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Cost-Effectiveness Analysis of Triple Therapy with Budesonide/ Glycopyrronium/ Formoterol Fumarate versus Dual Therapy in Patients with Chronic Obstructive Pulmonary Disease in Spain

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Objective: To evaluate the cost-effectiveness of Budesonide/Glycopyrronium/Formoterol (BUD/GLY/FOR) versus LAMA/LABA and ICS/LABA, respectively, in patients with moderate to severe COPD, from the Spanish National Healthcare System (NHS) perspective.

Methods: A lifetime Markov model with monthly cycle length was developed with baseline and treatment effect data from ETHOS clinical trial, together with utility values from literature and Spanish healthcare resource costs (€, 2021). A 3% annual discount rate was used for costs and benefits. The model comprised ten health states: nine forced expiratory volume in 1 second (FEV1)-related, which were divided by three levels of severity: moderate (FEV1 ≥50% and <80%); severe (FEV1 ≥30% and <50%) and very severe (FEV1 <30%) and a death state. Each FEV1-health state was divided into no exacerbation, moderate exacerbation, and severe exacerbations. An expert panel validated data and assumptions. Outcomes were measured as incremental cost per exacerbation avoided, per life year (LY) gained, and per quality-adjusted life-year (QALY) gained (ICUR). One-way (OWSA), scenario, and probabilistic sensitivity analyses (PSA) were performed.

Results: According to this cost-effectiveness analysis based on a Markov model, BUD/GLY/FOR was associated with a lower totals exacerbation per patient (12.80) compared to LAMA/LABA (13.36) and ICS/LABA (13.23) and higher LYs (10.32 vs 10.14 and 10.06, respectively) and QALYs (7.55 vs 7.41 and 7.32, respectively). The incremental costs were €850.95, and €2422.26, respectively, per exacerbation avoided, €2733.38 and €4111.15, respectively, per LY gained and €3461.19 and €4545.24 per QALY gained. OWSA showed that the model was most sensitive to the costs of treatments following discontinuation, but the ICUR remained below the cost-effectiveness threshold of €25,000 per QALY gained. In the PSA, the probability of BUD/GLY/FOR being cost-effective was 91.32% vs LAMA/LABA and 99.29% vs ICS/LABA.

Conclusion: BUD/GLY/FOR is a cost-effective treatment strategy for Spanish NHS patients with COPD compared to dual therapies.

Keywords: COPD, economic evaluation, exacerbation, inhaled bronchodilator, inhaled corticosteroid, single-inhaler triple therapy

Introduction

Chronic obstructive pulmonary disease (COPD) is one of the top three causes of death worldwide.[1] There is currently no cure for COPD, so treatment can help slow the progression of the condition and control the symptoms.[2] COPD is a chronic lung disease affecting men and women worldwide, characterized by persistent respiratory symptoms and airflow limitation due to airway and/or alveolar abnormalities.[1,3] Lung functional abnormalities lead to a limitation of the airflow, which could destroy parts of the mucus, blocking the airways and inflaming and swelling the airway lining.[3] Common symptoms of COPD include breathlessness, difficulty

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breathing, chronic cough, dyspnea, cough or sputum production, and fatigue.[1,3] These symptoms commonly lead to a reduction of quality of life due to the difficulties in developing normal activities, occasioned by breathlessness and acute worsening of respiratory symptoms.[3] COPD is a leading cause of morbidity and mortality and induces a substantial and increasing social and economic burden[1] with a considerable prevalence of 11.8% of adults over 40 years in 2019 and with a mortality of 26.8 deaths per 100,000 inhabitants in 2020.[4,5]

As a chronic and progressive disease, COPD is associated with significant concomitant chronic pathologies in most patients, which increase associated morbidity and mortality, creating a higher economic impact.[1] COPD represents one of the pathologies with the most important economic burden for the Spanish healthcare system, reaching 3000 million euros (€, 2011) per year.[6] The annual cost of COPD to the healthcare system is €3238 (~91%) per patient, with indirect costs amounting to €300 (~9%) per patient, bringing the total societal cost of the disease to €3538 per patient per year. Among the direct healthcare costs, hospitalizations caused by exacerbations account for the most significant proportion of expenditure, around 70–80%[7]. Mortality increases with the frequency of severe exacerbations, that could generate a 4.1 times greater mortality risk compared to patients with stable COPD, particularly if these require a hospital admission.[8]

The major objectives of COPD treatment are the reduction of disease symptoms, the reduction of the frequency and severity of exacerbations, and the improvement of the quality of life and patient survival.[9] Long-acting inhaled bronchodilator medications are recommended as initial maintenance therapy for many patients with COPD. These medications include long-acting muscarinic antagonists (LAMA) and long-acting β2-agonists (LABA). Combinations of long-acting bronchodilator agents (LAMA/LABA) and inhaled corticosteroids (ICS) combined with LABA (ICS/LABA) are also used as initial or follow-up therapy in patients with more severe symptoms or at risk of COPD exacerbations.[10] For patients who remain symptomatic despite dual therapy (a combination of ICS/LABA or LAMA/LABA) and are at high risk of exacerbations, the GOLD and the Spanish COPD guidelines recommend a triple combination of ICS/LAMA/LABA.[9,11]

ETHOS trial (Efficacy and Safety of Triple Therapy in Obstructive Lung Disease) was a randomized, double-blind, multi-centred, parallel-group study to assess the efficacy and safety of the ICS/LAMA/LABA triple-fixed therapy budesonide/glycopyrrolate/formoterol fumarate (BUD/GLY/FOR) relative to GLY/FOR (LAMA/LABA) and BUD/FOR (ICS/LABA) in over 52 weeks in patients with moderate to very severe COPD.[12] BUD/GLY/FOR are well-established pharmacological agents in the treatment of COPD, combined in a single metered-dose inhaler (MDI) device. BUD/GLY/FOR showed benefits over dual therapy with a LAMA/LABA or ICS/LABA combination concerning the annual rate of moderate or severe COPD exacerbations, symptoms, and health-related quality of life.[12]

The prevalence and burden of COPD are projected to increase over the coming decades due to continued exposure to COPD risk factors, disease characteristics, and aging of the population,[1] so having comparative evidence regarding the economic impacts of these therapies will be desirable. The present analysis aimed at assessing the cost-effectiveness of triple fixed-dose therapy BUD/GLY/FOR compared with dual therapies LAMA/LABA and ICS/LABA in patients with moderate to severe COPD, from the Spanish National Healthcare System (NHS) perspective.

