Cost-effectiveness analysis of umeclidinium bromide/vilanterol 62.5/25 mcg versus tiotropium/olodaterol 5/5 mcg in symptomatic patients with chronic obstructive pulmonary disease: a Spanish National Healthcare System perspective

M. T. Driessen¹, J. Whalen², B. Seewoodharry Buguth², L. A. Vallejo-Aparicio³, I. P. Naya⁴, Y. Asukai¹*, B. Alcázar-Navarrete⁵, M. Miravitlles⁶, F. García-Río⁷ and N. A. Risebrough⁸

Abstract

Background: A head-to-head study demonstrated the superiority of once-daily umeclidinium bromide/vilanterol (UMEC/VI) 62.5/25 mcg on trough forced expiratory volume in 1 s (FEV₁) versus once-daily tiotropium/olodaterol (TIO/OLO) 5/5 mcg in symptomatic patients with chronic obstructive pulmonary disease (COPD). This analysis evaluated the cost effectiveness of UMEC/VI versus TIO/OLO from a Spanish National Healthcare System perspective, using data from this study and Spanish literature.

Methods: This analysis was conducted from the perspective of the Spanish National Healthcare System with a 3-year horizon as base case. A disease progression model using a linked risk equation approach was used to estimate disease progression and associated healthcare costs, and quality-adjusted life years (QALYs). The Evaluation of COPD Longitudinally to Identify Predictive Surrogate Endpoints (ECLIPSE) study was used to develop the statistical risk equations for clinical endpoints, and costs were calculated using a health state approach (by dyspnea severity). Utilities for QALY calculation were estimated using patient baseline characteristics within a regression fit to Spanish observational data. Treatment effect, expressed as change from baseline in FEV₁, was obtained from the head-to-head study and used in the model (UMEC/VI minus TIO/OLO difference: + 52 mL [95% confidence interval: 28, 77]). Baseline patient characteristics were sourced from Spanish literature or the head-to-head study if unavailable. A scenario analysis using only the intent-to-treat (ITT) population from the head-to-head study, and sensitivity analyses (including probabilistic sensitivity analyses), were conducted. Direct healthcare costs (2017 Euro) were obtained from Spanish sources and costs and benefits were discounted at 3% per annum.

(Continued on next page)
Background
Chronic obstructive pulmonary disease (COPD) is a disabling respiratory disease characterized by airflow limitation and persistent breathing difficulties [1]. COPD is associated with a high clinical and economic burden worldwide, impacting the patient’s quality of life and causing significant costs, associated with clinical care [1]. In Spain, the prevalence of COPD in patients aged 40–80 years old is approximately 10.2% and prevalence is higher in men compared with women (15.1% versus 5.6%, respectively) [2]. Geographic variations in prevalence range from 6.2–16.9% [3]. The annual cost of COPD in Spain was estimated at €239 million in 1997 and €507 million in 2000 [4, 5].

Pharmacological treatment for COPD aims to improve patient symptoms and reduce the risk of exacerbation [1]. The cornerstone of pharmacological therapy for COPD is bronchodilatation with a long-acting muscarinic antagonist (LAMA), a long-acting $\beta_2$-agonist (LABA), or a LAMA/LABA combination either as initial therapy or escalation from monotherapy, depending on the severity of breathlessness and the patient’s risk of exacerbations [1, 6–8]. The Global Initiative for Chronic Obstructive Lung Disease (GOLD) 2018 report recommends dual LAMA/LABA therapy for patients initially on monotherapy who continue to experience exacerbations or patients with severe or persistent breathlessness [1].

The Spanish guidelines for pharmacological treatment of stable COPD (Guía española de la enfermedad pulmonar obstructiva crónica, GesEPOC) [9] include a number of GOLD principles and recommendations; however, GesEPOC follows an alternative suite of phenotype-based recommendations for the evaluation and treatment of COPD [9]. GesEPOC proposes four phenotypes that determine differential treatment: non-exacerbators; mixed COPD-asthma; exacerbators with emphysema; and exacerbators with chronic bronchitis [10]. Within this framework, dual LAMA/LABA therapy is recommended in non-exacerbators who remain symptomatic after bronchodilator monotherapy, and in patients with emphysema or chronic bronchitis at risk of exacerbations [10].

Various LAMA/LABA combinations are currently available in Spain. Umeclidinium/vilanterol 62.5/25 mcg (UMEC/VI) is a once-daily single inhaler LAMA/LABA therapy, approved for the treatment of COPD by the European Medicines Agency (EMA) in 2014 [11]. The safety and efficacy of UMEC/VI has been extensively investigated and studies have shown improvements in lung function with UMEC/VI compared with placebo [12, 13], UMEC or VI monotherapy [12, 14, 15], tiotropium (TIO) [14, 16, 17] and inhaled corticosteroid (ICS)/LABA combination therapy [18, 19]. TIO/olodaterol (TIO/OLO) was first approved as treatment for patients with COPD in 2015 [20]. A recent systematic literature review demonstrated that treatment with TIO/OLO provides significant improvement in lung function when compared with TIO and OLO monotherapies and when compared with ICS/LABA combination therapy [21].

Until recently, no direct comparison between once-daily LAMA/LABA combination therapies had been conducted, although indirect comparisons of double blind trials highlighted potential for efficacy differences within the LAMA/LABA treatment class in favor of UMEC/VI [22, 23]. A 12-week head-to-head study of UMEC and TIO monotherapies demonstrated that UMEC was superior to TIO in trough forced expiratory volume in 1 s (FEV$_1$), with a treatment difference of 59 mL (95% confidence interval [CI]:29, 88 mL) [24], and a recent open-label, 8-week crossover head-to-head study demonstrated that this superiority was maintained when UMEC and TIO were administered as part of a LAMA/LABA dual therapy [25]. This LAMA/LABA head-to-head study, UMEC/VI 62.5/25 mcg was compared with TIO/OLO 5/5 mcg in symptomatic patients with moderate COPD who were naïve to ICS at study entry [25]. The study showed that UMEC/VI was superior to TIO/OLO in the intent-to-treat population for FEV$_1$ improvement at 8 weeks with a treatment difference of 52 mL (95% CI: 28, 77 mL) [25].

UMEC/VI has already been shown to be cost effective when compared with TIO alone from a Spanish National Healthcare System perspective [26]. Following the
completion of the head-to-head study comparing UMEC/VI and TIO/OLO, this study aimed to assess the cost effectiveness of UMEC/VI versus TIO/OLO from a Spanish National Healthcare System perspective [25]. Given that the annual drug acquisition costs for UMEC/VI are lower than TIO/OLO in Spain, it was anticipated that this analysis would find that UMEC/VI dominated TIO/OLO (as a more effective and less expensive treatment). However, testing this hypothesis through sensitivity analyses is important to demonstrate the robustness of this assumption and to adequately inform healthcare decision makers.

