Early View

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Cost-effectiveness analysis of a single-inhaler triple therapy for COPD in the UK

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'Take home' message:
This cost-effectiveness analysis demonstrates that fluticasone furoate/umeclidinium/vilanterol provides a cost-effective treatment option *versus* budesonide/formoterol for patients with symptomatic chronic obstructive pulmonary disease in the United Kingdom

ABSTRACT

Introduction: United Kingdom management costs for chronic obstructive pulmonary disease, estimated at £1.9 billion/year, are rising. In the FULFIL (Lung Function and Quality of Life Assessment in Chronic Obstructive Pulmonary Disease with Closed Triple Therapy) study, single-inhaler triple therapy with fluticasone furoate/umeclidinium/vilanterol (100/62.5/25 µg) improved clinical outcomes *versus* budesonide/formoterol (400/12 µg) in patients with symptomatic chronic obstructive pulmonary disease at risk of exacerbations. We assessed the cost-effectiveness of fluticasone furoate/umeclidinium/vilanterol *versus* budesonide/formoterol for treating chronic obstructive pulmonary disease from a United Kingdom National Health Service perspective.

Methods: A model was developed combining a trial-based and Markov component and populated with baseline and treatment effect data from FULFIL, together with United Kingdom healthcare resource costs and disease-related utilities. Costs per life year and per quality-adjusted life year gained (costing year 2017) for fluticasone furoate/umeclidinium/vilanterol *versus* budesonide/formoterol were calculated for a lifetime horizon. Results were explored using deterministic sensitivity, scenario and probabilistic analyses.

Results: Fluticasone furoate/umeclidinium/vilanterol was associated with gains in life years (0.533) and quality-adjusted life years (0.506) *versus* budesonide/formoterol, but at slightly increased total costs (£26 416 *versus* £25 860). This translated to incremental cost-effectiveness ratios of £1042/life year and £1098/quality-adjusted life year for fluticasone furoate/umeclidinium/vilanterol *versus* budesonide/formoterol. In scenario analyses, incremental cost-effectiveness ratios ranged from dominant to £1547/quality-adjusted life year gained.

Conclusions: Fluticasone furoate/umeclidinium/vilanterol provides a cost-effective treatment option *versus* budesonide/formoterol for patients with symptomatic chronic obstructive pulmonary disease in the United Kingdom.

Introduction

The prevalence of chronic obstructive pulmonary disease (COPD) in the United Kingdom (UK) rose by approximately 27% between 2004 and 2012 [1] and this increase is predicted to continue [2]. Maintenance pharmacological therapy for COPD centres on the use of long-acting bronchodilators in the form of a long-acting muscarinic antagonist (LAMA) and/or long-acting β_2-agonist (LABA). For patients who remain symptomatic despite inhaled corticosteroid (ICS)/LABA or LAMA/LABA dual therapy and are at high risk of exacerbations, the Global Initiative for Chronic Obstructive Lung Disease (GOLD) recommends a triple combination of ICS plus a LAMA and LABA [3].

The Lung Function and Quality of Life Assessment in Chronic Obstructive Pulmonary Disease with Closed Triple Therapy (FULFIL) study was a phase III, randomised, double-blind, double-dummy trial (NCT02345161). FULFIL compared once-daily ICS/LAMA/LABA triple therapy using fluticasone furoate/umeclidinium/vilanterol 100/62.5/25 µg (FF/UMEC/VI) administered *via* the ELLIPTA inhaler with twice-daily ICS/LABA therapy with budesonide/formoterol 400/12 µg (BUD/FOR) administered *via* the Turbuhaler inhaler. The study was conducted in patients with advanced, symptomatic COPD, who were at risk of exacerbations [4]. The findings from FULFIL demonstrated a statistically significant benefit in terms of trough forced expiratory volume in 1 s (FEV_1) with FF/UMEC/VI within both the intent-to-treat (ITT) population, at 24 weeks, and a subpopulation of patients who remained on blinded treatment for an extended period of 52 weeks (extension [EXT] population) [4]. Thus, the clinical findings from FULFIL support the use of single-inhaler triple therapy over dual ICS/LABA therapy in patients with advanced, symptomatic COPD, who are at risk of exacerbations.

COPD represents a considerable cost to the UK economy; in 2017 this was estimated to be approximately £1.9 billion per year [5]. This, given the increasing prevalence of COPD, highlights the need to identify cost-effective therapeutic options with the potential to reduce exacerbations. Multiple models, capable of evaluating the cost-effectiveness of COPD treatments, have been developed [6]. These have

predominantly been Markov models, representing COPD in terms of lung function and exacerbations. The exception is the GALAXY model, which uses an interdependent system of risk equations to characterise a wider set of disease attributes over time, including COPD symptoms and exercise capacity, in addition to lung function and exacerbations [7–9]. For this analysis, we chose to use a trial-based assessment combined with a Markov model focussing on lung function and exacerbation risk, like many previous models, rather than an approach similar to the GALAXY model. This allows the assessment of treatment value based on these two key outcomes for clinical decision-making in COPD, utilises a structure (Markov) which is familiar to Health Technology Assessment bodies and is less data intensive than the GALAXY model, which requires data inputs for a broader range of baseline characteristics and treatment effects.

Here we present a description of the approach and its application in the assessment of the cost-effectiveness of FF/UMEC/VI compared with BUD/FOR in the treatment of advanced, symptomatic COPD, from the perspective of the UK National Health Service (NHS).

Methods

Model structure

The model comprised an initial decision tree, representing the trial period, followed by a Markov model, with a 1-year cycle length, to extrapolate outcomes beyond the trial period. The initial trial-based analysis directly reflected the baseline status and outcomes (24 weeks for the ITT population, and 52 weeks for the EXT population) in FULFIL [4].

The Markov model consisted of six health states, plus death (figure 1). These were based on three categories of COPD severity defined by FEV_1 status (moderate: FEV_1 percent predicted 50–<80%; severe: FEV_1 percent predicted 30–<50%; and very severe: FEV_1 percent predicted <30%), each with two categories (presence or absence) of recent (previous year) exacerbation. Exacerbations could be either moderate (requiring treatment with antibiotics and/or systemic corticosteroids) or

severe (requiring hospitalisation or resulting in death). Mild exacerbations were assumed to have a negligible impact on both clinical and economic outcomes, and therefore excluded. At the start of the Markov model, patients were assigned to one of the six health states in accordance with their FEV_1 status at the end of, and exacerbation history during, the trial period.