Methods

Model Overview

Given that COPD is a chronic progressive disease, a semi-Markov model was developed to estimate the costs and outcomes of moderate to severe COPD patients receiving three alternatives: triple fixed-dose therapy BUD/GLY/FOR; dual PT003 GLY/FOR (LAMA/LABA) MDI therapy; or dual PT009 BUD/FOR (ICS/LABA) MDI therapy. A lifetime horizon was used with a cycle length of 1-month following the natural history of the disease. The baseline characteristics of the modelled cohort were obtained from the ETHOS trial[13] (Table 1).

The model (Figure 1) comprised ten health states: nine forced expiratory volume in 1 second (FEV_1)-related health states and a death state. FEV_1 is a spirometry measure for assessing COPD and other lung diseases.[1] The FEV_1-related health states were divided by three levels of severity, defined according to the GOLD 2017 guidelines:[14] moderate

Table 1 Clinical Inputs Used in the Model

Clinical Inputs	All Treatments	BUD/GLY/FOR	LAMA/LABA	ICS/LABA	Reference
Population characteristics					
Mean age	64.7				ETHOS CSR[13]
Proportion of female (%)	40.3				ETHOS CSR[13]
FEV_1 health states					
Moderate FEV_1 no exacerbations (%)	28.55				ETHOS CSR[13]
Severe FEV_1 no exacerbations (%)	60.59				ETHOS CSR[13]
Very severe FEV_1 no exacerbations (%)	10.87				ETHOS CSR[13]
FEV_1 health state transitions					
Moderate FEV_1 to severe FEV_1 (%, CI 95%)		2.27 (1.82–2.73)	2.00 (1.59–2.38)	3.04 (2.43–3.65)	Data on file[15]
Severe FEV_1 to very severe FEV_1 (%, CI 95%)		0.60 (0.48–0.72)	0.71 (0,0.56–0.85)	1.25 (1.00–1.50)	Data on file[15]
Transitions from FEV_1 health states to exacerbation states					
Moderate FEV_1 no exacerbations to moderate exacerbation (%, CI 95%)		6.37 (5.13–7.60)	8.15 (6.57–9.70)	6.84 (5.51–8.15)	ETHOS CSR[13]
Moderate FEV_1 no exacerbations to severe exacerbation (%, CI 95%)		0.66 (0.53–0.80)	0.75 (0.60–0.90)	0.58 (0.47–0.70)	ETHOS CSR[13]
Severe FEV_1 no exacerbations to moderate exacerbation (%, CI 95%)		7.38 (5.95–8.79)	9.97 (8.06–11.84)	8.45 (6.82–0.06)	ETHOS CSR[13]
Severe FEV_1 no exacerbations to severe exacerbation (%, CI 95%)		1.24 (1.00–1.49)	1.49 (1.19–1.78)	1.49 (1.19–1.78)	ETHOS CSR[13]
Very severe FEV_1 no exacerbations to moderate exacerbation (%, CI 95%)		8.38 (6.76–9.97)	10.49 (8.48–12.45)	10.49 (8.48–2.45)	ETHOS CSR[13]
Very severe FEV_1 no exacerbations to severe exacerbation (%, CI 95%)		1.73 (1.39–2.08)	2.31 (1.85–2.76)	3.20 (2.57–3.82)	ETHOS CSR[13]
Initial risk of discontinuation					
Monthly risk (%)		1.85	2.42	2.15	Data on file[15]
Mortality					
First year					
Mortality - monthly (%)		0.118	0.223	0.158	ETHOS CSR[13]
Next years					
Moderate FEV_1 mortality - per cycle (%)	1.40				Shavelle et al 2009[16]
Severe FEV_1 mortality - per cycle (%)	2.55				Shavelle et al 2009[16], Assumption

(*Continued*)

Table 1 (Continued).

Clinical Inputs	All Treatments	BUD/GLY/FOR	LAMA/LABA	ICS/LABA	Reference
Very severe FEV_1 mortality - per cycle (%)	2.65				Shavelle et al 2009[16], Assumption
Severe exacerbation - only in the exacerbation cycle (%)	12.0				NICE 2017[18]; National COPD Audit Programme. Report 2014[19]
Utility value (EQ-5D-5L)					
Moderate FEV_1 utility	0.79				ETHOS CSR[13]
Severe FEV_1 utility	0.76				ETHOS CSR[13]
Very severe FEV_1 utility	0.72				ETHOS CSR[13]
Moderate exacerbation disutility	−0.010				NICE 2017[18]; Samyshkin 2014[20]
Severe exacerbation disutility	−0.042				NICE 2017[18]; Samyshkin 2014[20]

Abbreviations: BUD/GLY/FOR, budesonide/glycopyrrolate/formoterol fumarate; CI, confidence interval; FEV_1, forced expiratory volume in one second; ICS, inhaled corticosteroid; LABA, long-acting beta adrenoreceptor agonist; LAMA, long-acting muscarinic antagonist.

(GOLD 2): patients have post-bronchodilator FEV_1 ≥50% and <80% of predicted; severe (GOLD 3): patients have post-bronchodilator FEV_1 ≥30% and <50% of predicted; very severe (GOLD 4): patients have post-bronchodilator FEV_1 <30% of predicted. Each moderate, severe, and very severe FEV_1 health state was duplicated three times to separately capture patients who had experienced no, moderate, and severe exacerbations. Exacerbations health states were defined according to ETHOS trial.[12] A moderate exacerbation was characterized as an exacerbation requiring systemic corticosteroids or antibiotics for at least 3 days, and a severe exacerbation as requiring hospitalization or resulting in death.[12]

The risk of experiencing an exacerbation (or subsequent exacerbation) and the risk of death were differentiated between patients who had not experienced an event and those who had had a prior event. Differentiating FEV_1 health states by exacerbations permitted different risks, costs, and utility values to be applied, incorporating 'tunnel states'. These tunnel states were sub-states within each FEV_1 health state that permitted the increased resource use and utility decrease associated with moderate and severe exacerbations. Simulated patients entered each health state at the start of an exacerbation episode. A simulated patient only occupied the tunnel state for one model cycle; after that, the patient transitioned to either the post-exacerbation health state or the death state. A simulated cohort of patients entered the model in the no exacerbation health states (moderate, severe, and very severe FEV_1) according to the FEV_1 severity of patients at baseline in the ETHOS trial (Table 1).[13] The distribution of patients in the no exacerbation health states at baseline was assumed to be equivalent for all treatments.

