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Cost-effectiveness analysis of Anti-IL-5 therapies of severe eosinophilic asthma in Spain

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Author contributions:

FJGB, XMG, and JLIA José Luis Izquierdo-Alonso were involved in the interpretation of the data and or revising the paper critically for intellectual content.

SY and GVDW were involved in the conception and design of the analysis.

EM and AG were involved in the analysis and interpretation of the data and the drafting of the paper.

All authors approved the final version to be published; and all authors agree to be accountable for all aspects of the work.

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Aim: To analyse the cost-effectiveness of MEP with standard of care (SoC) versus other anti-IL-5 therapies approved for the treatment of severe eosinophilic asthma (SEA) patients, within the Spanish National Health System (NHS) perspective.

Methods: a Markov model with a 4-week cycle length was used to compare MEP with BEN and RES as therapies added to SoC in the management of SEA, in terms of cost per QALY gained and incremental cost-effectiveness ratio (ICER). Costs (€2019) were obtained from public sources, while utilities and transition probabilities were retrieved from literature, e.g. network meta-analysis. Continuation criteria for biological treatment and reduction of oral corticosteroids (OCS) was set at 50% minimum reduction of exacerbation rate. Adverse events related to chronic OCS use included diabetes, osteoporosis, cataracts, acute myocardial infarct, and peptic ulcer. The analysis was performed over a 5-year time horizon from the National Healthcare System (NHCS) perspective, with a yearly discount rate of 3% applied to both costs and QALYs. Probabilistic sensitivity analysis and univariate deterministic sensitivity analysis were performed to address uncertainty around the cost-effectiveness results.

Results: On top of SoC, the model indicates that MEP is dominant (lower cost, higher benefit) compared to BEN and RES: For BEN and RES respectively, treatment with MEP had a point estimate of 0.076 and 0.075 additional QALYs, and savings of 3,173.47€ and 7,772.95€ per patient. The findings were robust to variation as estimated using sensitivity analysis.

Conclusions: MEP is a cost-effective treatment in comparison with BEN and RES added to SoC for patients with SEA in the Spanish setting.

Keywords: Severe eosinophilic asthma, cost-effectiveness, mepolizumab, indirect treatment comparison, anti-IL-5

JEL codes: I10; I1; I; G14; G1; G

Short title: Cost-effectiveness analysis in severe eosinophilic asthma

Introduction

With the highest prevalence of chronic respiratory diseases (Soriano et al., 2017), asthma is described by the Global Initiative for Asthma (GINA) as a “heterogeneous disease, usually characterized by chronic airway inflammation. It is defined by the history of respiratory symptoms such as wheeze, shortness of breath, chest tightness and cough that vary over time and intensity, together with variable airflow limitation” (Asthma, 2020). With an estimated 358 million cases worldwide in 2015 (Soriano et al., 2017), rates of asthma have been observed to increase with adaptation of modern lifestyles, urbanicity, and ageing populations, and are therefore expected to continue growing over the coming years (Masoli et al., 2004). Combined with an expected rise in the direct and indirect costs associated per patient (*Global surveillance, prevention and control of chronic respiratory diseases. A comprehensive approach.*, 2007), the burden of asthma, both on patients and society, is large and growing.

Asthma is a complex heterogeneous condition, in which exacerbations, severity and frequency depend on patient characteristics and asthma phenotype (*Global surveillance, prevention and control of chronic respiratory diseases. A comprehensive approach.*, 2007; Melero Moreno et al., 2019). Effective and safe treatment, particularly for severe asthma, is recognized as an unmet need (Chung et al., 2014). Severe asthma with inadequate control is associated with high healthcare resources consumption (Chung et al., 2014; Melero Moreno et al., 2019) and substantial indirect costs (Puig-Junoy and Pascual-Argenté, 2017). Direct costs related to asthma management are mostly driven by medication costs, which are attributable to 45%-84% of direct costs in Europe, and 51%-68% in North America. (Souliotis et al., 2017) Severe asthma patients have been estimated to accrue annual costs ranging between €7,411-10,199 per patient in Spain (Melero Moreno et al., 2019).

Severe eosinophilic asthma (SEA) is a phenotype of asthma characterized by eosinophilic inflammation, which affects approximately 5% of asthma patients and up to 50% of severe asthma (Skolnik and Carnahan, 2019). Eosinophils, a type of white blood cells, cause lung inflammation in this subgroup of asthma patients, increasing the risk of suffering an exacerbation. SEA is identified in primary care based on measured historic blood eosinophils count of ≥ 150 -300 cells/ μ L (Bakakos et al., 2019). Due to persistent airflow limitation, distal inflammation with air trapping and continuous exacerbations, SEA leads to poor asthma control (Asthma, 2019; Busse et al., 2019).

Asthma management aims at limiting exposure to asthma triggers, to control and prevent the frequency and severity of exacerbations and to improve patients' quality of life (QoL). Optimal asthma treatment requires to correct identification of the relevant asthma phenotype for a proper control of the patients' condition. Due to its refractory nature, severe asthma requires treatment with high doses of inhaled corticosteroids (ICS) in addition to a long-acting β 2-agonist (LABA), leukotriene modifier or theophylline and/or continuous or near continuous systemic corticosteroids as background therapy (Asthma, 2019; Chung et al., 2014). Despite combined therapy, SEA remains difficult to treat (Chung et al., 2014), implies continuous or intermittent high-dose ICS treatment and may require emergency room visits and hospitalisation (Buhl et al., 2017).

Currently, SEA patients who continue to suffer multiple exacerbations can benefit from three different anti-interleukin-5 (anti-IL-5) therapies: Mepolizumab (MEP), Benralizumab (BEN), and Reslizumab (RES) (European Medicines Agency, 2018, 2016, 2015). Interleukin-5 (IL-5), a T-cell-derived cytokine, acts as a mediator in eosinophil activation (Buhl et al., 2017). As IL-5 levels are strongly correlated with asthma severity in SEA patients (Castillo et al., 2017), these biologic therapies offer a superior asthma control by reducing

eosinophils. (Cabon et al., 2017) Anti-IL-5 therapies added to standard of care (SoC) have established efficacy in SEA patients, have no serious safety concerns in clinical trials and have demonstrated favorable benefit–risk profiles (Buhl et al., 2017). Biologic treatments for severe asthma may also reduce the need for complementary therapy with continuous systemic corticosteroids, which often lead to several adverse events, the most frequently reported of which include diabetes, osteoporosis, cataract, acute myocardial infarction, and peptic ulcers (Bloechliger et al., 2018; Waljee et al., 2017). Evidence favors anti-IL-5 add-on treatment as they reduce exacerbation rates and hospitalizations at a similar level of efficacy. Guidelines in Spain recommend the use of MEP, BEN, and RES in those cases of severe eosinophilic asthma, specifically (Sociedad Española de Neumología y Cirugía Torácica, 2020), MEP and BEN for patients with eosinophils ≥ 500 cells/ μ L and those with < 500 cells/ μ L but who have suffered more than 2 severe exacerbations in the last year requiring at least 2 oral or systemic corticosteroid cycles or increasing maintaining corticosteroids for at least 3 days; or patients with more than one exacerbation requiring hospital admission, ICU admission or mechanical ventilation; this same restrictions are applied for the use of RES in those patients with eosinophils 400-500 cells/ μ L. (Agencia Española de Medicamentos y Productos Sanitarios, 2019, 2018, 2016)

Several indirect treatment comparisons have been carried out in order to determine differences in costs and effectiveness among available anti-IL-5 treatments (Busse et al., 2019; Cabon et al., 2017; Cockle et al., 2017; Henriksen et al., 2018). The study carried out by Busse et al. (Busse et al., 2019) reports that MEP was associated with significantly greater improvements in exacerbations and asthma control in comparison with RES or BEN in patients with similar blood eosinophil counts. However, there is a lack of comparative evidence regarding the economic impacts of these therapies (McQueen et al., 2018).

