ORIGINAL RESEARCH

Comparative Effectiveness of Umeclidinium/ Vilanterol versus Inhaled Corticosteroid/Long-Acting β₂-Agonist in Patients with Chronic Obstructive Pulmonary Disease in a Primary Care Setting in England

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Purpose: To compare adherence to once-daily umeclidinium/vilanterol (UMEC/VI), a long-acting muscarinic antagonist/long-acting β₂-agonist (LAMA/LABA), and twice-daily inhaled corticosteroids (ICS)/LABA single-inhaler dual therapy in patients with chronic obstructive pulmonary disease (COPD) in a primary care cohort in England.

Patients and Methods: Active comparator, new-user, retrospective cohort study using CPRD-Aurum primary care data and linked Hospital Episode Statistics secondary care administrative data. Patients without exacerbations in the previous year were indexed on first/earliest prescription date of once-daily UMEC/VI or twice-daily ICS/LABA as initial maintenance therapy between July 2014-September 2019. Primary outcome: medication adherence at 12 months post-index, defined as proportion of days covered (PDC) ≥80%. PDC represented proportion of time over the treatment duration that the patient was theoretically in possession of the medication. Secondary outcomes: adherence at 6, 18, and 24 months post-index, time-to-triple therapy, time-to-first on-treatment COPD exacerbation, COPD-related and all-cause healthcare resource utilization (HCRU), and direct health-care costs. A propensity score was generated and inverse probability of treatment weighting (IPTW) was used to balance potential confounders. Superiority was defined as >0% difference between treatment groups.

Results: In total, 6815 eligible patients were included (UMEC/VI:1623; ICS/LABA:5192). At 12 months post-index, weighted odds of a patient being adherent were significantly greater with UMEC/VI versus ICS/LABA (odds ratio [95% CI]: 1.71 [1.09, 2.66]; p=0.0185), demonstrating superiority of UMEC/VI. Patients taking UMEC/VI were statistically significantly more adherent than those taking ICS/LABA at 6, 18, and 24 months post-index (p<0.05). Differences in time-to-triple therapy, time-to-moderate COPD exacerbations, HCRU, and direct medical costs were not statistically significant between treatments after IPTW was applied.

Conclusion: At 12 months post-treatment initiation, once-daily UMEC/VI was superior to twice-daily ICS/LABA in medication adherence among patients with COPD without exacerbations in the previous year, newly initiating dual maintenance therapy in England. The finding was consistent at 6, 18, and 24 months.

Keywords: adherence, comparative effectiveness, chronic obstructive pulmonary disease (COPD) treatment, inhaled corticosteroid/long-actingβ₂-agonist (ICS/LABA) dual therapy, long-acting muscarinic antagonist (LAMA)/LABA dual therapy

Plain Language Summary

Chronic obstructive pulmonary disease (COPD) can be treated with a combination of two bronchodilators, such as umeclidinium/vilanterol (UMEC/VI), a long-acting muscarinic antagonist/long-acting β_2-agonist (LAMA/LABA) administered once daily, or a bronchodilator and an inhaled corticosteroid (ICS), such as an ICS/LABA administered twice daily. It is important to investigate how well patients adhere to their medications as studies have shown that patients who do not routinely take their medicines are more likely to suffer hospitalizations, greater mortality and morbidity, and reduced quality of life.

We analyzed data from patients with COPD of at least 35 years of age using a large database, the Clinical Practice Research Datalink, which includes information from patients treated in primary care in England, linked to the English secondary care database, Hospital Episode Statistics. In total, 6815 patients were included, among whom 1623 received UMEC/VI and 5192 received ICS/LABA. In the year after treatment initiation, we found that patients taking UMEC/VI had significantly greater adherence than those taking ICS/LABA in the short and long terms. Patients taking UMEC/VI were also more adherent than those taking ICS/LABA up to 2 years after initiating treatment. These results suggest that patients are more likely to adhere to their treatment and have better real-world outcomes when starting treatment with once-daily UMEC/VI over twice-daily ICS/LABA in a primary care setting in England.

Introduction

In 2019, chronic obstructive pulmonary disease (COPD) was the third leading cause of mortality globally.[1] In the UK, COPD affects 1.2 million people, making it the second most common lung disease after asthma.[2] The burden of COPD increases with overall frequency of symptoms and exacerbations, contributing to increased healthcare resource utilization (HCRU) and direct medical costs.[3,4] Adherence to inhaled therapy is critical to COPD management, with non-adherent patients experiencing significantly higher rates of COPD exacerbations, HCRU, and costs compared with adherent patients.[5–8] Poor adherence, as with other chronic diseases, is common in COPD and has been reported to increase morbidity rates, health-care costs, hospitalizations, mortality, escalation of therapy, and reduce quality of life.[9]

The Global Initiative for Chronic Obstructive Lung Disease (GOLD) strategic report and the National Institute for Health and Care Excellence (NICE) guideline in the UK recommend long-acting muscarinic antagonist (LAMA)/long-acting β_2-agonist (LABA) dual therapy as the initial maintenance treatment for patients with severe symptoms (COPD Assessment Test score ≥ 20) or for patients who continue to experience dyspnea and/or exacerbations despite short-acting bronchodilator use.[10,11] The GOLD 2023 strategy report no longer recommends inhaled corticosteroid (ICS)/LABA dual therapy for patients with COPD;[12] however, in the UK, NICE guideline still recommends ICS/LABA dual therapy for patients who have asthmatic features, remain breathless, or have exacerbations despite short-acting bronchodilator use.[11] Escalation to triple therapy with ICS/LAMA/LABA is recommended in patients who do not achieve adequate symptomatic relief with dual therapy.[10,11]

Umeclidinium/vilanterol (UMEC/VI) is a once-daily single-inhaler LAMA/LABA dual therapy approved in the UK for the treatment of COPD.[13] Retrospective studies in the US have demonstrated that patients with COPD who are infrequent exacerbators have higher adherence and a lower rate of severe COPD exacerbations after initiating UMEC/VI compared with patients initiating treatment with ICS/LABA dual therapy.[14–16] An administrative claims database study of patients initiating treatment for COPD in the US showed that those initiating a once-daily dosing treatment had significantly higher adherence and reduced HCRU than those initiating treatment on multiple daily dosing treatment, indicating that dosing regimen may be an important factor impacting adherence.[7] Other medication and regimen factors, such as inhaler device convenience and satisfaction, may also play an important role in determining adherence.[6] Moreover, adherence is lower for medications that do not have an immediate or direct effect on symptoms and drug side effects and medication costs may also impact adherence.[9]

There is no real-world evidence on adherence to once-daily LAMA/LABA in comparison with twice-daily ICS/LABA single-inhaler dual therapies in routine clinical practice in England. Therefore, this study aimed to assess adherence, escalation to triple therapy, COPD exacerbations, HCRU, and costs in patients with no prior exacerbations who were newly initiating maintenance therapy with once-daily UMEC/VI versus twice-daily ICS/LABA in a primary care setting in England.

Materials and Methods

Study Design

This was an active comparator and retrospective cohort study (GSK study ID: 214888) of patients with COPD who were new users of once-daily single-inhaler UMEC/VI or twice-daily single-inhaler ICS/LABA, using primary care medical data from the Clinical Practice Research Datalink (CPRD-Aurum) and linked secondary care administrative data from Hospital Episode Statistics (HES) in England (Figure 1). This study compared adherence between initial maintenance therapy (IMT) users without a history of moderate/severe exacerbation. IMT users were those without a prescription of COPD maintenance therapy (ie, any LAMA or LABA bronchodilator) at any time prior to index date. CPRD-Aurum is a longitudinal, representative anonymized electronic health record database of primary care interactions in England, containing data routinely collected from primary care practices using the EMIS Web® electronic patient record system software. For the purpose of this study, CPRD-Aurum was linked to the HES Admitted Patient Care (HES APC), and HES Accident and Emergency (HES A&E) datasets, to allow for a complete overview of the patient health-care pathway. HES APC includes basic patient demographics, date and method of hospital admission (emergency or planned)[17] and discharge, diagnoses (including primary diagnosis), specialists seen, and procedures undertaken with all diagnostic data captured using the International Classification of Diseases, Tenth Revision coding framework, as well as procedure information coded using the UK Office of Population, Census, and Surveys classification version 4.9. HES outpatient was excluded due to limited data availability at the time of the study, and the understanding that the majority of HCRU for COPD was in emergency and inpatient care settings.

