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Original research article

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Is single-inhaler triple therapy for COPD cost-effective in the UK? The IMPACT trial

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'Take home' message - 256 characters including spaces (currently 246):
This analysis demonstrates that fluticasone furoate/umeclidinium/vilanterol (FF/UMEC/VI) provides a cost-effective treatment option *versus* FF/VI or UMEC/VI for patients with symptomatic chronic obstructive pulmonary disease in the United Kingdom.

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Abstract

Background: The IMPACT trial demonstrated superior outcomes following 52 weeks of once-daily single-inhaler treatment with fluticasone furoate/umeclidinium/vilanterol (FF/UMEC/VI) 100/62.5/25 µg compared with once-daily FF/VI (100/25 µg) or UMEC/VI (62.5/25 µg). This study evaluates the cost-effectiveness of FF/UMEC/VI compared with FF/VI or UMEC/VI for the treatment of chronic obstructive pulmonary disease (COPD) from a United Kingdom National Health Service perspective.

Methods: Patient characteristics and treatment effects from IMPACT were populated into a hybrid decision tree/Markov economic model. Costs (GB£ inflated to 2018 equivalents) and health outcomes were modelled over a lifetime horizon, with a discount rate of 3.5% per annum applied to both. Sensitivity analyses were performed to test the robustness of key assumptions and input parameters.

Results: Compared with FF/VI and UMEC/VI, FF/UMEC/VI provided an additional 0.296 and 0.145 life years (LYs; discounted), and 0.275 and 0.118 quality-adjusted life years (QALYs), at an additional cost of £1129 and £760, respectively. Incremental cost-effectiveness ratios (ICERs) for FF/UMEC/VI were £4104/QALY and £3809/LY gained *versus* FF/VI and £6418/QALY and £5225/LY gained *versus* UMEC/VI. At a willingness-to-pay threshold of £20 000/QALY, the probability that FF/UMEC/VI was cost-effective was 96% *versus* FF/VI and 74% *versus* UMEC/VI. Results were similar in a subgroup reflecting patients recommended triple therapy in the 2019 National Institute for Health and Care Excellence COPD guideline.

Conclusions: FF/UMEC/VI single-inhaler triple therapy improved health outcomes and was a cost-effective option compared with FF/VI or UMEC/VI for patients with symptomatic COPD and a history of exacerbations in the UK at recognised cost-effectiveness threshold levels.

Keywords: COPD, triple therapy, cost-effectiveness, United Kingdom

Introduction

The Global Initiative for Chronic Obstructive Lung Disease (GOLD) has noted that the healthcare costs associated with chronic obstructive pulmonary disease (COPD) are substantial and increase with disease severity [1]. Patients who have advanced disease represent a subgroup of the COPD patient population typically associated with greater healthcare resource utilisation (HRU) [1].

GOLD recommends triple pharmacological therapy, comprising an inhaled corticosteroid (ICS), a long-acting β_2-agonist (LABA), and a long-acting muscarinic antagonist (LAMA), for patients with COPD who remain symptomatic or at risk of exacerbations despite treatment with dual regimens [1]. Similarly, the National Institute for Health and Care Excellence (NICE) 2019 Guideline on COPD recommended the use of triple therapy for patients receiving ICS/LABA if their day-to-day symptoms continue to adversely impact their quality of life, and for patients on either ICS/LABA or LAMA/LABA who experience a severe exacerbation requiring hospitalisation or two moderate exacerbations within a year [2]. Historically, triple therapy has been prescribed through multiple inhaler combination therapies, however, single-inhaler triple therapies (SITT) are now available [3-8]. There is currently a paucity of economic analyses comparing the use of SITT with dual therapies in the United Kingdom (UK) [9-11].

The Phase III InforMing the PAthway of COPD Treatment (IMPACT) trial was a randomised, double-blind, parallel-group, multicentre study [3, 12]. IMPACT demonstrated superior exacerbation reduction and lung function improvement over 52 weeks of once-daily single-inhaler ICS/LAMA/LABA treatment with a combination of fluticasone furoate (FF, 100 µg), umeclidinium (UMEC, 62.5 µg), and vilanterol (VI, 25 µg), compared with FF/VI (100/25 µg) or UMEC/VI (62.5/25 µg). The rate of COPD-related hospitalisations was also lower amongst those treated with FF/UMEC/VI compared with those who received UMEC/VI [3].

The aim of this study was to evaluate the cost-effectiveness of FF/UMEC/VI SITT compared with dual therapy with either FF/VI or UMEC/VI for the treatment of COPD, using data from the IMPACT clinical trial, from a UK National Health Service (NHS) perspective.

Methods

Cost-effectiveness model structure

The economic model used has been published previously [11]. Briefly, it comprised two parts: an initial decision tree representing clinical outcomes directly from IMPACT results for the one-year trial period, and a Markov model to extrapolate outcomes over the longer term (figure 1). The six health states in the Markov model are stratified according to recent exacerbation history (exacerbation/no exacerbation within the previous 12 months) and three categories of COPD severity. The categories of COPD severity were defined by percent predicted forced expiratory volume in 1 second ($PPFEV_1$) based on GOLD classifications (moderate: 50–<80%, severe: 30–<50%, and very severe: <30%) [11].

Patients started the Markov model in health states according to the distribution observed at the end of the IMPACT trial. The movement of patients to more severe states (FEV_1 decline) and exacerbation risk in each state (exacerbation risk increases with COPD severity and with a history of exacerbation within the previous 12 months) was predicted by risk equations, estimated using data from the 3-year Towards a Revolution in COPD Health (TORCH) study [13], as no data beyond 52 weeks were available from the IMPACT trial. Annual transition probabilities and annual risk of exacerbation by severity state are shown in supplementary table S1. Health-related quality of life (HRQoL) and HRU were assigned to health states (with more severe states having higher HRU and poorer HRQoL), and disutilities were applied to exacerbation and pneumonia events.

Model inputs

Patient population

Patient characteristics from the IMPACT trial intent-to-treat (ITT) population were used for this analysis [3]. A subgroup reflecting patients recommended for triple therapy in the 2019 National Institute for Health and Care Excellence COPD guideline was also examined [2]. Patients eligible for inclusion in the IMPACT study were ≥40 years of age with symptomatic advanced COPD, current or former smokers with a smoking history of ≥10 pack years, and had at least one moderate or severe exacerbation during the previous 12 months [3, 12].

Mean patient age was 65.3 years, with patients being predominantly male (66%). The distribution of baseline characteristics was similar across all three treatment groups, including the incidence of previous COPD exacerbations. Baseline patient characteristics from the TORCH trial [13] (supplementary table S2) were used to generate the risk equations for the annual FEV_1 decline and exacerbation rates.

Comparators

The comparators included in the model analysis were FF/UMEC/VI (100/62.5/25 µg); FF/VI (100/25 µg) and UMEC/VI (62.5/25 µg). These treatments were all administered once daily using the single-dose ELLIPTA inhaler (GlaxoSmithKline, Middlesex, UK).

Treatment effect

Treatment effect at 52 weeks in the IMPACT ITT population, by treatment arm, was used. For lung function, this was included as the change in distribution across COPD severity (defined by $PPFEV_1$) health states during the trial period, with trial-end defining patient distribution at the beginning of the Markov phase. No further effect on lung function was included, and FEV_1 declined in all patients at the rate for the health state occupied in each cycle.

Treatment effect on exacerbation reduction was incorporated directly during the within-trial period, and then, in the base case, indirectly in the longer term through more patients distributed to less severe COPD Markov states, or states without a recent exacerbation, which have a lower risk of exacerbation. In scenario analysis, directly including the exacerbation rate reduction with FF/UMEC/VI observed in IMPACT, in the longer term, was explored. Exacerbation rates from the IMPACT study [3] and health distributions at trial end/Markov initiation are shown in supplementary table S3.

