# Umeclidinium in patients with COPD: a randomised, placebo-controlled study

Roopa Trivedi, Nathalie Richard, Rashmi Mehta and Alison Church

**Affiliation:** Respiratory Medicines Development Center, GlaxoSmithKline, Research Triangle Park, NC, USA.

**Correspondence:** R. Trivedi, GlaxoSmithKline, 5 Moore Dr., Mailstop: 5.3317.1A, Research Triangle Park, 27709 NC, USA. E-mail: roopa.d.trivedi@gsk.com

ABSTRACT Efficacy and safety of umeclidinium administered in a dry power inhaler were evaluated in moderate-to-very-severe chronic obstructive pulmonary disease patients.

This was a randomised, placebo-controlled study assessing once-daily umeclidinium 62.5 and 125 μg over 12 weeks. The primary end-point was change from baseline in trough forced expiratory volume in 1 s ($FEV_1$) on day 85. Secondary end-points were 0–6-h weighted mean and serial forced expiratory volume in 1 s. Other end-points were transitional dyspnoea index, health outcomes (St George's Respiratory Questionnaire), pharmacokinetics and safety.

246 patients were enrolled; 168 completed the study. On day 85, umeclidinium 62.5 and 125 μg significantly improved least squares mean change from baseline in trough $FEV_1$ (127 and 152 mL, respectively; $p<0.001$) compared with placebo. On day 84, umeclidinium 62.5 and 125 μg significantly improved least squares mean change from baseline in 0–6-h weighted mean (166 and 191 mL, respectively; $p<0.001$) and serial $FEV_1$ at each time point ($p\leqslant0.003$). Significant improvement in least squares mean transitional dyspnoea index focal score (1.0 and 1.3 units, respectively; $p\leqslant0.05$) and change from baseline St George's Respiratory Questionnaire total score (-7.9 and -10.87 units, respectively; $p<0.001$) were noted compared with placebo at week 12. The incidence of adverse events was low and similar across treatments.

Umeclidinium 62.5 and 125 μg significantly improved lung function, dyspnoea and health status compared with placebo, and were well tolerated in chronic obstructive pulmonary disease patients over 12 weeks.

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## Introduction

Long-acting muscarinic agonists (LAMAs) are currently recommended as maintenance bronchodilator therapy for chronic obstructive pulmonary disease (COPD), as they allow less frequent dosing and provide improved efficacy compared with short-acting muscarinic antagonists [1]. Other LAMAs, including aclidinium bromide and tiotropium bromide, have shown improvements in lung function, dyspnoea measures and health outcomes, and were safe and well tolerated [2–5].

Umeclidinium bromide (UMEC; GSK573719) is a quinuclidine derivative in development as an inhaled LAMA for treatment of COPD. Statistically significant improvements in lung function were observed in patients with COPD in 7-day [6] (data on File, NCT01372410), 14-day [7] and 28-day [8] dose-ranging studies evaluating UMEC 15.6–1000 μg once daily and 15.6–250 μg twice daily. The overall incidence of adverse events (AEs) was generally similar to placebo at doses $\leqslant$125 μg once daily and increased at doses $\geqslant$250 μg once daily [7, 8].

The primary objective of this study was to compare the efficacy and safety of UMEC 62.5 and 125 μg once daily with placebo over 12 weeks in patients with moderate-to-very-severe COPD. The secondary objectives were to evaluate the effects of UMEC on health-related quality of life and pharmacokinetics.

## Methods

### Patients

Patients aged $\geqslant$40 years of age were included if they had a clinical history of COPD [9], were current or former (smoking-free $\geqslant$6 months) cigarette smokers with a smoking history of $\geqslant$10 pack-years, a post-salbutamol forced expiratory volume in 1 s ($FEV_1$)/forced vital capacity (FVC) ratio of $<$0.70 and a post-salbutamol $FEV_1$ of $<$70% predicted [10, 11], and a score of $\geqslant$2 on the modified Medical Research Council dyspnoea scale at visit 1.

Key exclusion criteria included current diagnosis of asthma or other clinically significant respiratory disorders other than COPD, any unstable, clinically significant disease, or hospitalisation for COPD or pneumonia within 12 weeks of screening. Patients were excluded if they used systemic, oral or parenteral corticosteroids within 6 weeks of screening or inhaled corticosteroids (ICSs) $>$1000 $\mu g \cdot day^{-1}$ of fluticasone propionate or equivalent within 30 days of screening. Patients receiving ICSs at baseline continued treatment at a stable dose during the run-in and treatment periods. All inhaled bronchodilators were discontinued prior to screening (long-acting $\beta_2$-agonists at least 48 h; tiotropium at least 14 days). Inhaled salbutamol was permitted as needed, but withheld for 4 h prior to and during study visits.

Withdrawal criteria included COPD exacerbation as defined by an acute worsening of symptoms of COPD requiring the use of any treatment beyond study drug or rescue salbutamol, a clinically important change in laboratory parameters including liver function, an abnormal and significant ECG finding, or a positive pregnancy test.

### Study design

This was a 12-week, randomised, double-blind, placebo-controlled, parallel-group study (protocol AC4115408, NCT01387230) conducted at 27 centres in the USA, Germany and Japan between July 16, 2011 and February 13, 2012. Written informed consent was obtained from each patient prior to study participation. The protocol was approved by the appropriate ethics committee or international review board, and the study was conducted in accordance with the Declaration of Helsinki 2008 [12] and ICH Good Clinical Practice guidelines [13].

Following screening and a 5–9-day run-in period to assess disease stability, patients were randomised 1:1:1 to receive UMEC 62.5 or 125 μg, or placebo once daily *via* identically appearing dry powder inhalers for 12 weeks. Treatment assignment was determined by a validated, computerised system (RandAll; GlaxoSmithKline, Slough, UK) and an automated, interactive telephone-based system (GlaxoSmithKline Registration and Medication Ordering System (RAMOS), GlaxoSmithKline, Harlow, UK). Patients and investigators were blinded to treatment assignment. Compliance was assessed by inhaler dose counter review between consecutive on-treatment clinic visits.