The index date was defined as the first prescription date of once-daily single-inhaler UMEC/VI or a twice-daily single-inhaler ICS/LABA within the indexing period (1 July 2014 to 30 September 2019). A 12-month baseline period and a variable follow-up of up to 24 months were applied. The end of the study period was 31 March 2020. While additional data were available beyond this timeline, the study period end date was set at 31 March 2020 to avoid any impact of the COVID-19 pandemic on the study results, as management of patients with COPD would not be representative during this period and the changes in HCRU were not under study.

Patients were divided into cohorts based on indexed medication (UMEC/VI or ICS/LABA).

The twice-daily ICS/LABA treatment arm included fluticasone propionate/salmeterol xinafoate (FP/SX), beclomethasone dipropionate/formoterol fumarate (BDP/FOR), budesonide/formoterol fumarate (BUD/FOR) and fluticasone propionate/formoterol (FP/FOR).

Patient demographics and characteristics were assessed at baseline (index inclusive). Other outcomes were assessed post-index for a maximum of 24 months.

Patient Population

All patients included in this study were required to have at least one primary care COPD diagnostic code at 35 years of age or above at any time in their history,[11] at least one prescription of single-inhaler once-daily UMEC/VI or twice-daily
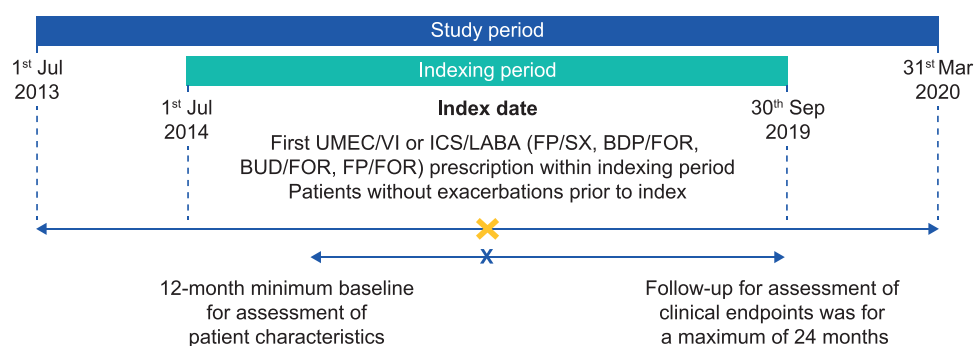

Figure 1 Study design.
Abbreviations: BDP, beclomethasone dipropionate; BUD, budesonide; ICS, inhaled corticosteroid; FOR, formoterol fumarate; FP, fluticasone propionate; LABA, long-acting β_2-agonist; SX, salmeterol xinafoate; UMEC, umeclidinium; VI, vilanterol.

ICS/LABA during the index period, forced expiratory volume in 1 s/forced vital capacity <0.7 at any time prior to index (inclusive), a minimum of 12 months of continuous registration pre-index with a general practitioner (GP), and data eligible for linkage to HES.

Patients were excluded if they had one or more diagnostic codes for medical conditions incompatible with a COPD diagnosis at any time prior to and including index, including but not limited to conditions related to lung or bronchial developmental anomalies, degenerative processes, pulmonary resection, or other significant respiratory disorders, one or more prescriptions of any COPD maintenance therapy (ie, use of any long-acting bronchodilator) prior to index, prescription for both UMEC/VI and ICS/LABA at index, concomitant use of ICS or LAMA-containing medications at index date in patients indexed for UMEC/VI and ICS/LABA, respectively, and ≥1 COPD exacerbation during the 12-month pre-index period (index date inclusive).

Study Outcomes

The primary outcome was medication adherence at 12 months after index. Adherence was defined as proportion of days covered (PDC) ≥80%, which is based on the threshold typically accepted in the literature.[14] PDC represented the proportion of time over the course of the patients' treatment that they theoretically were in possession of the medication; PDC was calculated by dividing the days covered by a fixed time interval (ie, 12 months): PDC = (number of covered days in period/number of days in period)x100 for all patients, regardless of treatment at index. Patients were considered "covered" for any given day in which they had a valid prescription for the relevant dual therapy.

Secondary endpoints included adherence (PDC≥80%) at 6, 18, and 24 months post-index, time-to-triple therapy initiation, time-to-first on-treatment COPD moderate-to-severe exacerbation, COPD-related and all-cause HCRU, and total COPD-related and all-cause direct health-care costs. All-cause HCRU comprised events reported for any reason. All-cause costs were the sum of all direct health-care costs accumulated within any given time period regardless of disease. As such, COPD-related HCRU and costs are a subset of all-cause HCRUs and costs. COPD-related HCRU was defined as a COPD-related event (ie, prescription for a COPD medication; GP consultation with a diagnostic code of COPD; hospital admission with COPD, unspecified acute lower respiratory infection, chronic bronchitis or emphysema diagnostic codes; and A&E admission with a diagnosis of respiratory conditions) recorded on the same day as the resource use; COPD-related costs were those associated with COPD-related HCRU. Prescriptions for COPD medications included short-acting β-agonist (SABA), short-acting muscarinic antagonist (SAMA), SABA/SAMA, ICS/SABA, ICS, LABA, LAMA, ICS/LABA, LAMA/LABA, methylxanthines, and inhaled phosphodiesterase 4 (PDE-4) inhibitors. Moderate-to-severe COPD exacerbations were identified according to an existing algorithm previously validated against physician notes.[18,19] A moderate exacerbation was one that required prescription of antibiotics and oral corticosteroids for 5–14 days, or the presence of respiratory symptoms and a prescription of antibiotics or oral corticosteroids on the same day, or a lower respiratory tract infection (LRTI) diagnosis using a specific LRTI medical code, or a COPD exacerbation-specific medical code. A severe exacerbation was one requiring hospitalization. The following COPD-related and all-cause health-care services were considered: primary care visits, hospitalizations, and A&E visits. COPD-related direct medical costs encompassed the sum of total medical costs, primary care costs (including costs for consultation and prescription medication), hospitalization costs, and A&E costs. Rescue medication use, defined as inhaled or nebulized short-acting β$_2$-agonist- or short-acting muscarinic antagonist-containing medication use and excluding those prescribed as part of a fixed-dose long-acting containing combination inhaler, at 6, 12, 18, and 24 months post-index was assessed as an exploratory outcome.

Sample Size and Statistical Analysis

A sample size of 1250 patients receiving UMEC/VI and 3000 patients receiving ICS/LABA was estimated to provide 80% power to detect at least a 5% difference in adherence among patients in the UMEC/VI versus ICS/LABA treatment arms. The superiority of UMEC/VI versus ICS/LABA in reducing medication adherence at 12 months post-index was defined with a margin of >0. A propensity score (PS) and an inverse probability of treatment weighting (IPTW)[20] approach were used for study outcome comparisons between treatment cohorts. A new PS, based on information observed, baseline demographic and clinical characteristics, was generated for each treatment comparison endpoint (and time interval where

relevant); the optimal method for applying the PS largely depended upon the ratio of patients within each treatment cohort, the extent of the overlap in the PS distribution between treatment cohorts, and any unknown confounders. IPTW was used to adjust for any differences in baseline characteristics between treatment groups, and per-patient probability weights were calculated as 1/PS for UMEC/VI and 1/(1-PS) for ICS/LABA. The weights derived from the PS for the IPTW models were used to create a pseudo-population, where the distribution of covariates in the population was independent of treatment assignment. This allowed an unbiased estimation of the average treatment effect (ATE) in the entire population by accounting for the influence of covariates on the results. Coefficients from each IPTW model were exponentiated to produce more familiar ATE, eg rate ratio and hazard ratio. A standardized mean difference (SMD) of less than 10% in the weighted cohort was indicative of adequate balance being achieved between the treatment cohorts, ie, considered quantitative evidence of relative balance of covariates.[21]

An on-treatment analysis was conducted to assess adherence, where patients were censored at the time of the first prescription for any non-indexed long-acting maintenance medication, or discontinuation of their indexed therapy. For all other endpoints, an intention-to-treat (ITT) analysis was conducted, where patients remained in their indexed treatment cohort for the entire follow-up period (maximum 24 months) and were only censored upon switching to the other indexed treatment. Time-to-triple therapy initiation and time-to-first in-treatment COPD exacerbation were assessed using Kaplan–Meier survival analysis. Both ITT and on-treatment analyses were conducted to compare COPD-related and all-cause HCRU and direct medical costs. The exploratory endpoint of rescue medication use was analyzed descriptively using descriptive analysis.

