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Dose response of umeclidinium administered once or twice daily in patients with COPD: a randomised cross-over study

Alison Church[1], Misba Beerahee[2*], Jean Brooks[3], Rashmi Mehta[1] and Palvi Shah[4]

Background: Umeclidinium bromide (UMEC) is an inhaled long-acting muscarinic antagonist in development for chronic obstructive pulmonary disease (COPD).

Methods: This was a multicentre, randomised, double-blind, placebo-controlled, three-way cross-over, incomplete block study to evaluate UMEC 15.6, 31.25, 62.5, and 125 μg administered once daily (QD), and UMEC 15.6 μg and 31.25 μg administered twice daily (BID), over 7 days in patients with COPD. Tiotropium was included as an open-label treatment arm. The primary efficacy endpoint was trough forced expiratory volume in 1 second (FEV_1) on Day 8. Secondary efficacy endpoints included weighted mean FEV_1 over 0 24 hours after morning dosing on Day 7, and serial FEV_1 at each time point over 24 hours after morning dosing on Day 7. Safety and pharmacokinetics were also examined.

Results: One hundred and sixty-three patients (mean age 59.5 years, 52% female) were randomised. Based on the population dose response model of trough FEV_1 data, the geometric mean potency (ED_{50}) of UMEC was 37 μg (95% confidence interval [CI]: 18, 57) with a predicted maximum intrinsic efficacy (E_{max}) at trough of 0.185 L (95% CI: 0.153, 0.218) after QD dosing. UMEC 125 μg QD demonstrated the greatest improvements in measure of lung function compared with doses of 62.5 μg and below. UMEC 125 μg QD exhibited more consistent increases in FEV_1 from baseline across serial time points over 24 hours compared with other UMEC doses and tiotropium. Increases in FEV_1 over 0 12 hours were similar to those observed over 12 24 hours after the second dose of UMEC was administered. UMEC was rapidly absorbed following inhaled dosing and eliminated from plasma. Adverse events, generally mild, were highest with UMEC 125 μg QD (18%) compared with placebo (8%), tiotropium (4%) and other UMEC doses (5 12%).

Conclusions: UMEC is a potent QD bronchodilator with geometric mean ED_{50} of 37 μg. A dose ordering over the range of UMEC 15.6 125 μg QD doses was observed, with UMEC 125 μg showing the greatest improvement in trough FEV_1.

Trial registration: GlaxoSmithKline funded (clinicaltrials.gov NCT01372410; GlaxoSmithKline study number AC4115321).

Keywords: Chronic obstructive pulmonary disease (COPD), Long-acting bronchodilators, Long-acting muscarinic antagonist (LAMA), Umeclidinium (UMEC), GSK573719

* Correspondence: misba.2.beerahee@gsk.com
[2]Clinical Pharmacology Modelling & Simulation, GlaxoSmithKline, Stevenage SG1 2NY, UK
Full list of author information is available at the end of the article

Background

Cholinergic tone is considered the major reversible component of airflow obstruction in patients with chronic obstructive pulmonary disease (COPD) [1]. Receptor antagonism by antimuscarinic agents facilitates relaxation of airway smooth muscle. These agents bind to muscarinic receptor subtypes M_1 and M_3 localised in airway smooth muscle and block the bronchoconstrictor response to cholinergic nerve stimulation [2,3], thereby improving airflow obstruction. Long-acting muscarinic antagonists (LAMAs) have been shown to be a more effective and convenient treatment for COPD than short-acting bronchodilators [4].

Umeclidinium bromide (UMEC; GSK573719) is an inhaled LAMA in development for the treatment of COPD. Pharmacology studies have demonstrated that single- and repeat-dose UMEC administration is well tolerated in healthy volunteers [5] and in patients with COPD [6,7]. Statistically significant improvements in change from baseline in trough forced expiratory volume in 1 second (FEV_1) were demonstrated compared with placebo [6,8]. Although the dose–response curve of UMEC from 62.5 μg to 1000 μg has been examined over 14 [6] and 28 days [8], the response obtained over this dosing range was relatively flat.

The current study examined the dose–response and safety of UMEC 15.6, 31.25, 62.5, and 125 μg administered once daily (QD), and UMEC 15.6 and 31.25 μg twice daily (BID). A model-based approach to the assessment of dose response has the advantage of utilising information within and across the range of doses studied for a more informed assessment of the drug's dose–response relationship [9]. Preliminary results have been presented in form [10].