Patients in the cohort could not transition back to the no exacerbation health states once they experienced an exacerbation (moderate or severe). Furthermore, since COPD is considered a progressive disease, patients could not experience an improvement in lung function and transition to a less severe FEV_1 health state. Death was the absorbing state to which patients could transition from all states.

All inputs were validated by an expert panel of three Spanish healthcare professionals (a pneumologist, a general practitioner, and a hospital pharmacist) to ensure the study perspective fits the current Spanish clinical practice.

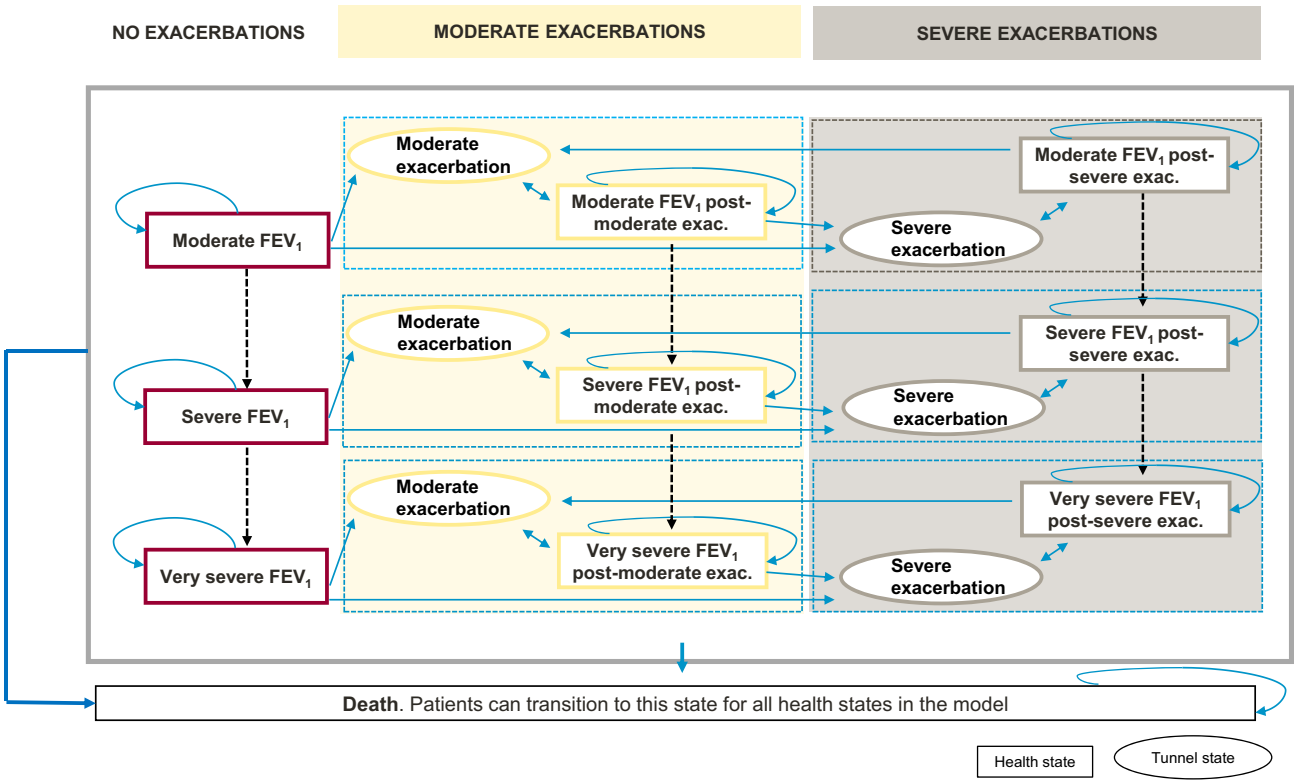

Figure 1 Model structure.
Dashed black arrows indicate the transition between more severe FEV_1 health states. Although not directly shown on this diagram, health state transitions between the moderate and very severe FEV_1 health states are permitted.
Abbreviations: Exac: exacerbation; FEV_1: forced expiratory volume in one second.

Efficacy

Lung Function (FEV_1) and Exacerbations

The transition probabilities between health states were calculated by reviewing the effect of each treatment over the simulated cohort of patients (Table 1). Based on ETHOS trial[15] data (Tables S1 and S2) at baseline, the rates of moderate and severe exacerbations were analysed for the overall patient population stratified by lung function (FEV_1) severity. A single rate ratio was applied for each type of exacerbation. It was assumed that there was no increased probability of presenting exacerbations after a previous exacerbation or no long-term decrease in the effect of treatment on lung function and exacerbations for each of the treatments. All 52-week data were transformed into monthly probabilities to reflect the model cycle length.

Treatment Discontinuation

The treatment discontinuation risk (monthly probability) (Table 1) for the therapies was derived from the ETHOS trial.[13] The reasons for premature treatment discontinuation were mainly adverse events, patients' withdrawal from the trial, or lack of efficacy. The risk of treatment discontinuation was applied for the lifetime horizon.

