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ORIGINAL RESEARCH

Economic Analysis of New Single-Inhaler Triple Therapies in Patients with COPD in the UK

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Purpose: Chronic obstructive pulmonary disease (COPD) is associated with a substantial economic burden in the UK. Although previous analyses have compared the cost-effectiveness of single-inhaler triple therapy (SITT) versus dual therapy or multiple-inhaler triple therapy, there are no studies investigating the cost-effectiveness of individual SITTs versus other SITTs. This study assessed the cost-effectiveness of SITT with fluticasone furoate/umeclidinium/vilanterol (FF/UMEC/VI) versus other SITTs for the treatment of COPD from a UK National Health Service perspective.

Patients and Methods: The validated GALAXY-COPD model was populated with patient baseline characteristics from the IMPACT study and treatment effect data from a network meta-analysis, which compared FF/UMEC/VI with budesonide/glycopyrrolate/formoterol fumarate (BUD/GLY/FOR; both 320 µg and 160 µg dosing; BUD320 and BUD160, respectively) and beclometasone dipropionate/formoterol fumarate/glycopyrrolate (BDP/FOR/GLY). UK healthcare resource unit and drug costs (Great British Pound, 2022) were applied, with costs and outcomes (except life years [LYs]) discounted at 3.5% annually. The base case was probabilistic (5000 iterations) with a lifetime horizon.

Results: FF/UMEC/VI provided an additional 0.620 (95% range: 0.255, 1.025) LYs and 0.283 (0.080, 0.501) quality-adjusted LYs (QALYs) with a cost saving of £1620 (£158, £3243) versus BUD320/GLY/FOR, an additional 0.627 (0.261, 1.053) LYs and 0.309 (0.097, 0.533) QALYs at a cost saving of £1721 (£261, £3345) versus BUD160/GLY/FOR, and an additional 0.328 (0.063, 0.654) LYs and 0.230 (0.035, 0.437) QALYs at a cost saving of £1221 (−£541, £2796) versus BDP/FOR/GLY. FF/UMEC/VI was less costly and showed higher QALYs in 98.2%, 98.9%, and 93.6% of simulations versus BUD360/GLY/FOR, BUD160/GLY/FOR, and BDP/FOR/GLY, respectively. At a willingness-to-pay threshold of £20,000 per QALY, the probability of FF/UMEC/VI being cost-effective was 99.9%, 100%, and 99.3% versus BUD320/GLY/FOR, BUD160/GLY/FOR, and BDP/FOR/GLY, respectively.

Conclusion: Based on this analysis, FF/UMEC/VI is a dominant (improved outcomes with cost savings) treatment option compared with other SITTs for the treatment of patients with COPD in the UK.

Keywords: chronic obstructive pulmonary disease, cost-effectiveness, fluticasone furoate/umeclidinium/vilanterol, GALAXY model, probabilistic

Introduction

Chronic obstructive pulmonary disease (COPD) affects approximately 3 million people in the UK and has been shown to reduce quality of life and increase mortality and morbidity.[1,2] COPD is also one of the costliest inpatient conditions treated by the UK National Health Service (NHS).[3] The estimated total cost to the NHS due to COPD in 2021 was £2 billion,[4] and this is predicted to increase annually in line with a predicted increase in prevalence of COPD in the UK.[4,5]

The Global Initiative for Chronic Obstructive Lung Disease (GOLD)[6] recommends triple therapy (long-acting β_2-agonist [LABA] + long-acting muscarinic antagonist [LAMA] + inhaled corticosteroid [ICS]) as initial maintenance therapy for patients with a history of exacerbations (≥2 moderate exacerbations or ≥1 exacerbation leading to hospitalization) and elevated

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blood eosinophil counts (≥300 cells/μL).[6] For patients who experience recurrent exacerbations while receiving mono or dual bronchodilator therapy, an escalation to triple therapy is recommended.[6]

Historically, triple therapy required the use of multiple inhalers, which was associated with poor persistence and adherence;[7,8] however, single-inhaler triple therapies (SITTs) are now available for use in the UK. These include fluticasone furoate/umeclidinium/vilanterol (FF/UMEC/VI),[9] budesonide/glycopyrrolate/formoterol fumarate (BUD/GLY/FOR),[10] and beclometasone dipropionate/formoterol fumarate/glycopyrrolate (BDP/FOR/GLY).[11]

Given the economic burden of COPD in the UK, the potential impact of prescribing SITT is of interest. Previous studies that compared the cost-effectiveness of SITT versus dual therapy demonstrated that SITT was a cost-effective treatment option that has a beneficial effect on patient outcomes by reducing the rate of exacerbations and improving health-related quality of life.[12–16] A recent analysis compared the cost-effectiveness of SITT with FF/UMEC/VI versus multiple-inhaler triple therapy (MITT) and showed improved health outcomes at reduced costs;[17] however, there are currently no studies investigating the cost-effectiveness of SITTs versus other SITTs. The GOLD currently recommends SITT over MITT due to the improved adherence that SITT offers.[6] The improved outcomes observed in patients who switch from MITT to SITT suggest that SITTs may become a more commonly prescribed treatment option. Therefore, comparing the effectiveness of SITTs in terms of cost-effectiveness and health outcomes could help healthcare providers to select the most appropriate SITT option for patients and could also help to reduce the economic burden of COPD.

A frequentist network meta-analysis (NMA) was previously conducted to understand the relative efficacy of FF/UMEC/VI compared with other SITTs (BUD/GLY/FOR and BDP/FOR/GLY) among patients with COPD.[18] Efficacy outcomes of interest in this NMA included forced expiratory volume in 1 second (FEV_1), annualized rate of combined moderate and severe exacerbations, St George's Respiratory Questionnaire (SGRQ) total score and SGRQ responders, transition dyspnea index focal score, and rescue medication use. The results showed that FF/UMEC/VI was statistically significantly more effective at increasing trough FEV_1 compared with most triple comparators and showed statistically significant improvements in the annualized rate of combined moderate or severe exacerbations versus BUD/GLY/FOR.

This current study used relevant, relative efficacy data from the NMA to assess the cost-effectiveness of SITT with FF/UMEC/VI versus BUD/GLY/FOR and BDP/FOR/GLY for the treatment of patients with moderate-to-severe COPD inadequately controlled with dual maintenance therapy from a UK NHS perspective.

Materials and Methods

Study Design

This analysis was conducted using the published and validated GALAXY-COPD disease progression model.[19–21] GALAXY uses linked risk equations to model associations between patient characteristics, treatment effects, disease progression, and cost and health outcomes (Figure 1). The model was adapted using patient characteristics from the IMPACT study.[22] IMPACT data were used as the sample size was large and the dataset was the most complete for the target population. For treatment effects, relevant efficacy data comparing FF/UMEC/VI versus BUD/GLY/FOR (320/18/9.6 μg and 160/18/9.6 μg dosing; BUD320/GLY/FOR and BUD160/GLY/FOR, respectively) and BDP/FOR/GLY were extracted from the NMA.

Model Inputs

Pooled baseline characteristics data from the IMPACT trial[22] were used for baseline parameter inputs across all treatment arms (this ensured that the starting population was the same across all comparator arms; Table 1[23,24]). For parameters that were not directly available from IMPACT trial data, estimates were made using risk equations or analogous data collected in the IMPACT trial (see Appendix 1).

