Mepolizumab (Nucala®, GlaxoSmithKline plc.) for the Treatment of Severe Asthma with Eosinophilia: Effectiveness, Value, and Value-Based Price Benchmarks

Draft Report

December 21, 2015

Institute for Clinical and Economic Review

AUTHORS: Jeffrey A. Tice, MD
Associate Professor of Medicine
University of California, San Francisco

Daniel A. Ollendorf, PhD
Chief Review Officer, Institute for Clinical and Economic Review

Jonathan D. Campbell, PhD
Assistant Professor, Department of Clinical Pharmacy,
Pharmaceutical Outcomes Research, University of Colorado, Denver

Rick Chapman, PhD, MS
Director of Health Economics, Institute for Clinical and Economic Review

Karen K. Shore, PhD
Program Director, Institute for Clinical and Economic Review

Jed Weissberg, MD, FACP
Senior Fellow, Institute for Clinical and Economic Review

Melanie Whittington, MS
Professional Research Assistant, University of Colorado, Denver

Steven D. Pearson, MD, MSc
President, Institute for Clinical and Economic Review

DATE OF PUBLICATION: December 21, 2015

We would also like to thank Matt Seidner, Elizabeth Russo, and Shanshan Liu of ICER for their contributions to this report.

About ICER

The Institute for Clinical and Economic Review (ICER) is an independent non-profit research organization that evaluates medical evidence and convenes public deliberative bodies to help stakeholders interpret and apply evidence to improve patient outcomes and control costs. ICER receives funding from government grants, non-profit foundations, health plans, provider groups, and health industry manufacturers. For a complete list of funders, visit http://www.icer-review.org/about/support/. Through all its work, ICER seeks to help create a future in which collaborative efforts to move evidence into action provide the foundation for a more effective, efficient, and just health care system. More information about ICER is available at http://www.icer-review.org

About CTAF

The California Technology Assessment Forum (CTAF) – a core program of ICER – provides a public venue in which the evidence on the effectiveness and value of health care services can be discussed with the input of all stakeholders. CTAF seeks to help patients, clinicians, insurers, and policymakers interpret and use evidence to improve the quality and value of health care.

The CTAF Panel is an independent committee of medical evidence experts from across California, with a mix of practicing clinicians, methodologists, and leaders in patient engagement and advocacy. All Panel members meet strict conflict of interest guidelines and are convened to discuss the evidence summarized in ICER reports and vote on the comparative clinical effectiveness and value of medical interventions. More information about CTAF is available at http://www.ctaf.org

Table of Contents

List of Acronyms Used in this Report

ACQ	Asthma Control Questionnaire
ACT	Asthma Control Test
AE	Adverse event
AQLQ	Asthma Quality of Life Questionnaire
BI	Budget impact
BSCA	Blue Shield of California
CDC	Centers for Disease Control and Prevention
CEA	Cost-effectiveness analysis
CI	Confidence interval
CMS	Centers for Medicare & Medicaid Services
DALY	Disability-adjusted life year
DHCS	Department of Health Care Services
ED	Emergency department
EQ-5D	European Quality of Life-5 Dimensions
FDA	Food and Drug Administration
FEV_1	Forced expiratory volume in one second
FVC	Forced vital capacity
GDP	Gross domestic product
ICER	Incremental cost-effectiveness ratio
ICS	Inhaled corticosteroids
ICU	Intensive care unit
IgE	Immunoglobulin E
IL-5	Interleukin 5
IV	Intravenous
LABA	Long-acting beta agonist
LCD	Local coverage determination
MAC	Medicare Administrative Contractor
NCD	National coverage determination
NHE	National health expenditures
NICE	National Institute for Health and Care Excellence
OCS	Oral corticosteroids
PEF	Peak expiratory flow
PICOTS	Population(s), Intervention(s), Comparator(s), Outcome(s), Timing, and Setting(s)
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
QALY	Quality-adjusted life-year
RCT	Randomized controlled trial
SABA	Short-acting beta agonists
SAE	Serious adverse event
SC	Subcutaneous
SGRQ	St. George's Respiratory Questionnaire
SoC	Standard of care
UHC	UnitedHealthcare
URI	Upper respiratory infection
USD	United States Dollars
USPSTF	United States Preventive Services Task Force
WAC	Wholesale acquisition cost

Executive Summary

Background

An estimated 22 million Americans have asthma,[1] which causes the airways of the lungs to narrow or become blocked, making it hard to breathe. Among both young and old, asthma can have a significant impact on health and limit the ability to pursue many activities. Although only 5-10% of people with asthma have severe asthma, they account for approximately 50% of all costs.[2] In addition to requiring daily inhaled corticosteroids (ICS) and long-acting beta agonist (LABA) therapy, these patients are often treated with oral corticosteroids, which may have detrimental clinical effects from long-term use.[3]

Topic in Context

In summarizing the contextual considerations for appraisal of a health care intervention, we seek to highlight the four following specific issues:

- Is there a particularly high burden/severity of illness?
- Do other acceptable treatments exist?
- Are other, equally or more effective treatments nearing introduction into practice?
- Would other societal values accord substantially more or less priority to providing access to this treatment for this patient population?

There are a number of treatments available for asthma.[4] Short-acting beta agonists (SABA), such as albuterol, are the primary treatment for mild intermittent asthma. ICS are usually added for persistent asthma. More severe asthma is treated with the combination of ICS and a LABA. Additional therapies for severe asthma include leukotriene inhibitors, theophylline, and omalizumab. Oral corticosteroids are used for short-term therapy to control asthma exacerbations and chronically for severe asthma that cannot be controlled without these drugs. Physicians try to avoid chronic oral corticosteroid therapy because it is associated with many long-term complications including growth suppression in children, osteoporosis, Cushing's syndrome, adrenal insufficiency, muscle weakness, diabetes, cataracts, joint necrosis, and an increased risk for infections.[5] Treatment is progressive from Step 1 (SABA as needed) to Step 3 (low dose ICS + LABA) to Step 5 (high dose ICS + LABA with consideration of omalizumab in patients with allergies). Finally, Step 6 is high dose ICS + LABA + oral corticosteroids.

Severe asthma is characterized by daily symptoms, awakening most nights due to symptoms, significant limitations in normal activities, forced expiratory volume in one second (FEV_1) <60% of the normal predicted volume, and two or more exacerbations requiring oral corticosteroids in the past year.[4] Well-controlled asthma is defined by symptoms ≤2 times per week, nocturnal awakening ≤2 times per month, no interference with normal activity, and an FEV_1 >80% of predicted.[4]

Asthma has been divided into subtypes, some of which are associated with airway inflammation with eosinophils.[6,7] About half of individuals with severe asthma exhibit the eosinophilic phenotype with elevated eosinophil levels (a marker of inflammation) in both the blood and airways.[6] Activated eosinophils can increase airway smooth muscle contraction and mucous secretion, which are hallmarks of asthma.[8,9] Interleukin-5 (IL-5) is an important cellular signal in eosinophilic inflammation.[10] Therapies that decrease IL-5 levels, and thus decrease eosinophils in lung tissue, are therefore being explored as treatments for asthma.

