
2. Asthma: A current diagnosis of asthma.
3. Other respiratory disorders: Known  $\alpha$ -1 antitrypsin deficiency, active lung infections (eg, tuberculosis) and lung cancer were absolute exclusionary conditions. A subject who had any other significant respiratory conditions in addition to COPD were excluded. Eg, clinically significant, bronchiectasis, pulmonary hypertension, sarcoidosis, or interstitial lung disease.
4. Other diseases/abnormalities: Subjects with historical or current evidence of clinically significant cardiovascular, neurological, psychiatric, renal, hepatic, immunological, endocrine (including uncontrolled diabetes or thyroid disease) or hematological abnormalities that were uncontrolled and/or a previous history of cancer in remission for  $< 5$  years prior to Visit 1 (localized carcinoma of the skin that has been resected for cure

was not exclusionary). Significant was defined as any disease that, in the opinion of the investigator, would put the safety of the subject at risk through participation, or which would have affected efficacy or safety analysis if the disease/condition exacerbated during the study.

5. Chest X-ray: A chest X-ray or computed tomography (CT) scan that revealed evidence of clinically significant abnormalities not believed to be due to the presence of COPD. A chest X-ray must have been taken at Visit 1 if a chest X-ray or CT scan was not available within 6 months prior to Visit 1.
6. Contraindications: history of allergy or hypersensitivity to any anticholinergic/muscarinic receptor antagonist,  $\beta_2$ -agonist, lactose/milk protein or magnesium stearate or a medical condition such as of narrow-angle glaucoma, prostatic hypertrophy, or bladder neck obstruction that contraindicated study participation or use of an inhaled anticholinergic.
7. Hospitalization: Hospitalization for COPD or pneumonia within 12 weeks prior to Visit 1.
8. Lung resection: Subjects with lung volume reduction surgery within the 12 months prior to Visit 1.
9. 12-lead ECG: An abnormal and significant ECG finding from the 12-lead ECG conducted at Visit 1, including the presence of a paced rhythm on a 12-lead ECG which caused the underlying rhythm and ECG to be obscured. Investigators were provided with ECG reviews conducted by a centralized independent cardiologist to assist in evaluation of subject eligibility.
10. Screening labs: Significantly abnormal finding from clinical chemistry and hematology tests at Visit 1.
11. Medication prior to spirometry: Unable to withhold albuterol for the 4-hour period required prior to spirometry testing at each study visit.
12. Medications prior to Screening: Use of the medications according to the defined time intervals prior to Visit 1 as shown in Table S1.

## Health-related quality of life assessments

### St George's Respiratory Questionnaire (SGRQ)

The SGRQ<sup>4</sup> is a disease-specific questionnaire designed to measure the impact of respiratory disease and its treatment on a subject's health related quality of life. As well as producing an overall summary score, it is also possible to calculate scores for the individual domains of symptoms, activity, and impacts. It has been widely used in studies of COPD and has been translated and validated for use in most major languages. Research has demonstrated that it is sensitive to change and interpretation of the results has been

**Table S1** Medications prior to screening: use of the medications according to the defined time intervals prior to visit 1

Medication	Time interval prior to visit 1
Depot corticosteroids	12 weeks
Systemic, oral, parenteral (intra-articular) corticosteroids	4 weeks
Antibiotics (for lower respiratory tract infection)	4 weeks
ICS/LABA combination products if ICS/LABA therapy is discontinued completely	30 days
Use of ICS at a dose > 1,000 mcg/day of fluticasone propionate or equivalent <sup>a</sup>	30 days
Initiation or discontinuation of ICS use <sup>a</sup>	30 days
PDE4 inhibitors (roflumilast)	14 days
Long-acting anticholinergics (eg, tiotropium)	7 days
Theophyllines <sup>b</sup>	12 hours (stable dose of theophylline alone allowed during the study but must be withheld 12 hours prior to each study visit)
Oral leukotriene inhibitors (zafirlukast, montelukast, zileuton)	48 hours
Oral beta <sub>2</sub> -agonists	
Long-acting	48 hours
Short-acting	12 hours
Inhaled long-acting beta <sub>2</sub> -agonists (LABA, eg, salmeterol, formoterol, indacaterol)	48 hours
LABA/ICS combination products only if discontinuing LABA therapy and switching to ICS monotherapy <sup>c</sup>	48 hours for LABA component
Inhaled sodium cromoglycate or nedocromil sodium	24 hours
Inhaled short-acting beta <sub>2</sub> -agonists <sup>d</sup>	4 hours
Inhaled short-acting anticholinergics <sup>b</sup> (eg, ipratropium bromide)	4 hours (stable dose of ipratropium alone allowed during the study, provided that the subject is on a stable dose regimen from screening [Visit 1 and remains so throughout the study] but must be withheld 4 hours prior to each study visit)
Inhaled short-acting anticholinergic/short-acting beta <sub>2</sub> -agonist combination products	4 hours
Any other investigational drug	30 days or 5 half-lives, whichever is longer