The main objective of this study was to estimate the economic and health-related impact of three anti-IL-5 treatments added to SoC in the management of adult SEA patients in Spain through an estimation of direct costs and quality-adjusted life years (QALYs) over a 5-year time horizon.

Methods

Study design

A cost-effectiveness analysis (CEA) was performed to compare both MEP with BEN and RES as add-ons to the SoC in SEA patients. All these three anti-IL-5 therapies are indicated for add-on, long-term treatment in SEA patients (Bakakos et al., 2019).

The incremental cost-effectiveness ratio for both scenarios was estimated for a 5-year time horizon. The analysis was carried out from the Spanish NHCS perspective and only direct healthcare costs were considered. In accordance with the main Spanish guidelines for economic evaluation (López-Bastida et al., 2010), the analyses used a yearly discount rate of 3% for both costs and QALYs, and a cost-effectiveness threshold of €30,000 to evaluate results (Sacristán et al., 2002).

Model structure

A 4-health state Markov model with a 4-week cycle length was used to simulate costs and QALY gains for a 5-year horizon (Figure 1). (National Institute for Health and Care Excellence, 2017) The model distinguishes between clinical response to anti-IL-5 (i.e. continuation criteria met or not met); mortality related to asthma and all-cause; three types of exacerbation events requiring (1) OCS burst, (2) emergency department (ED) visit, and (3) hospitalization. Transitions between on-treatment health states and asthma-related death

were caused by hospital exacerbations. All remaining deaths were considered as non-asthma related.

Population

According to the approved label, MEP is indicated for SEA in adults, adolescents, and children aged 6 years and older. MEP trials target population had a blood eosinophil count of ≥ 150 cells/ μL at baseline or ≥ 300 cells/ μL in the 12 months prior to screening. In contrast, BEN and RES are indicated only for adults, and the clinical trials for BEN and RES had baseline blood eosinophil counts in patients ≥ 300 cells/ μL (as primary analysis) and ≥ 400 cells/ μL , respectively. Consequently, two scenarios were analyzed:

- Patients with blood eosinophil ≥ 300 cells/ μL : MEP + SoC versus BEN + SoC
- Patients with blood eosinophil ≥ 400 cells/ μL : MEP + SoC versus RES + SoC.

Age and sex distributions were obtained from the Quirce et al. study (N=134) that analysed SEA patients aged ≥ 18 in Spain, mean age (95% CI) 54.07 years old (51.55-56.59), of whom 63.4% were female and 36.6% were male. (Quirce et al., 2021)

Probabilities

Efficacy and safety data about MEP came from three pivotal studies: DREAM (Pavord et al., 2012), MENSA (Ortega et al., 2014), and SIRIUS (Bel et al., 2014), relative efficacy of MEPO versus BEN and RES was based on the published network meta-analysis, that was conducted due to the absence of head-to-head trials directly comparing MEP versus BEN or RES comparing licensed doses of these treatments (Table 1). The relative efficacy of MEP, BEN, and RES in severe asthma was assessed by synthesising available RCT evidence via a

common comparator (placebo). The primary efficacy outcomes were clinically significant exacerbation reduction and asthma control. Here, clinically significant exacerbations were defined as exacerbations requiring oral/systemic corticosteroids, or at least a doubling of existing dose for maintenance OCS, and/or hospitalisation and/or emergency room treatment. Asthma control was measured with the Asthma Control Questionnaire (ACQ). In addition, lung function, measured as change from baseline pre-bronchodilator FEV1 was included as a secondary outcome. (Busse et al., 2019) Proportion of patients with $\geq 50\%$ exacerbation reduction was based on MENSA results (78.3% for ≥ 300 cells/ μL and 78.2% for ≥ 400 cells/ μL) (Ortega et al., 2014). Rate of clinically significant exacerbation rate for patients meeting continuation criteria (mCC) with MEP was 0.26 (SD 0.51) for ≥ 300 cells/ μL and 0.16 (SD 0.71) for ≥ 400 cells/ μL (Ortega et al., 2014). The clinically significant exacerbation rate was adjusted from the reduction factor observed for all patients with MEP and mCC (50% for ≥ 300 cells/ μL and 29.7% for ≥ 400 cells/ μL); for BEN and RES, an equivalent reduction with the same proportion was assumed. Once the number of exacerbations for each comparator was estimated, a distribution among the exacerbation type was done (OCS burst, ED visit, and hospitalization) (Table 1) (Ortega et al., 2014).

The probability of adverse events related to OCS was estimated according to the risk profile of the patients. An ad hoc analysis was carried out in the Clinical Practice Research Datalink (Herrett et al., 2015) following a logistic model adjusted by dose intensity, previous dose, age, gender, diabetes diagnosis, smoker status, high BMI, hypertension diagnosis, dyslipidemia diagnosis, impaired glucose tolerance and/or nonsteroidal anti-inflammatory drugs use. The probability of suffering adverse events according to the patient characteristics was then estimated.

- Cataract: it was assumed that 61.9% of the patients were males, 5.7% diabetic patients and 19.5% were smokers.
- Acute Myocardial infarction: assumptions, 62.1% males, 6.0% diabetic patients, 19.1% smokers, 25.9% with high BMI, 31.9% hypertensive, and 17.8% had dyspepsia.
- Gastroduodenal ulcer: assumptions, 62.1% males, 25.9% with high BMI of whom 4.7% with nonsteroidal anti-inflammatory drugs use.
- Osteoporosis: assumptions, 60.4% males and 42.5% age ≥ 60 .
- Diabetes without complications: assumptions, 62.4% males, 0.1% impaired glucose tolerance, and 22.8% high BMI.

Mortality

Asthma related mortality adjusted by age was obtained from Watson et al. (Watson et al., 2007) Based on National Review of Asthma Deaths (NRAD), asthma-related mortality was only linked to hospital exacerbation (Levy, 2015). All-cause mortality was obtained from 2017 from the Spanish Statistics Institute (Instituto Nacional de Estadística (INE), 2018).

Costs

Costs (expressed in €2019) were obtained from Spanish General Council of Official Pharmaceutical Colleges for drug cost, ("Base de Datos de Medicamentos, Consejo General de Colegios Oficiales de Farmacéuticos," n.d.) diagnosis-related group (DRG) for event cost (Ministerio de Sanidad, n.d.) and Spanish cost database e-salud (Table 2) (Gisbert and Brosa, 2007). Use of resources came from clinical trial and were validated in an expert panel.