Results based on small numbers of patients (n<5) were not reported, in line with standard CPRD reporting practices.

Results
Patient Population and Baseline Characteristics

In total, 6815 patients met the study eligibility criteria, of whom 1623 (23.8%) were indexed on once-daily UMEC/VI and 5192 (76.2%) were indexed on twice-daily ICS/LABA (Supplementary Figure 1). Mean (standard deviation [SD]) age was 68.2 (10.6) and 67.4 (11.2) years and 42.3% and 44.8% of patients were female in the UMEC/VI and ICS/LABA groups, respectively (Table 1). Differences in baseline patient demographic and clinical characteristics were observed between treatment groups. There was a smaller proportion of patients with a Medical Research Council (MRC) dyspnea scale score of 1 (10.9% vs 17.9%) and GOLD grade A (49.3% vs 64.4%) in the UMEC/VI versus ICS/LABA group. Regarding prescribing patterns between regions, 24.0% versus 10.5% of patients indexed on once-daily UMEC/VI versus twice-daily ICS/LABA were based in the South West, respectively. A similar trend was observed for Yorkshire and the Humber (11.1% of UMEC/VI patients vs 3.3% of ICS/LABA patients). While patients in London accounted for 15.4% of ICS/LABA patients, they only accounted for 7.0% of UMEC/VI patients. In terms of comorbidities, the UMEC/VI group included fewer patients with a current (7.4%) diagnosis of asthma than the ICS/LABA group (29.8%) (Table 1). More patients in the once-daily UMEC/VI versus twice-daily ICS/LABA group had no respiratory therapy use pre-index (24.8% vs 11.4%).

Adherence at 12 Months

The covariates listed in Supplementary Table 1 were imbalanced prior to PS weighting. While balance improved from pre- to post-PS weighting, sufficient balance (SMD≤10) was not achieved for all covariates. Unbalanced covariates were index year, region, socioeconomic, ethnicity, current asthma diagnosis, and baseline respiratory treatment covariates. At 12 months post-index, significantly more patients in the UMEC/VI versus ICS/LABA group were adherent (PDC≥80%) for both unweighted (54.5% vs 42.3%) and weighted (56.7% vs 43.4%) analyses (Figure 2A). The weighted odds of a patient being adherent versus not being adherent at 12 months post-index were significantly greater in the UMEC/VI versus ICS/LABA group (weighted odds ratio [95% confidence interval]: 1.71 [1.09, 2.66]; p=0.0185), thus demonstrating superiority of once-daily UMEC/VI versus twice-daily ICS/LABA (Figure 2B). Additional sensitivity analyses were conducted to support the findings in the main analysis, in consideration of insufficient PS model balance (all-defining adherence as PDC≥80%). These included trimming PS to region of overlap only, excluding patients with a current asthma diagnosis, removing ethnicity as a covariate (due to high volume of missing data), simultaneous exclusion of

Table 1 Patient Demographics and Clinical Characteristics

Characteristic	UMEC/VI (N=1623)	ICS/LABA (N=5192)
Age,[a] years, mean (SD)	68.2 (10.6)	67.4 (11.2)
Female, n (%)	686 (42.3)	2324 (44.8)
Patient region[a], n (%)		
East Midlands	22 (1.4)	132 (2.6)
East of England	49 (3.0)	207 (4.0)
London	113 (7.0)	797 (15.4)
North East	22 (1.4)	281 (5.4)
North West	308 (19.1)	1128 (21.8)
South Central	168 (10.4)	513 (9.9)
South East Coast	114 (7.1)	396 (7.7)
South West	386 (24.0)	541 (10.5)
West Midlands	250 (15.5)	1005 (19.4)
Yorkshire and The Humber	179 (11.1)	173 (3.3)
Multiple Deprivation Index,[a] n (%)		
Quintile 1 (least deprived)	252 (15.6)	737 (14.2)
Quintile 2	259 (16.0)	947 (18.3)
Quintile 3	289 (17.8)	992 (19.1)
Quintile 4	358 (22.1)	1160 (22.4)
Quintile 5 (most deprived)	462 (28.5)	1351 (26.0)
Smoking status,[b] n(%)		
Current smoker	973 (60.0)	2736 (52.7)
Former smoker	616 (38.0)	2161 (41.6)
Non-smoker	NR[c]	279 (5.4)
Unknown	NR[c]	16 (0.3)
FEV$_1$% predicted,[d] mean (SD)	58.6 (11.3)	59.7 (12.2)
GOLD 2019 grade,[e] n (%)		
A	800 (49.3)	2876 (64.4)
B	772 (47.6)	1419 (31.8)
C	25 (1.5)	97 (2.2)
D	26 (1.6)	77 (1.7)
MRC dyspnea scale score,[d] n (%)		
1[f]	177 (10.9)	927 (17.9)
2	648 (39.9)	2046 (39.4)
3	422 (26.0)	1119 (21.6)
4	143 (8.8)	317 (6.1)
5[g]	14 (0.9)	60 (1.2)
Unknown	219 (13.5)	723 (13.9)
Comorbidities,[h] n (%)		
Depression	515 (31.7)	1494 (28.8)
Rheumatoid/osteoarthritis	469 (28.9)	1518 (29.2)
Diabetes	306 (18.9)	865 (16.7)
Anxiety	276 (17.0)	900 (17.3)
Gastroesophageal reflux disease	261 (16.1)	890 (17.1)
Stroke	160 (9.9)	415 (8.0)
Acute myocardial infarction	140 (8.6)	448 (8.6)
Asthma[e]	117 (7.4)	1524 (29.8)

(Continued)

Table 1 (Continued).

Characteristic	UMEC/VI (N=1623)	ICS/LABA (N=5192)
Congestive heart failure	120 (7.4)	357 (6.9)
Dementia/cognitive impairment	91 (5.6)	326 (6.3)
Bronchiectasis	44 (2.7)	120 (2.3)
Lung cancer	16 (1.0)	35 (0.7)
Respiratory therapies received during baseline,[i] n (%)		
No use	402 (24.8)	592 (11.4)
Any use	1221 (75.2)	4600 (88.6)
ICS (not overlapping LABA or SABA)[j]	NR[c]	789 (15.2)
SABA (not overlapping SAMA)[j]	1153 (71.0)	4318 (83.2)
SAMA (not overlapping SABA or ICS)[j]	67 (4.1)	167 (3.2)
SAMA/SABA (FDC and open)[j]	61 (3.8)	227 (4.4)
ICS/SABA (FDC and open)[j]	85 (5.2)	3559 (68.5)
Xanthine	NR[c]	32 (0.6)
HCRU at baseline, mean (SD)		
Number of primary care visits	1.5 (1.3)	1.9 (1.5)
Number of hospitalisations	0.0 (0.0)	0.0 (0.0)
Number of A&E visits	0.0 (0.0)	0.0 (0.0)
Total medical costs at baseline, (GBP), mean (SD)	20.4 (62.9)	37.3 (81.5)

