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ORIGINAL RESEARCH

Cost-effectiveness of roflumilast as an add-on to triple inhaled therapy vs triple inhaled therapy in patients with severe and very severe COPD associated with chronic bronchitis in the UK

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Purpose: Patients with severe COPD are at high risk of experiencing disease exacerbations, which require additional treatment and are associated with elevated mortality and increased risk of future exacerbations. Some patients continue to experience exacerbations despite receiving triple inhaled therapy (ICS plus LAMA plus LABA). Roflumilast is recommended by the Global Initiative for Chronic Obstructive Lung Disease as add-on treatment to triple inhaled therapy for these patients. This cost-effectiveness analysis compared costs and quality-adjusted life-years for roflumilast plus triple inhaled therapy vs triple inhaled therapy alone, using data from the REACT and RE^{2}SPOND trials.

Patients and methods: Patients included in the analysis had severe to very severe COPD, FEV_1 <50% predicted, symptoms of chronic bronchitis and ≥2 exacerbations per year. Our model was adapted from a previously published and validated model, and the analyses conducted from a UK National Health Service perspective. A scenario analysis considered a subset of patients who had experienced at least one COPD-related hospitalization within the previous year.

Results: Roflumilast as add-on to triple inhaled therapy was associated with non-significant reductions in rates of both moderate and severe exacerbations compared with triple inhaled therapy alone. The incremental cost-effectiveness ratio (ICER) for roflumilast as add-on to triple inhaled therapy was £24,976. In patients who had experienced previous hospitalization, roflumilast was associated with a non-significant reduction in the rate of moderate exacerbations, and a statistically significant reduction in the rate of severe exacerbations. The ICER for roflumilast in this population was £7,087.

Conclusions: Roflumilast is a cost-effective treatment option for patients with severe or very severe COPD, chronic bronchitis, and a history of exacerbations. The availability of roflumilast as add-on treatment addresses an important unmet need in this patient population.

Keywords: National Health Service, National Institute for Health and Care Excellence, exacerbation rates

Introduction

COPD is characterized by persistent, often progressive, airflow limitation, with symptoms including cough, dyspnea, and sputum production. COPD is a leading cause of death worldwide, and imposes a considerable humanistic and economic burden.[1] Patients with severe COPD, defined as post-bronchodilator forced expiratory volume in 1 second (FEV_1) <50%,[2] are at particularly high risk of experiencing periods of disease exacerbation.[3] As well as requiring additional treatment, disease exacerbations

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contribute to a poor prognosis and increased mortality,[2] and are the most reliable predictor of future exacerbations, contributing to a worsened disease state.[3–5] Thus, a major part of COPD management in the more severe disease states is the treatment of exacerbations, to limit their impact and frequency.[2]

Treatment for COPD is based on bronchodilator therapy, often with a long-acting beta-2 agonist (LABA), which is also used in combination with a long-acting muscarinic antagonist (LAMA). Patients with severe or very severe COPD (defined as FEV_1 <50%) who experience exacerbations may have inhaled corticosteroids (ICS) added to their existing treatment, either in combination with LABA, or with LABA and LAMA as triple inhaled therapy.[2] Despite this, some of these patients continue to experience exacerbations, and require additional treatment. Roflumilast (AstraZeneca) is a phosphodiesterase type four inhibitor that blocks inflammatory pathways in COPD. It is recommended by the Global Initiative for Chronic Obstructive Lung Disease (GOLD) guidelines,[2] and is licensed by the European Medicines Agency,[6] as add-on maintenance treatment to bronchodilator therapy for patients with FEV_1 <50% predicted and chronic bronchitis who have had at least one exacerbation in the past year. Roflumilast is also approved by the Food and Drug Administration in the United States of America (USA) for patients with severe COPD associated with chronic bronchitis and a history of exacerbations.[7] In the United Kingdom (UK), the National Institute for Health and Care Excellence (NICE) has recently recommended roflumilast as an add-on to bronchodilator maintenance treatment for severe COPD (post-bronchodilator FEV_1 <50% predicted) in adult patients with chronic bronchitis and a history of exacerbations.[8]

The safety and efficacy of roflumilast as an add-on to ICS/LABA ± LAMA were examined in the 52-week Roflumilast and Exacerbation in patients receiving Appropriate Combination Therapy (REACT) study (NCT01329029) and the 52-week Roflumilast Effect on Exacerbations in Patients on Dual therapy (RE^2SPOND) study (NCT01443845).[9,10] Patients enrolled in both studies had severe COPD and chronic bronchitis, and had experienced at least two moderate or severe exacerbations in the past year. The primary endpoint, reduction in the rate of moderate-to-severe COPD exacerbations, was not met in either trial. A reduction in the rate of moderate-to-severe exacerbations was observed, but did not reach statistical significance.[9,10] Although the rates of adverse events were higher in the roflumilast group than in the placebo group in both trials, mortality was similar.

The objective of this analysis was to assess the lifetime costs, outcomes, and cost-effectiveness of roflumilast as an add-on to triple inhaled therapy, compared with triple inhaled therapy alone, in patients with FEV_1 <50% predicted and chronic bronchitis who continued to experience exacerbations while receiving triple inhaled therapy. Eligible patients were pooled from the intention-to-treat (ITT) populations of the REACT and RE^2SPOND studies, and the model used was adapted from a previously published and validated economic model by Samyshkin et al, 2014.[11]

Methods

Setting and patient population

This analysis compared costs and outcomes between patients with severe to very severe COPD with FEV_1 <50% predicted, symptoms of chronic bronchitis, and frequent exacerbations (≥2 per year), receiving either roflumilast maintenance treatment added on to triple inhaled therapy (ICS/LABA + LAMA), or triple inhaled therapy alone. The analysis was conducted from a UK National Health Service (NHS) and Personal Social Services perspective.

Patient-level data pooled from the ITT populations in the REACT and RE^2SPOND trials were used in this analysis. Patient baseline characteristics are shown in Table 1. Only patients who received LAMA in addition to ICS/LABA (70% of the REACT population; 47% of the RE^2SPOND population) were eligible for inclusion in this analysis. The 2018 GOLD guidelines recognize that roflumilast should be considered as an add-on to triple inhaled therapy in patients with an FEV_1 <50% predicted and chronic bronchitis, particularly if they have experienced at least one hospitalization for an exacerbation in the previous year, which represents the patient population used in this analysis.[2] This is supported by clinical data indicating that ~90% of patients who receive roflumilast in clinical practice do so as add-on to triple inhaled therapy.[12] Therefore, the data used in this analysis were from those patients who are most likely to benefit from roflumilast treatment. In total, 1,225 patients receiving roflumilast plus triple inhaled therapy and 1,215 patients receiving triple inhaled therapy alone were included in the base case analysis.