Treatment discontinuation

Treatment discontinuation was included in the initial decision-tree part of the model, using data obtained from the IMPACT trial at end of follow-up. Subsequent treatment discontinuation in the Markov model period was not included due to lack of long-term data. It was therefore assumed that patients remain on comparator treatment for

COPD for the duration of time in the Markov model. As patients were allowed to remain in the IMPACT trial after discontinuing therapy, the impact on treatment effect was considered to be accounted for in the ITT results, and discontinuation was assumed to only affect costs. Treatment costs were calculated assuming that patients who discontinued did so at the midpoint of the trial (i.e. they received 26 weeks of trial-assigned treatment and subsequently 26 weeks of replacement therapy). It was assumed that patients who discontinued remained on replacement therapy for the duration of the analysis time horizon. The cost of replacement therapy was based on the proportion of patients who received any of the four most common COPD medication classes used after discontinuation in IMPACT. In the base case, treatment arm-specific replacement treatment distributions were used; in the scenario analyses, the pooled replacement therapy distributions across all three treatment arms were applied across all initial treatments.

Pneumonia

Pneumonia was included as the only adverse event considered to potentially impact outcomes of the analysis. The rate of pneumonia was as reported for the IMPACT ITT population and in an additional post-hoc analyses for the subgroup [14]; in IMPACT, pneumonia incidence was analysed as a safety endpoint, and thus separately from the annual rate of moderate or severe exacerbations (primary endpoint in IMPACT). The rate of pneumonia was assumed to be dependent only on the treatment received, irrespective of COPD severity (supplementary table S3). Pneumonia mortality was assumed to be accounted for by the overall COPD excess mortality rates.

Mortality

Mortality occurring during the trial period was included within the base case and was as reported in the IMPACT trial (supplementary table S3). In the Markov model, mortality was estimated using COPD severity-specific risks (table 1), relative to patients without COPD, derived from a study of COPD mortality rates [21]. These were applied to rates from UK general population life tables [23] adjusted to exclude reported COPD deaths in the UK [24].

Costs

Health state, exacerbation, and drug costs are provided in table 1. All costs are in GB£ 2018 (inflated to 2018 costings using the Consumer Price Index [25] where applicable (supplementary table S4)). Drug costs were sourced from the Monthly Index of Medical Specialities (MIMS) [18].

HRU estimates for maintenance care at each level of COPD severity, and management of exacerbations, were taken from the available literature [19] and HRU unit cost from NHS reference costs (inflated to 2018) [16] and Personal Social Services Research Unit costs (inflated to 2018) [17] (supplementary table S4). For the cost of managing/treating pneumonia, ambulatory and inpatients unit costs from NHS references [16, 17] were weighted by the proportion of pneumonia cases hospitalised during the IMPACT trial (55%) [3], giving a weighted cost of £1087.98 per pneumonia event.

Costs of replacement therapies were based on weighted average use in 2018 UK market share data. Costs were estimated for the most commonly used therapies post-discontinuation in IMPACT, within each of the four therapy classes; £29.29 for LAMA monotherapy, £31.79 for ICS/LABA, £32.50 for LAMA/LABA, and £61.08 for ICS/LAMA/LABA [26]. The distribution of replacement therapies by class in IMPACT was similar for each treatment arm; resulting in 30-day replacement costs of £48.01, £48.54 and £49.34 for FF/UMEC/VI, UMEC/VI and FF/VI, respectively.

Societal costs (e.g. productivity losses due to absenteeism) were estimated according to the human capital approach, which can be broadly interpreted as estimating the lost gross value during time absent from usual activities [27], whether or not this means formal or paid employment. Societal costs were only included in the scenario analyses.

Health-related quality of life

During the trial period, utilities were calculated directly from EQ-5D data collected in IMPACT using the UK value set. The pooled baseline EQ-5D score was used for all treatments; treatment-specific utilities were then calculated by adding change from baseline in EQ-5D score at each time point where data were collected. Utilities for

health states and disutility for exacerbations and pneumonia for the Markov model were sourced from the literature [2, 15] (table 1).

Modelling assumptions

Only moderate and severe exacerbations were included, as it was assumed that mild exacerbations do not have a significant impact on clinical and economic outcomes. In the Markov model, it was assumed that individuals can only transition to increasingly severe health states, since COPD is a progressive disease.

Analyses

Base case

The base case analysis was conducted in the IMPACT ITT population over a lifetime (35 years) time horizon with costs and outcomes discounted at 3.5% per annum as per NICE guidance [28].

Subgroup analyses

In addition to the IMPACT ITT population, a subgroup analysis was conducted in the population of patients identified in the NICE COPD 2019 guidelines [2] as being appropriate for triple therapy, i.e. patients who experienced at least two moderate exacerbations or at least one severe exacerbation requiring hospitalisation in the previous year. IMPACT results for the subgroup are shown in supplementary table S3.

Scenario analyses

Scenario analyses were conducted with alternative model settings for discount rates, within-trial mortality, treatment discontinuation, time horizon, replacement therapy distribution, inclusion of societal costs and within-trial utility. Because the base case conservatively assumed no FF/UMEC/VI treatment effect on exacerbations beyond the trial period, scenario analyses were also conducted assuming treatment effect up to 5 years, both with constant full effect and with waning to zero, over that period.

Sensitivity analyses

Deterministic one-way sensitivity analyses were performed, varying a range of input parameters by ±20%, including the utility associated with very severe or moderate

COPD, exacerbation rates, risk of mortality, costs of FF/UMEC/VI, FF/VI and UMEC/VI, and COPD maintenance costs (supplementary table S5).

Probabilistic sensitivity analysis (PSA) was also conducted, with random sampling from distributions assigned to input parameters over 10 000 Monte Carlo simulations. Distributions used in the PSA are shown in supplementary table S6. Risk equation coefficients were included in the PSA via Cholesky decomposition. The findings were summarised as incremental cost-effectiveness ratio (ICER) scatter plots and cost-effectiveness acceptability curves.

Results

Compared with FF/VI, FF/UMEC/VI provided an additional 0.296 (95% confidence interval (CI) 0.198–0.399) life years (LYs; discounted) and 0.275 (0.033–0.512) quality-adjusted life years (QALYs), at an additional cost of £1129 (£683–£1533) (table 2), over the 35 year time horizon. The ICER in the base case was £4104 (£1646–£19 201) per QALY gained and £3809 (£2199–£6177) per LY gained (table 2). In one-way sensitivity analyses, ICERs ranged from £1320 to £6888 (figure 2), with results most sensitive to the cost of FF/UMEC/VI, utility associated with moderate COPD, and the cost of FF/VI. In scenario analyses, ICERs ranged from dominant (when the time horizon was restricted to the trial follow-up period) to £6234 (with no treatment discontinuation within or post trial) (table 3). In the PSA *versus* FF/VI, FF/UMEC/VI improved health outcomes and was more costly in the majority of simulations (figure 3a), with a probability of being cost-effective of 96%, at a willingness-to-pay (WTP) threshold of £20 000 per QALY [29] (figure 3b).

Compared with UMEC/VI, FF/UMEC/VI provided an additional 0.145 (0.041–0.253) LYs (discounted) and 0.118 (–0.124–0.355) QALYs, at an additional cost of £760 (£305–£1165) (table 2). This resulted in an ICER of £6418 (dominant (greater benefits at lower cost), £65 705) per QALY gained and £5225 (£1704–£19 702) per LY gained (table 2). In one-way sensitivity analyses, these results were shown to be most sensitive to the cost of both FF/UMEC/VI and UMEC/VI, and the utility associated with moderate COPD (figure 4); ICERs ranged from dominant to £12 888. Also, FF/UMEC/VI remained cost-effective when compared with UMEC/VI across all scenarios (table 3). In PSA, FF/UMEC/VI was associated with improved health

outcomes and was more costly than UMEC/VI in the majority of simulations (figure 5a) with a probability of being cost-effective compared with UMEC/VI of 74% at a WTP threshold of £20 000 per QALY gained (figure 5b).