**Notes:** <sup>a</sup>Use of a consistent dose of ICS was permitted provided the dose did not exceed 1,000 mcg of fluticasone propionate or equivalent; ICS use was not to be initiated or discontinued within 30 days prior to Visit 1. <sup>b</sup>Ipratropium bromide or theophylline was permitted, provided that the subject was on a stable dose from Screening (Visit 1) and remained on the stable dose throughout the study; however, ipratropium bromide must have been withheld for 4 hours; theophylline must have been withheld for 12 hours prior to and during each clinic visit. <sup>c</sup>Dose of ICS must have been consistent with that contained in the ICS/LABA combination product. <sup>d</sup>Use of study provided salbutamol was permitted during the study, except during the 4-hour period prior to spirometry testing.

**Abbreviations:** ICS, inhaled corticosteroid; LABA, long-acting  $\beta_2$ -agonist.

enhanced by determination of the score change necessary to achieve a clinically-meaningful improvement in quality of life.<sup>5</sup>

The SGRQ contains 76 items grouped into three domains (symptoms, activity, and impacts). The domain score is calculated as the sum of the weighted scores for the non-missing items within each domain, divided by the maximum possible score for those non-missing items and multiplied by 100. The SGRQ total score is calculated as the sum of the weighted scores from all 76 items, divided by the maximum possible score for the SGRQ, multiplied by 100. A lower SGRQ score indicates better health status. The minimum clinically-important difference for the SGRQ is a -4-unit difference.<sup>5</sup> The SGRQ was self-completed by subjects prior to spirometry at Visits 2, 4, 6, and 8.

### COPD assessment test (CAT)

The CAT is a subject-completed instrument designed to provide a simple and reliable measure of health status in COPD. The CAT was designed to measure overall COPD-related

health status for the assessment and long-term follow-up of individual subjects. The instrument consists of 8 items, each formatted as a semantic 6-point differential scale.<sup>6</sup>

The CAT was completed independently and without supervision by all subjects at Visits 2, 4, 6, and 8. The CAT was administered before any other study procedures were performed (including concurrent medication assessment or AE assessment, etc).

### COPD-related healthcare resource utilization assessment

All unscheduled COPD-related visits to a physician's office, urgent care facility, or emergency department, and COPD-related hospitalizations were recorded on the COPD-related healthcare resource use assessment worksheet within the subject's diary, by the subject. At Visits 2 through 9 or at the Early Withdrawal Visit, the resource utilization worksheet completed by the subject to record all health care contacts since the last visit, was reviewed by the investigator (or designee). The investigator (or designee) asked the subject

**Table S2** Analysis of SGRQ total score (ITT population)

	Placebo N=193	UMEC/VI 62.5/25 µg N=194	UMEC/VI 125/25 µg N=193
<b>Day 28</b>			
N (1)*	182	182	183
N (2)**	182	175	177
LS mean (SE)	38.19 (0.875)	35.83 (0.884)	34.18 (0.881)
LS mean change (SE)	-3.22 (0.875)	-5.59 (0.884)	-7.23 (0.881)
Column vs placebo difference (95% CI)		-2.36 (-4.81, 0.08)	-4.01 (-6.45, -1.57)
P-value		0.058	0.001
<b>Day 84</b>			
N (1)	182	182	183
N (2)	166	171	173
LS mean (SE)	36.62 (0.972)	33.30 (0.961)	31.72 (0.957)
LS mean change (SE)	-4.80 (0.972)	-8.11 (0.961)	-9.69 (0.957)
Column vs placebo difference (95% CI)		-3.32 (-6.00, -0.63)	-4.89 (-7.58, -2.21)
P-value		0.016	<0.001
<b>Day 168</b>			
N (1)	182	182	183
N (2)	158	157	163
LS mean (SE)	35.11 (1.035)	33.09 (1.035)	31.35 (1.022)
LS mean change (SE)	-6.30 (1.035)	-8.32 (1.035)	-10.06 (1.022)
Column vs placebo difference (95% CI)		-2.02 (-4.90, 0.86)	-3.76 (-6.62, -0.90)
P-value		0.168	0.010

**Notes:** Analysis performed using a repeated measures model with covariates of treatment, baseline (score prior to dosing on day 1), smoking status, country/region, day, day by baseline, and day by treatment interactions. \*N (1) represents number of subjects with analyzable data for one or more time points. \*\*N (2) represents number of subjects with analyzable data at the current time point.

**Abbreviations:** CI, confidence interval; ITT, intent-to-treat; LS, least squares; SE, standard error; SGRQ, St George's Respiratory Questionnaire; UMEC, umeclidinium; VI, vilanterol.

if any of the health care contacts recorded on the worksheets were due to COPD exacerbation. The investigator could refer to his/her records to verify or supplement information given by the subject if necessary. If any unscheduled health care contact was due to a COPD exacerbation, then the COPD exacerbation section of the electronic case report form was completed.

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