Mepolizumab

Mepolizumab (Nucala®, GlaxoSmithKline plc.) is a humanized monoclonal antibody to IL-5.[11] Mepolizumab binds to IL-5, which decreases IL-5 signaling leading to decreased eosinophils in the blood and tissue. The Food and Drug Administration (FDA) approved mepolizumab for the treatment of severe eosinophilic asthma in November 2015. Mepolizumab 100 mg is administered subcutaneously once every 4 weeks in a physician's office.[12] Office administration is required in order to monitor patients for hypersensitivity reactions, a common practice following administration of biologic agents.

In this review, we sought to assess the comparative clinical effectiveness and comparative value of adding mepolizumab to standard treatment for severe asthma (inhaled corticosteroids and other daily controller medications).

Comparative Clinical Effectiveness

The literature search for mepolizumab identified 147 potentially relevant references (see Appendix Figure A1), of which two randomized trials (MENSA, SIRIUS) met our inclusion criteria.[13,14] They are the only two trials that study the subcutaneous administration of mepolizumab. We searched clinicaltrials.gov and did not identify any additional completed trials. The MENSA trial was a double-blind randomized controlled trial (RCT) of 576 patients ages 12 years and older (mean age 50 years, 57% female, 25% chronic use of oral corticosteroids) with severe eosinophilic asthma and at least two asthma exacerbations in the past year.[14] The SIRIUS trial was a double-blind RCT of 135 patients ages 12 years and older (mean age 50 years, 55% female, 100% use of oral corticosteroids) with severe eosinophilic asthma who required 5 to 35 mg of prednisone daily for at least the prior six months.[13]

Results

Clinical Benefits

The average annual rate of significant exacerbations in the MENSA trial was 0.83 per patient in the mepolizumab 100 mg subcutaneous (SC) group and 1.74 per patient in the placebo group. Thus, mepolizumab was associated with a 53% reduction in asthma exacerbations compared with placebo (95% confidence interval [CI]: 36%, 65%; p<0.001). There were similar reductions in the annual per-patient rates of asthma exacerbations requiring emergency department (ED) visits or hospitalizations (61%; 95% CI: 17%, 82%; p=0.02) and hospitalizations only (69%; 95% CI: 9%, 89%; p=0.03). The SIRIUS trial reported asthma exacerbation rates as secondary outcomes. Mepolizumab reduced total annual per-patient exacerbations by 32% (95% CI: 1%, 53%; p=0.04).

The primary outcome in the SIRIUS trial was the percentage reduction in oral corticosteroid use. This is not of immediate clinical benefit but may reduce the long-term harms of oral corticosteroids (e.g., osteoporosis, muscle weakness, diabetes). The median percent reduction in oral corticosteroid dose was 50% in the mepolizumab group and 0% in the placebo group (p=0.007). The proportion of patients able to stop oral corticosteroids completely was 14% in the mepolizumab group and 8% in the placebo group, but this difference did not reach statistical significance.

The MENSA trial measured quality of life with the Asthma Control Questionnaire (ACQ) and the St. George's Respiratory Questionnaire (SGRQ). The ACQ is a 5-item questionnaire with a score ranging from 0 to 6 with higher numbers indicating worse asthma control. The ACQ score decreased 0.94 points in the mepolizumab 100 mg SC group and 0.50 points in the placebo group (difference -0.44; 95% CI: -0.63, -0.25; p<0.001). The SGRQ is a 50-item questionnaire with a score ranging from 0 to 100, in which higher scores indicate worse functioning. The SGRQ score decreased 16 points in the mepolizumab 100 mg SC group and 9 points in the placebo group (difference -7; 95% CI: -10.2, -3.8; p<0.001).

The SIRIUS trial also measured quality of life with the ACQ and the SGRQ. The difference in the ACQ score between the mepolizumab group and the placebo group was -0.52 (95% CI: -0.87, -0.17; p<0.004). Similarly, the SGRQ score decreased more in the mepolizumab group than in the placebo group (difference -5.8; 95% CI: -10.1, -1.0; p<0.02).

Harms

The total number of adverse events was similar in the mepolizumab groups and the placebo groups in the three large RCTs (Appendix Table F4).[13-15] Significant adverse events were more common in the placebo groups. Injection site reactions were more common in the group treated with mepolizumab (8% versus 3%). There were more herpes zoster infections in the group treated with

mepolizumab (2 versus 0), which may represent an increased risk for opportunistic infections or a chance finding.

Controversies and Uncertainties

The primary source of uncertainty in making a judgment of the comparative clinical effectiveness of mepolizumab is the relatively small number of patients and the short duration of follow-up of studies in the peer-reviewed literature. In the MENSA trial, 194 participants were treated with mepolizumab 100 mg SC for 32 weeks and in the SIRIUS trial, 69 participants were treated with mepolizumab 100 mg SC for 20 weeks. The greatest concern is that relatively uncommon side effects, such as opportunistic infections or anaphylaxis, will emerge as a larger group of patients is treated over several years. For example, post-marketing studies found that anaphylaxis occurs in about 1 per 1000 patients with severe asthma who are treated with omalizumab, a monoclonal antibody to immunoglobulin E (IgE).[16]

In addition, there were not enough patients studied who are of African descent or who are younger than 18 to draw any meaningful conclusions about the net health benefits of mepolizumab in these two important subgroups. The FDA is requiring the conduct of two post-marketing studies specifically in children aged 6-11.

Comparative Clinical Effectiveness: *Summary and Comment*

For adult patients with severe eosinophilic asthma, we judge there to be moderate certainty of a comparable or better net benefit for mepolizumab 100 mg SC every four weeks as add-on maintenance treatment compared with standard of care including high dose ICS, LABA, and additional controller medications. There is moderate certainty because both the MENSA trial, which demonstrated a significant reduction in asthma exacerbations, and the SIRIUS trial, which demonstrated a significant reduction in oral corticosteroids dosage, were relatively small studies of short duration. There remains uncertainty about the long-term durability of the benefits of the therapy and about the potential harms from modulation of the immune system. Ongoing post-marketing trials evaluating mepolizumab may demonstrate a wide variety of outcomes, from substantial net health benefit to a comparable net benefit given the potential harms associated with the monoclonal antibody (opportunist infections, anaphylaxis). Therefore, we judge the current body of evidence on mepolizumab to be “comparable or better” using the ICER Evidence Rating framework.

Other Benefits or Disadvantages

A major potential benefit of mepolizumab is a reduction in the long-term harms associated with chronic corticosteroid use. The SIRIUS trial was too small and too short in duration to capture these potential benefits.

Mepolizumab is a subcutaneous injection that requires an office visit every four weeks for administration. The burden of travel to a physician's office and the requirement for an injection may decrease long-term patient adherence to therapy. Conversely, the monitoring and opportunity for patient education at these visits may offer additional benefits.

Mepolizumab offers a new mechanism of action to treat a disease (severe asthma) that severely compromises patients' quality of life. No data were reported in clinical trial publications, but mepolizumab may lead to fewer days lost from school and/or work – two significant burdens borne by patients with severe asthma.

Comparative Value

To assess the incremental costs per outcomes achieved, we conducted a cost-effectiveness analysis (CEA) using a lifetime simulation model of asthma outcomes and costs in a representative population of candidates for mepolizumab therapy; the model structure was based on a previously published study of the cost-effectiveness of omalizumab,[17] an approved biologic agent also used in patients with severe allergic asthma, but with a different phenotype. We estimated the incremental cost-effectiveness of mepolizumab using estimates of reductions in asthma exacerbations and oral corticosteroid use from relevant clinical trial data and their corresponding effects on quality of life, survival, and costs of care. We employed a payer perspective (i.e., focus on direct health care costs only).

