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Respiratory Medicine (2015) 109, 63–73

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A randomized, three-period crossover study of umeclidinium as monotherapy in adult patients with asthma

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Available online 28 October 2014

KEYWORDS
Asthma;
Fixed-dose combination;
Muscarinic antagonist;
Inhaled corticosteroid;
Trough FEV_1

Summary

Background: To our knowledge, no studies in patients with asthma have assessed a long-acting muscarinic antagonist in the absence of inhaled corticosteroids (ICS).

Objective: Evaluate the dose–response, efficacy, and safety of umeclidinium (UMEC) in patients with asthma not receiving ICS.

Methods: In this double-blind, three-period crossover study, 350 subjects were randomized to a sequence of three of eight inhaled treatments: UMEC 15.6, 31.25, 62.5, 125, or 250 mcg once daily (OD), UMEC 15.6 or 31.25 mcg twice daily (BID), or placebo, administered for 14 days (12–14-day washout). Trough forced expiratory volume in one second (FEV_1), 0–24-h weighted mean (WM) FEV_1, and safety were assessed. Serial spirometry and pharmacokinetic assessments were performed in a subgroup.

Results: Subjects had a mean baseline pre- and post-bronchodilator FEV_1 of 71% and 88% predicted, respectively. Significant improvements in change from baseline trough FEV_1 were observed for UMEC 15.6 OD (0.066 L; $p = 0.036$) and UMEC 125 OD (0.088 L; $p = 0.005$) versus placebo, but not other OD or BID doses. UMEC increased 0–24-h WM FEV_1 versus placebo (0.068–0.121 L [$p \leq 0.017$] with no clear dose–response). Treatment

Abbreviations: Ae, amount of dose excreted unchanged in urine; AE, adverse event; ALT, alanine aminotransferase; AUC, area under the curve; BID, twice daily; bpm, beats per minute; CI, confidence interval; C_{max}, maximum plasma concentration; COPD, chronic obstructive pulmonary disease; ECG, electrocardiogram; Fe, percentage of total dose excreted in urine; FEV_1, forced expiratory volume in one second; GCP, Good Clinical Practice; HLQ, higher limit of quantification; ICS, inhaled corticosteroid; ICH, International Conference on Harmonisation; INR, international normalized ratio; LAMA, long-acting muscarinic antagonist; LLQ, lower limit of quantification; LS, least squares; NA, not available; NC, non-calculable; ND, not determined; NQ, non-quantifiable; OD, once daily; PEF, peak expiratory flow; PK, pharmacokinetic; PVC, premature ventricular contraction; SAE, serious adverse event; SD, standard deviation; SE, standard error; T_{last}, time of the last point with quantifiable concentration; T_{max}, time to maximum plasma concentration; ULN, upper limit of normal; UMEC, umeclidinium bromide; VPD, ventricular premature depolarization; WM, weighted mean.

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http://dx.doi.org/10.1016/j.rmed.2014.10.009

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differences were similar for corresponding OD and BID doses in serial assessments. UMEC was rapidly absorbed, with evidence of some accumulation. The incidence of on-treatment adverse events was 9—21% for UMEC and 12% for placebo. There were no treatment-related effects on laboratory parameters.
Conclusion: The modest trough FEV_1 improvements did not conclusively support a therapeutic benefit of UMEC in non-ICS treated patients with asthma.
ClinicalTrials.gov: NCT01641692.
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Introduction

Long-acting muscarinic antagonists (LAMAs) are well established in guidelines for the treatment of chronic obstructive pulmonary disease (COPD) [1]. Muscarinic antagonists bind to M_3 receptors, thereby blocking the action of vagally-derived acetylcholine and inhibiting airway smooth muscle contraction [2]. Given that parasympathetic nervous system dysfunction is well established in asthma, manifested as an increase in the magnitude of diurnal variation in pulmonary function, and increased airway hyper-responsiveness after viral infection or allergen exposure [3—5], LAMAs may also have therapeutic benefits in asthma. In support of this, recent studies have shown that the LAMA, tiotropium, improves asthma symptoms and/or lung function when used as add-on therapy to low- or medium-dose inhaled corticosteroid (ICS) [6,7], and reduces the risk of a severe asthma exacerbation when added to ICS and long-acting β-agonist therapy [8].

Umeclidinium (UMEC) is a quinuclidine derivative and potent anticholinergic with slow functional reversibility at the human M_3 receptor [9]. UMEC is approved as maintenance treatment for COPD in the US and EU. It is not indicated for treatment of asthma. Studies have shown that once-daily (OD) and twice-daily (BID) UMEC doses are well tolerated in patients with COPD, and significantly improve lung function, dyspnea, and health status in comparison with placebo [10—14].

To support the development program for an ICS/LAMA fixed-dose combination for the treatment of asthma, the objective of this study was to evaluate the dose—response, efficacy and safety of UMEC in adult patients with asthma.

Materials and methods

Study design

This was a multicenter, randomized, double-blind, placebo-controlled, three-period crossover incomplete block study (GlaxoSmithKline study: ALA116402; ClinicalTrials.gov identifier: NCT01641692 [May 2012—February 2013]). Patients were enrolled at 42 centers in Bulgaria, Germany, Mexico, Peru, Poland, and the United States.

During each 14-day treatment period there were three visits, at Days 1 and 14 of dosing and 24 h after the last dose. A follow-up visit was performed approximately 7 days following Treatment Period 3.

The study was approved by a local Ethics Committee/Institutional Review Board in each country, and was conducted in accordance with the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use, Good Clinical Practice (ICH-GCP) Guidelines, all applicable subject privacy requirements and the ethical principles outlined in the Declaration of Helsinki, 2008 [15,16]. Written, informed consent was obtained from each subject before any study procedures were performed.

