International Journal of COPD

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ORIGINAL RESEARCH

Cost-effectiveness analysis of umeclidinium/vilanterol for the management of patients with moderate to very severe COPD using an economic model

This article was published in the following Dove Press journal:
International Journal of COPD
24 March 2017
Number of times this article has been viewed

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Background: Bronchodilators such as long-acting muscarinic antagonists (LAMAs) and long-acting β_2-agonists (LABAs) are central to the pharmacological management of COPD. Dual bronchodilation with umeclidinium/vilanterol (UMEC/VI; 62.5/25 µg) is a novel LAMA/LABA combination approved for maintenance treatment for patients with COPD.

Objective: The objective of this study was to assess the cost-effectiveness of maintenance treatment with UMEC/VI compared with tiotropium (TIO) 18 µg, open dual LAMA + LABA treatment, or no long-acting bronchodilator treatment in patients with moderate to very severe COPD.

Methods: A Markov model was developed to estimate the costs and outcomes associated with UMEC/VI treatment in patients with moderate to very severe COPD (GSK study number: HO-13-13411). Clinical efficacy, costs, utilities, and mortality obtained from the published literature were used as the model inputs. Costs are presented in US dollars based on 2015 prices. The model outputs are total costs, drug costs, other medical costs, number of COPD exacerbations, and quality-adjusted life-years (QALYs). Costs and outcomes were discounted at a 3% annual rate. Incremental cost-effectiveness ratios were calculated. One-way and probabilistic sensitivity analyses were conducted to assess the effects of changing parameters on the uncertainty of the results.

Results: UMEC/VI treatment for moderate to very severe COPD was associated with lower lifetime medical costs ($82,344) compared with TIO ($88,822), open dual LAMA + LABA treatment ($114,442), and no long-acting bronchodilator ($86,751). Fewer exacerbations were predicted to occur with UMEC/VI treatment compared with no long-acting bronchodilator treatment. UMEC/VI provided an 0.11 and 0.25 increase in QALYs compared with TIO and no long-acting bronchodilator treatment, and as such, dominated these cost-effectiveness analyses. Sensitivity analyses confirmed that the results were robust.

Conclusion: The results from this model suggest that UMEC/VI treatment would be dominant compared with TIO and no long-acting bronchodilator treatment, and less costly than open dual LAMA + LABA treatment in patients with moderate to very severe COPD.

Keywords: umeclidinium, vilanterol, cost-effectiveness, tiotropium, COPD

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Introduction

COPD is a highly prevalent,[1,2] debilitating, chronic condition that has a significant impact on quality of life[3] and costs borne by health care systems.[4] In 2010, $32.1 billion direct medical costs were estimated to be attributable to COPD and its sequelae

in the USA and a further $3.9 billion to absenteeism costs.[5] Maintenance bronchodilator therapy is the foundation of stable COPD treatment, and combining bronchodilators is supported as a useful treatment option for patients with a higher symptom burden.[2]

The combination of the long-acting muscarinic antagonist (LAMA) umeclidinium (UMEC) with the long-acting β_2-agonist (LABA) vilanterol (VI) is an approved maintenance treatment for COPD in the USA, the EU, and several other countries.[6–8] Treatment with UMEC/VI increases lung function compared with tiotropium (TIO) monotherapy or placebo and has a clinically acceptable safety profile;[9–11] however, its cost-effectiveness remains unknown. A potential barrier to the use of dual bronchodilator therapy could be the cost and complexity of adding an additional inhaler to patients' treatments.

To address this, we examined the cost-effectiveness of UMEC/VI versus TIO, no long-acting bronchodilator treatment, and open dual (LAMA + LABA) bronchodilator treatment in patients with moderate to very severe COPD in the USA.

Methods

Analytic framework

A Markov model was developed with 1-year cycle times in which patients progressed through three COPD severity levels as defined by the 2013 COPD clinical guidelines.[12] Severity of COPD was classified according to the predicted postbronchodilator forced expiratory volume in 1 second (FEV_1) of patients, as shown in Figure 1.[12]

Data from an initial mix of patients in different disease severity health states were entered into the Markov model (GSK study number: HO-13-13411). This mix was obtained from a prevalence study[1] and from the Evaluation of COPD Longitudinally to Identify Predictive Surrogate Endpoints (ECLIPSE) observational study (NCT00292552).[13] Upon entering into the model, patients were prescribed a maintenance COPD treatment plus usual care. Each year in the model, patients remained in their current disease severity health state or moved to the next more severe health state.

