

Cost Effectiveness of Pharmacological Treatments for Asthma: A Systematic Review

Carlos E. Rodriguez-Martinez^{1,2}  · Monica P. Sossa-Briceño³ · Jose A. Castro-Rodriguez⁴

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Abstract

Objective The objective of this article was to summarize the findings of all the available studies on alternative pharmacological treatments for asthma and assess their methodological quality, as well as to identify the main drivers of the cost effectiveness of pharmacological treatments for the disease.

Methods A systematic review of the literature in seven electronic databases was conducted in order to identify all the available health economic evidence on alternative pharmacological treatments for asthma published up to April 2017. The reporting quality of the included studies was assessed using the Consolidated Health Economic Evaluation Reporting Standards (CHEERS) statement.

Results A total of 72 studies were included in the review, classified as follows: medications for acute asthma treatment ($n = 5$, 6.9%); inhaled corticosteroids (ICS) administered alone or in conjunction with long-acting β -agonists (LABA) or tiotropium for chronic asthma treatment ($n = 38$, 52.8%); direct comparisons between different combinations of ICS, ICS/LABA, leukotriene receptor antagonists (LTRA), and sodium cromoglycate for chronic asthma treatment ($n = 14$, 19.4%); and omalizumab for chronic asthma treatment ($n = 15$, 20.8%). ICS were reported to be cost effective when compared with LTRA for the management of persistent asthma. In patients with inadequately controlled asthma taking ICS, the addition of long-acting β -agonist (LABA) preparations has been demonstrated to be cost effective, especially when combinations of ICS/LABA containing formoterol are used for both maintenance and reliever therapy. In patients with uncontrolled severe persistent allergic asthma, omalizumab therapy could be cost effective in a carefully selected subgroup of patients with the more severe forms of the disease. The quality of reporting in the studies, according to the CHEERS checklist, was very uneven. The main cost-effectiveness drivers identified were the cost or rate of asthma exacerbations, the cost or rate of the use of asthma medications, the asthma mortality risk, and the rate of utilization of health services for asthma.

Conclusions The present findings are in line with the pharmacological recommendations for stepwise management of asthma given in the most recent evidence-based clinical practice guidelines for the disease. The identified reporting quality of the available health economic evidence is useful for identifying aspects where there is room for improvement in future asthma cost-effectiveness studies.

✉ Carlos E. Rodriguez-Martinez
carerodriguezmar@unal.edu.co

¹ Department of Pediatrics, School of Medicine, Universidad Nacional de Colombia, Carrera 45 No. 26–85, Bogota, Colombia

² Department of Pediatric Pulmonology and Pediatric Critical Care Medicine, School of Medicine, Universidad El Bosque, Av. Cra 9 No. 131A–02, Bogota, Colombia

³ Department of Internal Medicine, School of Medicine, Universidad Nacional de Colombia, Carrera 45 No. 26–85, Bogota, Colombia

⁴ Division of Pediatrics, School of Medicine, Pontificia Universidad Catolica de Chile, Av Libertador Bernardo O'Higgins 340, Santiago, Región Metropolitana, Chile

Key Points for Decision Makers

In acute asthma, nebulized magnesium sulphate (MgSO₄), oral dexamethasone, inhaled ipratropium bromide, and levalbuterol seem cost effective when contrasted with relevant comparators.

Inhaled corticosteroids (ICS) are cost effective when compared with leukotriene receptor antagonists (LTRA) for the management of persistent asthma. In patients with inadequately controlled asthma taking ICS, the addition of long-acting β -agonist (LABA) preparations has been shown to be cost effective when compared with other relevant strategies, such as the addition of LTRA to the same doses of ICS or doubling the doses of ICS. In patients with uncontrolled severe persistent allergic asthma, omalizumab therapy could be cost effective in a carefully selected subgroup of patients with the more severe forms of the disease when compared with standard therapy.

Overall, the findings from this systematic review of economic evidence are in line with the pharmacological recommendations for stepwise management of asthma given in the most recent evidence-based clinical practice guidelines for the disease.

1 Introduction

Asthma is a disease that remains an important and challenging public health problem worldwide, not only in children but also in adults [1]. This is because despite important advances in the knowledge of its physiopathology and the clinical aspects of its treatment, particularly over the past 20 years, the disease still produces a considerable clinical impact on patients and a significant economic burden to patients and their families, as well as to healthcare systems and to society as a whole [2]. The economic burden of the disease is considerable in terms of direct, indirect, and intangible costs [3].

A wide variety of pharmacological options have demonstrated efficacy for the prevention and treatment of asthma, potentially reducing the burden of the disease by reducing the costs of managing patients with poorly controlled disease [4, 5]. However, although pharmacological treatments have the potential of decreasing the burden and costs of asthma, they also represent the primary component

of direct medical expenditures [6], due to, among other factors, the availability in recent years of more expensive options, such as combination inhalers and biological treatments [7]. This fact underlines the importance of evaluating the costs and outcomes of the different pharmacological treatment options for asthma by means of economic evaluations [7]. Economic evaluations are increasingly being used for decision making because they offer crucial information for clinicians and decision makers in deciding the best treatment options for patients in a more rational and transparent form, therefore contributing to ensuring an efficient use of the available healthcare resources [8]. Among economic evaluations, asthma cost-effectiveness analyses (CEA) have been considered as pivotal in guiding the choice of the most efficient treatment option, measuring consequences in natural units (such as proportions of symptom-free days and episode-free days), or in terms of preference-based measures of health (such as quality-adjusted life-years [QALYs] or disability-adjusted life-years) in a variant of these studies, called cost-utility analysis (CUA) [8].

Several CEA and CUA studies of the various pharmacological treatment options for asthma have been published, making reading all of them a time-consuming process for busy clinicians and decision makers dealing with asthmatic patients. Therefore, it would be useful for most readers to have a summary of all this economic evidence in one manuscript. Although we acknowledge the publication of previous systematic reviews intended to summarize all the available evidence on the cost effectiveness, and other economic studies of the different pharmacological treatment options for asthma [7, 9–13], the most recent review was focused on evaluating the literature regarding the use of asthma-specific outcome measures instead of the identification of the main drivers of the cost effectiveness of pharmacological treatments for the disease [13]. Additionally, although some of the reviews have assessed the reporting quality of the primary included studies, none of these reviews has made this assessment, using a new and improved instrument (the Consolidated Health Economic Evaluation Reporting Standards [CHEERS] statement) that is designed to consolidate and update previous efforts for quality assurance of health economic studies [14].

Accordingly, there is a need for updated studies that summarize and assess the reporting quality of all the available evidence on economic studies of the different pharmacological treatment options for asthma using the above-mentioned instrument. This is essential for identifying the main drivers of pharmacological cost effectiveness, and contributing to ensuring an efficient use of the available healthcare resources when treating asthmatic patients.

As such, the objective of this article was to summarize the findings of all the available studies on alternative pharmacological treatments for asthma and assess their methodological quality, as well as to identify the main drivers of the cost effectiveness of pharmacological treatments for the disease.

2 Methods

2.1 Literature Search

A systematic review of the English and Spanish literature was conducted in order to identify articles published up to April 2017 that provided data on a comparative analysis of alternative pharmacological treatments for asthma in terms of both their costs and their consequences. The following electronic databases were searched: MEDLINE (PubMed), EMBASE, Cumulative Index to Nursing and Allied Health Literature (CINAHL), Tufts CEA Registry, SCOPUS, the NHS Economic Evaluation Database (NHS EED), and the Health Economic Evaluations Database (HEED). Additionally, we screened the reference lists of relevant reviews and included those studies that were identified.

The PubMed search strategy included the following search terms: ('Economics, Medical' OR 'Cost-Benefit Analysis') AND 'Asthma'. The Medical Subject Heading (MeSH) term 'Cost-Benefit Analysis' includes the following nested entry terms: Economic Evaluation; Economic Evaluations; Evaluation, Economic; Evaluations, Economic; Cost Effectiveness; Effectiveness, Cost; Cost-Effectiveness Analysis; Analysis, Cost-Effectiveness Analysis; Cost-Utility Analysis; Analyses, Cost-Utility; Analysis, Cost-Utility; Cost Utility Analysis; Cost-Utility Analyses; Analyses, Cost-Benefit; Analysis, Cost-Benefit; Cost-Benefit Analyses; Cost-Benefit Analysis; Analyses, Cost-Benefit; Analysis, Cost-Benefit; Cost-Benefit Analyses. To be included, studies had to meet all the following criteria: (1) a comparative analysis of alternative pharmacological treatments for acute and chronic asthma (including pharmacological treatment options suitable for both maintenance and reliever bronchodilator treatment); (2) comparative analyses in terms of both the cost and consequences of the alternatives (including cost-minimization studies); and (c) measurement and valuation of consequences, in terms of either natural units, preference-based measures of health, or monetary units. Studies were included irrespective of the setting and study perspective. Studies published solely in abstract form were excluded because the methods and results could not be fully analyzed. Likewise, studies dealing with alternative formulations, delivery methods, routes of administration,

and administration options for asthma medications without direct comparisons between alternative pharmacological treatments were excluded from this review.

Two review authors (CERM and JACR) independently screened the titles and abstracts of articles retrieved by the electronic and print searches for eligibility, according to the above-mentioned inclusion criteria. One of the review authors retrieved full-text articles of all those deemed potentially eligible, for closer examination. Disagreements on eligibility were resolved through discussion and, when disagreements could not be resolved, by seeking advice from the third author.

2.2 Data Extraction

We developed a standardized data collection form a priori to capture specific items of data needed for the review. We pilot tested the data extraction form with a sample of five included studies to guarantee clarity, completeness, and ease of use.

We extracted data on geographical region of study, target population/setting, details of the participants (including age group), comparators, type and duration of the interventions, type of economic evaluation, cost perspective, source of cost data, source of effectiveness data, method of cost calculation, funding source, time horizon, the incremental cost-effectiveness ratio (ICER), whether they were model-based versus trial-based, and whether discounting was performed. Base-case estimates for both costs and effectiveness were used if sensitivity analyses were performed. For studies that performed some type of sensitivity analysis, we identified and extracted any variable that may potentially have changed the study conclusions. Two review authors (CERM and JACR) independently extracted data from economic studies and recorded it on the specially designed form. Disagreements were discussed with the third reviewer and resolved by consensus.

In order to identify the main cost-effectiveness drivers, we first determined the studies that performed some type of sensitivity analysis, and thereafter we identified any variable that may potentially change the study conclusions.

2.3 Assessment of Quality and/or Reporting of the Primary Health Economic Studies

Two review authors (CERM and MPSB) independently assessed the reporting quality of the included studies. Disagreements were discussed with the third reviewer and resolved by consensus. The reporting quality of the economic studies included in the review was assessed using the CHEERS statement, an instrument that was designed to provide recommendations to optimize reporting of health

economic evaluations [14], in an attempt to consolidate and update previous similar efforts [15–23]. The CHEERS checklist is based on the format of the Consolidated Standards of Reporting Trials statement checklist and was developed by a task force supported by the International Society for Pharmacoeconomics and Outcomes Research in accordance with current recommendations for the development of reporting guidelines, using an international and multidisciplinary team of editors and content experts in economic evaluation and reporting [24]. The final recommendations are subdivided into six main categories: (1) title and abstract; (2) introduction; (3) methods; (4) results; (5) discussion; and (6) other. The recommendations are contained in a user-friendly, 24-item checklist (Table 9). Each item of the CHEERS checklist was graded from one to three (indicating studies that reported well, reported poorly, or did not report).

2.4 Drivers of Cost Effectiveness

In order to identify the main cost-effectiveness drivers, we first determined the studies that performed some type of deterministic sensitivity analysis, and thereafter we identified any variable that may potentially have changed the study conclusions after performing a critical evaluation of the methods and study characteristics (e.g. model structure, assumptions, comparator choice, discounting rate, mortality rates, exacerbation rates, sources of data, time horizon, etc.).

3 Results

3.1 Results of the Search

Figure 1 shows the study selection process. The systematic search of databases retrieved 532 references. Among those, we excluded 475 studies. The most common reasons for excluding studies that met our initial search were a language other than English or Spanish, outcomes not related to cost-effectiveness or other economic issues, studies not focused on pharmacological management of asthma, and studies not reporting primary data (editorials, reviews, letters, commentaries, discussion pieces, or methodological reports). We identified 21 additional potentially relevant studies from reference lists, of which 15 finally met the inclusion criteria. In the end, 72 cost-effectiveness and other economic studies evaluating alternative pharmacological treatments for acute asthma were included in the review.

3.2 Study Descriptions

3.2.1 Results by Pharmacological Group Class or Comparison Groups Evaluated

Tables 1, 2, 3, 4, 5, 6, 7 and 8 contain detailed information on each of the economic studies organized by the pharmacological group class or the comparison groups evaluated: medications for acute asthma treatment [25–29] (Tables 1, 2), inhaled corticosteroids (ICS) administered alone or in conjunction with long-acting β -agonist (LABA) preparations or tiotropium [30–67] (Tables 3, 4), direct comparisons between different combinations of ICS, ICS/LABA, leukotriene receptor antagonists (LTRA), and sodium cromoglycate [68–82] (Tables 5, 6), and omalizumab [83–97] (Tables 7, 8). Of the total 72 studies reviewed, 10 (13.8%) evaluated ICS [31, 32, 44, 53, 57, 60, 62, 98–100], 23 (31.9%) evaluated ICS/LABA combinations [30, 33–43, 45–48, 50, 51, 54, 55, 59, 65, 66], 15 (20.8%) evaluated omalizumab [83–97], and the remaining 24 (33.3%) tested several other different combinations of controller medications and medications for acute asthma treatment [25–29, 37, 47, 52, 54, 67–81].