Transitions between health states were determined by two risk equations, one predicting the rate of FEV_1 decline over time, and the second the probability of an exacerbation (see below and supplementary appendix for details), together with the likelihood of dying. Costs, health-related quality of life and utility were assigned to health states and events (exacerbations and pneumonia events).

Estimated coefficients for variables in each equation are provided in supplementary table S1 and supplementary table S2. Baseline characteristics for age, percentage male and height were used to estimate decline in FEV_1 percent predicted, from which the probability of transition to a more-severe state was calculated (supplementary table S3). The assumption was made that individuals could only transition to increasingly severe COPD. The second equation predicted the probability of an exacerbation. Experiencing an exacerbation within a 1-year cycle impacted the transition rate to the next FEV_1 percent predicted state, as well as the risk of an exacerbation, during the immediately subsequent cycle. Both risk equations were developed using data from the 3-year Towards a Revolution in COPD Health (TORCH) study [10, 11].

Model parameterisation

Patient characteristics

Baseline patient characteristics used within the model are shown in table 1. Age and height data were drawn from the FULFIL study [4], and were used to calculate FEV_1 percent predicted. The remaining baseline characteristics [10] required to populate the risk equations for predicting annual FEV_1 decline and exacerbation rate were derived from the TORCH study, since the data from this 3-year trial were used to develop the risk equations.

Treatment effect

Treatment effect was incorporated using results from FULFIL (supplementary table S4). This included, in addition to a reduction in within-trial exacerbations, a one-time shift in the distribution of the population across COPD severity health states, as a result of improvement in FEV_1 at the end of the trial period. This formed the starting distribution for the Markov model (supplementary table S4). In the base case, this was assumed to fully capture the effect of treatment on disease progression and exacerbation risk, and the direct reduction in exacerbation rate from FULFIL was not applied in the Markov model. For assignment of costs and utilities in the initial trial period, the population was assumed to occupy the baseline health-state distribution for the first half of the trial period and the end-of-trial distribution for the second half.

Treatment-specific discontinuation rates from FULFIL were included for the trial period, with an assumption that there would be no further discontinuation in the Markov model (supplementary table S5). The assumption was made that only costs needed to be adjusted to account for discontinuation, as treatment effects for the ITT population would already include the impact of discontinuation. For calculation of costs, patients were assumed to receive replacement therapy (detailed in the section below).

With the exception of pneumonia, FF/UMEC/VI and BUD/FOR showed comparable safety profiles in FULFIL [4]. Thus, pneumonia was the only adverse event included in the model, both in the trial period and Markov model, given the known association between ICS-containing treatment regimens and increased rates of pneumonia [12]. Rates for pneumonia were taken directly from FULFIL for the trial period; for the Markov model, annual probabilities based on data from TORCH were used [10, 13].

Resource use and unit costs
Drug acquisition costs for BUD/FOR were obtained from the British National Formulary (BNF 73, March 2017; www.bnf.org/); costs for FF/UMEC/VI were assumed to be the sum of the costs of FF/VI and UMEC as formal acquisition costs were not available at the time of the analysis. Based on the pack costs of £49.50 for 30 doses of FF/UMEC/VI and £38.00 for 60 doses of BUD/FOR, the weekly treatment costs in the trial-based model were calculated to be £11.55 and £8.87 for FF/UMEC/VI and BUD/FOR, respectively. In the trial period, patients who died or

discontinued were assumed to have done so halfway through the trial period. Thus, those discontinuing treatment received treatment costs for 12 weeks and replacement therapy costs for the remaining 12 weeks. In the Markov model, patients who discontinued in the trial-based part of the model were assigned costs of replacement therapy, and all others were assigned treatment costs, while alive. Replacement therapy costs were based on the proportions of patients who received each of the four most frequently reported COPD medications following discontinuation in the FULFIL trial (ICS/LABA, ICS/LAMA/LABA, LAMA/LABA and LAMA) [4].

Exacerbation and pneumonia costs were calculated from resource use and unit cost data (table 2). Resource use was obtained from the literature [14]. Unit costs were derived from the UK 2015/16 NHS Reference Costs [15] and the Personal Social Services Research Unit (PSSRU) 2016 schedule [16], and were inflated to 2017. For the societal perspective, productivity costs associated with exacerbations were determined by multiplying the estimated length of exacerbation in days by the mean daily wage (£99.80) [17].

Mortality

The base case included mortality during the trial period based directly on data from FULFIL, in which there were four reported on-treatment deaths for FF/UMEC/VI, and six for BUD/FOR, up to Week 24 of the study [4]. Because event rates were low for deaths, with the consequent likelihood of treatment differences due to chance, excluding deaths in the trial period was explored in scenario analyses. In the Markov phase, excess mortality due to COPD was modelled using severity-specific relative risks of death applied to background all-cause mortality from England and Wales life tables [18]. Relative risks were calculated from a study of mortality rates in moderate, severe and very severe COPD and non-COPD populations [19].

Health-related quality of life

Health-state utilities (table 3) were obtained from a previously published analysis [20] using data from the multinational Understanding Potential Long-term Impacts on Function with Tiotropium (UPLIFT) trial [21]. Utilities in the UPLIFT trial were elicited using the EQ-5D instrument from a subset of trial patients with characteristics similar

to those of the overall trial population [20]. Decrements in quality-adjusted life years (QALYs) were applied to exacerbation and pneumonia events and calculated using an area under the curve approach with each event assumed to last 12 weeks [22].

Analyses

Model outputs included numbers of exacerbations, costs (total and disaggregated), life years (LYs), QALYs and incremental cost-effectiveness ratios (ICERs) as incremental cost per LY or QALY gained. In order to capture all relevant costs and outcomes of treatments, a lifetime horizon was adopted for the base case. To align with the National Institute for Health and Care Excellence (NICE) reference case [23], a discount rate of 3.5% per annum was applied to both costs and benefits in the base case.