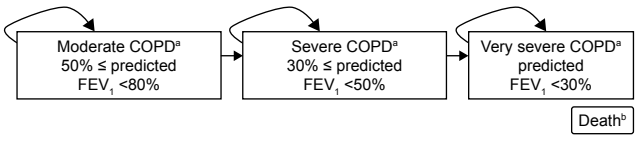

Figure 1 Structure of the decision model used.
Notes: [a]Within the health states, patients may experience either a severe or a nonsevere exacerbation. [b]Death could occur from any health status.
Abbreviation: FEV_1, forced expiratory volume in 1 second.

Within a year, patients could also experience an exacerbation or remain event free (ie, with no exacerbation). Death could occur from any health state according to the natural progression of the disease.[14]

The perspective of the analysis was that of a third-party payer in the USA where only direct medical costs were considered. A 20-year time horizon was assessed. Costs and outcomes were discounted at 3% per annum, and costs were reported in 2015 US dollars.

Patient population

Consistent with the patient populations studied in UMEC/VI clinical trials,[9–11] patients included in this analysis were aged 40 years or older, had moderate to very severe COPD, and were eligible for maintenance treatment with LAMA/LABA combination therapy.[6] Additional eligibility criteria included current smokers or ex-smokers with a smoking history of ≥10 pack-years, postalbuterol FEV_1/forced vital capacity (FVC) ≤0.70, FEV_1 ≤70% of predicted normal, and score of ≥2 using the Modified Medical Research Council Dyspnea Scale. Patients with a history of asthma or previous use of UMEC and/or VI were excluded.

Comparators

The following treatment regimens were compared: UMEC/VI (62.5/25 µg; delivering 55/22 µg administered once daily), TIO (18 µg; delivering 10 µg administered once daily), open dual LAMA + LABA therapy (TIO administered once daily and a LABA administered twice daily from separate inhalers), and no long-acting bronchodilator (where no such long-acting COPD maintenance treatment was administered).

TIO was chosen as the primary comparator for UMEC/VI, because it is one of the recommended first-line maintenance treatments for patients with moderate to very severe COPD[2] and one of the most commonly used long-acting bronchodilators in the USA and Canada for the treatment of patients with COPD.[15,16]

Model inputs

Change in trough FEV_1 efficacy

The model used 1) the improvement in lung function (ie, trough FEV_1) in the first 24–26 weeks of treatment (Table 1),[9–11,17] 2) patient characteristics, 3) average predicted FEV_1, and 4) annual rate of decline as observed among patients in the different disease severity health states to estimate the transition probabilities between the disease severity levels. Transitions between patients' disease severity health states were based on the method described by Spencer et al,[18] which used

Table 1 Clinical efficacy, including change in trough FEV_1, exacerbations, and AEs

Parameter	Values	Source/assumption
Mean change in trough FEV_1 in the first 24–26 weeks of treatment (L)		
UMEC/VI	0.200	Decramer et al (2014)[9] and Maleki-Yazdi et al (2014)[11]
TIO	0.112	Decramer et al (2014)[9] and Maleki-Yazdi et al (2014)[11]
No long-acting bronchodilator[a]	0.033	Jones (2013)[17] and Donohue et al (2013):[10] the placebo arm in this study was shown to have some effect on FEV_1, believed to be due to short-term treatment
Open dual LAMA + LABA	0.200	Assumed same as UMEC/VI[b]
Exacerbations per year (by disease severity)		
Total		
Moderate COPD	0.85	Hurst et al (2010)[13]
Severe COPD	1.34	
Very severe COPD	2.00	
Severe		
Moderate COPD	0.11	Hurst et al (2010)[13]
Severe COPD	0.25	
Very severe COPD	0.54	
Nonsevere		
Moderate COPD	0.74	Hurst et al (2010)[13]
Severe COPD	1.09	
Very severe COPD	1.46	

AE rates (%);[c] Decramer et al (2014),[9] Donohue et al (2013),[10] Maleki-Yazdi et al (2014),[11] and Celli et al (2014)[19]

	UMEC/VI	TIO (absolute difference: UMEC/VI – TIO)	No long-acting bronchodilator treatment (absolute difference: UMEC/VI – no long-acting bronchodilator)
N	1,296	874	555
Headache	8.95	6.29 (2.66)	10.45 (–1.50)
Musculoskeletal (back) pain	3.09	3.20 (–0.11)	3.60 (–0.51)
Nasopharyngitis	7.87	7.21 (0.66)	8.65 (–0.78)
Upper respiratory tract infection	2.31	2.97 (–0.66)	3.78 (–1.47)

Notes: [a]Mean change in FEV_1 for no long-acting bronchodilator treatment compared with UMEC/VI was extracted from Donohue et al.[10] [b]This was one of the key assumptions made for this model. [c]AEs are not shown for open dual LAMA + LABA therapy as they were assumed to be the same as for UMEC/VI.