3.2.2 Main Study Characteristics

Most of the studies were performed in North America ($n = 20$, 27.7%) and the UK ($n = 17$, 23.6%); only three (4.2%) of the studies were performed in a Latin American country.

In nearly half of the studies ($n = 30$, 41.7%), analyses included both pediatric and adult patients, and only 11 studies (15.0%) included exclusively pediatric patients.

The most frequent type of economic evaluation was the CEA in 57 (79.2%) studies, followed by the CUA in 23 (31.9%) studies (11 studies performed both types of analyses).

More than half of the studies ($n = 37$, 51.4%) used a healthcare provider cost perspective, while 19 (26.4%) studies used both a healthcare and a societal perspective, and 11 (15.3%) used a societal perspective for measuring costs.

Randomized clinical trials ($n = 37$, 51.4%) and literature review ($n = 11$, 15.3%) were the two most frequent methods for obtaining efficacy data.

Further characteristics of the included studies are listed in Tables 1, 2, 3, 4, 5, 6, 7 and 8.

3.2.3 Results for the Quality of Reporting of the Included Studies

As mentioned above, we assessed the reporting quality of the 72 included studies using the CHEERS checklist. The

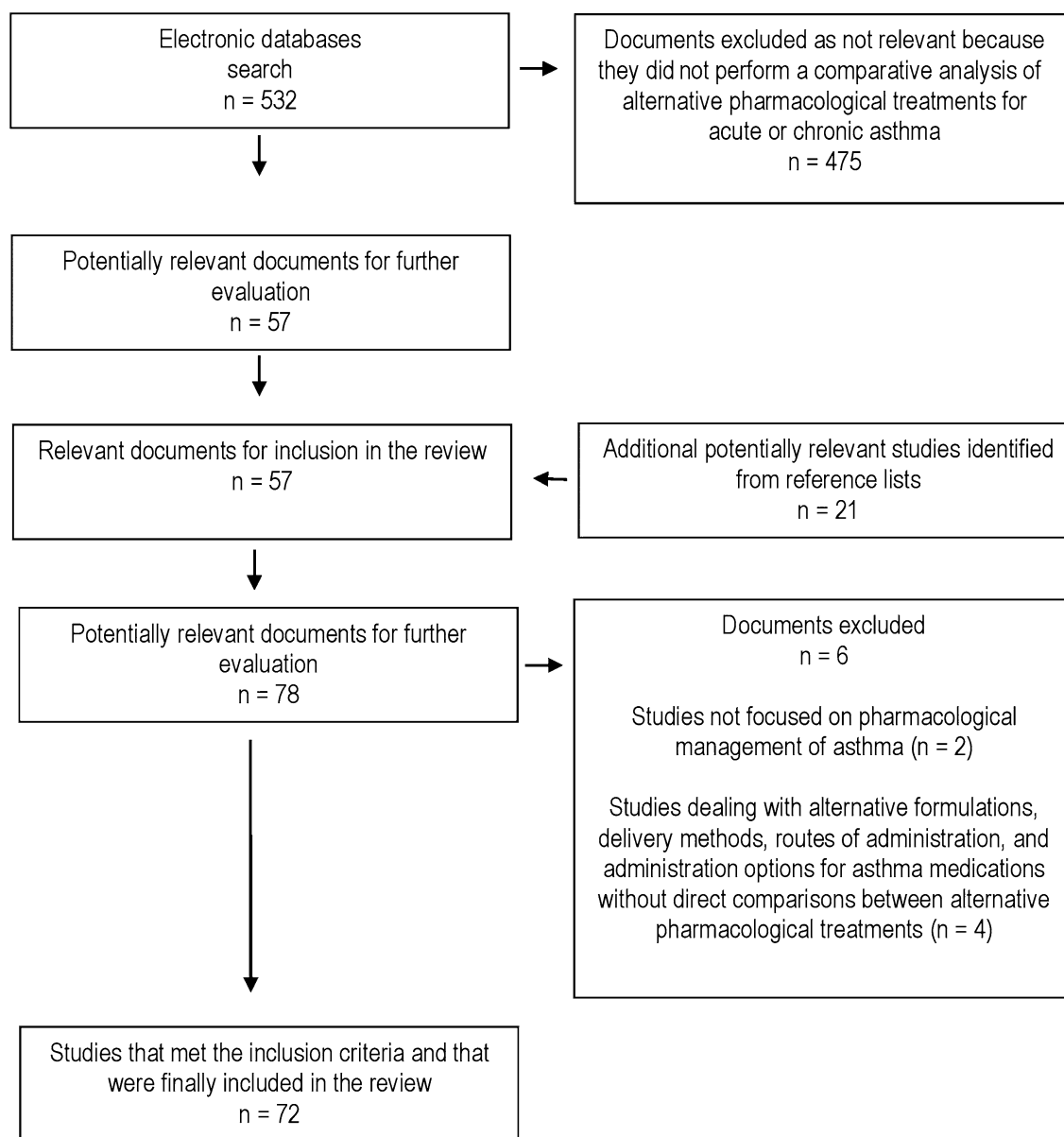


Fig. 1 Study selection process for studies reporting alternative pharmacological treatments for asthma

title of the majority of the articles ($n = 67$, 93.0%) identified the study as an economic evaluation. Most articles ($n = 66$, 91.7%) provided an explicit statement of the broader context for the study and presented the study question and its relevance for health policy or practice decisions. Although the articles generally described the perspective of the study and related this to the costs being evaluated, a specific statement regarding the perspective of the study was missing in 10 (13.9%) studies. The majority of the studies ($n = 46$, 63.9%) did not report the choice of discount rate(s) used for costs and outcomes, presumably because the majority of the studies had a time horizon of 1 year or less. A total of 53 (73.6%) studies properly reported the method used to measure effectiveness, and

nearly half of the studies ($n = 40$, 55.5%) reported any potential conflict of interest of the study contributors.

Further results of the quality of reporting for the included studies are listed in Table 9.

3.3 A Critical Review of Findings and Methodology

3.3.1 Medications for Acute Asthma Treatment

Only a few studies (5, 6.9%) have examined the cost effectiveness of medications for acute asthma treatment, being limited to evaluations of the value for money of nebulized magnesium sulphate (MgSO₄) [compared with isotonic saline] [26], oral dexamethasone (compared with

Table 1 Characteristics of economic studies evaluating medications for acute asthma treatment: methodology

Funding source	Scientific or academic	Scientific or academic	Scientific or academic	Funding source not explicitly stated	Scientific or academic
Sensitivity analyses	PSA	No PSA	No PSA	No PSA	No sensitivity analysis
Discounting, time horizon	Not necessary, 1 month	Not necessary, not explicitly stated	Not necessary, not explicitly stated	Not necessary, not explicitly stated	Not necessary, not explicitly stated
Source of effectiveness data	RCT. No justification for only one source of clinical data for treatment	Non-systematic literature review	Clinical trial	Literature reports	Medical records from two hospitals
Source of cost data	A variety of primary and secondary sources	A variety of primary and secondary sources	Maximum retail prices of the drugs	Not stated	Hospital charges submitted to patients
Source of resource-use data	Primary hospital attendances and postal questionnaires	Non-systematic literature review	CT	Medical records from two hospitals	Retrospective observational case review from two hospitals
Cost perspective	Third-party payer and a societal perspective. Productivity losses associated with time off work included	Third-party payer and a societal perspective. Productivity losses associated with time off work included.	Healthcare perspective	Healthcare perspective (analyses only considered prices of the drugs)	Healthcare perspective
Type of economic evaluation, model vs. trial-based study	CEA and CUA. Source of utility weights stated	CEA, model-based study (decision analysis model)	CMA, model-based study (decision analysis model)	CEA, trial-based study	CEA, trial-based study
Comparators	All relevant comparators	Selective comparators	All relevant comparators	Not explicitly stated the comparators	All relevant comparators
Type of interventions	Isotonic MgSO ₄ vs. isotonic saline	Oral dexamethasone vs. oral prednisone/prednisolone	4 mg of oral salbutamol or placebo as adjuvant treatment	The comparator was not stated	Racemic albuterol vs. levalbuterol in addition to standard treatments, e.g. corticosteroids and oxygen
Target population/setting, age	ED and children's assessment units at 30 hospitals, 2–15 years	Pediatric asthma cases with acute exacerbations at ED, < 19 years	Patients with seasonal or perennial asthma ≥ 50% of the days for at least 3 months/year for ≥ 2 years at outpatient clinics, ≥ 17 years	Adults with severe acute asthma, ≥ 14 years	Patients with a primary or secondary diagnosis of acute asthma who required nebulization with a SABA, ≥ 1 year
	Powell et al. (2013), UK [26]	Andrews et al. (2012), US [25]	Thomas et al. (1996), India, Canada [29]	Rodrigo and Rodrigo (2003), Uruguay [27]	Schreck and Babin (2005), US [28]

PSA probabilistic sensitivity analysis, RCT randomized controlled trial, CT clinical trial, CEA cost-effectiveness analysis, CUA cost-utility analysis, CMA cost-minimization analysis, MgSO₄ magnesium sulphate, ED Emergency Department, SABA short-acting β_2 -agonists

oral prednisone/prednisolone) [25], oral β -agonists as adjuvant therapy to inhaled β -agonist therapy (compared with placebo) [29], inhaled ipratropium bromide [27], and levalbuterol (compared with racemic albuterol) [28]. In

each case, the medication evaluated was claimed to be cost effective, except for the study that evaluated oral β -agonists, which reported that treatment with adjuvant oral β -agonists has little additional benefit for reducing

Table 2 Results of economic studies evaluating medications for acute asthma treatment

	Main drivers of cost effectiveness	ICERs	Conclusions of the study authors
Powell et al. (2013) [26]	Utility values	£189 per unit decrement in ASS £175,598 per QALY gained	Addition of MgSO ₄ to standard treatment may be more cost-effective than standard treatment only
Andrews et al. (2012) [25]	Admission rate and ED relapse rate	Not calculated. Dexamethasone dominates (more effective and less costly)	Two days of dexamethasone is both clinically more effective and cost saving than 5-days of prednisone/prednisolone
Thomas et al. (1996) [29]	Cost of salbutamol and probability of use of salbutamol	Not calculated	Adjuvant oral SABA are not cost-effective in asthmatics using an inhaled SABA
Rodrigo and Rodrigo (2003) [27]	Form of administration of ipratropium bromide (inhaled vs. nebulized)	Not calculated. Ipratropium bromide dominates (more effective and less costly)	Ipratropium bromide results cost effective, leading to a significant saving of resources in adults with severe exacerbation
Schreck and Babin (2005) [28]	No sensitivity analysis	Not calculated. Levalbuterol dominates (more effective and less costly)	Levalbuterol in the ED for patients with acute asthma may be a cost-effective alternative to racemic albuterol

ASS Asthma Severity Score, ED Emergency Department, MgSO₄ magnesium sulfate, QALY quality-adjusted life-year, SABA short-acting β_2 -agonists, ICER incremental cost-effectiveness ratio

bronchoconstriction or improving the quality of life in chronic asthmatics who are using inhaled short-acting β_2 -agonists (SABA), and it was associated with greater costs and side effects [29]. However, a few aspects deserve mention because they may have had an impact on the results of the studies. Although the majority of the studies included some kind of sensitivity analysis, only one performed a probabilistic sensitivity analysis (PSA), a useful analysis for determining the probability of making a correct overall decision. Additionally, none of the analyzed studies took a societal perspective, ignoring the impact on study results of lost work productivity and other costs not included when studies only take a health payer perspective. Two notable aspects that enhanced the overall transparency and credibility of the findings of the studies were that all but two of the studies assessed the cost effectiveness of all relevant comparators, and none of the studies was sponsored by a pharmaceutical company (although one study did not explicitly state the funding source).

3.3.2 Inhaled Corticosteroids (ICS) Administered Alone or in Conjunction with Long-Acting β -Agonists (LABA) or Tiotropium for Chronic Asthma Treatment

A number of studies have examined the cost effectiveness of ICS administered alone or in conjunction with LABA. Different studies have shown the cost effectiveness of ICS in patients with persistent asthma, even for developing countries with financial constraints [61, 66]. With respect to the choice among the different ICS, although there are reports that have shown that management with fluticasone

propionate (FP) is more cost effective than with budesonide (BUD) or with flunisolide [31, 57], a study performed in a developing country showed that FP could be more cost effective than beclomethasone dipropionate (BDP), depending on the willingness-to-pay threshold [53].