Scenario analyses explored the impact of alternative assumptions or model settings on the model results. The impact of uncertainty around input parameters and risk equation coefficients was explored in deterministic one-way sensitivity analyses (OWSA) and probabilistic analysis (PA). Supplementary table S6 provides upper and lower limits for input values of parameters included in the OWSA. The PA (10 000 Monte Carlo simulations) was conducted with random sampling from distributions assigned to input parameters (supplementary table S7). Risk equation coefficients were included in the PA *via* Cholesky decomposition [24].

Subgroup analyses were conducted for the EXT population and two other subgroups: patients whose COPD was severe or worse (defined as FEV_1 percent predicted <50%), and patients with an exacerbation history of ≥1 severe or ≥2 moderate exacerbations in the 12 months prior to randomisation.

Results

Base-case analysis

In the ITT population, FF/UMEC/VI was associated with fewer cumulative exacerbations per patient compared with BUD/FOR over a lifetime horizon (table 4). Total costs were slightly higher for FF/UMEC/VI than for BUD/FOR (incremental difference £556). Accumulated LYs and QALYs were also slightly greater with

FF/UMEC/VI compared with BUD/FOR (incremental LYs 0.533 and incremental QALYs 0.506). This led to an ICER of £1042 per LY gained and £1098 per QALY gained for FF/UMEC/VI compared with BUD/FOR.

Scenario and sensitivity analyses

In scenario analyses, ICERs for FF/UMEC/VI compared with BUD/FOR ranged from dominant (lower costs and better outcomes) to £1547 per QALY gained (table 5). Applying a direct post-trial treatment effect on exacerbations in the Markov model had the greatest impact on the ICER: assuming the duration of this effect to be 1 year resulted in an ICER of £255 per QALY gained; longer durations, with or without waning of treatment effect over time, resulted in FF/UMEC/VI dominating BUD/FOR. Restricting the time horizon of the model to equal that of the trial follow-up period also resulted in FF/UMEC/VI being dominant.

OWSA demonstrated that cost-effectiveness was most sensitive to drug acquisition costs (figure 2). Varying the costs of FF/UMEC/VI or BUD/FOR by ±20% resulted in ICERs ranging from dominant (–£829) to £3026 per QALY gained. Varying the utility of moderate COPD and the risk associated with mortality in very severe COPD by ±20% also had some impact on cost-effectiveness, with ICERs (cost per QALY gained) ranging from £796 to £1773, and £577 to £1447, respectively. The ICER remained below the accepted NICE cost-effectiveness threshold of £20 000 per QALY gained [23] in all of the deterministic sensitivity or scenario analyses.

Subgroup analyses

Results in the EXT population were similar to the base case, with FF/UMEC/VI associated with fewer cumulative exacerbations per patient compared with BUD/FOR over a lifetime horizon (supplementary table S8). Total costs of FF/UMEC/VI were lower than for BUD/FOR (incremental difference –£101). Accumulated LYs and QALYs were greater with FF/UMEC/VI compared with BUD/FOR with incremental gains of 0.666 and 0.643, respectively. In terms of cost-effectiveness, the ICERs per LY and QALY gained for FF/UMEC/VI compared with BUD/FOR were both dominant. Results in the two other subgroup populations – severe COPD or worse, and a history of exacerbations – were also similar to the

base case, with ICERs of £1172 and £864 per QALY gained, respectively (supplementary table S8).

Probabilistic analysis

In the PA, FF/UMEC/VI was associated with improved outcomes in all iterations, both for LYs (figure 3a; supplementary figure S1a) and QALYs (figure 3b; supplementary figure S1b). Furthermore, FF/UMEC/VI was associated with a 100% probability of cost-effectiveness at willingness-to-pay thresholds of £10 000 and £20 000 [23] in both the ITT (figure 3c) and EXT (supplementary figure S1c) patient populations.

Discussion

This analysis assessed the cost-effectiveness of treating patients with advanced, symptomatic COPD with FF/UMEC/VI or BUD/FOR from the UK NHS perspective, using data from the FULFIL study. Total costs were slightly higher with FF/UMEC/VI, but there were fewer COPD exacerbations and increased LYs and QALYs compared with BUD/FOR, with the result that FF/UMEC/VI was predicted to be highly cost-effective *versus* BUD/FOR. FF/UMEC/VI remained cost-effective across a series of sensitivity and scenario analyses, and in PA the probability of FF/UMEC/VI being cost-effective at the NICE willingness-to-pay threshold of £20 000/QALY gained [23] was 100%. Across all analyses, FF/UMEC/VI was associated with improved outcomes (in LYs and QALYs). Higher costs were due to increased costs associated with longer overall survival associated with FF/UMEC/VI while increased effectiveness was as a result of lower exacerbation incidence during the trial period across all patient populations. These findings are important for decisions on the treatment of COPD in the UK NHS.

It is helpful to understand how relevant the results of this analysis, which was based on data from a controlled trial, are for patients treated in real practice. FULFIL was designed to be highly inclusive and enrolled patients with COPD irrespective of whether they also had cardiovascular risk factors [4]; this contrasts with many other COPD clinical trials which often exclude such patients [25]. Patients did not have to

artificially withdraw from their usual medications to participate, thus the study population had similar characteristics to patients with COPD in the real-world setting. Furthermore, the mean age (63.9 years) and current smoking status (44%) of the ITT population in FULFIL [4] were similar to those reported in a large database study of 9219 patients with COPD in UK primary care [26]. This, together with the consistency of results across subgroups and the ITT population, strongly suggests that the findings of this analysis are generalisable to the population of patients with COPD in the UK.

The findings of this analysis are similar to those reported recently by Schroeder *et al.* (2019) in their analysis of the cost-effectiveness of FF/UMEC/VI *versus* BUD/FOR, also based on data from the FULFIL trial [27]. Using the GALAXY linked-risk equation model, FF/UMEC/VI resulted in gains in LYs (0.764) and QALYs (0.492), at an additional cost (£1652), compared with BUD/FOR; this translated to an ICER per QALY gained of £3357 [27]. A similar QALY gain (0.506) was observed in this analysis, but with a lower ICER per QALY gained (£1098). The current analysis used a Markov modelling approach that requires fewer input data, suggesting that the results derived may be more accessible to regulatory bodies. When considered alongside the findings reported by Schroeder *et al.* [27], this analysis demonstrates the cost-effectiveness of FF/UMEC/VI relative to BUD/FOR in the UK NHS setting.

