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

Roopa Trivedi, Nathalie Richard, Rashmi Mehta, Alison Church

Respiratory Medicines Development Center, GlaxoSmithKline, Research Triangle Park, NC, USA

Correspondence

Roopa Trivedi

GlaxoSmithKline

5 Moore Dr.

Mailstop: 5.3317.1A

Research Triangle Park

NC, USA 27709

Telephone: 919-483-9809

Fax: 919-483-4300

E-mail: roopa.d.trivedi@gsk.com

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ABSTRACT

Efficacy and safety of umeclidinium (UMEC) administered in a dry power inhaler were evaluated in moderate-to-very-severe COPD patients.

Randomised, placebo-controlled study assessing once-daily UMEC 62.5 and 125 mcg over 12 weeks. Primary end-point: change from baseline in trough FEV_1 on day 85. Secondary end-points: 0–6 h weighted mean (wm) and serial FEV_1. Other end-points: Transitional Dyspnoea Index (TDI), health outcomes (St. George's Respiratory Questionnaire [SGRQ]), pharmacokinetics and safety.

246 patients enrolled; 168 completed study. On day 85, UMEC 62.5 and 125 mcg significantly improved LSM change from baseline in trough FEV_1 (127 and 152 mL, respectively; $p<0.001$) compared with placebo. On day 84, UMEC 62.5 and 125 mcg significantly improved LSM change from baseline in 0–6 h wm (166 and 191 mL, respectively; $p<0.001$) and serial FEV_1 at each time point ($p\leq0.003$). Significant improvement in LSM TDI focal score (1.0 and 1.3 units, respectively; $p\leq0.05$) and change from baseline SGRQ 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.

UMEC 62.5 and 125 mcg significantly improved lung function, dyspnoea and health status compared with placebo and were well tolerated in COPD 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 long-acting muscarinic antagonist 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 mcg once daily (*q.d.*) and 15.6–250 mcg twice daily. The overall incidence of adverse events (AEs) was generally similar to placebo at doses ≤125 mcg *q.d.* and increased at doses ≥250 mcg *q.d.* [7, 8].

The primary objective of this study was to compare the efficacy and safety of UMEC 62.5 and 125 mcg *q.d.* 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 (PK).

METHODS

Patients

Patients ≥40 yrs of age were included if they had a clinical history of COPD [9], were current or former (smoking-free ≥6 months) cigarette smokers with a smoking history of ≥10 pack-yrs, a post-salbutamol forced expiratory volume in 1 second (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 ≥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 (ICS) >1000 mcg/day of fluticasone propionate or equivalent within 30 days of screening. Patients receiving ICS 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 β_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 electrocardiogram (ECG) finding, and 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 16 July 2011 and 13 February 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.

Following screening and a 5- to 9-day run-in period to assess disease stability, patients were randomised 1:1:1 to receive UMEC 62.5 or 125 mcg, or placebo *q.d.* via identical-appearing dry powder inhalers for 12 weeks. Treatment assignment was determined by a validated, computerised system (RandAll; GlaxoSmithKline, UK) and an automated, interactive telephone-based system (RAMOS). 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 FEV_1 ($wmFEV_1$) 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 [13], proportion of responders based on TDI score (improvement of ≥1 unit), trough FVC, weighted mean FVC, serial FVC, time to

onset (an increase of ≥100 mL above baseline in FEV_1) and rescue salbutamol use (percentage of rescue-free days and mean number of puffs/day) were also examined. Health outcomes were assessed by St. George's Respiratory Questionnaire (SGRQ) [14]. PK assessments included plasma UMEC concentrations and derived plasma PK parameters.

Safety was assessed by adverse events (AEs), 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) that met the performance recommendations of the American Thoracic Society [15]. The largest FEV_1 and FVC measurements obtained from three acceptable spirometry efforts were recorded. Trough spirometry for FEV_1 and FVC (defined as the mean of FEV_1 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.

Serial 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/day) in the last 24 h for relief of COPD symptoms.

Plasma PK samples were collected pre-dose and 5 and 15 min post-dose on days 1, 28 and 84 and used to determine plasma PK parameters. Pharmacokinetic-pharmacodynamic (PK-PD) assessment was conducted by visual inspection of the PK-PD 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 FEV_1 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 PK

population comprised all patients in the ITT population who were randomised to treatment with UMEC and for whom a PK sample was obtained and analysed.