Notes: [a]At index; [b]Most recent score in the 24 months prior to index; [c]Results based on small numbers of patients (n<5) were suppressed, as well as related values to protect primary suppression; [d]During the 24 months prior to index (inclusive); [e]During the 12 months prior to index (inclusive); [f]Not troubled by breathlessness except on strenuous exercise; [g]Too breathless to leave the house; [h]At any time in a patient history inclusive of the index date; [i]During the 12 months prior to and including the index date (excluding index prescriptions); [j]Percentages calculated for the full cohort.
Abbreviations: A&E, Accident and Emergency; FDC, fixed-dose combination; FEV_1, forced expiratory volume in one second; GBP, British Pound Sterling; GOLD; Global Initiative for Chronic Obstructive Lung Disease; HCRU, healthcare resource utilization; ICS, inhaled corticosteroid; LABA, long-acting β_2-agonist; MRC, Medical Research Council; NR, not reported; SABA, short-acting β_2-agonist; SAMA, short-acting muscarinic antagonist; SD, standard deviation; UMEC, umeclidinium; VI, vilanterol.

current asthma and the ethnicity covariate (rather than separately), and adding imbalanced covariates back into the final weighted outcomes regression. All sensitivity analyses results supported superiority of UMEC/VI for the adherence outcome at 12 months, except for the analysis where PS was trimmed. However, the observed was in the same direction as all other analyses, yet it did not reach statistical significance (ie, supporting once-daily UMEC/VI over twice-daily ICS/LABA; p=0.1294) (Supplementary Table 2).

Adherence at Other Timepoints
Across all timepoints, the proportion of patients adherent to once-daily UMEC/VI was consistently greater than that for twice-daily ICS/LABA in both unweighted and weighted analyses (Supplementary Table 3). The weighted odds of a patient being adherent at 6 and 24 months were significantly greater in the UMEC/VI versus ICS/LABA group (Figure 3).

Time-to-Triple Therapy
Before PS weighting, 25/46 covariates had insufficient balance (SMD≥10). After PS weighting, model balance improved, but 14/46 covariates still showed insufficient balance, with SMDs ranging from 10.1 to 54.1 (Supplementary Table 1). In the unweighted analysis, patients initiated triple therapy at a significantly lower rate in the UMEC/VI versus ICS/LABA group, although this difference was not observed in the weighted analysis (Supplementary Figure 2). The unweighted hazard ratio (HR) of triple therapy initiation was significantly lower with once-daily UMEC/VI compared with twice-daily ICS/LABA; however, the weighted HR was not statistically significant (Figure 4A). In the weighted analysis, at 18 months after treatment
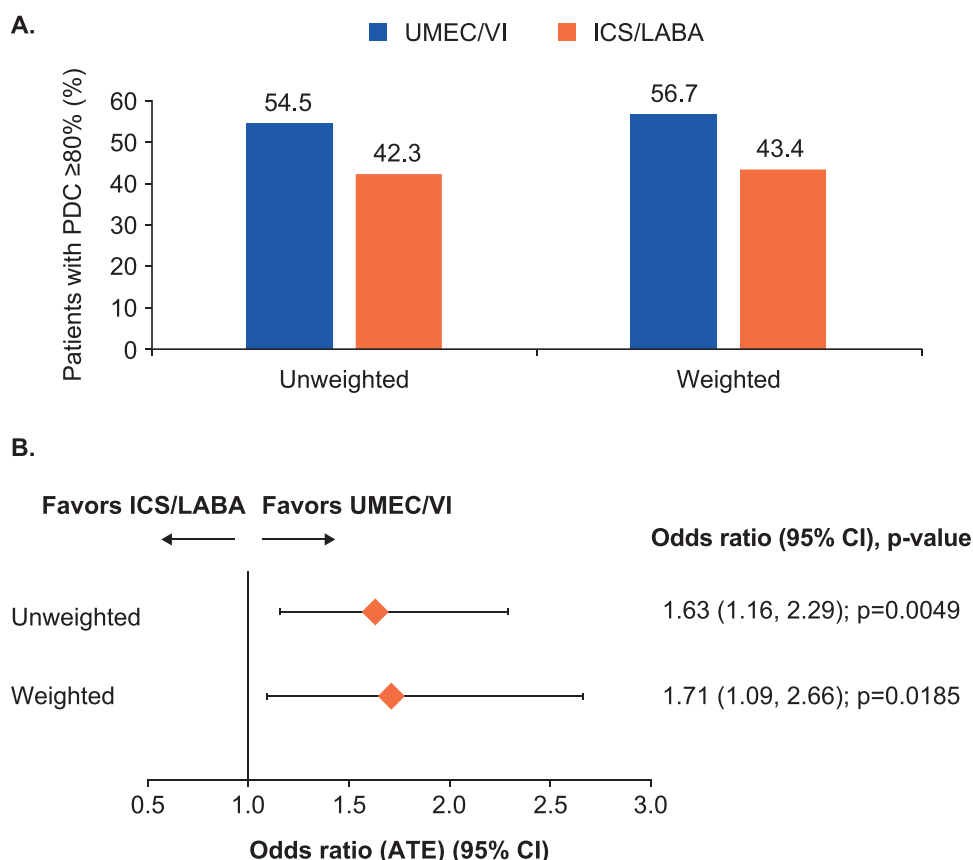
A.

B.

Figure 2 (**A**) Proportion of patients and (**B**) odds of adherence (PDC≥80%) at 12 months post-index.
Abbreviations: ATE, average treatment effect; CI, confidence interval; ICS, inhaled corticosteroid; LABA, long-actingβ_2-agonist; PCD, proportion of days covered; UMEC, umeclidinium; VI, vilanterol.
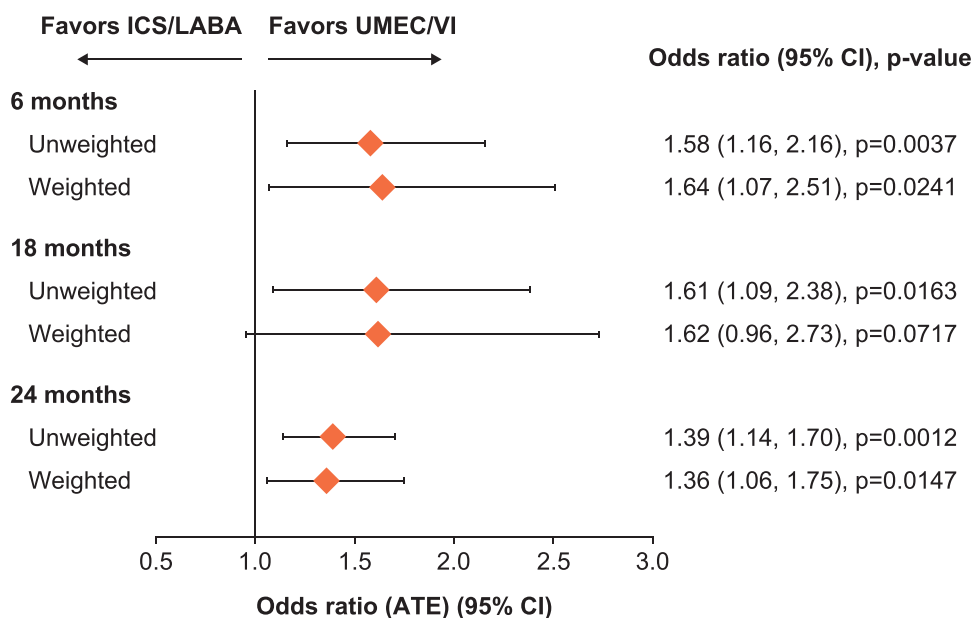

Figure 3 Odds of adherence (PDC≥80%) at 6, 18, and 24 months post-index.
Abbreviations: ATE, average treatment effect; CI, confidence interval; ICS, inhaled corticosteroid; LABA, long-actingβ_2-agonist; PCD, proportion of days covered; UMEC, umeclidinium; VI, vilanterol.

initiation, the UMEC/VI group showed a numerically lower rate of triple therapy initiation versus the ICS/LABA group, while median time-to-triple therapy was not reached for either treatment group. The on-treatment sensitivity analysis was consistent with the main ITT analysis (Supplementary Table 2).