### Outcomes and assessments

The primary efficacy end-point was trough $FEV_1$ on day 85 (defined as the mean of $FEV_1$ values obtained 23 and 24 h post-dose on day 84). Secondary end-points included weighted mean (wm)$FEV_1$ 0–6 h post-dose on days 1, 28 and 84, and serial $FEV_1$ at 1, 3, 6, 23 and 24 h post-dose on days 1 and 84. Transitional dyspnoea index (TDI) focal score [14], proportion of responders based on TDI score

(improvement of $\geqslant$1 unit), trough FVC, wmFVC, serial FVC, time to onset (an increase of $\geqslant$100 mL above baseline in FEV1) and rescue salbutamol use (percentage of rescue-free days and mean number of puffs per day) were also examined. Health outcomes were assessed by the St George's Respiratory Questionnaire (SGRQ) [15]. Pharmacokinetic assessments included plasma UMEC concentrations and derived plasma pharmacokinetic parameters.

Safety was assessed by AEs and COPD exacerbations (defined as acute worsening of COPD symptoms requiring the use of any treatment beyond study drug or rescue salbutamol, including antibiotics, systemic corticosteroids, and/or emergency treatment or hospitalisation), clinical chemistry and haematology parameters, vital signs (systolic and diastolic blood pressure and heart rate), and 12-lead ECGs.

### Measurements

Spirometric assessments were conducted using standardised equipment (eResearch Technology, Inc., Hoechberg, Germany) that met the performance recommendations of the American Thoracic Society [16]. The largest FEV1 and FVC measurements obtained from three acceptable spirometry efforts were recorded. Trough spirometry for FEV1 and FVC (defined as the mean of FEV1 or FVC values obtained 23 and 24 h after the previous day's morning dose) was conducted on days 2, 14, 28, 56, 84 and 85.

erial spirometry was performed pre-dose and post-dose at 1, 3 and 6 h on days 1, 28 and 84. On day 1, measurements were obtained at 30 and 5 min pre-dose. On days 28 and 84, when both serial and trough spirometry were measured, the pre-dose serial measurements consisted of the trough measurements obtained at 23 and 24 h after the previous day's morning dose. Dyspnoea assessments were performed using interviewer-administered instruments by trained individuals with advanced knowledge or training concerning dyspnoea in respiratory disease. On day 1, the severity of dyspnoea at baseline was assessed using the baseline dyspnoea index. At subsequent visits (days 28, 56 and 84), the change from baseline was assessed using the TDI. Disease-specific health status was evaluated using the subject-completed SGRQ. A patient-completed diary card recorded medical problems experienced and any medications used to treat those problems and rescue salbutamol use (puffs per day) in the last 24 h for relief of COPD symptoms.

Plasma pharmacokinetic samples were collected pre-dose and 5 and 15 min post-dose on days 1, 28 and 84 and used to determine plasma pharmacokinetic parameters. Pharmacokinetic–pharmacodynamic assessment was conducted by visual inspection of the pharmacokinetic–pharmacodynamic relationship in a data plot followed by linear regression analysis for UMEC with individual maximum concentration ($C_{max}$) plotted on the *x*-axis and change from baseline in pulse rate on the y-axis.

### Statistical analysis

A sample size of 56 evaluable patients per treatment arm was estimated to provide at least 90% power to detect a difference from placebo of 130 mL in trough FEV1 for the UMEC treatment arms on day 85 with a two-sided 5% significance level, assuming an estimate of residual standard deviation of 210 mL.

The intent-to-treat (ITT) population (all randomised patients who received at least one dose of study medication) was the primary population for all analyses. The pharmacokinetic population comprised all patients in the ITT population who were randomised to treatment with UMEC and for whom a pharmacokinetic sample was obtained and analysed.

Trough FEV1 on day 85 was analysed with a mixed model repeated measures (MMRM) analysis, including covariates of baseline FEV1 (calculated from the values measured 30 and 5 min pre-dose on day 1), smoking status at screening, day, centre group, treatment, day-by-baseline interaction and day by treatment interaction. The model used all available trough FEV1 values recorded on days 2, 14, 28, 56, 84 and 85. The 0–6-h wmFEV1 was analysed in a similar manner, using all available values recorded for days 1, 28 and 84.

Serial FEV1 at 1, 3, 6, 23 and 24 h after dosing on day 1, and pre-dose (24 h after previous day's dose) and 1, 3, 6, 23 and 24 h after dosing on day 84 were analysed separately by visit using a MMRM analysis. Covariates included baseline FEV1, smoking status at screening, centre group, treatment, time, time by baseline interaction and time-by-treatment interaction, where time represents the nominal time points. Other continuous efficacy and global health outcome end-points were analysed in a similar manner as the primary end-point or using ANCOVA with baseline FEV1, smoking status at screening, centre group and treatment included as covariates. Categorical end-points, such as responders to TDI, were analysed separately at each visit using a logistic regression including covariates of baseline score, smoking status at screening, centre group and treatment.