Methods
Objectives
A cost-effectiveness analysis was performed comparing once-daily UMEC/VI with once-daily TIO/OLO in symptomatic patients with stable COPD at low risk of exacerbations from the perspective of the Spanish National Healthcare System over a 3-year time horizon, using data from published literature and the head-to-head study of UMEC/VI versus TIO/OLO (study funded by GSK, study number 204990; NCT02799784) [25].

Design of the clinical study included in the analysis
The UMEC/VI versus TIO/OLO head-to-head study was a randomized, 8-week, open-label, two-period crossover study in symptomatic patients with moderate COPD [25]. To minimize the potential for bias in the assessment of the primary efficacy endpoint of trough FEV₁, given the open-label design, all spirometry assessments were performed by investigational staff blinded to treatment allocation throughout all study phases. Eligible patients were ≥40 years of age, with a diagnosis of COPD [27], a modified Medical Research Council (mMRC) dyspnea score of ≥2, a smoking history ≥10 pack-years, a post-bronchodilator FEV₁/forced vital capacity ratio < 0.70 and a post-bronchodilator FEV₁ ≤ 70% and ≥ 50% of predicted normal values.

Patients were randomized to receive UMEC/VI 62.5/25 mcg one inhalation once daily via the Ellipta dry powder inhaler for 8 weeks, followed by TIO/OLO 5/5 mcg (via two inhalations once daily of TIO/OLO 2.5/2.5 mcg) using the Respimat soft mist inhaler for 8 weeks, or vice versa, with an interim 3-week washout between each 8-week treatment period. The primary endpoint was trough FEV₁ at week 8 in both the ITT and per-protocol (PP) population, with a non-inferiority margin and superiority margin of −50 mL and 0 mL for the lower bound of the 95% CI in the PP and ITT populations, respectively. Other lung function and patient-reported outcomes were also assessed [25].

Cost-effectiveness model
The GALAXY COPD disease progression model was used to perform cost-effectiveness calculations; development of the model and internal/external validation, have been previously published [28–32]. A linked risk equation approach was used within the model to estimate disease progression. Associated healthcare costs such as drug costs, hospitalization costs and outpatient visits, as well as the impact on quality-adjusted life years (QALYs) and survival were estimated based on the resulting clinical outcomes. The model assigned general costs of follow-up based on the proportion of patients with various levels of dyspnea in each model cycle. Post hoc analyses of the Evaluation of COPD Longitudinally to Identify Predictive Surrogate Endpoints (ECLIPSE; NCT00292552) [33] study was used to develop the statistical risk equations for the epidemiological framework. The model uses a 1-year cycle length.

Ethics approval was not required for the study as data for the model were derived from previously conducted studies, for which ethical approval had been obtained.

Study perspective
The cost-effectiveness analyses were conducted from a Spanish National Healthcare System perspective and costs included direct healthcare-related costs, but not costs associated with a societal perspective (e.g. non-medical costs and indirect costs such as absenteeism and presenteeism).

Model inputs
Population
Patient characteristics for the base case analysis were based on two Spanish observational studies [34, 35], in order to analyze a population that is representative of the Spanish population initiating LAMA/LABA therapy. Where data could not be found, for example for clinical characteristics, data from the UMEC/VI versus TIO/OLO head-to-head study were used [25] (Table 1). All characteristics used for the base case analysis were validated by three clinical experts from Spain (initials of clinical experts: MM, BA-N, and FG-R). Data on baseline fibrinogen concentration and baseline 6-min walk test (6MWT) distance were not available from the UMEC/VI versus TIO/OLO head-to-head study; these data were estimated using equations developed within the model using baseline data from the ECLIPSE study [33] (Table 1).

Efficacy input parameters
Treatment effect was measured by change from baseline in post-bronchodilator FEV₁, using data from the UMEC/VI versus TIO/OLO head-to-head study (UMEC/VI: 180 mL; TIO/OLO: 128 mL; difference: 52 mL, 95% CI: 28, 77 mL) [25]. These absolute treatment effects (UMEC/VI: 180 mL; TIO/OLO: 128 mL) were applied to the
baseline FEV\textsubscript{1} and differential treatment effect (52 mL) was maintained over the time horizon as long as patients remained on therapy. The starting FEV\textsubscript{1} values and subsequent improvements in FEV\textsubscript{1} and other COPD disease factors built into the model at time 0 are outlined in Additional file 1.

**Cost inputs**

Total costs accounted for the drug acquisition costs, the costs of exacerbation events (moderate or severe) and the costs of follow-up according to the frequency of dyspnea symptoms. All costs were estimated in 2017 Euros and were adapted from Spanish sources.

National list prices for drug acquisition costs, including rescue medications, were sourced from each cost per pack at price to public plus value added tax (PTP + VAT), as listed in the 2017 catalogue of sanitary products included in the Spanish National Healthcare System (Table 2) [37]. The cost per pack for UMEC/VI and TIO/OLO was €70.25 and €81.49, respectively. Costs for rescue medications were also considered within the model; based on the results of the UMEC/VI versus TIO/OLO head-to-head study [25], salbutamol 1.77 inhalations per day and 1.51 inhalations per day were modeled into the TIO/OLO and UMEC/VI arms, respectively (cost per pack €2.69; Table 2).
The model assigned the unit cost of an exacerbation to the number of exacerbations experienced in each cycle. Cost for exacerbations and disease management were sourced from the previous cost-effectiveness analysis in Spain [26] and were inflated to 2017 Euro valuations using the Spanish Consumer Price Index [38]. The costs of a moderate and severe exacerbation were estimated to be €72.80 and €4470, respectively (Table 1) [26].

Annual disease management costs reflected the level of follow-up based on the proportion of patients with various levels of dyspnea in each model cycle (€524.87/year for a patient without dyspnea symptoms; €699.98/year for a patient experiencing dyspnea symptoms several days per week; €925.85/year for patients with dyspnea symptoms most days per week; Table 1) [26].

Utilities
In this Spanish cost-effectiveness analysis, the model estimated utilities in the base case analysis via linear regression for each cycle, using a utility equation developed for the previous cost-effectiveness analysis of UMEC/VI versus TIO [26], based on data from an observational study in Spain [39]. Details of the utility estimates used within this study, including any modifications made to the Spanish risk equation from the initial disease progression model [28–32], are available in Additional file 2.

Model assumptions
Given the disparity between the cycle length (1 year) and the total duration of the UMEC/VI versus TIO/OLO head-to-head study (8-week treatment periods) [25], it was assumed that treatment effects started at 0 months, i.e. a delay in treatment effect was not modeled. Clinically relevant effects have been seen after the first dose of treatment in favor of UMEC/VI, in studies performing serial FEV₁ assessment [40]. The model also assumed that treatment effects did not wane over the duration of the analysis and that the differential treatment effects observed within the UMEC/VI versus TIO/OLO head-to-head study were maintained over the time horizon, as long as patients remained on treatment. This assumption was validated by the Spanish clinical experts.