Abbreviations: AE, adverse event; FEV_1, forced expiratory volume in 1 second; LABA, long-acting β_2-agonist; LAMA, long-acting muscarinic antagonist; TIO, tiotropium; UMEC, umeclidinium; VI, vilanterol.

patients' average time in each health state (Supplementary materials and Tables S1–S4).

Changes in trough FEV_1 at 24–26 weeks for the different treatments were obtained from three studies for UMEC/VI (NCT01316900 [GSK study number DB2113360], NCT01316913 [DB2113374], and NCT01777334 [ZEP117115])[9,11] and one study for no long-acting bronchodilator (NCT01313650 [DB2113373])[10] (Table 1)[9–11,17]. Within these trials, the patient populations and methods used to measure relative changes in trough FEV_1 were similar.[9–11] It was therefore assumed that the relative changes in trough FEV_1 observed for UMEC/VI compared with TIO reported in the head-to-head trials[9,11] could be compared with the change in trough FEV_1 observed in the placebo-controlled trial.[10] It was also assumed that the change in trough FEV_1 was the same for the UMEC/VI and open dual LAMA + LABA therapies (Table 1)[9–11,17]. As the change in trough FEV_1 for each maintenance treatment was greater versus no long-acting treatment, patients in these groups remained in less severe health states longer than patients on no long-acting treatment.

Exacerbations

Exacerbations in this model were events that caused patients to seek health care. Patients could experience different levels of exacerbations or no exacerbations. Severe exacerbations were classified as events requiring hospitalization, and nonsevere exacerbations as events requiring a change in treatment such as systemic corticosteroids and/or antibiotics and/or contact with a health care provider. Patients were considered event free if they experienced no exacerbations.

Exacerbation risk was based on patient COPD severity and was obtained from the ECLIPSE study (Table 1).[13]

As a result, the impact that a treatment has on exacerbation was considered implicitly in the model. A treatment's direct impact on exacerbations was not modeled as the

clinical studies reporting the treatment effects were not powered to do so.

Adverse events (AEs)

AEs not associated with discontinuation were accounted for within the model. Specifically, AEs that occurred in at least 3% of patients and those deemed to result in significant costs were identified. AE rates for each treatment option were estimated using pooled data from the comparative trials of UMEC/VI (Table 1),[9–11,19] apart from the AE rates for open dual LAMA + LABA treatment that were assumed to be the same as UMEC/VI. It was also assumed that AEs occurred in year 1 of the model and subsequent AEs were accounted for in the discontinuation rates.

Discontinuations

Patients may discontinue treatment due to lack of efficacy and/or due to an occurrence of an intolerable AE. The clinical impact of discontinuations was captured in the clinical efficacy input and was assumed to be similar for open dual LAMA + LABA and UMEC/VI treatment. Patients who discontinued due to lack of efficacy were reverted to no treatment and were assumed to move to standard care (defined as no treatment with UMEC/VI) as seen in the trials. The cost of the respective treatments was reduced. However, additional drug costs were not captured. As a result, results may be considered to be conservative.

Mortality

Deaths (related to COPD and other causes) were considered in the model. Age-specific all-cause mortality was obtained from the US National Vital Statistics.[20] COPD-specific death was incorporated by applying relative risks for moderate COPD (relative risk =1.4) and severe and very severe COPD (relative risk =2.6) from Shavelle et al.[14] It was assumed that COPD-related mortality was only based on disease severity.

Drug costs

All costs included in the model were in US dollars and based on 2015 data. Estimations of monthly prescription costs were based on the recommended dosing of each treatment.[6,21] No long-acting bronchodilator treatment was assumed to be the cost of the short-acting bronchodilators ipratropium/albuterol (Combivent®).[22] Open dual LAMA + LABA treatment was assumed to include the cost of TIO and the estimated average cost of salmeterol and formoterol administered twice daily. All drug costs were obtained from Medi-Span 2.0 (Table 2).[23] Patients were assumed to be fully compliant with UMEC/VI or TIO treatments.