In the subgroup of patients who would be eligible to receive triple therapy according to NICE guideline recommendations [2], results were similar compared with the base case (table 2). The ICERs were £5642 (dominant, £37 302) per QALY gained and £5235 (£2997–£9662) per LY gained compared with FF/VI and £5495 (dominant, £61 459) per QALY gained and £4289 (£524–£21 488) per LY gained compared with UMEC/VI.

Discussion

This analysis of IMPACT data from the UK NHS perspective provides strong evidence to support the cost-effectiveness of prescribing FF/UMEC/VI for the treatment of patients with COPD who remain symptomatic or at risk of exacerbations, despite treatment with dual regimens in the UK. FF/UMEC/VI remained cost-effective across all sensitivity and scenario analyses and, importantly, FF/UMEC/VI was shown to be cost-effective compared with FF/VI or UMEC/VI in those patients for whom NICE guidelines [2] recommend the use of inhaled triple therapy.

These findings are consistent with evidence from other economic evaluations of FF/UMEC/VI. A study using the GALAXY model [30] to compare FF/UMEC/VI with budesonide/formoterol (BUD/FOR) dual therapy (based on data from the FULFIL trial) also demonstrated that FF/UMEC/VI is a cost-effective option for the treatment of patients with symptomatic COPD from a UK NHS perspective [31]. This analysis was repeated using the current model, as part of a comparison of the two models presented at ISPOR 2019 [32], with similar estimates of cost-effectiveness from both models. Similar findings from a Spanish National Healthcare System perspective have also been reported; a GALAXY model analysis using data from the FULFIL trial demonstrated that FF/UMEC/VI was cost-effective compared with BUD/FOR dual therapy over a 3-year time horizon [10]. In a study in a Canadian setting, also using the GALAXY model and based on data from the IMPACT study, FF/UMEC/VI was

shown to be cost-effective compared with FF/VI and UMEC/VI over a lifetime horizon from a Canadian healthcare system perspective [9].

The GALAXY model uses linked risk equations to predict long-term outcomes, the equations taking account of some baseline patient clinical characteristics in addition to treatment effect on FEV_1, exacerbations and SGRQ scores. The model used in this analysis, although including two risk equations, uses a Markov approach, predicting outcomes based on FEV_1, exacerbation history and age alone. Applying different modelling approaches for the same decision problem strengthens the evidence base and provides important corroborating evidence where results indicate a similar conclusion of cost-effectiveness. The current model design was chosen because the Markov approach is familiar to many reimbursement and health technology agencies. In addition, the economic analysis conducted in support of the most recent NICE COPD Guideline employed a Markov model [2]. A table comparing the features of the models can be found in the Supplementary Appendix (Table S7).

Total costs were higher with FF/UMEC/VI than either comparator, largely as a result of the higher acquisition cost of FF/UMEC/VI. This was offset to some extent by savings in medical management costs with FF/UMEC/VI, resulting from fewer exacerbations and less time spent in the more severe COPD states where HRU is higher. The potential for a reduction in healthcare costs with FF/UMEC/VI is corroborated by an analysis of HRU in the FULFIL study [33] and a US-based within-trial economic analysis of HRU costs in the IMPACT trial [34]. Of the two comparisons analysed in this paper, the ICER was lower for FF/UMEC/VI compared with UMEC/VI, despite total costs being lower with FF/VI than UMEC/VI. This is because outcomes in the Markov model are driven primarily by the distribution across health states defined by $PPFEV_1$. This results in the FF/VI arm (single bronchodilator) having the lowest QALYs, as FF/VI shows the least improvement in FEV_1, and consequently QALY gains are higher for FF/UMEC/VI *versus* FF/VI, compared with FF/UMEC/VI *versus* UMEC/VI (0.275 *versus* 0.118, respectively).

It should be noted that any potential effect of baseline eosinophil levels on cost-effectiveness of treatment was not examined in this analysis. In the prespecified analysis of the annual rate of moderate or severe exacerbations conducted within

IMPACT, the observed reduction in exacerbations with triple therapy *versus* dual therapy was statistically significant regardless of baseline eosinophil level [3]. Moreover, at the present time, discussions are ongoing regarding the most appropriate cut-off points for eosinophil count analyses [35]. Once these have been determined, it may then be appropriate for this to be considered within cost-effectiveness models.

Limitations of this study include the fact that, common to all analyses of cost-effectiveness using clinical trial data, results may not be generalisable to clinical practice. In addition, no long-term data (beyond 52 weeks) were available from the IMPACT study and thus, for long-term outcomes, risk equations based on data from the TORCH trial (with a 3-year follow up) were used. While the populations in the two trials were broadly similar, whether the results of TORCH are fully generalisable to the IMPACT population is not certain. However, the model-projected reduction in predicted exacerbations with FF/UMEC/VI post trial, based on lung function, was observed to be substantially smaller than that seen in IMPACT, and is therefore unlikely to over-estimate the benefit of FF/UMEC/VI. Scenario analyses showed that the results were sensitive to assumptions on post-trial exacerbation treatment effect, with a substantial reduction in the ICER if the trial effects were applied to longer time horizons. Restricting treatment discontinuation to the trial period may also be a limitation. It is reasonable to assume that the majority of discontinuation occurs early in treatment, but longer-term data on discontinuation patterns would be desirable. However, in all sensitivity and scenario analyses, FF/UMEC/VI was cost effective, suggesting that uncertainty around long-term effects does not substantially affect the study conclusion. Finally, comorbidity is not explicitly modelled in this analysis, despite the fact that it is likely to influence mortality risk as well as the severity and consequent healthcare costs of exacerbations and pneumonia in an individual patient. However, this is unlikely to affect analysis results for the following reason: IMPACT was a randomised study with a very large sample size, therefore distribution of comorbidities, and the consequent impact on mortality and healthcare costs, should be similar across treatments. Hence, comorbidity should not impact treatment comparisons of cost, health outcomes, and cost-effectiveness.

In addition to the robustness of results to sensitivity analysis, a strength of this study is that comparative efficacy and safety data were derived from a study (IMPACT), where all treatments evaluated consisted of the same component molecules administered via the same inhaler, and at the same dosing frequency. This uniquely allows for strict evaluation of the benefit of triple therapy with FF/UMEC/VI compared with dual therapy with LAMA/LABA or ICS/LABA. However, this does mean that any potential benefits of SITT compared with multiple-inhaler triple therapy (for example ease of use or adherence), or of once-daily dosing over more frequent dosing regimens, were not reflected in the analysis, and must be the subject of further research.

In conclusion, FF/UMEC/VI SITT was predicted to improve health outcomes and be a cost-effective option when compared with FF/VI or UMEC/VI for patients with symptomatic COPD and a history of exacerbations in the UK, at recognised cost-effectiveness threshold levels and in line with NICE COPD guidelines.

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Author contributions

All authors contributed to study conception or design, and/or data analysis and interpretation. All authors were involved in the writing, reviewing, final approval of the manuscript, and agree to be accountable for all aspects of the work.

Conflict of interest

A. Martin, G. Anley, G. Okorogheye, M. Schroeder and A.S. Ismaila are/were employees of, and shareholders in, GlaxoSmithKline. A.S. Ismaila is also an unpaid part-time professor at McMaster University, Canada. D. Shah, K. Ndirangu and N. Risebrough are employees of ICON plc. ICON plc. received funding from GlaxoSmithKline to conduct this study but were not paid for development of this manuscript.

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Data-sharing statement

Anonymised individual participant data and study documents can be requested for further research from www.clinicalstudydatarequest.com.