Discontinuation rates of 8.7% per year for each arm, were based on the rates observed in the Understanding Potential Long-Term Impacts on Function with Tiotropium (UPLIFT; NCT00144339) trial among GOLD stage 2 patients in the TIO arm [41]. Once patients discontinued their original treatment, the analysis assumed patients would escalate to multiple inhaler triple therapy (ICS, LAMA and LABA in combination). Spanish clinical experts confirmed the chosen escalation treatment in Spain as salbutamol/fluticasone propionate (SAL/FP) 50/500 mcg, two inhalations per day plus TIO 18 mcg, one inhalation per day. In the base case, the model assumed that the lung function of patients who escalated to triple therapy would not be subject to any lasting benefit from their initial treatment. Therefore, a +52 mL benefit in FEV₁ was applied for patients escalating from TIO/OLO to triple therapy (equal to the treatment difference between UMEC/VI and TIO/OLO) and no change in FEV₁ was

### Table 2 Drug acquisition costs

| Drug (brand)   | Drug (generic) | Dose (mcg) | Pack size | Pack cost (PTP + VAT) a [26] | Dosing                                   | Annual acquisition cost a |
|----------------|----------------|------------|-----------|-------------------------------|------------------------------------------|----------------------------|
| Spiolto Respimat TIO/OLO | TIO/OLO | 5/5 | 30 doses (60 pulsations) | €81.49 | 2 inhalations once daily | €992 |
| Anoro Ellipta UMEC/VI | 62.5/25 | 30 doses | €70.25 | 1 inhalation once daily | €855 |

**Comparator drug costs**

**Subsequent treatment and other drugs costs**

| Drug (brand)   | Drug (generic) | Dose (mcg) | Pack size | Pack cost (PTP + VAT) a [26] | Dosing                                   | Annual acquisition cost a |
|----------------|----------------|------------|-----------|-------------------------------|------------------------------------------|----------------------------|
| Spiriva Handihaler b  | TIO | 18 | 30 doses | €49.06 | 1 inhalation once daily | €597 |
| Seretide Accuhaler b  | SAR/FP | 50/500 | 60 doses | €41.28 | 1 inhalation twice daily | €503 |
| Flixotide Accuhaler c  | FP | 500 | 60 doses | €31.47 | 2 inhalations once daily | €383 |
| Ventolin d  | Salbutamol | 100 | 200 doses | €2.69 | | |

*Source: Pack cost is taken from the Ministerio de Sanidad, Servicios Sociales e Igualdad. Available at: https://www.msssi.gob.es/en/home.htm Accessed February 2018
*TIO + SAL/FP administered together as escalation treatment for both UMEC/VI and TIO/OLO arm in base case
*a added on to UMEC/VI in an escalation strategy tested in a sensitivity analysis
*b rescue medication, modeled based on data from the head-to-head study [25]: 1.77 dose inhalations per day for TIO/OLO, 1.51 dose inhalations per day for UMEC/VI
FP fluticasone propionate, PTP price to public, SAL salmeterol xinafoate, TIO/OLO tiotropium/olodaterol, UMEC/VI umeclidinium/vilanterol, VAT value added tax
applied for patients escalating from UMEC/VI to triple therapy, therefore cancelling the FEV1 benefit conferred by the initial treatment.

**Base case settings**
A time horizon of 3 years was employed to align with the previous UMEC/VI versus TIO cost-effectiveness analysis [26] and with another cost-effectiveness analysis performed on treatments for COPD [42]. Costs and benefits were discounted at 3% per year in line with Spanish guidelines for economic evaluation [43].

**Model outputs**
The model estimated: exacerbation rates (number of moderate and severe exacerbations per patient per year), costs (total, drug, non-drug; discounted), survival, life-years (LY) gained (undiscounted), QALYs gained (discounted), and incremental cost effectiveness per LY and per QALY gained (i.e. the cost effectiveness of each treatment for each year of survival [LY] and for each LY adjusted for quality of life [QALY]).

**Sensitivity and scenario analyses**
A scenario analysis was conducted using baseline characteristics from the ITT population from the UMEC/VI versus TIO/OLO head-to-head study (Table 1)[25]. All other parameters remained as per the base case, with the exception of utilities, which are outlined below.

In the ITT scenario analysis, utilities were estimated using the GALAXY model algorithm [28, 29], based on St. George's Respiratory Questionnaire for COPD patients (SGRQ-C) in each model cycle. First, the pooled baseline COPD Assessment Test (CAT) in the UMEC/VI versus TIO/OLO study (mean: 17.76, standard error [SE]: 0.46) was re-scaled to match the 0–100 range of SGRQ-C, by multiplying by 2.5 (estimated SGRQ-C: 44.4). Second, SGRQ-C was converted to SGRQ using the following conversion: $SGRQ = [SGRQ-C - 0.9] + 3.1 = 43.1$. At baseline, this provided an estimate for SGRQ value of 43.1. This baseline SGRQ value was transformed into an EuroQol-5 Dimension questionnaire (EQ-5D) utility estimate using the algorithm developed by Starkie et al. [44]: $EQ-5D = 0.9617 - 0.0013 \times SGRQ_{total} - 0.0001 \times SGRQ_{total}^2 + 0.0231 \times %\text{male}$. The corresponding baseline EQ-5D utility score was 0.743. Utilities in subsequent cycles were calculated from the SGRQ-C scores using the same approach.

Deterministic sensitivity analyses were conducted to examine the impact of changing certain model parameters estimates and are listed in Table 3. A threshold analysis was also conducted on the price