In patients with inadequately controlled asthma taking ICS, the cost effectiveness of adding LABA preparations (salmeterol or formoterol) to ICS (FP, BUD or BDP) has been claimed in several studies [30, 35, 40, 42]. These studies have reported that combined ICS and LABA preparations are more cost effective than ICS alone at the same doses, and even at double doses [35, 40]. Furthermore, the published literature indicates that fixed combinations of ICS and LABA are more cost effective than the same drugs delivered via separate inhalers [33]. With respect to the choice among the different LABA preparations, although an old study found no evidence to suggest that either LABA treatment (formoterol and salmeterol) administered alone was more cost effective than the other [54], more recent evidence has shown that combinations of ICS and formoterol could be cost effective when compared with combinations of ICS and salmeterol, being associated with cost savings and superior (or at least equivalent) clinical efficacy [38, 41]. The latter is especially true when the combination of ICS and formoterol (BUD/formoterol being the more extensively studied combination) is used for both maintenance and reliever therapy (SMART). A number of studies have shown that the SMART strategy could be cost effective when compared with other alternative strategies, such as fixed-dose FP/salmeterol plus as-needed salbutamol or terbutaline as reliever therapy [46]. Furthermore, a body of evidence has shown that the

Table 3 Characteristics of economic studies evaluating ICS administered alone or in conjunction with LABA preparations or tiotropium for chronic asthma treatment: methodology

	Target population/Setting, age	Type of interventions	Comparators	Type of economic evaluation, model vs. trial-based study	Cost perspective	Source of resource-use data
Miller and FitzGerald (2008), Canada [45]	Uncontrolled asthmatic patients using ≥ 500 $\mu\text{g/day}$ ICS ≥ 1 month, ≥ 12 years	Bud/form (SMART) vs. SFC	Selective comparators	CEA, trial-based study	Healthcare and societal perspective	CT and expert clinical panel. Insufficient detail on the methods of eliciting expert opinion
Wickstrom et al. (2009), Denmark [59]	Not stated, ≥ 4 years	Bud/Form (SMART) vs. higher dose ICS vs. ICS/LTRA vs. higher-dose ICS/LABA	Selective comparators	CEA, trial-based study	Healthcare and societal perspective	Five CTs
Price et al. (2007), 16 countries [51]	Asthmatic patients using ICS for ≥ 3 months at regular doses (> 500 $\mu\text{g/day}$) for > 12 years	Bud/Form (SMART) vs. Bud/Form + prn terbutaline vs. SFC + prn terbutaline	Selective comparators	CEA, trial-based study	Healthcare and societal perspective	CT
Miller et al., (2007) Canada [46]	Moderate to severe asthmatic patients, ≥ 12 years	Bud/Form (SMART) vs. FP/Salm + prn albuterol	Selective comparators	CEA, trial-based study	Healthcare and societal perspective	CT and expert clinical panel. Insufficient detail on the methods of eliciting expert opinion
Goossens et al. (2009), The Netherlands [39]	Mild-to-moderate persistent asthmatic patients with daily ICS, ≥ 18 years	Bud/Form (SMART) vs. medium daily doses ICS + prn terbutaline	Selective comparators	CEA, trial-based study	Healthcare and societal perspective	CT
Lundborg et al. (2006), Sweden [43]	Asthmatic patients not well-controlled with ICS alone or well-controlled with ICS + LABA, 6–82 years	Bud/Form (SMART) vs. higher fixed dose of bud/Form + prn Form	Selective comparators	CEA, trial-based study	Healthcare and societal perspective	CT
Stallberg et al. (2008), Sweden [55]	Asthmatic patients with daily ICS for > 30 days, ≥ 12 years	Bud/Form (SMART) + prn terbutaline vs. Bud/Form fixed + prn terbutaline vs. Bud/Form one inhalation	Selective comparators	CEA, trial-based study	Healthcare and societal perspective	CT
Sullivan et al. (2003), 5 countries [62]	Mild persistent asthma with ≤ 2 years of diagnosis, 5–66 years	Bud vs. usual therapy	Selective comparators	CEA, trial-based study	Healthcare and societal perspective	CT
Malone and Luskin (2003), USA [44]	Patients with ≥ 6 months of asthma, ≥ 12 years	HFA-Beclo vs. CFC-BDP	Selective comparators	CEA, trial-based study	Managed care organization	CT
Paggiaro et al. (2013), Italy [48]	Patients with ≥ 6 months of asthma, 18–65 years	Medium-dose FP/Salm dry powder vs. extrafine Beclo/Form pMDI	Selective comparators	CUA, model-based study (a patient-level simulation Markov model)	Health system perspective	CT
Ismaïla et al. (2014), Canada [40]	Uncontrolled asthma receiving low-, medium- or high-dose FP, not stated	FP vs. LABA/ICS	Selective comparators	CUA, model-based study (a decision model)	Public healthcare perspective	Patient data in GOAL trial

Table 3 continued

	Target population/Setting, age	Type of interventions	Comparators	Type of economic evaluation, model vs. trial-based study	Cost perspective	Source of resource-use data
Miyagawa et al. (2006), Japan [47]	Asthmatic patients on step 3–4 with ICS + LTRA and/or SRT, ≥ 16 years	Salm vs. not treated	Selective comparators	CEA, trial-based study	Healthcare payer perspective and societal perspective	Medical records
Bruggenjurgen et al. (2005), Germany [34]	Uncontrolled for ≥ 6 months mild to moderate asthmatic patients despite ICS, ≥ 16 years	Bud/Form (SMART) vs. Bud/Form fixed	Selective comparators	CMA, trial-based study	Health insurance and society	CT and expert clinical panel. Insufficient detail on the methods of eliciting expert opinion
Bruggenjurgen et al. (2010), Germany [33]	Moderate to severe asthma, ≥ 18 years	Fixed ICS + LABA compared with ICS and LABA delivered by separate inhalers	Selective comparators	CMA and CEA	Health insurance perspective	CT and expert clinical panel. Insufficient detail on the methods of eliciting expert opinion
Doull et al. (2007), UK [35]	Not adequately controlled with ICS and prn SABA, or adequately controlled on ICS/LABA in separate devices, ≥ 4 years	SFC vs. same dose ICS, SFC vs. increased dose ICS, SFC vs. ICS + LABA separate inhalers, SFC vs. Bud/Form	Selective comparators	CUA, model-based study (a decision model)	Not stated	CT
Gerzeli et al. (2012), Italy [38]	Moderate to severe persistent asthma, not stated	BDP/Form vs. SFC	Selective comparators	CEA and CUA, model-based study (Markov Model)	Italian National Health Service	Published studies, panel experts. Sufficient detail on the methods of eliciting expert opinion
Johansson et al. (2006), 4 countries [41]	Asthmatic patients receiving ≥ 500 $\mu\text{g/day}$ of Bud or FP (or ≥ 1000 $\mu\text{g/day}$ of another ICS) for at least 1 month, ≥ 12 years	SMART vs. SFC plus prn salbutamol	Selective comparators	CEA, trial-based study	Societal perspective	CT and patient notebooks
Ericsson et al. (2006), Germany, Netherlands [36]	Persistent asthma for at least 6 months, ≥ 18 years	Bud/Form single inhaler vs. FP	Selective comparators	CEA, trial-based study	Healthcare payer, societal perspective and drug budget holder	CT
Price et al. (2004), UK [50]	Established asthmatic patients maintained on ICS ≥ 400 $\mu\text{g/day}$, ≥ 18 years	Fixed Bud/Form vs. SMART strategy	Selective comparators	CEA, trial-based study	UK National Health Service	CT
Rodriguez-Martinez et al. (2013), Colombia [53]	Persistent asthma, < 18 years	Bud, FP, and ciclesonide vs. BDP	All relevant comparators	CUA, model-based study (Markov Model)	National healthcare system in Colombia	Medical records
Weiss et al. (2006), USA [58]	Mild persistent asthma, < 11 years	Bud added to usual care vs. usual care	Selective comparators	CEA, trial-based study	Healthcare payer's and societal perspective	CT

Table 3 continued

	Target population/Setting, age	Type of interventions	Comparators	Type of economic evaluation, model vs. trial-based study	Cost perspective	Source of resource-use data
Lundback et al. (2000), Sweden [42]	Symptomatic despite ICS at 800–1200 µg/day, ≥ 12 years	SFC vs. Bud	Selective comparators	CEA, trial-based study	Sweden healthcare system	CT
Stempel et al. (2000), USA [56]	All severities of asthma, ≥ 4 years	FP vs. bud	Selective comparators	CEA, trial-based study	US third-party payer	CT
Andersson et al. (2001), 3 countries [30]	Asthmatic for at least 6 months and treated with ICS for at least 3 months, ≥ 18 years	Low-dose Bud vs. low-dose Bud/Form vs. moderate-dose Bud/Form	Selective comparators	CEA, trial-based study	Societal perspective	Expert and CT. Sufficient detail on the methods of eliciting expert opinion
Everden et al. (2002), UK [37]	Symptomatic asthma receiving ICS + SABA, 6–17 years	Form by Turbohaler vs. salm by Accuhaler	Selective comparators	CEA, trial-based study	UK National Health Service	CT
Perera (1995), Sri Lanka [61]	With wheezing that disrupted their normal lives, not stated	BDP and Bud vs. no treatment with ICS	All relevant comparators	CEA, trial-based study	Societal perspective	Observational study
Bisgaard et al. (2001), Denmark [32]	Documented history of recurrent wheeze or asthma symptoms, 12–47 months	FP vs. placebo	Selective comparators	CEA, trial-based study	Danish healthcare system	CT
Price and Briggs (2002), UK [101]	FEV ₁ % predicted of 40–85% and receiving treatment, 12–70 years	SFC, FP, Salm, or placebo	Selective comparators	CUA, model-based study (Markov Model)	Healthcare system	CT
Johansson et al. (1999), Sweden [64]	Asthmatic, ≥ 12 years	SFC vs. FP	Selective comparators	CEA, trial-based study	Swedish healthcare system	CT
Palmqvist et al. (1999), Sweden [63]	Moderate to severe asthma	SFC vs. FP	Selective comparators	CEA, trial-based study	Swedish healthcare system	CT
Volmer et al. (1999), Germany [57]	Steroid-naïve patients with moderate asthma, 18–70 years	FP vs. flunisolide	Selective comparators	CEA, trial-based study	Third-party payer perspective	Two CTs
Rutten-van Mölken et al. (1998), 6 countries [54]	Asthma diagnosed more than 1 year before study entry, ≥ 18 years	Salm vs. Form	Selective comparators	CEA, trial-based study	Societal perspective	CT
Paltiel et al. (2001), USA [60]	Mild-to-moderate asthma, ≥ 18 years	SABA pm plus ICS vs. SABA pm	All relevant comparators	CEA and CUA, model-based study (Markov Model)	Societal perspective	Published resource utilization studies

Table 3 continued

	Target population/Setting, age	Type of interventions	Comparators	Type of economic evaluation, model vs. trial-based study	Cost perspective	Source of resource-use data
Price and Appleby (1998), UK [99]	Asthmatic patients registered at the practice and monitored regularly, not stated	FP vs. other therapies	All relevant comparators	CEA, trial-based study	Not stated	Observational study
Barnes et al. (1999), UK [31]	Asthmatic, not stated	FP vs. Bud	Selective comparators	CEA, trial-based study	Healthcare payer's perspective	CT
Stanciole et al. (2012), Africa, Asia [66]	Asthmatic, 0–80 years	Low-dose ICS, low-dose ICS and LABA, medium-dose ICS, and medium-dose ICS and LTRA	All relevant comparators	CUA, model-based study	Not stated	Published studies, WHO treatment guidelines and expert opinion
Price et al. (2013), UK [65]	Asthmatic, 18–80 years	SFC and eBDP-FOR	Selective comparators	CEA, trial-based study	Not stated	Medical records
Willson et al. (2014), UK [67]	Asthma patients who are uncontrolled despite treatment with ICS/LABA, not stated	Tiotropium add-on vs. usual care	Selective comparators	CUA, model-based study (Markov Model)	Healthcare payer's perspective	CT and experts' opinions
Miller and FitzGerald (2008), Canada [45]		Source of cost data	Source of effectiveness data	Discounting, time horizon	Sensitivity analyses	Funding source
	A variety of Canadian sources	CT		Not necessary, 6 months	No PSA	Funding source not explicitly stated
Wickstrom et al. (2009), Denmark [59]	Danish official tariffs, private and public	Five CTs		Not necessary, 1 year	No PSA	Pharmaceutical company
Price et al. (2007), 16 countries [51]	UK and Australian national registers and surveys	CT		Not necessary, 6 months	No PSA	Pharmaceutical company
Miller et al., (2007) Canada [46]	National or provincial (mostly Ontario) prices	CT		Not necessary, 1 year	No PSA	Pharmaceutical company
Goossens et al. (2009), The Netherlands [39]	Dutch manuals and databank by HealthCare Insurance Board	CT		Not necessary, 12 months	No PSA	Pharmaceutical company
Lundborg et al. (2006), Sweden [43]	Apoteket AB (Swedish pharmaceuticals) and literature	CT		Not necessary, 6 months	No sensitivity analysis	Pharmaceutical company

Table 3 continued

	Source of cost data	Source of effectiveness data	Discounting, time horizon	Sensitivity analyses	Funding source
Stallberg et al. (2008), Sweden [55]	Swedish Kronor and prices paid for medications and indirect resources, including social benefits	CT	Not necessary, 12 months	No PSA	Pharmaceutical company
Sullivan et al. (2003), 5 countries [62]	A medical and pharmacy database, US average wholesale prices, human capital approach	Medical records	Annual rate of 3%, 3 years	No PSA	Pharmaceutical company
Malone and Luskin (2003), USA [44]	Common Procedural Terminology codes, average wholesale prices	CT	Not necessary, 12 months	No PSA	Pharmaceutical company
Paggiaro et al. (2013), Italy [48]	Literature	CT	Not stated, 6 months	PSA	Pharmaceutical company
Ismaila et al. (2014), Canada [40]	Ontario schedule of benefits and Drug Benefit Formulary, and Alberta case costing report. Expert's opinion, with insufficient detail on the methods of eliciting expert opinion	Meta-analysis of RCTs	Not stated, 12 months	PSA	Pharmaceutical company
Miyagawa et al. (2006), Japan [47]	Medical records, human capital approach, and labor of Ministry of Health, Labour and Welfare	Medical records	Not stated, 1 year	PSA	Pharmaceutical company
Bruggenjurgen et al. (2005), Germany [34]	Rote Liste, Taschenbuch, Gesundheit Einheitlicher, Bewertungsmaßstab, Jahrbuch	CT	Not stated, 12 weeks	No sensitivity analysis	Funding source not explicitly stated
Bruggenjurgen et al. (2010), Germany [33]	Lauer Taxe ex pharmacy, Uniform Value Scale	CT	Not necessary, 24 weeks	No PSA	Pharmaceutical company