Methods

Patients

Study investigators enrolled eligible patients who were 40–80 years of age, had a clinical history of COPD as defined by the American Thoracic Society (ATS)/European Respiratory society [11], were current or former cigarette smokers with a history of cigarette smoking of ≥10 pack-years, and had a post-salbutamol FEV_1/forced vital capacity (FVC) ratio of <0.70 and a post-salbutamol FEV_1 of ≥35% and ≤70% of predicted normal values [12,13]. Patients were excluded if they had a current diagnosis of asthma, known α1-antitrypsin deficiency, active lung infections, lung cancer, any clinically significant uncontrolled disease, or an abnormal and significant electrocardiogram (ECG) or significantly abnormal clinical laboratory finding. Concomitant use of inhaled salbutamol as a rescue medication was allowed. Inhaled corticosteroids (ICS) at a dose up to 1000 μg/day of fluticasone propionate or equivalent were permitted, provided the dose remained stable throughout the treatment period. Initiation or discontinuation of ICS or long-acting β_2-agonist/ICS combinations within 30 days prior to screening was prohibited; however, patients were allowed to discontinue long-acting β_2-agonist/ICS up to 2 days prior to screening if ICS alone was continued.

Written consent was obtained prior to the start of study-specific procedures. The study (clinicaltrials.gov NCT01372410; GSK study number AC4115321) was approved by the local ethics review committee (Chesapeake IRB, Columbia, MD) and was conducted in accordance with the Declaration of Helsinki and Good Clinical Practice guidelines [14].

Study design and treatment

This randomised, incomplete block, three-period crossover, placebo-controlled study was conducted in 15 centres in the United States from 25 July 2011 to 27 October 2011. In accordance with the randomisation schedule, generated using SAS and RandAll version 2.5, patients were assigned to receive a sequence of three of eight potential treatments for a total of three treatment periods per patient. UMEC 15.6 μg QD, 31.25 μg QD, 62.5 μg QD, 125 μg QD, 15.6 μg BID, 31.25 μg BID, open-label tiotropium 18 μg QD, and placebo were evaluated. UMEC and matching placebo study medication were administered via the ELLIPTA™ dry powder inhaler [a] in a double-blind fashion where neither patients nor the study investigators knew which study medication was administered. Tiotropium was an open-label comparator administered via the Handihaler® [b]. To maintain blinding, patients taking QD treatments also took placebo in the evening. Treatment consisted of three 7-day treatment periods, with two intervening 10–14 day washout periods. A 7–9 day washout period followed the third treatment period, before a follow-up phone call.

Study withdrawal criteria included COPD exacerbation (defined as acute worsening of COPD symptoms requiring treatment beyond study medication or rescue salbutamol, including antibiotics or systemic corticosteroids, and/or hospitalisation or emergency treatment), clinically significant change in laboratory parameters, or elevated liver chemistry.

Treatment adherence was assessed on Day 7 of each treatment period using dose counters on the inhaler or by counting blister doses remaining (tiotropium).

Outcomes and assessments

The primary efficacy endpoint was trough FEV_1 on Day 8, defined as the mean of the FEV_1 values obtained 23 and 24 hours after morning dosing on Day 7 of each treatment period.

The secondary efficacy endpoints were weighted mean FEV_1 over 0–24 hours after morning dosing on Day 7, and serial FEV_1 over 24 hours after morning dosing on Day 7. Serial spirometry was measured 30 and 5 minutes

pre-morning dose, 1, 3, 6, 9, 12 (pre-evening dose), 13, 15, 23 and 24 hours after morning dosing.

Additional efficacy endpoints included trough FEV_1 at other time points, weighted mean FEV_1 over other time periods, serial FEV_1, trough FVC, weighted mean FVC, and rescue salbutamol use (mean number of puffs per day and percentage of rescue-free days). Safety assessments included incidence of adverse events (AEs), haematology and clinical chemistry evaluations, incidence of COPD exacerbations, and vital signs.