---

### Table 3 Deterministic sensitivity analyses

| Parameter                              | Base case                      | Sensitivity analysis                                      |
|----------------------------------------|--------------------------------|-----------------------------------------------------------|
| Time horizon                           | 3 years                        | 1.5 and 10 years lifetime (25 years) time horizons         |
| Discount rate                          | 3%                             | 0% and 5%                                                 |
| Patient population and utility estimation | Equation developed in the previous cost-effectiveness analysis [26], based on an observational Spanish study [39] | Base case population with utilities estimated from GALAXY utility algorithm |
|                                        |                                 | ITT study population with utilities estimated from GALAXY utility algorithm |
|                                        |                                 | ITT study population with utilities estimated from GALAXY utility algorithm over a lifetime horizon |
| FEV1 treatment effect                  | UMEC/VI 180 mL, TIO/OLO 128 mL  | Equal FEV1 treatment effect (128 mL) for UMEC/VI and TIO/OLO |
|                                        | (incremental FEV1 treatment effect of 52 mL (favoring UMEC/VI) | Incremental FEV1 treatment effect with UMEC/VI equal to the upper (+ 77 mL) and lower (+ 28 mL) 95% CI |
| Treatment discontinuation              | 8.7%                           | 50% for year 1 from population-based, retrospective, observational study in Catalonia [55] and 8.7% (from the UPLIFT trial [41]) for subsequent years |
| Subsequent treatment                   | SAL/FP 50/500 mcg, two inhalations per day + TIO 18 mcg | Patients on UMEC/VI add FP 500 mcg, two inhalations per day; patients on TIO/OLO escalate to SAL/FP 500/50 mcg, two inhalations per day + TIO 18 mcg, one inhalation per day |
| Costing for dyspnea                    | €524.87/year; €699.98/year; €925.85/year | Cost of level of dyspnea ±20% |
| Costing for exacerbations              | Moderate €72.76; severe €4466.09 | Cost of exacerbations ±20% |

CI confidence interval, ED emergency department, FEV1 forced expiratory volume in one second, FP fluticasone propionate, ITT intent-to-treat, OCS oral corticosteroid, SAL salmeterol xinafoate, TIO/OLO tiotropium/olodaterol, UMEC/VI umeclidinium vilanterol, UPLIFT Understanding Potential Long-Term Impacts on Function with Tiotropium

*This sensitivity analysis assumed that patients in both the UMEC/VI and TIO/OLO arms experienced the same FEV1 improvement upon escalating to triple therapy (assumed to be + 52 mL)

*Inflated to 2017 Euros using the Consumer Price Index [38]

"cost of OCS and/or antibiotics, one primary care visit and one ED visit for 4.3% patients

"cost of one primary care visit, one ED visit, and hospitalization for 8 days
of TIO/OLO, for UMEC/VI to be cost effective at €30,000/QALY.

Probabilistic sensitivity analysis
Probabilistic sensitivity analyses (PSA) were conducted to address the uncertainty in the model input values, by assigning distributions to input parameters and randomly sampling from these distributions over 2000 simulations. Two probabilistic analyses were conducted: one for the base case and one for the ITT scenario analysis. Discontinuation rates used beta distributions with SE equal to 20% of the point estimates. Treatment effects on FEV1 was assigned a normal distribution with SE equal to 20% of the point estimates. Exacerbation event costs and annual health state costs used a gamma distribution with SE equal to 20% of the point estimate. Risk equation coefficients were sampled using correlated draws from a Cholesky decomposition table, obtained from the covariance matrices for each equation [28].

Results
In the base case analysis, UMEC/VI was associated with fewer exacerbations (−0.014 per year) and improvements in survival (+0.004 LYs) and quality of life (+0.029 QALYs) over a 3-year time horizon, when compared with TIO/OLO. Treatment with UMEC/VI also resulted in a cost saving of €393 per patient (Table 4).

The results of the ITT scenario analysis were consistent with the base case, showing that UMEC/VI was associated with fewer exacerbations (−0.014 per year) and improvements in survival (+0.003 LYS) and quality of life (+0.009 QALY) over a 3-year time horizon, when compared with TIO/OLO, alongside cost savings of €396 per patient (Table 5).

The results of sensitivity analyses are presented in Table 6, looking at the impact of the time horizon, discount rates, patient population and utility estimation, treatment effect, discontinuation, subsequent treatment, and costings on the model outcomes. UMEC/VI was found to be dominant (better outcomes and reduced costs) compared with TIO/OLO in all analyses, with the exception of one analysis (equal FEV1 absolute treatment effect in both arms [128 mL]), whereby UMEC/VI was considered equally effective but less expensive (Table 6). A sensitivity analysis conducted on the price of TIO/OLO found that UMEC/VI was cost effective at a willingness-to-pay threshold of €30,000/QALY until the price of TIO/OLO fell to €39.66 (51% reduction from its current list price at €81.49).

The probabilistic sensitivity analyses showed UMEC/VI to be more effective and less expensive than TIO/OLO in 100% of the simulations in the cost-effectiveness scatter plot, in both the base case and ITT scenario analysis (Fig. 1). In the base case PSA, mean costs (95% CI) for UMEC/VI and TIO/OLO were €5660 (€5000, €6410) and €6060 (€5380, €6830), respectively. Mean QALYs (95% CI) were 2.15 (2.08, 2.21) and 2.05 (2.05, 2.18) for UMEC/VI and TIO/OLO, respectively. In the ITT scenario PSA, mean costs (95% CI) for UMEC/VI and TIO/OLO were €5740 (€5060, €6490) and €6140 (€5460, €6910), respectively. Mean QALYs (95% CI) were 2.06 (1.98, 2.13) and 2.05 (1.97, 2.12) for UMEC/VI and TIO/OLO, respectively.

Discussion
This study aimed to assess the cost effectiveness of UMEC/VI versus TIO/OLO from a Spanish National Healthcare System perspective. The results of this analysis with a Spanish population as base case, demonstrated that UMEC/VI dominated TIO/OLO, providing gains in LYS and QALYs (+0.004 and +0.029, respectively) alongside total cost savings of €393 per patient over 3 years. Drug costs were the main driver of the total costs savings, followed by non-drug costs, specifically costs associated with exacerbation events. The model also showed small numerical reductions in total exacerbation rates (−0.014 exacerbations per year) with UMEC/VI compared with TIO/OLO. The results within the ITT scenario analysis using the UMEC/VI versus TIO/OLO head-to-head study population were consistent with the base case, with UMEC/VI shown to be
In the base case results, patients gained more QALYs than LYs, indicating that the treatment effect of UMEC/VI on FEV₁ benefit was associated with improvement in quality of life, but little to no reduction in mortality, which is likely the result of modeling treatment effect based on FEV₁ benefit. These results are consistent with previous studies of UMEC/VI and with systematic reviews and meta-analyses of other therapies, which have found that FEV₁ benefit is associated with improvement in quality of life, but little to no reduction in mortality [12, 16, 45, 46]. A similar result was observed within the ITT scenario analysis; however, the magnitude of benefit was lower in this population compared with the base case, possibly due to the different approaches to utility estimation used within the base case and ITT analyses. The Spanish utility equation used within the base case, and the SGRQ-C equation used within the ITT analysis considered different variables and would therefore be sensitive to different parameters. In addition, the populations used within each equation would lead to different estimates of utility.