For the pharmacological costs of the biologic treatments, both posology and treatment schemes were considered (ex-factory price). For MEP, a mean daily dose of 100

mg, for BEN the dose was 30 mg, independently of the stage of induction or maintenance; and for RES a mean of 1.98 vials of 100 mg and 1.47 vials of 25 mg (a mean of 234.75 mg) (ANEXO I Ficha Técnica o resumen de las características del producto, Cinquaero, n.d., ANEXO I Ficha Técnica o Resumen de las Características del producto, Fasenra, n.d., ANEXO I Ficha Técnica o Resumen de las Características del producto, Nucala., n.d.). Additionally, the posology for BEN considered was an induction phase of 3 doses every 4 weeks and then a maintenance phase every 8 weeks. The annual discontinuation probability for biologic add-on therapy was assumed at 10% for all three drugs and constant throughout time based on expert opinion. Biologic treatment duration was set at 5 years, in a conservative approach. Continuation criteria for biological add-on therapy were set at 50% reduction in exacerbations according to expert panel.

SoC treatment was 100% fluticasone (0.0328 µg/day), 100% salmeterol (200 mg/day), 56.1% salbutamol (800 µg/day), 49.7% anti-leukotriene (10 mg/day), and 16.0% theophyllines (400 mg/day). From the study from Sicras-Mainar et al. (Sicras-Mainar et al., 2020), it was assumed that 30.2% of the patients maintained OCS treatment. Prednisolone dose was dependent on the approach: 13.20 mg/day if it was administered as an SoC, and 9.24 mg/day if it was administered as a biologic. To estimate the OCS dose in the patients treated with a biologic, an adjustment derived from the median OCS reduction of MEP vs. SoC (50% reduction) was applied (Bel et al., 2014; "SIRIUS Statistical Report, Data on file.," n.d.).

One medical visit a year was assumed for the administration of biological treatment and a monthly nurse visit for MEP and RES. For BEN, one medical visit and 6 nurse visits the first year and 5.5 nurse visits the following years, according to the treatment scheme. Likewise, one medical visit and 3 nurse visits a year were considered for SoC. In all the cases,

time for administration by the physician/nurse were 10 min. Medical visit cost was €242.04/hour and nurse visit cost was €26.55/hour (Gisbert and Brosa, 2007).

Data of resource use to manage exacerbations came from an internal analysis of MENSA and DREAM (Ortega et al., 2014; Pavord et al., 2012). Costs of telephone call (€18.74), home day visit (€65.80), home night visit (€123.93), practice visit (€38.22), outpatient attendance (€242.04), A&E attendance not admitted (€151.21), and hospitalization (length of stay cost per day adjusted to 10.9 days: €3,827.64) were taken into account. Additionally, the total rescue OCS for exacerbations was 350 mg for OCS burst (Asthma, 2015), 491 mg for ED visit (141 mg during ED (Edmonds et al., 2012), and 350 mg after visit (Asthma, 2015)), and 759 mg for hospitalization (409 mg during hospitalization and 350 mg after hospitalization (Asthma, 2015)).

Quality of life

Health related Quality of Life of asthma symptoms are based on St. George's Respiratory Questionnaire data collected in the MENSA trial, mapped to EQ-5D (Table 3) (Ortega et al., 2014; Starkie et al., 2011). Utilities for MEP and SoC came from MENSA (Ortega et al., 2014; Starkie et al., 2011) according to the subgroups of patients.

Differences in utility between MEP, BEN, and RES was estimated based on published differences in change from baseline ACQ score in the network meta-analysis. (Busse et al., 2019) A model selection step, including fractional polynomials up to the 2nd order (i.e. two terms), was performed to select a model which best predicts utility using ACQ-5 scores, using data from MUSCA. (Chupp et al., 2017) Published differences and associated 95% confidence intervals between anti-IL5 treatments (Busse et al., 2019) were then used to calculate the difference in utility between treatments using bootstrapping, which consider

both the uncertainty in the published differences in ACQ between treatments and the uncertainty in the model coefficients. The best fitting model, according to the described methods, in the primary population and most sub-populations was a 2nd order polynomial as follows: $Intercept + \beta_1 ACQ^{0.5} + \beta_2 ACQ^3$. Mean (SD) improvement in utility of MEP compared to BEN and RES were 0.023 (0.011) and 0.022 (0.009).

Exacerbation disutilities came from the Lloyd et al (Lloyd et al., 2007) study with the length of the MENSA study (12.680 days for OCS burst, 10.410 days for ED visit, and 20.7 days for hospitalization) (Ortega et al., 2014). We assumed that ED visit disutilities are the same as for OCS bursts.

Results were calculated in terms of cost per QALY gained and incremental cost-effectiveness ratio (ICER).

$$ICER = \frac{Costs_{MEP} - Costs_{RES}}{Effectiveness_{MEP} - Effectiveness_{RES}}$$

Sensitivity analysis

Deterministic and probabilistic sensitivity analyses were conducted to assess the robustness of the model results. Deterministic univariate sensitivity analyses (UDSA) were carried out by modifying all the parameters within a $\pm 20\%$ range. Additionally, different time horizons, and populations (sex and age) were evaluated.

A probabilistic sensitivity analyses (PSA) was carried out, with 2,000 cohorts simulated. This analysis allows the evaluation of the model results for the diverse typologies of patients, considering the distribution of each of the parameters in its natural range and the existing correlation. Used distributions were beta or Dirichlet for probabilities, lognormal for rates, gamma for resource use and costs, and beta for utilities.

All data inputs and model structure were validated by Spanish clinical experts in the field.

Results

Patients with blood eosinophil ≥ 300 cells/ μ L

In a 5-year time horizon, patients were treated with MEP for an average of 3.23 years, and with BEN 3.23 years (Table 4). This reflects as asthma related mortality of 0.92% for MEP and 1.10% for BEN. Additionally, a 17% reduction in the number of exacerbations was observed, that corresponded to a reduction of 0.64 exacerbations with MEP. Specifically, OCS exacerbations were 2.66 for MEP and 3.19 for BEN; ED exacerbations were 0.2 for MEP and 0.24 for BEN, and hospitalizations 0.34 for MEP and 0.41 for BEN.

Regarding the QoL over the 5-year time horizon, MEP resulted in 3.406 QALYs compared to 3.33 QALYs for BEN (Table 4). This improvement is caused by better utility because stronger efficacy in improving asthma control (3.43 QALYs for MEP, and 3.36 for BEN), and disutilities for exacerbations are greater for BEN, -0.0164 vs. -0.0137 for MEP.

Costs in MEP patients accounted for €47,706.59 and €50,880.06 for BEN patients over the period, with 89% related to intervention costs (Table 4). Savings from MEP are associated with reductions on intervention costs (€2,956), hospitalization (€269), OCS bursts (€27), and ED visits due to exacerbation (€8). However, a discrete increase in monitoring treatment costs (€85), and SoC costs (€2) was also observed.

In short, considering that MEP costs are lower (€3,173), and the QALYs and LY are similar or larger, MEP results were dominant vs. BEN (Table 4). With a time horizon set to lifetime, MEP was still dominant: MEP costs raised to €65,864.80 and BEN costs up to €69,009.58; QALYs to 12.873 for MEP and 12.780 for BEN.