Table 3 continued

	Source of cost data	Source of effectiveness data	Discounting, time horizon	Sensitivity analyses	Funding source
Doull et al. (2007), UK [35]	Online Drug Tariff, MIMS, and published sources for England and Wales	Systematic review of CTs	Not required, 1 year	PSA	Pharmaceutical company
Gerzeli et al. (2012), Italy [38]	Italian fees for healthcare services, retail prices for drugs	CT, Ministry of Health, published observational study	Not stated, 1 year	PSA	Pharmaceutical company
Johansson et al. (2006), 4 countries [41]	Official price from 4 European countries, and national registries, and literature and national average	CT	Not stated, 12 months	No sensitivity analysis	Pharmaceutical company
Ericsson et al. (2006), Germany, Netherlands [36]	German Marks and Dutch Guilders	CT	Not stated, 12 weeks	PSA	Pharmaceutical company
Price et al. (2004), UK [50]	Published sources, British National Formulary	CT	Not stated, 12 weeks	No PSA	Pharmaceutical company
Rodriguez-Martinez et al. (2013), Colombia [53]	National manual of drug prices, and hospitals' bills	Systematic review of RCTs	Not necessary, 12 months	PSA	Scientific or academic
Weiss et al. (2006), USA [58]	US average wholesale	CT	Annual rate of 3%, 3 years	No PSA	Funding source not explicitly stated
Lundback et al. (2000), Sweden [42]	Swedish government statistics	CT	Not stated, 24 weeks	No PSA	Funding source not explicitly stated
Stempel et al. (2000), USA [56]	Average whole sale prices, Current Procedural Terminology- 4	Systematic review of CTs	Not stated, 12 weeks	No PSA	Funding source not explicitly stated
Andersson et al. (2001), 3 countries [30]	Official price lists	CT	Not stated, 12 months	No PSA	Pharmaceutical company
Everden et al. (2002), UK [37]	Published sources, British National Formulary	CT	Not stated, 12 weeks	No PSA	Funding source not explicitly stated
Perera (1995), Sri Lanka [61]	Parentales interviews	Observational study	Not stated, 12 months	No sensitivity analysis	Funding source not explicitly stated
Bisgaard et al. (2001), Denmark [32]	Published sources	CT	Not stated, 12 weeks	No PSA	Pharmaceutical company
Price and Briggs (2002), UK [101]	Monthly Index of medical specialities and a published study	CT	Not stated, 12 weeks	PSA	Pharmaceutical company

Table 3 continued

	Source of cost data	Source of effectiveness data	Discounting, time horizon	Sensitivity analyses	Funding source
Johansson et al. (1999), Sweden [64]	Not stated	CT	Not stated, 12 weeks	No PSA	Funding source not explicitly stated
Palmqvist et al. (1999), Sweden [63]	Not stated	CT	Not stated, 12 weeks	No PSA	Funding source not explicitly stated
Volmer et al. (1999), Germany [57]	Rote Liste	Two CTs	Not stated, 8 weeks	No PSA	Pharmaceutical company
Rutten-van Mölken et al. (1998), 6 countries [54]	Various sources outside the trial	CT	Not stated, 6 months	No PSA	Pharmaceutical company
Paltiel et al. (2001), USA [60]	Published studies	Systematic review of the literature	Annual rate of 3%, 10 years	No PSA	Pharmaceutical company
Price and Appleby (1998), UK [99]	Practice/local authority estimates	Observational study	Not stated, 12 months	No sensitivity analysis	Funding source not explicitly stated
Barnes et al. (1999), UK [31]	British National Formulary and Office of Health Economics	CT	Not stated, 12 weeks	No PSA	Funding source not explicitly stated
Stanciole et al. (2012), Africa, Asia [66]	WHO-CHOICE 2005 database, International Drug Price Indicator Guide, and the drug price lists from the governments of New Zealand and Australia	Global Burden of Disease Study and the Dutch Disability Weight Study	Annual rate of 3%, lifetime horizon	PSA	No funding
Price et al. (2013), UK [65]	British National Formulary	Medical records	Not stated, 12 months	PSA	Pharmaceutical company
Willson et al. (2014), UK [67]	Health and Social Care, National Schedule of Reference Costs, and the British National Formulary	CT	Annual rate of 3.5%, lifetime horizon	PSA	Pharmaceutical company

ICS inhaled corticosteroids, *LABA* long-acting β -agonists, *PSA* probabilistic sensitivity analysis, *CT* clinical trial, *RCTs* randomized controlled trials, *CEA* cost-effectiveness analysis, *CUA* cost-utility analysis, *CMA* cost-minimization analysis, *Bud* budesonide, *SMART* single-inhaler maintenance and reliever therapy, *Form* formoterol, *SFC* salmeterol/fluticasone propionate, *LTRA* leukotriene receptor antagonists, *prm* as needed, *FP* fluticasone propionate, *Salm* salmeterol, *Beclo* beclomethasone, *CFC-BDP* chlorofluorocarbon-beclomethasone dipropionate, *pMDI* pressurized metered-dose inhaler, *SRT* slow-release theophylline, *eBDP-FOR* extra-fine particle beclomethasone dipropionate-formoterol, *FEV₁* forced expiratory volume in 1 s, *WHO* World Health Organization, *HFA* hydrofluoroalkane, *MIMS* Monthly Index of Medical Specialities

Table 4 Results of economic studies evaluating ICS administered alone or in conjunction with LABA preparations or tiotropium for chronic asthma treatment

	Main drivers of cost effectiveness	ICERs	Conclusions of the study authors
Miller and FitzGerald (2008) [45]	Number of SMART inhalations	Not calculated. SMART dominates (more effective and less costly)	SMART strategy is dominant over fixed higher dose Bud/Form plus prn terbutaline or fixed-dose SFC plus prn terbutaline
Wickstrom et al. (2009) [59]	–	Not calculated. SMART dominates (more effective and less costly)	SMART strategy is cost effective compared with higher dose of ICS, higher dose of ICS/LABA, and a similar dose of ICS/LABA
Price et al. (2007) [51]	Cost of Bud/Form	Not calculated. SMART dominates (more effective and less costly)	Compared with higher fixed-dose Bud/Form and SFC, SMART reduces severe exacerbations at a lower or similar overall cost and is cost effective
Miller et al. (2007) [46]	The annualized rate of exacerbations and the costs (excluding Bud/Form and SFC)	Not calculated. SMART dominates (more effective and less costly)	SMART strategy proved to be more effective and less expensive than a strategy of clinician-directed titration of SFC with salbutamol as reliever therapy
Goossens et al. (2009) [39]	Inclusion of productivity losses	Not calculated. SMART does not affect health outcomes and does not increase costs	SMART strategy instead of ICS plus bronchodilators does not affect health outcomes and does not increase costs
Lundborg et al. (2006) [43]	No sensitivity analysis	Not calculated. SMART is equally effective and less costly)	SMART strategy is equally effective and cheaper compared with double the maintenance dose of Bud/Form + Form prn
Stallberg et al. (2008) [55]	–	Not calculated. SMART is equally effective and less costly)	Direct cost savings with SMART strategy compared with conventional treatment regimens with at least equivalent efficacy
Sullivan et al. (2003) [62]	Drug and non-drug unit costs	\$11.30 (95% CI \$8.60–\$14.90) from the healthcare payer perspective and \$3.70 per symptom-free days gained (95% CI \$0.10–\$8.00) from the societal perspective	Bud appears to be cost effective in mild-persistent asthmatic of recent onset
Malone and Luskin (2003) [44]	Change in Bud effect over time, cost of ED visits and cost of office-based visits	–\$5.77 (95% CI –\$68.08 to –\$4.08) per symptom-free days gained	HFA-BDP was a dominant therapy (more effective, less costly) compared with CFC-BDP
Paggiaro et al. (2013) [48]	Form of formulation of SFC	High-dose dry powder SFC 1000/100 mg vs. extra-fine BDP/Form 400/24 mg was above £70,000 and €200,000/QALY. An ICER of £29,000/QALY and above €30,000/QALY was associated with medium-dose dry powder SFC 500/100 mg vs. BDP/F 400/24 mg	Stepping down from high-dose SFC to extra-fine BDP/Form is cost effective
Ismaila et al. (2014) [40]	Efficacy inputs	\$43,000 to \$54,400 per QALY gained for SFC compared with no FP dose change, and \$25,000–\$3500 per QALY gained compared with increased FP dose scenarios	SFC is cost effective compared with doubling FP dose
Miyagawa et al. (2006) [47]	–	Not calculated. ICS/salmeterol dominates (more effective and less costly)	ICS/salmeterol appears to be efficacious and cost effective
Bruggenjurgen et al. (2005) [34]	No sensitivity analysis	Not calculated. Adjustable maintenance dosing is equally effective and less costly)	Adjustable maintenance dosing strategy is similar for HRQoL, but at lower cost, than fixed dosing
Bruggenjurgen et al. (2010) [33]	Drug costs	€9.77 per additional day free of asthma symptoms	BDP/Form fixed combination is superior to BDP + Form delivered via separate inhalers

Table 4 continued

	Main drivers of cost effectiveness	ICERs	Conclusions of the study authors
Doull et al. (2007) [35]	–	Compared with an increased dose of SFC either ‘dominates’ (i.e. cheaper and more effective) FP or the cost per QALY is £6852	Is a cost-effective option to switch to SFC (at an equivalent ICS dose) compared with increasing ICS dose
Gerzeli et al. (2012) [38]	Drug costs	Not reported	BDP/Form compared with SFC strategy is associated with a cost reduction and equivalent clinical efficacy
Johansson et al. (2006) [41]	No sensitivity analysis	Not calculated. SMART dominates (more effective and less costly)	Compared with SFC, SMART may be cost effective from a societal perspective, providing a reduction of severe exacerbation
Ericsson et al. (2006) [36]	–	Not calculated.	Bud/Form in single inhaler is more effective than higher dose FP. It is cost-neutral and may provide cost savings in some countries
Price et al. (2004) [50]	Proportion of patients managed at Step 3, proportion of budesonide/Form patients currently self-managed, and one-off education costs	Not calculated. SMART is equally effective and less costly)	SMART strategy provided equivalent HRQoL to fixed dosing at lower cost
Rodriguez-Martinez et al. (2013) [53]	Cost of asthma exacerbation	The incremental cost-utility ratio of FP compared with BDP was £19,835.28 per QALY	BDP is the most cost effective when willingness to pay is less than £21,129.22/QALY, otherwise, FP is the most cost-effective therapy
Weiss et al. (2006) [58]	–	\$10.50 (95% CI \$1.20–33.30) per symptom-free days gained	Early intervention with once-daily Bud added to usual care is cost-saving from a societal perspective and is acceptably cost effective when viewed from a healthcare payer perspective
Lundback et al. (2000) [42]	–	Costs per additional successfully treated week, symptom-free day and episode-free day with SFC were SEK31.6 (\$US3.9), SEK9.2 (\$US1.1) and SEK7.7 (\$US0.9), respectively, relative to budesonide	SFC is a more cost effective treatment than Bud in the management of moderate to severe asthma
Stempel et al. (2000) [56]	The cost of Bud, and the length of hospital stay	FP dominates (more effective and less costly)	FP was more effective and less expensive than Bud
Andersson et al. (2001) [30]	Inclusion of productivity losses and cost of asthma exacerbations	The incremental cost per symptom-free days ranged between €2.51 in Spain and €6.60 in the UK.	Adding the inhaled, LABA formoterol to low–moderate doses of the ICS Bud generated gains in all outcome measures with partial or complete offset of costs, and can be considered cost effective
Everden et al. (2002) [37]	–	Not calculated. Eorm dominates (more effective and less costly)	Form by Turbohaler was more effective and less expensive than salmeterol by Accuhaler
Perera (1995) [61]	No sensitivity analysis	Not calculated	Even for developing countries with financial constraints, ICS treatment for prophylaxis of asthma is a cost-effective and rational form of treatment
Bisgaard et al. (2001) [32]	–	Not relevant. FP dominates (more effective and less costly)	FP is cost effective relative to standard therapy with bronchodilators alone
Price and Briggs (2002) [101]	Asthma management costs	The average incremental cost per successfully controlled week with SFC was £20.83	SFC is cost effective compared with FP at same doses
Johansson et al. (1999) [64]	–	The cost to achieve an additional successfully treated week with SFC was an additional SEK133.4 (\$US16.18) per week	SFC was more cost effective than FP

Table 4 continued

	Main drivers of cost effectiveness	ICERs	Conclusions of the study authors
Palmqvist et al. (1999) [63]	–	The additional costs to achieve an additional successfully treated week, symptom-free day and episode-free day were SEK12.6 (\$US1.53) per patient per week, SEK3.9 (\$US0.47) per patient per day and SEK3.9 (\$US0.47) per patient per day, respectively	SFC was more effective for a similar overall healthcare cost and was more cost effective than FP
Volmer et al. (1999) [57]	–	The additional costs per additional symptom-free day ranged between DM5.87 and DM6.04, and between DM2.61 and DM2.83 per each additional successfully treated patient per day	FP was more cost effective than flunisolide
Rutten-van Mölken et al. (1998) [54]	–	Not calculated (both costs and outcomes were not significantly different)	No evidence to suggest that either treatment (Form and salmeterol) was more cost effective than the other
Paltiel et al. (2001) [60]	The effect of ICS efficacy, and the percentage decrement in HRQoL because of side effects of ICS	Compared with quick relievers alone, an incremental cost of \$13,500 per QALY gained and \$7.50 per additional symptom-free day	ICS appear to deliver good comparative value
Price and Appleby (1998) [99]	No sensitivity analysis	Not calculated	Asthmatic patients with persistent symptoms and frequent exacerbations, switching to FP can bring improvement clinically and be cost effective
Barnes et al. (1999) [31]	–	Not relevant (FP is a dominant strategy)	FP is more effective and also cheaper, in terms of overall healthcare costs, than Bud
Stanciole et al. (2012) [66]	Age weights and the discount factor	Low-dose ICS most cost-effective Intervention, with average cost per DALY averted of \$2500	Low-dose ICS for mild–persistent asthma considered most cost-effective
Price et al. (2013) [65]	–	Using exacerbation prevention as treatment effective, eFBDP-FOR has 75% probability of cost effectiveness	Switching from SFC to eFBDP-FOR at equivalent or lower ICS dose is cost effective
Willson et al. (2014) [67]	The cost of the ‘uncontrolled asthma’ state	Add-on tiotropium therapy resulted in an ICER of £21,906 per QALY gained	Tiotropium add-on is cost effective for patients with uncontrolled asthma