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TABLE 1 Markov model health-state utilities [15], costs and QALY loss associated with each event [16]

Parameter	Input	Source
Health state costs		PSSRU 2019 [17]; NHS reference costs 2016/17 [16]; MIMS, 2019 [18]; Oostenbrink et al. 2005 [19]; ONS, 2018 [20]
Total cost (per annum)		
Moderate COPD	£216.82	
Severe COPD	£798.95	
Very severe COPD	£2297.98	
Relative risk of mortality		Afonso et al. 2011 [21]
Moderate COPD	1.89	
Severe COPD	3.63	
Very severe COPD	8.33	
Exacerbation costs		PSSRU 2019 [17]; NHS costs 2016/17 [16]; MIMS, 2019 [18]; Oostenbrink et al. 2005 [19]; ONS, 2018 [20]; Rutten-van Mölken et al.2006 [15]
Total cost (per event)		
Severe exacerbation	£6120.30	
Moderate exacerbation	£568.48	
Pneumonia*	£1087.98	
Drug costs		MIMS, July 2018 [18]
Cost per 30 days		
FF/UMEC/VI	£44.50	
FF/VI	£22.00	
UMEC/V	£32.50	
Health state utilities, utility (95% CI)		Rutten-van Mölken et al.2006 [15]
Moderate COPD (FEV_1 percent predicted 50–<80%)	0.787 (0.771–0.802)	
Severe COPD (FEV_1 percent predicted 30–<50%)	0.750 (0.731–0.786)	
Very severe COPD (FEV_1 percent predicted <30%)	0.647 (0.598–0.695)	
Event disutilities, QALY loss per event (95% CI)		NICE guidelines, 2010 [22]
Severe exacerbation	0.020 (0.020–0.030)	
Moderate exacerbation	0.011 (0.006–0.020)	
Pneumonia†	0.011 (0.006–0.020)	

*: weighted cost calculated using ambulatory and inpatient costs; †:assumption, equivalent to moderate exacerbation.
CI: confidence interval; COPD: chronic obstructive pulmonary disease; FEV_1: forced expiratory volume in 1 second; FF: fluticasone furoate; NICE: National Institute for Health and Care Excellence; QALY: quality-adjusted life year; UMEC, umeclidinium; VI, vilanterol.

TABLE 2**.** Results for FF/UMEC/VI compared with FF/VI or UMEC/VI base case ITT population and NICE recommended subgroup.

	FF/UMEC/VI	FF/VI	Incremental (FF/UMEC/VI *vs* FF/VI)	UMEC/VI	Incremental (FF/UMEC/VI *vs* UMEC/VI)
Base case ITT population					
Predicted exacerbations					
Moderate exacerbations	5.712	5.799	–0.087	5.888	–0.176
Severe exacerbations	1.371	1.378	–0.007	1.420	–0.049
Any moderate and/or severe exacerbation	7.083	7.177	–0.094	7.309	–0.225
Total LYs (discounted)	8.874	8.577	0.296 (0.198–0.399)	8.728	0.145 (0.041–0.253)
Total QALYs	6.564	6.289	0.275 (0.033–0.512)	6.446	0.118 (–0.124–0.355)
Costs					
Maintenance	£7926	£8479	–£552	£8030	–£104
Moderate exacerbations	£2666	£2738	–£72	£2776	–£110
Severe exacerbations	£6827	£6929	–£102	£7154	–£327
Pneumonia	£963	£940	£22	£606	£357
Treatment	£3881	£1759	£2122	£2546	£1335
Replacement therapy	£806	£1095	–£290	£1197	–£392
Total costs	£23 069	£21 941	£1129 (£683–£1533)	£22 310	£760 (£305–£1165)
ICER per LY gained			£3809 (£2199–£6177)		£5225 (£1704–£19 702)
ICER per QALY gained			£4104 (£1646–£19 201)		£6418 (dominant, £65 705)
Patients with ≥2 moderate or ≥1 severe exacerbation in the previous year					
Predicted exacerbations					
Moderate exacerbations	5.784	5.862	–0.078	5.983	–0.199
Severe exacerbations	1.384	1.396	–0.012	1.464	–0.080
Any moderate and/or severe exacerbation	7.168	7.258	–0.090	7.447	–0.279
Total LYs (discounted)	9.142	8.895	0.247 (0.148–0.356)	8.996	0.146 (0.029–0.266)
Total QALYs	6.800	6.571	0.229 (−0.013–0.473)	6.686	0.114 (−0.134–0.365)
Costs					
Maintenance	£7468	£7942	–£474	£7562	–£94
Moderate exacerbations	£2688	£2750	–£62	£2811	–£123
Severe exacerbations	£6856	£6978	–£122	£7369	–£514
Pneumonia	£1012	£965	£47	£640	£371
Treatment	£4026	£1843	£2183	£2624	£1402
Replacement therapy	£806	£1084	–£278	£1222	–£417
Total costs	£22 855	£21 562	£1293 (£873–£1686)	£22 228	£627 (£122–£1076)
ICER per LY gained			£5235 (£2997–£9662)		£4289 (£524–£21 488)
ICER per QALY gained			£5642 (dominant, £37 302)		£5495 (dominant, £61 459)

Outcomes and costs observed over the complete period (trial-based and Markov models). All ranges are 95% confidence intervals, unless otherwise stated. 95% confidence intervals were derived from the probabilistic sensitivity analysis. FF: fluticasone furoate; ICER: incremental cost-effectiveness ratio; LY: life year; QALY: quality-adjusted life year; UMEC: umeclidinium; VI: vilanterol.

TABLE 3**.** Scenario analyses (FF/UMEC/VI *versus* FF/VI or UMEC/VI) – ITT population

	Base case	**Scenario**	**FF/UMEC/VI *versus* FF/VI (ICER/QALY gained)**	**FF/UMEC/VI *versus* UMEC/VI (ICER/QALY gained)**
Base case			£4104	£6418
Discount rates (costs, benefits)	3.5%	0.0%	£4134	£6731
Discount rates (costs, benefits)	3.5%	5.0%	£4082	£6227
Within trial mortality	Included	Excluded	£4132	£8123
Post-trial treatment effect* – No waning	No direct effect	Direct effect for 1 year	£3293	£3301
Post-trial treatment effect – No waning	No direct effect	Direct effect for 3 years	£1951	Dominant
Post-trial treatment effect – No waning	No direct effect	Direct effect for 5 years	£891	Dominant
Post-trial treatment effect – With waning	No direct effect	Direct effect for 5 years	£1993	Dominant
Treatment discontinuation	Within trial treatment discontinuation applied	No treatment discontinuation within or post trial	£6234	£9455
Time horizon	Life-time	Trial follow-up	Dominant	Dominant
Replacement therapy	Replacement therapy specific per initial treatment	Average replacement therapy across all initial treatments	£4104	£6418
Perspective	Health service perspective	Societal perspective†	£3442	£3739
Utility for within trial period	EQ-5D data from IMPACT	Health state-specific utility data [15]	£4051	£6301

*: The post-trial treatment effect analyses applied the relative risk reductions in exacerbations observed during the IMPACT trial.

†: Indirect costs include productivity losses incurred by absenteeism. This was estimated according to the human capital approach, which can be broadly interpreted as estimating the lost gross value during time absent from usual activities.

FF: fluticasone furoate; ICER: incremental cost-effectiveness ratio; QALY: quality-adjusted life year; UMEC: umeclidinium; VI: vilanterol.