Trough FEV_1 on day 85 was analysed with a mixed model repeated measures (MMRM) analysis, including covariates of baseline FEV_1 (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 FEV_1 values recorded on days 2, 14, 28, 56, 84 and 85. The 0–6 h $wmFEV_1$ was analysed in a similar manner, using all available values recorded for days 1, 28 and 84.

Serial FEV_1 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 FEV_1, 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 an analysis of covariance with baseline, 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.

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 mcg and 10% for UMEC 62.5 mcg. The most common reason for withdrawal was lack of efficacy (12% placebo, 7% UMEC 125 mcg, 6% UMEC 62.5mcg) (see supplementary table 1). Baseline characteristics are summarised in table 1. Forty nine percent of patients in the placebo and UMEC 125 mcg groups were GOLD Stage II, with 36% at this stage for the UMEC 62.5 mcg treatment group. Similarly, 38% of patients in the placebo group, 36% in the UMEC 125 mcg group and 43% in the UMEC 62.5 mcg group were GOLD stage III. Overall, 24% of patients reported use of an inhaled corticosteroid at screening; similar usage was observed across treatment groups. Seventy-seven percent 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 mcg (127 mL, 95% confidence interval [CI] 52–202) and 125 mcg (152 mL [95% CI 76–229]) 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 mcg (102–145 mL) and 125 mcg (130–205 mL) compared with placebo (fig. 2a and supplementary table 2).

Statistically significant ($p<0.001$) improvements were observed in LSM change from baseline in 0–6 h wmFEV_1 on day 1 (125 mL [95% CI 83–166]; 147 mL [95% CI 105–188]), day 28 (165 mL [95% CI 105–224]; 196 mL [95% CI 135–256]) and day 84 (166 mL [95% CI 94–239]; 191 mL [95% CI 117–265]) for UMEC 62.5 and 125 mcg, 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 ($p\leq0.003$) (fig. 3). Statistically significant increases in LSM change from baseline were observed for UMEC 62.5 and 125 mcg compared with placebo in FVC measurements (see supplementary tables 3–4 and supplementary fig. 1). Most patients receiving UMEC 62.5 mcg (59%) and 125 mcg (64%) had an onset (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 during 0–6 h post-dose.

Dyspnoea and rescue medication use

The UMEC 62.5 and UMEC 125 mcg 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 [16] 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 mcg 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 mcg and 1.3 [95% CI

0.3–2.3]; p<0.05 for 125 mcg) which met the minimally clinically important difference for the TDI [16]. 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) [16] than a non-responder: UMEC 62.5 mcg odds ratio (OR) 3.4 (95% CI 1.3–8.4; p=0.009) and 125 mcg OR 3.4 (95% CI 1.4–8.6; p=0.009). See supplementary table 5 for proportion of responders according to TDI focal score.

The differences in rescue-treatment use from placebo were statistically significant for UMEC 62.5 mcg (-0.7 mean puffs/day [95% CI -1.3, -0.1]; p=0.025), but not 125 mcg (-0.6 mean puffs/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 mcg (9.0%) and 125 mcg (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 mcg), -3.14 (UMEC 62.5 mcg) and +4.75 (placebo). Statistically significant treatment differences (p<0.001) were observed for both doses (62.5 mcg: -7.90 [95% CI -12.20, -3.60]; 125 mcg, -10.87 [95% CI -15.25, -6.49]) compared with placebo on day 84 (fig. 5). Patients receiving 62.5 mcg (OR: 2.44 [95% CI 1.08–5.50]; p=0.032) or 125 mcg (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) [17] *versus* non-responder compared with placebo.

Pharmacokinetics and pharmacodynamics

UMEC absorption was rapid with C_{max} values approximately 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% CIs. No further accumulation occurred from day 28–84 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 adverse events

Overall incidence of AEs was similar across treatment groups (UMEC 62.5 mcg, 39%; UMEC 125 mcg, 41%; placebo, 35%). The most frequent AEs (≥3% of patients) are listed in table 2. Drug-related AEs included dry throat and dyspnoea (62.5 mcg), cough (125 mcg) and dysphonia (placebo); no drug-related AE was reported by more than 1 patient (1%) in any treatment group. Four patients reported an AE that was considered related to anticholinergic effects: dry mouth (1 patient, UMEC 125 mcg) and dysphagia, visual hallucination and pyrexia (1 patient each, placebo). Seven patients reported a cardiovascular AE: one AE of atrial fibrillation, tachyarrhythmia, coronary artery stenosis and hypertension (1 patient each, UMEC 125 mcg); one AE of supraventricular tachycardia and ventricular extrasystoles (1 patient each, UMEC 62.5 mcg); and atrioventricular block first degree (1 patient, placebo).