Model structure and clinical parameters

A cohort state transition (Markov) model adapted from a previous study by Samyshkin et al, 2014,[11] which examined the cost-effectiveness of roflumilast as add-on to LABA alone, was used in this analysis.[11] The model has three states: severe COPD, very severe COPD, and death. COPD severity

Table 1 Baseline characteristics in the pooled REACT/RE²SPOND population (ITT population receiving ICS/LABA + LAMA)

Characteristic	Roflumilast	Placebo
Baseline characteristics in the pooled REACT/RE²SPOND population[a]		
Population number	1,225	1,215
Proportion of patients aged ≤65 years, %	51.8	53.5
Proportion of patients aged ≥65 years, %	48.2	46.7
Proportion of men, %	70.6	68.6
Body mass index, %		
<18.5 kg/m²	5.3	5.9
18.5–<25 kg/m²	38.9	36.3
25–<30 kg/m²	30.9	34.1
≥30 kg/m²	24.9	23.7
Proportion of current smokers, %	37.3	41.2
Proportion of patients with severe COPD, %	61.3	64.8
Proportion of patients with very severe COPD, %	37.2	33.9
Proportion of patients with ≥1 prior hospitalization, %	36.2	33.3
Baseline characteristics of patients in the pooled REACT/RE²SPOND population with at least one COPD-related hospitalization[b]		
Population number	444	405
Proportion of patients aged ≤65 years, %	52.9	56.5
Proportion of patients aged ≥65 years, %	47.1	43.5
Proportion of men, %	72.7	67.2
Body mass index, %		
<18.5 kg/m²	5.9	5.9
18.5–<25 kg/m²	40.8	36.3
25–<30 kg/m²	30.2	33.3
≥30 kg/m²	23.2	24.4
Proportion of current smokers, %	44.8	48.1
Proportion of patients with severe COPD, %	56.1	60.2
Proportion of patients with very severe COPD, %	42.3	38.8
Proportion of patients with ≥1 prior hospitalization, %	100	100

Notes: [a]ITT population receiving ICS/LABA + LAMA. [b]Patients with severe COPD, who had experienced two or more exacerbations and at least one COPD-related hospitalization within the previous year, despite treatment with triple inhaled therapy.
Abbreviations: ICS, inhaled corticosteroid; ITT, intention to treat; LABA, long acting β_2-agonist; LAMA, long-acting muscarinic receptor agonist.

was defined by the GOLD airflow limitation criteria,[2] expressed as FEV_1 relative to the general population. COPD is characterized by chronic lung function decline; therefore, once patients had transitioned to the very severe state in the model, there was no possibility of this being reversed. In the base case analysis, all patients entered the model in the severe state; thus, patients could transition from severe COPD to very severe COPD, and from either COPD state to death. Key model inputs for the base case are given in Table 2.

Transition probabilities for progression from severe to very severe COPD were calculated using the estimated time taken to reach an FEV_1 of 30% predicted. The general population FEV_1 level was predicted separately for men and women,[13] using reference equations based on a previous study conducted in the USA, and actual FEV_1 was assumed to decline at a rate of 52 mL per year, based on the findings of Tantucci and Modina, 2012.[14] Transition probabilities were also estimated separately for men and women, weighted by the proportion of men and women in the model. The predicted average transition time to very severe COPD was 6.97 years, with a monthly transition probability from severe to very severe COPD of 1.2% (Figure 1).

Although roflumilast is associated with an improvement in lung function,[13] this is not included in the model base case, which adopted a common FEV_1 trajectory for both the roflumilast and placebo arms. Reductions in exacerbations in the model are therefore driven entirely by observed exacerbation rate ratios, and not by any possible effect through improved lung function.

Analysis of exacerbations

Patients could experience a moderate, a severe, or no exacerbation in each model cycle. Exacerbation rates were predicted using data from the pooled ITT populations from REACT and RE²SPOND. In these trials, a moderate exacerbation was defined as requiring treatment with oral or parenteral corticosteroids, and a severe exacerbation was defined as necessitating hospital admission or causing death.[9,10] In the

Table 2 Key model inputs for the base case

Parameter	Value
Mean FEV_1 for patients at the start of the model, %	40
Rate of moderate exacerbations in patients receiving triple inhaled therapy (95% CI)	0.84 (0.77–0.92)
Rate of severe exacerbations in patients receiving triple inhaled therapy (95% CI)	0.37 (0.32–0.43)
Rate of moderate exacerbations in patients receiving triple inhaled therapy + ROF (95% CI)	0.77 (0.70–0.85)
Rate of severe exacerbations in patients receiving triple inhaled therapy + ROF (95% CI)	0.32 (0.27–0.37)
Rate of moderate exacerbations in patients with ≥1 prior hospitalization receiving triple inhaled therapy (95% CI)	0.77 (0.65–0.91)
Rate of severe exacerbations in patients with ≥1 prior hospitalization receiving triple inhaled therapy (95% CI)	0.73 (0.60–0.89)
Rate of moderate exacerbations in patients with ≥1 prior hospitalization receiving triple inhaled therapy + ROF (95% CI)	0.66 (0.56–0.79)
Rate of severe exacerbations in patients with ≥1 prior hospitalization receiving triple inhaled therapy + ROF (95% CI)	0.48 (0.39–0.60)
FEV_1 decline per year for patients with COPD, mL (± SEM)	52 (±0.08)
Standardized mortality ratio for background mortality (excluding hospital deaths) for patients in the severe COPD state (SEM; 95% CI)[10]	2.5 (0.62; 1.4–3.9)
Standardized mortality ratio for background mortality (excluding hospital deaths) for patients in the very severe COPD state (SEM; 95% CI)[10]	3.85 (0.76; 2.5–5.5)
Hospital case fatality rates in patients aged 72 years, % (SEM)[25]	15.3 (0.09)
Utility for severe COPD (SEM; 95% CI)[a, 22]	0.75 (0.01; 0.73–0.77)
Utility for very severe COPD (SEM; 95% CI)[a, 22]	0.65 (0.03; 0.60–0.70)
Disutility for moderate exacerbation (SEM; 95% CI)[23]	–0.017 (0.002; –0.021, –0.012)
Disutility for severe exacerbation (SEM; 95% CI)[23]	–0.048 (0.009; –0.065, –0.031)
Monthly cost of ROF, £[b]	38.24
Monthly cost of ICS/LABA, £[b]	39.51
Monthly cost of LAMA, £[b]	33.97
Monthly maintenance costs for severe COPD, £[b]	32.57
Monthly maintenance costs for very severe COPD, £[b]	106.90
Average cost of moderate exacerbation, £[b]	103.85
Average cost of severe exacerbation, £[b]	1,724.43

