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Cost-effectiveness analysis of a single-inhaler triple therapy for patients with advanced chronic obstructive pulmonary disease (COPD) using the FULFIL trial: A UK perspective

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ABSTRACT

Objectives: The clinical benefit of once-daily fluticasone furoate/umeclidinium/vilanterol (FF/UMEC/VI) versus twice-daily budesonide/formoterol (BUD/FOR) for patients with symptomatic chronic obstructive pulmonary disease (COPD) was demonstrated in a clinical trial setting (FULFIL [NCT02345161]). The lifetime cost-effectiveness analysis of FF/UMEC/VI versus BUD/FOR, based on FULFIL data, is reported here.

Methods: A previously developed and validated GALAXY-COPD linked-risk equation model was used to assess the cost-effectiveness of FF/UMEC/VI from the UK National Health Service (NHS) perspective. Baseline characteristics and efficacy results from FULFIL and UK NHS reference cost data (2017) were included as inputs. Exacerbation rates (undiscounted), costs, life years (LYs; undiscounted) and quality-adjusted life years (QALYs), and the incremental cost-effectiveness ratio (ICER) were calculated over a lifetime horizon. Costs and QALYs were discounted at 3.5% per year, beyond one year, in accordance with National Institute for Health and Care Excellence (NICE) guidelines. Deterministic and probabilistic sensitivity analyses were performed to evaluate the robustness of the results.

Results: Predicted cumulative exacerbations per patient over a lifetime were 8.393 with FF/UMEC/VI and 10.456 with BUD/FOR. Patients receiving FF/UMEC/VI gained an additional 0.764 LYs and 0.492 QALYs, at an additional mean cost of £1,652, resulting in an ICER of £3,357 per QALY gained (95% confidence interval: £1,816, £5,194) compared with BUD/FOR. The ICER remained below £6,000 in all but one of the scenario and sensitivity analyses.

Conclusions: Compared with BUD/FOR, treatment with FF/UMEC/VI was predicted to improve health outcomes at an additional cost that suggests it would be cost-effective for patients with COPD in the UK.

1. Introduction

Chronic obstructive pulmonary disease (COPD) is characterized by persistent symptoms and airflow limitation and is one of the most common causes of preventable death worldwide [1–3]. COPD also imposes a high economic burden on healthcare systems due to physician visits, emergency room (ER) visits and hospitalizations [2,4]. In the United Kingdom (UK), the cost of COPD in 2011 was estimated to be £1.9 billion [5]. Based on patterns of COPD prevalence, these costs are likely to increase in future years. In addition to medical costs, the chronic and debilitating nature of COPD, particularly dyspnea and physical activity limitation, significantly reduces patients' health-related quality of life (HRQoL) [6–9].

The aim of pharmacological therapy in COPD is to reduce symptoms, reduce the risk and severity of exacerbations and improve HRQoL [3]. Escalating patients' therapy may be required to achieve treatment

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Abbreviations

6MWT	6-minute walk test
BMI	Body mass index
BUD	Budesonide
CAT	COPD Assessment Test
CEAC	Cost-effectiveness acceptability curve
CI	Confidence interval
COPD	Chronic obstructive pulmonary disease
CVD	Cardiovascular disease
DRG	Diagnosis related group
ECLIPSE	Evaluation of COPD Longitudinally to Identify Predictive Surrogate Endpoints
EQ-5D	EuroQol-5D
ER	Emergency room
EXACT-PRO	EXAcerbations of Chronic pulmonary disease Tool Patient-Reported Outcome
EXT	Extension
FEV_1	Forced expiratory volume in 1 s
FF	Fluticasone furoate
FP	Fluticasone propionate
FULFIL	Lung FUnction and quality of LiFe assessment in COPD with closed trIpLe therapy
FOR	Formoterol
GLY	Glycopyrronium
GOLD	Global Initiative for Chronic Obstructive Lung Disease
HRQoL	Health-related quality of life
HRU	Healthcare resource utilization
ICER	Incremental cost-effectiveness ratio
ICS	Inhaled corticosteroid
ICU	Intensive care unit
IMPACT	InforMing the PAthway of COPD Treatment
IND	Indacaterol
ITT	Intent to treat
LABA	Long-acting β_2-agonist
LAMA	Long-acting muscarinic antagonist
LY	Life year
mMRC	modified Medical Research Council
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
ONS	Office for National Statistics
PPPY	Per patient per year
PSA	Probabilistic sensitivity analysis
PSSRU	Personal Social Services Research Unit
QALY	Quality-adjusted life year
RR	Relative risk
SAL	Salmeterol
SALB	Salbutamol
SGRQ	St. George's Respiratory Questionnaire
SD	Standard deviation
SE	Standard error
SITT	Single-inhaler triple therapy
SLS	Salford Lung Study
SRC	Scheduled reference costs
TIO	Tiotropium
TORCH	TOwards a Revolution in COPD Health
UK	United Kingdom
UPLIFT	Understanding Potential Long-term Impacts on Function with Tiotropium
UMEC	Umeclidinium
VI	Vilanterol

goals. In patients with moderate-to-severe COPD, inhaled combination therapy of drugs with differing mechanisms of action has been shown to give better symptom reduction and a lower risk of exacerbations compared with monotherapy [3]. According to the most recent Global Initiative for Chronic Obstructive Lung Disease (GOLD) strategy document, an inhaled corticosteroid/long-acting muscarinic antagonist/long-acting β_2-agonist (ICS/LAMA/LABA) combination is recommended in patients with significant symptoms, despite combination therapy with ICS/LABA or LAMA/LABA, and who are at risk of frequent or severe exacerbations [3].