A potential limitation of this analysis is the absence of data on longer-term treatment effects in FULFIL. Risk equations, based on data from the 3-year TORCH trial, were used to bridge to longer-term outcomes. Although the populations in FULFIL and TORCH were quite similar with respect to age, lung function and smoking status, there may be limitations to how generalisable outcomes in TORCH are to the FULFIL or other populations. This is important to note, as sensitivity analyses within the model showed that results were sensitive to the duration and nature of long-term treatment effects on exacerbation frequency. However, longer-term differences between FF/UMEC/VI and BUD/FOR, predicted by the risk equations, were substantially smaller than those observed in FULFIL, suggesting that the base case is conservative. Furthermore, given all sensitivity and scenario analyses were well below the accepted willingness-to-pay threshold in the UK, uncertainty over long-

term effects does not appear to cast doubt on the findings of this analysis. Additionally, as treatment adherence in a clinical trial setting is typically greater than that observed in the real-world setting, it is possible that the full benefit of FF/UMEC/VI once-daily *versus* BUD/FOR twice-daily treatment was not fully realised in the original FULFIL trial. If this were the case, the results of this analysis would be conservative with respect to the cost-effectiveness of FF/UMEC/VI in routine practice.

Conclusions

Treatment with FF/UMEC/VI is predicted to improve long-term health outcomes and provide a cost-effective option for treatment of patients with advanced, symptomatic COPD when compared with BUD/FOR, in the UK.

References

1   Snell N, Strachan D, Hubbard R, Gibson J, Gruffydd-Jones K, Jarrold I. Epidemiology of chronic obstructive pulmonary disease (COPD) in the UK: findings from the British Lung Foundation's 'Respiratory Health of the Nation' project. Thorax 2016; 71: A20.

2   McLean S, Hoogendoorn M, Hoogenveen RT, Feenstra T, Wild S, Simpson CR, Rutten-van Mölken, Sheikh A. Projecting the COPD population and costs in England and Scotland: 2011 to 2030. Sci Rep 2016; 6: 31893.

3   Global Initiative for Chronic Obstructive Lung Disease (GOLD). Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease. 2020 report. https://goldcopd.org/wp-content/uploads/2019/11/GOLD-2020-REPORT-ver1.0wms.pdf. Date last updated: 2020. Date last accessed: January 2020.

4   Lipson DA, Barnacle H, Birk R, Brealey N, Locantore N, Lomas DA, Ludwig-Sengpiel A, Mohindra R, Tabberer M, Zhu C-Q, Pascoe SJ. FULFIL trial: once-daily triple therapy for patients with chronic obstructive pulmonary disease. Am J Respir Crit Care Med 2017; 196: 438-446.

5   British Lung Foundation. The battle for breath - the economic burden of lung disease. www.blf.org.uk/what-we-do/our-research/economic-burden. Date last updated: 2017. Date last accessed: January 2020.

6   Hoogendoorn M, Feenstra TL, Asukai Y, Briggs AH, Hansen RN, Leidl R, Risebrough N, Sanyshkin Y, Wacker M, Rutten-van Mölken MP. External validation of health economic decision models for chronic obstructive pulmonary disease (COPD): report of the third COPD modeling meeting. Value Health 2017; 20: 397-403.

7   Risebrough NA, Briggs A, Baker TM, Exuzides A, Colby C, Rutten van-Mölken M, Gonzalez McQuire S, Lomas D, Muellerova H, Tal-Singer R, Ismaila A. Validating a model to predict disease progression outcomes in patients with COPD. Value Health 2014; 17: A560-A561.

8   Briggs AH, Baker T, Risebrough NA, Chambers M, Gonzalez-McQuire S, Ismaila AS, Exuzides A, Colby C, Tabberer M, Muellerova H, Locantore N, Rutten-van Mölken MPMH, Lomas DA. Development of the Galaxy chronic obstructive pulmonary disease (COPD) model using data from ECLIPSE:

internal validation of a linked-equations cohort model. Med Decis Making 2017; 37: 469-480.

9   Exuzides A, Colby C, Briggs AH, Lomas DA, Rutten van-Mölken MPMH, Tabberer M, Chambers M, Muellerova H, Locantore N, Risebrough NA, Ismaila AS, Gonzalez-McQuire S. Statistical modeling of disease progression for chronic obstructive pulmonary disease using data from the ECLIPSE study. Med Decis Making 2017; 37: 453-468.

10   Calverley PM, Anderson JA, Celli B, Ferguson GT, Jenkins C, Jones PW, Yates JC, Vestbo J; TORCH investigators. Salmeterol and fluticasone propionate and survival in chronic obstructive pulmonary disease. N Engl J Med 2007; 356: 775-789.

11   Vestbo J, TORCH Study Group. The TORCH (towards a revolution in COPD health) survival study protocol. Eur Respir J 2004; 24: 206-210.

12   Morjaria JB, Rigby A, Morice AH. Inhaled corticosteroid use and the risk of pneumonia and COPD exacerbations in the UPLIFT study. Lung 2017; 195: 281-288.

13   Crim C, Calverley PM, Anderson JA, Celli B, Ferguson GT, Jenkins C, Jones PW, Willits LR, Yates JC, Vestbo J. Pneumonia risk in COPD patients receiving inhaled corticosteroids alone or in combination: TORCH study results. Eur Respir J 2009; 34: 641-647.

14   Oostenbrink JB, Rutten-van Mölken MP, Monz BU, FitzGerald JM. Probabilistic Markov model to assess the cost-effectiveness of bronchodilator therapy in COPD patients in different countries. Value Health 2005; 8: 32-46.

15   National Health Service (NHS). NHS reference costs collection guidance for 2015 to 2016. www.gov.uk/government/publications/nhs-reference-costs-collection-guidance-for-2015-to-2016. Date last updated: 2016. Date last accessed: January 2020.

16   Personal Social Services Research Unit. Unit costs of health and social care 2016. www.pssru.ac.uk/project-pages/unit-costs/2016/. Date last updated: 2016. Date last accessed: January 2020.

17   Office for National Statistics. Earnings and Working Hours. https://www.ons.gov.uk/employmentandlabourmarket/peopleinwork/earningsandworkinghours. Date last updated: December 2019. Date last accessed: January 2020.