Figure 1

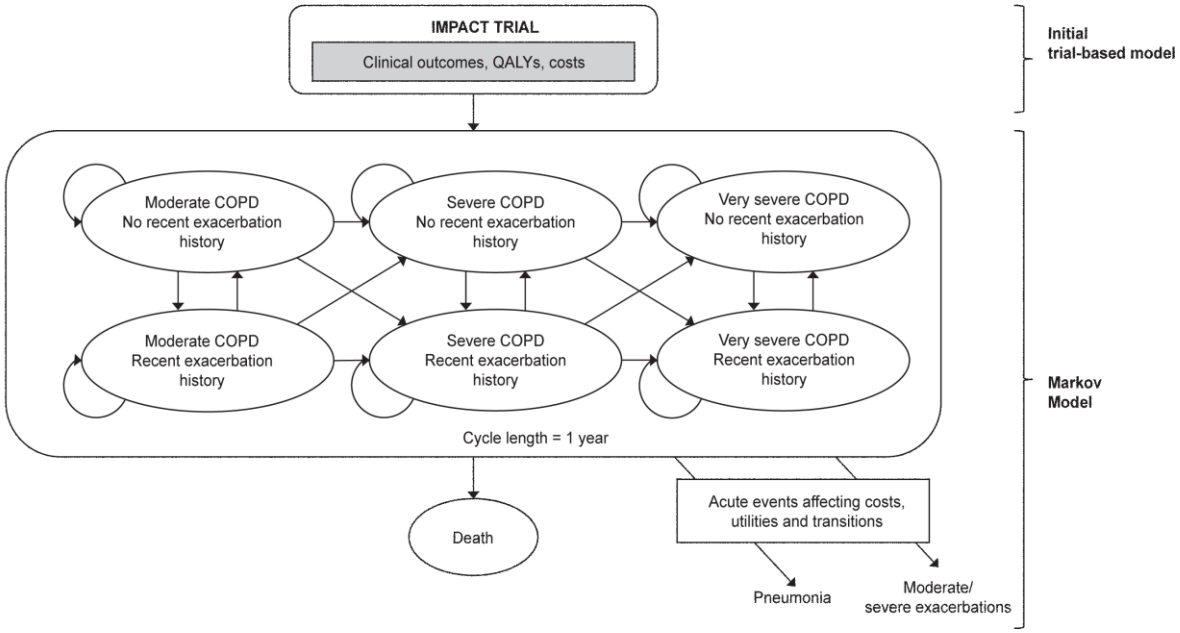

FIGURE 1 Conceptual COPD disease progression model

Moderate COPD (FEV_1 percent predicted 50–<80%); Severe COPD (FEV_1 percent predicted 30–<50%); Very severe COPD (FEV_1 percent predicted <30%). A recent exacerbation history is defined as an exacerbation occurring within the previous cycle.

COPD: chronic obstructive pulmonary disease; FEV_1: forced expiratory volume in 1 second; QALY: quality-adjusted life year.

Figure 2

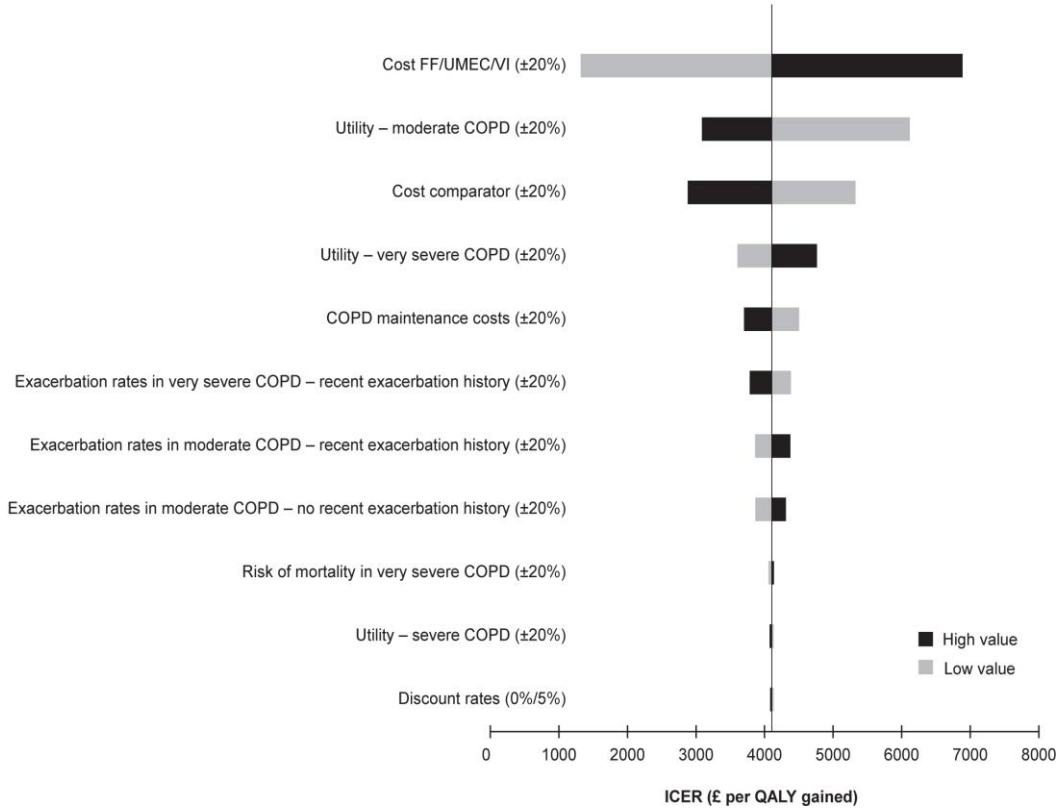

FIGURE 2 One-way sensitivity analysis plot for FF/UMEC/VI compared with FF/VI (QALYs; ITT population)

Moderate COPD (FEV_1 percent predicted 50–<80%); Severe COPD (FEV_1 percent predicted 30–<50%); Very severe COPD (FEV_1 percent predicted <30%).

COPD: chronic obstructive pulmonary disease; FEV_1: forced expiratory volume in 1 second; FF: fluticasone furoate; ICER: incremental cost-effectiveness ratio; ITT: intent-to-treat; OWSA: one-way sensitivity analysis; QALY: quality-adjusted life year; UMEC: umeclidinium; VI: vilanterol.