A triple therapy consisting of fluticasone furoate/umeclidinium/vilanterol (FF/UMEC/VI) 100 μg/62.5 μg/25 μg formulated as a single inhaler is indicated in the European Union for patients who are not adequately treated with combination ICS/LABA therapy [10]. Single-inhaler triple therapy (SITT) delivered as a once-daily dose may offer advantages in convenience, patient preference, and more consistent dosing, including in patients with multiple comorbidities, when compared with the three medications given in multiple inhalers [11–14].

FULFIL (lung FUnction and quality of LiFe assessment in COPD with closed trIpLe therapy; NCT02345161, GlaxoSmithKline plc. study CTT116853), a phase III, randomized, double-blind clinical trial, supported the registration of FF/UMEC/VI and compared the once-daily SITT (FF/UMEC/VI 100 μg/62.5 μg/25 μg delivered using the ELLIPTA inhaler) with twice-daily single-inhaler ICS/LABA therapy (budesonide/formoterol [BUD/FOR] 400 μg/12 μg, delivered using the Turbuhaler) in patients with COPD [11]. In this study, once-daily single-inhaler FF/UMEC/VI resulted in a statistically significant improvement in HRQoL and lung function (co-primary endpoints), compared with twice-daily single-inhaler BUD/FOR after 24 weeks of treatment. FF/UMEC/VI also resulted in a statistically significant reduction in the risk of exacerbations versus BUD/FOR. In a sub-population who were studied for 52 weeks, FF/UMEC/VI resulted in a statistically significant improvement in lung function and a statistically significant reduction in exacerbation risk, plus a numerical improvement in HRQoL, compared with BUD/FOR.

The current study was performed to compare the cost-effectiveness of once-daily FF/UMEC/VI with that of twice-daily BUD/FOR, from a UK National Health Service (NHS) perspective. The UK NHS now routinely requires evidence of cost-effectiveness, as well as clinical benefit, before adopting new technologies. This analysis used a validated COPD disease-progression model [15,16] and applied efficacy and treatment persistence data from FULFIL.

2. Methods

2.1. Cost-effectiveness model

Cost-effectiveness, based on the FULFIL data, was analyzed using the GALAXY-COPD disease progression model [15,16]. GALAXY-COPD uses a linked-risk equation approach to forecast disease natural history, including progression, associated healthcare costs (such as pharmacy costs and cost of ER visits, hospitalization and outpatient visits), and impact on quality-adjusted life years (QALYs) and survival. Statistical risk equations to predict COPD natural history over time were derived from the Evaluation of COPD Longitudinally to Identify Predictive Surrogate Endpoints (ECLIPSE) study [17]. Exacerbations, lung function (forced expiratory volume in 1 s [FEV_1]), symptoms (dyspnea, cough/sputum) and exercise capacity (based on the 6-minute walk test [6MWT]), at baseline and at the previous model cycle, were considered as independent variables. Statistical risk equations predicting healthcare resource utilization (HRU) were derived from the TOwards a Revolution in COPD Health (TORCH) study [18]. Full details of the GALAXY-COPD model and its validation have been published previously [15,16,19–21].

A UK NHS perspective was adopted for the analysis in the base case, with costs inflated to 2017. A lifetime horizon was used in the study base case, due to the chronic nature of COPD and based on guidance from the National Institute for Health and Care Excellence (NICE) [22]. Time horizons of five and 10 years were explored in scenario analyses. A 3.5% annual discount rate was applied for costs and benefits beyond one year, in accordance with NICE guidelines [22]. Life years (LYs) were kept undiscounted as a measure of predicted survival.

2.2. Model inputs

2.2.1. Population

Full details of patient inclusion criteria and other methods from the FULFIL trial have been previously published [11]. Briefly, patients (N = 1,810) were aged ≥40 years and suffered from advanced symptomatic COPD (FEV_1 < 50% predicted and COPD Assessment Test [CAT] score ≥10; or FEV_1 ≥50– < 80% predicted, CAT ≥10 and either ≥2 moderate exacerbations or ≥1 severe exacerbation in the previous 12 months) [11]. The inclusion criteria allowed the enrollment of patients with comorbidities, who make up a substantial proportion of the COPD population but who are often excluded from other trials. Patients were required to have been on maintenance COPD medication for ≥3 months prior to screening and could continue their pre-study maintenance therapy up to the time of randomization to mimic switch scenarios in clinical practice. The intent-to-treat (ITT) population included all randomized patients who received treatment, regardless of treatment duration. A subgroup of patients who were enrolled earliest were followed for a total of 52 weeks of treatment; these patients comprised the extension (EXT) population (n = 430).