18   Office for National Statistics. Deaths registered in England and Wales (2015). www.ons.gov.uk/peoplepopulationandcommunity/birthsdeathsandmarriages/deaths/bulletins/deathsregistrationsummarytables/2015. Date last updated: 2015. Date last accessed: January 2020.

19   Afonso AS, Verhamme KM, Sturkenboom MC, Brusselle GG. COPD in the general population: prevalence, incidence and survival. Respir Med 2011; 105: 1872-1884.

20   Rutten-van Mölken MP, Oostenbrink JB, Tashkin DP, Burkhart D, Monz BU. Does quality of life of COPD patients as measured by the generic EuroQol five-dimension questionnaire differentiate between COPD severity stages? Chest 2006; 130: 1117-1128.

21   Tashkin DP, Celli B, Senn S, Burkhart D, Kesten S, Menjoge S, Decramer M; UPLIFT Study Investigators. A 4-year trial of tiotropium in chronic obstructive pulmonary disease. N Engl J Med 2008; 359: 1543-1554.

22   National Institute for Health and Care Excellence. Chronic obstructive pulmonary disease: management of chronic obstructive pulmonary disease in adults in primary and secondary care (2010). https://www.nice.org.uk/guidance/cg101/documents/chronic-obstructive-pulmonary-disease-update-nice-draft-guideline2. Date last updated: 2010. Date last accessed: January 2020.

23   National Institute for Health and Care Excellence. The guidelines manual. Process and methods [PMG6]. 7. Assessing cost effectiveness (2012). www.nice.org.uk/process/pmg6/chapter/assessing-cost-effectiveness. Date last updated: 2012. Date last accessed: January 2020.

24   Weisstein EW. Cholesky decomposition. www.mathworld.wolfram.com/CholeskyDecomposition.html. Date last updated: January 2020. Date last accessed: January 2020.

25   Rabe KF, Hurst JR, Suissa S. Cardiovascular disease and COPD: dangerous liaisons? Eur Respir Rev 2018; 27: pii: 180057.

26   Haughney J, Gruffydd-Jones K, Roberts J, Lee AJ, Hardwell A, McGarvey L. The distribution of COPD in UK general practice using the new GOLD classification. Eur Respir J 2014; 43: 993-1002.

27   Schroeder S, Shah D, Risebrough N, Martin A, Zhang S, Ndirangu K, Briggs A, Ismaila AS. 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. Respir Med X 2019; 1: 100008.

Figures and tables

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 year

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

FIGURE 2 OWSA plot (QALYs; ITT population).

OWSA: one-way sensitivity analysis; QALY: quality-adjusted life year; ITT: intent to treat; FF: fluticasone furoate; UMEC: umeclidinium; VI: vilanterol; BUD: budesonide; FOR: formoterol; COPD: chronic obstructive pulmonary disease; ICER: incremental cost-effectiveness ratio.

FIGURE 3 Incremental cost-effectiveness of FF/UMEC/VI *versus* BUD/FOR: a) LYs plane;
b) QALYs plane; c) QALY cost-effectiveness acceptability curves (ITT population; PA).

a)

b)

c)

FF: fluticasone furoate; UMEC: umeclidinium; VI: vilanterol; BUD: budesonide; FOR: formoterol; LY:
life year; QALY: quality-adjusted life year; ITT: intent to treat; PA: probabilistic analysis.

TABLE 1 Baseline patient characteristics

Parameter	Mean	Source
Age at baseline, years (SD)	63.9 (6.39)	FULFIL [4]
Height, m (SD)	1.69 (0.08)	FULFIL [4]
Sex		
Male	75.8%	TORCH [10]
Age category, years		
<55	11.5%	TORCH [10]
55–<65	32.3%	TORCH [10]
65–<75	43.7%	TORCH [10]
>75	12.6%	TORCH [10]
Exacerbation history (moderate or severe, in the previous 12 months)		
0	43.0%	TORCH [10]
1	24.8%	TORCH [10]
≥2	32.3%	TORCH [10]
BMI, kg/m^2		
<20	13.5%	TORCH [10]
20–<25	37.6%	TORCH [10]
25–<29	26.9%	TORCH [10]
≥29	22.0%	TORCH [10]
SGRQ total score		
<38	28.8%	TORCH [10]
38–<50	25.7%	TORCH [10]
50–<62	22.9%	TORCH [10]
≥62	22.6%	TORCH [10]
FEV$_1$ percent predicted, baseline[#]		
<30%	12.9%	FULFIL [4]
30–<50%	54.5%	FULFIL [4]
50–<80%	32.6%	FULFIL [4]
≥80%	<1.0%	FULFIL [4]

SD: standard deviation; BMI: body mass index; SGRQ: St. George's Respiratory Questionnaire; FEV_1: forced expiratory volume in 1 s. [#]: FEV_1 percent predicted at baseline was not included in the model and is provided only as information describing lung function status at study entry.

TABLE 2 Itemised resource use and unit costs for COPD therapy and exacerbations

Cost category	Resource use (per annum)[#]	Unit cost (2017)[¶]	Overall cost
Moderate COPD			
Outpatient visit, respiratory physician	0.00	£149.35	£0.00
Outpatient visit, GP	2.00	£36.68	£73.37
Spirometry	2.00	£61.57	£123.15
Influenza vaccination	0.75	£9.05	£6.79
Oxygen therapy (days)	0.00	£16.98	£0.00
Total cost of moderate COPD (per annum)			**£203.30**
Severe COPD			
Outpatient visit, respiratory physician	2.00	£149.35	£298.71
Outpatient visit, GP	0.00	£36.68	£0.00
Spirometry	2.00	£61.57	£123.15
Influenza vaccination	0.75	£9.05	£6.79
Oxygen therapy (days)	14.60	£16.98	£247.86
Total cost of severe COPD (per annum)			**£676.51**
Very severe COPD			
Outpatient visit, respiratory physician	4.00	£149.35	£597.42
Outpatient visit, GP	0.00	£36.68	£0.00
Spirometry	4.00	£61.57	£246.29
Influenza vaccination	0.75	£9.05	£6.79
Oxygen therapy (days)	73.00	£16.98	£1239.32
Total cost of very severe COPD (per annum)			**£2089.82**