SAEs occurred in four patients; none were considered drug-related. Two of these patients (UMEC 125 mcg) reported SAEs that were severe in intensity and lead to

study withdrawal (coronary artery stenosis, COPD). The other two patients reported a lung neoplasm (1 patient, UMEC 62.5 mcg) that did not resolve and non-cardiac chest pain (1 patient, placebo), which was severe in intensity and lead to dose interruption and delay of treatment. Sixteen COPD exacerbations occurred (5 patients, UMEC 62.5 mcg; 4 patients, UMEC 125 mcg; 7 patients, 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 placebo. Mean absolute values for all clinical chemistry and haematology parameters were similar at baseline, day 28 and day 84. No clinically meaningful change from baseline in any clinical chemistry or haematology parameters occurred.

ECG findings

Mean observed changes in 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.

DISCUSSION

This placebo-controlled study of UMEC 62.5 and 125 mcg *q.d.* 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 FEV_1 compared with placebo were demonstrated, and improvements in 0–6 h $wmFEV_1$, serial FEV_1 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 mcg group compared with the other treatment groups, consistent improvements in trough FEV_1 were noted for UMEC 62.5 mcg compared with placebo. Overall, improvements in lung-function assessments over placebo were numerically greater with UMEC 125 mcg compared with 62.5 mcg.

The observed FEV_1 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 FEV_1 (UMEC 62.5 mcg, 124 mL; 125 mcg, 183 mL; $p<0.001$) and serial FEV_1 over 24 h compared with placebo (Data on File, NCT01372410). A 28-day study also reported significant improvements for UMEC 125 mcg *q.d.* in trough FEV_1 (159 mL; $p<0.001$), 0–6 h $wmFEV_1$ (211 mL; $p<0.001$), serial FEV_1 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 FEV_1 (UMEC 62.5 mcg, 128 mL; 125 mcg, 147 mL; $p<0.001$) and 0–24 h $wmFEV_1$ (UMEC 62.5 mcg, 143 mL; 125 mcg: 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 FEV_1 parameters compared with placebo [18] (Data on File, NCT00732472 and NCT00515502).

Results from our study are similar to those from studies of tiotropium, another LAMA used to treat COPD. The 4-yr Understanding Potential Long-Term Impacts on Function with Tiotropium (UPLIFT) study of tiotropium 18 mcg *q.d.* 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 *q.d.* 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 [19]. On day 84, both doses demonstrated clinically meaningful reductions in dyspnoea as measured by the TDI focal score compared with placebo; UMEC 125 mcg also demonstrated a clinically meaningful reduction compared with baseline and UMEC 62.5 mcg trended towards a clinically meaningful reduction. Over twice the proportion of patients receiving UMEC 62.5 mcg or 125 mcg achieved a TDI focal score of ≥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 mcg also demonstrated a clinically meaningful reduction from baseline with UMEC 62.5 mcg 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. Several other studies [20] of bronchodilators have also noted worsening of SGRQ scores with placebo treatment.

UMEC 62.5 and 125 mcg 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 study drug and non-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 et al. [21, 22]. 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 toward 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 [20] of bronchodilators for the treatment of COPD, patients were allowed to continue to use ICS 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 [21, 22]. In addition, imbalances due to ECG defining criteria for withdrawal were noted, 6 (9%) patients in placebo, none in the UMEC 62.5 mcg group and 5 (7 %) in the UMEC 125 mcg 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 mcg *q.d.* 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 *q.d.* COPD maintenance therapy.

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SUPPORT STATEMENT

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STATEMENT OF INTEREST

All authors are employees of and hold stock/shares in GlaxoSmithKline.