To ensure a uniform baseline population for the analysis, the baseline characteristics of the two treatment arms from FULFIL were pooled. In FULFIL, baseline characteristics were similar between treatment cohorts, including history of moderate/severe exacerbations in the previous 12 months. For FF/UMEC/VI compared with BUD/FOR, proportion of patients with: 0 exacerbations: 34% versus 35%, respectively; 1 exacerbation: 28% in each arm; ≥2 exacerbations: 38% versus 37%, respectively [11]. Thus, the proportion of frequent and infrequent exacerbators was virtually identical between the treatment arms. Additionally, total scores in the St. George's Respiratory Questionnaire (SGRQ) were similar between the arms: 53.0 (FF/UMEC/VI) versus

Table 1
Input characteristics (from FULFIL trial ITT population [11]).

Parameters	Value
Female (%)	26.0
Age (years)	63.9 (SD=8.64)
BMI low (<20, %)	7
BMI medium (20–30, %)	68
BMI high (>30, %)	25
Any CVD comorbidity (%)	40
Any other comorbidity (%)	58
No prior exacerbations at baseline (%)	35
mMRC dyspnea score ≥2 (%)*	43
Current smoker (%)	44
Height (cm)	169.5 (SD=8.8)
Fibrinogen (μg/dL)**	470.5 (SE=2.37)
No. of exacerbations in previous year (mean, SE assume 10% of mean)	1.1
No. of severe exacerbations in previous year (mean)	0.2
Starting SGRQ	51.3 (SE=0.4)
Starting FEV_1% predicted	45.3 (SD=13.30)
6MWT (m)**	370.7 (SE=5.37)
Treatment efficacy (FF/UMEC/VI versus BUD/FOR)	
FEV_1 increment (mL) (mean score difference)	171 (95% CI=148, 194)
SGRQ change (mean score difference)	–2.2 (95% CI=–3.5, –1.0)
Moderate exacerbation reduction (RR)	0.79 (95% CI=0.6, 1.04)
Severe exacerbation reduction (RR)	0.54 (95% CI=0.27, 1.08)
No. of occasions of rescue medication use per day (FF/UMEC/VI)	1.6 (95% CI=1.6, 1.7)
No. of occasions of rescue medication use per day (BUD/FOR)	1.8 (95% CI=1.8, 1.9)
Probability of discontinuation (FF/UMEC/VI) in first year (%)	8
Probability of discontinuation (BUD/FOR) in first year (%)	13

**Predicted, based on EXACT-PRO; **Predicted from risk equation.*
6MWT = 6-minute walk test, BMI = body mass index, BUD = budesonide, CI = confidence interval, CVD = cardiovascular disease, FEV_1 = forced expiratory volume in 1 second, FF = fluticasone furoate, FOR = formoterol, ITT = intent to treat, mMRC = modified Medical Research Council, RR = relative risk, SD = standard deviation, SE = standard error, SGRQ = St. George's Respiratory Questionnaire, UMEC = umeclidinium, VI = vilanterol.

50.8 (BUD/FOR). Pooling the baseline characteristics therefore accurately reflected the ITT population while avoiding noise in the analysis and any potential bias in the comparison of FF/UMEC/VI and BUD/FOR, although any such bias was unlikely to arise given the similarity of the treatment arms. Because the GALAXY-COPD model requires baseline values for dyspnea, fibrinogen and 6MWT scores, which were not measured in FULFIL, they were estimated as follows: (i) The proportion of patients with a baseline modified Medical Research Council (mMRC) dyspnea score ≥2 (not measured) was assumed to be the same as the proportion in FULFIL at baseline responding with '2' (breathless during light activity) or '3' (breathless when washing or dressing) to question eight of the EXAcerbations of Chronic pulmonary disease Tool Patient-Reported Outcome (EXACT-PRO, captured in FULFIL) questionnaire, 'Describe how breathless you were today'; (ii) baseline 6MWT scores were predicted using the model risk equation; and (iii) fibrinogen scores were predicted using an additional risk equation previously developed using ECLIPSE baseline data [17].

Table 1 shows the observed and estimated input parameter values for the analysis, based on the characteristics of the FULFIL 24-week ITT patient population; the same input parameter values were used for both comparator arms in the study. Characteristics of the EXT population (52 weeks) are shown in Supplementary Table 1 and were used to inform the model to conduct a subgroup analysis of the EXT population.

2.2.2. Treatment effect

The treatment effects, from FULFIL, used in the analysis were: change from baseline in post-bronchodilator FEV_1, change from baseline in SGRQ total score, and reduction in moderate and severe exacerbations. These have been published [11] or, in the case of exacerbations, relative risks for FF/UMEC/VI versus BUD/FOR were calculated separately for moderate and severe exacerbations in an unpublished post-hoc analysis of FULFIL data. These inputs modified the predicted outcomes of the first (annual) cycle of the model. After this, evolution of FEV_1 and exacerbation frequency, together with COPD symptoms and exercise capacity in each subsequent model cycle, were predicted by the model risk equations; based on baseline patient characteristics, treatment effect applied in the first cycle and predicted status at the end of the model cycle immediately preceding the current cycle. At each cycle, SGRQ was then predicted based on the predicted FEV_1, exacerbation frequency, COPD symptoms and exercise capacity status in that cycle. Outcomes were modeled for FF/UMEC/VI and BUD/FOR separately.