	Resource use (per exacerbation)	Unit cost (2017)[¶]	Cost (per exacerbation)
Moderate exacerbation			
ICU days	0.00	£1341.52	£0.00
Non-ICU days	1.01	£436.97	£441.34
ER visits	0.03	£200.94	£6.03
Outpatient visit, respiratory physician	0.34	£149.35	£50.78
Outpatient visit, GP	0.66	£36.68	£24.21
Visit other HCP	0.27	£98.52	£26.60
Antibiotics[¶]	7.94	£0.28	£2.21
Systemic steroids[¶]	7.94	£0.27	£2.11
Oxygen therapy	0.00	£16.98	£0.00
Total cost per moderate exacerbation			**£553.28**

Severe exacerbation

ICU days	0.86	£1341.52	£1153.71
Non-ICU days	11.08	£436.97	£4841.63
ER visits	0.25	£200.94	£50.24
Outpatient visit, respiratory physician	0.82	£149.35	£122.47
Outpatient visit, GP	0.70	£36.68	£25.68
Visit other HCP	0.50	£98.52	£49.26
Antibiotics[¶]	11.75	£0.56	£6.55
Systemic steroids[¶]	24.08	£0.27	£6.40
Oxygen therapy	0.21	£16.98	£3.57
Total cost per severe exacerbation			**£6259.49**
Cost per pneumonia event			**£6533.07**

COPD: chronic obstructive pulmonary disease; GP: general practitioner; ICU: intensive care unit; ER: emergency room; HCP: healthcare professional; PSSRU: Personal Social Services Research Unit. [#]: resource use estimates were based on Oostenbrink *et al.*, 2005 [14]; [¶]: unit cost represents the cost per day or visit, or per category.

Unit costs come from Oostenbrink *et al.*, 2005 [14], National Health Service Reference Costs 2015/16 [15], and PSSRU, 2016 [16]

TABLE 3 Health-state utilities and QALY loss associated with each event

Health state[#]	Utility	Lower 95% CI	Upper 95% CI
Moderate COPD	0.787	0.771	0.802
Severe COPD	0.750	0.731	0.768
Very severe COPD	0.647	0.598	0.695
Event	**QALY loss per event**	**Lower 95% CI**	**Upper 95% CI**
Moderate exacerbation[¶]	0.011	0.006	0.020
Severe exacerbation[¶]	0.020	0.020	0.030
Pneumonia[+]	0.011	0.006	0.020

QALY: quality-adjusted life year; CI: confidence interval; COPD: chronic obstructive pulmonary disease; NICE: National Institute for Health and Care Excellence. [#]: source: Rutten-van Molken *et al.*, 2006 [20]; [¶]: source: NICE Guidelines, 2010 [22]; [+]: assumption: equivalent to moderate exacerbation.

TABLE 4 Base-case results (lifetime horizon[#]) – ITT population

	FF/UMEC/VI	BUD/FOR	Incremental
Outcomes			
Predicted cumulative exacerbations			
Moderate exacerbations	5.793	5.804	–0.011
Severe exacerbations	1.422	1.434	–0.012
Any moderate and/or severe exacerbation	7.216	7.238	–0.023
Total LYs (discounted)	9.094	8.561	0.533
Total QALYs (discounted)	6.638	6.132	0.506
Costs			
Maintenance	£7531	£8495	–£965
Moderate exacerbation	£2459	£2484	–£25
Severe exacerbation	£6874	£6974	–£100
Pneumonia	£4261	£3927	£334
Treatment	£4887	£3339	£1549
Discontinuation	£404	£641	–£237
Total costs	£26 416	£25 860	£556
ICER per LY	£1042	Referent	–
ICER per QALY	£1098	Referent	–

ITT: intent to treat; FF: fluticasone furoate; UMEC: umeclidinium; VI: vilanterol; BUD: budesonide; FOR: formoterol; LY: life year; QALY: quality-adjusted life year; ICER: incremental cost-effectiveness ratio. [#]: outcomes and costs observed over the complete period (trial-based and Markov models).

TABLE 5 Scenario analyses (FF/UMEC/VI *versus* BUD/FOR) – ITT population

	Base case	Scenario	FF/UMEC/VI ICER (cost per QALY gained)
Base case			£1098
Discount rate (costs, benefits)	3.5%	0.0%	£1547
Discount rate (costs, benefits)	3.5%	5.0%	£900
Within-trial mortality	On	Off	£1011
Post-trial treatment effect	Off	On - 1 year	£255
Post-trial treatment effect	Off	On - 3 years	Dominant
Post-trial treatment effect	Off	On - 5 years	Dominant
Post-trial treatment effect - waning	Off	On - 5 years	Dominant
Overall treatment discontinuation	On	Off	£1414
Post-trial treatment discontinuation	On	Off	£1414
Time horizon	Lifetime	Trial follow-up	Dominant
Replacement therapy	By treatment arm	By overall trial	£1098
Perspective	Health service perspective	Societal perspective	£886

FF: fluticasone furoate; UMEC: umeclidinium; VI: vilanterol; BUD: budesonide; FOR: formoterol; ITT: intent to treat; ICER: incremental cost-effectiveness ratio; QALY: quality-adjusted life year.

FULFIL TRIAL

Clinical outcomes, QALYs, costs

Initial trial-based model

Moderate COPD
No recent exacerbation history

Severe COPD
No recent exacerbation history

Very severe COPD
No recent exacerbation history

Moderate COPD
Recent exacerbation history

Severe COPD
Recent exacerbation history

Very severe COPD
Recent exacerbation history

Cycle length = 1 year

Markov Model

Death

Acute events affecting costs, utilities and transitions

Pneumonia

Moderate/severe exacerbations

Cost FF/UMEC/VI (±20%)
Cost BUD/FOR (±20%)
Utility – moderate COPD (±20%)
Risk of mortality in very severe COPD (±20%)
COPD maintenance costs (±20%)
Discount rates (0%/5%)
Exacerbation rates in very severe COPD – recent exacerbation history (±20%)
Exacerbation rates in moderate COPD – recent exacerbation history (±20%)
Exacerbation rates in moderate COPD – no recent exacerbation history (±20%)
Utility – very severe COPD (±20%)

High value
Low value

-1000   -500   0   500   1000   1500   2000   2500   3000   3500

ICER (£)

Supplementary Appendix

SUPPLEMENTARY FIGURE S1 QALY cost-effectiveness acceptability curves of FF/UMEC/VI *versus* BUD/FOR (EXT population[#]; PA).