Mortality

The mortality rates for females and males in the general population were weighted by the proportion of females and males in the ETHOS trial overall population (Table 1).[13] The ETHOS trial collected data on patient mortality during the 52-week follow-up of the study.[15] These data were used for the first year (monthly probability was adjusted to align with the cycle duration) (Table 1). From the second year on and beyond, COPD-related mortality was presented as the increased risk of death due to COPD compared to the risk of death for the general population at the same age (Table 1). Relative risk of death by lung function (FEV_1) health state without exacerbation history were derived from the literature

(moderate FEV_1: 1.40; severe FEV_1: 2.60 and very severe FEV_1: 2.60)[16] and were adjusted according to the experts' recommendations (moderate FEV_1: 1.40; severe FEV_1: 2.55 and very severe FEV_1: 2.65). The general population all-cause mortality rates were sourced from the life tables of the Spanish National Statistics Institute.[17] It was also assumed that the risk of death by FEV_1 health state post-exacerbation was equivalent to the risk of death without an exacerbation history. Severe exacerbation-related deaths were modelled separately, only patients who experienced a severe exacerbation were at risk of severe exacerbation-related deaths. This risk was applied to these patients when an exacerbation occurred. A probability of 12% was considered and reflected the estimated mortality 90 days after hospitalization for a severe exacerbation (Table 1).[18,19] This input was set to 0% in the first year to avoid double-counting since overall mortality rates from the trial were used. Patients who experienced a moderate exacerbation had a risk of death depending on the FEV_1 health state when the exacerbation occurred.

Utility Values

Utility values for each lung function (FEV_1) severity state and utility decrements for exacerbations and AEs were included. The utility values ascribed to all FEV_1 health states (exacerbations and no exacerbations) were derived from the EuroQoL 5-dimension 5-level (EQ-5D-5L) questionnaire collected in the ETHOS trial (Table 1).[13] The loss of utility (dis-utility) associated with the exacerbation was applied as QALY losses per event in line with the roflumilast NICE assessment[18] and the publication by Samyskin et al[20] (Table 1). The QALY loss was assumed to occur during one cycle only, beyond which the patient's quality of life returned to the level associated with their lung function status.

In addition, disutilities associated with AEs were ascribed at the beginning of the model when the entire cohort was at risk of treatment-related AEs to ensure that the full impact of AEs was captured. The AEs-related disutility was assumed to be captured in the underlying EQ-5D-5L analysis of the ETHOS trial data.[13] Therefore, no additional AEs-related utility decrements were considered to avoid double-counting in the base-case analysis.

Costs

Costs included treatment-specific costs (drug acquisition and subsequent treatment, rescue medication, and adverse events) and disease management costs: by lung function (emergency room visit, specialist visit, primary care visit, nursing visit, telephone calls to physician, and telephone nursing consultation) and by exacerbation (hospitalization in the intensive care unit, hospitalization in the coronary care unit, hospitalization in the general ward, treatment with oral corticosteroids, ambulance transport, and primary care visit). All costs were estimated in euros 2021.

Drug acquisition costs were derived from an official database in Spain[21] (Table 2) (plus the rebate of 7.5% according to Spanish regulation RDL 8/2010, as appropriate[22]). All LAMA/LABA therapies had the same prices. However, ICS/LABA treatment costs were calculated as a price average.[21] Upon discontinuation of the initial drug, only drug acquisition costs were considered. They were calculated as weighted average costs based on market share determined by the experts. Patients receiving BUD/GLY/FOR assumed that 95% of cases continued to receive triple therapy treatment while receiving the additional subsequent treatment roflumilast.[23] The remaining 5% of patients de-escalated to double therapy (4% LAMA/LABA and 1% ICS/LABA). Patients that received LAMA/LABA treatment moved onto triple therapy in 90% of cases and received an ICS/LABA therapy as a subsequent treatment in 10%. Patients initially receiving ICS/LABA treatment moved onto triple therapy treatment in 100% of cases.

The number of inhalations per administration and the number of administrations per day by treatment were derived from the product summary of product characteristics (SmPC) for each treatment.[24] The efficacy of subsequent treatment was assumed equal to BUD/GLY/FOR triple therapy, and subsequent treatment cost to be the lowest of all triple therapies in the Botplus database[21] (Table 2). This assumption favoured the dual therapies opting for the most conservative approach. The rescue medication-related cost was included as the average number of rescue medication inhalations required per month per treatment and by FEV_1 state (Table 2). Rescue medication costs were calculated using the cost of salbutamol[21] and the mean daily number of rescue inhaler uses observed in ETHOS trial.[13] No rescue medication costs were applied after treatment discontinuation. The experts decided to include in the model those adverse events reported with a frequency greater than 3% and the cardiovascular events, both based on the ETHOS trial.[13] Therefore, nasopharyngitis, upper respiratory tract infection, confirmed pneumonia, bronchitis, and confirmed major adverse cardiovascular events were included. Unit costs were obtained

Table 2 Costs Inputs Used in the Model

Costs Inputs	All Treatments	BUD/GLY/FOR	LAMA/LABA	ICS/LABA	Reference
Drug acquisition					
LP-RDL (€)		44.95	41.63	26.82	BotPlus[21]; RDL 8/2010[22]
Number inhalations (per unit)		120	30	30	AEMPS-CIMA[24]
Number inhalations (per day)		4	2	2	AEMPS-CIMA[24]
Drug acquisition - monthly (€)		45.61	84.47	54.42	BotPlus[21]; RDL 8/2010[22]; AEMPS-CIMA
Subsequent treatment					
Subsequent treatment - monthly (€)		68.68	73.06	73.50	BotPlus[21]; RDL 8/2010[22]; AEMPS-CIMA[24]
Rescue medication					
Moderate FEV_1 cost- monthly (€)		54.80	67.00	60.90	BotPlus[21]
Severe FEV_1 cost- monthly (€)		82.20	91.30	91.30	BotPlus[21]
Very Severe FEV_1 cost- monthly (€)		115.70	124.80	137.00	BotPlus[21]
Adverse events					
Adverse events (€)		246.32	235.19	246.85	eSalud[25]
Cost for the FEV_1 health states (per cycle)					
Moderate FEV_1	14.27				eSalud[25]
Severe FEV_1	19.19				eSalud[25]
Very severe FEV_1	27.19				eSalud[25]
Cost for exacerbation					
Moderate exacerbation	54.43				eSalud[25]
Severe exacerbation	3724.24				eSalud[25]

Abbreviations: BUD/GLY/FOR, budesonide/glycopyrrolate/formoterol fumarate; FEV_1, forced expiratory volume in one second; ICS, inhaled corticosteroid; LABA, long-acting beta adrenoreceptor agonist; LAMA, long-acting muscarinic antagonist; LP, laboratory price; RDL, Royal Decree-Law.

from the Spanish healthcare costs database[25] (Table 2). More details about resource use and costs for AEs are shown in Table S3. The costs associated with AEs were ascribed in the first cycle only.