As the model predicts changes in SGRQ total score based on changes in FEV_1 and exacerbation frequency, and changes in exacerbation frequency based on changes in FEV_1, adjustments were made to prevent over or under prediction of outcomes compared with those observed. This adjustment was achieved by first inputting the FEV_1 treatment effect from FULFIL and then adjusting exacerbation treatment effects predicted by the model so that it was the same as that observed in FULFIL. The same procedure was then applied sequentially with the SGRQ treatment effect predicted by the model based on FEV_1 and exacerbation treatment effects. Predicted SGRQ for the first model cycle was calibrated to align with the change from baseline score observed in FULFIL, and the likelihood of measurement at 24 weeks coinciding with an exacerbation was small. Therefore, the risk of double counting the impact of exacerbations on QALYs, over the time horizon of this analysis, was very low.

2.2.3. Cost inputs

Costs were calculated using the resource-use risk equations in the GALAXY-COPD model [16]. Unit costs were applied to predicted annual counts of general ward days, intensive care unit (ICU) days, ER visits, office visits, day/night home visits, and outpatient visits. Unit costs (Table 2) were obtained from the 2016 Personal Social Services Research Unit (PSSRU) or the 2015/2016 NHS National Schedule of Reference costs [23,24]. Costs from 2015 were inflated to 2016 values using the PSSRU Hospital & Community Health Services Index [23] and subsequently inflated to 2017 values using the UK Consumer Price Index [25].

A scenario based on indirect costs utilized productivity losses incurred by sick leave, estimated according to the human capital approach, or gross value lost during time absent from usual activities. As data were not available from FULFIL, the Salford Lung Study (SLS) [26] was used to estimate the duration (mean [standard error, SE]) of moderate and severe exacerbations: 12.8 (0.38) days and 31.3 (0.71) days, respectively (calculated average across both treatment arms). The duration of exacerbations was assumed to be the same as the number of days absent from usual activities.

Medication costs were obtained from the online Monthly Index of Medical Specialities (2017) [27] and are shown in Table 3. Quantities of rescue medication were based on use in patients in the FULFIL ITT population (Table 1).

2.2.4. Utilities

A published algorithm was used to translate annual SGRQ total scores to an annual utility value [28], as follows:

EQ-5D = 0.9617 – (0.0013*SGRQ total) – (0.0001*[SGRQ total^2]) + (0.0231*male).

2.2.5. Model assumptions

No waning of treatment effect was considered in the analysis. Treatment discontinuation in the first year of therapy was assumed to be 8% with FF/UMEC/VI and 13% with BUD/FOR, based on results in the FULFIL ITT population at 24 weeks (no data on discontinuation at

Table 2
Unit costs for healthcare resource.

	2017 costs	Source	DRG description/methods summary
Hospital costs			
Cost per day in ICU	£1,340	NHS SRC	Adult critical care, 0–6 organs supported – code XC01Z-XC06Z
Cost per day in general ward	£436	NHS SRC	Weighted average costs by all COPD severities for non-elective long stay
ER visit	£201	NHS SRC	VB05Z, emergency medicine, category 2 investigation with category 3 treatment, type 1 non-admitted
Hospital outpatient visit – initial visit	£196	NHS SRC	CL, WF01B – respiratory medicine
Hospital outpatient visit – subsequent visit	£149	NHS SRC	CL, WF01A – respiratory medicine
Physician visit costs			
Daytime home visit	£133[a]	PSSRU 2011	(Home visit lasting 23.4 min)
Night time home visit	£133	Assumption	Assumed same as daytime home visit
Visit to physician's office	£68[a]	PSSRU 2015	(Clinical consultation lasting 17.2 min)
Telephone consultation	£28[a]	PSSRU 2015	(Clinical consultation lasting 7.1 min)

COPD = chronic obstructive pulmonary disease, DRG = diagnosis related group, ER = emergency room, ICU = intensive care unit, NHS = National Health Service, PSSRU = Personal Social Services Research Unit, SRC = scheduled reference costs.

[a] Inflated to 2016 £ (by using PSSRU [23] Hospital & Community Health Services Index 2016); 2016 costs were then updated to 2017 values using the Consumer Price Index data obtained from ONS [25].

Table 3
Drug unit costs.

