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Efficacy and safety of umeclidinium added to fluticasone furoate/vilanterol in chronic obstructive pulmonary disease: Results of two randomized studies

Thomas M. Siler [a, *], Edward Kerwin [b], Ana R. Sousa [c], Alison Donald [d], Rehan Ali [c], Alison Church [d]

[a] Midwest Chest Consultants, PC, 330 First Capitol Drive, Suite 470, St Charles, MO, USA
[b] Clinical Research Institute of Southern Oregon, Medford, OR, USA
[c] GSK, Respiratory Medicines Development Centre, Stockley Park, Middlesex, UK
[d] GSK, Respiratory and Immuno-Inflammation, Research Triangle Park, NC, USA

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ABSTRACT

Objective: The aim of these studies (NCT01957163; NCT02119286) was to evaluate the efficacy and safety of umeclidinium (UMEC 62.5 μg and 125 μg) added to fluticasone furoate/vilanterol (FF/VI, 100/25 μg) in chronic obstructive pulmonary disease (COPD).

Methods: These were 12-week, double-blind, placebo-controlled, parallel-group, multicenter studies. Eligible patients were randomized 1:1:1 to treatment with once-daily blinded UMEC 62.5 μg (delivering 55 μg), UMEC 125 μg (delivering 113 μg) or placebo (PBO) added to open-label FF/VI (delivering 92/22 μg; N = 1238 [intent-to-treat population]). The primary endpoint was trough forced expiratory volume in one second (FEV_1) on Day 85; the secondary endpoint was 0–6 h post-dose weighted mean (WM) FEV_1 at Day 84. Health-related quality of life was reported using St George's respiratory questionnaire (SGRQ). Adverse events (AEs) were also assessed.

Results: In both studies, trough FEV_1 was significantly improved with UMEC + FF/VI (62.5 μg and 125 μg) versus PBO + FF/VI (range: 0.111–0.128 L, all $p < 0.001$ [Day 85]), as was 0–6 h post-dose WM FEV_1 (range: 0.135–0.153 L, all $p < 0.001$ [Day 84]). SGRQ results were inconsistent, with statistically significant improvements with UMEC + FF/VI versus PBO + FF/VI in one study only and with UMEC 62.5 μg only (difference in SGRQ total score from baseline between treatments: −2.16, $p < 0.05$). Across all treatment groups, the overall incidences of AEs were similar (30–39%), as were cardiovascular AEs of special interest (<1–3%) and pneumonia AEs (0–1%).

Conclusion: Overall, the addition of UMEC to FF/VI therapy resulted in significant improvements in lung function compared with PBO + FF/VI in patients with COPD, with similar safety profiles, though SGRQ results were inconsistent.

Clinical relevance: The results from these two studies demonstrate that the addition of umeclidinium (62.5 μg and 125 μg) to FF/VI (100/25 μg) provides statistically significant and clinically meaningful improvements in lung function compared with placebo + FF/VI in patients with COPD. Statistically significant improvements in quality of life with UMEC + FF/VI versus placebo + FF/VI were reported in one study only. Safety profiles were consistent across all treatment groups in both studies. These studies support the use of triple therapy in COPD, providing physicians with an alternative treatment option.

Abbreviations: AE, adverse event; ASE, all subjects enrolled; CAT, COPD Assessment Test; CI, confidence interval; COPD, chronic obstructive pulmonary disease; FEV_1, forced expiratory volume in one second; FF, fluticasone furoate; FVC, forced vital capacity; GOLD, Global Initiative for Chronic Obstructive Lung Disease; HRQoL, health-related quality of life; ICS, inhaled corticosteroid; ITT, intent-to-treat; LABA, long-acting beta$_2$ agonist; LAMA, long-acting muscarinic agonist; LS, least squares; MedDRA, Medical Dictionary for Regulatory Activities; PBO, placebo; PRO, patient-reported outcome; QoL, quality of life; RI, run-in; SAE, serious adverse event; SGRQ, St George's Respiratory Questionnaire; UMEC, umeclidinium; VI, vilanterol; WM, weighted mean.

* Corresponding author. Midwest Chest Consultants, 330 First Capitol Drive, Suite 470, St Charles, MO, USA.
E-mail address: thomas.siler.md@midwestchest.com (T.M. Siler).

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1. Introduction

Chronic obstructive pulmonary disease (COPD) is characterized by persistent airflow limitation, is a substantial contributor to morbidity and mortality worldwide, and imparts a high economic burden [1,2]. Central to the pharmacological management of COPD are inhaled bronchodilators, such as muscarinic antagonists and beta$_2$-agonists [1] and inhaled anti-inflammatory agents, such as corticosteroids [1].

As disease severity increases, COPD treatment guidelines recommend an incremental approach to pharmacological treatment, involving the use of combinations of drug classes with different or complementary mechanisms of action [1,3]. Long-acting muscarinic antagonists (LAMAs) have been shown to improve lung function, relieve symptoms, increase exercise capacity, improve quality of life (QoL) and reduce COPD exacerbations to a greater extent than short-acting bronchodilators alone [1,4,5]. Inhaled corticosteroid (ICS)/long-acting beta$_2$ agonist (LABA) combination products have been shown to improve lung function, health status and reduce COPD exacerbations compared with either agent alone [1].