Outputs from this model were also used to inform a population-based analysis of the one- and five-year potential budgetary impact of mepolizumab at a national level. Potential budgetary impact included estimates of costs saved from averted asthma exacerbations and was calculated assuming an uptake pattern for mepolizumab if covered for the FDA-labeled indications without payer or provider efforts to restrain utilization. Based on long-term incremental cost-effectiveness ratios and a threshold for potential budget impact related to net health care cost growth at the national level, we also define a "value-based price benchmark" for mepolizumab. Details on methods and inputs for all analyses can be found in the full report and appendices.

Incremental Costs per Outcomes Achieved: *Results*

Over a lifetime treatment horizon, the model estimated that 23.96 exacerbations would be averted (non-discounted) per patient receiving mepolizumab versus standard of care (SoC) alone. Avoidance of exacerbations and the reduction in chronic oral corticosteroid use resulted in over $18,000 in cost offsets among those receiving mepolizumab, but treatment costs were increased by over $600,000. The resulting incremental cost per exacerbation averted was $24,626 (this estimate discounted costs but not exacerbations averted). Treatment with mepolizumab resulted in a gain of 1.53 quality-adjusted life-years (QALYs) relative to SoC alone, approximately 70% of which was due

to quality of life improvement alone (1.1 versus 0.43 for improved survival). This resulted in a cost-effectiveness estimate of $385,546 per QALY gained (see Table ES1 below).

Table ES1. Base-Case Clinical and Economic Outcomes from the Payer Perspective: Lifetime Treatment Horizon

	QALYs	Treatment Costs	Non-Treatment Costs	ICER ($/QALY)
Mepolizumab + SoC	15.12	$706,111	$15,465	$385,546/QALY
SoC alone	13.59	$98,083	$33,552	--

Notes: Future costs and QALYs are discounted 3% a year. Treatment costs include the cost of Mepolizumab and SoC. Non-treatment costs include the cost of exacerbations and chronic oral corticosteroid use.
ICER: Incremental cost-effectiveness ratio

Sensitivity Analyses

Findings from sensitivity analyses are described in detail in the full report. Results were most sensitive to changes in estimates of the quality of life benefit from reduced asthma exacerbations, the impact on quality of life of a short-term course of high-dose oral corticosteroids, and the annual exacerbation rate for mepolizumab + SoC. In all situations, however, cost-effectiveness estimates remained well above commonly-cited thresholds (i.e., $50,000, $100,000, or $150,000 per QALY gained). We also varied the treatment time horizon from 1 to 50 years but found little difference across this range (cost-effectiveness from $350,000-$450,000 per QALY gained), as outcomes and costs of interest accrue on a relatively constant basis over time.

Threshold Analyses

To achieve a cost-effectiveness ratio of $150,000 per QALY gained, the price per mepolizumab vial would need to be $932 ($12,116 annually), a 63% discount from the $2,500 wholesale acquisition cost (WAC) of $32,500 per year (see Table ES2). To achieve $100,000 per QALY gained, a price of $599 per vial would be required (a 76% discount). Finally, a discount of 89% would be necessary ($266 per vial) to reach a threshold of $50,000 per QALY gained.

Table ES2. Threshold Analysis for Cost of Mepolizumab

ICER	Price per Vial (% of base-case)	Price per Year
$50,000/QALY	$266 (10.6%)	$3,458
$100,000/QALY	$599 (24.0%)	$7,787
$150,000/QALY	$932 (37.3%)	$12,116
$385,546/QALY (base-case)	$2,500	$32,500

Potential Budgetary Impact Model: *Results*

Based on prior analyses, we assumed that 10% of the US population with asthma has severe disease,[18,19] and that 19.9% of those with severe asthma have had at least two exacerbations in the past year.[20] We also assumed that 72% of patients with severe asthma and two or more exacerbations have eosinophilic inflammation.[20] This resulted in a candidate population size of approximately 320,000 individuals in the US.

Based on several criteria, we estimated that the theoretical "unmanaged" uptake of mepolizumab would lead to approximately 10% of eligible patients using the drug by year five following its introduction. Mepolizumab is the first anti-IL-5 treatment for adults and adolescents with severe asthma featuring an eosinophilic phenotype. However, requirements for office-administered injection might dampen enthusiasm among some patients, and clinical evidence suggests that even standard treatments for severe asthma may provide benefit in this phenotype. Finally, another anti-IL-5 agent for eosinophilic asthma is under review by the FDA, with potential approval and market entry as early as March 2016.[21,22]

Table ES3 below presents the potential budgetary impact of mepolizumab in the candidate population, assuming the uptake pattern previously described. Results are presented for both one-year and five-year time horizons. An estimated 6,407 individuals would receive mepolizumab in the first year. After one year of treatment, with net annual costs of $31,388 per patient, one-year budget impact is estimated to be $201.1 million.

Table ES3. Estimated Total Potential Budget Impact (BI) of Mepolizumab

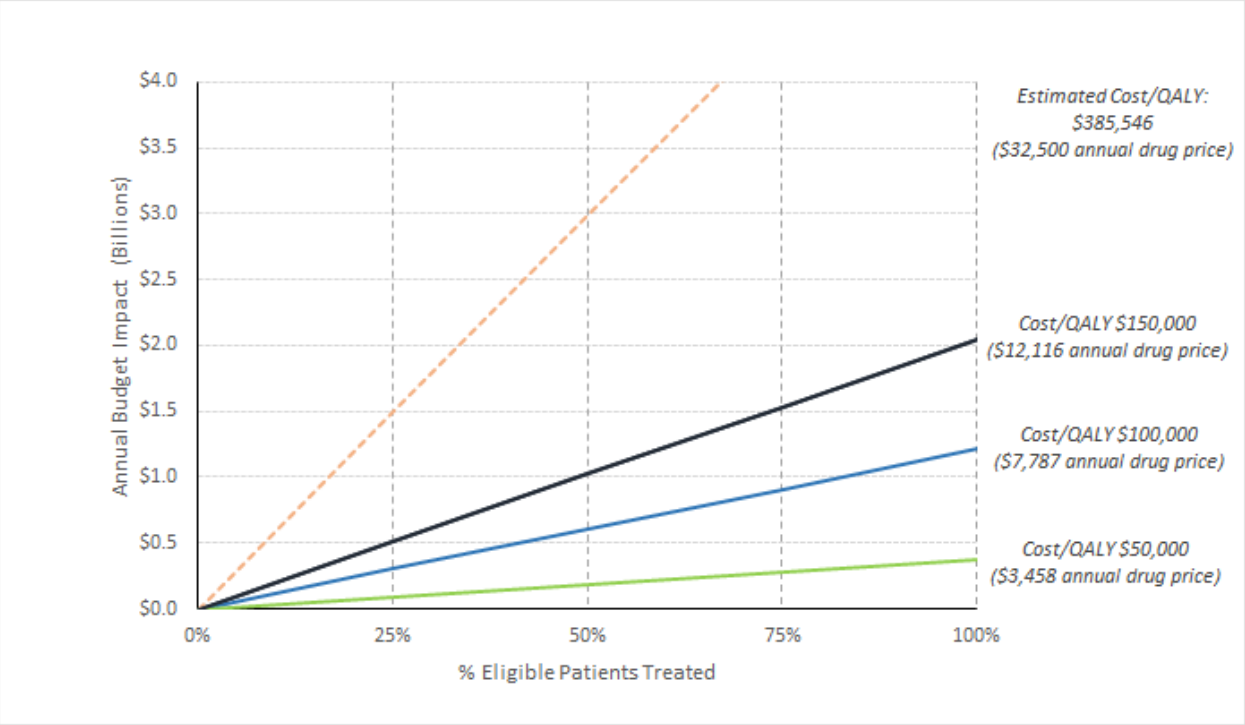
		Analytic Horizon = 1 Year			Analytic Horizon = 5 Years		
	Eligible Population (thousands)	Number Treated (thousands)	Annual BI per Patient ($)*	Total BI (millions)	Number Treated (thousands)	Weighted BI per Patient ($)*	Average BI per year (millions)
Mepolizumab	320	6.4	$31,388	$201.1	32.0	$93,043	$596.1