Treatment effect parameters from the NMA included in the model were change from baseline in FEV_1, absolute change from baseline in SGRQ score, and relative risk for moderate and severe exacerbations (Table 2). No comparison of treatment effect on moderate and severe exacerbation reduction, separately, was possible in the NMA,[18] so the estimates for overall exacerbation reduction were used for both moderate and severe exacerbation reductions in the

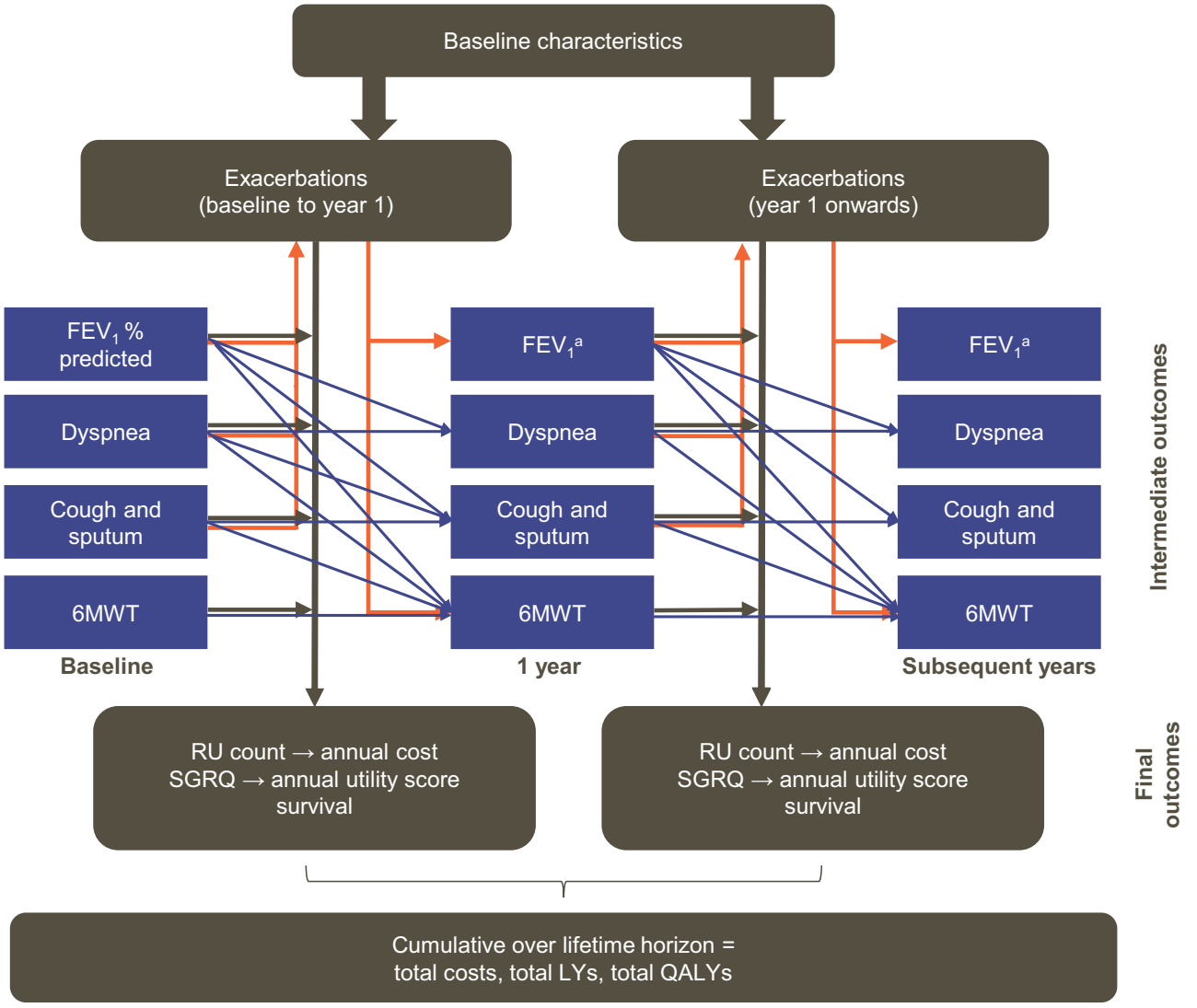

Figure 1 GALAXY model.

Notes: [a]Calculated (in mL) using the risk equation at 1 year and converted to FEV_1% predicted based on the cohort profile. Purple lines indicate the relationship between the central attributes in the different time periods. Orange lines indicate the relationship between intermediate outcomes and exacerbations. Grey lines indicate the relationship between the central attributes and the final health outcomes. Adapted with permission from: Andrew H Briggs, Timothy Baker, Nancy A Risebrough, Mike Chambers, Sebastian Gonzalez-McQuire, Afisi S Ismaila, Alex Exuzides, Chris Colby, Maggie Tabberer, Hana Muellerova, Nicholas Locantore, Maureen P M H Rutten van Mölken, David A Lomas. *Med Decis Making* 2017; 37: 469–480.

Abbreviations: 6MWT, six-minute walking test; COPD, chronic obstructive pulmonary disease; FEV_1, forced expiratory volume in 1 second; LY, life year; QALY, quality-adjusted life year; RU, resource utilization; SGRQ, St George's Respiratory Questionnaire.

model. Prior to fitting the model, SGRQ score was converted to SGRQ for COPD patients (SGRQ-C) score based on the SGRQ-C manual.[25]

In the base case, treatment-specific discontinuation data from clinical trials (IMPACT for FF/UMEC/VI,[22] ETHOS for BUD/GLY/FOR [both doses],[26] and TRIBUTE for BDP/FOR/GLY[27]) at 52 weeks were used for the first year. For subsequent years, discontinuation rates were assumed to be zero for all treatment arms. In the model, all patients who discontinued their initial treatment (FF/UMEC/VI or other SITT) switched to subsequent treatment. Subsequent treatment was based on the four most common classes of treatment taken after discontinuation of randomized treatment in IMPACT (ICS/LABA/LAMA, ICS/LABA, LAMA/LABA, and LAMA).[22] The proportion of patients receiving each class was renormalized in line with the assumption of 100% of patients receiving subsequent treatment. The efficacy of subsequent treatment was assumed to be the same as the reference treatment (other SITT) for patients discontinuing FF/

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Table 1 Model Inputs for Patient Characteristics – Base Case

Characteristic	IMPACT (ITT – Pooled Data)	Source
Female, %	34	IMPACT clinical trial supplementary materials[23]
Age, years	65.3	IMPACT clinical trial supplementary materials[23]
BMI low (<21), %	17	IMPACT clinical trial supplementary materials[23]
BMI medium (21–30), %	58	IMPACT clinical trial supplementary materials[23]
BMI high (>30), %	25	IMPACT clinical trial supplementary materials[23]
Any CVD comorbidity, %	44	IMPACT clinical trial supplementary materials[23]
Any other comorbidity, %	57	IMPACT clinical trial supplementary materials[23]
History of exacerbation, 1 or more, %	100	IMPACT clinical trial supplementary materials[23]
mMRC score ≥2, %	37	IMPACT clinical trial supplementary materials[23]
Current smokers, %	35	IMPACT clinical trial supplementary materials[23]
Height, cm	167.5	IMPACT clinical trial supplementary materials[23]
Fibrinogen[a], μg/dL	477.5	Not available from IMPACT, derived from a risk equation
6MWD[a], m	365.8	Not available from IMPACT, derived from a risk equation
Dyspnea (none)[a], %	1.5	Not available from IMPACT, derived from a risk equation
Dyspnea (several days per week)[a], %	30.3	Not available from IMPACT, derived from a risk equation
Dyspnea (most days per week)[a], %	68.2	Not available from IMPACT, derived from a risk equation
Cough or sputum (most days per week)[a], %	54.1	Not available from IMPACT, derived from a risk equation
Mean number of exacerbations in previous year	1.71	IMPACT clinical trial supplementary materials[23]
Mean number of moderate exacerbations	1.41	IMPACT clinical trial supplementary materials[23]
Mean number of severe exacerbations	0.30	IMPACT clinical trial supplementary materials[23]
Starting FEV_1% predicted	45.5	IMPACT clinical trial supplementary materials[23]
Starting FEV_1 (mL), predicted by the GALAXY model	1215.3	Based on FEV_1% reported in IMPACT[22] and formulae based on ECLIPSE[24] to back calculate the starting FEV_1 value
Mean starting SGRQ total score	50.7	IMPACT clinical trial supplementary materials[23]
Resulting HRQoL utility value	0.654	Calculated from SGRQ-C score by algorithm