Brand name	*Molecule*	*Dose*	*Pack size*	*Pack cost*	*Cost per dose*	*Cost per day*	*Label dosing*[a]
Trelegy	FF/UMEC/VI	100μg/62.5μg/25 μg	30	£49.50	£1.65	£1.65	1 inhalation per day
BUD/FOR							
Symbicort, (Symb 400)[b]	BUD/FOR	400μg/12 μg	60	£38.00	£0.63	£1.27	1 inhalation twice daily
DuoResp Spiromax (DuoR 320)[c]	BUD/FOR	320μg/9 μg	60	£29.97	£0.50	£1.00	1 inhalation twice daily
Subsequent therapy medications							
Tiotropium (Spiriva)	TIO	18 μg	30	£34.87	£1.16	£1.16	1 inhalation per day
Seretide Accuhaler (SertA500)	SAL/FP	500μg/50 μg	60	£40.92	£0.68	£1.36	1 inhalation twice daily
Ultibro Breezhaler	IND/GLY	110μg/50 μg	30	£32.50	£1.08	£1.08	1 inhalation per day
Anoro ELLIPTA	UMEC/VI	62.5μg/25 μg	30	£32.50	£1.08	£1.08	1 inhalation per day
Rescue medication							
Ventolin Accuhaler	SALB	200 μg	60	£3.60	£0.06	£0.06	1

According to Monthly Index of Medical Specialties 2017 [27].
BUD = budesonide, FOR = formoterol, FF = fluticasone furoate, FP = fluticasone propionate, GLY = glycopyrronium, IND = indacaterol, SAL = salmeterol, SALB = salbutamol, TIO = tiotropium, UMEC = umeclidinium, VI = vilanterol.
[a] Label dosing was obtained from the Monthly Index of Medical Specialties 2017 [27].
[b] Used for costing of interventions in the model, unless other otherwise specified (i.e., in scenario analyses).
[c] This is equivalent to a metered dose of 400μg/12 μg for BUD/FOR (based on product monograph) used for scenario analyses where the generic price for BUD/FOR was tested.

52 weeks were available; see also Supplementary Appendix). Thereafter, treatment discontinuation was assumed to be 0% in all subsequent years; it is reasonable to assume that after the first year, patients are unlikely to discontinue, since COPD is chronic and treatment usually additive. For cost of subsequent therapy (Table 3), all patients discontinuing treatment were assumed to switch to other classes of medication, in the same proportions as observed in FULFIL for the combined treatment groups. Under these assumptions, subsequent treatment was: ICS/LABA, 40%; ICS/LAMA/LABA, 36%; LAMA/LABA, 15%; and LAMA, 9%. Costs for each treatment class were based on the treatment most frequently prescribed within each class in the UK (Supplementary Table 2). The efficacy of all subsequent treatments was assumed to be equivalent to BUD/FOR.

2.3. Model outputs

Model outputs included moderate and severe exacerbation rates, LYs gained, QALYs gained, and an incremental cost-effectiveness ratio (ICER), presented as incremental cost per QALY gained.

2.4. Scenario analyses

Scenario analyses examined the effect of alternative populations, assumptions and model settings on the base-case results. These were as follows: using patient baseline characteristics and results for the EXT population from FULFIL (52-week follow-up; see Supplementary Table 1), time horizon of five or 10 years, discount rate (both costs and outcomes) of 0% and 5%, duration of treatment effect of three years, alternative discontinuation rates (ongoing treatment discontinuation at the same rate as the first year [FF/UMEC/VI, 8%; BUD/FOR, 13%] and no discontinuation in the first and subsequent years), generic cost for BUD/FOR, and inclusion of indirect costs (patient productivity).

2.5. One-way sensitivity analyses

Sensitivity analyses were conducted on baseline covariate values that were not available from FULFIL data (baseline values for fibrinogen, 6MWT and mMRC dyspnea scores) and on treatment effects (FEV_1, SGRQ and exacerbations) (Supplementary Table 3). The variations explored were as follows: upper and lower bands of 95% confidence intervals (CIs) around the base-case treatment effects on FEV_1, SGRQ, moderate exacerbation reduction, and severe exacerbation reduction. For the predicted values for parameters not obtainable from FULFIL, fibrinogen and 6MWT values were varied to 95% CI limits approximated using data from the ECLIPSE study, and ± 25% limits were used for mMRC dyspnea score due to the analogous nature of the data.

2.6. Probabilistic sensitivity analysis

A probabilistic sensitivity analysis (PSA) was conducted to address the uncertainty in the parameters used within the model by assigning distributions to input parameters (Supplementary Table 4) and randomly sampling over 1,000 Monte Carlo simulations from these distributions (see also Supplementary Appendix). Normal/log-normal distributions were used for treatment effects, and coefficients for the risk equations were sampled using correlated draws from a Cholesky decomposition table, developed from the covariance matrices for each equation. The outputs of this analysis were summarized as 95% ranges, scatter plots of incremental cost-effectiveness, and cost-effectiveness acceptability curves (CEAC), for FF/UMEC/VI versus BUD/FOR. While statistical distributions for the coefficients in the algorithm for mapping SGRQ total score to EQ-5D were not available, the coefficients for the risk equation predicting SGRQ were included in the PSA. Uncertainty around HRQoL benefit was therefore tested in the following two ways: 1) directly by prediction of SGRQ and uncertainty in the specific risk equation [16]; and 2) with the treatment effect and 95% CI around the treatment effect on the clinical outcomes based upon which SGRQ was predicted. Uncertainty in predicted QALYs was, therefore, explored.

3. Results

3.1. Base case

The predicted cumulative total number of moderate and severe exacerbations per patient over a lifetime was lower with FF/UMEC/VI compared with BUD/FOR (Table 4), with the FF/UMEC/VI group experiencing 2.06 (95% CI: −3.76, −0.39) fewer moderate and severe exacerbations versus the BUD/FOR group.