*Weighted budget impact calculated by subtracting cost offsets from drug costs for one-year horizon. For five-year horizon, drug costs and cost offsets apportioned assuming 20% of patients in uptake target initiate therapy each year. Those initiating in year 1 receive full drug costs and cost offsets, those initiating in year 2 receive 80% of drug costs and cost offsets, etc.

Over the entire five-year time horizon, we estimate that "unmanaged" uptake would lead to approximately 32,000 persons taking mepolizumab. Across this timeframe, the weighted budgetary impact (i.e., adjusted for differing periods of drug utilization and associated cost-offsets) is approximately $93,000 per patient. Total budgetary impact over five years is approximately $3 billion, with an average budget impact per year of approximately $596 million.

Figure ES1 below demonstrates different potential budget impact levels associated with different pricing and patient uptake assumptions. As shown in the figure, the dashed line – representing the potential annual budget impact for mepolizumab at list price – shows that annualized potential budget impact increases from $596 million at our assumed 10% uptake to $1.5 billion at 25% of eligible patients treated, and further up to approximately $6 billion if 100% of eligible patients were treated. In addition, if the annual price for mepolizumab was lowered to $12,116 to meet a cost-effectiveness threshold of $150,000/QALY, 50% of eligible patients could be treated at an annualized potential budget impact of less than $1 billion.

Figure ES1. Combined Cost-effectiveness and Potential Budget Impact Graph for Mepolizumab



Note: Colored lines represent the annualized budget impact of different uptake patterns (eligible patients treated) at the actual list price of the drug (dashed line), and at drug prices needed to achieve common incremental cost-effectiveness ratios.

Draft Value-Based Price Benchmark

As shown in Table ES4, the annual price range for mepolizumab to meet a cost-effectiveness range of $100,000-$150,000/QALY is $7,787 to $12,116. This is the price range that ICER designates as a long-term "care value" price. For mepolizumab, if it were priced in alignment with this long-term care value range, it would not exceed a short-term (five-year) potential budget impact threshold linked to national growth targets.

Therefore, the draft ICER value-based price benchmark for mepolizumab is $7,787 to $12,116 per year, which represents a 63-76% discount from the full list price ($32,500 per year).

Table ES4. Draft Value-based Price Benchmark for Mepolizumab

Population	Price to Achieve $100K/QALY	Price to Achieve $150K/QALY	Exceeds Potential Budget Impact Threshold?	Draft Value-Based Price Benchmark
Mepolizumab (n=32,035)	**$7,787/year**	**$12,116/year**	**No**	**$7,787 to $12,116/year**

Comparative Value: *Summary and Comment*

Adding mepolizumab to standard care for adult patients with severe eosinophilic asthma appears to confer clinical benefits in terms of reduced rates of exacerbation and improved quality of life relative to standard care alone. However, at the current wholesale acquisition cost, the estimated cost-effectiveness of mepolizumab exceeds commonly-cited thresholds. Achieving levels of value more closely aligned with patient benefit would require discounts of two-thirds to three-quarters from the current list price of mepolizumab.

1. Background

1.1 Introduction

Background

The Centers for Disease Control and Prevention (CDC) estimates that 39.5 million Americans have been diagnosed with asthma at some time and that 22 million currently have asthma.[1] Asthma causes the airways of the lungs to narrow or become blocked, making it hard to breathe. Many processes contribute to the narrowing, including tightening of the muscles around the airways, inflamed tissue lining the airways, and mucous plugging the airways. The disease follows a waxing and waning course with exacerbations initiated by allergens, cold weather, exercise, pollution, and other triggers. This leads to approximately 14.2 million office visits, 1.8 million emergency department visits, and 440,000 hospitalizations each year in the US; total direct medical costs are estimated to be about $50 billion annually.[1] Individuals with severe asthma represent less than 5-10% of all individuals with asthma but account for approximately 50% of all costs.[2] In addition to requiring daily inhaled corticosteroids (ICS) and long-acting beta agonist (LABA) therapy, these patients are often treated with oral corticosteroids (OCS).[3] About half of individuals with severe asthma exhibit the eosinophilic phenotype with elevated eosinophil levels in both the blood and airways.[6] Mepolizumab is a humanized monoclonal antibody to interleukin 5 (IL-5), a cell messenger that controls eosinophilic inflammation, and has been studied to determine if reduction in such inflammation leads to corresponding reductions in asthma exacerbation episodes and improved asthma control.