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TABLE 1 Patient demographics

Demographic Characteristic	Placebo n=68	UMEC 62.5 mcg n=69	UMEC 125 mcg n=69	Total N=206
Age (yrs)				
Mean (SD)	62.5 (8.72)	62.3 (9.50)	64.6 (7.96)	63.1 (8.77)
Sex				
Female, n (%)	26 (38)	25 (36)	27 (39)	78 (38)
Male, n (%)	42 (62)	44 (64)	42 (61)	128 (62)
Race				
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) Mean (SD)	170.3 (8.34)	170.5 (9.44)	169.3 (8.92)	170.0 (8.89)
Weight (kg) Mean (SD)	81.53 (19.461)	80.70 (24.272)	73.12 (15.381)	78.44 (20.300)
Body mass index (kg/m^2) Mean (SD)	27.96 (5.509)	27.58 (7.414)	25.45 (4.688)	26.99 (6.055)
Current smokers Mean (%)	36 (53)	37 (54)	39 (57)	112 (54)
Mean smoking pack-year history Mean (SD)	52.3 (30.2)	45.2 (21.2)	47.5 (18.6)	48.3 (23.9)
Pre-bronchodilator FEV_1 (mL), n	1247 (429.9)	1303 (605.9)	1252 (435.7)	1267 (495.1)
Post-salbutamol FEV_1 (mL), n Mean (SD)	1388 (454.7)	1366 (595.7)	1356 (454.4)	1370 (504.0)

Post-salbutamol FEV_1/FVC				
Mean (SD)	46.021 (10.6635)	47.971 (11.4884)	48.377 (10.5899)	47.463 (10.9179)
Post-salbutamol % predicted FEV_1				
Mean (SD)	47.0 (13.05)	44.5 (13.99)	47.9 (14.42)	46.5 (13.84)
GOLD stage, n (%)[a]				
Stage I (≥80%)	0	0	0	0
Stage II (≥50% to <80%)	33 (49)	25 (36)	34 (49)	92 (45)
Stage III (≥30% to <50%)	26 (38)	30 (43)	25 (36)	81 (39)
Stage IV (<30%)	9 (13)	14 (20)	10 (14)	33 (16)

[a]Gold stage is based on % predicted FEV_1.

FEV_1: forced expiratory volume in 1 second; FVC: forced vital capacity; GOLD: Global Initiative for Obstructive Lung Disease; SD: standard deviation; UMEC: umeclidinium bromide.

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

	Number (%) of patients		
Preferred term	**Placebo n=68**	**UMEC 62.5 mcg n=69**	**UMEC 125 mcg n=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
Chronic obstructive pulmonary disease[a]	0	0	2 (3)

[a]Chronic Obstructive Disease 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.

UMEC: umeclidinium bromide.

Figure legends

FIGURE 1. Patient disposition and CONSORT flow chart. ITT: intent-to-treat; ECG; electrocardiograph; PK: pharmacokinetic; UMEC: umeclidinium bromide.