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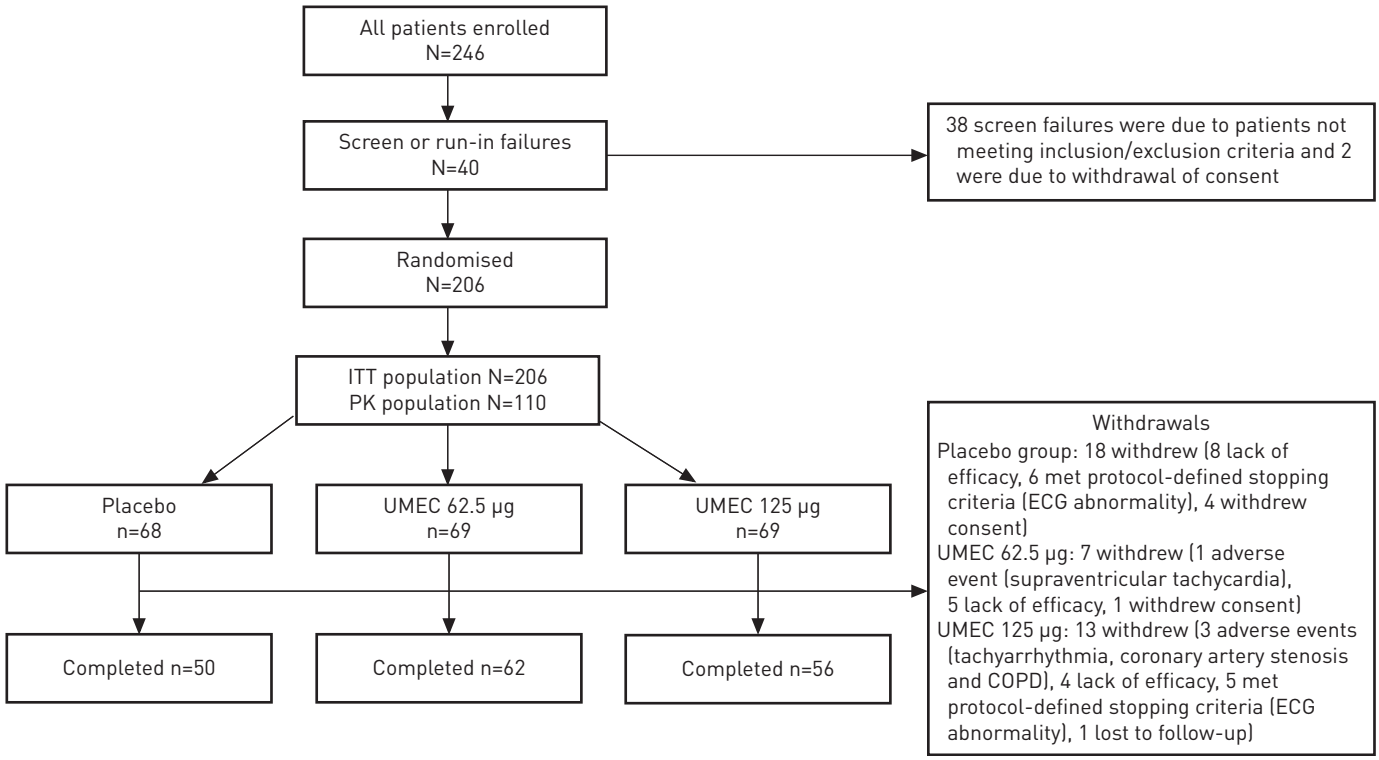


FIGURE 1 Patient disposition and Consolidated Standards of Reporting Trials flow chart. ITT: intent-to-treat; PK: pharmacokinetic; UMEC: umeclidinium bromide; COPD: chronic obstructive pulmonary disease.

## Results

### *Study population*

246 patients were enrolled, 206 were randomised (ITT population) and 168 completed the study (fig. 1). Withdrawal rates were 26% for placebo, 19% for UMEC 125 µg and 10% for UMEC 62.5 µg. The most common reason for withdrawal was lack of efficacy (12% placebo, 7% UMEC 125 µg and 6% UMEC 62.5 µg) (online supplementary table S1). Baseline characteristics are summarised in table 1. 49% of patients in the placebo and UMEC 125 µg groups were Global Initiative for Chronic Obstructive Lung Disease (GOLD) stage II, with 36% at this stage for the UMEC 62.5 µg treatment group. Similarly, 38% of patients in the placebo group, 36% in the UMEC 125 µg group and 43% in the UMEC 62.5 µg group were GOLD stage III. Overall, 24% of patients reported use of an inhaled corticosteroid at screening; similar usage was observed across treatment groups. 77% of patients reported use of a non-COPD medication at screening; the most commonly reported medication class was cardiovascular.

### *Efficacy*

#### *Lung function*

At day 85, statistically significant ($p<0.001$) improvements in least squares mean (LSM) change from baseline in trough $FEV_1$ were observed for UMEC 62.5 µg (127 mL, 95% CI 52–202 mL) and 125 µg (152 mL, 95% CI 76–229 mL) compared with placebo. Statistically significant improvements in LSM change from baseline in trough $FEV_1$ were observed for all time points measured from day 2–84 for UMEC 62.5 µg (95% CI 102–145 mL) and 125 µg (95% CI 130–205 mL) compared with placebo (fig. 2a and online supplementary table S2).

Statistically significant ($p<0.001$) improvements were observed in LSM change from baseline (95% CI) in 0–6-h $wmFEV_1$ on day 1 (125 (83–166) mL; 147 (105–188) mL), day 28 (165 (105–224) mL; 196 (135–256) mL) and day 84 (166 (94–239) mL; 191 (117–265) mL) for UMEC 62.5 and 125 µg, respectively, compared with placebo (fig. 2b). Improvements were also observed in LSM change from baseline in 24-h serial $FEV_1$ for each dose of UMEC compared with placebo at all post-dose time points measured on days 1 and 84 ($p\leqslant0.003$) (fig. 3). Statistically significant increases in LSM change from baseline were observed for UMEC 62.5 and 125 µg compared with placebo in FVC measurements (see supplementary tables S3 and S4 and supplementary fig. S1). Most patients receiving UMEC 62.5 µg (59%) and 125 µg (64%) had an onset