Plasma and urine samples were collected for pharmacokinetic (PK) analysis. Assessments included area under concentration-time curve from time 0 to time t ($AUC_{(0\text{-}t)}$), maximum observed plasma concentration (C_{max}), time of maximum observed plasma concentration (t_{max}), amount of drug excreted unchanged in urine, and fraction of dose excreted unchanged in urine. Accumulation was calculated using plasma C_{max}, plasma AUC using a common sampling time and amount excreted in urine over the same time interval on Day 7 versus Day 1.

Spirometry measurements

Measurements for FEV_1 and FVC were obtained using standard spirometry equipment that met or exceeded the minimal ATS performance recommendations [15]. Spirometry was performed at screening, during a 6-hour interval on the first day of each treatment period, and during a 24-hour interval on the last day of each treatment period. A minimum of three acceptable spirometry efforts were obtained for FEV_1 and FVC, and the highest measurement was recorded. Pre- and post-salbutamol spirometry measures at screening determined patient eligibility.

Sample size determination

The sample size for the population model-based dose response analysis was determined using the Monte-Carlo Mapped Power approach for mixed effects [16]. The dose response from a UMEC dose-ranging study was used as reference [6]. Using a model-based approach for a cross-over design study, 16 patients would provide at least 90% power to show a significant dose response with 25 patients showing ~95% power. The sample size was increased to reduce the risk of a false positive result for the lower UMEC doses – a sample size of 40 patients per arm would provide <10% chance that lower doses of UMEC would falsely show a trough FEV_1 response of >100 mL. This number of patients would also provide approximately 85% power for the comparison of active treatments with placebo for the primary efficacy endpoint on Day 8 (ANCOVA analysis). This calculation assumes a two-sided 5% significance level, a within-patient standard deviation of 0.170 L (based on Donohue et al. [6]) and a treatment difference from placebo of 0.130 L. Therefore, approximately 160 patients were recruited to compensate for a possible 30% dropout rate.

Study population

The primary population for all efficacy and safety analyses was the modified intent-to-treat (mITT) population, comprising all patients who were randomised and received at least one dose of study medication. The population was modified in that outcomes were analysed based on the actual treatment received rather than the randomised treatment. The PK population comprised all patients in the mITT population for whom a PK sample was obtained and analysed.

Model-based and statistical analysis

Two approaches were used to characterise the relationship between dose and trough FEV_1. The first approach (i.e., the primary analysis) was a model-based analysis whereby an E_{max} model was selected from a suite of dose response shape models to describe the observed trough FEV_1 data as a function of dose. Two key parameters were estimated from this model - E_{max} which is an estimate of the maximum response predicted by the model given the observed trough FEV_1 and ED_{50} which represents the dose that achieves 50% of E_{max}. The modelling approach investigated the impact of the inter-patient variability in trough FEV_1 by examining the influence of patient demographic and physiologic factors (Additional file 1), and the effect of QD and BID regimen on the model parameters. Established model diagnostics were derived [17,18] to demonstrate the suitability of the chosen dose–response model. Using the population E_{max} model, the predictive distribution of trough FEV_1 across treatments was derived by simulating 1000 sets of individual model parameters using the covariance matrix (model uncertainty and random effects) of parameter estimates from the model. Key outputs included median trough FEV_1 (95th percentiles) for QD and BID regimens, the probability of achieving a certain target trough FEV_1 with each dose (adjusted for baseline and placebo), and median estimates of trough FEV_1 (adjusted for baseline and placebo) across the dose range and by dose regimen. Both mean baseline FEV_1 and period were included as covariates.

A Day 8 dataset and a pooled dataset for Days 7 and 8 (*post-hoc* analysis) were analysed and reported for the primary efficacy analysis. The rationale for pooling Day 7 and Day 8 was to ensure informative interpretation of FEV_1 response as function of dose, given the repeated measures for trough FEV_1 response within each patient on different days.

The second approach (also referred to as the secondary analysis) involved comparison of trough FEV_1 at each dose versus placebo using Analysis of Covariance (ANCOVA). The change from baseline FEV_1 (defined as the mean of

the two pre-morning dose assessments at Day 1) to trough FEV_1 at Day 8 was analysed using a mixed model which included period baseline FEV_1, mean baseline FEV_1, treatment and period as fixed effects, and patient as a random effect. A similar methodology was used to analyse weighted mean FEV_1 and trough and weighted mean FVC endpoints. Serial FEV_1 was analysed using a similar mixed model. Sensitivity analyses were conducted to assess the effect of any interaction of treatment with mean baseline, period baseline or period by repeating the analysis of trough FEV_1 on Day 8 and adding a variable to indicate the previous treatment received, removing baselines from the model or both.