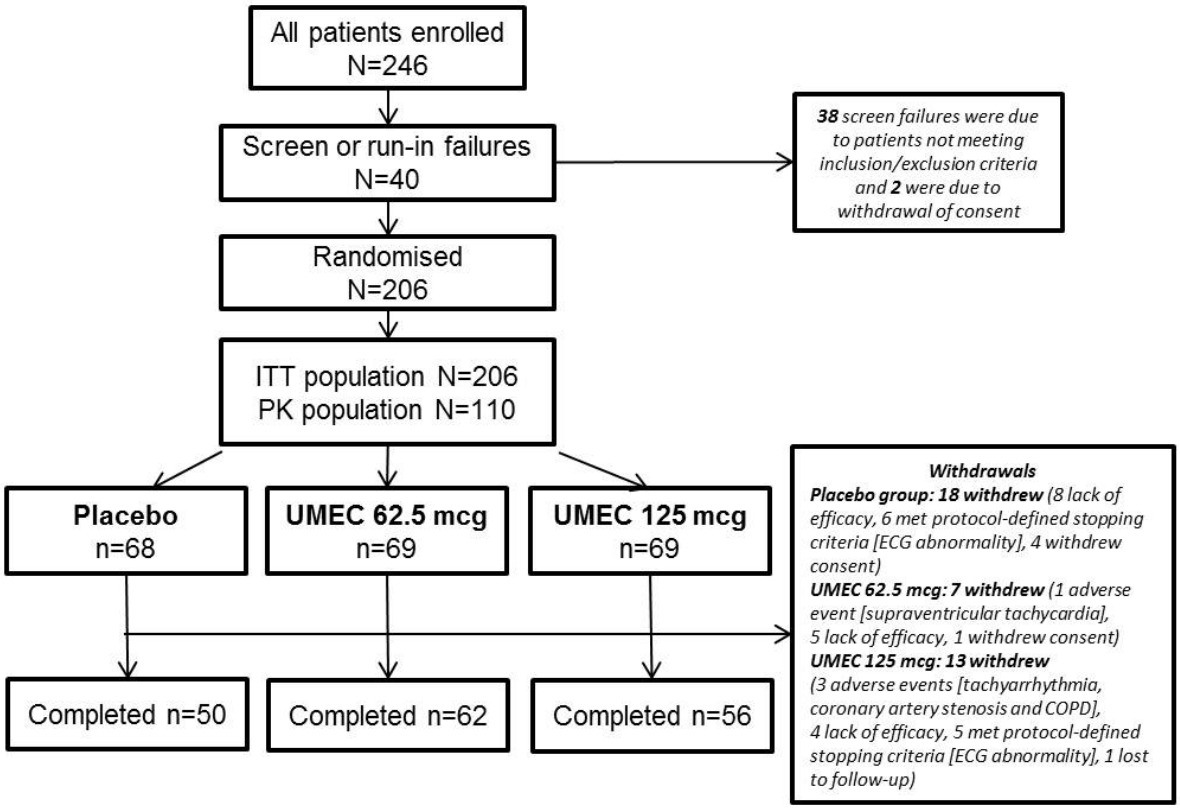

FIGURE 2. Least squares mean change from baseline in (a) trough forced expiratory volume in 1 second (mL) and (b) 0–6 h weighted mean forced expiratory volume in 1 second (mL) (intent-to-treat population). CI: confidence interval; LSM: least squares mean; UMEC: umeclidinium bromide.