Time-to-First on-Treatment Moderate-to-Severe COPD Exacerbation

Before PS weighting, 38/60 covariates had insufficient balance (SMD≥10); after PS weighting, model balance improved, but 19/60 still showed insufficient balance (Supplementary Table 1). Patients receiving once-daily UMEC/VI versus twice-daily ICS/LABA had a numerically lower risk of a first on-treatment moderate-to-severe COPD exacerbation in both unweighted and weighted analyses (Supplementary Figure 3). The unweighted HR of time-to-first on-treatment moderate-to-severe COPD exacerbation was statistically significantly different between treatment groups (Figure 4B). The on-treatment sensitivity analysis was consistent with the main ITT analysis (Supplementary Table 2).

HCRU

Before PS weighting, at 12 months post-index, 48.9–67.3% and 31.7–62.1% of covariates had insufficient balance (SMD≥10) in the COPD-related and all-cause models, respectively; after PS weighting, model balance improved, but 6.4–31.4% and 31.0–45.1% of covariates still showed insufficient balance (Supplementary Table 1). Across both COPD-related and all-cause analyses, the weighted incidence and rate ratio of HCRU were similar between treatment groups (Supplementary Table 4; Figure 5). In general, similar results were obtained with the on-treatment sensitivity analyses (Supplementary Table 2).

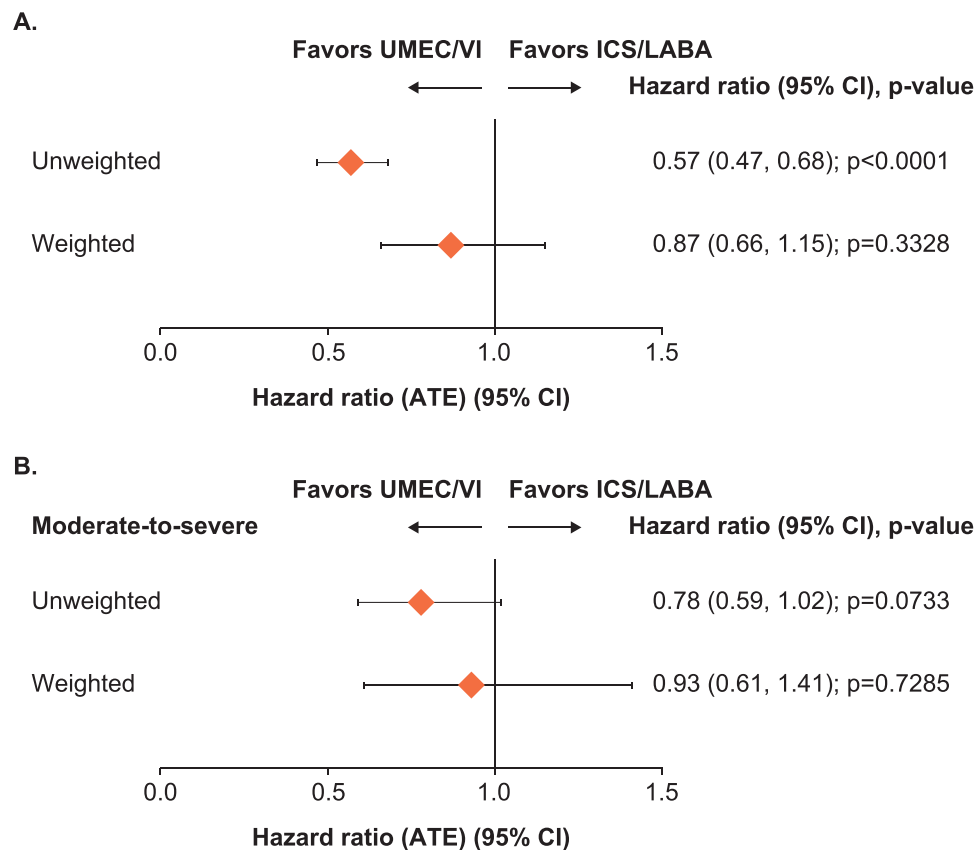**Figure 4** (**A**) Time-to-first triple therapy and (**B**) time-to-first moderate-to-severe COPD exacerbation.
Abbreviations: ATE, average treatment effect; CI, confidence interval; ICS, inhaled corticosteroid; LABA, long-actingβ₂-agonist; UMEC, umeclidinium; VI, vilanterol.
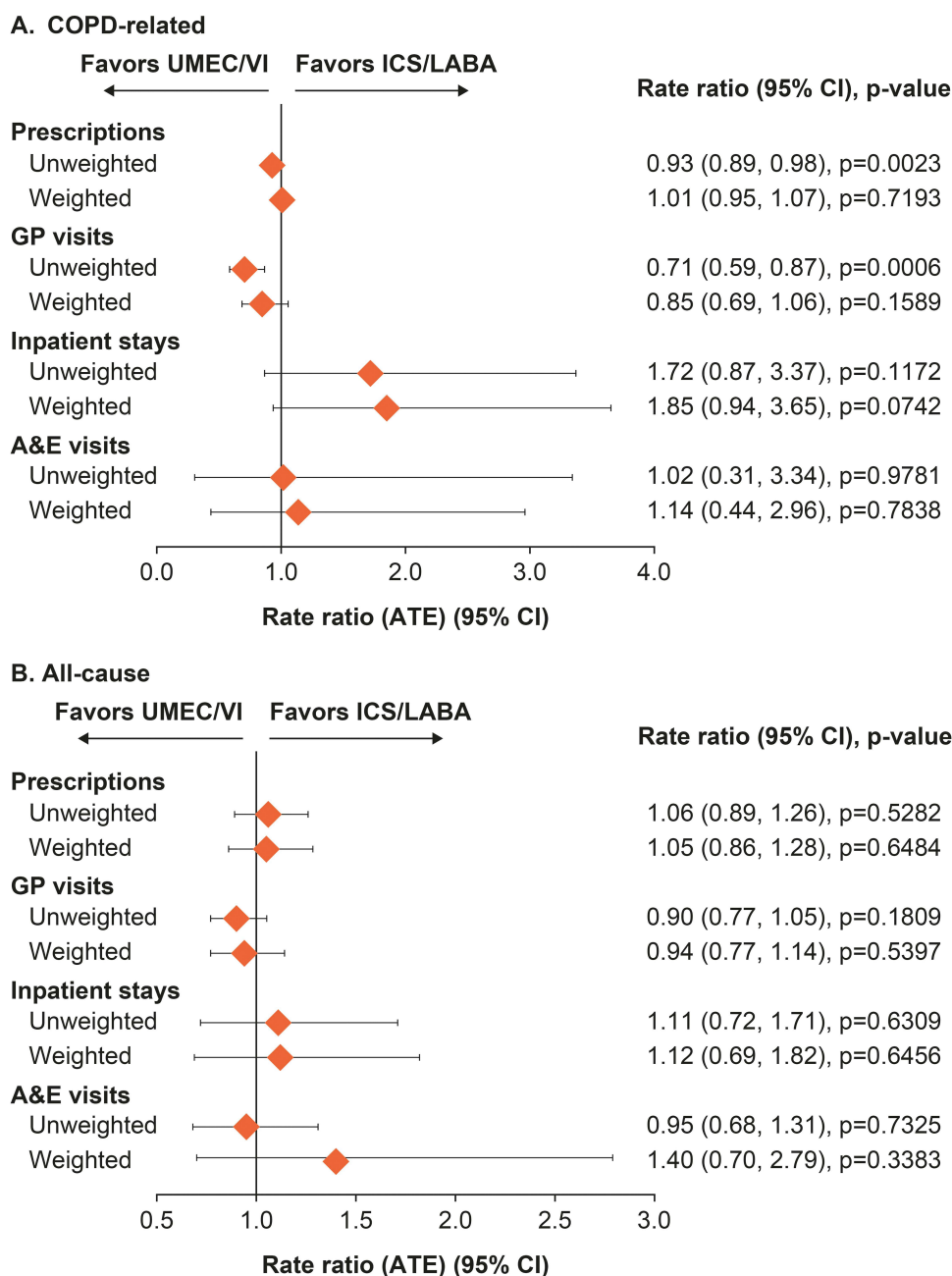
Figure 5 Rate ratio of (**A**) COPD-related and (**B**) all-cause HCRU use at 12 months post-index.
Abbreviations: A&E, Accident and Emergency; ATE, average treatment effect; CI, confidence interval; COPD, chronic obstructive pulmonary disease; GP, general practitioner; HCRU, healthcare resource utilization; ICS, inhaled corticosteroid; LABA, long-actingβ₂-agonist; UMEC, umeclidinium; VI, vilanterol.