Notes: [a]Data not available from IMPACT,[22,23] based on predicted values at baseline from the risk equations in the GALAXY model.
Abbreviations: 6MWD, six-minute walk distance; BMI, body mass index; COPD, chronic obstructive pulmonary disease; CVD, cardiovascular disease; FEV_1, forced expiratory volume in 1 second; HRQoL, health-related quality of life; ITT, intent-to-treat; mMRC, modified Medical Research Council; SGRQ, St George's Respiratory Questionnaire; SGRQ-C, St George's Respiratory Questionnaire for COPD patients.

UMEC/VI or other SITT. Thus, there was residual benefit included in the analysis after discontinuation of FF/UMEC/VI, like patients would have received one of the other SITTs.

Utilities

The GALAXY model predicts SGRQ-C scores for each annual cycle based on COPD disease status. Utilities were derived by translating predicted SGRQ-C scores to a utility value using a published algorithm based on a mapping from SGRQ-C to EuroQol 5-Dimensions 3-level index scores.[28]

Table 2 Model Inputs for Treatment Effects – Base Case

Comparator Treatment	FF/UMEC/VI Versus Comparator, Mean Difference		
	Change from Baseline in FEV_1, mL	Change from Baseline in SGRQ	Relative Risk for Moderate and Severe Exacerbations
BUD320/GLY/FOR	111.22 (79.80, 142.63)	−0.66 (−2.53, 1.21)	0.62 (0.45, 0.86)
BUD160/GLY/FOR	110.77 (71.78, 149.76)	−0.92 (−2.84, 1.00)	0.61 (0.44, 0.85)
BDP/FOR/GLY[a]	46.70 (15.21, 78.20)	−1.43 (−3.47, 0.61)	0.73 (0.51, 1.04)

Notes: Source adapted from[18]. [a]12-week analysis available only. Data are mean (95% CI), unless otherwise stated.
Abbreviations: BDP/FOR/GLY, beclometasone dipropionate/formoterol fumarate/glycopyrrolate; BUD160, budesonide 160 µg dosing; BUD320, budesonide 320 µg dosing; CI, confidence interval; FEV_1, forced expiratory volume in 1 second; FF/UMEC/VI, fluticasone furoate/umeclidinium/vilanterol; GLY/FOR, glycopyrrolate/formoterol fumarate; SGRQ, St George's Respiratory Questionnaire.

Costs

Medication costs were obtained from the British National Formulary.[29] Dose, pack size, and cost per pack were used to calculate the cost per day (Table 3). The cost of each subsequent treatment was calculated as the weighted average of all

Table 3 Primary Treatment Costs, Subsequent Treatment Costs, and Health State and Exacerbation Costs (2022, GBP)

Drug	Dose (µg)	Pack Size	Pack Cost (£)	Cost per Dose (£)	Cost per Day (£)	Label Dosing
FF/UMEC/VI	100/62.5/25	30	44.5	1.48	1.48	1 daily by inhalation
BUD320/GLY/FOR	182/10.4/5.8	120	44.5	0.37	1.48	2 inhalations twice daily
BUD160/GLY/FOR	182/10.4/5.8	120	44.5	0.37	1.48	2 inhalations twice daily
BDP/FOR/GLY	100/6/12.5	120	44.5	0.37	1.48	2 inhalations twice daily
Subsequent therapy		**Renormalized percentage of patients receiving treatment in IMPACT (all comparators)**			**Weighted average cost per day (£)**	
ICS/LABA/LAMA		57.9			1.72	
ICS/LABA		25.1			0.93	
LAMA/LABA		10.3			1.01	
LAMA		6.7			0.92	
Total		100.0			1.40	
Parameter					**Total management cost (£)**	
Health state						
Moderate to severe (FEV_1% predicted 80–50%)					128	
Severe (FEV_1% predicted <50–30%)					850	
Very severe (FEV_1% predicted <30%)					1578	
Exacerbation					**Cost per exacerbation (£)**	
Moderate					88	
Severe					2379	

Source[23,29–31].
Abbreviations: BDP/FOR/GLY, beclometasone dipropionate/formoterol fumarate/glycopyrrolate; BUD160, budesonide 160 µg dosing; BUD320, budesonide 320 µg dosing; FEV_1, forced expiratory volume in 1 second; FF/UMEC/VI, fluticasone furoate/umeclidinium/vilanterol; GBP, Great British Pound; GLY/FOR, glycopyrrolate/formoterol fumarate; ICS, inhaled corticosteroid; LABA, long-acting β_2-agonist; LAMA, long-acting muscarinic antagonist.

available products (weighted by their volume) in the treatment class, based on the renormalized percentage of patients receiving each class (Table 3). The cost of rescue medication was included in the analyses and clinical trial data were used where available (IMPACT[22] for FF/UMEC/VI and TRIBUTE[27] for BDP/FOR/GLY). Where clinical trial data were unavailable, calculations using NMA data were used (BUD/GLY/FOR; see Appendix 1).[18] Rescue medication costs were only applied to patients while they were receiving their initial treatment regimen (ie, no rescue medication costs were applied after initial treatment discontinuation).

For healthcare costs, three health states based on categories of COPD severity were defined (moderate to severe [FEV_1% predicted 80–50%], severe [FEV_1% predicted <50–30%], and very severe [FEV_1% predicted <30%]).[30] The model calculated the proportion of the cohort in each health state for each cycle, and appropriate annual costs were applied. Events (moderate or severe exacerbations) were costed individually. Resource utilization estimates and unit costs for healthcare items in each health state and for exacerbation events were obtained from a published economic model report (2018) from the National Institute for Health and Care Excellence (NICE).[30] Costs were inflated to 2022 values using Consumer Price Index data obtained from the Office of National Statistics[31] (Table 3).

Indirect costs (including productivity losses incurred by sick leave) included in scenario analyses were estimated according to the human capital approach. This is broadly interpreted as estimated lost gross value during time absent from usual activities (ie, although a proportion of patients may be unemployed or retired, they would still be unable to continue their usual activities and may need to hire help).[32] Average UK earning per day was used to calculate the cost of each day absent from usual activities.[33]

Analyses

The analysis was conducted from a UK NHS perspective over a lifetime horizon, with a 3.5% discount rate (for costs and benefits) in accordance with guidelines from NICE.[34] Cumulative exacerbation rate per person per year (PPPY), life years (LYs), quality-adjusted LYs (QALYs), and disaggregated costs for each treatment were calculated from the annual cycle health and cost outcomes predicted for the model to give the following outputs: disaggregated direct costs (COPD medications, non-drug costs); total direct costs; total exacerbations (moderate and severe); total LYs gained; and total QALYs gained. Incremental costs and QALYs were calculated using the cumulative costs and QALYs at the selected timeframe.