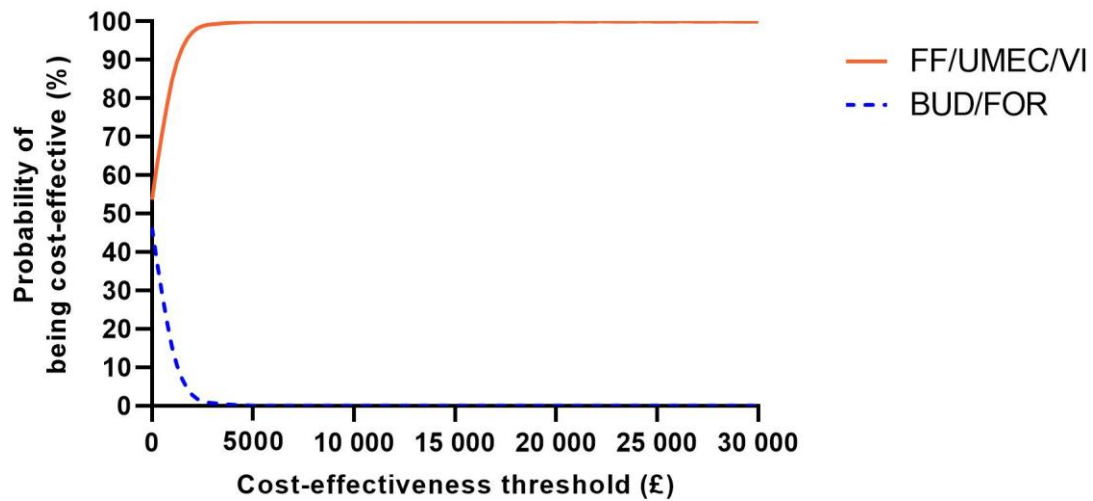FF: fluticasone furoate; UMEC: umeclidinium; VI: vilanterol; BUD: budesonide; FOR: formoterol; PA: probabilistic analysis; QALY: quality-adjusted life year; EXT: extension. [#]: patients treated for up to 52 weeks.

SUPPLEMENTARY TABLE S1 Coefficients estimated within the FEV_1 (mL) random intercept equation fit using data from TORCH[#]

Variable	Point estimate	Standard error
Intercept	1275.6	35.9
Slope (years)	−40.9	4.5
Recent exacerbation history*	−30.6	5.9
Age, years		
<55	Referent	
55–<65	−203.0	23.6
65–<75	−326.5	23.1
≥75	−402.6	29.5
Sex		
Male	293.9	17.1
Female	Referent	
BMI, kg/m²		
<20	Referent	
20–<25	153.3	24.5
25–<29	244.5	25.4
≥29	348.7	25.9
Exacerbation history (moderate or severe, in the previous 12 months)		
0	Referent	
1	−0.03	17.7
≥2	−55.0	17.4
Baseline SGRQ total score		
<38	Referent	
38–<50	−93.9	19.4
50–<62	−161.1	20.0
≥62	−185.9	20.7

FEV_1: forced expiratory volume in 1 s; BMI: body mass index; SGRQ: St. George's Respiratory Questionnaire. [#]: source: Calverley *et al.*, 2007 [10] and Vestbo *et al.*, 2004 [11]; *a recent exacerbation history is defined as an exacerbation occurring within the previous year.

SUPPLEMENTARY TABLE S2 Coefficients estimated within the exacerbation random intercept equation fit using data from TORCH[#]

Variable	Point estimate	Standard error
Intercept	–0.96	0.11
Treatment arm[¶]		
ICS/LABA	Referent	
Placebo	0.03	0.07
ICS alone	–0.12	0.07
LABA alone	0.05	0.07
Recent exacerbation history*	0.9	0.06
FEV$_1$ percent predicted		
<30% (very severe COPD)	Referent	
30–<50% (severe COPD)	–0.14	0.06
50–<80% (moderate COPD)	–0.49	0.08
>80% (non-COPD)	–0.98	0.22
Sex		
Male	–0.16	
Female	Referent	
Exacerbation history (moderate or severe, in the previous 12 months)		
0	Referent	
1	0.26	0.07
≥2	0.43	0.06
Baseline SGRQ total score		
<38	Referent	
38–<50	0.20	0.07
50–<62	0.22	0.07
≥62	0.26	0.07

ICS: inhaled corticosteroid; LABA: long-acting β$_2$-agonist; FEV$_1$: forced expiratory volume in 1 s; COPD: chronic obstructive pulmonary disease; SGRQ: St. George's Respiratory Questionnaire. [#]: source: Calverley *et al.*, 2007 [10] and Vestbo *et al.*, 2004 [11]; [¶]: it was assumed that all patients were treated with at least an ICS/LABA; *: a recent exacerbation history is defined as an exacerbation occurring within the previous year.

SUPPLEMENTARY TABLE S3 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)	0.041
Moderate COPD to Severe COPD (recent exacerbation history)	0.088
Severe COPD to Very severe COPD (no recent exacerbation history)	0.070
Severe COPD to Very severe COPD (recent exacerbation history)	0.143

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 year

FEV$_1$: forced expiratory volume in 1 s; COPD: chronic obstructive pulmonary disease.

SUPPLEMENTARY TABLE S4 Treatment effect and patient distribution across the health states defined by FEV_1 and exacerbation status at the end of the FULFIL trial (week 24, ITT population)

	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)	
	FF/UMEC/VI	**BUD/FOR**
No within-trial exacerbations		
Very severe COPD (FEV_1 percent predicted<30%)	11.0%	16.0%
Severe COPD (FEV_1 percent predicted 30–<50%)	38.9%	45.6%
Moderate COPD (FEV_1 percent predicted 50–<80%)	39.9%	25.4%
With within-trial exacerbations		
Very severe COPD (FEV_1 percent predicted<30%)	1.5%	3.9%
Severe COPD (FEV_1 percent predicted 30–<50%)	5.0%	6.2%
Moderate COPD (FEV_1 percent predicted 50–<80%)	3.2%	2.3%
Deaths	0.4%	0.7%
Mean moderate exacerbations per patient	0.11	0.15
Mean severe exacerbations per patient	0.01	0.03
Mean pneumonia per patient	0.02	0.01

FEV_1: forced expiratory volume in 1 s; ITT: intent to treat; FF: fluticasone furoate; UMEC: umeclidinium; VI: vilanterol; BUD: budesonide; FOR: formoterol; CI: confidence interval; SGRQ: St. George's Respiratory Questionnaire; RR: relative risk.