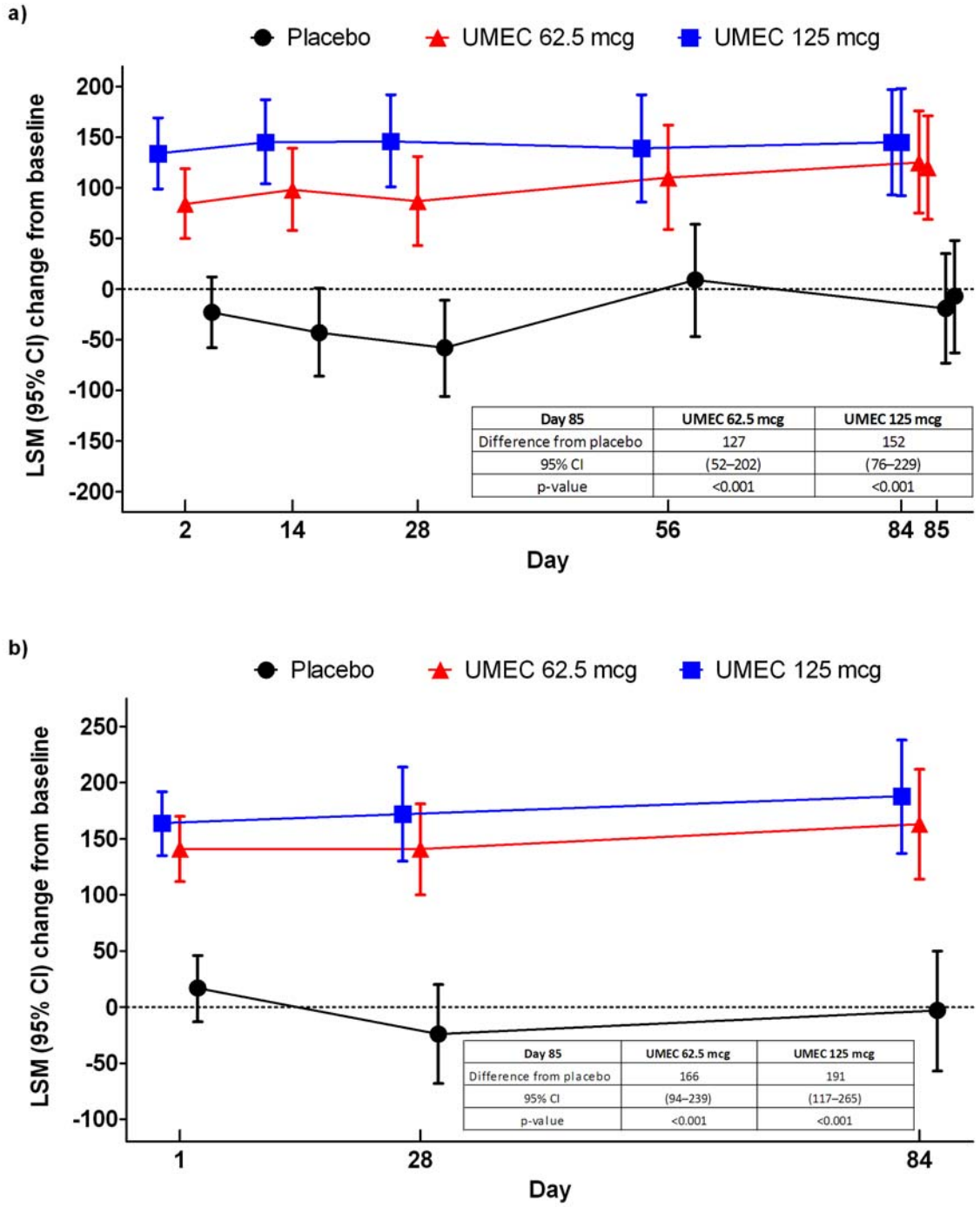

FIGURE 3. Least squares mean change from baseline in serial forced expiratory volume in 1 second (mL) over time at (a) day 1 and (b) day 84 (intent-to-treat population). CI: confidence interval; LSM: least squares mean; UMEC: umeclidinium bromide.