Total costs were greater with FF/UMEC/VI compared with BUD/FOR (£20,842 versus £19,190), mainly as a result of higher drug costs. The longer survival of patients in the FF/UMEC/VI group contributed to the higher non-drug costs (£15,542 for FF/UMEC/VI versus £15,153 for BUD/FOR). Overall, treatment with FF/UMEC/VI resulted in an additional 0.764 LYs (undiscounted) and 0.492 QALYs gained, at an additional mean cost per patient treated of £1,652 (95% CI: £723, £2,462) compared with BUD/FOR, resulting in an ICER of £3,357 (95% CI: £1,816, £5,194) per QALY gained.

Table 4
Accumulated outcomes (lifetime time horizon).

	FF/UMEC/VI	BUD/FOR
Cumulative number of exacerbations over timeframe (discounted[a]):		
Moderate	6.629	7.664
Severe	1.764	2.792
Total	**8.393**	**10.456**
Severe exacerbations PPPY	0.174	0.299
Total exacerbations PPPY	0.830	1.119
Outcomes at end of timeframe		
Accumulated LYs (undiscounted)	10.107	9.343
Accumulated QALYs (discounted[a])	5.150	4.657
Costs at end of timeframe (discounted[a])		
Drug costs	£5,300	£4,037
Total non-drug costs	£15,542	£15,153
Hospital costs	£14,316	£13,973
Outpatient/hospital/clinic costs	£799	£766
Physician visits (office, home, day or night)	£427	£414
Total accumulated costs	£20,842	£19,190
Incremental results (mean, 95% CI)		
Incremental cost	£1,652 (£723, £2,462)	
Incremental LYs	0.764 (0.33, 1.17)	
Incremental QALYs	0.492 (0.29, 0.69)	
ICER (per QALY gained)	£3,357 (£1,816, £5,194)	

BUD = budesonide, CI = confidence interval, FF = fluticasone furoate, FOR = formoterol, ICER = incremental cost-effectiveness ratio, LY = life year, PPPY = per patient per year, QALY = quality-adjusted life year, UMEC = umeclidinium, VI = vilanterol.
[a] Discounts applied at 3.5%.

3.2. Scenario and sensitivity analyses

In most of the scenarios analyzed, the ICER was between £2,000 and £5,000 per QALY gained (Table 5); two scenarios were outside of this range: (1) considering a three-year duration of treatment effect, and (2) including patient productivity costs.

Alternative assumptions about discount rate, treatment discontinuation rate, or time horizon resulted in relatively small changes to the ICER. The ICER was lower (£2,262 per QALY gained) if baseline characteristics and results for the FULFIL EXT population were used in place of those for the ITT population analysis, and was greater (£4,718) if generic BUD/FOR cost was substituted in. The scenario associated with the highest ICER (£9,902) was limiting the duration of treatment effect to three years. In contrast, FF/UMEC/VI was dominant over BUD/FOR (i.e., FF/UMEC/VI was less costly and more effective) if patient productivity costs were included in the model. As with the base-case lifetime horizon, the predicted lifetime cumulative total number of moderate and severe exacerbations per patient was lower with FF/UMEC/VI compared with BUD/FOR, for both five-year (3.6 versus 4.7, respectively) and 10-year (6.2 versus 8.1, respectively) time horizons (Supplementary Fig. 1). Predicted survival rates were higher with FF/UMEC/VI compared with BUD/FOR after five and 10 years (80.3% versus 77.5%, and 49.2% versus 43.3%, respectively; Supplementary Table 5).

Results of one-way sensitivity analyses are shown in Table 6.

The results were most sensitive to changes in SGRQ and severe exacerbation treatment effects. Applying the upper and lower 95% confidence limits for risk reduction of severe exacerbation gave the largest ICER range, from £2,466 to £5,556. The PSA found that FF/UMEC/VI had a higher cost and produced more QALYs than BUD/FOR in all simulations (Fig. 1A). Overall, the results of the scenario and sensitivity analyses were all below the cost-effectiveness threshold of £20,000 [29].

For 95% of the 1,000 simulations, the ICER lay between £1,816 and £5,194; the probability of FF/UMEC/VI being cost-effective at a willingness-to-pay threshold of £20,000 was 100% (Fig. 1B).

4. Discussion

In this study, we used the previously developed and validated GALAXY-COPD linked-risk equation model to assess the cost-effectiveness of treating moderate-to-severe COPD with once-daily FF/UMEC/VI versus twice-daily BUD/FOR from a UK NHS perspective. FF/UMEC/VI was associated with increases in LYs and QALYs, but also with higher costs, compared with BUD/FOR. Non-drug costs were higher for patients receiving FF/UMEC/VI compared with those receiving BUD/FOR, despite lower rates of moderate and severe exacerbations. A major contributor to this was the longer survival in the cohort on FF/UMEC/VI, illustrated in a scenario analysis at a shorter time horizon of five years, where non-drug costs were higher with BUD/FOR (£7,761) compared with FF/UMEC/VI (£7,639). This suggests that the higher acquisition cost of FF/UMEC/VI would be offset by health service savings elsewhere, particularly as a result of the difference in the per-patient yearly rate of severe exacerbations (requiring hospital admission), which was 42% lower in the FF/UMEC/VI group compared with the BUD/FOR group (see Table 4). The ICER of £3,357 per QALY gained in the base case and equivalent costs in the scenario and sensitivity analyses were all within the willingness-to-pay threshold of £20,000 that is generally considered to be a cost-effective use of healthcare resources in the UK [29]; thus, the health gain with FF/UMEC/VI versus BUD/FOR justifies the higher treatment acquisition cost. The base-case study was conducted from a UK NHS perspective, according to NICE guidelines [22], and did not include estimates of effects on productivity.