TABLE 1 Patient demographics

| Demographic characteristic | Placebo | UMEC 62.5 μg | UMEC 125 μg | Total |
|---|---|---|---|---|
| **Subjects** | 68 | 69 | 69 | 206 |
| **Age years** | 62.5±8.72 | 62.3±9.50 | 64.6±7.96 | 63.1±8.77 |
| **Sex** | | | | |
| Female | 26 (38) | 25 (36) | 27 (39) | 78 (38) |
| Male | 42 (62) | 44 (64) | 42 (61) | 128 (62) |
| **Ethnicity** | | | | |
| African American/African heritage | 1 (1) | 1 (1) | 2 (3) | 4 (2) |
| Asian | 8 (12) | 7 (10) | 6 (9) | 21 (10) |
| Japanese/East Asian heritage/Southeast Asian heritage | 8 (12) | 7 (10) | 6 (9) | 21 (10) |
| White | 59 (87) | 61 (88) | 61 (88) | 181 (88) |
| **Height cm** | 170.3±8.34 | 170.5±9.44 | 169.3±8.92 | 170.0±8.89 |
| **Weight kg** | 81.53±19.461 | 80.70±24.272 | 73.12±15.381 | 78.44±20.300 |
| **BMI kg·m$^{-2}$** | 27.96±5.509 | 27.58±7.414 | 25.45±4.688 | 26.99±6.055 |
| **Current smokers** | 36 (53) | 37 (54) | 39 (57) | 112 (54) |
| **Smoking pack-year history** | 52.3±30.2 | 45.2±21.2 | 47.5±18.6 | 48.3±23.9 |
| **Pre-bronchodilator FEV$_1$ mL** | 1247±429.9 | 1303±605.9 | 1252±435.7 | 1267±495.1 |
| **Post-salbutamol FEV$_1$ mL** | 1388±454.7 | 1366±595.7 | 1356±454.4 | 1370±504.0 |
| **Post-salbutamol FEV$_1$/FVC** | 46.021±10.6635 | 47.971±11.4884 | 48.377±10.5899 | 47.463±10.9179 |
| **Post-salbutamol % pred FEV$_1$** | 47.0±13.05 | 44.5±13.99 | 47.9±14.42 | 46.5±13.84 |
| **GOLD stage** | | | | |
| I[#] | 0 | 0 | 0 | 0 |
| II[¶] | 33 (49) | 25 (36) | 34 (49) | 92 (45) |
| III[+] | 26 (38) | 30 (43) | 25 (36) | 81 (39) |
| IV[§] | 9 (13) | 14 (20) | 10 (14) | 33 (16) |

Data are presented as n, mean±SD or n (%). UMEC: umeclidinium bromide; BMI: body mass index; FEV$_1$: forced expiratory volume in 1 s; FVC: forced vital capacity; % pred: % predicted; GOLD: Global Initiative for Obstructive Lung Disease. [#]: FEV$_1$ ⩾80% pred; [¶]: FEV$_1$ ⩾50 to <80% pred; [+]: FEV$_1$ ⩾30 to <50% pred; [§]: FEV$_1$ <30% pred.

(increase of ⩾100 mL above baseline in FEV$_1$) at 1 h (earliest scheduled time point) post-dose on day 1; 66% of patients receiving placebo did not reach an increase of ⩾100 mL from baseline any time 0–6 h post-dose.

### *Dyspnoea and rescue medication use*

The UMEC 62.5 and 125 μg treatment groups exhibited an LSM TDI focal score of 0.7 and 1.0 units, respectively, which is approximate to the clinically meaningful improvement 1 unit [17], whereas the placebo group had an LSM TDI focal score of -0.3, reflecting a worsening compared to baseline. Patients receiving UMEC demonstrated significant improvements in LSM TDI focal score compared with placebo at all time points (fig. 4). On day 84, UMEC 62.5 and 125 μg demonstrated statistically significant improvements in LSM TDI focal score compared with placebo (1.0 (95% CI 0.0–2.0), p=0.05 for 62.5 μg and 1.3 (95% CI 0.3–2.3), p<0.05 for 125 μg), which met the minimal clinically important difference (MCID) for the TDI [17]. Compared with placebo on day 84, patients receiving either dose of UMEC had statistically significantly higher odds of being classified as a responder with a clinically meaningful improvement in TDI (⩾1 unit) [17] than a nonresponder: UMEC 62.5 μg odds ratio 3.4 (95% CI 1.3–8.4) (p=0.009) and 125 μg odds ratio 3.4 (95% CI 1.4–8.6) (p=0.009). See supplementary table S5 for proportion of responders according to TDI focal score.

The differences in rescue-treatment use from placebo were statistically significant for UMEC 62.5 μg (mean -0.7 puffs per day (95% CI -1.3– -0.1), p=0.025), but not 125 μg (mean -0.6 puffs per day (95% CI -1.2–0.0), p=0.069). The percentage of rescue-free days over 12 weeks increased from baseline for UMEC 62.5 μg (9.0%) and 125 μg (8.3%) but decreased with placebo (-4.2%).

### *Health outcomes*

On day 84, the LSM change from baseline in SGRQ total score was -6.12 (UMEC 125 μg), -3.14 (UMEC 62.5 μg) and +4.75 (placebo). Statistically significant treatment differences (p<0.001) were observed for both doses (62.5 μg: -7.90 (95% CI -12.20– -3.60); 125 μg, -10.87 (95% CI -15.25– -6.49)) compared with


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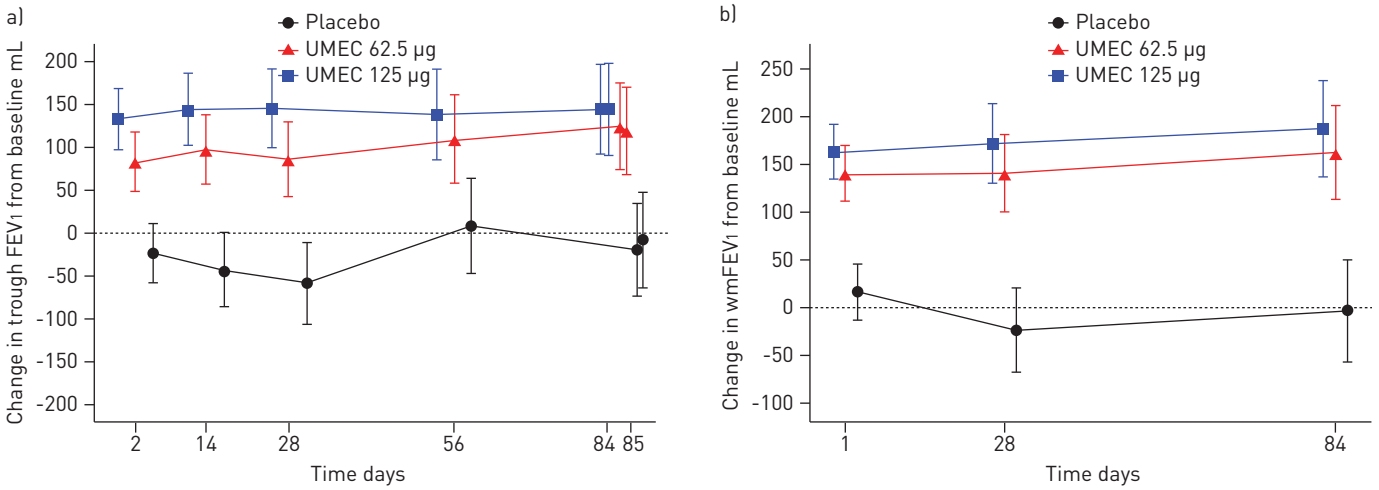