The use of combinations of drug classes with complementary mechanisms of action addresses the multi-component, inflammatory and progressive nature of COPD [1]. Recent studies involving the LAMA tiotropium in patients with COPD have shown that the addition of a LAMA to an ICS/LABA combination was well tolerated and associated with improvements in pulmonary, symptomatic and health-related QoL (HRQoL) endpoints [6–10]. Based on the results of several trials, the Global Initiative for Chronic Obstructive Lung Disease (GOLD) guidelines now include a recommendation for the use of a LAMA plus an ICS/LABA product as a secondary treatment option for symptomatic COPD with severe airflow obstruction and a high risk of exacerbations [1].

Although guidelines recommend a LAMA plus ICS/LABA as a treatment for patients with very severe COPD, physician prescribing practices differ from treatment guidelines, which may reflect differences in clinical judgement of the severity of COPD disease. In one study that examined the GOLD strategy in a real-world COPD population, 22.2% of patients categorized as having moderate COPD (according to the GOLD 2010 and 2011 criteria) received treatment with a LAMA plus an ICS/LABA, whereas 58.4% of patients with very severe COPD received a LAMA plus an ICS/LABA [11].

Umeclidinium bromide 62.5 μg (UMEC, GSK573719; GSK, London, UK) is a LAMA indicated for the treatment of COPD [4,12]. Fluticasone furoate/vilanterol (FF/VI) is a once-daily ICS/LABA combination indicated for the treatment of patients with COPD [13]. Here, we present the results of two clinical studies investigating the efficacy and safety of once-daily UMEC (62.5 μg and 125 μg) in addition to once-daily FF/VI (100/25 μg) in patients with moderate-to-very-severe COPD.

2. Materials and methods

2.1. Study designs

Two replicate, 12-week, randomized, double-blind, placebo-controlled parallel-group studies were completed between October 2013 and April 2014. Study 1 (ClinicalTrials.gov registration number: NCT01957163; GSK study number: 200109) was conducted in Argentina, Canada, Chile, Romania and the USA. Study 2 (ClinicalTrials.gov registration number: NCT02119286; GSK study number: 200110) was conducted in the Czech Republic, Germany, the Republic of Korea and the USA. Both studies were conducted in accordance with the Declaration of Helsinki [14] and Good Clinical Practice guidelines, were approved by the relevant local ethics review committees, and all patients provided written, informed consent before study participation.

2.2. Patients

Eligible patients were: ≥40 years of age with a clinically established history of COPD [3]; current or former cigarette smokers with ≥10-pack-years smoking history; had a pre- and post-salbutamol (albuterol) forced expiratory volume in one second (FEV_1)/forced vital capacity (FVC) ratio of <0.7 and predicted FEV_1 ≤70%; and had a modified Medical Research Council dyspnea scale score ≥2. Exclusion criteria included: current diagnosis of asthma or other known respiratory disease, hospitalization in the 12 weeks previous to Visit 1 for COPD or pneumonia, pregnancy, or use of long-term oxygen therapy. Patients previously receiving COPD medications were eligible provided they adhered to the following exclusion periods prior to Visit 1 and subsequently avoided their use throughout the study: ICS use was permitted to Visit 1, LAMA use required a 7-day exclusion period and the use of ICS/LABA combination therapies required a 48-h exclusion period (further details of inclusion/exclusion criteria, permitted/prohibited medications and washout periods are provided in Supplementary Materials).

2.3. Treatment

Following screening at Visit 1, patients underwent 4 weeks' run-in treatment with open-label FF/VI 100/25 μg (delivering 92/22 μg) prior to the 12-week treatment period (Visits 2–7). Eligible patients were randomized 1:1:1–12 weeks' treatment with once-daily UMEC 62.5 μg (delivering 55 μg), UMEC 125 μg (delivering 113 μg), or placebo (PBO), plus FF/VI (100/25 μg once daily) administered via the ELLIPTA™ dry powder inhaler. UMEC and PBO treatments were double-blind; FF/VI treatment was open label.

Randomization codes were generated by GSK using a validated computerized system (RandAll v2.13). Concurrent use of salbutamol as rescue medication was permitted throughout the study, except during the 4 h prior to spirometry testing.

2.4. Outcomes and assessments

In both studies, the primary efficacy endpoint was trough FEV_1 at Day 85 (defined as the mean of the FEV_1 values obtained 23 and 24 h after dosing on Day 84). An increase of 0.100 L was considered as the minimal clinically important difference (MCID) for this endpoint [15,16]. The secondary efficacy endpoint was weighted-mean (WM) FEV_1 over 0–6 h obtained post-dose on Day 84. Other lung function endpoints included: proportion of patients achieving an increase of ≥0.100 L above baseline in trough FEV_1; lung function endpoints (trough FEV_1 and WM FEV_1 over 0–6 h post-dose) at other timepoints; the proportion of patients achieving an increase in FEV_1 of ≥12% and ≥0.200 L above baseline at any time during 0–6 h post-dose at Day 1; serial FEV_1 over 0–6 h (at each timepoint); peak FEV_1 at Days 1, 28 and 84; time to onset of treatment response (defined as an increase of 0.100 L above baseline in FEV_1 [not specified in the original protocol]); and serial and trough FVC at each timepoint.

Other endpoints included rescue medication, as assessed by the percentage of rescue-free days and puffs/day (descriptive data only). HRQoL endpoints included the COPD Assessment Test (CAT; descriptive data only) [17,18] and St George's Respiratory Questionnaire for COPD Patients (SGRQ-C) [19]. SGRQ scores were calculated from the SGRQ-C-scores using standardized adjustment. Safety assessments included adverse events (AEs), vital signs (including pulse rate and systolic and diastolic blood pressure) and