Due to issues with Good Clinical Practice at one investigator site, a decision was made after unblinding to re-evaluate the dose–response model and ANCOVA analysis of trough FEV_1 on Day 8, excluding all patients enrolled at that site.

A Bayesian analysis of the primary endpoint (using the same covariates as the original mixed- model analysis) provided the posterior probability distribution of the treatment difference of each treatment against placebo, i.e. the distribution of the true treatment difference given the data observed in the study.

Results

Study population

Two hundred and forty-four patients were screened, 163 were randomised (mITT population; Figure 1), and 90% completed the study. Mean treatment compliance was ≥99.3% across all treatment periods.

Patient demographics and baseline clinical characteristics are summarised in Table 1. Overall, the study population had moderate to severely impaired airflow obstruction at screening, as evident by values for mean post-bronchodilator FEV_1 and FEV_1/FVC ratio, and mean post-salbutamol FEV_1 and FVC. Across treatment groups, 20–32% of patients took concomitant COPD medication, most often ICSs (18–30%) followed by oxygen (4–8%).

Efficacy

Final dose–response model

The physiological E_{max} model (see Additional file 2) was optimal in defining the relationship between UMEC doses

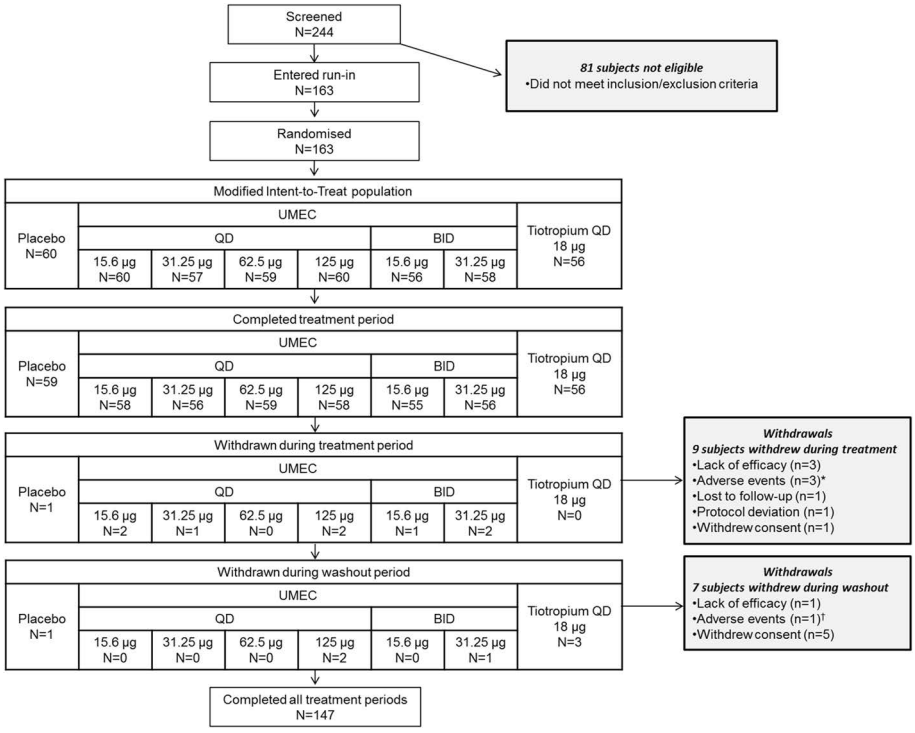

Figure 1 Patient disposition and CONSORT flow chart. *1 patient each in UMEC 15.6 µg QD (acute respiratory failure), UMEC 31.25 µg QD (myocardial infarction), and UMEC 31.25 µg BID (dizziness) during active treatment. †1patient in UMEC 125 µg QD (nasopharyngitis) during washout. Number of patients (*N*) for completed treatment period, withdrawn during treatment period, and withdrawn during washout period reflects the total number of patients in each treatment group across all three treatment periods who completed the treatment period, withdrew during the treatment period, or withdrew during the washout period; two patients included in the counts for 'withdrawn during a treatment period' and not included in the counts and percentages for 'withdrawn during a washout period' actually withdrew during a washout period. BID, twice daily; QD, once daily; UMEC, umeclidinium bromide.