FIGURE 2 Change from baseline in a) trough forced expiratory volume in 1 s ($FEV_1$) and b) 0–6-h weighted mean $FEV_1$ (wm$FEV_1$) (intent-to-treat population). Data are presented as least squares means with 95% confidence intervals. UMEC: umeclidinium bromide.

placebo on day 84 (fig. 5). Patients receiving 62.5 µg (OR 2.44, 95% CI 1.08–5.50; p=0.032) or 125 µg (OR 3.20, 95% CI 1.40–7.34; p=0.006) had statistically significantly higher odds of being a SGRQ responder (⩾4-unit reduction) [18] *versus* a nonresponder compared with placebo.

### *Pharmacokinetics and pharmacodynamics*

UMEC absorption was rapid, with $C_{max}$ values ~5–15 min post-dose on all study days. Accumulation ratios for day 1–28 ranged from 1.4–1.9; day 1 and day 84 ranged from 1.6–1.8 with overlapping 90% confidence intervals. No further accumulation occurred from day 28 to 84 for either dose. Evaluation of individual steady-state $C_{max}$ and change from baseline in pulse rate on day 84 showed no obvious trends for either UMEC dose, and changes from baseline were similar to placebo (fig. 6).

### *Safety*

#### *On-treatment AEs*

Overall incidence of AEs was similar across treatment groups (UMEC 62.5 µg, 39%; UMEC 125 µg, 41%; and placebo, 35%). The most frequent AEs (⩾3% of patients) are listed in table 2. Drug-related AEs included dry throat and dyspnoea (62.5 µg), cough (125 µg) and dysphonia (placebo); no drug-related AE was reported by more than one patient (1%) in any treatment group. Four patients reported an AE that was considered to be related to anticholinergic effects: dry mouth (one patient on UMEC 125 µg), and

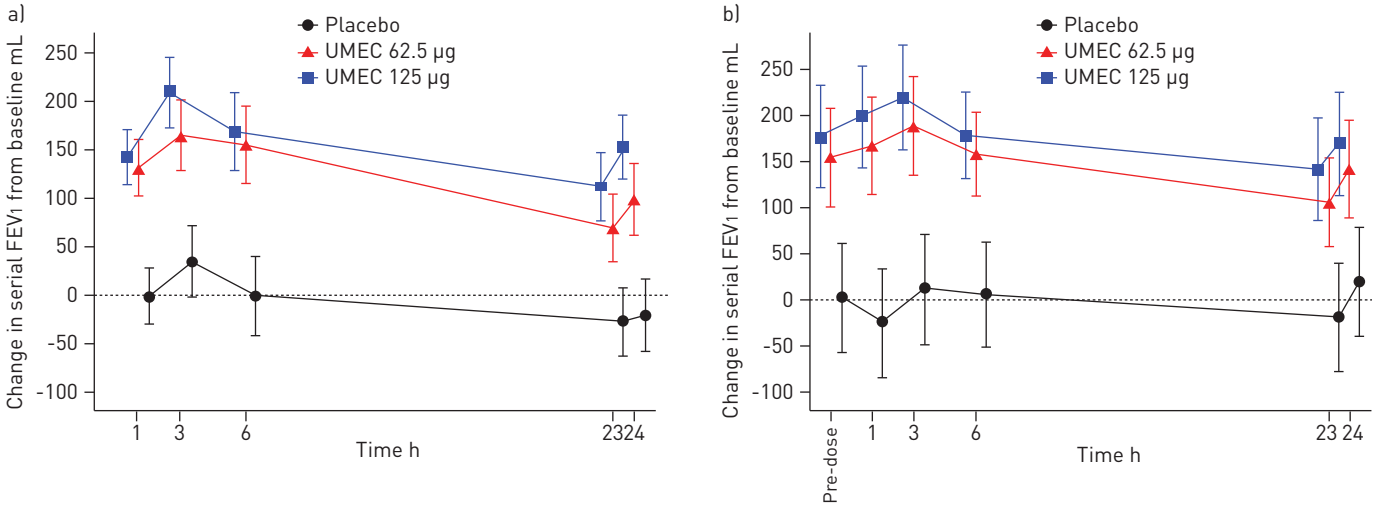


FIGURE 3 Change from baseline in serial forced expiratory volume in 1 s ($FEV_1$) over time at a) day 1 and b) day 84 (intent-to-treat population). Data are presented as least squares means with 95% confidence intervals. UMEC: umeclidinium bromide.