The univariate sensitivity analysis indicated MEP mCC exacerbation rate 50% (0.0101-1.3860), BEN overall RR exacerbation (0.41-0.86), MEP discontinuation (6.43%-14.24%), BEN mCC RR exacerbation (0.3326-0.7228), and SoC overall exacerbation rate (1.0758-1.8693), were the parameters primarily influencing the results. MEP was dominant across all these analyses (Supplemental. Figure 1). Probabilistic analysis verified MEP dominance for thresholds of €20,000/QALY and €30,000/QALY (Figure 2).

Patients with blood eosinophil ≥ 400 cells/ μ L

In the comparison between patients treated with MEP or RES, over a 5-years' time horizon, patients were treated with MEP for an average of 3.23 years and with RES for 3.22 years, respectively (Table 4); reflecting an asthma related mortality of 0.95% for MEP and 1.19% for RES. Moreover, number of exacerbations were reduced by 20.5% for those being treated with MEP corresponding to 0.849 incremental exacerbations. OCS exacerbations were 2.71 for MEP and 3.42 for RES; ED exacerbations 0.2 for MEP and 0.25 for RES; and hospitalizations 0.35 for MEP and 0.44 for RES.

Regarding QoL over a 5-year time horizon, the differences between MEP and RES increased slightly, with 3.373 QALYs for MEP vs. 3.298 QALYs for RES (Table 4); caused by more patients on mCC health state (2.37 QALYs for MEP and 2.30 for RES) and that disutilities for exacerbations related to RES are higher than those for MEP (-0.0176 vs. -0.0140).

Costs for MEP patients in the aforementioned period were €47,739.84 and €55,512.79 for RES patients, being 90% of it, intervention costs (Table 4). MEP savings were related to reductions in intervention costs (€7,367), hospitalization for exacerbations (€362), OCS burst (€35), and ED visits for exacerbation (€11). However, there was a slight increase in costs for SoC costs (€3), monitoring treatment costs (€0.5), and OCS related AE costs (€0.04).

Considering that MEP's costs are lower (€7,773), and QALYs and LY are similar or greater, MEP is dominant vs. RES (Table 4). If the time horizon is set to a lifetime, MEP will remain dominant: MEP costs increases to € 67,298.27 and RES costs to €75,029.34; QALYs were 12.616 for MEP and 12.518 for RES.

Univariate sensitivity analysis indicated that the parameters with greatest influence on the results were, MEP exacerbation rate for mCC patients 50% (0.0011-1.0668), MEP discontinuation (6.43%-14.24%), patients with $\geq 50\%$ exacerbation reduction (66.36%-88.03%) and, RES overall RR exacerbation rate (0.40-0.62). MEP dominance was robust to all tested variance (Supplemental. Figure 2). Probabilistic analysis verified MEP dominance for ICER thresholds of €20,000/QALY and €30,000/QALY (Figure 2).

Scenario analysis

All the scenarios were consistent with the previous results, MEP was dominant over RES and BEN for both sexes, all age groups tested (mean age 65, 75, 85, and 95) for both patient's profiles (≥ 300 cells/ μ L and ≥ 400 cells/ μ L) (Supplemental Tables 1-6).

Discussion

Economic evaluations have proven to be fundamental tools to guide resource allocation efficiently along with improving the public health in a resource-constrained health care system (Bodrogi and Kaló, 2010; Chisholm and Evans, 2007; Drummond et al., 2005). Given the general increase in the pressure of health services worldwide (OECD, 2019), economic evaluations are essential to decision making in the publicly funded health care benefits, particularly for health conditions that impose substantial socioeconomic burden, such as SEA (Bodrogi and Kaló, 2010; Chisholm and Evans, 2007; OECD, 2019). In this CEA, the economic value of MEP and the comparators BEN and RES were assessed for the Spanish

healthcare setting.

As the Busse et al. (Busse et al., 2019) analysis indicated, anti-IL5 biologic therapies for SEA patients, MEP, BEN, and RES, all significantly reduced asthma exacerbations and improved overall asthma control. However, the indirect comparison of MEP versus BEN and RES concluded that MEP offered greater improvements both in SEA exacerbations and control in patients with similar blood eosinophil counts. Taking into account the ITC and the results of the model, we observed a reduction in OCS therapy for the patients being treated with MEP, as was recently demonstrated by Llanos et al. in a real-world retrospective study of 346 patients (Llanos et al., 2020). Reduction in OCS therapy leads to down-stream benefits in terms of reductions in OCS-related adverse events (Buhl et al., 2017).

Additionally, the beneficial response to biologic therapies appears to increase with higher blood eosinophil levels. This is of great importance, as patients with higher eosinophil levels have a higher frequency of exacerbations and comparatively poorer disease control and this implies higher costs for the national healthcare system. (Buhl et al., 2017)

In this CEA, the disutilities linked to exacerbations and health states and asthma-related mortality have been handled as recommended by McQueen et al (McQueen et al., 2018) in their systematic literature review of cost-effectiveness analyses for biological asthma treatments. Reflecting the chronic nature of asthma, and in accordance with recommendations by the same authors, data for a 5-year time horizon is presented as the main case, with results for 10-years and a lifetime horizon as sensitivity analyses.

In this study MEP was found to be dominant when compared with BEN and RES, with more QALYs gained and lower costs in the different time horizons evaluated (5-, 10- and a lifetime horizon).

The main strength of this study is that the analysis was conservative in order to obtain a lower bound for improvements associated with MEP use. However, the study has limitations, for instance, the study assumed 100% adherence to SOC, but in real-world, adherence to standard therapy may be inadequate can impact SEA control (Illic et al., 2016). In 2019, the EMA's human medicines committee (CHMP) approved the self-administering method of MEP in SEA patients (European Medicines Agency, 2019). This decision may result in a reduction of administration costs for this treatment arm, which would result in MEP being more cost-effective. These results highlight the necessity to prioritize MEP vs de other biologic treatments due to its efficiency for the healthcare system in Spain, moreover, from the social point of view, this treatment improves clinical outcomes which imply an improvement in patients' QoL. This data should be considered cautiously as the unit costs and QoL are country-dependant.

Conclusions

The CEA model results suggest that MEP as an add-on therapy to SoC is a cost-effective alternative for Spanish SEA patients, with better clinical outcomes and lower cost than BEN and RES.

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Table 1. Clinical data.