BDP beclomethasone dipropionate, *Bud* budesonide, *CFC* chlorofluorocarbon, *CI* confidence interval, *DM* Deutsche Mark, *efBDP-FOR* extra-fine particle beclomethasone dipropionate-formoterol *Form* formoterol, *DALY* disability-adjusted life-years, *ED* Emergency Department, *FP* fluticasone propionate, *HFA-BDP* hydrofluoroalkane-134a-beclomethasone dipropionate extrafine aerosol, *HRQoL* health-related quality of life, *ICERs* incremental cost-effectiveness ratios, *ICS* inhaled corticosteroids, *LABA* long-acting β_2 -agonists, *prn* as needed, *QALY* quality-adjusted life-year, *Salm* salmeterol, *SEK* Swedish Krona, *SFC* salmeterol/fluticasone propionate, *SMART* single-inhaler maintenance and reliever therapy

SMART strategy is cost effective over other strategies that use formoterol as the LABA component, such as fixed higher-dose BUD/formoterol plus as-needed salbutamol or terbutaline as reliever therapy [45, 51] and doubling the maintenance dose of BUD/formoterol plus formoterol as needed [43].

One study evaluated the cost effectiveness of tiotropium as add-on to the usual care in asthma patients who are uncontrolled despite treatment with an ICS/LABA combination, showing that tiotropium was cost effective, resulting in an ICER of £21,906 per QALY gained [67].

Although most of these studies reported that their interventions were cost effective, in our opinion this was not always supported by the methodology of the studies, for several reasons. First, most of the studies used clinical

trial efficacy data instead of effectiveness data, making it possible that they did not truly represent real-life health outcomes. For example, it has been well-documented that real-life patients often have poor inhalation technique and suboptimal adherence levels to inhaled medications, which are associated with worse health outcomes. Therefore, the use of clinical trial efficacy data could have led to overestimation of the actual benefits of the intervention of interest. Along the same line, two other common aspects that could have also resulted in overestimation of the actual benefits of these interventions are the assessment of a limited and selective number of comparators and sponsorship by a pharmaceutical company. Specifically, all of the 10 studies that compared ICS with some combination of ICS and LABA [30, 35, 36, 39, 40, 42, 59, 63, 64, 101]

Table 5 Characteristics of economic studies evaluating direct comparisons between different combinations of ICS, ICS/LABA, LTRA, and sodium cromoglycate for chronic asthma treatment: methodology

	Target population/setting, age	Type of interventions	Comparators	Type of economic evaluation, model vs. trial-based study	Cost perspective	Source of resource-use data
Tan et al. (2009), US [79]	At least 1 medical claim for asthma and at least 1 prescription claim for an asthma controller medication, 18–64 yrs	ICS, LTRA, LABA, and combinations	All relevant comparators, 12 months	CEA, trial-based study	Healthcare perspective and societal perspective	Administrative claims data
Stempel et al. (2007), US [78]	Documented asthma diagnosis and index prescription claim for FP or MONT, 4–17 years	FP and MONT	Selective comparators, 12 months	CEA, trial-based study	Healthcare perspective	Medical and pharmaceutical claims in a national database
Wang et al. (2011), US [80]	Mild-to-moderate persistent asthma, 6–14 years	FP and MONT	Selective comparators, 48 weeks	CEA, trial-based study	Healthcare payer perspective and societal perspective	CT
Rely et al. (2011), Mexico [75]	Symptomatic asthma receiving ICS, 6–14 years	SFC and MONT	Selective comparators, 12 weeks	CEA, trial-based study	Public healthcare perspective	CT, panel expert. Insufficient detail on the methods of eliciting expert opinion
Price et al. (2011), UK [74]	Uncontrolled by SABA (Step 2) or ICS (Step 3) and a score ≤ 6 points on Mini AQLQ and/or ≥ 1 point on ACQ, 12–80 years	LTRA vs. ICS as initial controller, and LTRA vs. LABA as add-on therapy to ICS	All relevant comparators, 2 months and 2 years	CEA and CUA, trial-based study	Healthcare and societal perspectives	CT
Shih et al. (2007), US [77]	Mild-to-moderate persistent asthmatic, not stated	Single-inhaler SFC, FP, non-FP and LTRA	All relevant comparators, 12 months	CEA, model-based study (a decision model)	Managed care organizations payer perspective	Published clinical trials and observational studies
Borker et al. (2005), US [69]	Persistent asthma uncontrolled with a SABA alone, ≥ 15 years	SFC vs. MONT	Selective comparators, 12 weeks	CEA, trial-based study	Payer's perspective	CT
Heaton et al. (2006), US [70]	Asthmatic, at least 1 pharmacy claim for an asthma medication in the 6 months prior to their asthma diagnosis, ≥ 18 years	LTRA vs. non-LTRA	Selective comparators, 270 days	CBA, trial-based study	Third-party payer	Ohio Medicaid database
O'Connor et al. (2004), US [72]	Asthmatic patients for at least 6 months symptomatic despite ICS, ≥ 15 years	SFC vs. FP + MONT	Selective comparators, 12 weeks	CEA and CMA, trial-based study	US third-party payer's perspective	CT
Wilson et al. (2010), UK [81]	Uncontrolled asthmatic despite low-dose ICS, 12–80 years	LTRA vs. LABA as add-on to ICS	Selective comparators, 2 years	CEA and CUA, trial-based study	UK National Health Service and societal perspective included	CT (GP practice data, patient-diary cards)
O'Connor et al. (2002), US [73]	Primary or secondary diagnosis of asthma that had switched from ICS monotherapy to dual therapy, ≥ 12 years	SFC, ICS non-FP + salmeterol, and ICS + LTRA	Selective comparators, 12 months	CEA, trial-based study	Payer's perspective	Observational study, Health Net and Physician Health Services

Table 5 continued

	Target population/setting, age	Type of interventions	Comparators	Type of economic evaluation, model vs. trial-based study	Cost perspective	Source of resource-use data
Sheth et al. (2002), US [76]	Asthma for at least 6 months, ≥ 15 years	SFC vs. MONT	Selective comparators, 12 weeks	CEA, trial-based study	Payer's perspective	CT
Andersson et al. (2001), Sweden [68]	Unstable asthma not previously treated with ICS or cromones, 5–11 years	Bud vs. sodium cromoglycate	Selective comparators, 12 months	CEA, trial-based study	Societal perspective	CT
Menendez et al. (2001), US [71]	Persistent asthma currently receiving SABA alone, ≥ 12 years	FP vs. zafirlukast	Selective comparators, 12 weeks	CEA, trial-based study	Third-party payor	CT
	Source of cost data	Source of effectiveness data	Discounting, time horizon	Sensitivity analyses	Funding source	
Tan et al. (2009), US [79]	Administrative claims data	Administrative data	Not stated, 12 months	No PSA	Insurance company	
Stempel et al. (2007), US [78]	Medical and pharmaceutical claims in a national database	Medical and pharmaceutical claims in a national database	Not stated, 12 months	No sensitivity analysis	Pharmaceutical company	
Wang et al. (2011), US [80]	Drug Topics Red Book, the human-capital approach	CT	Not stated, 48 weeks	PSA	Scientific or academic	
Rely et al. (2011), Mexico [75]	Mexican Social Security Institute, panel expert	CT	Not necessary, 12 weeks	PSA	Funding source not explicitly stated	
Price et al. (2011), UK [74]	PSSRU, NHS Reference Costs, and published sources	CT	Annual rate of 3.5%, 2 months and 2 years	No sensitivity analysis	Scientific or academic	
Shih et al. (2007), US [77]	HealthCare Consultants of America, Physician Fee and Coding Guide, Red Book, published studies	Published clinical trials and observational studies	Not stated, 12 months	PSA	Pharmaceutical company	
Borker et al. (2005), US [69]	Various published sources	CT	Not stated, 12 weeks	No PSA	Pharmaceutical company	
Heaton et al. (2006), US [70]	Ohio Medicaid database	Ohio Medicaid database	Not stated, 270 days	No sensitivity analysis	Scientific or academic	
O'Connor et al. (2004), US [72]	Various published sources	CT	Not stated, 12 weeks	PSA	Pharmaceutical company	

Table 5 continued

	Source of cost data	Source of effectiveness data	Discounting, time horizon	Sensitivity analyses	Funding source
Wilson et al. (2010), UK [81]	British National Formulary code, pharmacy websites, NHS costs, and national average gross hourly wage	CT	Annual rate of 3.5%, 2 years	PSA	Scientific or academic
O'Connor et al. (2002), US [73]	Average wholesale price of the prescription and any applicable co-pays, Health Net providers	Observational study	Not stated, 12 months	No sensitivity analysis	Pharmaceutical company
Sheth et al. (2002), US [76]	First DataBank database report and Drug Topics Red Book, Current Procedural Terminology-4, and published study	CT	Not stated, 12 weeks	PSA	Pharmaceutical company
Andersson et al. (2001), Sweden [68]	Swedish physicians' drug manual, statistics Sweden	CT	Not stated, 12 months	No PSA	Funding source not explicitly stated
Menendez et al. (2001), US [71]	Average wholesale price, a national survey of reimbursements and published consumer price index for healthcare	CT	Not stated, 12 weeks	No PSA	Pharmaceutical company

ICS inhaled corticosteroids, *LABA* long-acting β_2 -agonists, *LTRA* leukotriene receptors antagonists, *PSA* probabilistic sensitivity analysis, *CT* clinical trial, *PSSRU* Personal Social Services Research Unit, *NHS* National Health Service, *GP* general practitioner, *CEA* cost-effectiveness analysis, *CUA* cost-utility analysis, *CMA* cost-minimization analysis, *FP* fluticasone propionate, *MONT* montelukast, *SFC* salmeterol/fluticasone propionate, *Bud* budesonide, *SABA* short-acting β_2 -agonists, *AQLQ* Asthma Quality of Life Questionnaire, *ACQ* Asthma Control Questionnaire

Table 6 Results of economic studies evaluating direct comparisons between different combinations of ICS, ICS/LABA, LTRA, and sodium cromoglycate for chronic asthma treatment

	Main drivers of cost effectiveness	ICERs	Conclusions of the study authors
Tan et al. (2009) [79]	–	Not calculated	ICS are associated with greater efficacy and a lower cost if adherence was achieved, otherwise, LTRA may be a reasonable alternative. ICS/LABA is associated with better or equivalent clinical, economic, and patient-reported outcomes
Stempel et al. (2007) [78]	No sensitivity analysis	Not relevant (FP is a dominant strategy)	FP is associated with better outcomes and lower cost than MONT
Wang et al. (2011) [80]	–	Not relevant (FP is a dominant strategy)	Low-dose FP had lower cost and higher effectiveness than MONT, especially in those with more airway inflammation
Rely et al. (2011) [75]	Percentage of patients with adequate control of asthma, percentage of asthma exacerbations, and percentage and duration of hospitalizations for asthma exacerbations	Not relevant (SFC is a dominant strategy)	Compared with MONT, SFC may be cost saving
Price et al. (2011) [74]	No sensitivity analysis	LTRA are equally effective than ICS and more costly	LTRA are unlikely to be a cost-effective alternative to ICS. LTRA were clinically equivalent to ICS as initial controller therapy, and to LABA as add-on to ICS in terms of HRQoL at 2 months; equivalence was not proven at 2 years
Shih et al. (2007) [77]	Medication adherence	The cost to achieve an additional symptom-free day with SFC vs. FP was \$US9.55, and \$US8.93 per rescue medication-free day	The additional costs for achieving incremental effectiveness with SFC vs. FP and non-FPC may be lower than the commonly accepted benchmark value for cost effectiveness. FP/Salm may also be more cost effective than LTRA
Borker et al. (2005) [69]	–	\$2.87 (95% CI –\$1.08 to \$6.65) per day for an additional symptom-free day, and \$1.79 (95% CI –\$0.72 to \$3.86) per day to achieve a lung function improvement of $\geq 12\%$ from baseline	SFC is more cost effective than MONT as initial maintenance therapy
Heaton et al. (2006) [70]	No sensitivity analysis	Not relevant (non-use of LTRA is a dominant strategy)	Use of LTRA was not associated with clinical effectiveness in asthma control, but was associated with higher total costs for asthma care
O'Connor et al. (2004) [72]	–	Not relevant (SFC is a dominant strategy)	Treating persistent asthma with SFC may not only be a more cost-effective strategy but may actually lead to cost savings compared with the addition of MONT to low-dose FP
Wilson et al. (2010) [81]	–	The incremental cost per QALY gained (LTRA vs. LABA) was £22589 from the societal perspective, and £11919 from the NHS perspective	The results marginally favor the repositioning of LTRA as a cost-effective alternative to LABA as add-on therapy to ICS for asthma
O'Connor et al. (2002) [73]	No sensitivity analysis	Not relevant (SFC is a dominant strategy)	Compared with ICS + MONT, SFC provides superior clinical benefit, as evidenced by lower ED and hospitalization as at substantially lower costs