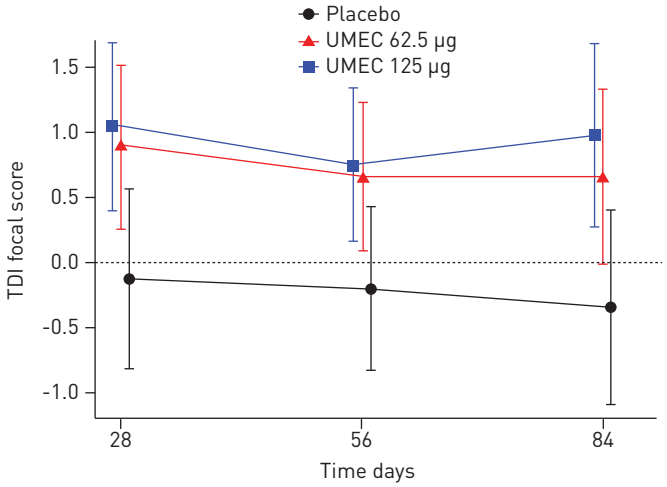


FIGURE 4 Transitional dyspnoea index (TDI) focal score (intent-to-treat population). Data are presented as least squares means with 95% confidence intervals. UMEC: umeclidinium bromide.

dysphagia, visual hallucination and pyrexia (one patient each, placebo). Seven patients reported a cardiovascular AE: one AE of atrial fibrillation, tachyarrhythmia, coronary artery stenosis and hypertension (one patient each, all on UMEC 125 µg); one AE of supraventricular tachycardia and ventricular extrasystoles (one patient each, both on UMEC 62.5 µg) and atrioventricular block first degree (one patient on placebo).

Serious AEs occurred in four patients; none were considered drug-related. Two of these patients (UMEC 125 mg) reported serious AEs that were severe in intensity and led to study withdrawal (coronary artery stenosis and COPD). The other two patients reported a lung neoplasm (one patient on UMEC 62.5 µg) that did not resolve and noncardiac chest pain (one patient on placebo), which was severe in intensity and led to dose interruption and delay of treatment. 16 COPD exacerbations occurred (in five patients on UMEC 62.5 µg, four patients on UMEC 125 µg and seven patients on placebo) during treatment.

### *Vital signs and clinical laboratories*

Overall, there was little change in systolic or diastolic blood pressures or pulse rate over the treatment period, and mean changes from baseline were small and similar across treatments. No notable treatment-related changes in vital-sign assessments were observed in UMEC groups and the placebo group. Mean absolute values for all clinical chemistry and haematology parameters were similar at baseline, and on days 28 and 84. No clinically meaningful change from baseline in any clinical chemistry or haematology parameters occurred.

### *ECG findings*

Mean observed changes in corrected QT (QTc(F)) were small, not considered clinically significant and similar across treatment groups at all time points. There was no consistent pattern of increase in QTc(F) with UMEC.

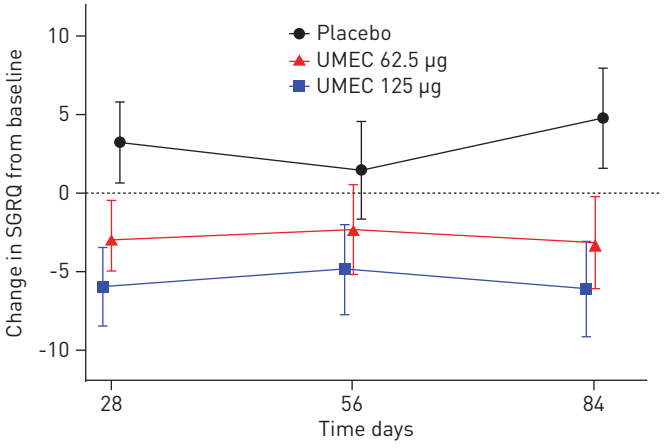


FIGURE 5 Change from baseline in St George's Respiratory Questionnaire (SGRQ) total score (intent-to-treat population). Data are presented as least squares means with 95% confidence intervals. UMEC: umeclidinium bromide.


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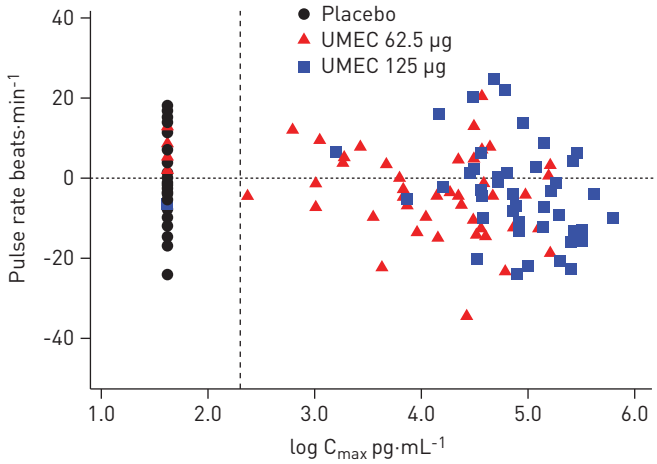


FIGURE 6 Individual change from baseline in maximum pulse rate (beats·min$^{-1}$) *versus* umeclidinium bromide (UMEC) maximum concentration ($C_{max}$) at day 84 (intent-to-treat population).

## Discussion

This placebo-controlled study of UMEC 62.5 and 125 µg once daily demonstrated clinically and statistically significant improvements in lung function compared with placebo in patients with moderate-to-very-severe COPD over 12 weeks of treatment. Improvements in change from baseline in trough FEV1 compared with placebo were demonstrated, and improvements in 0–6 h wmFEV1, serial FEV1 measurements over 24 h and FVC further supported the primary end-point. Lung function improved on day 1 in patients receiving UMEC and improvements were sustained over the treatment period. Despite a greater percentage of GOLD stage III patients in the UMEC 62.5 µg group compared with the other treatment groups, consistent improvements in trough FEV1 were noted for UMEC 62.5 µg compared with placebo. Overall, improvements in lung-function assessments over placebo were numerically greater with UMEC 125 µg compared with 62.5 µg.