Figure 3

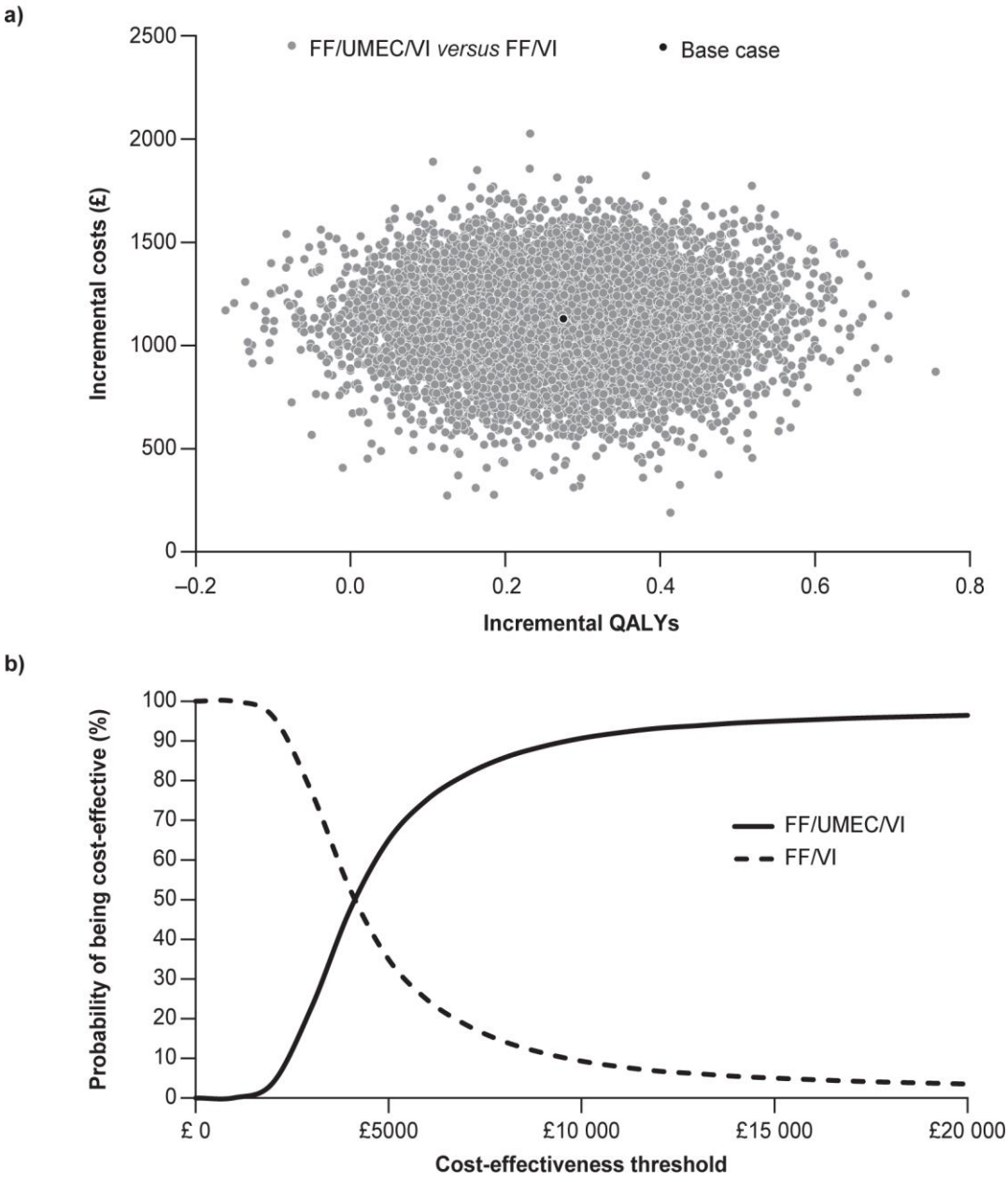

FIGURE 3 a) ICER scatter plot (QALYs) and b) cost-effectiveness acceptability curve for FF/UMEC/VI compared with FF/VI

FF: fluticasone furoate; ICER: incremental cost-effectiveness ratio; QALY: quality-adjusted life year; UMEC: umeclidinium; VI: vilanterol

Figure 4

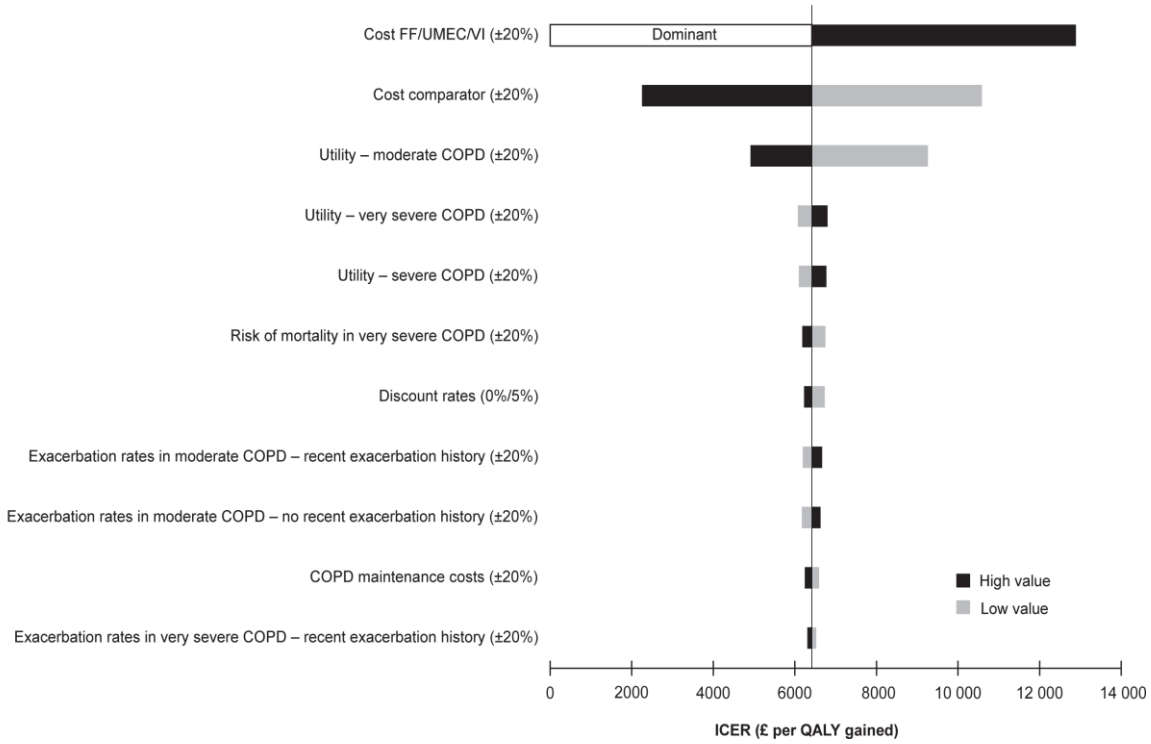

FIGURE 4 One-way sensitivity analysis plot for FF/UMEC/VI compared with UMEC/VI (QALYs; ITT population)

Moderate COPD (FEV_1 percent predicted 50–<80%); Severe COPD (FEV_1 percent predicted 30–<50%); Very severe COPD (FEV_1 percent predicted <30%).

COPD: chronic obstructive pulmonary disease; FEV_1: forced expiratory volume in 1 second; FF: fluticasone furoate; ICER: incremental cost-effectiveness ratio; ITT: intent-to-treat; OWSA: one-way sensitivity analysis; QALY: quality-adjusted life year; UMEC: umeclidinium; VI: vilanterol.