Lung function and exacerbation management costs, such as resource use (annual frequency), were derived from the ETHOS trial[13] and were validated according to the experts' recommendations. In addition, unit costs were obtained from the Spanish healthcare costs database[25] (Table 2). More details about resource use and costs for lung function and exacerbation management are shown in Table S4. Disease management costs were ascribed separately for patients who discontinued and were not included as a subsequent treatment cost.

Model Outputs

The outputs were measured as total costs, the number of exacerbations, life years (LYs), and quality-adjusted life-years (QALYs). The cost-effectiveness was expressed as incremental cost effectiveness ratio (ICER) per exacerbation avoided and per life year (LY) gained, and per quality-adjusted life-year (QALY) gained (ICUR). Cost-effectiveness was assessed using a willingness-to-pay (WTP) threshold of €25,000/QALY.[26]

An annual discount rate of 3% was applied to costs and benefits, following Spanish guidelines.[27]

Sensitivity Analysis

One-way (OWSA), scenario, and probabilistic sensitivity analyses (PSA) were conducted to explore the parameter uncertainty of the model inputs. OWSA was estimated using 95% CI from ETHOS trial or ±20% the value defined for the base case. The result of the OWSA was plotted on a tornado diagram with the 10 most sensitive parameters presented.

Two scenario analysis was performed based on experts' opinions. In the first one, the characteristics of the population (average age of patients and rates for females and males) were modified. Although patients from Spanish centers participated in the ETHOS trial, including data from the Spanish population was considered necessary, taking into account the perspective of our analysis; Therefore, instead of the data from the ETHOS trial (64.7 and 40.3% female, respectively), data from an epidemiological study on COPD (60 and 52.6% female, respectively) in the Spanish population were used.[28]

As the ETHOS trial lasted only 52 weeks, a second scenario analysis with a 1-year time horizon was performed, calculating the annual costs and showing the differences between treatments on an annual basis.

The PSA was performed using a Monte Carlo simulation with 10,000 iterations. The gamma distribution was used for cost and resource use. The beta distribution was used for probabilities and utilities. Finally, a log-normal distribution was applied to the relative treatment effects (relative risk/rate ratio).

Results

Base-Case Analysis

Over a lifetime horizon, the rate of exacerbations was lower with BUD/GLY/FOR (12.80) than LAMA/LABA (13.36) and ICS/LABA (13.23). In addition, BUD/GLY/FOR had more LYs and QALYs (10.32 and 7.55, respectively) compared to LAMA/LABA (10.14 and 7.41, respectively) and ICS/LABA (10.06 and 7.32, respectively). The total costs were higher for the BUD/GLY/FOR (€, 16,520.45) vs LAMA/LABA (€, 16,044.47) and vs ICS/LABA (€, 15,489.48). Drug initial costs were lower in the BUF/GLY/FOR (€, 1,893.19) than LAMA/LABA (€, 2,814.86) and similar to ICS/LABA (€, 1,978.51) (Table 3). Subsequent treatment was the only cost higher for BUD/GLY/FOR. The estimated incremental cost per exacerbation avoided for BUD/GLY/FOR was €850.95 vs LAMA/LABA and €2,422.26 vs ICS/LABA (Table 3). The incremental cost per LY gained (ICER) for BUD/GLY/FOR vs LAMA/LABA and vs ICS/LABA was €2,733.38 and €4,111.15, and the ICUR was €3,461.19 and €4,545.24, both respectively.

Table 3 Results of the Base-Case Analysis

	BUD/GLY/FOR	LAMA/LABA	ICS/LABA
Effectiveness			
Total exacerbations	12.80	13.36 (Δ=−0.56)	13.23 (Δ=−0.43)
LYs	10.32	10.14 (Δ=0.17)	10.06 (Δ=0.25)
QALYs	7.55	7.41 (Δ=0.14)	7.32 (Δ=0.23)
Costs (€)			
Total	16,520.45	16,044.47 (Δ=475.98)	15,489.48 (Δ=1030.97)
Disease-specific costs	8704.84	8863.46 (Δ=−158.62)	9387.46 (Δ=−682.62)
Treatment-specific costs			
Initial treatment	1893.19	2814.86 (Δ=−921.67)	1978.51 (Δ=−85.32)
Rescue medication	26.19	22.63 (Δ=3.56)	26.50 (Δ=−0.31)
Adverse events	246.32	235.19 (Δ=11.13)	246.85 (Δ=−0.53)
Subsequent treatment	5649.91	4108.33 (Δ=1541.58)	3850.15 (Δ=1799.76)
Incremental cost per exacerbation avoided		850.95	2422.26
Incremental cost per LY gained		2733.38	4111.15
Incremental cost per QALY gained		3461.19	4545.24

Note: Δ BUD/GLY/FOR vs dual therapy.

Abbreviations: BUD/GLY/FOR, budesonide/glycopyrrolate/formoterol fumarate; FEV1, forced expiratory volume in one second; ICS, inhaled corticosteroid; LABA, long-acting beta adrenoreceptor agonist; LAMA, long-acting muscarinic antagonist; Lys, life years; QALYs, quality-adjusted life-year.

Sensitivity Analyses

The OWSA showed that base-case results were robust to changes in input parameters. The most sensitive parameter was the subsequent treatment costs for BUD/GLY/FOR and LAMA/LABA or ICS/LABA (Figures 2 and Figure 3); even so, BUD/GLY/FOR continued to be cost-effective.