The observed FEV1 improvements in the current study are consistent with smaller UMEC studies. A 7-day crossover study showed statistically significant improvements for once-daily doses in trough FEV1 (UMEC 62.5 µg, 124 mL; 125 µg, 183 mL; $p<0.001$) and serial FEV1 over 24 h compared with placebo (data on file at www.ClinicalTrials.gov identifier number NCT01372410). A 28-day study also reported significant improvements for UMEC 125 µg once daily in trough FEV1 (159 mL; $p<0.001$), 0–6-h wmFEV1 (211 mL; $p<0.001$), serial FEV1 over 24 h and FVC measurements compared with placebo [8]. A further 14-day crossover study also demonstrated significant improvements for once-daily doses in trough FEV1 (UMEC 62.5 µg, 128 mL; 125 µg, 147 mL; $p<0.001$) and 0–24-h wmFEV1 (UMEC 62.5 µg, 143 mL; 125 µg, 136 mL; $p<0.001$) compared with placebo [7]. Other placebo-controlled, parallel-group studies of both healthy volunteers and patients with COPD have shown similar results with significant improvements in FEV1 parameters compared with placebo [19] (data on file at at www.ClinicalTrials.gov identifier numbers NCT00732472 and NCT00515502).

TABLE 2 Overall adverse events occurring in ⩾3% of patients (intent-to-treat population)

| | Placebo | UMEC 62.5 µg | UMEC 125 µg |
|---|---|---|---|
| **Subjects** | 68 | 69 | 69 |
| **Headache** | 7 (10) | 5 (7) | 10 (14) |
| **Nasopharyngitis** | 7 (10) | 8 (12) | 7 (10) |
| **Back pain** | 4 (6) | 2 (3) | 0 |
| **Cough** | 1 (1) | 0 | 5 (7) |
| **Upper respiratory tract infection** | 0 | 2 (3) | 2 (3) |
| **Oropharyngeal pain** | 1 (1) | 0 | 2 (3) |
| **Bursitis** | 0 | 2 (3) | 0 |
| **COPD#** | 0 | 0 | 2 (3) |

Data are presented as n or n (%). UMEC: umeclidinium bromide; COPD: chronic obstructive pulmonary disease. #: COPD was the disease under study and, therefore, signs and symptoms of COPD were not to be recorded as an AE unless they met the definition of a serious AE as specified in the protocol.

Results from our study are similar to those from studies of tiotropium, another LAMA used to treat COPD. The 4-year Understanding Potential Long-Term Impacts on Function with Tiotropium (UPLIFT) study of tiotropium 18 μg once daily demonstrated improvements in trough $FEV_1$ of 87–103 mL compared with placebo [3]. Similarly, 6-month [4] and 48-week [5] placebo-controlled studies of the same tiotropium once daily dose demonstrated improvements in trough $FEV_1$ of 107–120 mL.

In addition to spirometric measurements, the effects of therapy on health status and TDI are also important and robust clinical outcomes in COPD research [20]. On day 84, both doses demonstrated clinically meaningful reductions in dyspnoea as measured by the TDI focal score compared with placebo; UMEC 125 μg also demonstrated a clinically meaningful reduction compared with baseline and UMEC 62.5 μg trended towards a clinically meaningful reduction. More than twice the proportion of patients receiving UMEC 62.5 μg or 125 μg achieved a TDI focal score of $\geqslant 1$ unit compared with placebo on day 84. Interestingly, the placebo group demonstrated a slight worsening in dyspnoea as assessed by TDI focal score. Though the majority of placebo patients had a TDI focal score of 0 (no change) on day 84, the mean score may have been impacted by those patients reporting a worsening, such as the two patients who reported a score of -9 at day 84. Despite the results in the placebo group, mean TDI scores support an improvement in dyspnoea in the UMEC group. Additionally, patients receiving UMEC also demonstrated a reduction in rescue salbutamol use compared with placebo.

Improvements in lung function and reductions in dyspnoea were further supported by clinically meaningful SGRQ reductions (exceeding MCID of -4 units) in both doses compared with placebo on day 84; UMEC 125 μg also demonstrated a clinically meaningful reduction from baseline with UMEC 62.5 μg trending towards a clinically meaningful reduction. It should be noted that patients in the placebo group reported worsening of the SGRQ score (LSM change from baseline of 4.75 units), making the treatment differences from placebo particularly high. Worsening of SGRQ scores with placebo treatment has been previously observed with other bronchodilators [21, 22].

UMEC 62.5 and 125 μg were well tolerated across 12 weeks of treatment with no notable differences in safety findings between doses. The overall incidence of AEs was similar across all treatment groups. Cardiovascular effects were closely evaluated due to potential effects on cardiovascular function through cholinergic blockade. All cardiovascular AEs were unrelated to the study drug and were not serious. Previous UMEC studies did not report a treatment-related effect on cardiovascular-related AEs and the present findings confirm and extend the tolerability with longer-term treatment [6–8].

Withdrawal rates for the placebo group of patients were higher than reported in other 12-week studies of bronchodilators for COPD, although the withdrawal rates for patients on UMEC were similar to those reported in studies by KERWIN and co-workers [23, 24]. The primary reason for withdrawal from any treatment group was lack of efficacy, with COPD exacerbation as the most common cause. A dose-related trend towards fewer discontinuations due to lack of efficacy and COPD exacerbations was noted with UMEC compared with placebo. No clear reason for the rate of COPD exacerbations in placebo patients was identified. The majority of patients in all three treatment groups did not have a history of exacerbations in the last year and no imbalances were noted. As in other studies [21, 25, 26] of bronchodilators for the treatment of COPD, patients were allowed to continue to use ICSs at a stable dose during the duration of the study and patients with an acute exacerbation requiring hospitalisation within 12 weeks of the study were excluded [23, 24]. In addition, imbalances due to ECG-defining criteria for withdrawal were noted: six (9%) patients in the placebo group, none in the UMEC 62.5 μg group and five (7%) in the UMEC 125 μg group. No pattern in the ECG criteria was noted in these patients taking UMEC compared with placebo; the majority of these ECG stopping criteria were met before they were dosed with study medication on day 1.

In conclusion, treatment with inhaled UMEC 62.5 and 125 μg once daily was well tolerated and provided significant improvement in lung function, dyspnoea and health status over 12 weeks of treatment. This study demonstrated that both doses of UMEC provide meaningful value as a once daily COPD maintenance therapy.