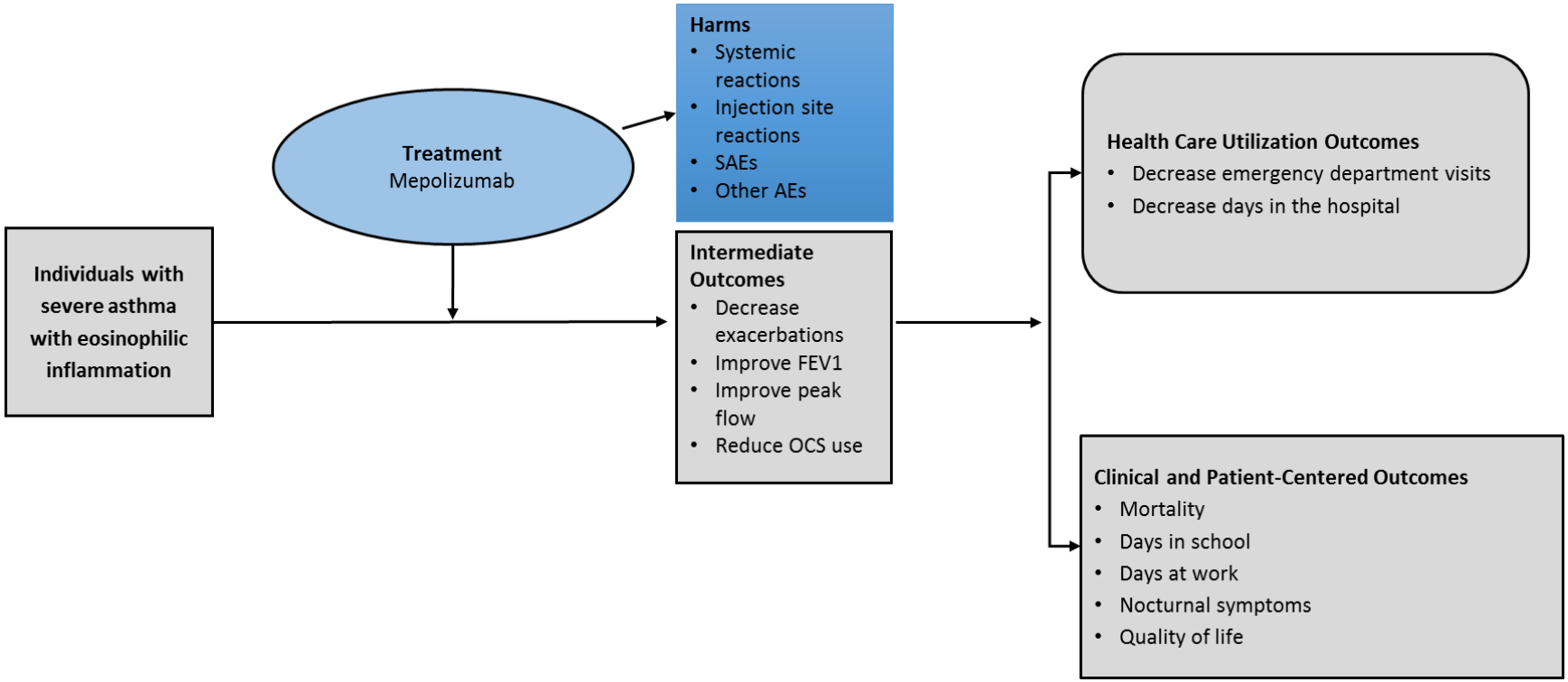
Scope of the Assessment

The scope for this assessment is described below using the PICOTS (Population, Intervention, Comparators, Outcomes, Timing, and Settings) framework. Evidence was culled from Phase II or III randomized controlled trials (RCTs) and comparative cohort studies as well as high-quality systematic reviews where available. We also included case series that meet certain quality criteria (e.g., sample retention, consecutive patients, clearly-defined entry criteria).

Analytic Framework

The analytic framework for this assessment is depicted in Figure 1.

Figure 1. Analytic Framework: Asthma Management with Mepolizumab



Note: SAEs: serious adverse events; AEs: adverse events; FEV_1: forced expiratory volume in 1 second; OCS: oral corticosteroid

Populations

The population of focus for the review included adults and children ages 12 years and older with severe, uncontrolled asthma and evidence of eosinophilic inflammation. Severe asthma was defined as asthma requiring either OCS for >50% of the year or the combination of high dose ICS and a LABA or other controller medication (leukotriene inhibitor/theophylline) to maintain control.[18] Uncontrolled asthma was defined by at least one of the following: frequent exacerbations (two or more bursts of oral corticosteroid therapy lasting at least four days); serious exacerbations (hospitalization, intensive care unit [ICU] stay, or mechanical ventilation); airflow limitation (forced expiratory volume in one second [FEV_1] <80% of predicted); or poor symptom control (Asthma Control Questionnaire [ACQ] >1.5; Asthma Control Test [ACT] score <20).[18] Eosinophilic inflammation was defined as a blood eosinophil level ≥150 cells/µL at initiation of therapy or ≥300 cells/µL in the prior 12 months. All individuals with uncontrolled asthma should be treated with high-dose ICS therapy and at least one additional controller medication (e.g., LABAs, leukotriene agonists, theophylline, OCS).

Interventions

The intervention of interest was mepolizumab 100 mg by subcutaneous (SC) injection once every four weeks, in conjunction with daily ICS and other controller therapy.

Comparators

The comparators of interest were placebo or OCS added to daily ICS and other controller therapy alone (control arms in the mepolizumab trials also received placebo injection). Omalizumab (Xolair®, Genentech Inc. and Novartis AG) a monoclonal antibody to immunoglobulin E [IgE]) was considered as a comparator for patients with severe eosinophilic asthma and elevated IgE levels.

Outcomes

This review examined both clinical and health care utilization outcomes related to asthma. Listed below are the outcomes of interest:

- Asthma control assessed by standard questionnaires (ACQ or ACT)
- Asthma exacerbations
- Asthma-related hospitalizations and emergency department (ED) visits
- Mortality (asthma-specific and total)
- Use of oral corticosteroids including a reduction in dose for those on chronic oral corticosteroids
- Peak flow
- FEV_1

- Absence from school
- Absence from work
- Symptom scale, including nocturnal symptoms
- Health-related quality of live (Asthma Quality of Life Questionnaire [AQLQ] or St. George's Respiratory Questionnaire [SGRQ])

Timing

Evidence on intervention effectiveness and harms were derived from studies of any duration.

Settings

All relevant settings were considered, including inpatient, clinic, and outpatient settings.

2. The Topic in Context

Asthma severity is defined as intermittent or persistent, with persistent asthma subdivided into mild, moderate, and severe.[4] These categories are defined by the frequency of symptoms, lung function, and frequency of exacerbations requiring OCS. Severe asthma is characterized by daily symptoms, awakening most nights due to symptoms, significant limitations in normal activities, FEV_1 <60% of the normal predicted volume, and two or more exacerbations requiring OCS.[4] Well-controlled asthma is defined by symptoms ≤2 times per week, nocturnal awakening ≤2 times per month, no interference with normal activity, and an FEV_1 >80% of predicted.[4]

There are a number of treatments available for asthma.[4] Short-acting beta agonists (SABA), such as albuterol, are the primary treatment for mild intermittent asthma. ICS are usually added for persistent asthma. More severe asthma is treated with the combination of ICS and a LABA. Additional therapies for severe asthma include leukotriene inhibitors, theophylline, and omalizumab. OCS are used for short-term therapy to control asthma exacerbations and chronically for severe asthma that cannot be controlled without OCS. Physicians try to avoid chronic OCS therapy because it is associated with many long-term complications including growth suppression in children, osteoporosis, Cushing's syndrome, adrenal insufficiency, muscle weakness, diabetes, cataracts, joint necrosis, and an increased risk for infections.[5] Treatment is progressive from Step 1 (SABA as needed) to Step 3 (low dose ICS + LABA) to Step 5 (high dose ICS + LABA with consideration of omalizumab in patients with allergies). Finally, Step 6 is high dose ICS + LABA + OCS.

Asthma has been divided into subtypes, some of which are associated with airway inflammation with eosinophils.[6,7] Activated eosinophils can increase airway smooth muscle contraction and mucous secretion, which are hallmarks of asthma.[8,9] Interleukin-5 (IL-5) is an important cellular signal in eosinophilic inflammation.[10] Therapies that decrease IL-5 levels may be useful in the treatment of asthma by decreasing eosinophils in lung tissue.

Mepolizumab

Mepolizumab is a humanized monoclonal antibody to IL-5, which is one of the primary cytokines regulating blood and tissue eosinophils.[11] Mepolizumab binds to IL-5, which decreases IL-5 signaling leading to decreased eosinophils in the blood and tissue. It has been studied as a treatment for asthma, eosinophilic esophagitis, Churg-Strauss disease, and nasal polyposis. The Food and Drug Administration (FDA) approved mepolizumab for the treatment of severe eosinophilic asthma in November 2015. Mepolizumab 100 mg is administered subcutaneously once every four weeks in a physician's office.[12]

A second monoclonal antibody to IL-5, reslizumab (Teva Pharmaceutical Industries Ltd.), is currently under evaluation by the FDA for patients with asthma and elevated eosinophil levels.