Table 6 continued

	Main drivers of cost effectiveness	ICERs	Conclusions of the study authors
Sheth et al. (2002) [76]	–	\$1.33 (95% CI 0.80–2.02) per percentage change in FEV ₁ from baseline, and \$1.69 (95% CI 1.01–2.48) per percentage symptom-free days	SFC bid is more cost effective than MONT od as initial therapy
Andersson et al. (2001) [68]	Asthma drug costs	Not relevant (Bud is a dominant strategy)	Bud for continued maintenance, after an initial period of stabilizing with Bud, resulted in lower costs and less drug switches than a strategy with sodium cromoglycate

bid twice daily, *Bud* budesonide, *CI* confidence interval, *ED* Emergency Department, *FEV₁* forced expiratory volume in 1 s, *FP* fluticasone propionate, *HRQoL* health-related quality of life, *ICERs* incremental cost-effectiveness ratios, *ICS* inhaled corticosteroids, *LABA* long-acting β_2 -agonists, *LTRA* leukotriene receptor antagonists, *MONT* montelukast, *NHS* National Health Service, *od* once daily, *QALY* quality-adjusted life-year, *Salm* salmeterol, *SFC* salmeterol and fluticasone propionate

used clinical trial efficacy data and compared a limited and selective number of comparators. Additionally, 7 of these 10 studies were sponsored by a pharmaceutical company (in the remaining three studies, the funding source was not explicitly stated). Likewise, all of the studies that compared any combination of ICS and formoterol with any combination of ICS and salmeterol [35, 38, 41, 46, 48, 51], and all of those that compared combinations containing formoterol used for both maintenance and reliever therapy (SMART strategy) with combinations containing formoterol or salmeterol used in fixed maintenance doses [34, 41, 43, 45, 46, 50, 51, 55, 59], used clinical trial efficacy data (except one study, which used real-life effectiveness data [55]), assessed a limited and selective number of comparators, and were sponsored by a pharmaceutical company. The study that evaluated tiotropium also used clinical trial efficacy, compared a limited and selective number of comparators, and was sponsored by a pharmaceutical company [67]. An important additional aspect that should be taken into account when interpreting the results of the studies is the time horizon. This is because limited time horizons cannot appropriately capture all the significant benefits and consequences of interest, nor can they account for the seasonality of asthma. Among all the studies that compared ICS with some combination of ICS and LABA, studies that compared any combination of ICS and formoterol with any combination of ICS and salmeterol, and studies that compared the SMART strategy with combinations containing formoterol or salmeterol used in fixed maintenance doses, 5/10 [36, 42, 63, 64, 101], 2/6 [48, 51] and 5/9 [34, 43, 45, 50, 51], respectively, had time horizons of < 1 year, ranging from 12 to 24 weeks. On the contrary, the study that evaluated tiotropium had a lifetime horizon [67].

An important aspect that serves as a support for helping decision makers or clinicians to make a rational

interpretation of study findings is the ICER result. Among all the studies that compared ICS with some combination of ICS and LABA, the studies that compared any combination of ICS and formoterol with any combination of ICS and salmeterol, and the studies that compared the SMART strategy with combinations containing formoterol or salmeterol used in fixed maintenance doses, 7/10 [30, 35, 40, 42, 63, 64, 101], 2/6 [35, 51], and 0/9, respectively, reported an ICER result, although in the majority of cases in which it was not calculated this was due to the dominance of the intervention of interest. The study that evaluated tiotropium reported an ICER of £21,906 per QALY gained [67]. The ICER results of each of the included studies are shown in Table 4.

3.3.3 Direct Comparisons between Different Combinations of ICS, ICS/LABA, Leukotriene Receptor Antagonists, and Sodium Cromoglycate for Chronic Asthma Treatment

In pediatric patients with unstable asthma, it seems more cost effective to use ICS (e.g. BUD) than sodium cromoglycate [68]. In the same way, different studies have shown that in patients with mild-to-moderate persistent asthma, ICS have lower costs and higher effectiveness compared with LTRA preparations such as montelukast (MON) or zafirlukast [71, 80], with it being unlikely that LTRA preparations are a cost-effective alternative to ICS [74]. An exception to this statement might occur in case ICS adherence cannot be achieved, in which case an economic evaluation based on administrative claims data from US commercial health plans found that LTRA may be a reasonable choice for monotherapy [79]. Similarly, a number of studies have shown that in patients with asthma inadequately controlled through ICS, the addition of LABA preparations (e.g. salmeterol) to ICS (e.g. FP) is cost

Table 7 Characteristics of economic studies evaluating omalizumab for severe chronic asthma treatment: methodology

	Target population/setting, age	Type of interventions	Comparators	Type of economic evaluation, model vs. trial-based study	Cost perspective	Source of resource-use data
Wu et al. (2007), US [92]	Severe asthma, not stated	ICS + SABA prn and ICS + SABA prn + OMA	All relevant comparators	CEA, model-based study (Markov Model)	Societal perspective	Published resource-use studies
Faria et al. (2014), UK [86]	Severe persistent allergic asthma, ≥ 6 years	OMA and standard asthma care	All relevant comparators	CUA, model-based study (Markov Model)	Healthcare perspective	Systematic review of the literature
Dal Negro et al. (2012), Italy [85]	Severe, persistent atopic asthma on chronic high-dose antiasthmatic treatments, ≥ 12 years	OMA and standard asthma care	All relevant comparators	CUA, trial-based study	Healthcare perspective	Institutional database
van Nooten et al. (2013), Nether [90]	Uncontrolled allergic (IgE-mediated) asthma despite treatment with high-dose ICS and LABA, ≥ 12 years	OMA and standard asthma therapy	All relevant comparators	CUA, model-based study (Markov Model)	Healthcare and societal perspectives	Observational study
Norman et al. (2013), UK [88]	Severe persistent allergic asthma, ≥ 6 years	OMA as an add-on therapy to standard care vs. standard therapy alone	All relevant comparators	CEA and CUA, model-based study (Markov Model)	Healthcare perspective	CT
Brown et al. (2007), Canada [83]	Severe persistent allergic asthma, not stated	OMA and standard therapy	All relevant comparators	CEA and CUA, model-based study (Markov Model)	Health insurance perspective	CT
Campbell et al. (2010), US [84]	Moderate-to-severe persistent asthma, a positive SPT or in vitro reactivity to a perennial aeroallergen, and uncontrolled with ICS, mean 40 years	OMA plus usual care vs. usual care alone	All relevant comparators	CUA, model-based study (Markov Model)	Payer perspective	Meta-analysis of the best-available evidence
Levy et al. (2015), Spain [87]	Uncontrolled severe allergic persistent asthma, ≥ 14 years	OMA vs. routine clinical practice	All relevant comparators	CEA and CUA, trial-based study	Spanish National Health System	Observational CT
Oba and Salzman (2004), US [89]	Moderate-to-severe, suboptimally controlled allergic asthma, ≥ 15 years	OMA vs. placebo	All relevant comparators	CEA, trial-based study	Third-party payer's perspective	CT
Venera et al. (2016), Spain [91]	Severe persistent allergic asthma uncontrolled by standard treatment, ≥ 17 years	OMA vs. standard treatment	All relevant comparators	CEA, trial-based study	Societal perspective	Observational study
Yoshikawa et al. (2016), Japan [93]	Severe asthma, 9–14 years	OMA vs. conventional treatment	All relevant comparators	CEA, trial-based study	Not stated	Clinical data
Devilde et al. (2006), Sweden [96]	Adult patients with severe persistent allergic asthma who are uncontrolled despite GINA Step 4 therapy, mean 43 years	OMA vs. standard therapy	All relevant comparators	CEA and CUA, model-based study (Markov Model)	Societal perspective	INNOVATE trial and from a UK observational study

Table 7 continued

	Target population/setting, age	Type of interventions	Comparators	Type of economic evaluation, model vs. trial-based study	Cost perspective	Source of resource-use data
Zafari et al. (2016), Canada [97]	Adults with moderate-to-severe allergic asthma whose asthma remained uncontrolled despite treatment with high-dose ICS with or without LABA, 18–65 years	OMA vs. standard therapy vs. BT	All relevant comparators	CEA and CUA, model-based study (Markov Model)	Healthcare perspective	Published literature
Dal Negro et al. (2011), Italy [95]	Adults with severe difficult asthma, 27–70 years	OMA vs. standard therapy	All relevant comparators	CEA and CUA, trial-based study	Healthcare perspective	Institutional database
Morishima et al. (2013), Japan [94]	Patients with moderate-to-severe persistent asthma despite high-dose ICS and other controller medication, 27–70 years	OMA vs. standard therapy	All relevant comparators	CUA, model-based study (Markov Model)	Societal perspective	Department's Quality Indicator/Improvement Project
	Source of cost data	Source of effectiveness data	Discounting, time horizon	Sensitivity analyses	Funding source	
Wu et al. (2007), US [92]	Published studies	Literature review	Annual discount rate of 3%, 10 years	No PSA	Scientific or academic	
Faria et al. (2014), UK [86]	Published sources	Literature review	Both costs and QALYs were discounted at 3.5% per annum, lifetime horizon	PSA	Scientific or academic	
Dal Negro et al. (2012), Italy [85]	Ex-factory prices, reference prices, and retail prices	Institutional database	Not stated, 36 months	No sensitivity analysis	Funding source not explicitly stated	
van Nooten et al. (2013), Nether [90]	Dutch sources	Observational study	Annual discount rate for outcomes 1.5%, and 4% for costs, lifetime horizon	PSA	Pharmaceutical company	
Norman et al. (2013), UK [88]	NHS reference costs and the PSSRU	CT	Annual discount rate of 3.5%, lifetime horizon	PSA	Scientific or academic	
Brown et al. (2007), Canada [83]	CTs, Ontario Schedule of Benefits and Fees, and Canadian Institute of Health Information	CT	Annual discount rate of 5%, lifetime horizon	PSA	Pharmaceutical company	
Campbell et al. (2010), US [84]	Market-Scan data, and Wholesale Acquisition Cost	Meta-analysis of the best available evidence	Annual discount rate of 3%, lifetime horizon	PSA	Pharmaceutical company	
Levy et al. (2015), Spain [87]	Clinical registries and a published source	Observational clinical data, self-administered questionnaire	Not stated, 10 months	No PSA	Pharmaceutical company	

Table 7 continued

	Source of cost data	Source of effectiveness data	Discounting, time horizon	Sensitivity analyses	Funding source
Oba and Salzman (2004), US [89]	Wholesale acquisition cost, published study, and Current Procedural Terminology-4 codes	CT	Not stated, 52 weeks	No PSA	Funding source not explicitly stated
Vennera et al. (2016), Spain [91]	Database of Spanish healthcare costs, Ministry of Health, Social Services and Equality Minimum Basic Data Set-Hospital Discharge, and General Council of Official Colleges Pharmacist	Observational study	Not stated, 12 months	PSA	Pharmaceutical company
Yoshikawa et al. (2016), Japan [93]	Ministry of Health, Labour and Welfare, Japan	CT	Not stated, 2 years	No sensitivity analysis	Funding source not explicitly stated
Dewilde et al. (2006), Sweden [96]	Swedish unit costs	CT	Annual discount rate of 3%, lifetime horizon	PSA	Pharmaceutical company
Zafari et al. (2016), Canada [97]	Published literature	Literature review with meta-analysis	Annual discount rate of 3%, 5 years	PSA	Scientific or academic
Dal Negro et al. (2011), Italy [95]	DRG-based remuneration tariff granted to hospitals in the Veneto Region, regional specialists' tariffs, and published literature and sources	Institutional database	Not stated, 10 months	No sensitivity analysis	Funding source not explicitly stated
Morishima et al. (2013), Japan [94]	Japan's official database and department's Quality Indicator/Improvement Project	CT	Annual discount rate of 3%, lifetime horizon	PSA	Scientific or academic

PSSRU Personal Social Services Research Unit, *QALYs* quality-adjusted life-years, *CT* clinical trial, *NHS* National Health Service, *CEA* cost-effectiveness analysis, *CUA* cost-utility analysis, *SABA* short-acting β_2 -agonists, *ICS* inhaled corticosteroids, *LABA* long-acting β_2 -agonists, *pm* as needed, *Ig* immunoglobulin, *SPT* skin prick test, *OMA* omalizumab, *BT* bronchial thermoplasty, *GINA* Global Initiative for Asthma, *PSA* probabilistic sensitivity analysis, *DRG* Diagnosis related group

Table 8 Results of economic studies evaluating omalizumab for severe chronic asthma treatment: results