Medical Costs

At 12 months after treatment initiation, before PS weighting, 33.3–66.7% and 56.8–69.2% of covariates, respectively, had insufficient balance (SMD≥10) in the COPD-related and all-cause models; after PS weighting, model balance improved, but 2.2–31.5% and 4.5–36.7% of covariates still showed insufficient balance, with the lowest balance for number of prescriptions (Supplementary Table 1). COPD-related and all-cause unweighted and weighted HCRU element costs were similar across both cohorts (Supplementary Table 5). COPD-related prescription costs (unweighted and weighted analyses) and GP visits (unweighted analysis) were significantly greater in the UMEC/VI versus ICS/LABA group; statistically significant differences were not observed for any all-cause HCRU element costs at 12 months (Figure 6). In general, results from the on-treatment sensitivity analyses found no statistically significant differences
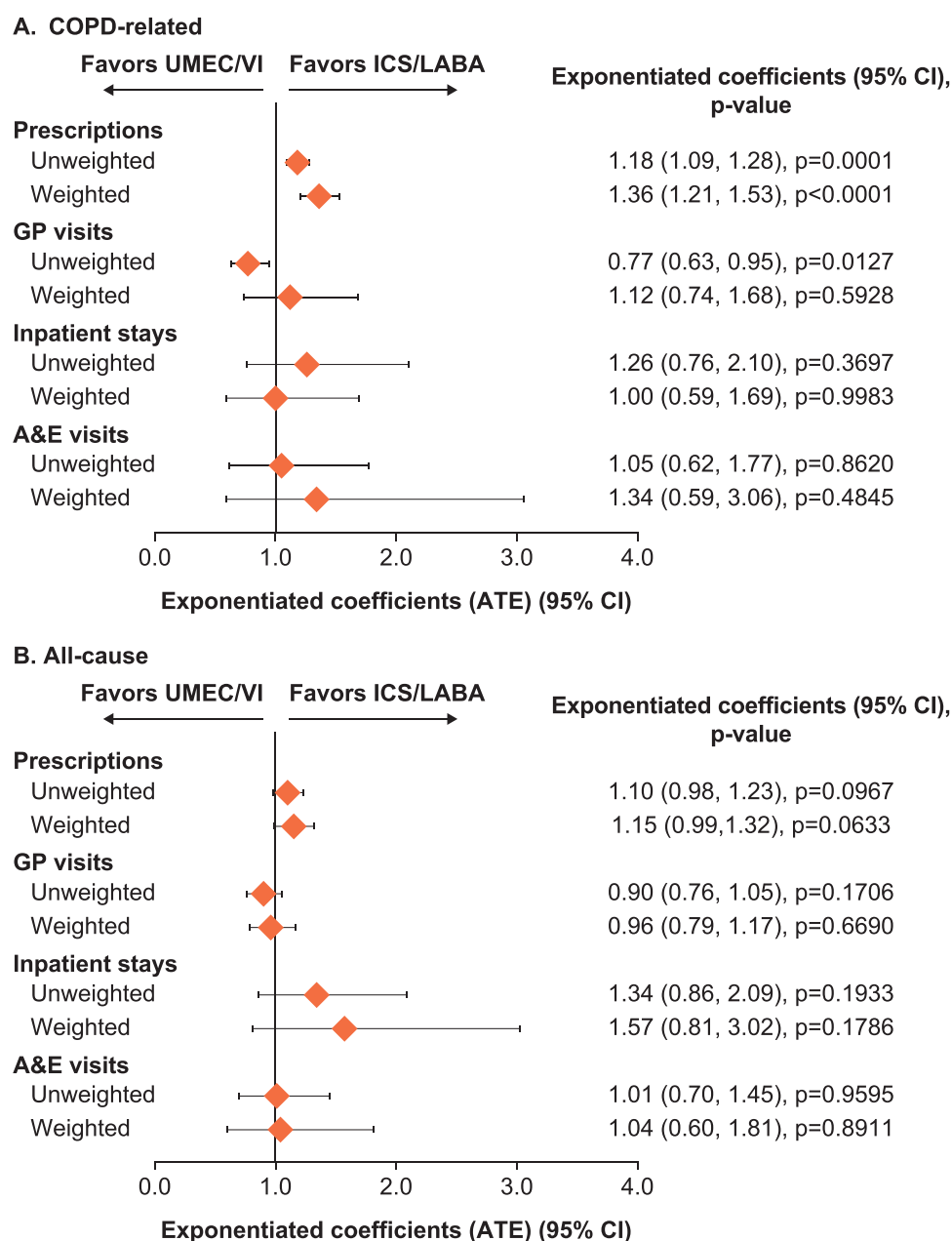
A. COPD-related

Favors UMEC/VI   Favors ICS/LABA   **Exponentiated coefficients (95% CI), p-value**

Prescriptions
Unweighted   1.18 (1.09, 1.28), p=0.0001
Weighted   1.36 (1.21, 1.53), p<0.0001

GP visits
Unweighted   0.77 (0.63, 0.95), p=0.0127
Weighted   1.12 (0.74, 1.68), p=0.5928

Inpatient stays
Unweighted   1.26 (0.76, 2.10), p=0.3697
Weighted   1.00 (0.59, 1.69), p=0.9983

A&E visits
Unweighted   1.05 (0.62, 1.77), p=0.8620
Weighted   1.34 (0.59, 3.06), p=0.4845

0.0   1.0   2.0   3.0   4.0

Exponentiated coefficients (ATE) (95% CI)

B. All-cause

Favors UMEC/VI   Favors ICS/LABA   **Exponentiated coefficients (95% CI), p-value**

Prescriptions
Unweighted   1.10 (0.98, 1.23), p=0.0967
Weighted   1.15 (0.99,1.32), p=0.0633

GP visits
Unweighted   0.90 (0.76, 1.05), p=0.1706
Weighted   0.96 (0.79, 1.17), p=0.6690

Inpatient stays
Unweighted   1.34 (0.86, 2.09), p=0.1933
Weighted   1.57 (0.81, 3.02), p=0.1786

A&E visits
Unweighted   1.01 (0.70, 1.45), p=0.9595
Weighted   1.04 (0.60, 1.81), p=0.8911

0.0   1.0   2.0   3.0   4.0

Exponentiated coefficients (ATE) (95% CI)

Figure 6 (**A**) COPD-related and (**B**) all-cause direct healthcare costs at 12 months post-index.
Abbreviations: ATE, average treatment effect; A&E, Accident and Emergency; CI, confidence interval; COPD, chronic obstructive pulmonary disease; GP, general practitioner; HCRU, healthcare resource utilization; ICS, inhaled corticosteroid; LABA, long-actingβ_2-agonist; UMEC, umeclidinium; VI, vilanterol.

between treatments, except for lower COPD-related and all-cause GP consultation costs and all-cause A&E visits with once-daily UMEC/VI versus twice-daily ICS/LABA (Supplementary Table 2).