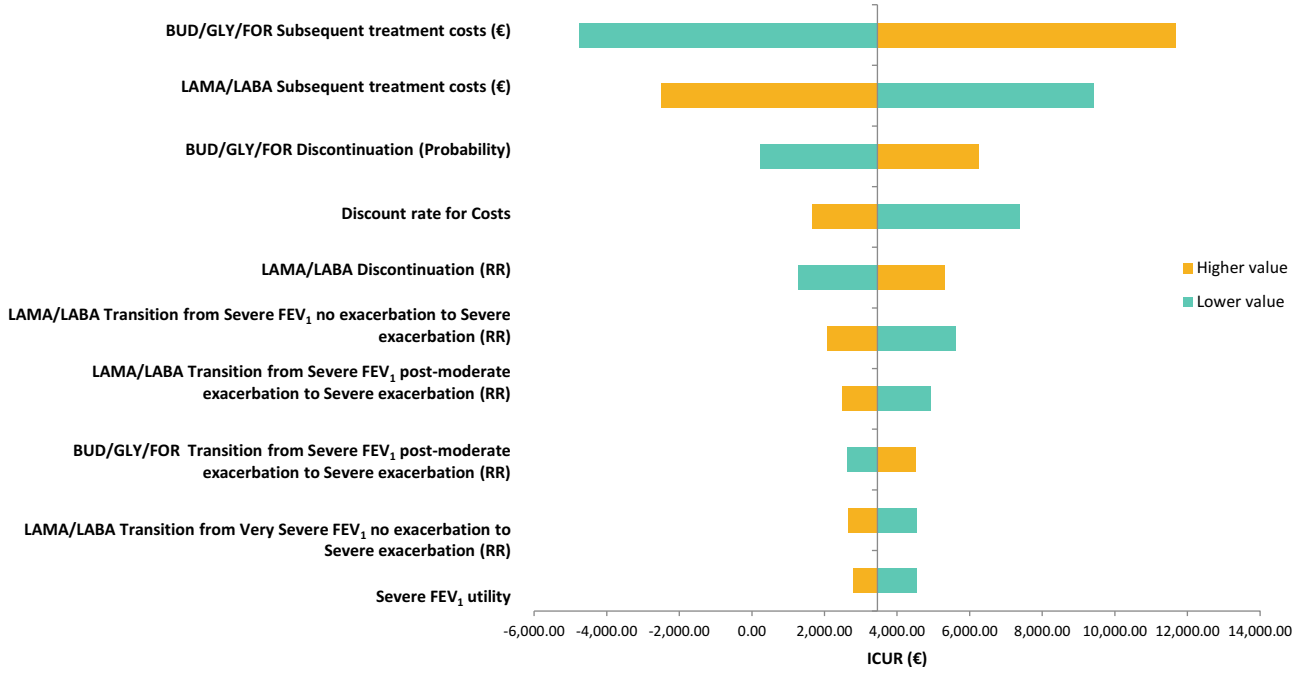

Figure 2 OWSA BUD/GLY/FOR vs LAMA/LABA.

Abbreviations: BUD/GLY/FOR: budesonide/glycopyrrolate/formoterol fumarate. FEV_1: forced expiratory volume in one second; ICS: inhaled corticosteroid; ICUR: incremental cost-utility ratio; LABA: long-acting beta adrenoreceptor agonist; LAMA: long-acting muscarinic antagonist. RR: Relative Risks.

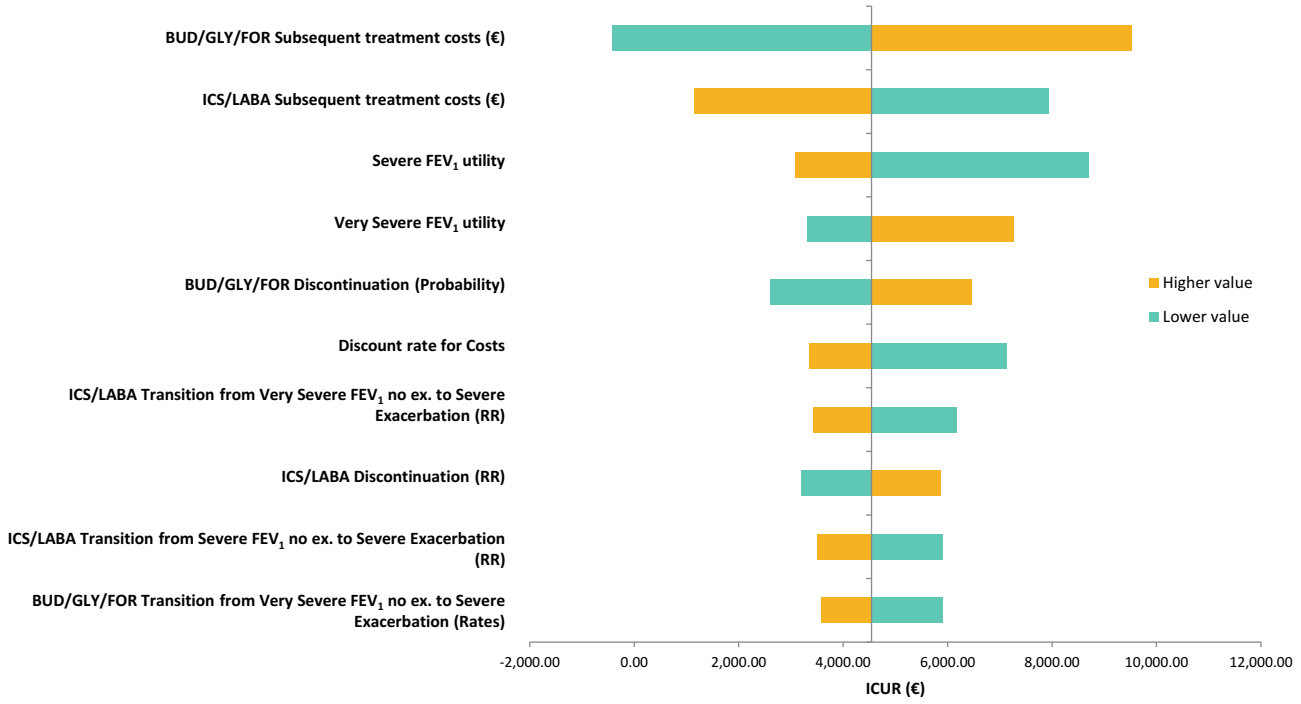

Figure 3 OWSA BUD/GLY/FOR vs ICS/LABA.