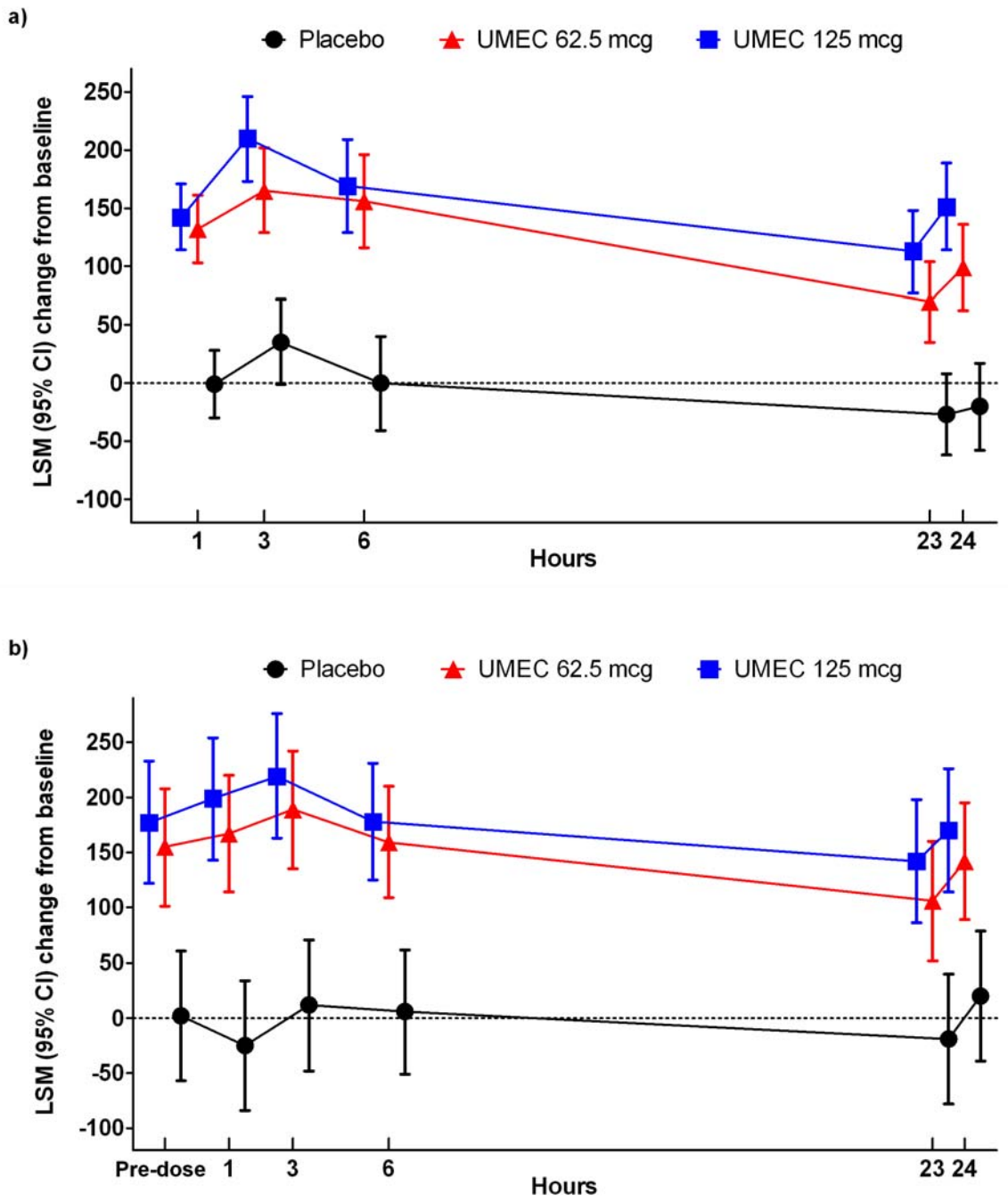

FIGURE 4. Least squares mean Transitional Dyspnoea Index focal score (intent-to-treat population). CI: confidence interval; LSM: least squares mean; UMEC: umeclidinium bromide.

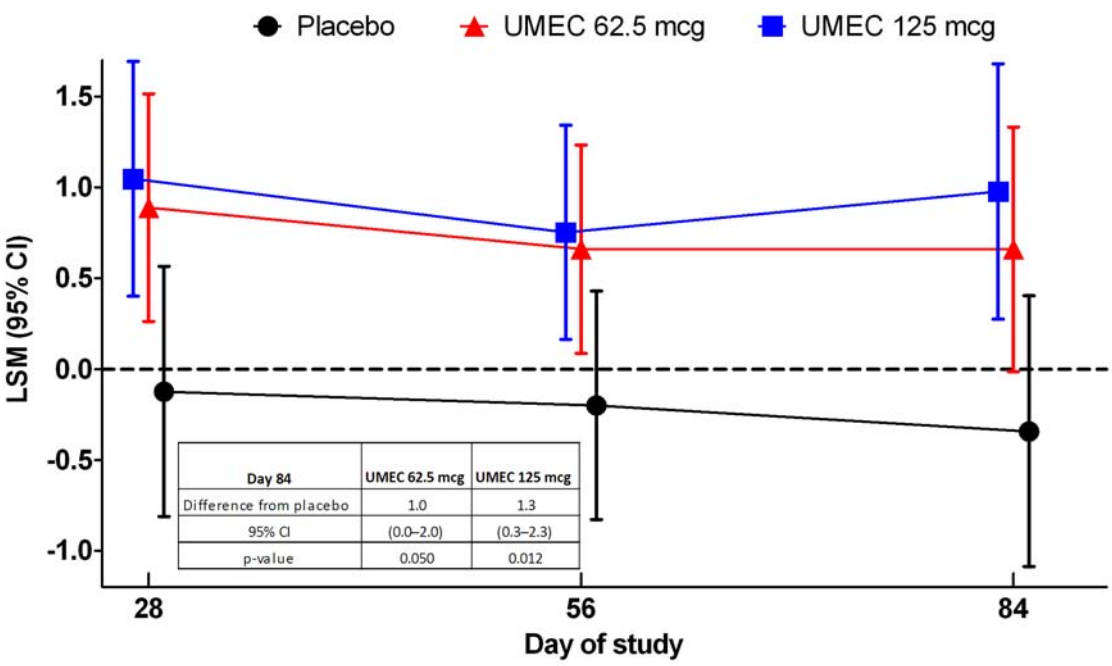

FIGURE 5. Least squares mean change from baseline in St. George's Respiratory Questionnaire total score (intent-to-treat population). CI: confidence interval; LSM: least squares mean; UMEC: umeclidinium bromide.