One of the strengths of the GALAXY-COPD model is that it draws on a wide range of patient characteristics and clinical measures to extrapolate to longer-term outcomes from shorter-term data, in this case, the 24-week ITT data from FULFIL. However, the need to make assumptions regarding the duration of treatment effect and treatment discontinuation after one year may be considered as limitations of the analysis. Results were sensitive to the duration of treatment effect, with the ICER increasing to £9,902 if the duration of treatment effect was limited to three years compared with the base case, where treatment effect was assumed to continue for the time

Table 5
Scenario analyses for FF/UMEC/VI versus BUD/FOR.

Scenario	Incremental costs	Incremental QALYs	ICER (cost per QALY gained)
Base case	**£1,652**	**0.492**	**£3,357**
EXT population[a]	£1,327	0.587	£2,262
Patient productivity costs	–£2,177	0.492	Dominant
Discount rate 0%	£2,299	0.666	£3,454
Discount rate 5%	£1,455	0.438	£3,323
Duration of treatment effect: three years	£862	0.087	£9,902
Treatment discontinuation excluded in first and subsequent years	£1,841	0.525	£3,507
Treatment discontinuation included in first and subsequent years	£986	0.347	£2,840
Generic price for Symbicort (DuoResp 320 [BUD/FOR])	£2,321	0.492	£4,718
Time horizon: five years	£422	0.135	£3,134
Time horizon: 10 years	£892	0.298	£2,992

BUD = budesonide, FOR = formoterol, ICER = incremental cost-effectiveness ratio, QALY = quality-adjusted life year.
[a] EXT = 52-week extension population of the FULFIL trial [11].

Table 6
One-way sensitivity analyses for FF/UMEC/VI versus BUD/FOR.

	Upper confidence limit			Lower confidence limit		
	Incremental costs	Incremental QALYs	ICER (cost per QALY gained)	Incremental costs	Incremental QALYs	ICER (cost per QALY gained)
Base case	**£1,652**	**0.492**	**£3,357**	–	–	–
Fibrinogen (465.9–475.2 µg/dL)	£1,638	0.490	£3,346	£1,659	0.493	£3,362
6MWT (365.3–376.1 m)	£1,731	0.519	£3,334	£1,717	0.515	£3,337
mMRC dyspnea score ≥2 (32–53%)	£1,621	0.488	£3,324	£1,677	0.495	£3,386
Incremental FEV_1 (148–194 mL)	£1,806	0.521	£3,468	£1,492	0.462	£3,227
RR for moderate exacerbation (0.6–1.04)	£1,399	0.461	£3,034	£1,841	0.515	£3,578
RR for severe exacerbation (0.27–1.08)	£2,422	0.436	£5,556	£1,282	0.520	£2,466
SGRQ change (−3.5 to −1)	£1,652	0.370	£4,466	£1,652	0.622	£2,656

6MWT = 6-minute walk test, FEV_1 = forced expiratory volume in 1 s, ICER = incremental cost-effectiveness ratio, mMRC = modified Medical Research Council, QALY = quality-adjusted life year, RR = relative risk, SGRQ = St. George's Respiratory Questionnaire.