Total Direct Costs

Before PS weighting, 48.8–50.0% and 50.0–51.1% of covariates, respectively, had insufficient balance (SMD≥10) in the COPD-related and all-cause models; after PS weighting, model balance improved, but 11.6–11.9% and 8.9–13.0% of covariates still showed insufficient balance (Supplementary Table 1). At all timepoints, COPD-related and all-cause mean total costs per patient per year were greater in the UMEC/VI versus ICS/LABA group for both unweighted and weighted analyses, with the exception of weighted COPD-related total costs at 6 months in which mean total costs were similar between cohorts (Supplementary Table 6). Total all-cause costs were numerically greater with once-daily UMEC/VI

versus twice-daily ICS/LABA for both unweighted and weighted analyses, with total costs being statistically significantly greater with once-daily UMEC/VI versus twice-daily ICS/LABA at 24 months in the weighted analysis (Figure 7). In general, the on-treatment sensitivity analysis was consistent with the main ITT analysis (Supplementary Table 2).

Rescue Medicine Use

Across all timepoints, patients in the UMEC/VI versus ICS/LABA group had a numerically lower mean number of rescue medication prescriptions (Supplementary Table 7). At all timepoints, numerically fewer patients in the UMEC/VI versus ICS/LABA group had a rescue medication prescription (at 6 months UMEC/VI: 39.1%, ICS/LABA: 31.6%) (Supplementary Table 8).
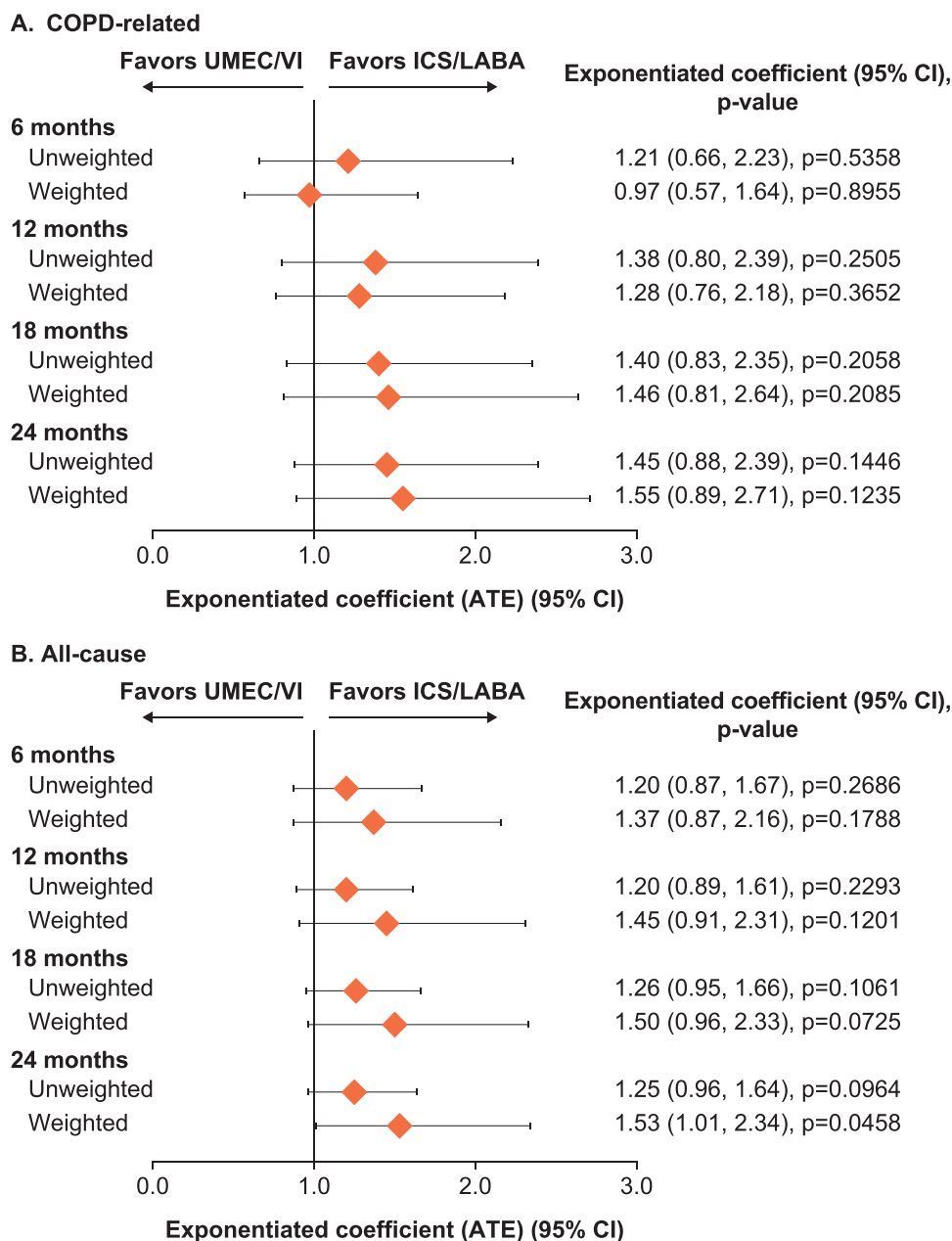
Figure 7 (**A**) COPD-related and (**B**) all-cause and total costs at 6, 12, 18, and 24 months post-index.
Abbreviations: ATE, average treatment effect; CI, confidence interval; COPD, chronic obstructive pulmonary disease; HCRU, healthcare resource utilization; ICS, inhaled corticosteroid; LABA, long-actingβ_2-agonist; UMEC, umeclidinium; VI, vilanterol.

Discussion

This study is the first to compare real-world treatment adherence to once-daily UMEC/VI and twice-daily ICS/LABA dual therapy in patients with no prior exacerbations in the previous year, newly initiating dual-maintenance therapy in a primary care cohort England. Our results suggest that patients taking once-daily UMEC/VI had greater medication adherence than those taking twice-daily ICS/LABA after 12 months of treatment. At all timepoints, the odds of a patient being adherent (PDC≥80%) versus not being adherent was greater with once-daily UMEC/VI versus twice-daily ICS/ LABA. While demographic characteristics were largely similar between treatment cohorts, differences noted in age and comorbidities such as depression could impact treatment adherence. Most patients (over 90%) included in this study were GOLD 2019 grade A or B patients; this was expected as unlike GOLD 2022 Strategy Report, UK NICE guidelines recommend dual therapy as initial maintenance therapy instead of monotherapy with a LAMA or a LABA for patients with COPD.[11] A greater proportion of patients with currently diagnosed asthma were in the ICS/LABA cohort, which is expected as UK NICE guidelines recommend ICS/LABA for patients with COPD with asthmatic features.[11] PS models achieved relatively low balance, with a large number of covariates insufficiently balanced by the IPTW method. This was expected due to different treatment classes being compared; in fact, NICE guidelines recommend LAMA/LABA and ICS/LABA dual therapy for patients with differing symptoms of COPD.[11] In response to the low model balance observed and to add unbalanced covariates to the PS model, a range of sensitivity analyses were conducted, varying either the definition of the outcome or the patient sample being assessed. Sensitivity analyses supported the findings in the main analysis; suggesting that the results of the primary objective were not an artefact of the PS model used.

The findings of this study are in accordance with a previous retrospective claims study in the US, which found that adherence decreased with increased frequency in dosing.[7] This suggests that once-daily inhalers reduce complexity of treatment for patients with COPD compared with twice-daily inhalers, which is an important factor in improving medication adherence.[7] Greater medication adherence is associated with better disease symptoms and clinical outcomes.[22] Other factors such as lower risk of experiencing a first exacerbation observed in this study with UMEC/VI compared with ICS/LABA have also been shown to improve with greater adherence,[6,23] and a trend towards a decreased rate of exacerbations with greater medication adherence has also been shown in a randomized controlled trial in patients with COPD.[24]

Once-daily UMEC/VI showed longer time-to-triple therapy and time-to-first COPD exacerbations than twice-daily ICS/LABA, but after PS weighting the differences for these outcomes were not statistically significant. Contrastingly, a database study in the US showed that non-adherent patients (PDC<50%) had significantly higher rates of COPD exacerbations and significantly higher all-cause costs versus those who adhered to their treatment, suggesting that adherence may affect COPD exacerbation rates.[5] The differences between our study and the US study may be due to the differing definitions of adherence.[5] Of note, while ICS is predominantly used for the prevention of exacerbations;[10] LAMA/LABA has been recommended as first-line treatment for patients with COPD who continue to experience exacerbations[10] and rate of moderate or severe exacerbations has been reported to be lower with indacaterol/glycopyrronium (a LAMA/LABA) than with salmeterol/fluticasone (an ICS/LABA),[25] so that therapeutic class differences could also explain efficacy differences between the LAMA/LABA and ICS/LABA regimens investigated in this study on COPD exacerbations and also rescue medication use as outlined below. Additionally, the results presented here suggest that UMEC/VI may be a better option for certain patients with COPD at low risk of exacerbations due to greater adherence compared with ICS/LABA.