	Subgroup ≥ 300 cells/ μ L	Subgroup ≥ 400 cells/ μ L	Source
Clinically significant exacerbation rate			
Mepolizumab + SoC			
All patients	0.37 (0.35)	0.32 (0.41)	MENSA
mCC	0.26 (0.51)	0.16 (0.71)	MENSA
Standard of Care			
All patients	1.43 (0.20)	1.64 (0.20)	MENSA
Patients with $\geq 50\%$ exacerbation reduction	78.3%	78.2%	MENSA
Network meta-analysis: relative effects			
Mepolizumab + SoC RR			
All patients	0.036 (0.27-0.49)	0.028 (0.19-0.4)	NMA
Benralizumab+SoC RR			
All patients	0.59 (0.41-0.86)	0.50 (0.39-0.65)	NMA
mCC	0.41 (0.29-0.60)	0.25 (0.20-0.33)	Adjusted by the same factor detected on MEP all patients/meeting CC
Reslizumab RR			
All patients	-	0.50 (0.4-0.62)	NMA
mCC	-	0.25 (0.20-0.31)	Adjusted by the same factor detected on MEP all patients/meeting CC
Distribution over type of exacerbation			
Exacerbation: OCS burst	83.2%	83.2%	MENSA
Exacerbation: ED visit	6.1%	6.0%	MENSA
Exacerbation: Hospitalization	10.6%	10.7%	MENSA

mCC, meeting continuation criteria; RR: Risk Ratio; NMA: Network Meta-analysis; SoC: Standard of Care.

Table 2. Costs of drugs, monitoring, exacerbations, and adverse events.

Costs		
Intervention, drug costs		
Mepolizumab	€ 1,086.00	Botplus
Benralizumab	€ 2,172.00	Botplus.
Reslizumab	€ 1,274.68	
Standard of Care		
Biologics	€ 35.86/cycle	Botplus (pooled: ICS, LABA, SABA, Anti-leukotriene, Theophyllines and prednisolone)
SoC	€ 35.93/cycle	Botplus (pooled: ICS, LABA, SABA, Anti-leukotriene, Theophyllines and prednisolone)
Monitoring treatment (average cost)		
Mepolizumab	€ 7.19/cycle	e-salud 2019 (1 physician visit and 12 nurse visits, annually)
Benralizumab		
Year 1	€ 9.56/cycle	e-salud 2019 (1 physician visit and 6 nurse visits, annually)
Year 1+	€ 9.95/cycle	
Reslizumab	€ 7.19/cycle	e-salud 2019 (1 physician visit and 5.5 nurse visits, annually)
SoC	€ 13.40/cycle	e-salud 2019 (1 physician visit and 12 nurse visits, annually)
Exacerbations		
OCS burst	€ 50.49/event	Bot-plus and e-salud 2019
ED visit	€ 218.65/event	Bot-plus and e-salud 2019
Hospitalisation	€ 3,975.28/event	Bot-plus and e-salud 2019
Adverse Events		
Cataract	€ 2,334.09	GRD-APR 70 (Ministerio de Sanidad, n.d.)
Acute myocardial infarction	€ 5,496.75	GRD-APR 190 (Ministerio de Sanidad, n.d.)
Gastroduodenal ulcer	€ 5,578.97	GRD-APR 241 (Ministerio de Sanidad, n.d.)
Osteoporosis	€ 6.40	Botplus ("Base de Datos de Medicamentos, Consejo General de Colegios Oficiales de Farmacéuticos," n.d.)
Diabetes (without complications)	€ 4,108.42	Crespo et al. 2013 (Crespo et al., 2013)

Table 3. Utility values.

Parameters	Value		Source
Health state Utilities	Subgroup ≥300 cells/μL	Subgroup ≥400 cells/μL	
Mepolizumab (all)	0.777	0.775	MENSA
Mepolizumab (mCC)	0.790	0.783	MENSA Adjusted by the patients with ≥50% exacerbation reduction
Benralizumab (all)	0.754	-	MUSCA
Benralizumab (mCC)	0.767	-	MUSCA
Reslizumab (all)	-	0.753	MUSCA
Reslizumab (mCC)	-	0.761	MUSCA
SoC	0.671	0.661	MENSA
Exacerbations			
Disutilities			
OCS burst	-0.100 (12.68 days)		Lloyd, 2007 utilites and MENSA days
ED visit	-0.100 (10.41 days)		Assume equal utility of OCs burst in Lloyd, 2007 and MENSA days
Hospitalization	-0.200 (20.70 days)		Lloyd, 2007 utilites and MENSA days
Adverse events, disutility values			
Cataract	-0.0271		Sullivan 2011
Acute myocardial infarction	-0.0557		Sullivan 2011
Gastroduodenal ulcer	-0.0552		Sullivan 2011
Osteoporosis	-0.0418		Sullivan 2011
Diabetes (without complications)	-0.0621		Sullivan 2011

mCC, meeting continuation criteria; nmCC, not meeting continuation criteria; SoC: Standard of Care; OCS: Oral Corticosteroids; ED: Emergency Department.

Table 4. Results of the cost-effectiveness analysis at 5 years.

	Subgroup ≥300 cells/μL		Subgroup ≥400 cells/μL	
EFFECTIVENESS	MEP	BEN	MEP	RES
Asthma related mortality	0.92%	1.10%	0.95%	1.19%
OCS, n exacerbations	2.66	3.19	2.71	3.42
ED, n exacerbations	0.20	0.24	0.20	0.25
Hospitalization, n exacerbations	0.34	0.41	0.35	0.44
Life years	4.596	4.591	4.596	4.590
QALYs	3.406	3.330	3.373	3.298
COST (€)				
Total Costs	47,706.59	50,880.06	47,739.84	55,512.79
Intervention costs	42,886	45,842	42,874	50,241
Monitoring treatment costs	367	282	367	367
SoC costs	2,147	2,145	2,147	2,144
Exacerbation: OCS burst	134	161	137	172
Exacerbation: ED visit	43	51	43	54
Exacerbation: Hospitalization	1,348	1,617	1,390	1,752
OCS related AE costs	782	782	782	782
INCREMENTALS				
Costs	-€3,173.47		-€7,772.95	
QALYs	0.076		0.075	
Incremental cost-effectiveness	Dominant		Dominant	

QALYs: Quality Adjusted life-years. OCS: Oral Corticosteroids; ED: Emergency Department.