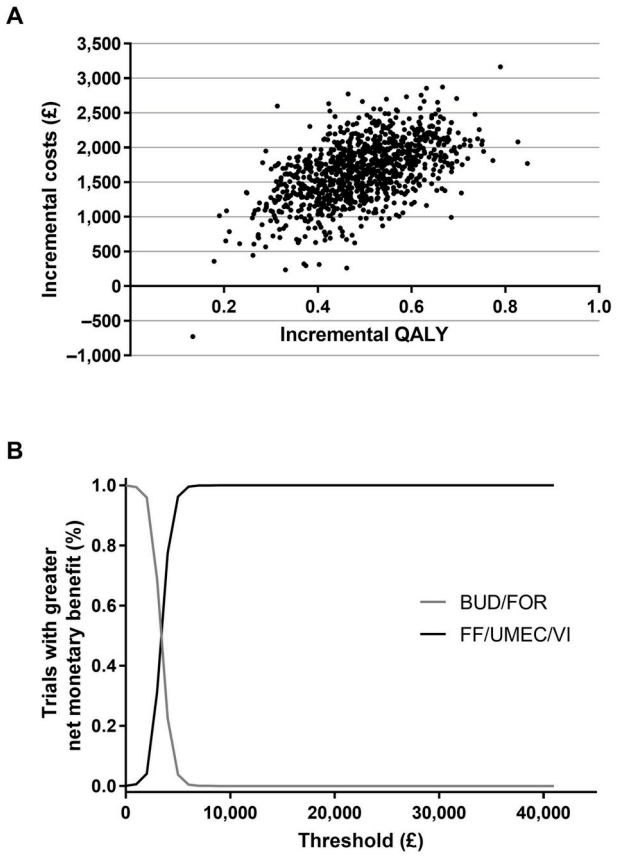

Fig. 1. Probabilistic sensitivity analysis results for FF/UMEC/VI versus BUD/FOR showing a) base case, incremental cost-effectiveness plane and b) cost-effectiveness acceptability curve.
BUD = budesonide, FF = fluticasone furoate, FOR = formoterol, QALY = quality-adjusted life year, UMEC = umeclidinium, VI = vilanterol.

patients remained on treatment. However, a longer efficacy duration is a reasonable assumption, based on the findings of the Understanding Potential Long-Term Impacts on Function with Tiotropium (UPLIFT) trial that reported four-year sustained efficacy with a LAMA [30]. In addition, the scenario using 52-week results from the FULFIL EXT population showed a 33% reduction in the ICER compared with the base case. This reflects the greater relative benefit, particularly on exacerbation reduction and improvement in SGRQ, seen with FF/UMEC/VI in the EXT population at 52 weeks, compared with at 24 weeks in the ITT population. Thus, the findings of other studies and the analysis in the EXT population also increase confidence in the results of the base-case analysis based on ITT data. While the assumption that no treatment discontinuation would occur after one year was based on limited evidence from longer studies [17,18], it was also seen as reasonable from a clinical perspective since discontinuation due to lack of efficacy or due to treatment-related adverse events is most likely to occur in the first year; in scenario analyses, the assumption of ongoing treatment discontinuation for all years did not greatly affect the ICER.

Other limitations of the study were, first, that the evaluation of cost-effectiveness was based solely on clinical efficacy observed in the FULFIL study. A comparison of FF/UMEC/VI with ICS/LABA combinations other than BUD/FOR could potentially provide differing levels of cost-effectiveness, although the recent Informing the Pathway of COPD Treatment (IMPACT) trial, which favorably compared FF/UMEC/VI with FF/VI [31], further substantiates the benefit of ICS/LAMA/LABA versus ICS/LABA. Second, was the need to estimate required parameters for the GALAXY-COPD model as they were unavailable from the FULFIL data. Although responses to the EXACT-PRO were a suitable substitute for mMRC dyspnea score, the 6MWT and plasma fibrinogen were predicted based on values from the published ECLIPSE study [17]. While the use of predicted values based on a single study might not be considered ideal, varying the baseline parameters for the 6MWT or fibrinogen in the one-way sensitivity analyses in the current study had only limited effects on the ICER for FF/UMEC/VI treatment compared with BUD/FOR. With this in mind, future clinical trials may consider including the 6MWT as an outcome and fibrinogen as a baseline characteristic, due to their prognostic value for the modelling of long-term treatment effects. Third, the effectiveness of subsequent therapy was not known and was assumed in this analysis to be similar to the reference treatment. However, triple therapy may have been more effective than the reference treatment, and it is possible that this assumption decreased the total benefit to a greater extent in the BUD/FOR arm (which had the higher discontinuation rate) than the FF/UMEC/VI arm. Thus, assuming the effectiveness of subsequent therapy to have been closer to triple therapy could have reduced incremental QALYs and increased the ICER. Nonetheless, given that discontinuation was only applied in the first year, the effect of this assumption was likely to have been small. Fourth, the population of TORCH, from which the risk equations for HRU were developed, was not specifically a UK population. Similar to other large COPD studies suitable for disease modelling, TORCH was multi-national; however, with 50% of patients from Europe and 31% of patients from Western Europe [18], the HRU rates in TORCH were likely similar to those of the UK. Furthermore, the coefficients of the HRU risk equations were included in the PSA. Finally, FULFIL only included patients who were considered GOLD group D at enrollment (FEV_1 < 50% predicted and CAT score ≥10; or FEV_1 ≥50– < 80% predicted, CAT ≥10 and either ≥2 moderate exacerbations or ≥1 severe exacerbation in the previous 12 months) [11], limiting the population included in the study. Accordingly, the results of this economic evaluation are only generalizable to this limited patient population.

5. Conclusions

In conclusion, treatment with FF/UMEC/VI compared with BUD/FOR

resulted in a reduction in the total cumulative number of exacerbations, including severe events. This economic analysis found FF/UMEC/VI to be cost-effective for the UK NHS, compared with BUD/FOR, in patients with COPD who are symptomatic and at risk of an exacerbation. Sensitivity analyses showed that variation in key input parameters did not alter the results. These results may be useful for informing drug listing decision-making processes in the UK healthcare system.

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Declaration of interests

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests:

Zhang S: GlaxoSmithKline plc. employee and holds shares.

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Ismaila AS: GlaxoSmithKline plc. employee and holds shares. ASI is also an unpaid professor at McMaster University in Canada.

Appendix A. Supplementary data

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