At 12 months after treatment initiation, HCRU was similar in patients initiating UMEC/VI and ICS/LABA, which may be expected given the similar time-to-first COPD exacerbations after index in both treatment groups. A retrospective database analysis in the US showed similar results for patients treated with once-daily versus twice-daily ICS/LABA.[26] Patients who initiated treatment with once-daily fluticasone furoate/VI had 9% lower risk of having a COPD-related moderate or severe exacerbation and significantly better adherence (PDC≥80%) than those who initiated treatment with twice-daily BUD/FOR. Despite lower exacerbation risk and better adherence to a once-daily ICS/LABA, there were no statistically significant differences between COPD-related and all-cause costs between groups.[26]

Rescue medication use was lower in patients initiating UMEC/VI versus ICS/LABA throughout the 24-month follow-up period. Noting the potential for differences in efficacy between the therapeutic classes highlighted above, this may suggest

that patients initiating treatment with UMEC/VI had better symptom control and better lung function[27] versus those initiating treatment with ICS/LABA, as there is evidence that reduced rescue medication can be a surrogate marker of symptomatic benefit in this patient population.[28]

This study has several strengths. The range of sensitivity analyses that were conducted supported the findings in the main analysis. Additionally, in testing for suitable covariates for inclusion into the PS models using an extensive and robust process, results where sufficient covariate balance for effective comparison between treatment groups have been presented. The CPRD-Aurum database provided real-world data for study adherence rather than clinical trial data, which enabled the assessment of this endpoint under optimal conditions.[29] However, this study has several limitations. The primary limitation is the use of a retrospective database methodology, as adherence could have been overestimated if the medication was not dispensed and/or the patient did not consume the medication as prescribed. However, the use of prescription data to assess adherence, measured as PDC, is generally considered an acceptable proxy measure for adherence as long as its limitations are considered when interpreting results.[30] The CPRD-Aurum data represents approximately 15% of England's GPs; however, the linked CPRD-HES data source covers nearly 70% of England's population, and therefore the findings presented here are considered to be representative of the population in England.[31] Additionally, medications prescribed in secondary care were not captured, and missing data were common for some characteristics such as ethnicity, MRC, and GOLD. There was a potential for patients with asthma to be misidentified as having COPD; however, a previous study using the CPRD database indicated that Read codes can be used to accurately identify patients with asthma, suggesting that patients included in this study had COPD and any recording for asthma is therefore likely to be comorbid COPD and asthma.[32] A validation study of COPD diagnosis in CPRD has shown that patients with COPD can be identified by a combination of COPD diagnostic code plus a code that supports diagnosis such as smoking status or spirometry.[33] Rescue medication use was observed as a proxy for frequency of short-term worsening of symptoms and was defined as prescriptions for medications and doses. However, the frequency of rescue medication prescriptions may not directly correlate with the frequency of rescue medication used by the patients for worsened symptoms as this data does not account for unused prescriptions.

Conclusion

Overall, the data from this study indicate that once-daily UMEC/VI was superior to twice-daily ICS/LABA in medication adherence among patients with COPD and no prior recent exacerbations newly initiating dual maintenance therapy in England. The finding was consistent at 6, 18, and 24 months. Furthermore, numerical trends in reducing time-to-first COPD exacerbations, and numerical lower use of rescue medications was seen with UMEC/VI. Small differences between treatment groups and in varying directions were observed for all HCRU and cost outcomes.

Abbreviations

A&E, Accident and Emergency; ACL, aclidinium; APC, Admitted Patient Care; ATE, average treatment effect; BDP, beclomethasone dipropionate; BUD, budesonide; CI, confidence interval; COPD, chronic obstructive pulmonary disease; COVID, coronavirus; CPRD, Clinical Practice Research Datalink; FDC, fixed-dose combination; FEV_1, forced expiratory volume in 1 s; FOR, formoterol; FP, fluticasone propionate; FVC, forced vital capacity; GBP, British Pound Sterling; GOLD; Global Initiative for Chronic Obstructive Lung Disease; GP, general practitioner; HCRU, healthcare resource utilization; HES; Hospital Episode Statistics; HR, hazard ratio; ICS; inhaled corticosteroid; IMT, initial maintenance therapy; IPTW, inverse probability of treatment weighting; ITT, intention-to-treat; LABA, long-acting β_2-agonist; LAMA, long-acting muscarinic antagonist; LRTI, lower respiratory tract infection; MRC, Medical Research Council; NICE, National Institute for Health and Care Excellence; PDC, proportion of days covered; PDE-4, phosphodiesterase 4; PS, propensity score; SABA, short-acting β_2-agonist; SAMA, short-acting muscarinic antagonist; SD, standard deviation; SMD, standardized mean difference; SX, salmeterol xinafoate; UK, United Kingdom; UMEC; umeclidinium; US, United States; VI, vilanterol.

Data Sharing Statement

This study is based in part on data from CPRD obtained under licence from the UK Medicines and Healthcare products Regulatory Agency. The data are provided by patients and collected by the National Health Service as part of their care and support. The interpretation and conclusions contained in this study are those of the author/s alone. Data from HES Copyright © (2022), re-used with the permission of The Health & Social Care Information Centre. All rights are reserved. Authors had access to the study data for the purposes of this work only. Data were accessed through an existing GSK license to address pre-specified research questions only. Therefore, the data cannot be broadly disclosed or made publicly available at this time. Access to each database can be requested via the respective websites (EMIS Web® electronic patient record system and CPRD-Aurum).

Ethics Approval and Informed Consent

This study was approved by the GSK Protocol Review Committee and by the CPRD Research Data Governance process, which reviewed the protocol and approved access to CPRD data (protocol no. 21_000617). This study complied with all applicable laws regarding subject privacy. No direct subject contact or primary collection of individual human subject data occurred. Personal identifiers and personal identifiable information were removed by the database provider prior to receipt by the study team. Study results are in tabular form and aggregate analyses that omit subject identification, therefore informed consent, ethics committee, or Institutional Review Board (IRB) approval were not required. This study was designed, implemented, and reported in accordance with the Guidelines for Good Pharmacoepidemiology Practices (GPP) of the International Society for Pharmacoepidemiology (ISPE 2008), the STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) guidelines, and with the ethical principles laid down in the Declaration of Helsinki.

Disclosure

AC, GR, CC, KJR, and ASI are employees of GSK and hold stock and shares at GSK. ASI also holds an unpaid faculty position at McMaster University in Canada. FH is an employee of the Translational Lung Research Center Heidelberg, part of the Germany lung research Foundation (DZL) and he also reports lecturing and adboard activities for GSK. JKQ holds a position at Imperial College London. CMC, TT, RWo, and RWi are employees of Adelphi Real World. VB is currently an employee of Bayer AG UK and holds stock and shares there. VB and JY were employees of Adelphi Real

World at the time of the study. Adelphi Real World is a business that provides consulting and other research services to pharmaceutical, device, government, and non-government organizations, which received funding from GSK to conduct the study. Adelphi Real World employees work with a variety of companies and organizations and are expressly prohibited from receiving any payment or honoraria directly from these organizations for services rendered. The authors report no other conflicts of interest in this work.

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