Abbreviations: BUD/GLY/FOR: budesonide/glycopyrrolate/formoterol fumarate. FEV_1: forced expiratory volume in one second; ICS: inhaled corticosteroid; ICUR: incremental cost-utility ratio; LABA: long-acting beta adrenoreceptor agonist; LAMA: long-acting muscarinic antagonist. RR: Relative Risks.

In the model developed, the QALY difference observed between compared treatments resulted from different utility values for each lung function (FEV_1) severity state and utility decrements for exacerbations and AEs. Therefore, a lower utility value of severe FEV_1 health status would lead to fewer QALYs and higher ICUR. However, contrary to expectations, with ICS/LABA, a lower utility value of the very severe health state FEV_1 caused QALYs to be higher. This is because the probability of progressing to a very severe FEV_1 state in ICS/LABA treatment was faster than in BUD/GLY/FOR. Therefore, the number of individuals accumulated in very severe FEV_1 state is higher and QALYs are higher too in ICS/LABA treatment.

In the first alternative scenario, the characteristics of the population (ETHOS clinical trial population in base-case) were changed for the characteristics of Spanish population. In this case, the ICUR of BUD/GLY/FOR versus LAMA/LABA was €1,707.76, and versus ICS/LABA was €3,935.68, remaining lower than the WTP threshold (25,000€/QALY), which also supports the results' robustness. The second alternative scenario (1-year time horizon) showed that LAMA/LABA and ICS/LABA were dominated by BUD/GLY/FOR so, BUD/GLY/FOR is both clinically superior and cost saving.

The PSA showed that 91.32% vs LAMA/LABA and 99.29% vs ICS/LABA of simulations were in the northeast quadrant, indicating that BUD/GLY/FOR was cost-effectiveness vs dual therapies by a willingness to pay (WTP) threshold of €25,000 per QALY gained (Figures 4 and Figure 5).

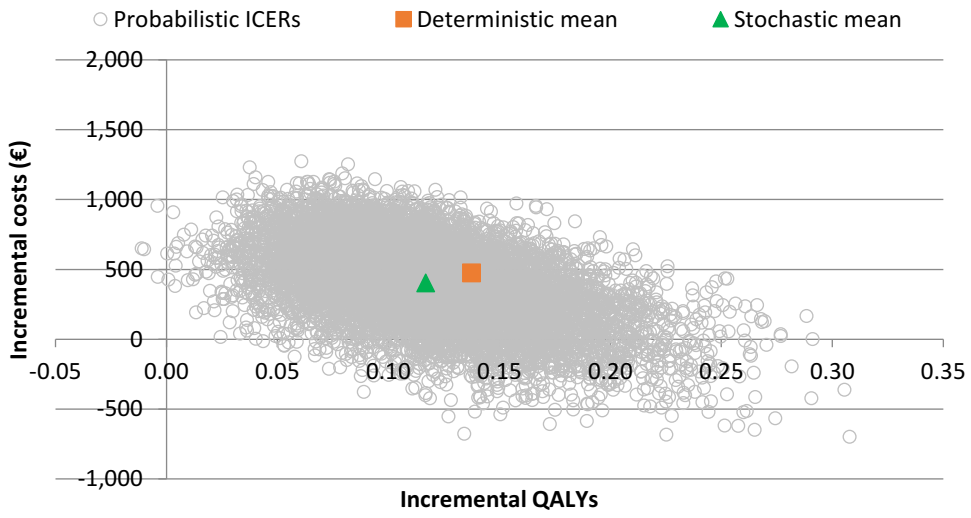

Figure 4 PSA BUD/GLY/FOR vs LAMA/LABA.
Abbreviations: ICER: incremental cost-effectiveness ratio; QALYs: quality-adjusted life-year.

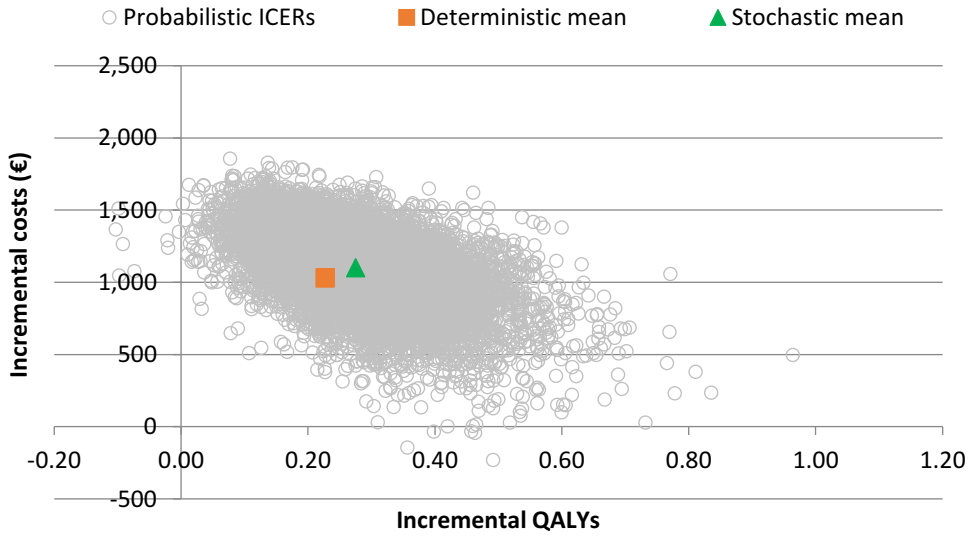

Figure 5 PSA BUD/GLY/FOR vs ICS/LABA.
Abbreviations: ICER: incremental cost-effectiveness ratio; QALYs: quality-adjusted life-year.