Patients

Eligible patients: were ≥18 years of age; had a history of asthma for ≥6 months prior to Visit 1 (as defined by the National Institutes of Health [17]); were using a non-corticosteroid controller and/or a short-acting β-agonist (ICS use was prohibited for ≥4 weeks prior to study start); had a forced expiratory volume in one second (FEV_1) of 60—85% predicted normal (as determined by Nutrition Health and Examination Survey III reference equations) [18]; demonstrated ≥12% and ≥0.200 L reversibility to albuterol at Visit 1; and were capable of withholding albuterol for ≥4 h prior to any study visit.

Patients were excluded if they: were of childbearing potential (unless practicing acceptable birth control methods); had a history of life-threatening asthma within the last 5 years; had experienced an asthma exacerbation within the 4 weeks prior to Visit 1 that required oral or injected corticosteroids for ≥3 days, or an in-patient hospitalization or emergency department visit due to asthma that required systemic corticosteroids; had a respiratory infection within 4 weeks of Visit 1; had any concurrent respiratory disease or disease preventing the use of anticholinergics or where the use of an anticholinergic could be deleterious; had used tobacco products in the 6 months prior to Visit 1 or a smoking history ≥10 pack-years; had a severe milk protein allergy or specific drug allergies; had used any prohibited medications; or had a condition that would affect their ability to participate in the study according to protocol specifications.

Subjects who did not meet the inclusion criteria at the end of the run-in period were not eligible for randomization. Additional exclusion criteria at randomization included: clinically significant abnormal laboratory tests during Visit 1, which were still abnormal upon repeat analysis; a severe asthma exacerbation requiring the use of systemic corticosteroids for ≥3 days; in-patient

hospitalization or an emergency department visit due to asthma that required systemic corticosteroids between Visits 1 and 3; or evidence of a significant abnormality in the 12-lead electrocardiogram (ECG) performed at Visit 1 or 12-lead Holter monitoring over a 24-h period prior to randomisation.

Procedures

For subjects meeting eligibility criteria, non-corticosteroid controller medications were ceased ≥48 h before the screening visit. Subjects were permitted to use a short-acting β-agonist as needed until the day of screening (Visit 1). Subjects entered a 9—14-day run-in period after screening, during which reversibility testing to ipratropium bromide was performed (Visit 2). Subjects received four puffs of ipratropium bromide, with FEV_1 assessments performed pre-dose and within 40 min post-dose. Eligible subjects were stratified in a 1:2:2 ratio according to age (18—29, 30—49 and ≥50 years), and were randomized at Visit 3 to a sequence of three of eight potential treatments: UMEC 15.6, 31.25, 62.5, 125, or 250 mcg OD, UMEC 15.6 or 31.25 mcg BID, or placebo. The 14-day treatment periods were separated by 12—14-day washout periods. Treatment Period 3 was followed by a 5—9-day washout period before a follow-up visit.

All treatments were self-administered via dry powder inhaler in the morning and evening from distinct inhalers labeled 'AM' and 'PM'. In order to maintain blinding, subjects who were randomized to receive an OD dose in the morning also received a placebo in the evening. All subjects had albuterol provided as rescue medication throughout the study, including during washout periods.

Subjects were randomized using SAS®-generated codes imported into a validated computerized system (Randall Version 2.5, GlaxoSmithKline). The Registration and Medication Ordering System was used to register and randomize subjects.

Outcomes and assessments

Efficacy endpoints

The primary efficacy endpoint was change from baseline in trough FEV_1 on Day 15 of each treatment period. Baseline was the pre-dose FEV_1 on Day 1; trough FEV_1 was obtained 24 h after morning dosing on Day 14. Changes in morning and evening peak expiratory flow (PEF) and rescue albuterol use were assessed as secondary endpoints. Change from baseline in morning pre-dose FEV_1 (Day 14) was assessed as an additional efficacy endpoint.

Weighted mean (WM) FEV_1 24 h after morning dosing on Day 14 and serial FEV_1 at each time point over 24 h after morning dosing on Day 14 were additional secondary endpoints examined in a serial assessment subgroup (consisting of approximately 30% of the total population). Additional spirometry parameters in the serial assessment subgroup included WM FEV_1 0—6 h after morning dosing (Days 1 and 14), WM FEV_1 0—12 h after morning and evening dosing (Day 14), and serial FEV_1 over 6 h after morning dosing (Days 1 and Day 14).

Spirometry measurements (excluding those in the serial assessment subgroup) were performed in the morning at all clinic visits (Day 1, Day 14, and Day 15 of each treatment period, and at follow-up). In the serial assessment subgroup, measurements were performed pre-dose on Day 1 (within 1 h prior to dosing) and at 5, 15, and 30 min, and 1, 3, and 6 h post-dose. On Day 14 (continuing into Day 15), FEV_1 was measured pre-dose (within 1 h prior to dosing) and at 5, 15, and 30 min, and 1, 3, 6, 9, 12, 16, 20, 23, and 24 h post-dose. PEF, asthma symptoms, and rescue albuterol use were recorded using electronic diaries throughout the study, including screening and washout periods, to identify any periods of asthma worsening.

Exploratory analyses

Exploratory analyses examined possible predictors of change from baseline in trough FEV_1, including age, sex, body mass index, asthma duration, screening FEV_1 and FEV_1/forced vital capacity (FVC) ratio, albuterol reversibility, ipratropium reversibility, heart rate, systolic and diastolic blood pressure, and the asthma control test [19].

Pharmacokinetic (PK) analyses

PK analyses on UMEC were performed on blood and urine samples taken from the serial assessment subgroup. Blood samples were collected pre-dose on Day 1 of each treatment period (within 1 h prior to dosing) and at 5 and 15 min, and 2 h post-dose. On Day 14, samples were collected pre-dose and at 5 and 15 min, and 2 and 12 h after each of the morning and evening doses. Urine samples were collected on Day 1 of each treatment period at 0—6 h post-dose and on Day 14 of each treatment period at 0—6 h, 6—9 h, 9—12 h, 12—14 h, and 14—24 h following the morning dose.