Two sets of analyses were conducted: probabilistic and deterministic. Incremental cost-effectiveness ratios (ICERs) were calculated by dividing the mean incremental costs by the mean incremental QALYs for the probabilistic analyses and by dividing the incremental costs by the incremental QALYs for the deterministic analyses.

Probabilistic analyses were conducted with random sampling from distributions assigned to input parameters over 5000 simulations. The output was summarized using 95% confidence intervals,[35] a scatterplot of incremental costs and effectiveness, and net benefit acceptability curves for competing treatments included in the model. Further details can be found in Appendix 1 and Supplementary Table S1.

Scenario and Sensitivity Analyses

Scenario analyses were performed to examine the impact of alternative populations, assumptions, and model settings on the base case results (Table 4). Both probabilistic and deterministic analyses were conducted for these scenarios.

One-way sensitivity analyses were conducted on baseline covariate values that were not available from IMPACT data and FF/UMEC/VI treatment effects on exacerbation, SGRQ response, and FEV_1 (see Appendix 1 and Supplementary Table S2).

Results

Base Case Analyses

Using data from the IMPACT trial[22,23] for the model inputs for patient demographics, 34% of patients in the base case analysis of this NMA were female and all patients had previously experienced ≥1 exacerbation. Patients had a starting predicted FEV_1 of 1215.3 mL and a mean starting SGRQ total score of 50.7.

Table 4 Summary of Model Settings – Base Case and Scenario Analyses

Parameter	Base Case	Scenario Analyses
Time horizon	Lifetime (25 years)	5 years, 10 years
Discount rates	3.5%	0%, 5%
Patient characteristics	IMPACT ITT data	Data from comparator pivotal trials 1. KRONOS[36,37] 2. ETHOS[26] 3. TRILOGY[35]
Treatment discontinuation and subsequent treatment	Include, only in first year	1. Exclude 2. Include in first and subsequent years
Cost of each treatment class used for subsequent treatment	Weighted average of all available products in each treatment class	1. Assume 100% market share of product with highest cost in each treatment class 2. Assume 100% market share of product with lowest cost in each treatment class
Rescue drug use costs	Include, based on NMA results and IMPACT data	Exclude
Patient productivity costs	Exclude	Include

Abbreviations: ITT, intent-to-treat; NMA, network meta-analysis.

In the probabilistic analyses, FF/UMEC/VI provided an additional 0.620 (95% range: 0.255, 1.025) LYs and 0.283 (0.080, 0.501) QALYs with a cost saving of £1620 (£158, £3243) versus BUD320/GLY/FOR, an additional 0.627 (0.261, 1.053) LYs and 0.309 (0.097, 0.533) QALYs at a cost saving of £1721 (£261, £3345) versus BUD160/GLY/FOR, and an additional 0.328 (0.063, 0.654) LYs and 0.230 (0.035, 0.437) QALYs at a cost saving of £1221 (−£541, £2796) versus BDP/FOR/GLY (Tables 5–7). In all three cases, FF/UMEC/VI resulted in higher drug costs versus the comparator,

Table 5 FF/UMEC/VI versus BUD320/GLY/FOR – Base Case (Probabilistic), 2022 GBP

Probabilistic (Lifetime)	BUD320/GLY/FOR	FF/UMEC/VI	Incremental
Cumulative number of exacerbations over timeframe			
Moderate	11.234	8.209	−3.025
Severe	3.620	2.701	−0.919
Total	14.854	10.911	−3.944
Severe exacerbations PPPY	0.407	0.284	−0.123
Total exacerbations PPPY	1.670	1.147	−0.523
Outcomes at end of timeframe			
Accumulated LYs (undiscounted)	8.892	9.512	0.620
Accumulated QALYs	4.465	4.748	0.283
Costs at end of timeframe			
Accumulated costs total	£18,372	£16,751	−£1620
Drug costs	£4071	£4292	£221
Total non-drug costs	£14,301	£12,459	−£1842

(*Continued*)

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Table 5 (Continued).

Probabilistic (Lifetime)	BUD320/GLY/FOR	FF/UMEC/VI	Incremental
Incremental results (mean, 95% range)			
Incremental cost			−£1620 (−£3243, −£158)
Incremental LYs (undiscounted)			0.620 (0.255, 1.025)
Incremental QALYs			0.283 (0.080, 0.501)
Incremental cost-effectiveness ratio, QALY			Dominant (dominant, dominant)

Abbreviations: BUD320/GLY/FOR, budesonide 320 µg dosing/glycopyrrolate/formoterol fumarate; FF/UMEC/VI, fluticasone furoate/umeclidinium/vilanterol; GBP, Great British Pound; LY, life year; PPPY, per person per year; QALY, quality-adjusted life year.

Table 6 FF/UMEC/VI versus BUD160/GLY/FOR – Base Case (Probabilistic), 2022 GBP

Probabilistic (Lifetime)	BUD160/GLY/FOR	FF/UMEC/VI	Incremental
Cumulative number of exacerbations over timeframe			
Moderate	11.255	8.141	−3.114
Severe	3.635	2.687	−0.948
Total	14.890	10.828	−4.061
Severe exacerbations PPPY	0.408	0.282	−0.126
Total exacerbations PPPY	1.671	1.135	−0.536
Outcomes at end of timeframe			
Survival at end of time horizon, %	0.2	0.6	0.35
Accumulated LYs (undiscounted)	8.910	9.536	0.627
Accumulated QALYs	4.469	4.778	0.309
Costs at end of timeframe			
Accumulated costs total	£18,421	£16,700	−£1721
Drug costs	£4082	£4300	£218
Total non-drug costs	£14,339	£12,400	−£1939
Incremental results (mean, 95% range)			
Incremental cost			−£1721 (−£3345, −£261)
Incremental LYs (undiscounted)			0.627 (0.261, 1.053)
Incremental QALYs			0.309 (0.097, 0.533)
Incremental cost-effectiveness ratio, QALY			Dominant (dominant, dominant)

Abbreviations: BUD160/GLY/FOR, budesonide 160 µg dosing/glycopyrrolate/formoterol fumarate; FF/UMEC/VI, fluticasone furoate/umeclidinium/vilanterol; GBP, Great British Pound; LY, life year; PPPY, per person per year; QALY, quality-adjusted life year.

Table 7 FF/UMEC/VI versus BDP/FOR/GLY – Base Case (Probabilistic), 2022 GBP

Probabilistic (Lifetime)	BDP/FOR/GLY	FF/UMEC/VI	Incremental
Cumulative number of exacerbations over timeframe			
Moderate	11.260	9.126	−2.134
Severe	3.639	2.985	−0.655
Total	14.899	12.111	−2.788
Severe exacerbations PPPY	0.408	0.322	−0.085
Total exacerbations PPPY	1.669	1.308	−0.360
Outcomes at end of timeframe			
Accumulated LYs (undiscounted)	8.930	9.257	0.328
Accumulated QALYs	4.480	4.710	0.230
Costs at end of timeframe			
Accumulated costs total	£18,460	£17,239	−£1221
Drug costs	£4101	£4199	£98
Total non-drug costs	£14,359	£13,039	−£1319
Incremental results (mean, 95% range)			
Incremental cost			−£1221 (−£2796, £541)
Incremental LYs (undiscounted)			0.328 (0.063, 0.654)
Incremental QALYs			0.230 (0.035, 0.437)
Incremental cost-effectiveness ratio, QALY			Dominant (dominant, £4241)

Abbreviations: BDP/FOR/GLY, beclometasone dipropionate/formoterol fumarate/glycopyrrolate; FF/UMEC/VI, fluticasone furoate/umeclidinium/vilanterol; GBP, Great British Pound; LY, life year; PPPY, per person per year; QALY, quality-adjusted life year.

mainly due to patients receiving FF/UMEC/VI accumulating more LYs; however, non-drug costs were lower for FF/UMEC/VI versus all three comparators. Patients receiving FF/UMEC/VI had fewer exacerbations PPPY with reductions of 0.523, 0.536, and 0.360 versus BUD360/GLY/FOR, BUD160/GLY/FOR, and BDP/FOR/GLY, respectively. Hence, compared with other SITTs, FF/UMEC/VI was the dominant treatment option (improved outcomes with cost savings) in all base case analyses. Similar results were seen in the deterministic analyses with FF/UMEC/VI being the dominant treatment option versus other SITTs across all base case analyses (Supplementary Tables S3–5).