SUPPLEMENTARY TABLE S5 Summary of analysis assumptions

Detail
The patient population in the FULFIL trial is representative of the target UK COPD population, eligible for treatment with FF/UMEC/VI
Treatment effect for the reduction in exacerbations with FF/UMEC/VI is limited only to the duration of the trial
In the Markov model, exacerbation treatment effect is incorporated indirectly as a result of the shift in FEV_1 percent predicted health-state distribution
Risk of an exacerbation increases with increasing COPD severity (defined by decreasing FEV_1 percent predicted), and is higher for individuals who experienced an exacerbation during the previous year
Of all predicted exacerbations by COPD category, it is assumed that 80% are moderate and 20% are severe
Treatment discontinuation only occurs within the trial period; no further discontinuation was included after the FULFIL trial duration
Mortality rate in the EXT population (follow-up 52 weeks) for FULFIL is unknown, thus it was assumed to occur at the same rate as the ITT population (follow-up 24 weeks)
Pneumonia does not have a direct impact on mortality

UK: United Kingdom; COPD: chronic obstructive pulmonary disease; FF: fluticasone furoate; UMEC: umeclidinium; VI: vilanterol; FEV_1: forced expiratory volume in 1 s; EXT: extension; ITT: intent to treat.

SUPPLEMENTARY TABLE S6 OWSA: pre-specified upper and lower limits for pre-selected parameters, Markov model

Parameter	Base case	Lower limit	Upper limit
Utility - moderate COPD (±20%)	0.787	0.630	0.944
Utility - severe COPD (±20%)	0.750	0.600	0.900
Utility - very severe COPD (±20%)	0.647	0.518	0.776
Pneumonia disutility (±20%)	–0.011	–0.013	–0.009
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
Exacerbation rates in very severe COPD - recent exacerbation history (±20%)	1.200	0.960	1.440
Risk of mortality in very severe COPD (±20%)	8.330	6.664	9.996
Discount rates	3.5%	0.0%	5.0%
Cost BUD/FOR (±20%)	£38.00	£30.40	£45.60
Cost FF/UMEC/VI (±20%)	£49.50	£39.60	£59.40
COPD maintenance costs (±20%)			
Moderate COPD	£203	£163	£244
Severe COPD	£677	£541	£812
Very severe COPD	£2090	£1672	£2508

OWSA: one-way sensitivity analysis; COPD: chronic obstructive pulmonary disease; BUD: budesonide; FOR: formoterol; FF: fluticasone furoate; UMEC: umeclidinium; VI: vilanterol.

A recent exacerbation history is defined as an exacerbation occurring within the previous year

SUPPLEMENTARY TABLE S7 Distributions used in the PA

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
Regression parameters[+]	Multivariate normal	To capture correlation between normally distributed regression parameters
Other 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
Health-state utilities	Beta	Constrained on interval 0 and 1
QALY loss	Gamma	Constrained on interval of 0 to positive infinity

PA: probabilistic analysis; COPD: chronic obstructive pulmonary disease; QALY: quality-adjusted life year; FEV_1: forced expiratory volume in 1 s. [#]: age, height; [¶]: COPD mortality, exacerbations; [+]: FEV_1 decline, exacerbations.

SUPPLEMENTARY TABLE S8 Base-case results: EXT (lifetime horizon[#]) population and ITT subgroup populations

	EXT population[#]			Severe COPD or worse[¶]			History of exacerbations[+]		
	FF/UMEC/VI	BUD/FOR	Incremental	FF/UMEC/VI	BUD/FOR	Incremental	FF/UMEC/VI	BUD/FOR	Incremental
Outcomes									
Predicted cumulative exacerbations									
Moderate exacerbations	5.940	6.007	−0.067	5.751	5.739	0.011	5.797	5.846	−0.049
Severe exacerbations	1.478	1.615	−0.137	1.414	1.421	−0.007	1.435	1.458	−0.022
Any moderate and/or severe exacerbation	7.417	7.622	−0.205	7.165	7.160	0.005	7.232	7.304	−0.072
Total LYs (discounted)	9.643	8.977	0.666	8.409	7.916	0.493	9.725	9.121	0.604
Total QALYs (discounted)	7.054	6.411	0.643	5.982	5.512	0.470	7.242	6.671	0.571
Costs									
Maintenance	£7850	£9190	−£1340	£8871	£9784	−£913	£6296	£7377	−£1081
Moderate exacerbation	£2502	£2544	−£42	£2484	£2492	−£8	£2427	£2475	−£48
Severe exacerbation	£7054	£7552	−£497	£6955	£7008	−£52	£6823	£6989	−£166
Pneumonia	£4285	£3955	£331	£3952	£3637	£315	£4545	£4179	£365
Treatment	£5219	£3545	£1675	£4500	£3075	£1425	£5244	£3568	£1676
Discontinuation	£405	£631	−£227	£370	£587	−£217	£435	£688	−£253
Total costs	£27 316	£27 416	−£101	£27 133	£26 582	£551	£25 769	£25 276	£494
ICER (cost/LY gained)	Dominant	Referent	–	£1118	Referent	–	£817	Referent	–
ICER (cost/QALY gained)	Dominant	Referent	–	£1172	Referent	–	£864	Referent	–

EXT: extension; ITT: intent to treat; COPD: chronic obstructive pulmonary disease; FF: fluticasone furoate; UMEC: umeclidinium; VI: vilanterol; BUD: budesonide; FOR: formoterol; LY: life year; QALY: quality-adjusted life year; ICER: incremental cost-effectiveness ratio; FEV_1: forced expiratory volume in 1 s. [#]: patients treated for up to 52 weeks; [¶]: patients with FEV_1 percent predicted <50% at screening, with 24 weeks' follow-up; [+]: patients with ≥1 severe or ≥2 moderate exacerbations in the 12 months prior to randomisation.