Plasma and urine samples were analyzed using validated analytical method based on solid phase extraction, followed by high-performance liquid chromatography with tandem mass spectrometry. The lower limit of quantification for UMEC in plasma and urine was 10.0 pg/mL, while the higher limit of quantification was 2000 pg/mL in plasma and 5000 pg/mL in urine (York Bioanalytical Solutions, York, UK).

Safety

Safety assessments in all subjects included adverse events (AEs), liver function, vital signs (including pulse and systolic/diastolic pressure), clinical chemistry, hematology and urinalysis parameters, 12-lead ECG parameters, and severe asthma exacerbations. In addition, serial ECG assessments and 24-h Holter monitoring were performed in the serial assessment subgroup.

Sample sizes and statistical analyses

The study design provided 95% power to detect a 0.150 L difference in FEV_1 between any two treatments. It was assumed that $\alpha = 0.05$, that the within-patient standard deviation of FEV_1 was 0.290 L, and that testing was two-sided. A total of 350 subjects were randomized to ensure that ≥270 completed all three double-blind treatment periods.

Analyses were conducted in the intent-to-treat (ITT) population (subjects randomized to treatment and

receiving ≥1 dose of study medication) or the PK population (subjects in the ITT population for whom a PK sample was obtained and analyzed). Dose–response analyses (using linear and non-linear mixed-effects modeling) were conducted for the primary endpoint. Other efficacy endpoints were analyzed using mixed-model methods. Descriptive statistics summarized safety data. WM FEV_1 was defined as the area under the FEV_1 versus time curve (calculated using the trapezoidal rule) divided by the relevant time interval.

PK parameters were derived by standard non-compartmental analyses via Phoenix WinNONLIN Version 6.3 (Pharsight Corporation, California, USA). All other analyses were performed via SAS® Version 9 or NONMEM Version 7.1.

Results

Subjects

Of the 529 patients screened, 350 were randomized to treatment and included in the ITT population, across 42 centers (United States, $n = 95$ [27%]; Peru, $n = 87$ [25%]; Bulgaria, $n = 61$ [17%]; Poland, $n = 42$ [12%]; Germany, $n = 36$ [10%], and Mexico, $n = 29$ [8%]) (Fig. 1). In total, 298 subjects completed the study and 52 subjects were withdrawn. The most common reason for withdrawal over the course of the study (including treatment periods, washout and follow-up) was reaching protocol-defined stopping criteria ($n = 22$ [6%]), including ECG abnormalities ($n = 15$ [4%]) and Holter abnormalities ($n = 8$ [2%]; one subject was recorded with both an ECG abnormality and a Holter abnormality) (further details in Supplementary Tables 1 and 2).

The serial spirometry, PK, and ECG assessments, and 24-h Holter monitoring were performed in subjects randomized at a subset of centers (128 subjects: United States, $n = 37$; Germany, $n = 28$, Bulgaria, $n = 24$; Poland, $n = 21$; and Peru, $n = 18$).

The majority of subjects in the ITT population were White, female, and had a diagnosis of asthma for ≥10 years (Table 1). Most subjects (71%) had an asthma control test score <20 at screening. Subjects had mild impairment in airflow (mean pre-albuterol FEV_1, 71%) and were reversible