This study is the first to compare two LAMA/LABA dual therapies using direct head-to-head data from a randomized, 12-week study [24], which is the most
reliable set of data to include within a cost-effectiveness model [24]. Other studies have compared LAMA/LABA dual therapy using models with assumptions based on network meta-analyses [47, 48], or have used head-to-head data to compare UMEC/VI with TIO monotherapy [26, 49]. For example, a UK cost-effectiveness analysis of TIO/OLO found that costs and QALYs associated with TIO/OLO were equal to those of UMEC/VI and IND/GLY. However, this study was based on indirect data from a network meta-analysis and assumed equal efficacy and equal acquisition costs for LAMA/LABA comparators [48]. Similarly, a cost-effectiveness analysis conducted in Spain used efficacy inputs derived from a meta-analysis and found that aclidinium/formoterol (ACL/FF) 400/12 mcg provided the same health benefits as TIO/OLO in terms of LYs (4.073) and QALYs (2.928), but that ACL/FF was associated with lower costs (−€332) over a 5-year time horizon [47]. An additional cost-effectiveness analysis conducted in the US found UMEC/VI to be equally effective but less costly compared with open dual LAMA/LABA combination, with efficacy inputs derived from two clinical studies [14, 16, 49].

### Table 6 Model results: sensitivity analyses

| Sensitivity analyses | Incremental costs (€) | Incremental QALYs | ICER (€ per QALY gained) |
|---------------------|-----------------------|-------------------|--------------------------|
| **Base case**       | −€393                 | 0.029             | Dominant                 |
| **Time horizon**    |                       |                   |                          |
| 1 year              | −€152                 | 0.010             | Dominant                 |
| 5 years             | −€562                 | 0.043             | Dominant                 |
| 10 years            | −€752                 | 0.071             | Dominant                 |
| Lifetime (25 years) | −€774                 | 0.091             | Dominant                 |
| **Discount rate**   |                       |                   |                          |
| 0%                  | −€405                 | 0.029             | Dominant                 |
| 5%                  | −€388                 | 0.027             | Dominant                 |
| **Patient population and utility estimation** | | | |
| Base case population with utilities estimated from the GALAXY utility algorithm | −€393 | 0.010 | Dominant |
| Use ITT study population with utilities estimated from the GALAXY utility algorithm | −€396 | 0.009 | Dominant |
| Use ITT study population with utilities estimated from the GALAXY utility algorithm with life time horizon | −€781 | 0.052 | Dominant |
| **Treatment effect** |                       |                   |                          |
| Analysis with equal FEV₁ treatment effect (128 mL) across UMEC/VI and TIO/OLO arms after initiating therapy | −€338 | 0.000 | Equally effective; less expensive |
| Incremental FEV₁ treatment effect with UMEC/VI after initiating therapy equal to the upper 95% CI (+ 77 mL) | −€420 | 0.041 | Dominant |
| Incremental FEV₁ treatment effect with UMEC/VI after initiating therapy equal to the lower 95% CI (+ 28 mL) | −€362 | 0.012 | Dominant |
| **Treatment discontinuation** | | | |
| Treatment discontinuation rates from first year sourced from population-based, retrospective, observational study in Catalonia (50%) and from the UPLIFT trial for subsequent years (8.7%) | −€252 | 0.018 | Dominant |
| **Subsequent treatment** | | | |
| Patients on UMEC/VI escalate to UMEC/VI and FP 500 mcg, two inhalations per day while patients on TIO/OLO escalate to SAL/FP 500/50 mcg, two inhalations per day + TIO 18 mcg, one inhalation per day | −€355 | 0.032 | Dominant |
| **Costing** | | | |
| Cost of level of dyspnea plus 20% | −€397 | 0.029 | Dominant |
| Cost of level of dyspnea minus 20% | −€392 | 0.029 | Dominant |
| Cost of exacerbations plus 20% | −€404 | 0.029 | Dominant |
| Cost of exacerbations minus 20% | −€385 | 0.029 | Dominant |

CI confidence interval, FEV₁ forced expiratory volume in one second, FP fluticasone propionate, ICER incremental cost-effectiveness ratio, ITT intention-to-treat, LY life years, QALY quality-adjusted life-year; SAL salmeterol xinafoate, TIO/OLO tiotropium/olodaterol, UMEC/VI umeclidinium/vilanterol, UPLIFT Understanding Potential Long-Term Impacts on Function with Tiotropium
Several cost-effectiveness analyses have been conducted from a Spanish National Healthcare System perspective, using direct head-to-head data. One study compared UMEC and TIO [50], using direct head-to-head data from a 12-week study whereby in which UMEC was found to be superior to TIO for trough FEV\textsubscript{1} in the ITT population (treatment difference: 53 mL, 95% CI: 25, 81 mL; \(p < 0.001\)) [24]. Results from this cost-effectiveness analysis using direct head-to-head data from the UMEC and TIO study showed results comparable to our study, whereby UMEC dominated TIO, gaining similar 0.014 QALYs and demonstrating cost savings of €192 [50]. Another Spanish cost-effectiveness analysis of UMEC/VI versus TIO alone estimated 3-year costs of €6215 and QALYs of 2.025 for patients treated with UMEC/VI and found UMEC/VI to be more effective and costlier than TIO monotherapy, with an incremental cost-effectiveness ratio (ICER) of €21,475/QALY [26]. The higher QALYs and lower costs for UMEC/VI in our base case analysis reflect the patient population characteristics at baseline. The Spanish population in our analysis had fewer current smokers, was less obese, had a lower cardiovascular disease comorbidity, experienced fewer exacerbations and had a higher FEV\textsubscript{1}% predicted at baseline compared with the population in the Spanish cost-effectiveness analysis of UMEC/VI versus TIO [26].

The cost effectiveness analysis presented here could be a conservative estimate, as some medical costs such as costs associated with inhaler misuse, were not taken into account within the model [51, 52]. Poor inhalation technique can lead to poor disease control and the costs associated with critical errors are considerable [51, 52]. In Spain, total costs associated with poor inhalation technique were estimated at €155 million in 2015, representing 15.5% of the total costs associated with unscheduled healthcare visits [51]. A recent study compared the Ellipta device with other commonly used inhaler devices, and the results demonstrated that fewer patients had at least one critical error using the Ellipta device compared with five alternative inhalers [53]. In addition, the Ellipta inhaler received more positive patient feedback in terms of ease of use in the UMEC/VI versus TIO/OLO head-to-head study, compared with the Respimat inhaler [25]. Inhaler training was provided in the UMEC/VI versus TIO/OLO head-to-head study, and inhaler technique was routinely checked, thus reiterating how the results of this cost-effectiveness analysis are likely to be a conservative estimate of treatment difference, as they do not fully reflect the development of poor technique over time and variation in inhaler training seen in a real-world setting.