FF/UMEC/VI was less costly and showed higher QALYs in 98.2%, 98.9%, and 93.6% of simulations versus BUD360/GLY/FOR, BUD160/GLY/FOR, and BDP/FOR/GLY, respectively (Figure 2). At a willingness-to-pay threshold of £20,000 per QALY, the probability of FF/UMEC/VI being cost-effective was 99.9%, 100%, and 99.3% versus BUD320/GLY/FOR, BUD160/GLY/FOR, and BDP/FOR/GLY, respectively (Figure 3).

Scenario Analyses

The mean results showed that FF/UMEC/VI remained a dominant treatment option across all probabilistic scenario analyses (Table 8). Versus all three comparators, the cost savings of FF/UMEC/VI were highest in the scenario where patient lost productivity costs were included and lowest in the scenario where same discontinuation data were applied for the first year and subsequent years. In the two scenario analyses conducted; one where discontinuation rates for

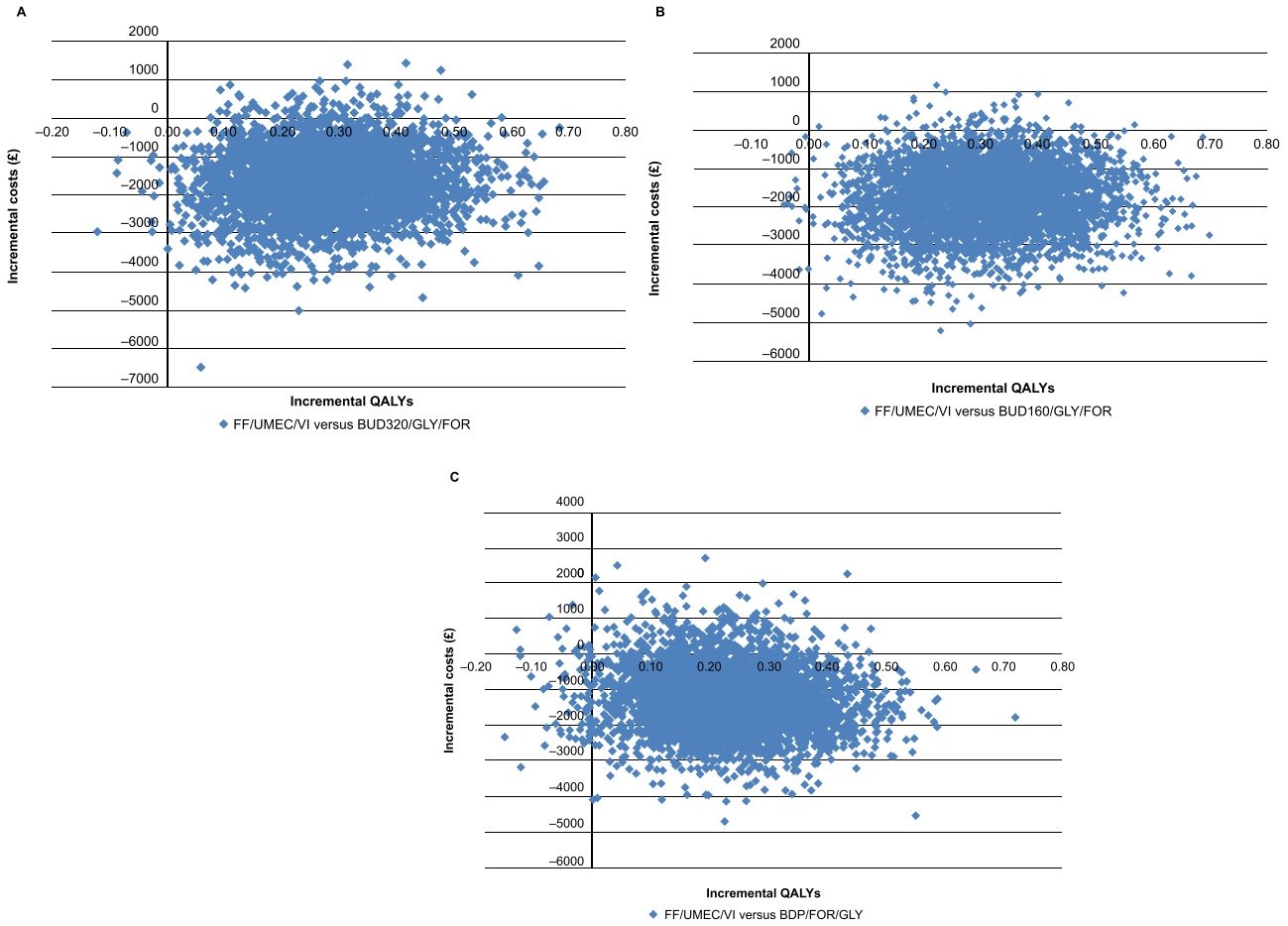

Figure 2 Incremental cost-effectiveness planes for FF/UMEC/VI versus (**A**) BUD320/GLY/FOR, (**B**) BUD160/GLY/FOR, and (**C**) BDP/FOR/GLY – base case (probabilistic).
Abbreviations: BDP/FOR/GLY, beclometasone dipropionate/formoterol fumarate/glycopyrrolate; BUD160, budesonide 160 µg dosing; BUD320, budesonide 320 µg dosing; FF/UMEC/VI, fluticasone furoate/umeclidinium/vilanterol; GLY/FOR, glycopyrrolate/formoterol fumarate; QALY, quality-adjusted life year.

subsequent years were assumed to be the same as the first year, and one where the discontinuation rate was assumed to be zero in the first and subsequent years, the overall results did not differ when compared with the base case (FF/UMEC/VI remained the dominant treatment option). In deterministic analyses, FF/UMEC/VI remained the dominant treatment across all scenario analyses (Supplementary Table S6).

One-Way Sensitivity Analyses (Deterministic)

FF/UMEC/VI remained the dominant treatment across all one-way sensitivity analyses, except for one (Table 9). For the FF/UMEC/VI versus BDP/FOR/GLY analysis where the smallest treatment effect on exacerbation reduction was assumed, using the upper CI value of the relative risk from the NMA, FF/UMEC/VI resulted in an additional cost of £417 and an incremental QALY of 0.147, resulting in an ICER of £2847/QALY. However, at a willingness-to-pay threshold of £20,000 per QALY, FF/UMEC/VI remained highly cost-effective.