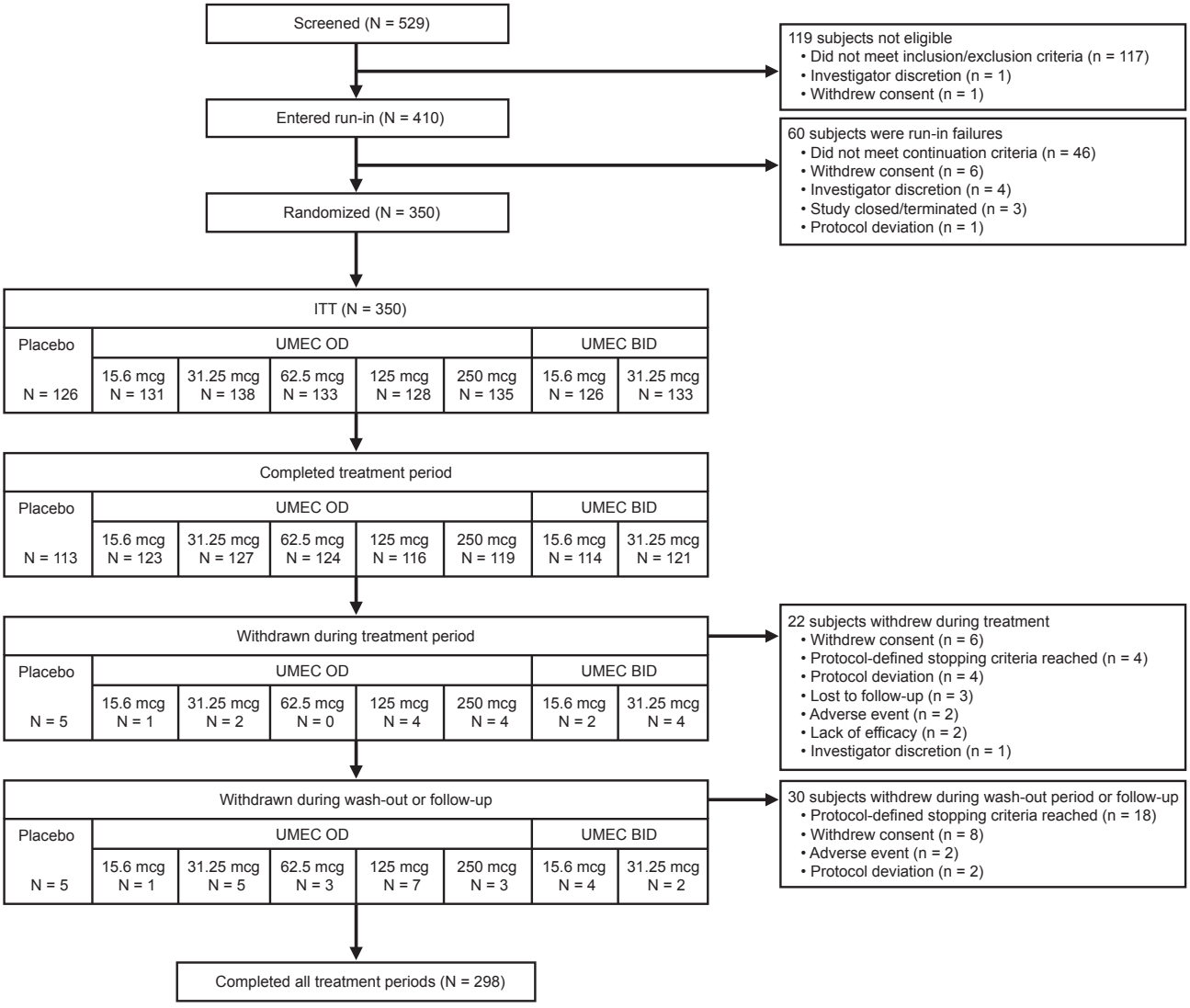

Figure 1 Subject disposition. BID, twice daily; ITT, intent-to-treat; OD, once daily; UMEC, umeclidinium.

Table 1 Baseline subject demographics and characteristics.

Demographic characteristic	Total ($N = 350$)
Sex, n (%)	
Female	232 (66)
Male	118 (34)
Age, years	
Mean (SD)	42.6 (14.84)
Age group, *n* (%)	
18–29	83 (24)
30–49	149 (43)
≥50	118 (34)
Race, *n* (%)	
White	197 (56)
American Indian or Alaska Native	85 (24)
Black or African-American	33 (9)
Multiple	31 (9)
Asian	4 (1)
Ethnicity, *n* (%)	
Hispanic/Latino	123 (35)
Not Hispanic/Latino	227 (65)
Body size, mean (SD)	
BMI (kg/m^2)	28.5 (6.42)
Asthma duration	
≥6 months to <1 year	3 (<1)
≥1–<2 years	7 (2)
≥2–<5 years	26 (7)
≥5–<10 years	70 (20)
≥10–<15 years	54 (15)
≥15–<20 years	52 (15)
≥20–<25 years	54 (15)
≥25 years	84 (24)
Asthma control test score	
Mean (SD)	16.6 (4.24)
Pre-albuterol FEV_1 (L)	
Mean (SD)	2.268 (0.5539)
Predicted pre-albuterol FEV_1 (%)	
Mean (SD)	71.33 (6.766)
Post-albuterol FEV_1 (L)	
Mean (SD)	2.794 (0.6880)
Predicted post-albuterol FEV_1 (%)	
Mean (SD)	87.91 (9.538)
Pre-ipratropium FEV_1 (L)	
Mean (SD)	2.330 (0.6139)
Post-ipratropium FEV_1 (L)	($n = 349$)
Mean (SD)	2.622 (0.6902)
FEV_1 reversibility to albuterol (%)	
Mean (SD)	23.46 (10.211)
FEV_1 reversibility to ipratropium (%)	($n = 349$)
Mean (SD)	13.21 (13.220)

BMI, body mass index; FEV_1, forced expiratory volume in one second; L, liters; SD, standard deviation.

to albuterol (mean reversibility, 23.46% [$n = 350$]) and ipratropium (mean reversibility 13.21% [$n = 349$]). Further details on the asthma history of subjects are provided in Supplementary Table 3. In the 30 days prior to Screening Visit 1, asthma medications were used by 91% of subjects. The medications used most frequently in this period were albuterol (71% of subjects), montelukast/montelukast sodium (18%), and theophylline (5%).

Efficacy outcomes

Trough FEV_1 increased for all UMEC doses versus placebo in the range of 0.011–0.088 L, but the least squares (LS) mean change from baseline was statistically significantly different from placebo only for UMEC 15.6 OD and UMEC 125 OD at Day 15 (Fig. 2; Table 2). Overall, treatment differences were similar for corresponding OD and BID doses, and there was no clear dose–response in the change from baseline in trough FEV_1.

There were no statistically significant differences for any UMEC dose versus placebo for morning PEF. UMEC 15.6 OD, 125 OD, 250 OD, and 31.25 BID produced statistically significant improvements in evening PEF versus placebo, with no clear dose–response (Supplementary Table 4). Small reductions in rescue albuterol use were observed (0.2–0.5 puffs/day), but the reductions were not significantly different for UMEC versus placebo. Improvements in the change from baseline in morning pre-dose FEV_1 (Day 14) were not statistically significant compared with placebo (difference versus placebo: 0.005–0.050 L).

Serial spirometry assessments

In the subgroup of subjects with serial spirometry assessments, all UMEC doses produced statistically significant increases in 0–24-h WM FEV_1 versus placebo (0.068–0.121 L) (Table 3). The largest increases in FEV_1 were observed at 3 h post-dose, and these improvements were statistically significant compared with placebo ($p \leq 0.005$), but there was no apparent dose-ordering (Fig. 3). Responses to UMEC administered BID were similar to those following the corresponding OD doses. All UMEC doses produced statistically significant increases in 0–6 h WM FEV_1 versus placebo on Day 1 (except OD UMEC 31.25 and both BID doses) and on Day 14 (Supplementary Table 5). Similar results were seen for WM FEV_1 0–12 h after morning and evening dosing on Day 14 (Supplementary Table 6). There was no clear dose–response in any of the serial spirometry assessments.