The results of this study are based on data from the 8-week UMEC/VI versus TIO/OLO head-to-head study [25]. Future studies to confirm the results observed within this direct treatment comparison, and to compare the cost effectiveness of LAMA/LABA dual therapies over a longer duration, would be beneficial in further helping payers make informed judgements on the cost effectiveness of LAMA/LABA therapies.
As there are currently no clinical studies providing data on the use of LAMA/LABA combination therapy for a longer duration than the timeframes considered within this analysis (3 years, 5 years, 10 years and lifetime), certain assumptions were made within this model. One such assumption was that treatment effects began at the outset of the analysis (month 0) in both arms. This assumption is supported by data from studies that demonstrated observable, significant improvement in FEV _1_ from the first dose [12, 40]. The model also assumed that treatment effect remained constant for the duration of the study, as long as patients remained on treatment. Treatment effect differences between UMEC/VI and TIO/OLO may be driven by the differences seen between the LAMA components UMEC and TIO. A randomized, blinded, 12-week parallel group study demonstrated superiority of UMEC over TIO on the primary endpoint of trough FEV _1_. The model also assumed that treatment effect remained constant for the duration of the study, as long as patients remained on treatment. Treatment effect differences between UMEC/VI and TIO/OLO were maintained over 10 years [24, 54]. This was shown in both the overall population [54] and the subgroup of patients with GOLD stage II COPD [41], as included in the analysis presented here. An additional study demonstrated significant improvement in FEV _1_ for patients treated with UMEC/VI, and this treatment benefit was maintained over 6 months [12]. Based on these previous studies, it was therefore reasonable to assume that the differential treatment effect seen between UMEC/VI and TIO/OLO would be maintained over a 3-year time period [24, 54].

Discontinuation rates used within the base case were based on data from the UPLIFT study [41], as it provides data over a 4-year follow-up, and this approach was validated by Spanish clinical experts [41]. Nevertheless, a sensitivity analysis was conducted using 50% discontinuation rates sourced from an observational study in Catalonia [55], and UMEC/VI remained dominant compared with TIO/OLO. Data on escalation to triple therapy from LAMA/LABA therapy are also not available from previous clinical studies, therefore it was necessary to make an assumption regarding the changes in FEV _1_ once a patient escalated to subsequent triple therapy (LAMA/LABA+ICS). The base case assumed that patients would escalate to the same triple therapy regimen, and that FEV _1_ treatment effect once on triple therapy would be the same between arms. This may have been a conservative assumption as it assumed that patients treated with UMEC/VI did not experience a change in FEV _1_ after they initiated ICS therapy. Indeed, this assumption was tested in a sensitivity analysis and an increase in QALY gains of 0.004 versus the base case was observed. Finally, data on baseline fibrinogen concentration and 6MWT distances were not available from the sources used for this analysis and had to be estimated within the model. It may be informative to collect and include such data within future studies to assist further cost-effectiveness evaluations.

### Conclusions

This analysis has shown UMEC/VI to be both more effective and less expensive than TIO/OLO for patients with symptomatic COPD in Spain, providing small additional gains in LY (0.004) and QALY (0.029), as well as a cost saving of €393 per patient over a 3-year time period. Scenario and sensitivity analyses demonstrated results consistent with the base case. These data may aid payers in making judgements on which LAMA/LABA treatments can be considered cost effective in a Spanish setting.

### Additional files

**Additional file 1:** Improvement in COPD disease factors in the model at time = 0. Description of the improvements in COPD disease factors built into the model at time 0 (i.e. the beginning of the cycle), when FEV _1_ benefit has been included. (DOCX 13 kb)

**Additional file 2:** Utilities. Description of the utilities used within the study, including any modifications. (DOCX 13 kb)

### Abbreviations

6MW: 6-min walk test; CAT: COPD Assessment Test; CI: Confidence interval; COPD: Chronic obstructive pulmonary disease; ECLIPSE: Evaluation of COPD Longitudinally to Identify Predictive Surrogate Endpoints; EMA: European Medicines Agency; EQ 5D: EuroQol-5 Dimension questionnaire; FEV _1_: Forced expiratory volume in 1 s; FP: Fluticasone propionate; GesEPOC: Guia española de la enfermedad pulmonar obstructiva crónica; GOLD: Global Initiative for Chronic Obstructive Lung Disease; ICS: Inhaled corticosteroid; ITT: Intent to treat; LABA: Long-acting β2-agonist; LAMA: Long-acting muscarinic antagonist; LY: Life-years; mMRC: Modified Medical Research Council; OLO: Olodaterol; PP: Per-protocol; PSA: Probabilistic sensitivity analyses; PTP: Price to public; QALYs: Quality-adjusted life years; SAL: Salbutamol; SE: Standard error; SGRQ-C: St. George's Respiratory Questionnaire for COPD patients; TIO: Tiotropium; UPLIFT: Understanding Potential Long-Term Impacts on Function with Tiotropium; VAT: Value added tax; VI: Vilanterol

### Acknowledgments

Editorial support (in the form of writing assistance, assembling tables and figures, collating author comments, grammatical editing and referencing) was provided by Emma Hargreaves at Fishawack Indicia Ltd., UK, and was funded by GSK.

### Funding

This study was funded by GSK (study number HO-17-17500). The funders of the study had a role in study design, data analysis, data interpretation, and writing of the report. Data analysis was conducted by ICON Health Economics and funded by GSK. No funding was provided to employees of ICON Health Economics for manuscript development. The corresponding author had full access to all the data and the final responsibility to submit for publication.

### Availability of data and materials

GSK makes available anonymized individual participant data and associated documents from interventional clinical studies which evaluate medicines, upon approval of proposals submitted to www.clinicaltrialdatarequest.com. To access data for other types of GSK sponsored research, for study documents without patient-level data and for clinical studies not listed, please submit an enquiry via the website.
Authors' contributions

MTD, IPN, YA, LAV-A, JW, BSB and NAR contributed to the concept or design of the study and data analysis and interpretation. BA-N, MM and FG-R contributed to data analysis and interpretation. All authors read and approved the final manuscript.

Ethics approval and consent to participate

No ethics approval was required for the study as data were taken from previously conducted studies that had obtained ethical approval.

Consent for publication

Not applicable.

Competing interests

IPN and YA are employees of GSK and hold stocks/shares in the company. MTD was an employee of GSK and held stocks/shares in the company, at the time of the study. LAV-A is an employee of GSK. JW, BSB and NAR are employees of ICON Health Economics, who were contracted by GSK to provide data analysis for the study. JW was an employee of ICON Health Economics at the time of the study. No funding was provided to employees of ICON Health Economics for manuscript development. BA-N received personal fees and nonfinancial support from GlaxoSmithKline grants, personal fees, and nonfinancial support from Novartis AG, personal fees and nonfinancial support from Boehringer Ingelheim, personal fees and nonfinancial support from Boehringer Ingelheim, personal fees and nonfinancial support from Laboratorios Menarini, personal fees from Gebro, and personal fees from AstraZeneca outside the submitted work. In addition, BA-N has a patent (P201730724) pending. JW has received speaker fees from Boehringer Ingelheim, Chiesi, Cipla, Menarini, Rovi, Grifols and Novartis, and consulting fees from Boehringer Ingelheim, Chiesi, GlaxoSmithKline, Gebro Pharma, CSL Behring, Novartis and Grifols. FG-R has received speaker fees from Boehringer Ingelheim, Novartis, Chiesi and Rovi, and consulting fees from Boehringer Ingelheim, GlaxoSmithKline, Gebro Pharma, AstraZeneca, Menarini, and Novartis.