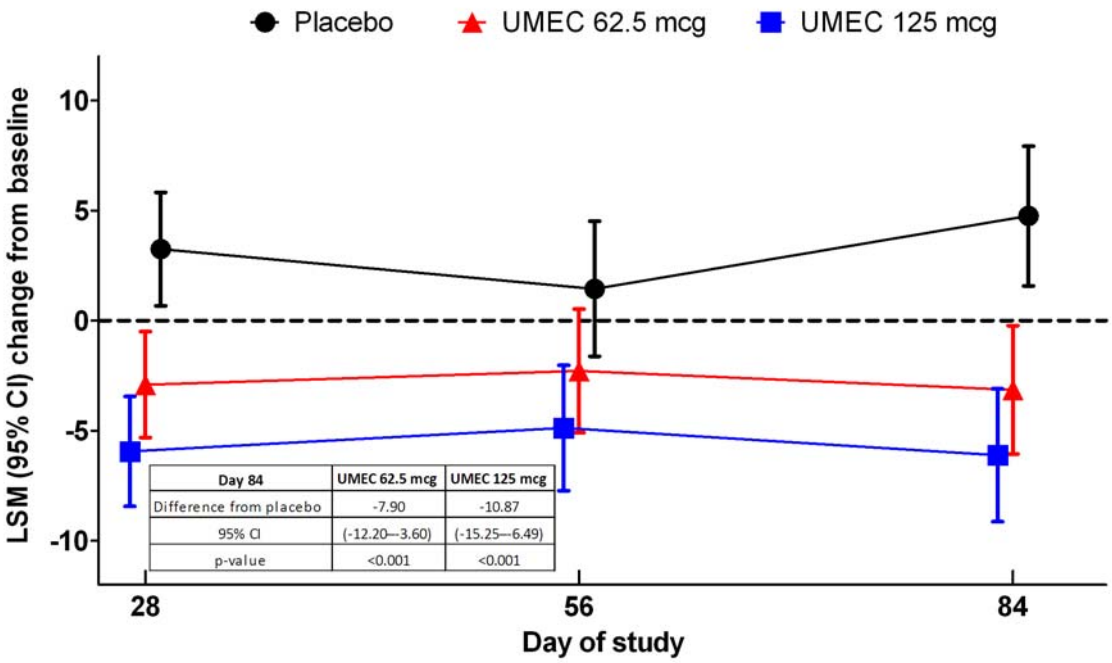
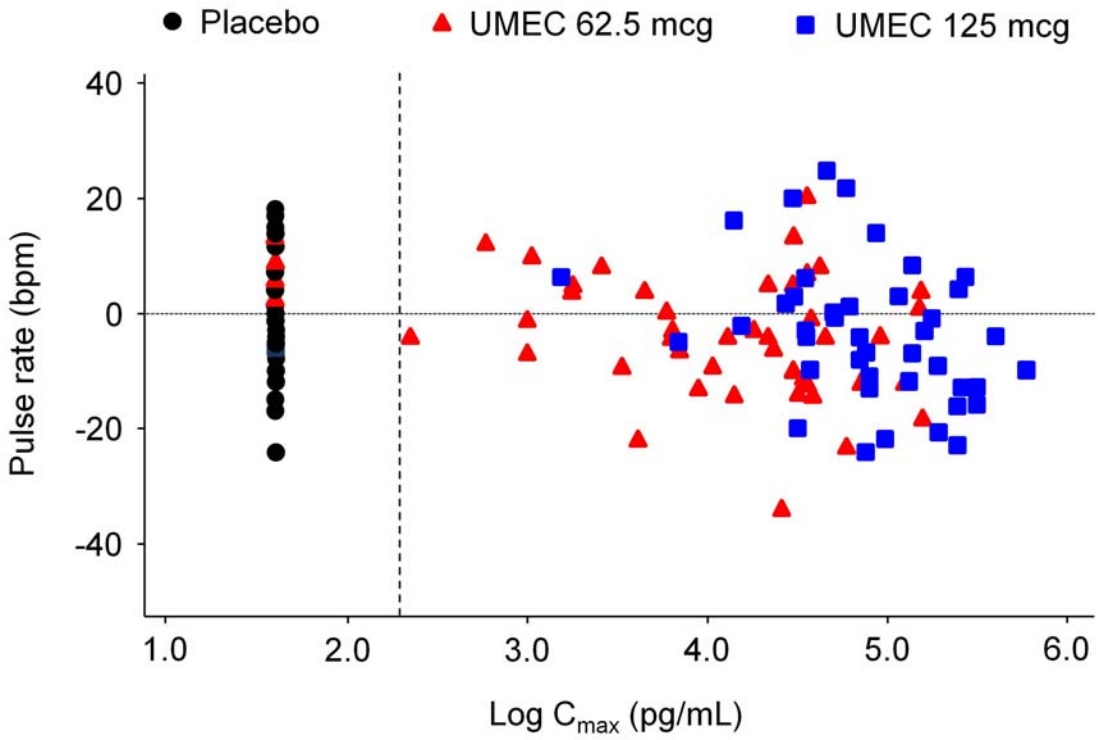
FIGURE 6. Individual change from baseline in maximum pulse rate (beats per minute) *versus* umeclidinium maximum concentration at day 84 (intent-to-treat population). bpm: beats per minute; C_{max}: maximum concentration; UMEC: umeclidinium bromide.