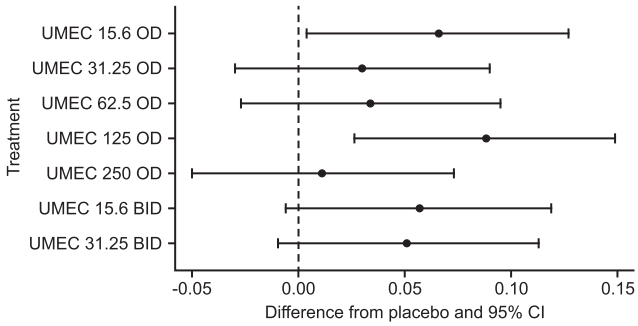

Figure 2 Adjusted mean differences from placebo (95% CI) in change from baseline in trough FEV_1 (L) on Day 15. CI, confidence interval; BID, twice daily; FEV_1, forced expiratory volume in one second; OD, once daily; UMEC, umeclidinium.

Table 2 Statistical analysis of change from baseline in trough FEV_1 (L) at Day 15.

Trough FEV_1 (L)	Placebo	UMEC OD				
		15.6 mcg	31.25 mcg	62.5 mcg	125 mcg	250 mcg
n	110	120	124	122	113	117
LS mean (SE)	2.398 (0.0235)	2.464 (0.0226)	2.428 (0.0222)	2.432 (0.0224)	2.486 (0.0232)	2.409 (0.0228)
LS mean change (SE)	0.046 (0.0235)	0.112 (0.0226)	0.076 (0.0222)	0.080 (0.0224)	0.134 (0.0232)	0.057 (0.0228)
Treatment vs Placebo						
Difference		0.066	0.030	0.034	0.088	0.011
95% CI		0.004, 0.127	−0.030, 0.090	−0.027, 0.095	0.026, 0.149	−0.050, 0.073
p-value		0.036	0.331	0.272	0.005	0.722
Trough FEV_1 (L)			UMEC BID			
			15.6 mcg			31.25 mcg
n			113			118
LS mean (SE)			2.455 (0.0232)			2.449 (0.0227)
LS mean change (SE)			0.103 (0.0232)			0.097 (0.0227)
Treatment vs Placebo						
Difference			0.057			0.051
95% CI			−0.006, 0.119			−0.010, 0.113
p-value			0.076			0.101

Analysis performed using a mixed model, including treatment, period, period baseline FEV_1 and mean baseline FEV_1 as fixed effects and subject as a random effect.
BID, twice daily; CI, confidence interval; FEV_1, forced expiratory volume in one second; L, liters; LS, least squares; OD, once daily; SE, standard error; UMEC, umeclidinium.

Exploratory analyses

Multiple statistically significant predictors of trough FEV_1 response were identified in linear regression models (Supplementary Table 7a). However, the Pearson correlation coefficients for overall data and by treatment were low (range: −0.245 to 0.365) and the data did not indicate any clinically-relevant predictors of response. When the significant predictors from the linear regression models were included in multiple regression models (overall and by treatment), few significant predictors were identified and the model multiple correlation coefficients were low

Table 3 0–24-h WM FEV_1 at Day 14.

WM FEV_1 (L)	Placebo	UMEC OD				
		15.6 mcg	31.25 mcg	62.5 mcg	125 mcg	250 mcg
n	33	35	49	42	45	38
LS mean (SE)	2.309 (0.0255)	2.394 (0.0249)	2.410 (0.0222)	2.426 (0.0232)	2.427 (0.0229)	2.382 (0.0243)
LS mean change (SE)	−0.025 (0.0255)	0.060 (0.0249)	0.077 (0.0222)	0.092 (0.0232)	0.094 (0.0229)	0.048 (0.0243)
Treatment vs placebo						
Difference		0.085	0.101	0.117	0.119	0.073
95% CI		0.025, 0.145	0.047, 0.156	0.061, 0.173	0.064, 0.174	0.015, 0.131
p-value		0.006	<0.001	<0.001	<0.001	0.014
WM FEV_1 (L)			UMEC BID			
			15.6 mcg			31.25 mcg
n			35			43
LS mean (SE)			2.430 (0.0252)			2.377 (0.0231)
LS mean change (SE)			0.097 (0.0252)			0.043 (0.0231)
Treatment vs placebo						
Difference			0.121			0.068
95% CI			0.061, 0.182			0.012, 0.124
p-value			<0.001			0.017

Note: Analysis performed using a mixed model, including treatment, period, period baseline FEV_1 and mean baseline FEV_1 as fixed effects and subject as a random effect.
BID, twice daily; CI, confidence interval; FEV_1, forced expiratory volume in one second; L, liters; LS, least squares; OD, once daily; SE, standard error; UMEC, umeclidinium; WM, weighted mean.

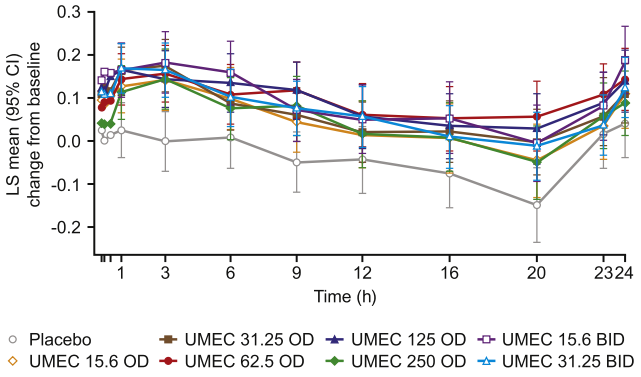

Figure 3 Adjusted mean change from baseline (95% CI) in 0—24-h serial FEV_1 on Day 14. BID, twice daily; CI, confidence interval; FEV_1, forced expiratory volume in one second; LS, least squares; OD, once daily; UMEC, umeclidinium.

(overall, $R^2 = 0.161$ [Supplementary Table 7b]; by treatment, all $R^2 < 0.227$). Based on these findings, no predictors of trough FEV_1 response were carried forward for further inferential analysis.