Table 1 Summary of patient population (mITT population), (a) demographic characteristics (b) screening parameters

a.

Characteristic	Total
	N = 163
Age (yr)	
Mean (SD)	59.5 (9.21)
Sex, *n* (%)	
Male	78 (48)
Ethnicity, *n* (%)	
Hispanic/Latino	1 (<1)
Non-Hispanic/Latino	162 (>99)
Race, *n* (%)	
White	145 (89)
African American/African heritage	16 (10)
African American/African heritage and White	1 (<1)
American Indian or Alaskan native	1 (<1)
Height (cm)	
Mean (SD)	170.2 (9.20)
Weight (kg)	
Mean (SD)	79.55 (17.539)
Body mass index (kg/m^2)	
Mean (SD)	27.36 (5.115)

b.

Parameter	Total *N* = 163	
	Pre-salbutamol	Post-salbutamol
% predicted FEV_1 (%)		
n	162	163
Mean (SD)	47.0 (12.84)	51.1 (10.16)
FEV_1/FVC (%)		
n	162	163
Mean (SD)	51.1 (11.65)	52.3 (10.62)
FEV_1 (L)		
n	162	163
Mean (SD)	1.429 (0.5179)	1.554 (0.4727)
FVC (L)		
n	162	163
Mean (SD)	2.803 (0.7948)	3.001 (0.8073)
Reversibility to salbutamol (%)		
n	162	
Mean (SD)	11.8 (15.31)	
Reversibility to salbutamol (mL)		
n	162	
Mean (SD)	124.2 (212.56)	
Mean baseline FEV_1 (L)		
n	163	
Mean (SD)	1.408 (0.5282)	
Mean baseline FVC (L)		
n	163	
Mean (SD)	2.763 (0.7920)	

Note: mean baseline was defined as the mean of the baseline values from each treatment period. If one or more values were missing, the mean baseline was the mean of the non-missing values.
FEV_1, forced expiratory volume in 1 second; FVC, forced vital capacity; mITT, modified intent-to-treat; SD, standard deviation; UMEC, umeclidinium bromide.

and the primary endpoint of trough FEV_1 on Day 8; the parameters of the model were estimated with high precision (coefficient of variation <30%). The ED_{50} for UMEC QD dosing was 37 μg (95% CI: 18–57). The predicted E_{max} was 0.185 L (95% CI: 0.153, 0.218). Model diagnostics show suitability of the final model in describing the dose–response relationship (see Additional file 3). Pooled data from Day 7 and Day 8 were similar: ED_{50} of 38 μg and predicted E_{max} of 0.156 L.

The model-based simulated median estimates of FEV_1 for the QD regimen were plotted together with the observed least square (LS) mean FEV_1 treatment differences (ANCOVA analysis) (Figure 2a). Both methods showed reasonable agreement in the FEV_1 response with dose with the model-based analysis showing a clear monotonic dose response. The dose–response curve suggests that trough FEV_1 response did not plateau at the highest dose. Results of the *post-hoc* model analysis excluding one investigator site (due to issues of Good Clinical Practice) were generally consistent with those for the mITT population (Figure 2b). Similar trends were also observed for the BID regimen in the mITT (Figure 2c) and the *post-hoc* model analysis excluding one investigator site (Figure 2d).

Simulation based on the final dose–response model was used to estimate the probability of achieving a particular response at a given dose (Table 2); this application of the model utilised the integrated variability between- and within-patients across doses to provide a better insight into the dose–response relationship. Thus, UMEC 62.5 μg and 125 μg QD had a ≥87% probability of exceeding the minimum clinically relevant target of 0.100 L trough FEV_1 [6] and a ≥77% probability of exceeding a 0.120 L trough FEV_1 (Table 2). Based on the total daily UMEC dose, the model-based analysis suggests that although there were small numerical differences between the 31.25 μg QD and 15.6 μg BID dosing regimens, the probability of exceeding the target response with the 31.25 μg BID dose is markedly lower than that for the 62.5 μg QD dose (Table 2).