Definitions

Severe asthma is defined as asthma that requires either OCS for >50% of the year or the combination of high dose ICS and a LABA or other controller medication (leukotriene inhibitor/theophylline) to maintain control.[18]

Uncontrolled asthma is defined by at least one of the following:

- Frequent exacerbations (two or more bursts of oral corticosteroid therapy lasting at least four days)
- Serious exacerbations (hospitalization, ICU stay or mechanical ventilation)
- Airflow limitation (FEV_1 <80% predicted)
- Poor symptom control (Asthma Control Questionnaire >1.5; Asthma Control Test <20)[18]

Eosinophilic inflammation is defined as a blood eosinophil level ≥150 cells/µL at initiation of therapy or ≥300 cells/µL in the prior 12 months.

Asthma Control Questionnaire (ACQ) scores range from 0 to 6 with higher scores indicating worse control and a change of 0.5 points being the minimal clinically important difference.

St George's Respiratory Questionnaire (SGRQ) scores range from 0 to 100 with higher scores indicating worse function and a change of 4 points being the minimal clinically important difference.

3. Summary of Coverage Policies

To understand the insurance landscape for therapies for severe, uncontrolled asthma, we reviewed the publicly available coverage policies and formularies of the Centers for Medicare & Medicaid Services (CMS), California Department of Health Care Services (DHCS), Aetna, Anthem, CIGNA, Humana, UnitedHealthcare (UHC), Health Net, Blue Shield of California (BSCA), and CVS Caremark. We supplemented our search for coverage policy on mepolizumab with summaries of existing policies on omalizumab as a model for office-administered antibody therapy for severe asthma.

We were unable to locate any National Coverage Determinations (NCDs) or Local Coverage Determinations (LCDs) for California issued by CMS or Medicare Administrative Contractors (MACs) in California for mepolizumab or omalizumab. The California DHCS does not include omalizumab or mepolizumab in its contract drug list.[20]

At the time of publication for the initial draft report, Aetna, Anthem, and Humana have released coverage policies for mepolizumab.[23-25] All three payers cover mepolizumab for patients over the age of 12 with severe eosinophilic asthma uncontrolled by therapy with the combination of an ICS and one or more additional agents. Anthem requires patients to demonstrate blood eosinophil counts ≥150 cells/µL at initiation of therapy or ≥300 cells/µL in the previous year, while Humana requires a blood eosinophil count of ≥300 cells/µL. Aetna and Anthem require the demonstration of FEV_1 <80% of predicted volume, and FEV_1 reversibility of at least 12% and 200 ml after the use of albuterol or salbutamol.

Aetna, Anthem, CIGNA, and Humana provide coverage for omalizumab in some of their plans and place the drug in higher tiers designated for brand-name drugs.[24,26-29] Each of the aforementioned payers requires prior authorization for the drug and requires patients to demonstrate moderate to severe persistent asthma, positive skin or in vitro reactivity tests to a perennial allergen, and asthma inadequately controlled through therapy with ICS use. Aetna and UHC both require patients to have baseline plasma immunoglobulin E (IgE) levels of 30 to 1,500 IU/ml, Humana requires levels between 30 and 700 IU/ml, and Anthem requires levels of at least 30 IU/ml.[26,27,30] Aetna and Anthem additionally require patients to demonstrate reduced pulmonary function through measurements of peak expiratory flow (PEF) or FEV_1. We were unable to find publicly-available documentation relating to private coverage for omalizumab from Health Net or CVS Caremark.

Payer coverage policies are summarized in Table 1 and described in detail in Appendix C.

Table 1: Representative Public and Private Payer Policies for Omalizumab and Mepolizumab

	Aetna	Anthem	CIGNA	Humana	UHC	Health Net	BSCA
Mepolizumab							
Covered?	Yes	Yes	--	Yes	--	--	--
Prior Authorization	Precertification	--	--	Yes	--	--	--
Step Therapy	--	Yes	--	--	--	--	--
Eosinophil level	--	≥150 cells/µL ≥300 cells/µL	--	≥300 cells/µL	--	--	--
Omalizumab							
Covered?	In some plans	In some plans	Yes	In some plans	--	Yes	--
Tier	2, 4	Non-formulary, 3, 4	2, 4, 5	4, 5	--	--	--
Prior Authorization	Precertification	Yes	Yes	Yes	--	--	--
IgE level	30 – 1,500 IU/ml	≥30 IU/ml	--	30 – 700 IU/ml	30 – 1,500 IU/ml	>30 IU/ml	--

--: Not mentioned in coverage policy.

Note: The information in this table is extracted from publicly available documents as of December 17, 2015 and is meant to summarize key details from these documents. For a more detailed summary of individual payer policies, see Appendix C.

4. Comparative Clinical Effectiveness

4.1 Overview

To inform our analysis of the comparative clinical effectiveness of mepolizumab added to standard of care (SoC) versus SoC alone, we abstracted evidence from RCTs of individuals ages 12 years and older with severe eosinophilic asthma. The comparator treatment for each intervention of interest included SoC treatment with ICS and LABA. Our review focused on clinical benefits (i.e., asthma exacerbations, ED visits, hospitalizations, quality of life) as well as potential harms (drug-related adverse events).

4.2 Methods

Data Sources and Searches

Procedures for the systematic literature review assessing the evidence on mepolizumab for severe asthma followed established best methods used in systematic review research.[31] We conducted the review in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.[32] The PRISMA guidelines include a checklist of 27 items, further detail of which is available in Appendix Table A1.

The timeframe for our search spanned the period from January 1990 to the most recently published data available and focused on MEDLINE, EMBASE, and Cochrane-indexed articles. We limited each search to studies of human subjects and excluded articles indexed as guidelines, letters, editorials, narrative reviews, case reports, conference abstracts, or news items. To supplement the above searches and ensure optimal and complete literature retrieval, we performed a manual check of the references of recent relevant reviews and meta-analyses. Further details on the search algorithm are available in Appendix Table A2.

Study Selection

We performed screening at both the abstract and full-text level. A single investigator screened all abstracts identified through electronic searches according to the inclusion and exclusion criteria described earlier. We did not exclude any study at abstract-level screening due to insufficient information. For example, an abstract that did not report an outcome of interest would be accepted for further review in full text.

We retrieved the citations that were accepted during abstract-level screening for full text appraisal. One investigator reviewed full papers and provided justification for exclusion of each excluded study.

We also included FDA documents related to mepolizumab. These included the manufacturer's submission to the agency, internal FDA review documents, and the transcript of Advisory Committee deliberations and discussions. All literature that did not undergo a formal peer review process is described separately.