	Main drivers of cost-effectiveness	ICERs	Conclusions of the study authors
Wu 2007 [92]	The monthly cost of omalizumab and improvement in HR-QOL	\$821,000 per QALY gained, and \$120 per symptom-free day gained	OMA is not cost-effective for most patients with severe asthma
Faria 2014 [86]	The asthma mortality risk, and the effect of improvements in HR-QOL with omalizumab.	The incremental cost-effectiveness ratio varied from £30,109 to 57,557 per QALY gained depending on the population considered using the PAS price	OMA represents good value for money only in severe subgroups and under optimistic assumptions regarding asthma mortality and improvement in HR-QOL
Dal Negro 2012 [85]	No sensitivity analysis	Incremental cost/utility ratio of €23,880 per QALY gained	36-month add-on OMA persistently improved all clinical outcomes in difficult-to-treat asthmatic patients. Costs were also optimized and related to the extent of long-term health benefits achieved
van Nooten 2013 [90]	Cost of omalizumab, time horizon, estimation of work loss.	ICER of €38,371 per QALY	OMA was found to have an attractive cost-effectiveness ratio
Norman 2013 [88]	Asthma-related mortality risk, HRQoL improvement and OCS-related adverse effects	The ICER for adults and adolescents is £83,822 per QALY gained, and £78,009 per QALY gained for children.	OMA improve the health outcomes of patients with uncontrolled severe persistent allergic asthma but it also substantially increases the costs. The ICER estimates are more favourable in the severe subgroup population of maintenance OCS compared with the overall population. However, the ICERs remain above conventional NICE thresholds of cost-effectiveness.
Brown 2007 [83]	—	ICER of €31,209 per QALY	Add-on OMA is cost-effective in patients with severe persistent allergic asthma
Campbell 2010 [84]	The difference in treatment-specific utilities for the chronic state, exacerbation-associated mortality, omalizumab price, exacerbation rates, and response definition	ICER of \$287, 200 per QALY gained and \$172, 300 per QALY gained in responders	Adding OMA to usual care improves QALYs at an increase in direct medical costs. The cost-effectiveness of OMA is similar to other chronic disease biologics.
Levy 2015 [87]	The change in the extrapolation multiplication factor and unit costs	ICER of €462.08 (347.65–606.22) per exacerbation avoided and €26 864.89 (21 632.07–33 859.49) per QALY gained	Adding OMA to uncontrolled severe asthmatic reduces the number of exacerbations with ED visits and increases HR-QOL after 10 months of treatment and produces ICERs favorable to OMA and acceptable from the health system perspective
Oba 2004 [89]	Efficacy parameters	ICER of \$523 per additional successfully controlled day and \$378 to achieve at least a 0.5-point increase in AQLQ score	OMA could be cost saving if given to nonsmoking patients who are hospitalized 5 or more times or 20 days or longer per year despite maximal asthma therapy
Vennera 2016 [91]	—	ICER of €1130.93 (909.08–1392.86) per exacerbation avoided, and €4124.79 (3281.69–5186.73) per 3-point increase in the ACT	Adding OMA to standard therapy in uncontrolled severe persistent asthma, and the incremental cost observed after 1 year of OMA might be considered OMA as attractive from the societal perspective, and good value for money
Yoshikawa 2016 [93]	No sensitivity analysis	JPY 20,868 per additional hospital-free day	Add-on OMA can reduce both the costs of hospitalization of pediatric patients with severe asthma and the total medical costs of the patients with a history of frequent and prolonged hospitalization, with reduction in hospitalization

Table 8 continued

	Main drivers of cost-effectiveness	ICERs	Conclusions of the study authors
Dewilde 2006 [96]	The exacerbation-related mortality rate, the time horizon and the discount rates	ICER of €56,091 per QALY	OMA provides cost offsets, improves HR-QOL and may have an attractive ICER in treating the severe allergic asthma population
Zafari 2016 [97]	Cost of BT and cost of omalizumab	ICER of BT versus standard therapy and OMA versus BT was \$78,700/QALY and \$3.86 million/QALY, respectively	There is more than 60% chance that BT becomes cost-effective relative to OMA and standard therapy at the WTP of \$100,000/QALY in patients with moderate-to-severe allergic asthma
Dal Negro 2011 [95]	No sensitivity analysis	Incremental cost/utility ratio of 26,000 €/QALY	OMA added to an optimised therapy significantly improves clinical outcomes in difficult-to-treat, persistent allergic asthma. Costs also increased but proved justified by health benefits achieved
Morishima 2013 [94]	Asthma-related mortality, exacerbation risk, and OMA cost	ICER for OMA was US\$755,200 (\$614,200–1,298,500) per QALY gained	With a WTP of \$45,000 per QALY, OMA was not cost-effective. Confining OMA to previously predicted responders may be a reasonable strategy to reduce the ICER

ACT Asthma control test, *BT* bronchial thermoplasty, *CEA* cost-effectiveness analysis, *CMA* cost minimization analysis, *CT* clinical trial, *CUA* cost utility analysis, *ED* emergency department, *HR-QOL* Health related-quality of life, *QALY* quality-adjusted life-year, *ICER* incremental cost-effectiveness ratios, *ICS* Inhaled corticosteroids, *JPY* Japanese Yen, *LABA* long acting beta 2 agonists, *Nether* The Netherlands, *OCS* Oral corticosteroids, *OMA* omalizumab, *PAS* probabilistic sensitivity analysis, *QALY* quality adjusted life year, *SABA* short active beta 2 agonists, *SPT* skin prick test, *WTP* willingness to pay

effective when compared with the addition of LTRA (e.g. MON) to the same doses of ICS [72]. The results of a unique economic evaluation based on a pragmatic trial marginally favor the repositioning of LTRAs as a cost-effective alternative to LABA as add-on therapy to ICS [81].

Some economic studies have focused on comparing the cost effectiveness of salmeterol/FP (SFC) to an LTRA alone (e.g. MON) as initial maintenance therapy for persistent asthma in patients treated with SABA only [69, 75, 76]. In each case, the treatment with SFC was claimed to be cost effective, affording a greater proportion of symptom-free days, a greater percentage of asthma-controlled week with no SABA use during the study period, and a greater proportion of patients who achieved a 12% or greater increase in forced expiratory volume in 1 s (FEV₁) from baseline.

As mentioned above, the use of clinical trial efficacy data, the assessment of a limited and selective number of comparators, sponsorship by a pharmaceutical company, the time horizon, and the ICER results are important aspects that serve as a support in helping decision makers or clinicians to make a rational interpretation of study findings. Among all the studies that compared ICS with LTRA preparations, 3/6 used clinical trial efficacy data [71, 77, 80], 3/6 assessed a limited and selective number of comparators [71, 78, 80], 3/6 were sponsored by a

pharmaceutical company [71, 77, 78], 2/6 had time horizons of < 1 year [71, 80], and 0/9 reported an ICER result (this last mainly due to the fact that ICS were the dominant strategy). Likewise, among all the studies that compared the addition of LABA preparations to ICS with the addition of LTRA to the same doses of ICS, 1/4 used clinical trial efficacy data [72], 3/4 assessed a limited and selective number of comparators [72, 73, 81], 2/4 were sponsored by a pharmaceutical company [72, 73], 1/4 had a time horizon of < 1 year [72], and 1/4 studies reported an ICER result [81].

We should sound a note of caution with regard to economic studies that have focused on comparing the cost effectiveness of SFC to an LTRA alone as initial maintenance therapy for persistent asthma in patients treated with SABA only [69, 75, 76], for two reasons. First, all these studies evaluated lung function rather than patient-centered outcomes, and it is not unexpected that a medication containing a bronchodilator will produce greater improvements in lung function outcomes (e.g. FEV₁) than a medication that does not contain a bronchodilator, such as MON. Second, and more importantly, SFC versus LTRA is not a logical comparison, nor does it match the decisions that must be made in real life, because, unlike LTRA, SFC combination therapy should not be used as first-line asthma therapy; it is a second-line therapy reserved for patients with asthma inadequately controlled through ICS.

Table 9 Assessment of the reporting quality of included studies using the CHEERS checklist

Domain/item	Number of studies (%) reporting		
	Well	Poorly	Not
Title and abstract			
Title	67 (93.1)	3 (4.2)	2 (2.7)
Abstract	53 (73.6)	16 (22.2)	3 (4.2)
Introduction			
Background and objectives	66 (91.7)	6 (8.3)	0 (0)
Methods			
Target population and subgroups	61 (84.7)	11 (15.3)	0 (0)
Setting and location	43 (59.7)	29 (40.3)	0 (0)
Study perspective	59 (81.9)	3 (4.2)	10 (13.8)
Comparators	66 (91.7)	5 (6.9)	1 (1.4)
Time horizon	61 (84.7)	4 (5.5)	7 (9.7)
Discount rate	26 (36.1)	0 (0)	46 (63.9)
Choice of health outcomes	67 (93.1)	5 (6.9)	0 (0)
Measurement of effectiveness	53 (73.6)	15 (20.8)	4 (5.5)
Measurement and valuation of preference-based outcomes	23 (31.9)	2 (2.8)	47 (65.3)
Estimating resources and costs	43 (59.7)	28 (38.9)	1 (1.4)
Currency, price date, and conversion	48 (66.7)	9 (12.5)	15 (20.8)
Choice of model	59 (81.9)	10 (13.9)	3 (4.2)
Assumptions	38 (52.8)	26 (36.1)	8 (11.1)
Analytical methods	35 (48.6)	26 (35.1)	11 (15.3)
Results			
Study parameters	50 (69.4)	21 (29.2)	1 (1.4)
Incremental costs and outcomes	60 (83.3)	6 (8.3)	6 (8.3)
Characterizing uncertainty	59 (81.9)	2 (2.8)	11 (15.3)
Characterizing heterogeneity	23 (31.9)	6 (8.3)	43 (59.7)
Discussion			
Study findings, limitations, generalizability, and current knowledge	61 (84.7)	11 (15.3)	0 (0)
Other			
Source of funding	53 (73.6)	0 (0)	19 (26.4)
Conflicts of interest	40 (55.5)	1 (1.4)	31 (43.1)

CHEERS Consolidated Health Economic Evaluation Reporting Standards

3.3.4 Omalizumab for Chronic Asthma Treatment

A number of studies have evaluated the cost effectiveness of omalizumab in patients with uncontrolled severe persistent allergic asthma, and, in all cases, omalizumab therapy has been associated with improvement of a variety of clinical outcomes, such as number of exacerbations with Emergency Department (ED) visits [87], health-related quality of life (HRQoL) [86, 87], and QALY [84], but with increasing direct medical costs [84]. Although when interpreting ICERs some authors proclaim omalizumab therapy to be cost effective [85, 87, 90], other authors have concluded that omalizumab has a better cost-effectiveness profile under certain conditions or with subgroups of patients [88, 89, 93, 94], or even that it is not cost effective at all [92]. Authors who found a better cost-effectiveness

profile under certain conditions or with subgroups of patients have concluded that omalizumab use could be cost effective in the severe subgroup population of maintenance oral corticosteroids, non-smoking patients who are hospitalized five or more times or 20 days or longer per year despite maximal asthma therapy [89], patients who previously had been predicted to be likely to respond to omalizumab [94], and patients with a history of frequent and prolonged hospitalization [93].

Among the studies that compared ICS with LTRA preparations, 5/15 used effectiveness data [85, 87, 90, 91, 95], 0/15 assessed a limited and selective number of comparators, 7/15 were sponsored by a pharmaceutical company [83, 84, 87, 88, 90, 91, 96], 2/15 had time horizons of < 1 year [87, 95], and all studies reported an ICER result [83–90, 92–97].

3.4 Drivers of Cost Effectiveness

A total of 58 (80.6%) studies conducted some type of sensitivity analysis (Tables 1, 2, 3, 4, 5, 6, 7, 8). Among these, 32 (55.2%) studies conducted a PSA, either alone or with a one-, two-, or multiway deterministic sensitivity analysis. The most common variables subjected to a sensitivity analysis were efficacy and cost parameters. Among the studies that performed some type of sensitivity analysis, 35 (60.3%) identified any variable that may potentially change the study conclusions. The main cost-effectiveness drivers identified in these studies were the utility values [26, 84], rate of utilization of health services for asthma [25, 46, 75, 84], length of stay for asthma exacerbations [56, 75], rate or cost of asthma exacerbations [30, 44, 46, 53, 75, 84], cost or rate of use of asthma medications [29, 33, 38, 45, 50, 51, 56, 62, 68, 71, 84, 90, 92, 94, 97], form of administration of medications [27, 48], inclusion or form of estimation of productivity losses [30, 39, 90], time horizon [90, 96], medication adherence [77], discount rates [66, 96], asthma mortality risk [84, 86, 88, 94, 96], and efficacy parameters such as the rate of adequate asthma control and improvement in HRQoL [40, 44, 60, 75, 86, 88, 89, 92].

4 Discussion

4.1 Overview of the Systematic Review Findings

This systematic review assesses the content and quality of reporting of the published economic evidence in the pharmacologic treatment of asthma, and helps to identify the main drivers of the cost effectiveness of alternative pharmacological options for this disease. The findings of the present review indicate that economic evaluations in the area of asthma have determined the cost effectiveness of a wide range of pharmacological treatments, including medications for treating acute asthmatic episodes and medications for controlling chronic symptoms. We found that medications such as nebulized MgSO₄, oral dexamethasone (compared with oral prednisone/prednisolone), inhaled ipratropium bromide, and levalbuterol (compared with racemic albuterol) have been shown to be cost effective when used for treating patients with acute asthma exacerbations. Although the clinical efficacy of ICS and their superiority over other medications such as LTRA and sodium cromoglycate for the management of persistent asthma have been known for years, the present review provides additional information about their high cost-effectiveness profile. In patients with inadequately controlled asthma taking ICS, the addition of a LABA preparation has been shown to be cost effective when compared with other

alternative strategies, with some studies showing that when the combinations of ICS and LABA are administered in a single inhaler, and that when the combinations containing formoterol are used for both maintenance and reliever therapy (SMART strategy), a better cost-effectiveness profile can be achieved. Tiotropium has been shown to be cost effective when added to usual care in patients who remain uncontrolled despite treatment with high-dose ICS/LABA, although more economic evidence is needed to conclusively demonstrate its cost effectiveness. Finally, in patients with uncontrolled severe persistent allergic asthma, omalizumab therapy could be cost effective in a carefully selected subgroup of patients with the highest morbidity or the more severe forms of the disease. The quality of reporting in the studies, according to the CHEERS checklist, was very uneven. While the majority of studies reported the items related to the title (item 1), background and objectives (item 3), and choice of health outcomes (item 10) well, only a minority of them reported the items related to discount rate (item 9), measurement and valuation of preference-based outcomes (item 12), and characterizing heterogeneity (item 21) well. However, it is important to mention that the measurement and evaluation of preference-based outcomes is only applicable to CUA.