Discussion

This analysis estimated the cost-utility (cost per QALY gained) of initiating FF/UMEC/VI versus other SITTs (BUD/GLY/FOR [320 and 160 µg doses] and BDP/FOR/GLY) over a lifetime horizon for the treatment of patients with moderate-to-severe COPD from a UK NHS perspective. Overall, treatment with FF/UMEC/VI resulted in an increase in clinical benefit (reduction in exacerbations and gains in overall survival and QALYs), coupled with cost-savings versus BUD/GLY/FOR (both doses) and BDP/FOR/GLY. The additional LYs and QALYs provided by FF/UMEC/VI were largely due to its favorable treatment effects for FEV_1 and SGRQ. Although FF/UMEC/VI resulted in slightly higher

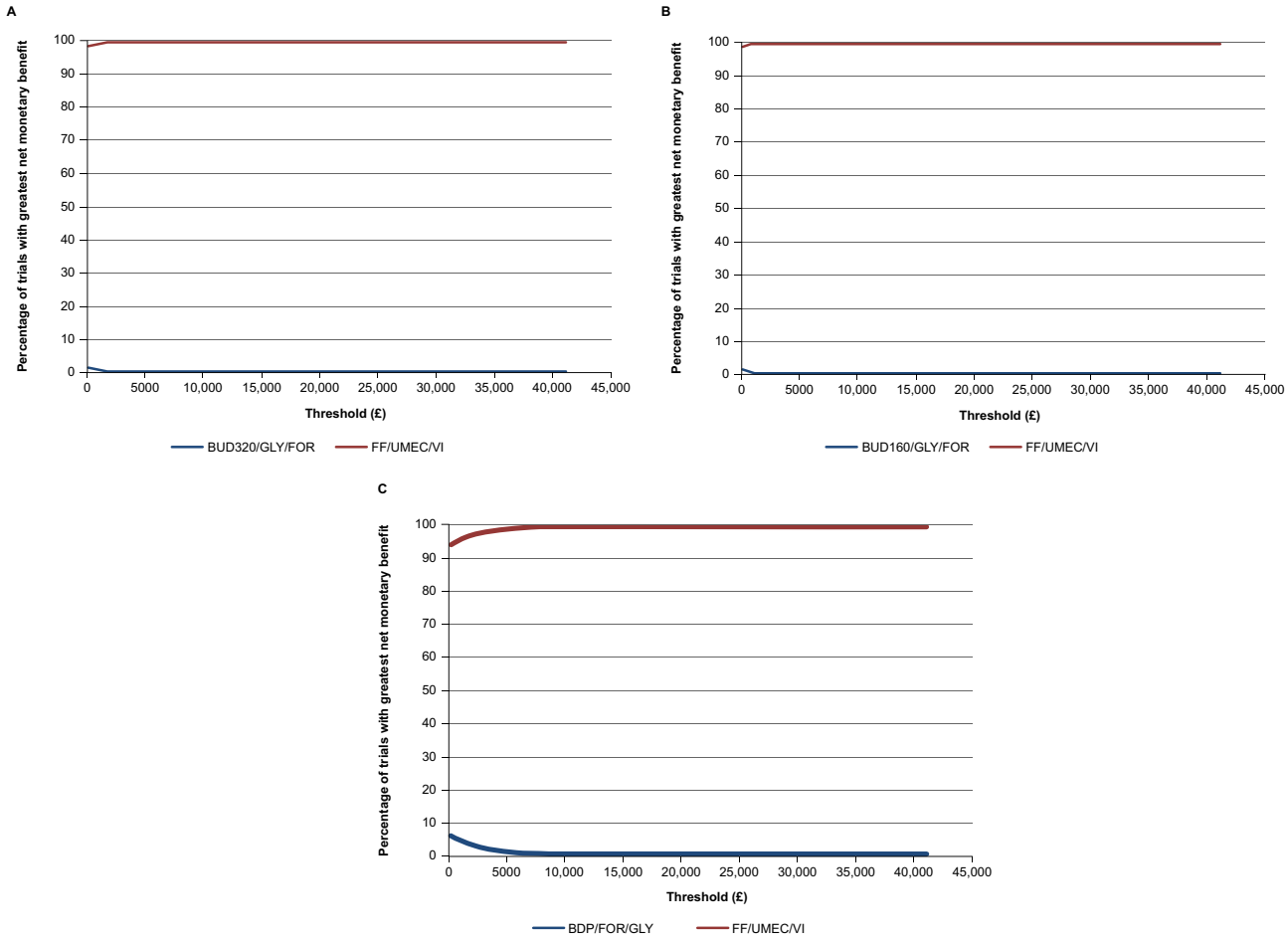

Figure 3 Net benefit acceptability curves for FF/UMEC/VI versus (**A**) BUD320/GLY/FOR, (**B**) BUD160/GLY/FOR, and (**C**) BDP/FOR/GLY – base case (probabilistic).
Abbreviations: BDP/FOR/GLY, beclometasone dipropionate/formoterol fumarate/glycopyrrolate; BUD160, budesonide 160 µg dosing; BUD320, budesonide 320 µg dosing; FF/UMEC/VI, fluticasone furoate/umeclidinium/vilanterol; GLY/FOR, glycopyrrolate/formoterol fumarate.

drug costs versus comparators, the total accumulated costs for FF/UMEC/VI were lower compared with comparators as the increased drug costs were outweighed by savings in non-drug costs. As patients who were treated with FF/UMEC/VI had fewer exacerbations, the healthcare resource use costs were lower with FF/UMEC/VI compared with comparators.

Table 8 Scenario Analyses (Probabilistic – Mean [95% CI]), 2022 GBP

	Incremental QALYs	Incremental Costs (£)	ICER/QALY
FF/UMEC/VI versus BUD320/GLY/FOR			
Base case	0.283 (0.080, 0.501)	−1620 (−3243, −158)	Dominant (dominant, dominant)
Time horizon (5 years)	0.057 (−0.017, 0.130)	−1040 (−1778, −426)	Dominant (dominant, £97,610)
Time horizon (10 years)	0.157 (0.017, 0.300)	−1544 (−2537, −455)	Dominant (dominant, dominant)
Discount rates (0%)	0.396 (0.116, 0.703)	−1831 (−4109, 28)	Dominant (dominant, £85)
Discount rates (5%)	0.250 (0.068, 0.442)	−1552 (−2970, −262)	Dominant (dominant, dominant)
Baseline characteristics (KRONOS[36,37])	0.246 (0.060, 0.452)	−3164 (−4238, −2147)	Dominant (dominant, dominant)
Baseline characteristics (ETHOS[26])	0.283 (0.081, 0.502)	−1759 (−3458, −226)	Dominant (dominant, dominant)

(*Continued*)

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Table 8 (Continued).