Figure 5

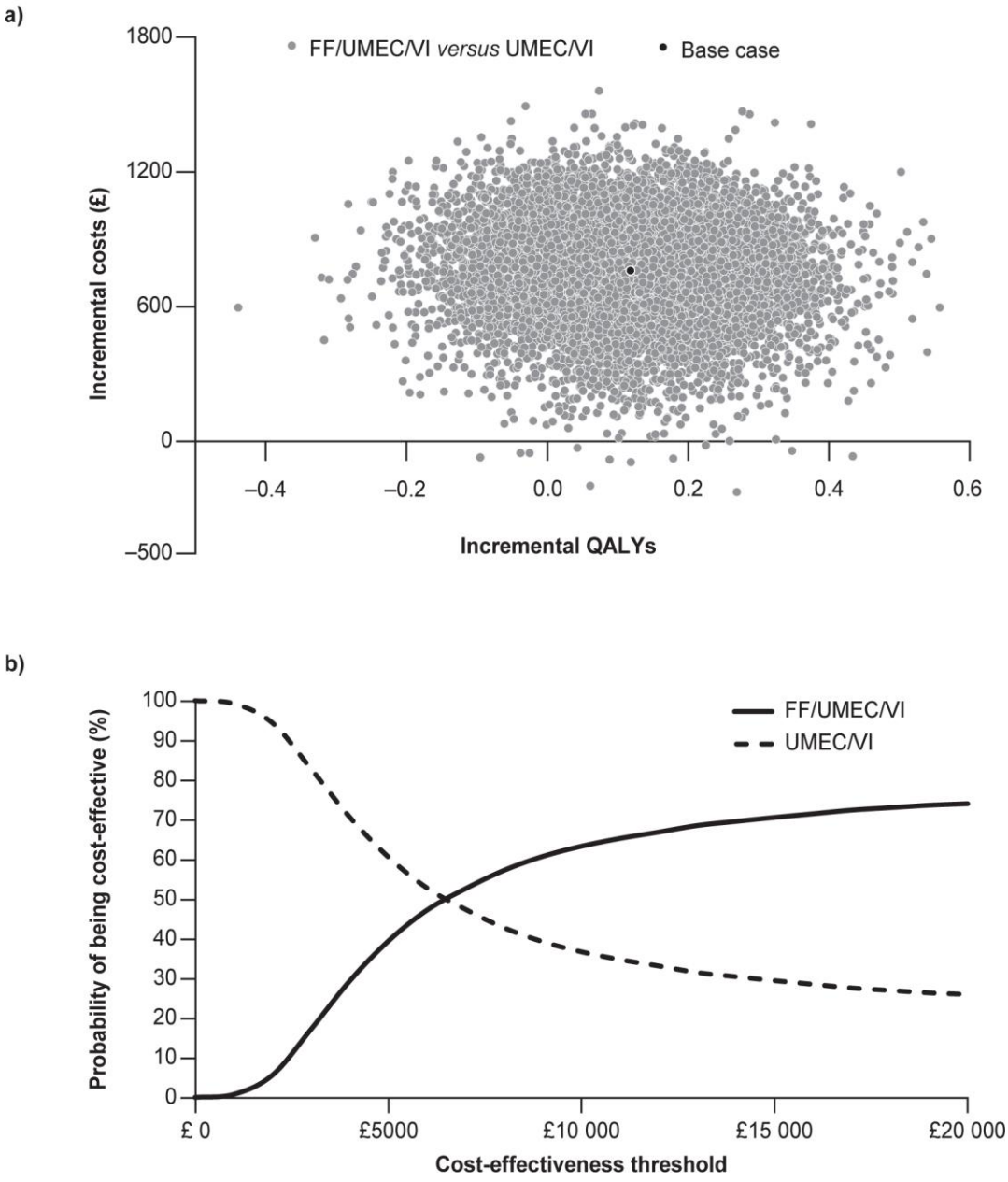

FIGURE 5 a) ICER scatter plot (QALYs) and b) cost-effectiveness acceptability curve for FF/UMEC/VI compared with UMEC/VI

FF: fluticasone furoate; ICER: incremental cost-effectiveness ratio; QALY: quality-adjusted life year; UMEC: umeclidinium; VI: vilanterol.

Supplementary appendix

SUPPLEMENTARY TABLE S1 Annual transition probabilities (based on statistical equations for FEV_1 decline over time)

COPD severity health state transition	Transition probability
Moderate COPD to Severe COPD (no recent exacerbation history)	4.11%
Moderate COPD to Severe COPD (recent exacerbation history)	8.83%
Severe COPD to Very severe COPD (no recent exacerbation history)	7.83%
Severe COPD to Very severe COPD (recent exacerbation history)	14.28%

Moderate COPD (FEV_1 percent predicted 50–<80%); Severe COPD (FEV_1 percent predicted 30–<50%); Very severe COPD (FEV_1 percent predicted <30%). A recent exacerbation history is defined as an exacerbation occurring within the previous cycle.

COPD: chronic obstructive pulmonary disease; FEV_1: forced expiratory volume in 1 second.

SUPPLEMENTARY TABLE S2 Baseline patient characteristics

Parameter		Source
Sex		
Male	75.8%	TORCH [1]
Age category, years		
<55	11.5%	TORCH, data on file
55–<65	32.3%	TORCH, data on file
65–<75	43.7%	TORCH, data on file
≥75	12.6%	TORCH, data on file
Exacerbation history (moderate or severe, in the previous 12 months)		
0	43.0%	TORCH, data on file
1	24.8%	TORCH, data on file
≥2	32.3%	TORCH, data on file
BMI, kg/m^2		
<20	13.5%	TORCH, data on file
20–<25	37.6%	TORCH, data on file
25–<29	26.9%	TORCH, data on file
≥29	22.0%	TORCH, data on file
SGRQ total score		
<38	28.8%	TORCH, data on file
38–<50	25.7%	TORCH, data on file
50–<62	22.9%	TORCH, data on file
≥62	22.6%	TORCH, data on file

SD: standard deviation; BMI: body mass index; SGRQ: St. George's Respiratory Questionnaire; FEV_1: forced expiratory volume in 1 second.

SUPPLEMENTARY TABLE S3 Model inputs: trial outcomes and health-state distribution at end of trial/start of Markov model

	FF/UMEC/VI	FF/VI	UMEC/VI
IMPACT ITT population			
Trial outcomes (on-treatment event analysis)			
Annual rate of moderate COPD exacerbations (95% CI)	0.75 (0.71–0.79)	0.89 (0.85–0.93)	0.97 (0.91–1.04)
Annual rate of severe COPD exacerbations (95% CI)	0.13 (0.12–0.14)	0.15 (0.13–0.16)	0.19 (0.17–0.22)
Pneumonia (rate/1000 patient-years)	95.8	96.6	61.2
Deaths (n, %)*	70 (1.7)	78 (1.9)	50 (2.4)
Utility inputs			
Baseline (pooled)†	0.788	0.788	0.788
28-week change from baseline	0.017	0.014	0.013
52-week change from baseline	0.013	0.006	0.002
Health-state distribution at end of trial/start of Markov model			
No within-trial exacerbations (%)			
Moderate COPD (FEV_1 percent predicted 50–<80%)	27.7	23.1	25.2
Severe COPD (FEV_1 percent predicted 30–<50%)	19.6	19.5	21.1
Very severe COPD (FEV_1 percent predicted <30%)	5.2	7.5	6.0
With within-trial exacerbations (%)			
Moderate COPD (FEV_1 percent predicted 50–<80%)	17.3	13.9	16.6
Severe COPD (FEV_1 percent predicted 30–<50%)	19.9	23.0	20.5
Very severe COPD (FEV_1 percent predicted <30%)	8.6	11.1	8.1
Treatment discontinuation (%)	18.3	25.2	27.3

	FF/UMEC/VI	FF/VI	UMEC/VI
IMPACT subgroup: ≥2 moderate exacerbations or ≥1 severe exacerbation			
Trial outcomes			
Annual rate of within-trial moderate COPD exacerbations	0.77 (0.73–0.81)	0.88 (0.84–0.94)	1.01 (0.94–1.10)
Annual rate of within-trial severe COPD exacerbations	0.13 (0.11–0.14)	0.15 (0.13–0.17)	0.22 (0.19–0.25)
Pneumonia (rate/1000 patient-years)‡	97.9	95.8	62.9
Deaths (n, %)*	31 (1.1)	34 (1.2)	27 (1.9)
Utility inputs			
Baseline (pooled)	0.788	0.788	0.788
28-week change from baseline	0.018	0.016	0.017
52-week change from baseline	0.015	0.011	0.010
Health-state distribution at end of trial/start of Markov model			
No within-trial exacerbations (%)			
Moderate COPD (FEV_1 percent predicted 50–<80%)	31.8%	28.1%	29.7%
Severe COPD (FEV_1 percent predicted 30–<50%)	15.6%	16.6%	15.8%
Very severe COPD (FEV_1 percent predicted <30%)	4.0%	5.1%	4.2%
With within-trial exacerbations (%)			
Moderate COPD (FEV_1 percent predicted 50–<80%)	21.4%	17.5%	20.3%
Severe COPD (FEV_1 percent predicted 30–<50%)	18.0%	21.7%	20.3%
Very severe COPD (FEV_1 percent predicted <30%)	8.1%	9.8%	7.8%
Treatment discontinuation (%)	17.6	24.0	27.3

*: From adjudicated fatal serious adverse events; †: Pooled utility for all three treatment arms in the IMPACT trial was used at baseline; ‡: GlaxoSmithKline, data on file.