Add-on therapy

Add-on therapy was considered in the model to account for the additional costs incurred by patients who progress to triple therapy. The additional costs were for fluticasone propionate/salmeterol (Advair®) for patients in the TIO and no long-acting bronchodilation groups and also for fluticasone for UMEC/VI and open dual LAMA + LABA therapy groups. It should be noted that the percentage of patients who progressed to triple therapy was assumed to be related to disease severity and not to specific treatments, with the percentages used within this assumption obtained from a treatment pattern analysis (Table 2, GSK data on file).

Additional medical costs

Medical costs (other than those detailed previously) were also included and were assumed to be specific to exacerbations. These medical costs included inpatient, emergency room, outpatient, and "other" medical costs. "Other" medical costs were those not previously covered, such as home visits and skilled nursing facility services. Total medical costs for a severe exacerbation, nonsevere exacerbation, and no exacerbation were estimated according to Yu et al.[24] The costs included those of the index exacerbation visit and those of any subsequent treatments. The costs of an AE resulting from the COPD maintenance treatments (the cost per AE assumed one physician visit and antibiotics as applicable; Table 2)[25–27] were also considered within the model.

Utility weights

The annual utility weights used within the model were derived from those previously published and were related to disease severity and exacerbation events (Table 2).[18] Severe exacerbations and nonsevere exacerbations were assumed to have a duration of 28 days and 10.5 days, respectively. These utility values were used to estimate quality-adjusted life-years (QALYs) by multiplying the number of accrued life-years within a particular health state by the disease severity's utility weight.

Model calculations

The following outputs were estimated by the model: total costs, drug costs, other medical costs, number of exacerbations (total, nonsevere, and severe), life-years, and QALYs.

The cost-effectiveness of UMEC/VI versus each comparator was determined by calculating the incremental total cost per life-year or QALY gained: $(C_i - C_s)/(E_i - E_s)$, where C_i is the cost accrued by the treatment of interest, C_s is the cost accrued by the status quo treatment, E_i is the effectiveness

Table 2 Costs included as model inputs and the utility values for COPD severity and exacerbation severity

Parameter	Value	Source/assumption	
Exacerbation costs	**Quarterly costs**		
Severe exacerbation	$8,116.88	Yu et al (2011)[24] and US BLS (2015)[27]	
Nonsevere exacerbation	$1,401.56	Yu et al (2011)[24] and US BLS (2015)[27]	
No exacerbation	$527.76	Yu et al (2011)[24] and US BLS (2015)[27]	
AE	**Costs[a] (per reported AE)**		
Headache	$73.99	Physician visit at $73.99 (RBRVS, [Ingenix, 2013][26]); US BLS (2015)[27]	
Musculoskeletal (back) pain	$73.99	Physician visit at $73.99 (RBRVS, [Ingenix, 2013][26]); US BLS (2015)[27]	
Nasopharyngitis	$73.99	Physician visit at $73.99 (RBRVS, [Ingenix, 2013][26]); US BLS (2015)[27]	
Upper respiratory tract infection	$75.36	Physician visit at $73.99 (RBRVS, [Ingenix, 2013][26]) and penicillin V antibiotic treatment at $13.00 applied to 10% of patients with strep-positive diagnosis (CDC);[25] US BLS (2015)[27]	
Drug costs	**Monthly prescription costs (WAC)**		
UMEC/VI	$297.81	Medi-Span (2015)[23]	
TIO	$315.68	Medi-Span (2015)[23]	
No long-acting bronchodilator	$295.71	Assumed price of ipratropium/albuterol[23]	
LAMA	$315.68	Assumed price of TIO[23]	
LABA	$261.74	Assumed price of salmeterol and formoterol[23]	
Add-on drug costs			
ICS	$179.70	Assumed price of fluticasone propionate; applied to UMEC/VI and open dual after 1 year of primary treatment	
ICS/LABA	$309.84	Assumed price of fluticasone propionate/salmeterol; applied to TIO and no long-acting bronchodilator after 1 year of primary treatment	
Add-on uptake	**%**		
Moderate COPD	27	GSK, data on file	
Severe COPD	40		
Very severe COPD	45		
Disease severity	**Utility (SE)[b]**	**By exacerbation: mean modeled utility (SE)[b]**	
		Requiring primary care treatment with oral corticosteroids and/or antibacterials (nonsevere)	**Requiring hospital admission (severe)**
Moderate COPD	0.810 (0.02)	0.720 (0.02)	0.519 (0.02)
Severe COPD	0.720 (0.03)	0.658 (0.03)	0.447 (0.07)
Very severe COPD	0.670 (0.05)	0.475 (0.05)	0.408 (0.05)

Notes: [a]The physician visit cost was estimated to be $73.99 using CPT code 99213, which is described as in RBRVS, Ingenix, 2013.[26] CPT codes were obtained from the American Medical Association (2013).[39] [b]Disease severity and exacerbation-specific utilities were derived by Spencer (2005) et al.[18] Costs are presented in US dollars based on 2015 prices.