Notes: [a]Utilities were derived using UK general population preference weights. [b]Drug costs were taken from the British National Formulary.[16]
Abbreviations: FEV_1, forced expiratory volume in 1 second; ICS, inhaled corticosteroid; LABA, long-acting β_2-agonist; LAMA, long-acting muscarinic receptor agonist; ROF, roflumilast; SEM, standard error of the mean.

cost-effectiveness model the rate of moderate or severe exacerbations was predicted using a predefined negative binomial regression model. Explanatory variables included randomized treatment, background treatment stratum (LAMA or no LAMA), trial (REACT, RE^2SPOND) and COPD severity (defined by GOLD status).

Note that the primary efficacy analysis in the REACT trial employed a Poisson regression model. This was consistent

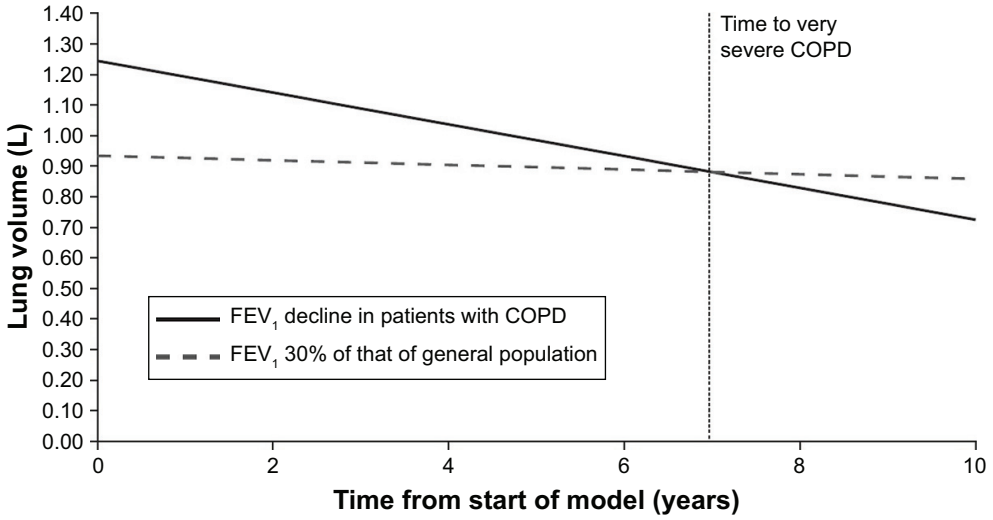

Figure 1 Calculation of average time to very severe COPD state, used to calculate transition probabilities.
Abbreviations: FEV_1, forced expiratory volume in 1 second; L, litres.

with the pivotal M2-124 and M2-125 trials and the approach to determine the sample size (following regulatory guidance). This model did not find significant differences between the groups; however, a predefined sensitivity analysis using a negative binomial regression to assess the robustness of the primary analysis showed that the effect was statistically significant.[9] A negative binomial regression model was preferred in the RE^{2}SPOND trial, and there were no significant differences between the two treatments for the primary efficacy variable.[10]

The lack of significant treatment effect for roflumilast in RE^{2}SPOND might be due to the fact that patients in this study had less severe COPD than the study population in REACT. Two key differences between the study populations suggest that there may have been a disparity in disease severity. Firstly, a lower proportion of patients in RE^{2}SPOND received triple inhaled therapy (47%) than in REACT (70%), and secondly patients were only required to have received LAMA for 3 months prior to randomization in RE^{2}SPOND, whereas patients in REACT had received LAMA for at least 12 months.

Cost-effectiveness, time horizon and discounting

Cost-effectiveness was expressed as incremental cost per quality-adjusted life year (QALY) gained. The base case time horizon was 40 years, representing a lifetime time horizon, and costs and outcomes were discounted at 3.5% per annum in line with NICE guidance.[15]

Resource use and costs

Drug costs and dosing for roflumilast, LAMA, ICS/LABA, and prednisolone (used in the treatment of moderate exacerbations), were taken from the British National Formulary (July 2016).[16] Resource use and monthly maintenance costs for severe and very severe COPD were taken from British Medical Journal (BMJ) Best Practice Guidance (2016) and previous publications,[17,18] and included General Practitioner (GP) consultations, spirometry, influenza vaccinations, and oxygen therapy. Resource use and costs associated with exacerbations were taken from BMJ Best Practice Guidance (2016), NHS reference costs, and previous publications,[17,19–21] and included GP consultations, taken as one visit for a moderate exacerbation and none for a severe exacerbation; prednisolone treatment; and, for severe exacerbations, hospital admission and ambulance costs. Full details of costs and resource use are included in Tables S1 and S2.

Utilities

Health-related quality of life weights (utilities) associated with COPD health states were taken from the study of Rutten-van Mölken et al, 2006,[22] which sampled 1,235 patients in 13 countries using the 5-dimension EuroQoL questionnaire (EQ-5D) and applied the UK general population tariff. All patients in this study had FEV_1 less than 70%, and approximately 49% of the population had severe or very severe COPD. Decrements (disutilities) associated with exacerbations were taken from Hoogendoorn et al, 2011, based on patient-reported EQ-5D scores using the UK tariff.[23]

Mortality

Within the model, death could occur as a consequence of a severe exacerbation or from a cause not related to COPD (background mortality). Mortality due to a severe exacerbation was obtained from the UK National COPD Audit Report,[24] with an adjustment for patient age.[11] Background mortality for severe and very severe COPD was calculated using age- and sex-specific UK life tables and standardized mortality ratios as employed in the previous study by Samyshkin et al, 2014.[11] We also included a 90-day post-COPD hospitalization mortality risk of 15.3% (Connolly et al, 2006).[25] This modification arose in the context of the recent appraisal of roflumilast by NICE. Rather than modify the model to accommodate tunnel states (during which additional mortality could apply) in the post-discharge period, this was applied as an immediate mortality penalty at the point of exacerbation.

Treatment-emergent adverse events

Rates of treatment-emergent severe adverse events were obtained from the ITT populations of the REACT and RE^{2}SPOND trials. Adverse events occurred in approximately 16% of patients, and were comparable between treatment groups. The most frequently reported grade three adverse events were pneumonia, diarrhea, nausea, and weight decrease. The incidence of pneumonia was similar between the roflumilast and placebo groups, but comparatively more patients in the roflumilast group reported nausea, weight decrease, and abdominal pain.