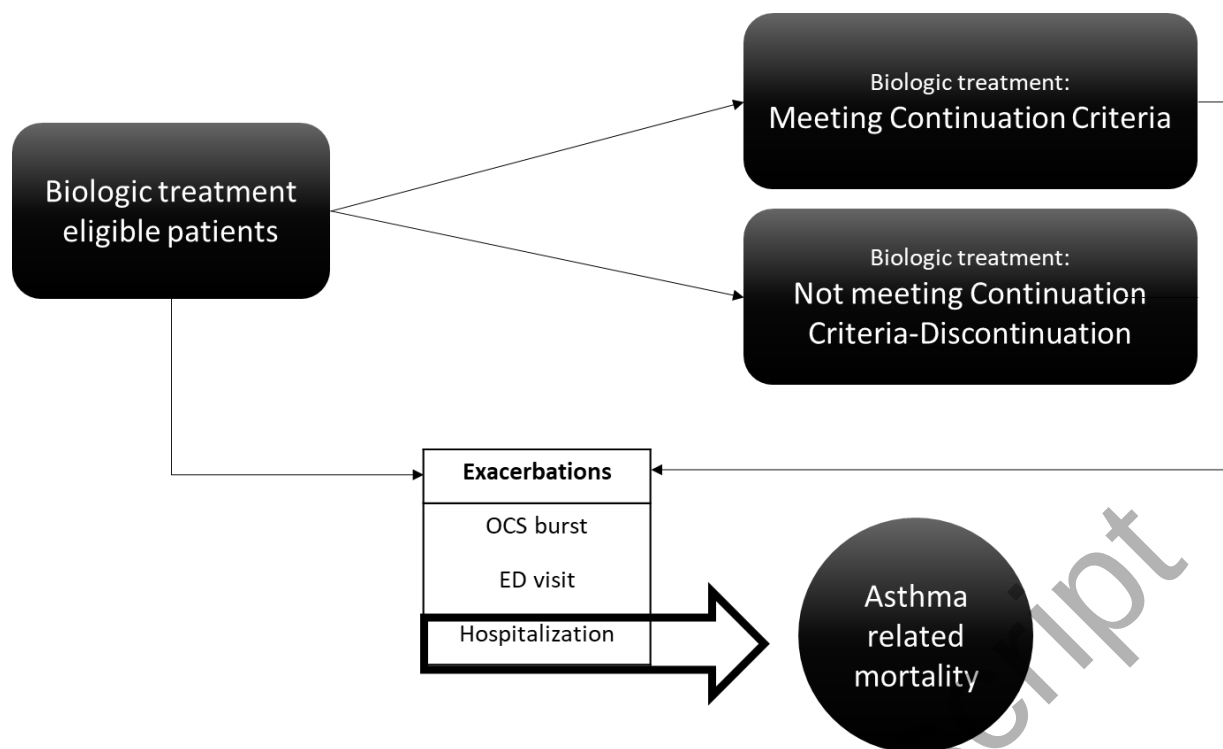


Figure 1.

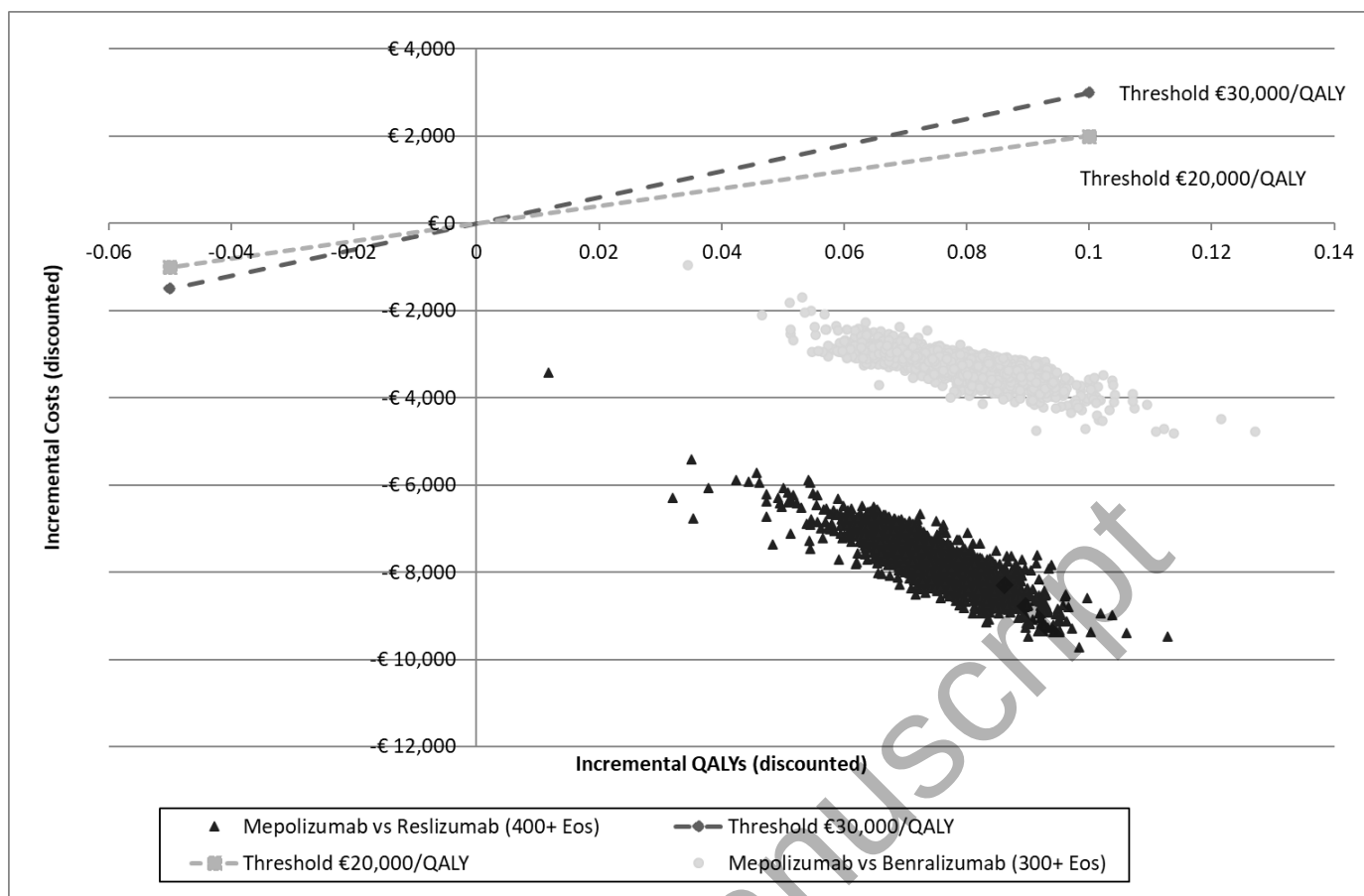


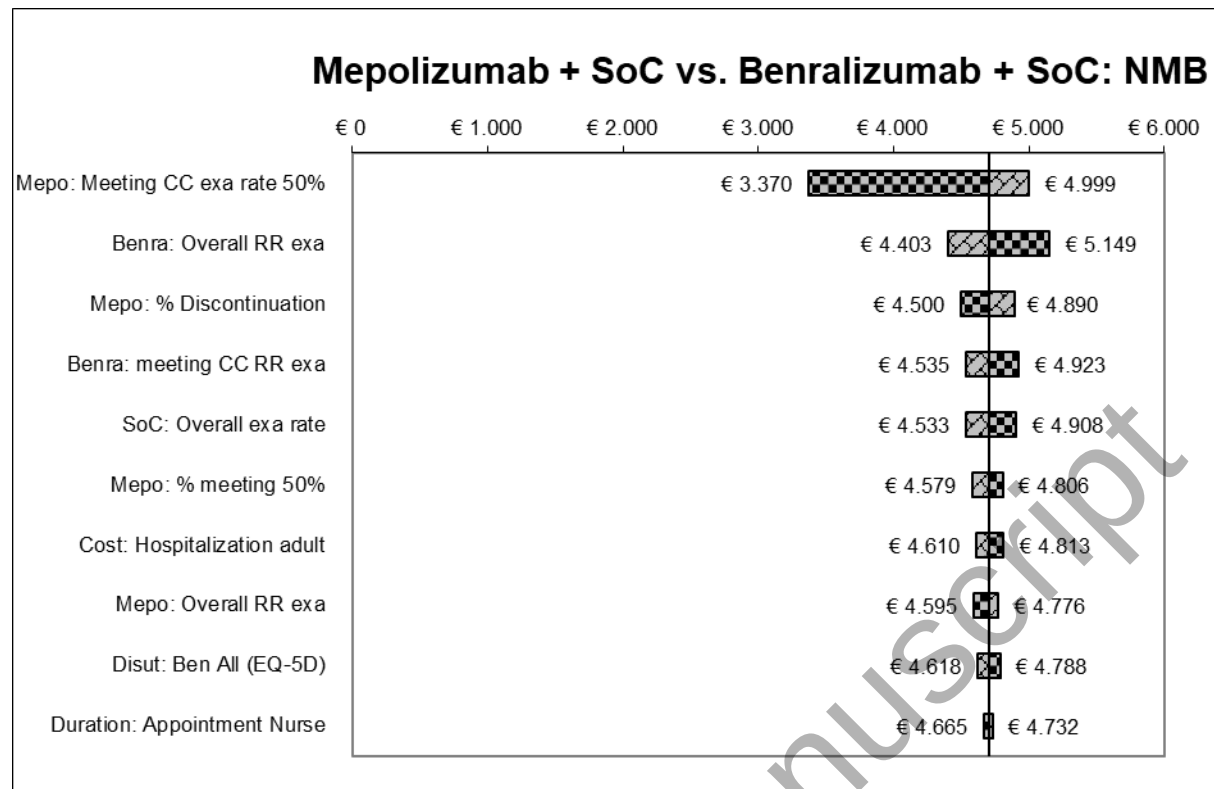
Figure 2.