Data Extraction and Quality Assessment

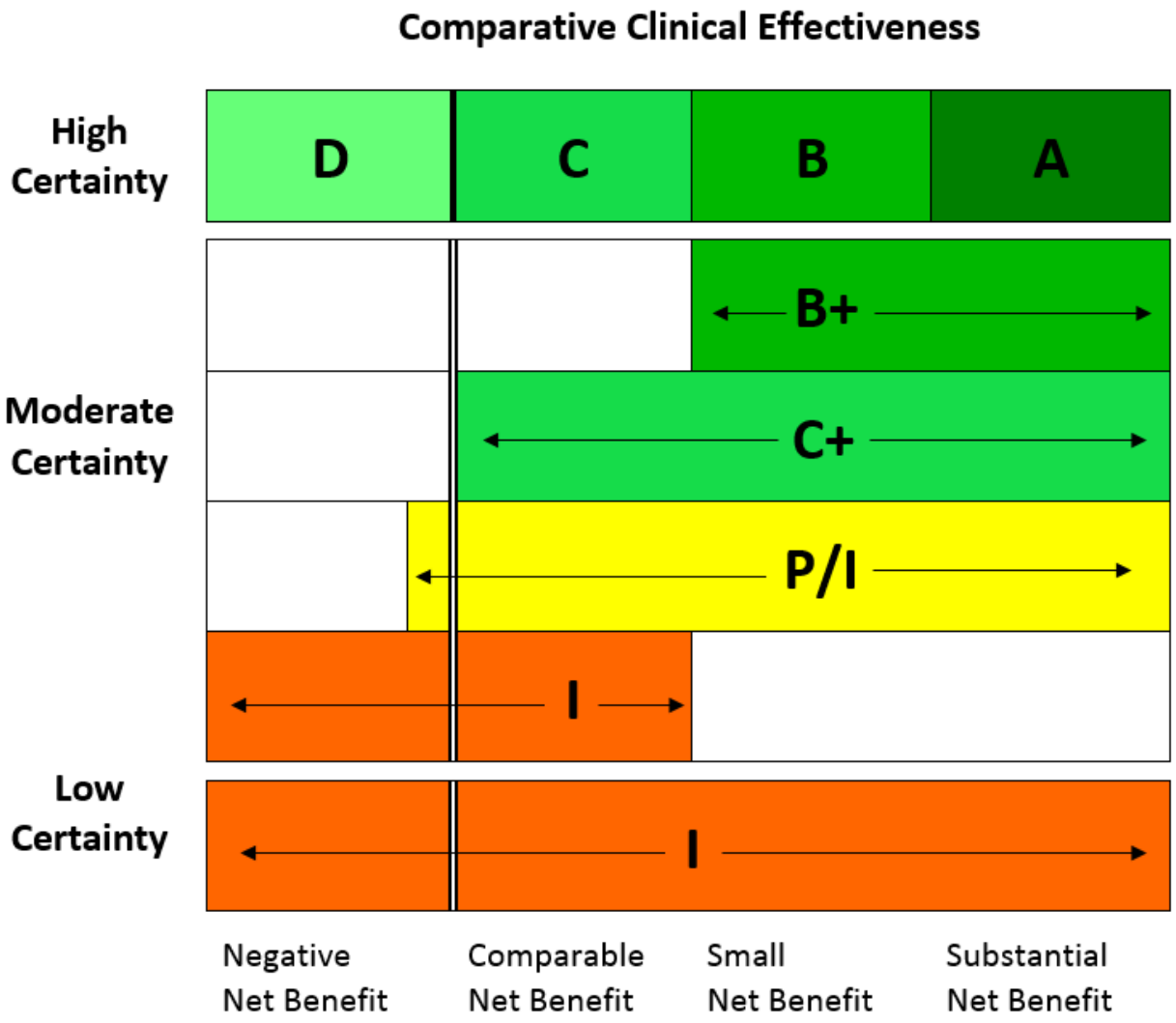
Our data extraction and review process is detailed in Appendix F. Summary tables are available in Appendix Tables F1 through F4. We abstracted outcome data for the subcutaneous dosing regimen, which is the FDA-approved route of administration. Data on adverse events in patients treated with intravenous (IV) dosing were included to ensure that potential adverse events were not missed. We used criteria published by the US Preventive Services Task Force (USPSTF) to assess the quality of RCTs and comparative cohort studies, using the categories "good," "fair," or "poor."[33]

Assessment of Level of Certainty in Evidence

We used the ICER Evidence Rating Matrix (see Figure 2) to evaluate the evidence for a variety of outcomes. The evidence rating reflects a joint judgment of two critical components:

a) The **magnitude** of the difference between a therapeutic agent and its comparator in "net health benefit" – the balance between clinical benefits and risks and/or adverse effects AND
b) The level of **certainty** in the best point estimate of net health benefit.[34]

Figure 2. ICER Evidence Rating Matrix



A = "Superior" **-** High certainty of a substantial (moderate-large) net health benefit
B = "Incremental" **-** High certainty of a small net health benefit
C = "Comparable"**-** High certainty of a comparable net health benefit
D="Negative"**-** High certainty of an inferior net health benefit
B+="Incremental or Better" **–** Moderate certainty of a small net health benefit, with high certainty of at least incremental net health benefit
C+="Comparable or Better" **-** Moderate certainty of a comparable net health benefit, with high certainty of at least comparable net health benefit
P/I = "Promising but Inconclusive" - Moderate certainty of a small or substantial net health benefit, small (but nonzero) likelihood of a negative net health benefit
I = "Insufficient" **–** Either moderate certainty that the best point estimate of comparative net health benefit is comparable or inferior; or any situation in which the level of certainty in the evidence is low

Assessment of Bias

As part of our quality assessment, we evaluated the evidence base for the presence of potential publication bias represented by general or specific study designs used in the assessment of each intervention. Given the emerging nature of the evidence base for newer treatments, we performed an assessment of publication bias using the clinicaltrials.gov database of trials. We scanned the site to identify studies completed more than two years ago that would have met our inclusion criteria and for which no findings have been published. Any such studies identified provided qualitative evidence for use in ascertaining whether there was a biased representation of study results in the published literature.

Data Synthesis and Statistical Analyses

Given the small numbers of relevant studies for mepolizumab, we judged that it would not be helpful or appropriate to perform formal meta-analysis to generate pooled estimates of treatment effect.

4.3 Results

Study Selection

The literature search for mepolizumab identified 147 potentially relevant references (see Appendix Figure A1), of which two randomized trials (MENSA, SIRIUS) met our inclusion criteria.[13,14] Only two trials studied the subcutaneous administration of mepolizumab that is the FDA-approved route of administration. We abstracted data from a third randomized trial (DREAM) of IV formulations of mepolizumab for additional data on potential harms.[15] The DREAM trial did not study the FDA-approved SC formulation of mepolizumab, but it was included in the FDA evaluation of mepolizumab and provides useful information on adverse events of the medication. We specifically looked for studies comparing mepolizumab to omalizumab, another monoclonal antibody that has FDA approval for the treatment of patients with severe asthma, but found no studies in the literature. Details of the included studies are summarized in Appendix Tables F1 through F4.

Scanning of the ClinicalTrials.gov site to identify additional studies completed more than two years ago that would have met our inclusion criteria but have not been published revealed no such studies (see Appendix E for ongoing studies).