Uncertainty

Probabilistic sensitivity analyses (10,000 iterations) were performed to assess uncertainty in the model inputs for the base case scenario. One-way deterministic sensitivity analyses were also used to assess the impact of varying individual parameters. Probability distributions for relevant model inputs are given in Table S3.

Two scenario analyses were also performed:

Post-hospitalization mortality

Scenario analyses were conducted to assess the impact of mortality assumptions on the incremental cost-effectiveness

ratio (ICER) by varying mortality risk. Mortality risks were taken from Roberts et al, 2002 (90-day post-hospitalization mortality risk of 13.7%),[26] Soler-Cataluna et al, 2005 (permanent post-hospitalization hazard ratio of 2.235),[27] Hartl et al, 2016 (90-day post-hospitalization mortality risk of 10.8%),[28] and Wildman et al, 2009 (180-day post-hospitalization mortality risk of 37.9%),[29] termed scenarios 1–4 respectively.

Patients with severe COPD and prior hospitalization

A second scenario analysis assessed the effect of roflumilast in a subgroup of patients with severe COPD, who had experienced two or more exacerbations and at least one COPD-related hospitalization within the previous year, despite treatment with triple inhaled therapy. Data were available for 444 patients randomized to roflumilast and 405 patients randomized to placebo. Baseline characteristics for this population are shown in Table 1. Treatment-emergent adverse events were reported by 23% of this population: 20.5% of patients receiving roflumilast and 24.9% of patients receiving placebo. The most frequently reported adverse effect was pneumonia, followed by diarrhea and nausea.

Software

The model in our analysis was developed in Microsoft Excel. Regression analyses were performed in SAS 9.2 (SAS Institute, Cary, NC, USA).

Results

Exacerbation rates in the REACT/RE²SPOND pooled population

Exacerbation rates for the base case analysis are shown in Table 3. It was estimated that roflumilast as an add-on to triple inhaled therapy was associated with a non-significant reduction in the combined rate of moderate or severe exacerbations, compared with triple inhaled therapy alone (rate ratio [RR]: 0.89, 95% CI: 0.78–1.00, *P*=0.056, 11% reduction). When considered separately, estimates for both moderate (RR: 0.92, 95% CI: 0.81–1.05, *P*=0.220; 8% reduction) and severe exacerbation rates (RR: 0.86, 95% CI: 0.70–1.05, *P*=0.137; 14% reduction) were also lower with roflumilast than with triple therapy alone, although without statistical significance.

Cost-effectiveness in the REACT/RE²SPOND pooled population (base case)

In the full patient population, triple inhaled therapy+ roflumilast accumulated total costs of £19,524 and 5.23 QALYs, whereas triple inhaled therapy alone accumulated costs of £16,016 and 5.09 QALYs (Table 4). This equated to an additional 0.14 QALYs at an incremental cost of £3,508 for triple inhaled therapy+ roflumilast, generating a deterministic ICER of £24,976. In probabilistic analyses, triple inhaled therapy+ roflumilast accumulated an additional 0.14 QALYs at an incremental cost of £3,528, generating an ICER of £24,682 (Table 4 and Figure 2). Triple inhaled therapy had a 15% probability of being cost-effective at a threshold of £20,000 per QALY gained, increasing to 81% at £30,000 per QALY gained (Figure 2).

Deterministic sensitivity analyses showed that the most influential parameter in the model was the starting age of the patient. Other influential parameters were the transition from the severe to very severe state in those receiving tripled inhaled therapy alone and the discount rate. The ICER remained under £35,000 per QALY gained for all sensitivity analyses (Figure 3).

Table 3 Exacerbation rates in the pooled REACT and RE²SPOND population (base case) and in the scenario analyses

Exacerbation severity	Exacerbation rate (95% CI)		Rate ratio (triple inhaled therapy + ROF vs triple inhaled therapy alone) (95% CI)	*P*-value
	Triple inhaled therapy + ROF	Triple inhaled therapy alone		
Base case analysis				
Moderate or severe	1.21 (1.11–1.33)[a]	1.37 (1.26–1.49)[b]	0.89 (0.78–1.00)	0.056
Moderate	0.77 (0.70–0.85)[a]	0.84 (0.77–0.92)[b]	0.92 (0.81–1.05)	0.220
Severe	0.32 (0.27–0.37)[a]	0.37 (0.32–0.43)[b]	0.86 (0.70–1.05)	0.137
Scenario analysis in patient population with prior hospitalization				
Moderate or severe	1.28 (1.10–1.49)[c]	1.72 (1.49–1.99)[d]	0.74 (0.60–0.92)	0.005
Moderate	0.66 (0.56–0.79)[c]	0.77 (0.65–0.91)[d]	0.86 (0.68–1.09)	0.214
Severe	0.48 (0.39–0.60)[c]	0.73 (0.60–0.89)[d]	0.66 (0.49–0.88)	0.004

Notes: [a]n=1,225; [b]n=1,215; [c]n=444; [d]n=405.
Abbreviation: ROF, roflumilast.

Table 4 Costs and QALYs in the pooled REACT and RE²SPOND population (base case) and in the scenario analyses

Scenario (where applicable)	Treatment group	Total costs, £	Total QALYs	Incremental costs, £	Incremental QALYs	ICER, £ per QALY gained
Base case (deterministic)						
	Triple inhaled therapy + ROF	19,524	5.23			
	Triple inhaled therapy	16,016	5.09	3,508	0.14	24,976
Sensitivity analysis of the base case (probabilistic)						
	Triple inhaled therapy + ROF	19,599	5.25			
	Triple inhaled therapy	16,071	5.11	3,528	0.14	24,682
Scenario analyses varying post-hospitalization mortality (deterministic)						
Scenario 1 Roberts et al (2002)[26]	Triple inhaled therapy + ROF	19,883	5.31			
	Triple inhaled therapy	16,358	5.17	3,525	0.13	26,526
Scenario 2 Soler-Cataluña et al (2005)[27]	Triple inhaled therapy + ROF	17,606	4.82			
	Triple inhaled therapy	14,509	4.72	3,097	0.10	31,202
Scenario 3 Hartl et al (2016)[28]	Triple inhaled therapy + ROF	20,578	5.46			
	Triple inhaled therapy	17,027	5.34	3,552	0.12	30,349
Scenario 4 Wildman et al (2009)[29]	Triple inhaled therapy + ROF	15,760	4.38			
	Triple inhaled therapy	12,545	4.18	3,214	0.20	16,293
Scenario analysis in patient population with prior hospitalization (deterministic)						
	Triple inhaled therapy + ROF	20,173	5.16			
	Triple inhaled therapy	16,773	4.68	3,401	0.48	7,087

Abbreviations: ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life year; ROF, roflumilast.