Figure 1. Markov model. OCS: oral corticosteroid, ED: emergency department. All-cause mortality not shown for simplification purposes of the figure. All health states are associated with general population mortality.

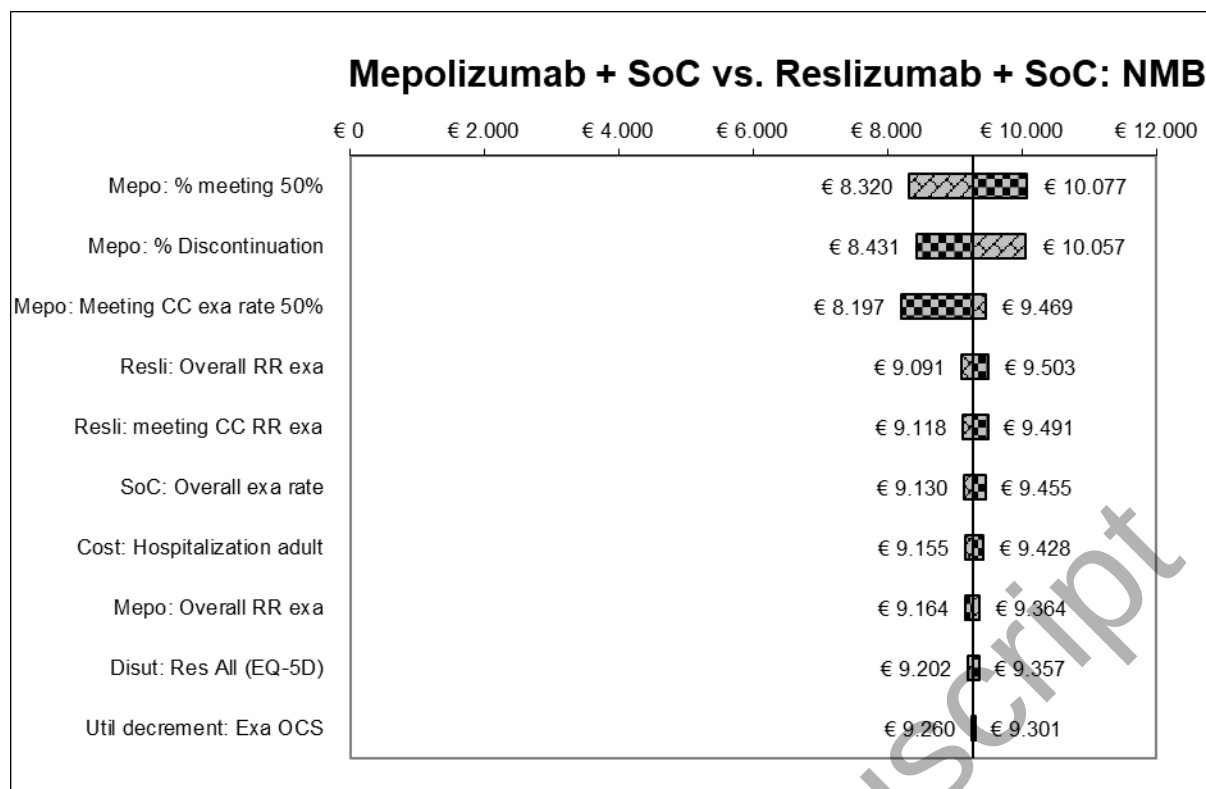
Figure 2. Cost-effectiveness plane.

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Supplemental Material



Supplemental Figure 1. Tornado analysis (Mepolizumab vs Benralizumab). NMB: Net Monetary Benefit. NMB is positive if the incremental cost-effectiveness ratio is below the willingness to pay threshold (€20,000) of a quality-adjusted life-year and MEP is cost-effective.



Supplemental Figure 2. Tornado analysis (Mepolizumab vs Reslizumab). NMB: Net Monetary Benefit. NMB is positive if the incremental cost-effectiveness ratio is below the willingness to pay threshold (€20,000) of a quality-adjusted life-year and MEP is cost-effective.

Supplemental Table 1. Results of the cost-effectiveness analysis at 5 years for women.

	Subgroup ≥300 cells/μL		Subgroup ≥400 cells/μL	
EFFECTIVENESS	MEP	BEN	MEP	RES
Asthma related mortality	0.92%	1.10%	0.96%	1.20%
OCS, n exacerbations	2.67	3.20	2.72	3.42
ED, n exacerbations	0.20	0.24	0.20	0.25
Hospitalization, n exacerbations	0.34	0.41	0.35	0.44
Life years	4.607	4.602	4.607	4.601
QALYs	3.414	3.337	3.381	3.306
COST (€)				
Total Costs	47,803.32	50,978.30	47,836.76	55,625.28
Intervention costs	42,972	45,930	42,961	50,343
Monitoring treatment costs	368	283	368	368
SoC costs	2,153	2,150	2,152	2,149
Exacerbation: OCS burst	135	161	137	173
Exacerbation: ED visit	43	52	43	54
Exacerbation: Hospitalization	1,351	1,621	1,393	1,756
OCS related AE costs	782	782	782	782
INCREMENTALS				
Costs	-€ 3,174.98		-€ 7,788.51	
QALYs	0.077		0.075	
Incremental cost-effectiveness	Dominant		Dominant	

Supplemental Table 2. Results of the cost-effectiveness analysis at 5 years for men.