Author details

1Value Evidence and Outcomes, GSK, 980 Great West Road, Brentford, Middlesex TW8 9GK, UK. 2ICON Health Economics, ICON plc, Abingdon, UK. 3Departamento de Evaluación de Medicamentos, GSK, Tres Cantos, Madrid, Spain. 4Global Respiratory Franchise, GSK, Brentford, Middlesex, UK. 5Hospital de Alta Resolución de Loja, Granada, Spain. 6Pneumology Department, Hospital Universitari Vall d’Hebron, Barcelona, Spain. 7Hospital Universitari La Paz-Idiapaz, Madrid, Spain. 8ICON Health Economics, ICON, Toronto, ON, Canada.

Received: 12 June 2018 Accepted: 18 October 2018

Published online: 20 November 2018

References

1 Global Initiative for Chronic Obstructive Lung Disease. Global Strategy for the Diagnosis, Management and Prevention of Chronic Obstructive Pulmonary Disease. 2018. http://goldcopd.org/wp-content/uploads/2017/11/GOLD-2018-v6.0-FINAL-revised-20-Nov_WMSf.pdf. Accessed April 2018.

2 Miravitlles M, Soriano JB, Garcia-Rio F, Muñoz L, Duran-Tauleria E, Sanchez G, et al. Prevalence of COPD in Spain: impact of undiagnosed COPD on quality of life and daily life activities. Thorax. 2009;64:863–8.

3 Soriano JB, Miravitlles M, BORDERAS L, Duran-Tauleria E, Rio FG, Martinez J, et al. Geographical variations in the prevalence of COPD in Spain: relationship to smoking, death rates and other determining factors. Arch Bronconeumol (English Edition). 2010;46:522–30.

4 Masa J, Sobradillo V, Villasante C, Jiménez-Ruiz C, Fernández-Fau L, Viejo J, et al. Costes de la EPOC en España. Estimación a partir de un estudio epidemiológico poblacional. Arch Bronconeumol. 2004;40:72–9.

5 Miravitlles M, Murio C, Guerrero T, Gisbert R. Costs of chronic bronchitis and COPD: a 1-year follow-up study. Chest. 2003;123:784–91.

6 Cazzola M, Page CP, Calzetta L, Matera MG. Pharmacology and therapeutic agents of bronchodilators. Pharmacol Rev. 2012;64:450–504.

7 Tashkin DP, Cooper CB. The role of long-acting bronchodilators in the management of stable COPD. Chest. 2004;125:249–59.

8 Tashkin DP, Ferguson GT. Combination bronchodilator therapy in the management of chronic obstructive pulmonary disease. Respir Res. 2013;14:49.

9 Miravitlles M, Soler-Cataluña JJ, Calle M, Molina J, Almagro P, Quintano JA, et al. Spanish COPD guidelines (GesEPOC) 2017. Pharmacological treatment of stable chronic obstructive pulmonary disease. Arch Bronconeumol. 2017;53:334–5.

10 Miravitlles M, Soler-Cataluña JJ, Calle M, Molina J, Almagro P, Quintano JA, et al. Spanish COPD guidelines (GesEPOC). pharmacological treatment of stable COPD. Arch Bronconeumol (English Edition). 2012;48:247–57.

11 European Medicines Agency (EMA). Anoro: umeclidinium bromide/ vilanterol. 2014. http://www.ema.europa.eu/ema/index.jsp?curl=pages/ medicines/human/medicines/002751/human_med_001754.jsp&xmlid= WC0b01ac058001d124. Accessed April 2018.

12 Donohue JF, Maleki-Yazdi M, Kilbride S, Mehta R, Kalberg C, Church A. Efficacy and safety of once-daily umeclidiniumVilanterol 62.5/25 mcg in COPD. Respir Med. 2013;107:1538–46.

13 Sier TM, Donald AC, O’Dell D, Church A, Fahy WA. A randomized, parallel-group study to evaluate the efficacy of umeclidinium/vilanterol 62.5/25 μg on health-related quality of life in patients with COPD. Int J Chron Obstruct Pulmon Dis. 2016;11:971–9.

14 Decramer M, Arauzo A, Kerwin E, Kaelin T, Richard N, Crater G, et al. Efficacy and safety of umclidinium plus vilanterol versus tiotropium, vilanterol, or umclidinium monotherapies over 24 weeks in patients with chronic obstructive pulmonary disease results from two multicentre, blinded, randomised controlled trials. Lancet Respir Med. 2014;2:472–86.

15 Donohue JF, Singh D, Munuz C, Kilbride S, Church A. Magnitude of umclidinium/vilanterol lung function effect depends on monotherapy responses: results from two randomised controlled trials. Respir Med. 2016;112:65–74.

16 Maleki-Yazdi MR, Kaelin T, Richard N, Zvarich M, Church A. Efficacy and safety of umclidinium/vilanterol 62.5/25 mcg and tiotropium 18 mcg in chronic obstructive pulmonary disease results of a 24-week, randomized, controlled trial. Respir Med. 2014;108:1752–60.

17 Kervin EM, Kalberg CJ, Galkin DV, Zhu C-Q, Church A, Riley JH, et al. Umeclidinium/Vilanterol as step-up therapy from tiotropium in patients with moderate COPD: a randomized, parallel-group, 12-week study. Int J Chron Obstruct Pulmon Dis. 2017;12:745–55.

18 Donohue JF, Worsley S, Zhu CQ, Hardaker L, Church A. Improvements in lung function with umclidinium/vilanterol versus fluticasone propionate/ salmeterol in patients with moderate-to-severe COPD and infrequent exacerbations. Respir Med. 2015;109:870–81.

19 Singh D, Worsley S, Zhu CQ, Hardaker L, Church A. Umeclidinium/vilanterol versus fluticasone propionate/salmeterol in COPD: a randomised trial. Pulm Med. 2015;1:91.

20 Boehringer Ingelheim. New advance in COPD maintenance treatment, Spiolto® Respirat®, approved in first European countries. 2015. https://www. boehringer-ingelheim.com/press-release/new-advance-copd-maintenance -treatment-spiolto-respirat-approved-first-european. Accessed April 2018.