	Incremental QALYs	Incremental Costs (£)	ICER/QALY
Baseline characteristics (TRILOGY[35])	0.277 (0.075, 0.490)	−2038 (−3817, −445)	Dominant (dominant, dominant)
Treatment discontinuation (subsequent years same as first year)	0.112 (0.023, 0.205)	−801 (−1514, −171)	Dominant (dominant, dominant)
Treatment discontinuation (excluded)	0.349 (0.096, 0.620)	−1956 (−3868, −195)	Dominant (dominant, dominant)
Subsequent treatment cost (100% market share of product with highest cost in each class)	0.286 (0.088, 0.498)	−1640 (−3275, −131)	Dominant (dominant, dominant)
Subsequent treatment cost (100% market share of product with lowest cost in each class)	0.286 (0.082, 0.502)	−1608 (−3218, −129)	Dominant (dominant, dominant)
Rescue drug use (exclude)	0.285 (0.084, 0.502)	−1630 (−3219, −166)	Dominant (dominant, dominant)
Patient productivity costs (include)	0.283 (0.085, 0.498)	−6170 (−9651, −2774)	Dominant (dominant, dominant)
FF/UMEC/VI versus BUD160/GLY/FOR			
Base case	0.309 (0.097, 0.533)	−1721 (−3345, −261)	Dominant (dominant, dominant)
Time horizon (5 years)	0.065 (−0.012, 0.141)	−1093 (−1975, −440)	Dominant (dominant, £70,688)
Time horizon (10 years)	0.174 (0.024, 0.327)	−1644 (−2794, −492)	Dominant (dominant, dominant)
Discount rates (0%)	0.428 (0.148, 0.753)	−1971 (−4221, −69)	Dominant (dominant, dominant)
Discount rates (5%)	0.270 (0.082, 0.474)	−1654 (−3177, −264)	Dominant (dominant, dominant)
Baseline characteristics (KRONOS[36,37])	0.267 (0.075, 0.475)	−3180 (−4301, −2131)	Dominant (dominant, dominant)
Baseline characteristics (ETHOS[26])	0.306 (0.095, 0.532)	−1803 (−3460, −223)	Dominant (dominant, dominant)
Baseline characteristics (TRILOGY[35])	0.301 (0.095, 0.524)	−2093 (−3908, −443)	Dominant (dominant, dominant)
Treatment discontinuation (subsequent years same as first year)	0.121 (0.031, 0.216)	−857 (−1617, −186)	Dominant (dominant, dominant)
Treatment discontinuation (excluded)	0.377 (0.118, 0.660)	−2095 (−4155, −302)	Dominant (dominant, dominant)
Subsequent treatment cost (100% market share of product with highest cost in each class)	0.307 (0.096, 0.528)	−1736 (−3393, −243)	Dominant (dominant, dominant)
Subsequent treatment cost (100% market share of product with lowest cost in each class)	0.307 (0.095, 0.529)	−1724 (−3369, −222)	Dominant (dominant, dominant)
Rescue drug use (exclude)	0.305 (0.101, 0.534)	−1711 (−3361, −223)	Dominant (dominant, dominant)
Patient productivity costs (include)	0.307 (0.097, 0.526)	−6425 (−10,070, −2952)	Dominant (dominant, dominant)
FF/UMEC/VI versus BDP/FOR/GLY			
Base case	0.230 (0.035, 0.437)	−1221 (−2796, 541)	Dominant (dominant, £4241)
Time horizon (5 years)	0.068 (−0.010, 0.144)	−722 (−1320, 79)	Dominant (dominant, £31,634)
Time horizon (10 years)	0.148 (0.008, 0.288)	−1102 (−2206, 238)	Dominant (dominant, £4680)
Discount rates (0%)	0.303 (0.045, 0.581)	−1383 (−3489, 730)	Dominant (dominant, £3838)
Discount rates (5%)	0.205 (0.025, 0.392)	−1141 (−2544, 350)	Dominant (dominant, £3931)
Baseline characteristics (KRONOS[36,37])	0.193 (0.020, 0.372)	−1824 (−2948, −686)	Dominant (dominant, dominant)
Baseline characteristics (ETHOS[26])	0.230 (0.042, 0.439)	−1297 (−3037, 389)	Dominant (dominant, £2766)
Baseline characteristics (TRILOGY[35])	0.223 (0.030, 0.427)	−1478 (−3268, 357)	Dominant (dominant, £3479)
Treatment discontinuation (subsequent years same as first year)	0.097 (0.009, 0.189)	−600 (−1244, 198)	Dominant (dominant, £4984)
Treatment discontinuation (excluded)	0.278 (0.038, 0.531)	−1431 (−3402, 599)	Dominant (dominant, £3779)
Subsequent treatment cost (100% market share of product with highest cost in each class)	0.230 (0.040, 0.435)	−1156 (−2733, 535)	Dominant (dominant, £4081)
Subsequent treatment cost (100% market share of product with lowest cost in each class)	0.231 (0.037, 0.435)	−1291 (−2928, 377)	Dominant (dominant, £3228)

(*Continued*)

Table 8 (Continued).

	Incremental QALYs	Incremental Costs (£)	ICER/QALY
Rescue drug use (exclude)	0.230 (0.039, 0.432)	−1226 (−2830, 532)	Dominant (dominant, £4023)
Patient productivity costs (include)	0.228 (0.036, 0.432)	−4411 (−8153, −428)	Dominant (dominant, dominant)

Abbreviations: BDP/FOR/GLY, beclometasone dipropionate/formoterol fumarate/glycopyrrolate; BUD160, budesonide 160 µg dosing; BUD320, budesonide 320 µg dosing; CI, confidence interval; FF/UMEC/VI, fluticasone furoate/umeclidinium/vilanterol; GBP, Great British Pound; GLY/FOR, glycopyrrolate/formoterol fumarate; ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life year.

Table 9 One-Way Sensitivity Analyses (Deterministic), 2022 GBP

	Using Lower Value			Using Higher Value		
	Incremental QALYs	Incremental Costs (£)	ICER	Incremental QALYs	Incremental Costs (£)	ICER
FF/UMEC/VI versus BUD320/GLY/FOR						
Fibrinogen, µg/dL (95% CI using ECLIPSE[24] data)	0.288	−1605	Dominant	0.289	−1586	Dominant
6MWT (95% CI using ECLIPSE[24] data)	0.288	−1574	Dominant	0.289	−1617	Dominant
mMRC score ≥2, % (+/− 25%)	0.290	−1630	Dominant	0.289	−1607	Dominant
Treatment effects						
FEV_1 increment, mL (95% CI)	0.251	−1719	Dominant	0.328	−2105	Dominant
Exacerbation reduction (RR) (95% CI)	0.338	−2586	Dominant	0.221	−240	Dominant
SGRQ change (converted to SGRQ-C change) (95% CI)	0.428	−1590	Dominant	0.146	−1590	Dominant
FF/UMEC/VI versus BUD160/GLY/FOR						
Fibrinogen, µg/dL (95% CI using ECLIPSE[24] data)	0.311	−1670	Dominant	0.311	−1650	Dominant
6MWT (95% CI using ECLIPSE[24] data)	0.310	−1638	Dominant	0.311	−1682	Dominant
mMRC score ≥2, % (+/− 25%)	0.312	−1695	Dominant	0.311	−1672	Dominant
Treatment effects						
FEV_1 increment, mL (95% CI)	0.263	−1820	Dominant	0.360	−2133	Dominant
Exacerbation reduction (RR) (95% CI)	0.360	−2652	Dominant	0.243	−302	Dominant
SGRQ change (converted to SGRQ-C change) (95% CI)	0.453	−1655	Dominant	0.164	−1655	Dominant
FF/UMEC/VI versus BDP/FOR/GLY						
Fibrinogen, µg/dL (95% CI using ECLIPSE[24] data)	0.234	−1279	Dominant	0.234	−1262	Dominant
6MWT (95% CI using ECLIPSE[24] data)	0.233	−1253	Dominant	0.234	−1288	Dominant
mMRC score ≥2, % (+/− 25%)	0.236	−1288	Dominant	0.234	−1280	Dominant
Treatment effects						
FEV_1 increment, mL (95% CI)	0.196	−1385	Dominant	0.274	−1127	Dominant
Exacerbation reduction (RR) (95% CI)	0.298	−2485	Dominant	0.147	417	£2847
SGRQ change (converted to SGRQ-C change) (95% CI)	0.379	−1265	Dominant	0.085	−1265	Dominant

Abbreviations: 6MWT, six-minute walking test; BDP/FOR/GLY, beclometasone dipropionate/formoterol fumarate/glycopyrrolate; BUD160, budesonide 160 µg dosing; BUD320, budesonide 320 µg dosing; CI, confidence interval; FEV_1, forced expiratory volume in 1 second; FF/UMEC/VI, fluticasone furoate/umeclidinium/vilanterol; GBP, Great British Pound; GLY/FOR, glycopyrrolate/formoterol fumarate; ICER, incremental cost-effectiveness ratio; mMRC, modified Medical Research Council; QALY, quality-adjusted life year; RR, relative risk; SGRQ, St George's Respiratory Questionnaire; SGRQ-C, St George's Respiratory Questionnaire for chronic obstructive pulmonary disease patients.