Pharmacokinetics

UMEC plasma concentrations peaked at approximately 5 min post-dose on Days 1 and 14. The median of the last time point with quantifiable concentration (t_{last}) was 0.242—2.00 h for UMEC 15.6—250 OD on Day 1, and 0.250—24.00 h on Day 14. The median t_{last} was similar for UMEC 15.6—31.25 BID on Day 1 and 14, at 0.233—0.250 h and 0.233—0.275 h, respectively (Table 4). The mean maximum plasma concentration (C_{max}) was higher on Day 14 than Day 1 for all OD and BID UMEC doses (C_{max} was non-calculable for UMEC 15.6 OD) (Table 4).

The approximate dose proportionality of UMEC was assessed based on C_{max}, area under the curve 0—2 h (AUC_{0-2}) in plasma and amount of UMEC excreted unchanged (Ae) in the urine with power models. For C_{max} with OD dosing, the adjusted mean slopes (90% confidence intervals [CI]) were 1.03 (0.90—1.16) on Day 1, and 1.20 (1.06—1.34) on Day 14 (only 62.5, 125, and 250 mcg doses were analyzed due to the high proportion of non-calculable values on other doses). It was not possible to calculate the adjusted mean slope for AUC_{0-2} on Day 1 due to the high proportion of non-quantifiable concentrations. At Day 14, for AUC_{0-2}, the adjusted mean slope was 1.11 (1.01—1.21). Ae values on Day 14 indicated dose-proportionality for OD doses of 15.6—250 mcg: Ae_{0-6} 1.06 (0.92—1.20); Ae_{0-24} 1.07 (1.00—1.14).

On Day 1 and Day 14, percentage of total UMEC dose excreted in urine 0—6 h was approximately 0.5—1.4% of the dose administered for all treatments. Over 24 h, the median amount of UMEC excreted was approximately 3% of the dose after repeated administration of UMEC (Table 4).

Safety

The incidence of on-treatment AEs across all treatment periods was 9—21% for UMEC, and 12% for placebo. The most frequently reported on-treatment AE was headache (UMEC, 2—5%; placebo, 2%) and 'product taste abnormal' was more common at higher UMEC doses (Table 5).

Four subjects experienced on-treatment asthma exacerbations during the study (UMEC 15.6 BID, $n = 1$; UMEC 31.25 BID, $n = 1$; placebo, $n = 2$). Two non-fatal serious AEs (SAEs) were reported, one spontaneous abortion identified at the end of Treatment Period 3 (UMEC 250 OD) and one asthma exacerbation post-treatment (UMEC 62.5 OD). None of the non-fatal SAEs was considered related to study treatment by the investigator and there were no deaths during the study. Four subjects had non-serious on-treatment AEs that led to study withdrawal (UMEC 125 OD, $n = 1$ [supraventricular tachycardia, an ECG stopping criterion]; placebo, $n = 3$ [ECG T-wave inversion, throat irritation, and myalgia/eyelid edema).

There was no indication of treatment- or dose-related changes in clinical chemistry, hematology, urinalysis parameters or liver function tests over the course of the study. However, for diastolic blood pressure it was noted that the mean change from baseline in diastolic blood pressure was greater in the placebo group (−2.1 mmHg) than the UMEC treatment groups (range: −0.8 to 0.6 mmHg). The difference was statistically significant between placebo and all UMEC OD treatment groups (except UMEC 31.25 OD) and UMEC 15.6 BID (1.7—2.7 mmHg, $p \leq 0.030$).

Post-treatment ECG abnormalities occurred at a similar rate across the treatment groups (UMEC, 38—48 subjects [30—38%]; placebo, 38 subjects [30%]). The most common abnormal finding was depolarization/repolarization (frequent ventricular premature depolarization [≥3]), which occurred in 20—32 subjects [15—25%] following UMEC treatment and 21 subjects [17%] following placebo. A similar incidence of Holter abnormalities were reported at Day 14 in the placebo group (6 subjects [15%]) and UMEC treatment groups (7—8 subjects [14—19%]), with the exception of UMEC 15.6 OD where the incidence was lower (3 subjects [7%]). Overall, there was no indication of treatment-related effects in relation to ECG and Holter findings.

Discussion

The utility of LAMAs is well established in the treatment of COPD, and tiotropium data in patients with asthma uncontrolled on an ICS-containing therapy are emerging [1,6,8]. In the present study, the change in trough FEV_1 at Day 15 was <0.090 L for all UMEC doses compared with placebo, with no consistency in the magnitude of the effect or apparent dose—ordered response. All UMEC doses were associated with significant improvements in 0—24-h WM FEV_1 (0.068—0.121 L) compared with placebo yet also without a dose—ordered response. There was no indication that BID dosing offered additional benefit over OD dosing. These results are in line with studies of tiotropium in asthma, which have failed to demonstrate a convincing dose—response with the doses established for use in COPD [20,21]. However, the data are in contrast to studies in COPD where UMEC demonstrated a dose—ordered response in trough FEV_1 across a similar range of OD doses [14]. It is possible that the contrasting results may be explained by

Table 4 Summary of key UMEC pharmacokinetic parameters (plasma and urine) following morning dosing on Days 1 and 14.