21 Miravitlles M, Urrutia G, Mathoudakis AG, Ancochea J. Efficacy and safety of tiotropium and olodaterol in COPD: a systematic review and meta-analysis. Respir Res. 2018;18:196.

22 Calzetta L, Rogliani P, Matera MG, Cazzola M. A systematic review with meta-analysis of dual bronchodilatation with LAMA/LABA for the treatment of stable COPD. Chest. 2016;149:1181–96.

23 Sion KY, Huisman EL, Punekar YS, Naya I, Ismaila AS. A network meta-analysis of long-acting muscarinic antagonist (LAMA) and long-acting β2-agonist (LABA) combinations in COPD. Pulm Ther. 2017;3:297–316.

24 Feldman G, Maltais F, Khindri S, Vahdati-Bolouri M, Church A, Fahy WA, et al. A randomized, blinded study to evaluate the efficacy and safety of umclidinium 62.5 μg compared with tiotropium 18 μg in patients with COPD. Int J Chron Obstruct Pulmon Dis. 2016;11:719.

25 Feldman GJ, Sousa AR, Lipson DA, Tomas L, Barnes N, Riley JH, et al. Comparative efficacy of once-daily Umclidinium/Vilanterol and tiotropium/ Olodaterol therapy in symptomatic chronic obstructive pulmonary disease: a randomized study. Adv Ther. 2017;34:2518–33.

26 Miravitlles M, Gildz B, Huerta A, Vilcampa A, Cardoso D, Garcia-Rio F. Cost-effectiveness of combination therapy umclidinium/Vilanterol versus tiotropium in symptomatic COPD Spanish patients. Int J Chron Obstruct Pulmon Dis. 2016;11:123.
27. Celli BR, MacNee W, Force AE. Standards for the diagnosis and treatment of patients with COPD: a summary of the ATS/ERS position paper. Eur Respir J. 2004;23:932–46.
28. Briggs AH, Baker T, Risebrough NA, Chambers M, Gonzalez-McQuire S, Ismaila AS, et al. Development of the Galaxy chronic obstructive pulmonary disease (COPD) model using data from ECLIPSE: internal validation of a linked-equations cohort model. Med Decis Mak. 2017;37:469–80.
29. Ezuzides A, Colby C, Briggs AH, Lomas DA, Rutten-van-Molken MP, Tabberer M, et al. Statistical modeling of disease progression for chronic obstructive pulmonary disease using data from the ECLIPSE study. Med Decis Mak. 2017;37:453–68.
30. Risebrough NA, Briggs A, Baker TM, Ezuzides A, Colby C, Rutten-van-Molken MP, et al. Validating a model to predict disease progression outcomes in patients with COPD. Value Health. 2014;17:A560–1.
31. Tabberer M, Gonzalez-McQuire S, Mueblerova H, Briggs AH, Rutten-van-Molken MP, Chambers M, et al. Development of a conceptual model of disease progression for use in economic modeling of chronic obstructive pulmonary disease. Med Decis Mak. 2017;37:440–52.
32. Hoogendoorn M, Feenstra TL, Asukai Y, Briggs AH, Hansen RN, Leidi R, et al. 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.
33. Agusti A, Calverley PM, Celli B, Coxon HO, Edwards LD, Lomas DA, et al. Characterisation of COPD heterogeneity in the ECLIPSE cohort. Respir Res. 2010;11:122.
34. Calle Rubio M, Casamor R, Miravitlles M. Identification and distribution of COPD phenotypes in clinical practice according to Spanish COPD guidelines: the FENEPOCO study. Int J Chron Obstruct Pulmon Dis. 2017;12:1617.
35. Calle Rubio M, Alcázar Navarrete B, Soriaño JB, Soler-Cataluña JJ, González-Moro JM, Ferrer MEF, et al. Clinical audit of COPD in outpatient respiratory clinics in Spain: the EPOCONSUL study. Int J Chron Obstruct Pulmon Dis. 2017;12:417.
36. Spanish Ministry of Health. Spanish National Health Survey 2011–2012. 2012. https://www.msssi.gob.es/en/profesionales/nomenclador.do. Accessed April 2018.
37. Ministerio de Sanidad SSal. Information about the products included in the pharmaceutical provision of the SNS (dispensable through pharmacies). 2018. http://www.msssi.gob.es/en/profesionales/nomenclador.do. Accessed April 2018.
38. National Statistics Institute. Consumer Price Index (CPI). 2017. http://www.ine.es/dyngs/INEbase/es/operacion.htm?c=Estadistica_C&cid=12547361768028&menu=ultDatos&idp=1254735976607. Accessed April 2018.
39. Miravitlles M, Huerta A, Fernández-Villar JA, Alcázar B, Villa G, Formé C, et al. Generic utilities in chronic obstructive pulmonary disease patients stratified according to different staging systems. Health Qual Life Outcomes. 2014;12:120.
40. Maltais F, Singh S, Donald AC, Crater G, Church A, Goh AH, et al. Effects of a combination of umeclidinium/vilanterol on exercise endurance in patients with chronic obstructive pulmonary disease: two randomized, double-blind clinical trials. Ther Adv Respir Dis. 2014;8:169–81.
41. Decramer M, Celli B, Kesten S, Lustig T, Mehra S, Taskin DP. Effect of tiotropium on outcomes in patients with moderate chronic obstructive pulmonary disease (UPLIFT): a prespecified subgroup analysis of a randomised controlled trial. Lancet. 2009;374:1171–8.
42. Rutten-van Molken MP, Goossens LM. Cost-effectiveness of pharmacological maintenance treatment for chronic obstructive pulmonary disease: a review of the evidence and methodological issues. PharmacoEconomics. 2012;30:271–302.
43. López-Bastida J, Oliva J, Antoranansas F, García-Altés A, Gisbert R, Mar J, et al. Spanish recommendations on economic evaluation of health technologies. Eur J Health Econ. 2010;11:513–20.
44. Starkie HJ, Briggs AH, Chambers MG, Jones P. Predicting EQ-5D values using the SGRQ. Value Health. 2011;14:435–60.
45. Horita N, Goto A, Shibata Y, Ota E, Nakashima K, Nagai K, et al. Long-acting muscarinic antagonist (LAMA) plus long-acting beta-agonist (LABA) versus LABA plus inhaled corticosteroid (ICS) for stable chronic obstructive pulmonary disease (COPD). Cochrane Database Syst Rev. 2017;10:CD012066.
46. Kamer C, Cheng J, Foke P. Tiotropium versus placebo for chronic obstructive pulmonary disease. Cochrane Database Syst Rev. 2012;11: CD009285.
47. Capel M, Mareque M, Alvarez CJ, Lindner L, Oyagüez I. Cost-effectiveness of fixed-dose combinations therapies for COPD in Spain. Eur Respir J. 2017; 50(Suppl 61):PA2792.