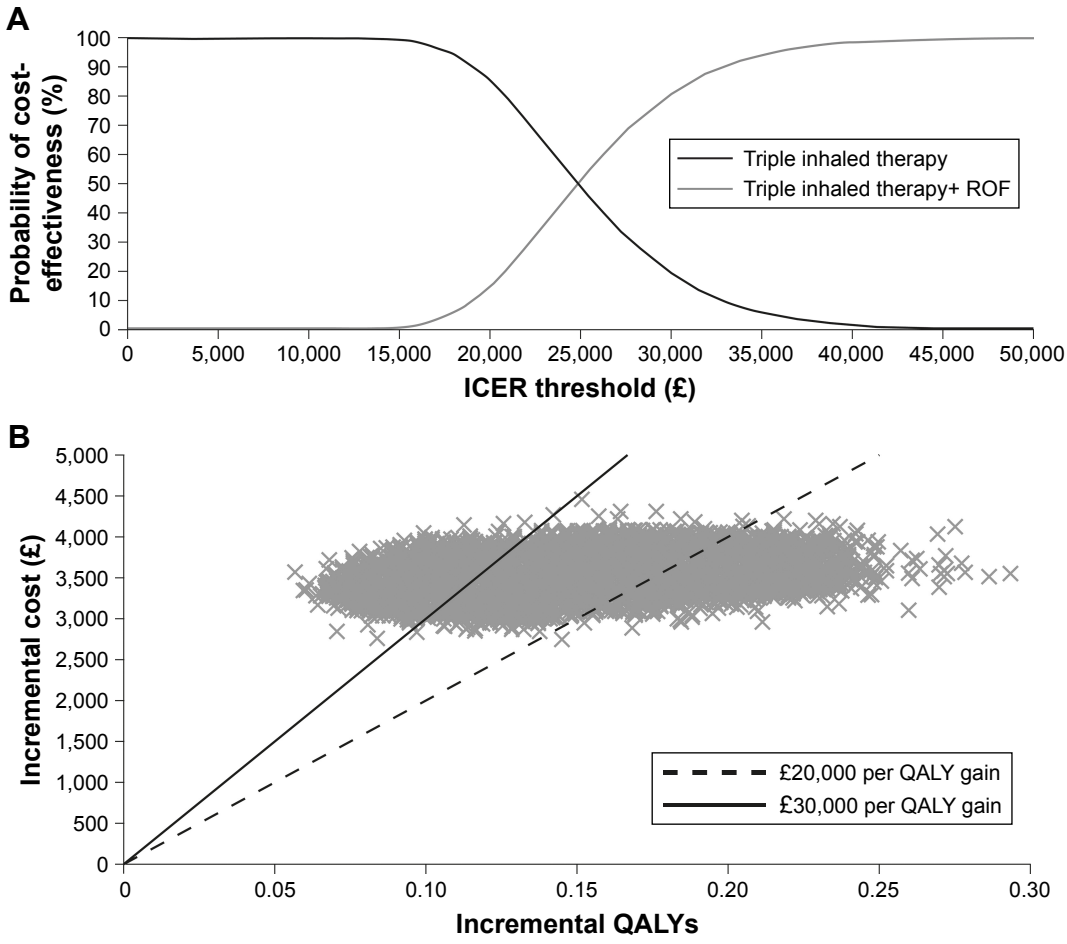

Figure 2 Probabilistic sensitivity analyses for the base case scenario.
Note: (**A**) Cost-effectiveness acceptability curve and (**B**) incremental cost-effectiveness scatter plot.
Abbreviations: ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life year; ROF, roflumilast.