	UMEC treatment	*N*	Day 1			Day 14		
			n	*n**	Median (Range)	*n*	*n**	Median (Range)
Plasma parameters								
t_{max} (h)	15.6 OD	44	16	25	0.083 (0.05—0.25)	23	18	0.083 (0—12.05)
	31.25 OD	55	37	15	0.083 (0—0.30)	45	6	0.083 (0—0.28)
	62.5 OD	48	44	2	0.083 (0—0.25)	46	0	0.083 (0—12.25)
	125 OD	53	49	0	0.083 (0.05—0.28)	45	1	0.083 (0—0.27)
	250 OD	48	43	2	0.083 (0.05—0.33)	42	0	0.083 (0—0.25)
	15.6 BID	42	20	20	0.083 (0—0.27)	30	9	0.083 (0—2.00)
	31.25 BID	52	41	9	0.083 (0.05—0.25)	44	5	0.083 (0—2.00)
t_{last} (h)	15.6 OD	44	16	25	0.242 (0.05—0.25)	23	18	0.250 (0.05—12.05)
	31.25 OD	55	37	15	0.250 (0.05—2.08)	45	6	0.250 (0.07—12.13)
	62.5 OD	48	44	2	0.250 (0.08—2.08)	46	0	2.00 (0.18—24.17)
	125 OD	53	49	0	2.00 (0.05—2.17)	45	1	23.967 (0.23—24.27)
	250 OD	48	43	2	2.00 (0.27—2.15)	42	0	24.00 (2.07—24.5)
	15.6 BID	42	20	20	0.233 (0.05—2.03)	30	9	0.233 (0.07—11.75)
	31.25 BID	52	41	9	0.250 (0.05—0.25)	44	5	0.275 (0.05—11.95)
					Geometric mean (95% CI)			**Geometric mean (95% CI)**
C_{max} (pg/mL)	15.6 OD	44	41	25	NA	41	18	10.52 (NC, 13.33)
	31.25 OD	55	52	15	14.53 (11.57, 18.25)	51	6	24.04 (19.27, 29.98)
	62.5 OD	48	46	2	48.42 (39.08, 59.98)	46	0	66.21 (55.75, 78.63)
	125 OD	53	49	0	115.41 (96.03, 138.71)	46	1	131.65 (105.39, 164.44)
	250 OD	48	45	2	183.78 (136.91, 246.7)	42	0	339.65 (282.16, 408.85)
	15.6 BID	42	40	20	NA (NC, 10.93)	39	9	12.43 (10.29, 15.01)
	31.25 BID	52	50	9	17.35 (13.93, 21.62)	49	5	28.91 (22.35, 37.39)
AUC_{0-2} (pg h/mL)	15.6 OD	44	33	33	NA	27	27	NA
	31.25 OD	55	29	28	NA	17	12	NA
	62.5 OD	48	11	3	38.02 (20.79, 69.52)	36	2	55.46 (46.27, 66.46)
	125 OD	53	41	2	94.1 (77.34, 114.49)	44	1	124.29 (105.36, 146.64)
	250 OD	48	44	2	169.71 (135.32, 212.85)	42	0	290.6 (257.15, 328.4)
	15.6 BID	42	31	29	NA	26	23	NA
	31.25 BID	52	20	20	NA	29	9	27.75 (21.03, 36.62)
Urine parameters								
					Geometric mean (95% CI)			**Geometric mean (95% CI)**
Ae_{0-6} (mcg)	15.6 OD	44	39	2	0.092 (0.07, 0.120)	39	2	0.134 (0.106, 0.171)
	31.25 OD	55	52	0	0.122 (0.07, 0.208)	51	0	0.288 (0.244, 0.340)
	62.5 OD	48	46	0	0.032 (0.25, 0.40)	46	0	0. 532 (0.412, 0.688)
	125 OD	53	49	0	0.868 (0.07, 1.07)	46	0	0.999 (0.506, 1.974)
	250 OD	48	44	0	1.936 (1.60, 2.34)	42	0	3.278 (2.790, 3.850)
	15.6 BID	42	40	0	0.094 (0.07, 0.12)	39	0	0.181 (0.145, 0.228)
	31.25 BID	52	50	0	0.160 (0.13, 0.20)	48	1	0.286 (0.158, 0.519)
Ae_{0-24} (mcg)	15.6 OD	44	NA	NA	NA	38	1	0.376 (0.270, 0.523)
	31.25 OD	55	NA	NA	NA	51	0	0.797 (0.688, 0.924)
	62.5 OD	48	NA	NA	NA	45	0	1.815 (1.563, 2.107)
	125 OD	53	NA	NA	NA	43	0	3.567 (2.781, 4.574)
	250 OD	48	NA	NA	NA	40	0	7.812 (6.759, 9.029)
	15.6 BID	42	NA	NA	NA	39	0	0.484 (0.394, 0.595)
	31.25 BID	52	NA	NA	NA	48	0	1.014 (0.834, 1.232)
					Median (Range)			**Median (Range)**
Fe_{0-6} (%)	15.6 OD	44	39	2	0.516 (0.03—3.46)	39	2	1.014 (0.10—3.43)
	31.25 OD	55	52	0	0.473 (0.00—4.14)	51	0	0.911 (0.17—2.81)
	62.5 OD	48	46	0	0.631 (0.06—1.99)	46	0	1.001 (0.03—2.32)
	125 OD	53	49	0	0.750 (0.08—2.74)	46	0	1.263 (0.00—5.29)
	250 OD	48	44	0	0.769 (0.14—2.64)	42	0	1.266 (0.49—4.08)
	15.6 BID	42	40	0	0.638 (0.10—3.69)	39	0	1.269 (0.20—5.30)
	31.25 BID	52	50	0	0.517 (0.12—2.36)	48	1	1.378 (0.00—3.90)
Fe_{0-24} (%)	15.6 OD	44	NA	NA	NA	38	1	2.885 (0.03—9.39)
	31.25 OD	55	NA	NA	NA	51	0	2.614 (0.50—8.39)

Table 4 (*continued*)

	UMEC treatment	*N*	Day 1			Day 14		
			n	*n**	Median (Range)	*n*	*n**	Median (Range)
	62.5 OD	48	NA	NA	NA	45	0	3.352 (0.71–6.99)
	125 OD	53	NA	NA	NA	43	0	3.243 (0.14–9.24)
	250 OD	48	NA	NA	NA	40	0	3.044 (1.30–7.87)
	15.6 BID	42	NA	NA	NA	39	0	1.510 (0.39–5.36)
	31.25 BID	52	NA	NA	NA	48	0	1.681 (0.32–7.62)

Geometric mean and CIs were not calculated if there were over 50% and 30% NC values, respectively. AUC was imputed with half the lowest observed AUC, C_{max} was imputed with half the LLQ (LLQ, 10 pg/mL).
Ae, amount of UMEC excreted unchanged in urine; AUC, area under the curve; BID, twice daily; CI, confidence interval; C_{max}, maximum plasma concentration; Fe, percentage of total UMEC dose excreted in urine; LLQ, lower limit of quantification; *n*, number of non-missing values (including imputed NC values); *n**, number of NC values; NA, not available; NC, non-calculable (due to presence of NQ values); ND, not determined; NQ, non-quantifiable concentration measured as below LLQ; OD, once daily; t_{last}, time of the last point with quantifiable concentration; t_{max}, time to maximum plasma concentration; UMEC, umeclidinium.

differences in the levels of functional agonism in different health and disease states.