Abbreviations: AE, adverse event; BLS, Bureau of Labor Statistics; CDC, Centers for Disease Control and Prevention; CPT, current procedural terminology; ICS, inhaled corticosteroids; LABA, long-acting β_2-agonist; LAMA, long-acting muscarinic antagonist; RBRVS, Resource Based Relative Value Scale; SE, standard error; TIO, tiotropium; UMEC, umeclidinium; VI, vilanterol; WAC, wholesale acquisition cost.

accrued by the treatment of interest (life-year or QALY), and E_s is the effectiveness accrued by the status quo treatment (life-year or QALY); all over a lifetime horizon. Cost and health outcomes were discounted at a 3% rate per year.

The effect of changing parameters was examined in one-way sensitivity analyses to test the robustness of the model assumptions and specific parameters. The results of sensitivity analysis for each input were ranked from most sensitive to least sensitive and plotted on tornado diagrams, with the 15 most sensitive parameters presented.

Probabilistic sensitivity analyses (second-order Monte Carlo simulation), in which all parameters in the model were varied at the same time, were also performed. Analyses were run 10,000 times to capture stability in the results for each relevant scenario and presented using scatter plots.

Results

Base-case analysis

Treatment of patients with moderate to very severe COPD with UMEC/VI resulted in total remaining lifetime medical

costs of $82,344 compared with $88,822 for TIO, $114,442 for open dual LAMA + LABA treatment, and $86,751 for no long-acting bronchodilator treatment (Table 3). Patients treated with UMEC/VI also experienced fewer exacerbations (due to initial improvements in lung function) compared with patients receiving no long-acting bronchodilator treatment.

Due to the assumptions used in the model, patients receiving UMEC/VI and open dual LAMA + LABA treatment experienced the same total life-years and QALYs. However, patients treated with UMEC/VI gained 0.16 life-years and 0.11 QALYs compared with TIO treatment and 0.35 life-years and 0.25 QALYs compared with no long-acting bronchodilator treatment. As UMEC/VI treatment was also less costly and was associated with fewer exacerbations compared with both TIO and no long-acting bronchodilator treatment, it was dominant to both (Table 3).

One-way sensitivity analyses

One-way sensitivity analyses showed that UMEC/VI treatment remained the dominant treatment compared with TIO and no long-acting bronchodilator treatment within the range of uncertainty applied to all variables in the model. UMEC/VI also had lower total costs compared with open dual LAMA + LABA within the range of uncertainty for all variables, mainly due to a lower acquisition cost.

Probabilistic sensitivity analyses

The probabilistic sensitivity analyses demonstrated that UMEC/VI was dominant 81.5% of the time, was not dominant but was cost-effective (incremental cost per QALY <$50,000) 13.8% of the time, and was cost-effective 95.3% of the time compared with TIO (Figure 2A). Compared with no bronchodilator treatment, UMEC/VI was dominant 71.1% of the time, was not dominant but was cost-effective 27.8% of the time, and was cost-effective 98.9% of the time (Figure 2B). The safety and efficacy of open dual LAMA + LABA was assumed to be the same as UMEC/VI making a probabilistic sensitivity analysis for this particular comparison unnecessary.

Discussion

This analysis estimated the cost-effectiveness of UMEC/VI compared with other bronchodilator treatments for patients with moderate to very severe COPD and included a comparator of no long-acting bronchodilator treatment in which only short-acting rescue medication was permitted. In the base-case analysis, UMEC/VI was found to be dominant compared with TIO and no long-acting bronchodilator treatment. Furthermore, when UMEC/VI was compared with open dual LAMA + LABA treatment, both were assumed to have the same efficacy, but UMEC/VI was found to be less costly. Sensitivity analyses demonstrated that all cost-effectiveness findings were robust. Future analyses could investigate the cost-effectiveness of UMEC/VI compared with other closed dual bronchodilator treatments (eg, QVA149).

Since the approval of TIO as the first LAMA for the treatment of patients with COPD, several cost-effectiveness studies have been completed with different comparators.[28–32] In this study, TIO cost more than no long-acting bronchodilation treatment but had an increased QALY of 0.14. An improvement in QALYs on TIO treatment has been reported in other studies comparing TIO with other treatments in COPD (0.051–0.15 QALYs),[28–32] supporting the model assumptions used.