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## References

1 Global Initiative for Chronic Obstructive Lung Disease. Global strategy for the diagnosis, management and prevention of chronic obstructive pulmonary disease. www.goldcopd.org/uploads/users/files/GOLD_Report_2011_Feb21.pdf. Date last updated: 2011. Date last accessed: June 4, 2013.


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2 Jones PW, Rennard SI, Agusti A, *et al.* Efficacy and safety of once-daily aclidinium in chronic obstructive pulmonary disease. *Respir Res* 2011; 12: 55.
3 Tashkin DP, Celli B, Senn S, *et al.* A 4-year trial of tiotropium in chronic obstructive pulmonary disease. *N Engl J Med* 2008; 359: 1543–1554.
4 Brusasco V, Hodder R, Miravitlles M, *et al.* Health outcomes following treatment for six months with once daily tiotropium compared with twice daily salmeterol in patients with COPD. *Thorax* 2003; 58: 399–404.
5 Chan CK, Maltais F, Sigouin C, *et al.* A randomized controlled trial to assess the efficacy of tiotropium in Canadian patients with chronic obstructive pulmonary disease. *Can Respir J* 2007; 14: 465–472.
6 Church A, Beerahee M, Brooks J, *et al.* Umeclidinium (GSK573719) dose response and dosing interval in COPD. *Eur Respir J* 2012; 40: Suppl. 56, 377.
7 Donohue JF, Anzueto A, Brooks J, *et al.* A randomized, double-blind, dose-ranging study of the novel LAMA GSK573719 in patients with COPD. *Respir Med* 2012; 106: 970–979.
8 Decramer M, Maltais F, Feldman G, *et al.* Bronchodilation of umeclidinium, a new long-acting muscarinic antagonist, in COPD patients. *Respir Physiol Neurobiol* 2013; 185: 393–399.
9 Celli BR, MacNee W, ATS/ERS Task Force. Standards for the diagnosis and treatment of patients with COPD: a summary of the ATS/ERS position paper. *Eur Respir J* 2004; 23: 932–946.
10 Hankinson JL, Odencrantz JR, Fedan KB. Spirometric reference values from a sample of the general U.S. population. *Am J Respir Crit Care Med* 1999; 159: 179–187.
11 Hankinson JL, Kawut SM, Shahar E, *et al.* Performance of American Thoracic Society-recommended spirometry reference values in a multiethnic sample of adults: the multi-ethnic study of atherosclerosis (MESA) lung study. *Chest* 2010; 137: 138–145.
12 WMA Declaration of Helsinki – Ethical Principles for Medical Research Involving Human Subjects. Adopted by the 18th WMA General Assembly, Helsinki, Finland, June 1964 and amended (latest) by the 59th WMA General Assembly, Seoul, Korea, October 2008. www.wma.net/en/30publications/10policies/b3/index.html Date last updated: October 2008. Date last accessed: June 4, 2013.
13 International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH). ICH Good Clinical Practice guidelines. www.ich.org/products/guidelines/efficacy/efficacy-single/article/good-clinical-practice.html Date last accessed: November 6, 2013.
14 Mahler DA, Weinberg DH, Wells CK, *et al.* The measurement of dyspnea. Contents, interobserver agreement, and physiologic correlates of two new clinical indexes. *Chest* 1984; 85: 751–758.
15 Jones PW, Quirk FH, Baveystock CM, *et al.* A self-complete measure of health status for chronic airflow limitation. The St. George's Respiratory Questionnaire. *Am Rev Respir Dis* 1992; 145: 1321–1327.
16 Miller MR, Hankinson J, Brusasco V, *et al.* Standardisation for spirometry. *Eur Respir J* 2005; 26: 319–338.
17 Mahler DA, Witek TJ Jr. The MCID of the transition dyspnea index is a total score of one unit. *COPD* 2005; 2: 99–103.
18 Jones PW. St George's Respiratory Questionnaire: MCID. *COPD* 2005; 2: 75–79.
19 Cahn A, Lovick R, Newlands A, *et al.* Safety, tolerability, pharmacodynamics (PD) and pharmacokinetics (PK) of GSK573719 in healthy subjects. *Eur Respir J* 2011; 38: Suppl. 55, 723.
20 Cazzola M, MacNee W, Martinez FJ, *et al.* Outcomes for COPD pharmacological trials: from lung function to biomarkers. *Eur Respir J* 2008; 31: 416–469.
21 Donohue JF, van Noord JA, Bateman ED, *et al.* 6-month, placebo-controlled study comparing lung function and health status changes in COPD patients treated with tiotropium or salmeterol. *Chest* 2002; 122: 47–55.
22 Burge PS, Calverley PM, Jones PW, *et al.* Randomised, double blind, placebo controlled study of fluticasone propionate in patients with moderate to severe chronic obstructive pulmonary disease: the ISOLDE trial. *BMJ* 2000; 320: 1297–1303.
23 Kerwin EM, D'Urzo AD, Gelb AF, *et al.* ACCORD I study investigators. Efficacy and safety of a 12-week treatment with twice-daily aclidinium bromide in COPD patients (ACCORD COPD I). *COPD* 2012; 9: 90–101.
24 Kerwin EM, Gotfried MH, Lawrence D, *et al.* Efficacy and tolerability of indacaterol 75 μg once daily in patients aged $\geqslant$40 years with chronic obstructive pulmonary disease: results from 2 double-blind, placebo-controlled 12-week studies. *Clin Ther* 2011; 33: 1974–1984.
25 Vincken W, van Noord JA, Greefhorst AP, *et al.* Improved health outcomes in patients with COPD during 1 yr's treatment with tiotropium. *Eur Respir J* 2002; 19: 209–216.
26 Casaburi R, Mahler DA, Jones PW, *et al.* A long-term evaluation of once-daily inhaled tiotropium in chronic obstructive pulmonary disease. *Eur Respir J* 2002; 19: 217–224.