	Subgroup ≥300 cells/μL		Subgroup ≥400 cells/μL	
EFFECTIVENESS	MEP	BEN	MEP	RES
Asthma related mortality	0.92%	1.09%	0.95%	1.19%
OCS, n exacerbations	2.65	3.18	2.70	3.40
ED, n exacerbations	0.20	0.23	0.20	0.25
Hospitalization, n exacerbations	0.34	0.41	0.35	0.44
Life years	4.578	4.572	4.577	4.571
QALYs	3.392	3.316	3.360	3.285
COST (€)				
Total Costs	47,539.52	50,710.38	47,572.44	55,318.50
Intervention costs	42,736	45,690	42,724	50,066
Monitoring treatment costs	366	281	366	365
SoC costs	2,139	2,136	2,139	2,136
Exacerbation: OCS burst	134	160	136	172
Exacerbation: ED visit	43	51	43	54
Exacerbation: Hospitalization	1,342	1,610	1,383	1,745
OCS related AE costs	781	781	781	781
INCREMENTALS				
Costs	-€ 3,170.86		-€ 7,746.06	
QALYs	0.076		0.075	
Incremental cost-effectiveness	Dominant		Dominant	

Supplemental Table 3. Results of the cost-effectiveness analysis at 5 years for patients with a mean

	Subgroup ≥300 cells/μL		Subgroup ≥400 cells/μL	
EFFECTIVENESS	MEP	BEN	MEP	RES
Asthma related mortality	0.91%	1.08%	0.94%	1.18%
OCS, n exacerbations	2.62	3.15	2.67	3.37
ED, n exacerbations	0.19	0.23	0.19	0.24
Hospitalization, n exacerbations	0.33	0.40	0.34	0.44
Life years	4.541	4.536	4.541	4.534
QALYs	3.358	3.282	3.326	3.251
COST (€)				
Total Costs	47,608.77	50,774.66	47,641.03	55,334.52
Intervention costs	42,442	45,393	42,431	49,723
Monitoring treatment costs	363	279	363	363
SoC costs	2,122	2,119	2,121	2,118
Exacerbation: OCS burst	132	159	135	170
Exacerbation: ED visit	42	51	42	54
Exacerbation: Hospitalization	1,330	1,597	1,371	1,730
OCS related AE costs	1,177	1,177	1,177	1,177
INCREMENTALS				
Costs	-€3,165.89		-€7,693.49	
QALYs	0.076		0.074	
Incremental cost-effectiveness	Dominant		Dominant	

age 65.

Supplemental Table 4. Results of the cost-effectiveness analysis at 5 years for patients with a mean

	Subgroup ≥300 cells/μL		Subgroup ≥400 cells/μL	
EFFECTIVENESS	MEP	BEN	MEP	RES
Asthma related mortality	0.87%	1.05%	0.90%	1.13%
OCS, n exacerbations	2.53	3.05	2.58	3.26
ED, n exacerbations	0.19	0.23	0.19	0.24
Hospitalization, n exacerbations	0.32	0.39	0.33	0.42
Life years	4.395	4.390	4.395	4.389
QALYs	3.239	3.166	3.208	3.136
COST (€)				
Total Costs	46,937.04	50,082.47	46,966.60	54,452.76
Intervention costs	41,285	44,219	41,274	48,368
Monitoring treatment costs	352	270	352	352
SoC costs	2,053	2,051	2,053	2,050
Exacerbation: OCS burst	128	154	130	165
Exacerbation: ED visit	41	49	41	52
Exacerbation: Hospitalization	1,284	1,545	1,322	1,673
OCS related AE costs	1,794	1,794	1,794	1,794
INCREMENTALS				
Costs	-€3,145.43		-€7,486.16	
QALYs	0.074		0.072	
Incremental cost-effectiveness	Dominant		Dominant	

age 75.

Supplemental Table 5. Results of the cost-effectiveness analysis at 5 years for patients with a mean

	Subgroup ≥300 cells/μL		Subgroup ≥400 cells/μL	
EFFECTIVENESS	MEP	BEN	MEP	RES
Asthma related mortality	0.73%	0.89%	0.75%	0.96%
OCS, n exacerbations	2.15	2.62	2.18	2.79
ED, n exacerbations	0.16	0.19	0.16	0.20
Hospitalization, n exacerbations	0.27	0.33	0.28	0.36
Life years	3.784	3.780	3.784	3.779
QALYs	2.772	2.707	2.746	2.682
COST (€)				
Total Costs	42,569.99	45,634.05	42,588.85	49,197.10
Intervention costs	36,389	39,259	36,379	42,636
Monitoring treatment costs	306	233	306	305
SoC costs	1,768	1,766	1,768	1,766
Exacerbation: OCS burst	109	132	110	141
Exacerbation: ED visit	35	42	35	44
Exacerbation: Hospitalization	1,091	1,328	1,119	1,432
OCS related AE costs	2,873	2,873	2,873	2,873
INCREMENTALS				
Costs	-€3,064.06		-€6,608.26	
QALYs	0.065		0.064	
Incremental cost-effectiveness	Dominant		Dominant	

age 85.

Supplemental Table 6. Results of the cost-effectiveness analysis at 5 years for patients with a mean

	Subgroup ≥300 cells/μL		Subgroup ≥400 cells/μL	
EFFECTIVENESS	MEP	BEN	MEP	RES
Asthma related mortality	0.47%	0.59%	0.48%	0.63%
OCS, n exacerbations	1.43	1.79	1.43	1.89
ED, n exacerbations	0.11	0.13	0.10	0.14
Hospitalization, n exacerbations	0.18	0.23	0.18	0.24
Life years	2.597	2.594	2.597	2.594
QALYs	1.864	1.817	1.848	1.802
COST (€)				
Total Costs	33,580.81	36,502.61	33,582.25	38,414.43
Intervention costs	26,507	29,272	26,500	31,065
Monitoring treatment costs	214	162	214	214
SoC costs	1,213	1,212	1,213	1,212
Exacerbation: OCS burst	72	91	72	95
Exacerbation: ED visit	23	29	23	30
Exacerbation: Hospitalization	723	909	731	969
OCS related AE costs	4,829	4,829	4,829	4,829
INCREMENTALS				
Costs	-€2,921.80		-€4,832.18	
QALYs	0.047		0.046	
Incremental cost-effectiveness	Dominant		Dominant	

age 95.

Supplemental Table 6. Results of the cost-effectiveness analysis at a lifetime horizon.

	Subgroup ≥300 cells/μL		Subgroup ≥400 cells/μL	
EFFECTIVENESS	MEP	BEN	MEP	RES
Asthma related mortality	10.05%	10.21%	11.44%	11.65%
OCS, n exacerbations	19.65	20,16	22.05	22.71
ED, n exacerbations	1.45	1.49	1.60	1.65
Hospitalization, n exacerbations	2.51	2.57	2.85	2.93
Life years	18.867	18.836	18.761	18.720
QALYs	12.873	12.780	12.616	12.518
COST				
Total Costs	65,864.80	69,009.58	67,298	75,029
Intervention costs	42,886	45,842	42,874	50,241
Monitoring treatment costs	1,133	1,046	1,127	1,124
SoC costs	8,824	8,810	8,775	8,756
Exacerbation: OCS burst	992	1,018	1,113	1,147
Exacerbation: ED visit	317	325	350	360
Exacerbation: Hospitalization	9,963	10,219	11,310	11,651
OCS related AE costs	1,750	1,750	1,750	1,750
INCREMENTALS				
Costs	-€3,144.78		-€7,731.07	
QALYs	0.094		0.098	
Incremental cost-effectiveness	Dominant		Dominant	