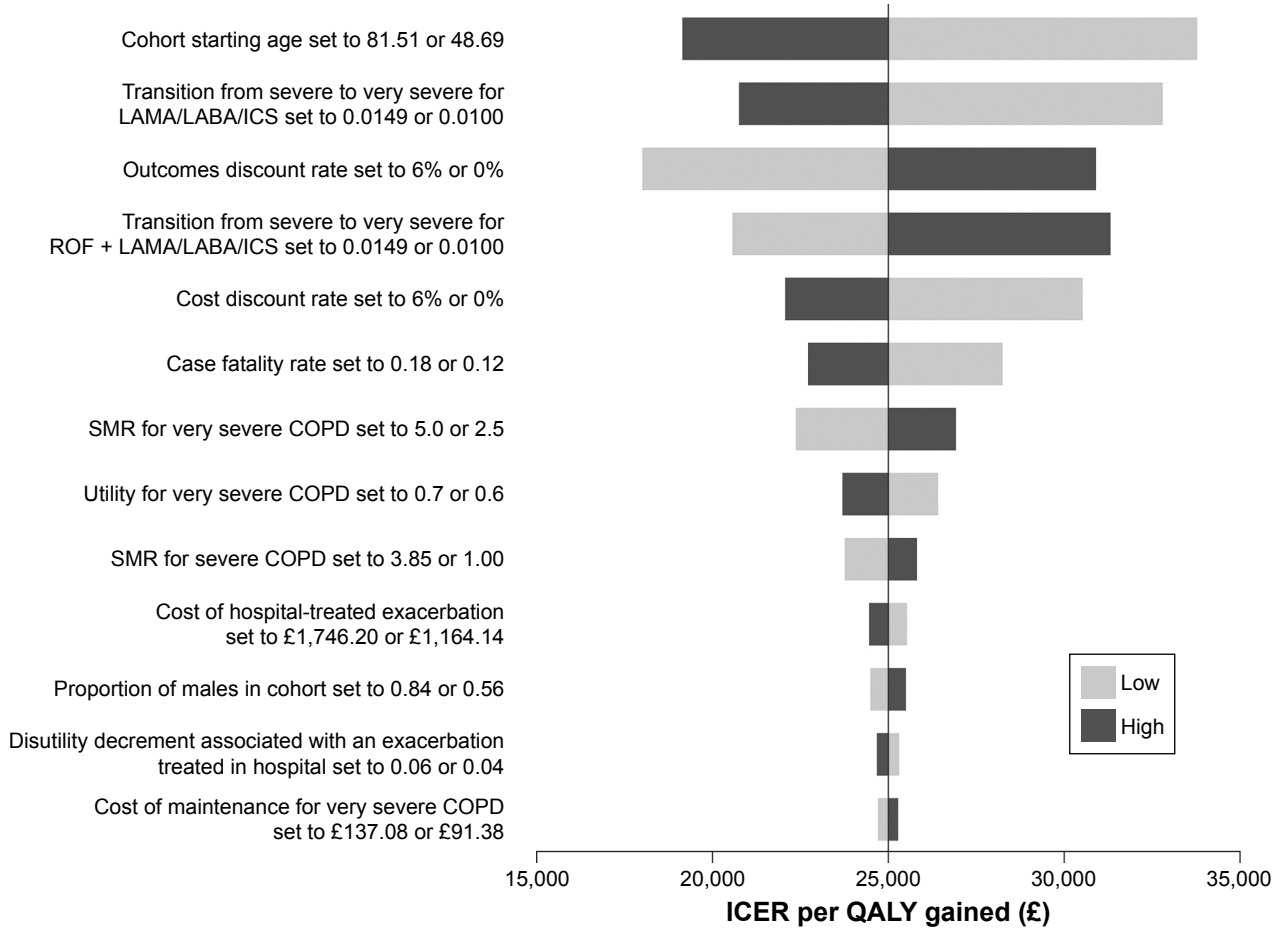

Figure 3 Tornado diagram for base case one-way sensitivity analysis.
Abbreviations: ICS, inhaled corticosteroids; LABA, long-acting beta-2 agonist; LAMA, long-acting muscarinic antagonist; SMR, standardized mortality rate; ROF, roflumilast.

Scenario analyses varying the assumptions made for post-hospitalization mortality

The ICERs generated for four populations using different post-hospitalization mortality assumptions are shown in Table 4. The lowest ICER generated was £16,293 in scenario 4, using the 180-day post-hospitalization mortality rate in Wildman et al, 2009,[29] and the highest ICER generated was £31,202 in scenario 2, using the permanent post-hospitalization hazard ratio in Soler-Cataluna et al, 2005.[27]

Scenario analysis including a subpopulation of patients with prior hospitalization

Exacerbation rates

In the patient population with prior hospitalization it was estimated that, in comparison to placebo, the addition of roflumilast to triple inhaled therapy was associated with a significant reduction in the combined rate of moderate or severe exacerbations (RR: 0.74, CI: 0.60–0.92, *P*=0.005; 26% reduction; Table 3). In this analysis, the addition of roflumilast to triple inhaled therapy was also associated with a statistically significant reduction in the rate of severe exacerbations (RR: 0.66, CI: 0.49–0.88, *P*=0.004; 34% reduction), and a non-statistically significant reduction in the rate of moderate exacerbations (RR: 0.86, CI: 0.68–1.09, *P*=0.214, 14% reduction).

Cost-effectiveness analysis

When all patients who entered the model had experienced prior hospitalization due to COPD, triple inhaled therapy+ roflumilast was associated with an additional 0.48 QALYs at an incremental cost of £3,401, generating an ICER of £7,087 (Table 4).

Discussion

Roflumilast as an add-on to triple inhaled therapy was found to be cost-effective for the treatment of patients in the UK with severe to very severe COPD, chronic bronchitis, and

a history of exacerbations, compared with triple inhaled therapy alone. This analysis formed part of the submission to NICE to support the reimbursement of roflumilast, following which NICE updated its guidance (Technology Appraisal guidance 461 [TA461]) to recommend the use of roflumilast in England and Wales as an add-on to triple inhaled therapy for patients with severe COPD and a history of two or more exacerbations in the previous 12 months despite receiving triple inhaled therapy.

This analysis is the first to assess exacerbation rates and cost-effectiveness specifically in a patient population receiving roflumilast in addition to triple inhaled therapy. Although no statistically significant interaction was found between roflumilast and the use of LAMA in addition to ICS/LABA on exacerbation rate, patients receiving concomitant LAMA were pre-specified as a subgroup prior to the unblinding of both the REACT and RE^{2}SPOND trials, justifying the use of this population in our analysis. The analysis was conducted using a de novo economic model based on a previously published and validated model by Samyshkin et al, 2014.[11] Although previous analyses also used data from the REACT[9] and RE^{2}SPOND[10] trials, they included a mixed population of patients receiving roflumilast as an add-on to ICS/LABA with or without concomitant LAMA. In our analysis, roflumilast as add-on to triple inhaled therapy was associated with a reduction in the rate of moderate/severe COPD disease exacerbations compared with triple inhaled therapy alone; the *P*-value for this comparison was 0.056, indicating that the difference between groups is just outside the boundaries of conventional statistical significance. The deterministic ICER for roflumilast was £24,976 per QALY gained, and probabilistic analyses generated an ICER of £24,682.

The earlier analysis by Samyshkin et al, 2014 examined the cost-effectiveness of roflumilast as add-on treatment to ICS/LABA in a patient population with chronic bronchitis and a history of exacerbations, using data from the pivotal M2-124 and M2-125 trials, and reported an ICER of £19,505 per QALY gained for roflumilast as add-on therapy.[11] The model structure used by Samyshkin et al, 2014, formed the basis of the model in our study; however, there were important differences between the models, not limited to the alternative clinical evidence bases. Although exacerbation case-fatality was an important feature in Samyshkin et al, 2014, and the general mortality risk in patients with COPD relative to the general population was incorporated in the model, mortality in the period following hospital discharge was not addressed. During the recent NICE appraisal of roflumilast, an interest was expressed in considering post-discharge mortality in the model. We therefore modified the model to incorporate a 90-day post-hospitalization mortality risk. Our model also used different utility values from those in the previous study, and adopted a slightly longer time horizon. A reconciliation with the original model was successfully performed, however, and indicated that the models were comparable.

The effect of roflumilast in improving lung function was not incorporated in our model, which may have meant that the treatment benefit of roflumilast was underestimated. Furthermore, the model included the assumption that the occurrence of an exacerbation did not affect FEV_1 or increase the probability of future exacerbations, meaning that the true impact of exacerbations may also have been underestimated. Therefore, the treatment effect and cost-effectiveness of roflumilast generated by our analyses may be conservative estimates.

The results of scenario analyses indicated that varying the post-hospitalization mortality risk incorporated into the model impacts the ICER generated. As the post-hospitalization mortality assumption used in the base case analysis may be an underestimate of mortality, the ICER generated in this study may be a conservative estimate of cost-effectiveness.