COPD, chronic obstructive pulmonary disease; FEV_1, forced expiratory volume in 1 second; FF, fluticasone furoate; ITT, intent-to-treat; UMEC, umeclidinium; VI, vilanterol

SUPPLEMENTARY TABLE S4 Itemised resource use and unit costs for COPD management and exacerbations

Cost category	Resource use (per annum)*	Unit cost (2018)‡	Overall cost
Moderate COPD management			
Outpatient visit GP [2]	2.00	£39.01	£78.02
Spirometry [3]	2.00	£66.40	£132.81
Influenza vaccination [4]	0.75	£8.00	£6.00
Total cost of moderate COPD (per annum)			**£216.82**
Severe COPD management			
Outpatient visit, respiratory physician [3]	2.00	£212.39	£424.78
Spirometry [3]	2.00	£66.40	£132.81
Influenza vaccination [4]	0.75	£8.00	£6.00
Oxygen therapy (days) [5]	14.60	£16.12	£235.36
Total cost of severe COPD (per annum)			**£798.95**
Very severe COPD management			
Outpatient visit RP [3]	4.00	£212.39	£849.56
Spirometry [3]	4.00	£66.40	£265.61
Influenza vaccination [4]	0.75	£8.00	£6.00
Oxygen therapy (days) [5]	73.00	£16.12	£1176.81
Total cost of very severe COPD (per annum)			**£2297.98**
	Resource use (per exacerbation)*	Unit cost (2018)	Cost (per exacerbation)
Moderate exacerbation			
Non-ICU days [3]	1.01	£413.90	£418.04
ER visits [3]	0.03	£221.68	£6.65
Outpatient visit, RP [3]	0.34	£212.39	£72.21
Outpatient visit, GP [2]	0.66	£39.01	£25.75
Visit other healthcare provider [3]	0.27	£153.70	£41.50
Antibiotics† [4]	7.94	£0.45	£3.54
Systemic steroids† [4]	7.94	£0.10	£0.80
Total cost per moderate exacerbation			**£568.48**
Severe exacerbation			
ICU days [3]	0.86	£1377.43	£1184.59
Non-ICU days [3]	11.08	£413.90	£4586.01
ER visits [3]	0.25	£221.68	£55.42
Outpatient visit, respiratory physician [3]	0.82	£212.39	£174.16
Outpatient visit, GP [2]	0.70	£39.01	£27.31
Visit other healthcare provider [3]	0.50	£153.70	£76.85
Antibiotics† [4]	11.75	£0.9	£10.16

Systemic steroids† [4]	24.08	£0.1	£2.43
Oxygen therapy [5]	0.21	£16.1	£3.39
Total cost per severe exacerbation			**£6120.30**

Moderate COPD (FEV_1 percent predicted 50–<80%); Severe COPD (FEV_1 percent predicted 30–<50%); Very severe COPD (FEV_1 percent predicted <30%).

*: Resource use estimates come from Oostenbrink et al (2005) [5]; †: Unit cost represents the cost per days or visit or per category; ‡: All costs were updated to 2018 using the Office on National Statistics inflation and price indices [6].

COPD: chronic obstructive pulmonary disease; ER: emergency room; FEV_1: forced expiratory volume in 1 second; GP: general practitioner; ICU: intensive care unit; RP: respiratory physician.

SUPPLEMENTARY TABLE S5 one-way sensitivity analysis: pre-specified upper and lower limits for pre-selected parameters, Markov model

Parameter	Range	Base case	Lower limit	Upper limit
Utility associated with very severe COPD	±20%	0.647	0.518	0.776
Utility associated with severe COPD	±20%	0.750	0.600	0.900
Utility associated with moderate COPD	±20%	0.787	0.630	0.944
Exacerbation rates in very severe COPD - recent exacerbation history	±20%	1.200	0.960	1.440
Exacerbation rates in moderate COPD - no recent exacerbation history	±20%	0.299	0.239	0.359
Exacerbation rates in moderate COPD - recent exacerbation history	±20%	0.735	0.588	0.882
Risk of mortality in very severe COPD	±20%	8.33	6.664	9.996
Discount rates for costs and benefits	–	3.5%	0%	5%
Cost of comparator	±20%			
FF/VI		£22.00	£17.60	£26.40
UMEC/VI		£32.50	£26.00	£39.00
Cost FF/UMEC/VI	±20%	£44.50	£35.60	£53.40
COPD maintenance cost	±20%			
Moderate COPD (FEV_1 percent predicted 50–<80%)		£216.82	£173.46	£260.19
Severe COPD (FEV_1 percent predicted 30–<50%)		£798.95	£639.16	£958.74
Very severe COPD (FEV_1 percent predicted <30%)		£2297.98	£1838.38	£2757.57

Moderate COPD (FEV_1 percent predicted 50–<80%); Severe COPD (FEV_1 percent predicted 30–<50%); Very severe COPD (FEV_1 percent predicted <30%).

COPD: chronic obstructive pulmonary disease; FEV_1: forced expiratory volume in 1 second; FF: fluticasone furoate; OWSA: one-way sensitivity analysis; UMEC: umeclidinium; VI: vilanterol.

SUPPLEMENTARY TABLE S6 Distributions used in the PSA

Parameter	**Distribution**	**Justification**
Patient characteristics*	Normal	Assumed normally distributed in the population
COPD mortality rates	Log normal	
Relative risk†	Log normal	Ratio, additive on log scale
Trial-based model probabilities	Beta/Dirichlet	Constrained on interval of 0 to 1
Risk equation coefficients‡	Multivariate normal with Cholesky decomposition	To capture correlation between normally distributed regression coefficients
Unit costs	Gamma	Constrained on interval of 0 to positive infinity
Resource use rates	Gamma	Constrained on interval of 0 to positive infinity
Resource use probabilities	Beta	Constrained on interval of 0 to 1
Utilities	Beta	Constrained on interval 0 and 1
QALY loss	Gamma	Constrained on interval of 0 to positive infinity

*: Age, height; †: COPD mortality, exacerbations; ‡: FEV_1 decline, exacerbations.

COPD: chronic obstructive pulmonary disease; PSA: probabilistic sensitivity analysis; QALY: quality-adjusted life years

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SUPPLEMENTARY TABLE S7 Comparison of the Markov and GALAXY models

	Markov	**GALAXY**
Structure	Decision tree followed by Markov model	Linked-risk equations
Treatment effects	FEV_1 effect applied at the start of the Markov phase; exacerbation risk determined by FEV_1 status. Direct exacerbation treatment effect not applied	Applied at each annual model cycle to FEV_1, SGRQ score, and moderate/severe exacerbations
Risk equations	Based on TORCH [7] and applied to cohort by health state (according to COPD severity)	Based on ECLIPSE [8,9] (clinical) and TORCH [7] (resource use) and applied across the cohort
Utility	Derived from EQ-5D data collected in UPLIFT [10] and applied to health states, exacerbation events, and pneumonia events	SGRQ score predicted per annual cycle (based on lung function, recent exacerbations, symptoms, and baseline factors) and then mapped to utility using a validated algorithm [11]
Disease progression	Risk equations predict rate of FEV_1 decline (FEV_1 health state transitions) and risk of exacerbations, based on baseline covariates, COPD severity, and history of exacerbations in previous cycle	FEV_1, exacerbations, symptoms, and exercise capacity are predicted by risk equations based on baseline covariates and disease status in previous cycle
Mortality	Risk of death derived from mortality tables, with specific health-state excess risk multipliers	Estimated survival in each year based on predicted clinical status that year
Costs	Directly assigns HRU (rates from literature [5]) and associated costs to health states and exacerbation and pneumonia events	Costs applied to cohort mean HRU rates predicted by risk equations based on baseline covariates, disease status, and exacerbation events
Baseline inputs	**Markov**	**GALAXY**
Common to both	Age, sex, BMI, FEV_1, exacerbation history, SGRQ score	
Differ between models	BMI, SGRQ, and age categorized differently than in GALAXY to predict FEV_1 decline and exacerbation count, and applied across health states.	FULFIL demographics [12] (CVD comorbidity, other comorbidities, mMRC dyspnea score, current smoking status), estimated 6MWT distance, estimated fibrinogen levels used to predict FEV_1 decline, exacerbation count, SGRQ decline and survival for patient cohort

	TORCH population demographics [7] (sex, BMI, SGRQ score, and baseline exacerbation history) used as a data source	

6MWT, 6-minute walk test; BMI, body mass index; CVD, cardiovascular disease; EQ-5D, EuroQol-5D health questionnaire; HRU, healthcare resource utilization; mMRC, modified Medical Research Council

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