In scenario and sensitivity analyses, FF/UMEC/VI remained the dominant treatment option across all analyses, except the one where the most pessimistic treatment effect on exacerbation reduction was used when comparing FF/UMEC/VI with BDP/FOR/GLY. In this case, the comparison of FF/UMEC/VI versus BDP/FOR/GLY resulted in an ICER of £2847/QALY; however, at a willingness-to-pay threshold of £20,000 per QALY, FF/UMEC/VI remained highly cost-effective.

The cost-effectiveness of SITT with FF/UMEC/VI versus dual therapies for the treatment of patients with symptomatic COPD from a UK NHS perspective has previously been shown; FF/UMEC/VI improved health outcomes (gains in LYs and QALYs) and was a cost-effective treatment option versus fluticasone furoate/vilanterol, umeclidinium/vilanterol, and budesonide/formoterol fumarate.[13–15] In some studies, gains in LYs (0.533) and QALYs (0.506) were shown to be associated with slightly increased total costs (ICERs of £1042/LY and £1098/QALY for FF/UMEC/VI versus BUD/FOR).[14] Similar trends were observed in the study by Schroeder et al (0.764 LYs and 0.492 QALYs), at an additional mean cost of £1652 resulting in an ICER of £3357/QALY gained compared with BUD/FOR.[15] In a recent analysis using the GALAXY model adapted with patient characteristics and treatment effect data from the INTREPID study,[38] FF/UMEC/VI was shown to be associated with an improvement in LYs (additional 0.174) and QALYs (additional 0.253) coupled with a cost saving of £1764 per patient compared with MITT in a UK setting.[17] Overall, the data suggest that FF/UMEC/VI is a cost-effective treatment option for patients with moderate-to-severe COPD in the UK.

There are a few limitations of the NMA that were included in this analysis that should be considered. First, some differences existed in the study design and inclusion/exclusion criteria of the trials included in the analyses and clinical heterogeneity between the participants included in each study. Results from such trials would not necessarily cause bias; however, the methodology of each included trial would need to be fully examined. Ideally, a randomized controlled trial comparing two SITTs would have been included in our cost-effectiveness analysis; however, a head-to-head randomized controlled trial is not available, hence the need for an NMA. Also, some baseline parameters, including mMRC Dyspnea Scale, 6-minute walking test, and fibrinogen, were not available from IMPACT data and values were instead predicted by risk equations or estimated using analogous data. However, the results of the sensitivity analyses for the model parameters taken from the IMPACT trial showed that the incremental QALYs and costs did not change substantially compared to the deterministic results; the IMPACT trial was chosen as it included the necessary variables and was a large-scale study where baseline and demographic characteristics were considered to be relatively representative. Model inputs for patient characteristics were taken from the IMPACT trial, which was conducted in 37 countries, and costs were applied from a UK perspective. Therefore, the findings of this study may not be generalizable outside of the UK population. Finally, only 1-year discontinuation rates were available from clinical trial data. Discontinuation rates were assumed to be zero for all subsequent years in the analysis; this was tested during the scenario analyses with the overall results remaining unaffected. Thus, discontinuation rates did not substantially influence the cost-effectiveness of FF/UMEC/VI. There is limited exploration of long-term treatment adherence in NMAs, and no assumptions were made about adherence in this study.

The findings of the base-case analysis demonstrate that FF/UMEC/VI was the dominant treatment option, and the sensitivity analyses do not detract from the base-case analysis results. Studies have shown the positive impact of FF/UMEC/VI on reducing the risk of exacerbations and reducing healthcare resource utilization and costs,[12–15] hence our findings are important for clinician and policymaker decision-making on the effective treatment of COPD. Moreover, patients on SITT or newly initiating SITT, particularly FF/UMEC/VI, have been shown to have greater medication adherence and persistence compared with those on MITT or initiating MITT, or other SITTs, suggesting additional clinical benefits.[39–41] These findings, along with the favorable effects for FEV_1, suggest that FF/UMEC/VI may be an appropriate treatment option in terms of cost savings and for improving clinical outcomes.

Conclusion

Based on this analysis, FF/UMEC/VI is a dominant (improved outcomes with cost savings) treatment option compared with other SITTs for the treatment of patients with COPD in the UK. Therefore, FF/UMEC/VI may reduce the economic burden of COPD and may be considered by physicians as a preferred treatment option.

Abbreviations

6MWD, six-minute walking distance; 6MWT, six-minute walking test; BDP, beclometasone dipropionate; BMI, body mass index; BUD160, budesonide 160 μg dosing; BUD320, budesonide 320 μg dosing; BUD, budesonide; CI, confidence interval; COPD, chronic obstructive pulmonary disease; CVD, cardiovascular disease; FEV_1, forced expiratory volume in 1 second; FF, fluticasone furoate; FOR, formoterol fumarate; GBP, Great British Pound; GLY, glycopyrrolate; GOLD, Global Initiative for Chronic Obstructive Lung Disease; HRQoL, health-related quality of life; ICER, incremental cost-effectiveness ratio; ICS, inhaled corticosteroid; ITT, intent-to-treat; LABA, long-acting β_2-agonist; LAMA, long-acting muscarinic antagonist; LY, life year; MITT, multiple-inhaler triple therapy; mMRC, modified Medical Research Council; NHS, National Health Service; NICE, National Institute for Health and Care Excellence; NMA, network meta-analysis; PPPY, per person per year; QALY, quality-adjusted life year; RR, relative risk; RU, resource utilization; SGRQ, St George's Respiratory Questionnaire; SGRQ-C, St George's Respiratory Questionnaire for COPD patients; SITT, single-inhaler triple therapy; UMEC, umeclidinium; VI, vilanterol.

Data Sharing Statement

Data used in this analysis are available from the corresponding author on reasonable request.

Ethics Approval and Informed Consent

Ethics committee approval and patient informed consent were not required for this analysis. The analysis was conducted using patient characteristics and treatment effects from a previously published study; therefore, no direct patient contact or primary collection of individual patient data were required.

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Author Contributions

All authors made a significant contribution to the work reported, whether that was in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising, or critically reviewing the manuscript; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

AAM and ASI are employees of and/or hold financial equities in GSK. AI is also a part-time unpaid faculty member at McMaster University, Hamilton, ON, Canada. CC was an employee of and/or held financial equities in GSK at the time of study. RC is now an employee of Parexel but was an employee of ICON plc at the time of study. YG, NAR, and KH are/were employees of ICON plc at the time of the analysis. ICON plc received funding from GSK to conduct the analysis but not for manuscript development. DMGH reports personal fees from AstraZeneca, personal fees and non-

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