In the scenario analysis in which all patients had previously experienced hospitalization following an exacerbation, roflumilast as an add-on to triple therapy was associated with a significant reduction in exacerbation rates compared with triple therapy alone. Roflumilast as add-on to triple therapy was also considered a cost-effective treatment option. Hospitalizations following an exacerbation are associated with a poor long-term prognosis, higher mortality, and increased resource use.[2] Furthermore, the incidence of an exacerbation is itself considered to perpetuate future exacerbations, leading to a further decline in lung function and a worsened health state.[4] This indicates that roflumilast is cost-effective in a patient population that may be at a particularly high risk of adverse outcomes.

Conclusion

In this analysis, roflumilast as an add-on to triple inhaled therapy was associated with a reduction in both moderate and severe exacerbations, and was a cost-effective option when compared with triple inhaled therapy alone. This analysis formed the basis of the submission to NICE, which has since made a positive recommendation for the use of roflumilast as an add-on to triple inhaled therapy in patients with severe COPD, chronic bronchitis, and a history of exacerbations.[8] Disease exacerbations can impose a considerable burden on

individuals with COPD, resulting in reduced quality of life, elevated risk of future exacerbations and increased mortality. Therefore, the availability of a new add-on treatment shown to reduce exacerbation rates addresses an important unmet need for patients in this subgroup.

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Disclosures

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References

1. World Health Organization. Chronic obstructive pulmonary disease (COPD). *Fact sheet*. 2016. Available from: http://www.who.int/mediacentre/factsheets/fs315/en/. Accessed June 2017.
2. Global Initiative for Chronic Obstructive Lung Disease. *Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease – 2018*. Available from: http://goldcopd.org/wp-content/uploads/2017/11/GOLD-2018-v6.0-FINAL-revised-20-Nov_WMS.pdf. Accessed December 2017.
3. Hurst JR, Vestbo J, Anzueto A, et al. Susceptibility to exacerbation in chronic obstructive pulmonary disease. *N Engl J Med*. 2010;363(12):1128–1138.
4. Hurst JR, Donaldson GC, Quint JK, Goldring JJ, Baghai-Ravary R, Wedzicha JA. Temporal clustering of exacerbations in chronic obstructive pulmonary disease. *Am J Respir Crit Care Med*. 2009;179(5):369–374.
5. Suissa S, Dell'aniello S, Ernst P. Long-term natural history of chronic obstructive pulmonary disease: severe exacerbations and mortality. *Thorax*. 2012;67(11):957–963.
6. European Medicines Agency. Roflumilast. *Summary of Product Characteristics 18 November 2016*. Available from: http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/001179/WC500095209.pdf. Accessed June 2017.
7. Food and Drug Administration. *Daliresp (roflumilast) highlights of prescribing information*; 2011. Available from: https://www.accessdata.fda.gov/drugsatfda_docs/label/2013/022522s003lbl.pdf. Accessed June 2017.
8. National Institute for Health and Care Excellence. *Roflumilast for treating chronic obstructive pulmonary disease*; *2017*. Available from: https://www.nice.org.uk/guidance/ta461. Accessed August 27, 2018.
9. Martinez FJ, Calverley PM, Goehring UM, Brose M, Fabbri LM, Rabe KF. Effect of roflumilast on exacerbations in patients with severe chronic obstructive pulmonary disease uncontrolled by combination therapy (REACT): a multicentre randomised controlled trial. *Lancet*. 2015;385(9971):857–866.
10. Martinez FJ, Rabe KF, Sethi S, et al. Effect of Roflumilast and Inhaled Corticosteroid/Long-Acting β2-Agonist on Chronic Obstructive Pulmonary Disease Exacerbations (RE(2)SPOND). A Randomized Clinical Trial. *Am J Respir Crit Care Med*. 2016;194(5):559–567.
11. Samyshkin Y, Kotchie RW, Mörk AC, Briggs AH, Bateman ED. Cost-effectiveness of roflumilast as an add-on treatment to long-acting bronchodilators in the treatment of COPD associated with chronic bronchitis in the United Kingdom. *Eur J Health Econ*. 2014;15(1):69–82.
12. National Institute for Health and Care Excellence. *Appraisal consultation document*. *Roflumilast for treating chronic obstructive pulmonary disease*. *January 2017*. Available from: https://www.nice.org.uk/guidance/GID-TA10062/documents/appraisal-consultation-document. Accessed June 2017.
13. Crapo RO, Morris AH, Gardner RM. Reference spirometric values using techniques and equipment that meet ATS recommendations. *Am Rev Respir Dis*. 1981;123(6):659–664.
14. Tantucci C, Modina D. Lung function decline in COPD. *Int J Chron Obstruct Pulmon Dis*. 2012;7:95–99.
15. National Institute for Health and Care Excellence. *Guide to the methods of technology appraisal*; 2013. Available from: https://www.nice.org.uk/process/pmg9/chapter/foreword. Accessed June 2017.
16. Joint Formulary Committee. *British National Formulary*; 2016.
17. British Medical Journal. *Best Practice*. *COPD*. 2016. Available from: http://bestpractice.bmj.com/best-practice/monograph/7.html. Accessed June 2017.
18. 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(1):32–46.
19. Curtis L, Burns A. *Unit costs of health and social care. Canterbury: personal social services research unit.*; 2015. Available from: http://www.pssru.ac.uk/project-pages/unit-costs/2015/. Accessed June 2017.
20. Department of Health. *NHS reference costs 2014–2015*. Available from: https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/477919/2014-15_Reference_costs_publication.pdf. Accessed December 2017.
21. Thomas M, Radwan A, Stonham C, Marshall S. COPD exacerbation frequency, pharmacotherapy and resource use: an observational study in UK primary care. *COPD*. 2014;11(3):300–309.
22. 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(4):1117–1128.
23. Hoogendoorn M, Hoogenveen RT, Rutten-van Mölken MP, Vestbo J, Feenstra TL. Case fatality of COPD exacerbations: a meta-analysis and statistical modelling approach. *Eur Respir J*. 2011;37(3):508–515.
24. National COPD Audit Programme. *National COPD Audit Programme*. *COPD: Who cares matters National Chronic Obstructive Pulmonary Disease (COPD) Audit Programme: Clinical audit of COPD exacerbations admitted to acute units in England and Wales 2014*. *National clinical audit report*; 2015. Available from: http://www.hqip.org.uk/public/cms/253/625/24/77/COPD%20National%20audit%20report%20-%20exacerbations%20-%202015.PDF?realName=zTtPO9.pdf. Accessed August 27, 2018.