A strength of this analysis is that it incorporated progression to triple therapy (inhaled corticosteroids [ICS] +

Table 3 Base-case analysis results over a lifetime horizon

Parameter	UMEC/VI	TIO	No long-acting bronchodilator	Open dual LAMA + LABA
Costs				
Drug costs	$40,229	$46,342	$43,715	$72,327
Other medical costs	$42,115	$42,480	$43,036	$42,115
Total costs	$82,344	$88,822	$86,751	$114,442
Number of exacerbations				
Nonsevere	10.866	10.938	11.045	10.866
Severe	2.347	2.433	2.552	2.347
Total exacerbations	13.214	13.371	13.597	13.214
Life-years	11.843	11.687	11.493	11.843
QALYs	7.304	7.195	7.055	7.304
Incremental cost-effectiveness ratio				
Cost per life-year gained	–	UMEC/VI dominates	UMEC/VI dominates	Not defined[a]
Cost per QALY gained	–	UMEC/VI dominates	UMEC/VI dominates	Not defined[a]

Notes: [a]Incremental cost-effectiveness ratio not defined as the effectiveness of open dual LAMA + LABA was assumed to be the same as UMEC/VI. Costs are presented in US dollars based on 2015 prices.

Abbreviations: LABA, long-acting β_2-agonist; LAMA, long-acting muscarinic antagonist; QALY, quality-adjusted life-year; TIO, tiotropium; UMEC, umeclidinium; VI, vilanterol.

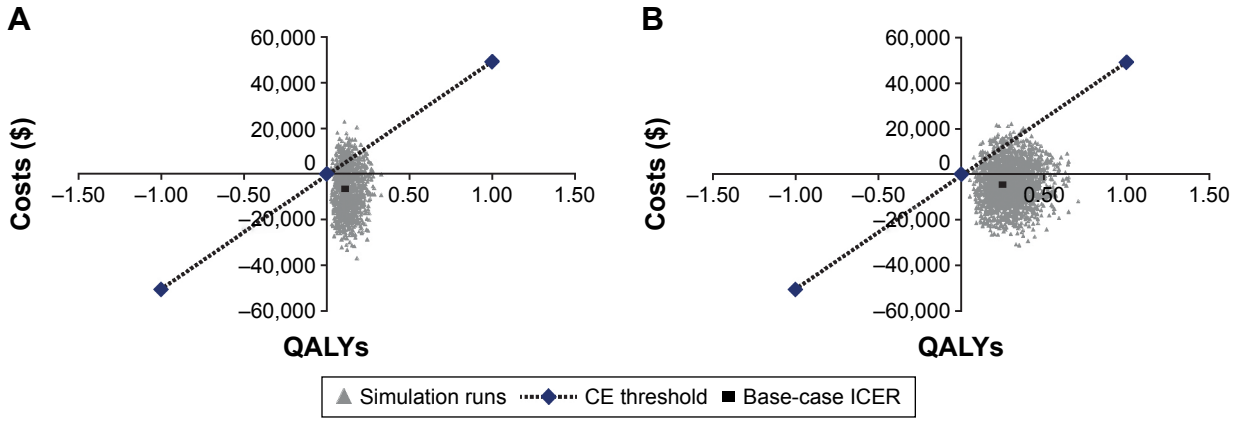

Figure 2 Cost-effectiveness of UMEC/VI treatment in patients with moderate to very severe COPD: probabilistic sensitivity analyses (**A**) UMEC/VI compared with TIO and (**B**) UMEC/VI compared with no long-acting bronchodilator.
Note: Costs are presented in US dollars based on 2015 prices.
Abbreviations: CE, cost-effectiveness; ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life-year; TIO, tiotropium; UMEC, umeclidinium; VI, vilanterol.

LAMA + LABA) for patients with COPD. This progression was based on disease severity and not specific treatments. A study in the UK found that patients with COPD often progress quickly to triple therapy[33] and a second study in Japan found that more than half of patients who progress to triple therapy do so because of the need for additional symptom improvement.[34] Progression to triple therapy incurs additional drug costs for COPD treatment, which this model accounted for in all treatment arms. Therefore, the reported cost-effectiveness for UMEC/VI includes this important aspect of COPD treatment.