The present study demonstrated a bronchodilator effect of UMEC in subjects with asthma not requiring ICS treatment, which was of a similar nature to that seen in healthy volunteers (data on file). To our knowledge, no other trials have evaluated LAMAs for the treatment of asthma in the absence of ICS therapy. The modest improvement in pulmonary function could be a reflection of an asthma study population in whom parasympathetic nervous system dysfunction does not predominate. Supportive evidence for the benefit of anticholinergic medications in asthma exists in selected asthma populations, including those with nocturnal symptoms, or fixed airway obstruction, and in murine models of chronic asthma, rather than across the broad spectrum of asthma severity [22–24]. Furthermore, a study of UMEC combined with an OD ICS (fluticasone furoate) demonstrated convincing evidence of a bronchodilating effect of UMEC in patients with asthma uncontrolled on ICS, and further showed that the effect was greater in patients with fixed versus non-fixed obstruction [25].

Overall, the PK of UMEC in terms of both plasma concentration and urine extraction were consistent with previous studies of UMEC in healthy volunteers and patients with COPD [11,14,26,27]. On Day 14, the high proportion of non-quantifiable values for UMEC C_{max} and AUC_{0-2} prevented an accurate interpretation of dose proportionality. However, in contrast to the plasma PK parameters, the urinary recovery of unchanged UMEC over 24 h following repeat dosing did show evidence of dose proportionality for

Table 5 On-treatment AEs reported by ≥3% of subjects in any treatment group.

Preferred term	Number of subjects, *n* (%)					
	Placebo *N* = 126	UMEC OD				
		15.6 mcg *N* = 131	31.25 mcg *N* = 138	62.5 mcg *N* = 133	125 mcg *N* = 128	250 mcg *N* = 135
Any AE	15 (12)	12 (9)	13 (9)	21 (16)	26 (20)	28 (21)
Headache	2 (2)	5 (4)	4 (3)	5 (4)	4 (3)	6 (4)
Nasopharyngitis	1 (<1)	3 (2)	0	1 (<1)	3 (2)	1 (<1)
Product taste abnormal	0	0	2 (1)	1 (<1)	4 (3)	5 (4)
Pharyngitis	1 (<1)	0	1 (<1)	5 (4)	0	1 (<1)

Preferred term	UMEC BID	
	15.6 mcg *N* = 126	31.25 mcg *N* = 133
Any AE	16 (13)	12 (9)
Headache	2 (2)	6 (5)
Nasopharyngitis	4 (3)	2 (2)
Product taste abnormal	1 (<1)	0
Pharyngitis	1 (<1)	0

On-treatment AEs were defined as AEs with onset within the period beginning with the first day of study drug administration through the day after the last day of study drug administration.
AE, adverse event; BID, twice daily; OD, once daily; UMEC, umeclidinium.

OD doses. There was some evidence of accumulation with repeat dosing, further studies would be needed to determine whether this had reached a plateau by Day 14 as observed in the previous studies [11,26].

No safety concerns were identified from the clinical chemistry and hematology data. Cardiovascular safety was closely monitored in the study, particularly in the serial subgroup where serial ECGs and 24-h Holter recording were performed. Holter abnormalities (that did not meet exclusion criteria) were identified in 20 of the subjects (16%) with available Holter counts during screening (most commonly recorded as ectopic supraventricular beats, other abnormality/cardiologist comments and ventricular premature depolarization), indicating a background incidence of findings in the population studied. Most subjects included in the study population had normal ECG or Holter assessments at screening, although a high proportion of abnormal ECGs not requiring exclusion were observed over the study. Overall, the ECG and Holter data did not raise safety concerns, as judged by the study investigators, consistent with studies of UMEC in patients with COPD [11].

Conclusions

In conclusion, the modest improvements in trough FEV_1 following UMEC treatment were not dose-related or consistent in magnitude, and therefore did not conclusively support a therapeutic benefit of UMEC monotherapy in patients with asthma not requiring ICS treatment. The results of this study, the first to evaluate LAMA monotherapy in asthma, should be balanced with the preponderance of data for LAMAs in the management of COPD [1] and emerging evidence for their benefit in patients with persistent asthma [6,8,25]. As LAMAs may not provide effective bronchodilation in patients with asthma who do not exhibit features of high cholinergic tone, adequate characterization of the dose—response of UMEC in asthma requires careful consideration of the subjects' phenotype.

Role of the funding source

The work presented here, including the conduct of the study, data analysis and interpretation, was supported by GlaxoSmithKline.

Author contributions

All authors participated in the conception and design of the research study; SY and LDE analyzed data and performed statistical analyses; all authors contributed to the writing of the paper and participated in the review and interpretation of the data. All authors read and approved the final manuscript.

Conflicts of interest

AB, LDE, LAL, SP, and SY are employees of GlaxoSmithKline and hold stocks/shares in the company.

Acknowledgments

Editorial assistance in the preparation of the manuscript (provided by Natasha Thomas, PhD, of Fishawack Indicia Ltd) was funded by GlaxoSmithKline.

Appendix A. Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.rmed.2014.10.009.

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