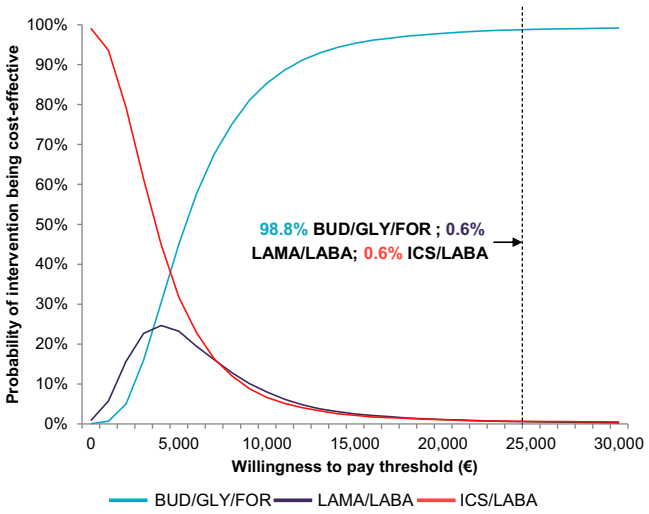

Figure 6 Cost-effectiveness acceptability curve.
Abbreviations: BUD/GLY/FOR: budesonide/glycopyrrolate/formoterol fumarate.ICS: inhaled corticosteroid; LABA: long-acting beta adrenoreceptor agonist; LAMA: long-acting muscarinic antagonist.

The cost-effectiveness acceptability curve showed that BUD/GLY/FOR (98.8%) has a higher probability of being cost-effectiveness than LAMA/LABA (0.6%) and ICS/LABA (0.6%) at a WTP threshold of €25,000/QALY (Figure 6).

Discussion

COPD is a highly prevalent chronic disease that produces a great economic impact and is projected to increase over the coming decades, so strategies to address this disease are necessary.[1] The results of this cost-effectiveness analysis based on a Markov model showed that triple therapy BUD/GLY/FOR is dominant with a 1-year time horizon and cost-effective treatment option over lifetime horizon for patients with moderate to severe COPD compared to dual therapies LAMA/LABA and ICS/LABA from the Spanish NHS perspective. BUD/GLY/FOR was associated with a lower total exacerbation per patient (12.80) than LAMA/LABA (13.36) and ICS/LABA (13.23) and more LYs (10.32 vs 10.14 and 10.06, respectively) and QALYs (7.55 vs 7.41 and 7.32, respectively) per patient gained. The analysis resulted in an ICER of €2,733.38 and €4111.15 per LY gained, and an ICUR of €3,461.19 and €4,545.24 per QALY gained, for BUD/GLY/FOR vs LAMA/LABA and ICS/LABA respectively, both below the threshold of €25,000/QALY. Furthermore, the results were robust to various sensitivity analyses and showed that variation in critical parameters did not impact the results in a great deal.

Others cost-effectiveness analyses of different single-inhaler triple therapy in patients with COPD and risk of exacerbations versus dual therapies were identified.[29–31] All of them showed triple therapy was cost-effective vs dual therapies with an ICUR of £ 6418 (£ 2018, UK),[29] £ 4104 (£ 2018, UK),[29] £ 1098 (£ 2015/2016, UK)[28] for a lifetime horizon in line with our analysis, including one from the Spanish perspective with an ICUR of € 642 (€ 2019) over a 3-year time horizon.[31] Results of different modelling approaches for the same decision problem showed similar outcomes as our study, strengthening the robustness of our results. Furthermore, these findings suggest that the data on cost-effectiveness in the UK and Spain may extend to other countries.

This study has some limitations, common to all cost-effectiveness analyses using clinical trial data and Markov models, mainly due to assumptions such as QALY loss was assumed to occur during one cycle only. Although validated by clinical experts, these assumptions introduce uncertainty into the findings. Firstly, the time horizon was for a lifetime; however, the ETHOS trial duration was 52 weeks, so it was assumed that there was no long-term decrease in the treatment effect on lung function and exacerbations for each of the treatments and the efficacy of subsequent treatment was equalled to BUD/GLY/FOR triple therapy. Alternatively, several sensitivity analyses were conducted to ascertain the impact of long-term efficacy assumptions and confirmed that the results were not impacted. Specifically, in the scenario where the time horizon was one year, the results favoured BUD/GLY/FOR therapy.

Secondly, the approach does not fully capture the link between exacerbations, symptoms, lung function and the exact exacerbation history to the extent that a patient-level simulation model would. A Markov model is unable to ascribe probabilities of future health state transitions according to the nature or timing of past events.[32] However, overcoming this was possible due to "tunnel states", allowing the analysis to capture exacerbation management costs and the utility decrement and increased risk of mortality associated with the exacerbation events experienced in an individual cycle. In addition, the model underestimates the mortality risk for patients with multiple exacerbations. In this regard, the experts indicated that the probability of presenting an exacerbation after the "post-exacerbation" health state does not depend only on the previous exacerbation, as there are other issues to consider (eg, smoking, corticosteroid treatments, etc.). Therefore, the experts assumed that the best approach was not to include it in any of the comparators. Thirdly, subsequent treatment discontinuation was not considered. Patients who went from double to triple therapy stayed there until the end, and those who were on BUF/GLU/FOR went on to BUF/GLU/FOR plus roflumilast (95%) until the end of their lives. Therefore, those who received dual therapy would never receive BUF/GLU/FOR plus roflumilast, from which they could benefit from so that this model can be considered conservative. Nevertheless, BUD/GLU/FOR remained a cost-effective treatment option considering a number of uncertainties across all sensitivity and scenario analyses, suggesting that the results were robust when adapting to the reality of COPD management in clinical practice and that the developed model is reliable.

In addition to the robustness of the sensitivity analysis results, a strength of this study is that the proposed economic model structure was appropriate for the decision problem. The model considered the inclusion of different severity levels of exacerbation which allowed to include costs and HRQoL decrements as captured. In addition, this allowed different risk of disease progression for patients who have experienced an exacerbation after initiation of treatment.

Moreover, all inputs were validated according to the experts' recommendations.

Our study demonstrated a beneficial effect of BUD/GLY/FOR vs dual therapies on the annual rate of exacerbations, symptoms, and health-related quality of life following guidelines' recommendations[9] and, consequently, demonstrating to be cost-effective in terms of LYs and QALYs.

In conclusion, the results of this cost-effectiveness analysis based on a Markov model showed that treatment with the fixed-dose combination of BUD/GLY/FOR was cost-effective compared with dual therapies. These results may help inform future decision-making processes in the Spanish NHS.

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