A limitation of the study is that no formal statistical adjustments were made for the efficacy data of the treatments considered in this analysis, because of limited data on FEV_1, comparative exacerbations, and treatment-related and exacerbation-related mortality. However, the sensitivity analysis that varied these parameters in the model showed that UMEC/VI remained cost-effective irrespective of variation in efficacy parameters.

Previous studies have shown that the major economic impact of maintenance treatment for COPD was in reducing exacerbations.[29,31,32] While in this model, data were used from the ECLIPSE study[13] that related FEV_1 status to frequency of exacerbation events, other factors are also known to impact on exacerbation rate such as prior exacerbation history and heartburn.[13] Furthermore, though disease severity has often been assessed using FEV_1 performance in the past, recent clinical developments indicate that many other disease characteristics should be considered when assessing COPD severity. These factors were not directly accounted for in the model, and the analysis may need adjusting in the future once further data are available.

Another limitation is that COPD-related mortality was assumed to be disease severity specific and only indirectly accounted for treatment and exacerbation status, which is not necessarily the case and may have impacted the outcomes.[35,36] Soler-Cataluna et al[35] demonstrated that mortality is correlated with increasing severe exacerbations. However, as the impact of UMEC/VI on exacerbations has not yet been fully determined,[9] this could not be fully included in the current model. Inclusion of treatment-specific impact on exacerbations and the associated mortality risk for exacerbations could affect the results, but it is unclear in which direction the effect would be without observing the exacerbation data for UMEC/VI. However, the data used within the model were the most accurately available at the time the analysis was undertaken and mortality was included. Finally, the assumption that patients would be fully compliant with the prescribed treatment regimens is unlikely to be true. While adherence with a once-daily TIO regimen is known to be high,[37] it has not yet been directly evaluated with once-daily UMEC/VI. Adherence is likely to be similar as both treatments are once-daily inhalers, so it is unlikely to have an impact on the cost-effectiveness of UMEC/VI over TIO. Adherence to these once-daily LAMA treatments is likely to be much higher compared with adherence to any open dual regimen, as found in the recent real-world study comparing once-daily TIO with twice-daily budesonide/formoterol.[38]

Conclusion

The results from this model suggest that UMEC/VI treatment would be dominant compared with TIO and no long-acting bronchodilator treatment and be less costly than open dual LAMA + LABA treatment in patients with moderate to very

severe COPD. Compared with TIO and no long-acting bronchodilator treatment, UMEC/VI was associated with fewer exacerbations as well as gains in life-years and QALYs.

Acknowledgments

GSK funded this study (study number HO-13-13411). Editorial assistance was provided by Gillian Groeger, PhD, Fishawack Indicia Ltd (UK), which was funded by GSK.

Author contributions

MRW, JGP, AC, CLM, RHS, and SRE contributed to the concept and design of this study and undertook data analysis and interpretation. All authors contributed toward data analysis, drafting and critically revising the paper and agree to be accountable for all aspects of the work.

Disclosure

MRW, CLM, and SRE are employees of RTI Health Solutions, an independent contract research organization that has received funding from GSK for this and other studies and from other pharmaceutical companies that market drugs for the treatment of patients with COPD and other medical conditions. AC and RHS are employees of GSK and holders of GSK stock. JGP was an employee of GSK and holder of GSK stock at the time of the study. JGP is now employed by Amgen. The authors report no other conflicts of interest in this work.

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Supplementary materials

Methods

Estimates of disease transitions were based on age, average height, percentage of the COPD population that was female, average percentage predicted forced expiratory volume in 1 second (FEV_1) among patients in the health state at start of model, average predicted normal FEV_1, and annual rate of decline as observed among patients in the different disease severity health states in the ECLIPSE study. Reference equations were also used to estimate predicted normal FEV_1 in males and females (included subsequently).

To calculate disease progression transition probabilities, the method detailed in Spencer et al[1] was followed (Tables S1–S4).

- $T = (predFEV_1 \times (gamma - tau))/(delta - tau \times beta)$ where $predFEV_1$ is the predicted normal FEV_1 patient population, gamma is the percentage that actual FEV_1 at baseline is of predicted normal FEV_1, delta is the annual decline in lung function in patients with COPD, T is the time (in years) from when patients start in a health state until patients change to a new health state, tau is the percentage of predicted FEV_1 threshold at which patients enter a new health state, beta is the rate of decline for a normal patient without COPD.