25. Connolly MJ, Lowe D, Anstey K, et al. Admissions to hospital with exacerbations of chronic obstructive pulmonary disease: Effect of age related factors and service organisation. *Thorax*. 2006;61(10):843–848.
26. Roberts CM, Lowe D, Bucknall CE, Ryland I, Kelly Y, Pearson MG. Clinical audit indicators of outcome following admission to hospital with acute exacerbation of chronic obstructive pulmonary disease. *Thorax*. 2002;57(2):137–141.
27. Soler-Cataluña JJ, Martínez-García MA, Román Sánchez P, Salcedo E, Navarro M, Ochando R. Severe acute exacerbations and mortality in patients with chronic obstructive pulmonary disease. *Thorax*. 2005;60(11):925–931.
28. Hartl S, Lopez-Campos JL, Pozo-Rodriguez F, et al. Risk of death and readmission of hospital-admitted COPD exacerbations: European COPD Audit. *Eur Respir J*. 2016;47(1):113–121.
29. Wildman MJ, Sanderson CF, Groves J, et al. Survival and quality of life for patients with COPD or asthma admitted to intensive care in a UK multicentre cohort: the COPD and Asthma Outcome Study (CAOS). *Thorax*. 2009;64(2):128–132.

Supplementary materials

Table S1 Drug costs used in the model

Drug	Pack size	Pack cost	Cost per dose
Roflumilast			
Roflumilast 500 µg	30	£37.71	£1.26
Roflumilast 500 µg	90	£113.14	£1.26
Average cost			
LAMA			
Tiotropium bromide 18 µg	30	£33.50	£1.12
ICS/LABA			
Budesonide/formoterol fumerate dihydrate (200/6) (x2)	120	£38.00	£0.63
Budesonide/formoterol fumerate dihydrate (400/12)	60	£38.00	£0.63
Fluticasone propionate/salmetrol 500	60	£40.92	£0.68
Average cost (x2)[a]			£1.30
Prednisolone[b]			
Prednisolone 5 mg	28	£1.24	£0.04
Prednisolone 25 mg	56	£75.00	£1.34
Combined cost (30 mg dose)			£1.38
Monthly drug costs			
Drug	**Average cost per pill/tablet**	**Days of treatment**	**Cost per month**
Roflumilast	£1.26	30.42[c]	£38.24
LAMA	£1.12	30.42[c]	£33.97
ICS/LABA	£1.30	30.42[c]	£39.51
Prednisolone 30 mg	£1.38	7	£9.69
Prednisolone 30 mg	£1.38	14	£19.37

Notes: [a]Unit costs doubled to ensure correct dosage. [b]Lowest bill burden for patients via this combination. [c]Number of days in each model cycle equivalent to 365/12.
Abbreviations: ICS, inhaled corticosteroid; LABA, long-acting beta-2 agonist; LAMA, long-acting muscarinic receptor antagonist.

Table S2 Costs associated with COPD maintenance and exacerbations

Maintenance costs							
Component	**Resource use (severe COPD)**	**Resource use (very severe COPD)**	**Cost per use**	**Cost per month (severe COPD)**	**Cost per month (very severe COPD)**	**Resource use source**	**Cost source**
GP consultations, per year (per month, SEM)	2 (0.17, 0.05)	2 (0.17, 0.05)	£44.00	£7.33	£7.33	BMJ Best Practice (2016)[17]	PSSRU (2015)[19]
Spirometry, days per year (days per month)	2 (0.17, 0.001)	4 (0.33, 0.03)	£50.05[a]	£8.34	£16.68	Oostenbrink et al (2005)[18]	Samyshkin et al (2014)[11]
Influenza vaccination, % of patients (per month, SEM)	75 (6.25, 0.01)	75 (6.25, 0.01)	£6.29	£0.39	£0.39	Oostenbrink et al (2005)[18]	BNF (July 2016)[16]
Oxygen therapy, days per month (SEM)	1.22 (0.23)	6.08 (1.04)	£13.56[b]	£16.50	£82.49	Oostenbrink et al (2005)[18]	Oostenbrink et al (2005)[18]
Total monthly cost				**£32.57**	**£106.90**		

Exacerbation costs					
Component	**Mean value**	**Cost per use**	**Cost per exacerbation**	**Resource use reference**	**Cost reference**
Moderate exacerbations					
Excess GP consultations, per year (SEM)	2.03 (0.61)	£44.00 (£9.76)	£89.32	BMJ Best Practice (2016)[17] Thomas et al (2014)[21]	PSSRU (2015)[19]
Prednisolone (7 days) (% of patients)	50	£9.69	£4.84	Assumption[c]	BNF (July 2016)[16]
Prednisolone (14 days) (% of patients)	50	£19.37	£9.69	Assumption[c]	BNF (July 2016)[16]
Total cost			**£103.85**		
Severe exacerbations					
Excess GP consultations, per year (SEM)	8.03 (2.42)	£44.00 (£9.76)	£353.32	BMJ Best Practice (2016)[17] Thomas et al (2014)[21]	PSSRU (2015)[19]
Hospital admission (% of patients)	100	£1,183.06 (£102.99)	£1,183.06	By definition	NHS reference costs (DZ65)[d]
Ambulance transport (% of patients)	90	£223.02 (£15.22)	£209.72	Assumption	NHS reference costs (ASS02)
Total cost			**£1,724.43**		

Notes: [a]Indexed to 2015. [b]Indexed to 2015 and converted at PPP exchange rate. [c]Assumed that 50% of patients will receive treatment with prednisolone for 7 days and 50% for 14 days when they have had a moderate exacerbation. [d]Weighted average of non-elective short stay and long stay.
Abbreviations: BMJ, British Medical Journal; BNF, British National Formulary; GP, general practitioner; NHS, National Health Service; PPP, Purchasing Power Parity; PSSRU, Personal Social Services Research Unit.

Table S3 Probability distributions used in probabilistic sensitivity analyses

Parameter	**Distribution**
FEV_1 decline per annum	Gamma
Covariates in the exacerbation regression equations	Normal
Rates of treatment-emergent adverse events and treatment-emergent severe adverse events	Beta
Resource use, except prednisolone use, hospital admission and ambulance transport	Beta or gamma
Unit costs, except spirometry, influenza vaccination and oxygen therapy	Gamma
COPD health state utilities and COPD exacerbation disutilities	Beta
Standardized mortality ratios	Gamma
Case fatality rate for severe exacerbations	Beta

Note: For parameterization, alpha and beta were calculated from the mean and standard error for all parameters except covariates in the exacerbation regression equations, for which a covariance matrix was used.
Abbreviation: FEV_1, forced expiratory volume in 1 second.