4.2 Implications of the Systematic Review Findings

The most remarkable result to emerge from the data is that overall the findings from this systematic review of economic evidence are in line with the pharmacological recommendations for stepwise management of asthma given in the most recent and higher-quality evidence-based clinical practice guidelines (CPGs) for the disease [102, 103]. Although these recommendations are mainly based on efficacy-driven studies, the concordance between the recommendations given in these CPGs and the main findings in the present study suggests that when following the pharmacological recommendations for stepwise management of asthma given in the most recent evidence-based asthma CPGs, an efficient allocation of resources is achieved.

In this regard, our study provides additional and important support for the recommendation that in all age groups, ICS remain the preferred first-line choice for therapy for the management of patients with persistent asthma, and LTRA medications may be used as an alternative preventer therapy in such patients, especially in those who are unable or unwilling to take ICS and in those who experience intolerable side effects from ICS [103]. Similarly, in adult and adolescent patients with inadequately controlled asthma taking ICS, the recommendation that the first choice and preferred option as add-on therapy to ICS should be an inhaled LABA (which should be

considered before increasing the dose of ICS) [102], considering in particular the combination ICS/formoterol (BUD or BDP) as both maintenance and reliever treatment, is in line with the findings of the present review [103]. On the other hand, in pediatric patients aged 5 years and over with inadequately controlled asthma taking low-dose ICS, the recommendation that either a LABA preparation or an LTRA can equally be considered as initial add-on therapy [102], or the recommendation that the preferred option in these patients is moderate-dose ICS plus as-needed SABA [103], are less supported by the economic studies identified in our review. In the same manner, the recommendation of administering LTRA as an alternative preventer in children under 5 years of age who are unable to take ICS [102] continues to be widely applied without the support of a sound cost-effectiveness study. Consequently, future economic evaluations should address the most cost-effective strategy for pediatric patients with inadequately controlled asthma taking low-dose ICS.

With respect to the use of anti-immunoglobulin (Ig) E monoclonal antibodies, our review provides support for the recommendation in the CPGs that omalizumab may be considered in patients with a high corticosteroid burden [102] or in patients aged ≥ 6 years with moderate or severe allergic asthma that is uncontrolled on Step 4 treatment [103]. However, the findings from our review that omalizumab use could be cost effective in a severe subgroup population of maintenance oral corticosteroids, non-smoking patients who are hospitalized five or more times or 20 days or longer per year despite maximal asthma therapy, patients who previously had been predicted to be likely to respond to omalizumab, and patients with a history of frequent and prolonged hospitalization could be used to more precisely define the subgroup of patients in which omalizumab could be recommended to be used in future CPGs in order to be a cost-effective therapy. This concurs well with a recent real-world, within-person, repeated-measures matched cohort study, which concluded that the use of omalizumab was associated with increased costs but that there was no evidence of lower rates of clinically important outcomes, and that further studies should explore subsets of patients most likely to benefit from omalizumab therapy [104].

4.3 Critique of the Methods Adopted by the Economic Studies

Regarding the quality of reporting in the studies, the fact that only nearly half of the studies reported the items related to analytical methods, assumptions, and conflicts of interest well is noteworthy. Although all items assessed by the CHEERS checklist are important, these three items have been increasingly recognized as major issues in

promoting transparency in cost-effectiveness studies, reducing the risk of manipulation of the model until the desired result is obtained, and finally encouraging the development of high-quality, cost-effectiveness studies [105, 106]. These findings are potentially useful for identifying aspects or domains where there is room for improvement in future asthma cost-effectiveness studies, and could assist authors of these studies in the development and dissemination of high-quality analyses.

A crucial aspect when analyzing the findings of the present review is the range of interventions compared in each economic study. In 46 (63.9%) studies, the authors assessed the cost effectiveness of a limited and selective number of comparators instead of the cost effectiveness of all relevant comparators. This fact means that they may have potentially overestimated the cost effectiveness of the comparators of interest. It is important to note that the great majority of the studies sponsored by a pharmaceutical company had the above-mentioned shortcoming of a limited number of comparisons involved, thereby reducing the overall transparency and credibility of the findings and conclusions of these studies. Furthermore, these sponsored studies generally involve potential conflicts of interest and may be biased in the conduct and interpretation of their results, reducing their credibility even further. Therefore, it is not surprising that almost all of these sponsored studies reported a favorable cost-effectiveness profile for the comparator of interest. This is a relevant topic because of the total number of studies included, 38 (52.8%) were sponsored by a pharmaceutical company.

Regarding the perspective used in the included studies, although it can vary depending on country-specific health economic guidelines, in general it has been recommended that economic analyses in healthcare adopt a broad societal perspective and look to incorporate indirect costs, such as those associated with lost work productivity, traveling to and from healthcare appointments, waiting in the ED and in physician's offices, and the cost incurred by carers [107]. However, the perspective of most of the analyses (37, 51.4%) was that of the health payer, including only the costs of interventions of interest and wider healthcare costs. Of the studies that took a societal perspective, the costs included were primarily the productivity losses associated with time off work. The fact of not adopting a broad societal perspective may potentially have caused an underestimation of the cost effectiveness of more effective medications since better health outcomes are expected to reduce the time off work, thereby improving productivity levels.

An important consideration when interpreting the findings of economic evaluations is whether researchers performed a sensitivity analysis to explore the robustness of the results. Toward this aim, ideally researchers should

perform a PSA, conceivably the most appropriate form of sensitivity analysis, because, among other factors, it allows the researchers to calculate the ICER confidence intervals and to calculate the probability of a treatment being cost effective compared with the control [108]. Additionally, ideally sensitivity analyses should assess the uncertainty not only in the parameters used but also in the methodological, structural, and heterogeneity components. Although the majority of identified studies (58, 80.6%) performed some type of sensitivity analysis, only a limited number of studies (32, 44.4%) performed PSA in order to explore the uncertainty in their results. Furthermore, the majority of the studies that performed some type of sensitivity analysis assessed uncertainty in the parameters used, but only one-third of them (20, 34.5%) also assessed uncertainty in the methodological, structural or heterogeneity components. Among the studies that performed PSA, only a minority reported sufficiently on the ranges and the justification of the distributions used, consequently reducing the usefulness of this analysis.

One important aspect of economic evaluations is the time horizon of the economic evaluations. Although time horizons usually vary widely among different economic evaluations, one crucial consideration that must be taken into account when deciding on the time horizon is that it should capture all important benefits and consequences of interest [109]. Considering this aspect, it is important to take into account that asthma is a chronic episodic disease, characterized by acute, symptomatic episodes of varying severity, with a high risk of recurrence over time. Consequently, limited time horizons would probably not reflect all the health and economic consequences relevant for the different pharmacological options for the treatment of asthma. Additionally, limited time horizons could fail to appropriately account for the seasonality of asthma [110]. In this respect, although a lifetime time horizon may not be always necessary, the chronic episodic nature of asthma indicates the need for an extended time period to be analyzed, generally using a modeling approach to go beyond the limited time horizons of randomized controlled trials (RCTs). An additional factor that must be considered is the discount rate for costs and health effects when the time horizon is longer than 1 year. In the present review, the time horizon varied widely across studies, ranging from the duration of the acute asthma exacerbation to a lifetime. As expected, studies assessing the cost effectiveness of medications for acute asthma treatment had shorter time horizons than those evaluating chronic asthma treatment since they were generally limited to the duration of the acute asthma exacerbation. However, it is surprising that the majority of studies included in this review (50, 69.4%) used limited time horizons, generally being limited to the duration of an RCT, almost always < 1 year. All included

studies with a time horizon longer than 1 year used a discount rate for costs and health effects (ranging between 3 and 5% annually), except two studies with time horizons > 1 year that did not report any discount rate [85, 93]. Consequently, in the majority of studies, the time horizon was judged to be too short to capture all the costs and benefits associated with the treatments evaluated.

Closely related to the time horizon is the consideration of undertaking the economic evaluation alongside an RCT, or using decision analysis, economic modeling techniques. As stated above, with the latter it is possible to not only go beyond the limited time horizons of an RCT but also to simulate more appropriately the chronic episodic and cyclic nature of asthma over a long period of time [111]. All included studies that used a modeling approach employed Markov models to compare the long-term effectiveness of alternative comparators, except eight studies that used simple decision trees [25, 26, 29, 33, 35, 40, 66, 77]. Although simple decision trees may be appropriate for modeling the effectiveness of medications for acute asthma treatment, they are not suitable for the modeling of recurrent events over a long period of time, as occurs in chronic asthma. On the other hand, all 49 studies that undertook economic evaluation alongside an RCT performed a selective use of RCT efficacy data without reporting the rationale for the choice of the RCT, instead of a systematic review of the literature for identification of clinical evidence. This may have introduced bias into the economic evaluations, thus potentially overestimating the cost effectiveness of the comparators of interest.

When a new intervention is both clinically superior and cost saving, it is referred to as an economically 'dominant' strategy. However, the majority of new interventions are clinically superior but at increased cost. In this case, it is necessary to calculate an ICER to determine whether the health benefits gained from a new intervention outweigh the costs. Although no single threshold incremental ICER exists to determine whether a new intervention is considered to be cost effective, there are at least three recognized threshold ICERs that are generally considered attractive when studies use the QALY as the measure of outcome (cost-utility studies): ICERs of < \$50,000 per QALY gained within the US; ICERs of < £30,000 per QALY gained within the UK; and values based on local gross domestic product per capita for developing countries [112]. However, when studies use different natural units as the measure of outcome (cost-effectiveness studies), the comparison of cost effectiveness across studies is practically impossible, and the decision as to whether or not the health benefits gained from a new intervention outweigh the costs often requires a considered judgment. In the present review, a total of 23 (31.9%) studies used the QALY as an outcome measure. On the other hand, a total of 57 (79.2%)

studies used different natural units as the measure of outcome.

An important issue necessary to allow robust cross-study comparisons is the use of outcomes in the economic studies. Among the three classes of asthma-specific outcomes recommended by the National Institutes for Health (core, supplemental, and emerging) [113], the findings of our review agree well with those reported in a recent review of asthma cost-effectiveness studies, which found that the great majority of asthma economic studies included at least one core outcome (hospitalizations, ED visits, outpatient visits, medication, intervention costs), but that there is still room for improvement in using supplemental and emerging outcomes [13].

An important additional aspect that needs to be considered is whether the studies included in the review used efficacy-based or effectiveness-based evidence. In line with a recent review that focused on this subject [114], the majority of CEA studies evaluating asthma medications have used efficacy-based evidence. This is important because it has been well-established that efficacy asthma evidence trends toward being less likely to produce cost-effective findings than effectiveness asthma evidence [114].

4.4 Limitations of the Systematic Review

We are aware that our research may have two limitations. The first is related to the scope of the CHEERS checklist itself. Assessment with this instrument explores the reporting of a number of important and critical domains in the health economic evaluations, but does not ensure the quality of the final products nor the accuracy of their findings. However, we consider that the fact that the CHEERS checklist was developed in accordance with current recommendations for the development of reporting guidelines, using an international and multidisciplinary team of editors and content experts in economic evaluation and reporting, is a valid argument favoring the choice to use the instrument to assess the reporting quality of economic evaluations over many other existing instruments or checklists. The second is that we did not include an evaluation of economic evaluations of other important issues in the management of asthmatic patients, such as implementation of asthma management strategies or disease management programs. However, evaluation assessment of non-pharmacological treatments for the disease was not an objective in the original protocol. Despite these limitations, we can nevertheless conclude that our review is useful for assessing the reporting quality of all the available health economic evidence of alternative pharmacological treatments for asthma, and for identifying the main drivers of

the cost effectiveness of pharmacological treatments for the disease.

5 Conclusions

Available health economic evidence of alternative pharmacological treatments for asthma is an important input for clinicians and other decision-making authorities for ensuring the efficient use of the available healthcare resources. In general, the findings from the present review reveal that most studies reported that their intervention of interest was cost effective and that their conclusions are in line with the pharmacological recommendations for step-wise management of asthma given in the most recent and higher-quality evidence-based CPGs of the disease. However, our findings need to be interpreted with caution. This is mainly because we judged many studies as having several flaws in many important aspects of the design and execution, which may have introduced bias into the economic evaluations, such as the interventions assessed and the comparisons made, perspective used, sensitivity analyses performed, modeling techniques, and time horizon. Management alternatives such as the use of combination therapy with ICS-LABA, tiotropium, or omalizumab, when administered according to their current therapeutic indications, could be cost effective. Additionally, the identified reporting quality of all the available health economic evidence, and the use of standardized outcomes, are potentially useful for identifying aspects or domains where there is room for improvement in future asthma CEA studies.

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Author Contributions Dr. RM conceptualized and designed the study, carried out the initial analyses, drafted the initial manuscript, and approved the final version as submitted. Dr. SB critically reviewed and revised the manuscript, and approved the final version as submitted. Dr. CR carried out the initial analyses, reviewed and revised the manuscript, and approved the final version as submitted. All authors approved the final version of the manuscript as submitted and agree to be accountable for all aspects of the work.

Compliance with Ethical Standards

Conflicts of interest Carlos E. Rodriguez-Martinez, Monica P. Sossa-Briceno, and Jose A. Castro-Rodriguez declare that they have no conflicts of interest.

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