The following National Health and Nutrition Examination Survey/Hankinson reference equation was also used:[2]

- Predicted $FEV_1\%$ = predicted FEV_1/predicted forced vital capacity (FVC)

  Predicted FVC men, age to 19
  $= -0.2584 - 0.20415 \times Age + 0.010133 \times Age \times Age + 0.00018642 \times Height\ (in\ cm) \times Height\ (in\ cm)$
  Predicted FVC men, age 20+
  $= -0.1933 + 0.00064 \times Age - 0.000269 \times Age \times Age + 0.00018642 \times Height\ (in\ cm) \times Height\ (in\ cm)$
  Predicted FVC women
  $= -0.3560 + 0.01870 \times Age - 0.000382 \times Age \times Age + 0.00014815 \times Height\ (in\ cm) \times Height\ (in\ cm)$
  Predicted FEV_1 men, age to 19
  $= -0.7453 - 0.04106 \times Age + 0.004477 \times Age \times Age + 0.00014098 \times Height\ (in\ cm) \times Height\ (in\ cm)$
  Predicted FEV_1 men, age 20+
  $= 0.5536 - 0.01303 \times Age - 0.000172 \times Age \times Age + 0.00014098 \times Height\ (in\ cm) \times Height\ (in\ cm)$
  Predicted FEV_1 women
  $= 0.4333 - 0.00361 \times Age - 0.000194 \times Age \times Age + 0.00011496 \times Height\ (in\ cm) \times Height\ (in\ cm)$

Change in trough FEV_1 (L) compared with no long-acting treatment for each maintenance treatment was used to increase FEV_1 upon initiation of treatment and thus patients on maintenance treatment remained in less severe health states longer than patients on no long-acting treatment. The changes in trough FEV_1 (at 24 hours) for umeclidinium/vilanterol (UMEC/VI) compared with tiotropium were obtained from the three clinical studies, and the estimate of change in trough FEV_1 for no long-acting beta-2 agonist treatment was taken from GSK study DB113373, which compared UMEC/VI with a no-treatment arm where short-acting maintenance was allowed to treat short-term symptoms. Transition probabilities in years subsequent to year 1 were adjusted based on increased risk of death due to age.

The "moderate base" case represents transition probabilities of patients at the start of the model, in the context of their improvements in FEV_1, which would be specific to their therapy regimen. The "moderate new" case, on the other hand, represents transition probabilities for patients newly transitioned into a given health state during the course of the

Table S1 Transition probabilities for UMEC/VI

From	To								
	Mild base	Moderate base	Severe base	Very severe base	New moderate	New severe	New very severe	CV death	Death
Mild base	–				–				–
Moderate base		0.944				0.031			0.026
Severe base			0.922				0.030		0.048
Very severe base				0.952					0.048
New moderate					0.948	0.026			0.026
New severe						0.909	0.043		0.048
New very severe							0.952		0.048
Death								0.000	1.000

Abbreviations: CV, cardiovascular; UMEC/VI, umeclidinium/vilanterol.

Table S2 Transition probabilities for tiotropium bromide

From	To								
	Mild base	Moderate base	Severe base	Very severe base	New moderate	New severe	New very severe	CV death	Death
Mild base	–				–				–
Moderate base		0.936				0.038			0.026
Severe base			0.911				0.041		0.048
Very severe base				0.952					0.048
New moderate					0.948	0.026			0.026
New severe						0.909	0.043		0.048
New very severe							0.952		0.048
Death								0.000	1.000

Abbreviation: CV, cardiovascular.

Table S3 Transition probabilities for open dual LAMA + LABA

From	To								
	Mild base	Moderate base	Severe base	Very severe base	New moderate	New severe	New very severe	CV death	Death
Mild base	–				–				–
Moderate base		0.944				0.031			0.026
Severe base			0.922				0.030		0.048
Very severe base				0.952					0.048
New moderate					0.948	0.026			0.026
New severe						0.909	0.043		0.048
New very severe							0.952		0.048
Death								0.000	1.000

Abbreviations: CV, cardiovascular; LABA, long-acting β_2-agonist; LAMA, long-acting muscarinic antagonist.

Table S4 Transition probabilities for no long-acting bronchodilator

From	To								
	Mild base	Moderate base	Severe base	Very severe base	New moderate	New severe	New very severe	CV death	Death
Mild base	–				–				–
Moderate base		0.925				0.0490			0.026
Severe base			0.890				0.062		0.048
Very severe base				0.952					0.048
New moderate					0.948	0.026			0.026
New severe						0.909	0.043		0.048
New very severe							0.952		0.048
Death								0.000	1.000

Abbreviation: CV, cardiovascular.

model time horizon. Since these probabilities are not specific to a given drug, the values are the same for all drugs.

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