Key Studies

The MENSA trial was a double-blind RCT of 576 patients ages 12 years and older (mean age 50 years, 57% female, 25% chronic use of OCS, mean eosinophil count 300 cells/µL) with severe

eosinophilic asthma and at least two asthma exacerbations in the past year.[14] Severe asthma is defined as asthma that requires either OCS for >50% of the year or the combination of high-dose ICS and a LABA or other controller medication (leukotriene inhibitor/theophylline) to maintain control.[18] The participants were randomized to one of three groups: mepolizumab 75 mg IV, mepolizumab 100 mg SC, or identical placebo every four weeks for 32 weeks. All patients also received SoC therapy for severe asthma as described above. The study drugs were prepared by staff who were not involved in the study assessments. All patients, the staff administering the medications, and the staff performing outcomes assessment were blinded to the group assignment. The primary outcome was the annualized frequency of severe exacerbations defined by worsening asthma requiring at least three days of systemic corticosteroids (i.e., steroid "burst"), an ED visit, or hospitalization through 32 weeks of follow-up.

The SIRIUS trial was a double-blind RCT of 135 patients ages 12 years and older (mean age 50 years, 55% female, 100% use of oral corticosteroids, mean eosinophil count 240 cells/µL) with severe eosinophilic asthma who required 5 to 35 mg of prednisone daily for at least the prior six months.[13] The participants were randomized to either mepolizumab 100 mg SC or identical placebo (along with SoC therapy) every four weeks for 20 weeks. The study drugs were prepared by staff who were not involved in the study assessments. All patients, the staff administering the medications, and the staff performing outcomes assessment were blinded to the group assignment. The primary outcome was the percentage reduction in daily OCS dose during weeks 20-24 compared to baseline.

Quality of Individual Studies

As noted earlier, we used criteria from USPSTF to rate the quality of the trials. Based on these criteria, we considered both the MENSA and SIRIUS trials to be of good quality, as study arms were comparable at baseline, the authors used valid instruments to evaluate outcomes, and no differential attrition occurred during the double-blind assessment for outcomes. The earlier dose-finding DREAM trial, which did not include a group treated with mepolizumab 100 mg SC, was also of good quality.

Clinical Benefits

The annual rate of significant exacerbations in the MENSA trial was 0.83 in the mepolizumab 100 mg SC group and 1.74 in the placebo group. Thus, mepolizumab was associated with a 53% reduction in asthma exacerbations compared with placebo (95% confidence interval [CI]: 36%, 65%; p<0.001). There were similar reductions in the rates of asthma exacerbations requiring ED visits or hospitalizations (61%; 95% CI: 17%, 82%; p=0.02) and hospitalizations (69%; 95% CI: 9%, 89%; p=0.03). The SIRIUS trial reported asthma exacerbation rates as secondary outcomes. Mepolizumab reduced total exacerbations by 32% (95% CI: 1%, 53%; p=0.04).

The primary outcome in the SIRIUS trial was the percentage reduction in OCS use. This is not of direct clinical benefit but should reduce the long-term harms of OCS use (e.g., osteoporosis, muscle weakness, diabetes). The median percent reduction in OCS dose was 50% in the mepolizumab group and 0% in the placebo group (p=0.007). The proportion of patients able to completely stop OCS was 14% in the mepolizumab group and 8% in the placebo group, but this did not differ statistically.

In both trials, the blood eosinophil counts decreased by more than 80% in the groups treated with mepolizumab (p<0.001 in both trials).

The MENSA trial measured quality of life with the ACQ and the SGRQ. The ACQ is a 5-item questionnaire with a score ranging from 0 to 6 with higher numbers indicating worse asthma control. The ACQ score decreased 0.94 points in the mepolizumab 100 mg SC group and 0.50 points in the placebo group (difference -0.44; 95% CI: -0.63, -0.25; p<0.001). A difference of 0.50 points on the ACQ is considered clinically significant, so the difference between the two groups, while statistically significant, is of only borderline clinical significance. The SGRQ is a 50-item questionnaire with a score ranging from 0 to 100, in which higher scores indicate worse functioning. The SGRQ score decreased 16 points in the mepolizumab 100 mg SC group and 9 points in the placebo group (difference -7; 95% CI: -10.2, -3.8; p<0.001). A difference of 4 points on the SGRQ is considered clinically significant.

The SIRIUS trial also measured quality of life with the ACQ and the SGRQ. The difference in the ACQ score between the mepolizumab group and the placebo group was -0.52 (95% CI: -0.87, -0.17; p<0.004). Similarly, the SGRQ score decreased more in the mepolizumab group than in the placebo group (difference -5.8; 95% CI: -10.1, -1.0; p<0.02).

Harms

The total number of adverse events was similar in the mepolizumab groups and the placebo groups in the three large RCTs (Appendix Table F4).[13-15] Significant adverse events were more common in the placebo groups. The most common adverse events in patients treated with mepolizumab 100 mg SC were headache, back pain, and fatigue, and they were not significantly associated with mepolizumab (see Table 2). Injection site reactions were more common in the group treated with mepolizumab (8% versus 3%).

Table 2: Common Adverse Events in Patients Treated with Mepolizumab 100 mg SC

Adverse Event	Mepolizumab 100 mg SC (N = 263)	Placebo (N =257)
Headache	19%	18%
Injection site reaction	8%	3%
Back pain	5%	4%
Fatigue	5%	4%

Hypersensitivity reactions (angioedema, bronchospasm, hypotension, urticaria, rash) are a concern with the administration of any monoclonal antibody. They have been reported with mepolizumab, but they occurred less often in the mepolizumab group than in the control group (1% versus 2%). Omalizumab, another monoclonal antibody approved to treat a subgroup of patients with severe asthma, carries a black box warning for anaphylaxis because about 1/1000 patients receiving omalizumab developed anaphylaxis.[16]

Opportunistic infections are also a concern with therapies such as mepolizumab that modulate the immune system. Patients with known parasitic infections were excluded from the clinical trials of mepolizumab. It is not known if mepolizumab would blunt the effectiveness of treatments for parasitic infections. Herpes zoster occurred in 2 of 263 patients treated with mepolizumab in clinical trials compared to 0 of 257 placebo patients. This may be a chance finding but should be monitored in phase IV studies.

Subgroup Analyses

Two subgroups of interest in severe asthma include African Americans and children ages 12 to 17 years. African Americans are hospitalized and die from asthma with more frequency than other races/ethnicities. Adolescent eosinophilic asthma may also represent a different phenotype than that of adults. Neither subgroup was described in the published literature, but data are presented in the FDA Advisory Committee Meeting Briefing Document that is publically available.

The DREAM and MENSA trials, including their IV mepolizumab groups, randomized a total of 39 individuals of African descent. In this subgroup, the rate ratio for asthma exacerbations with mepolizumab compared to placebo (0.58; 95% CI: 0.27, 1.25) was similar to that observed in pooled data for the two trials (0.53; 95% CI: 0.44, 0.62), but it was not statistically significant. No patients of African descent were randomized in the OCS dose reduction study (SIRIUS).

Similarly, the DREAM and MENSA trials, including their IV mepolizumab groups, randomized a total of 25 individuals between the ages of 12 and 17 years. In these adolescents, the rate ratio for asthma exacerbations with mepolizumab compared to placebo (0.56; 95% CI: 0.09, 3.45) was also similar to that observed in pooled data for the two trials (0.53; 95% CI: 0.44, 0.62), but it was not statistically significant. The SIRIUS study randomized two participants ages 12-17 years to

mepolizumab 100 mg SC and no similarly aged participants to placebo, so no subgroup analysis is possible in this study of OCS dose reduction.

Controversies and Uncertainties

The primary source of uncertainty is the paucity of peer-reviewed data in the literature on mepolizumab, particularly using the FDA-approved SC therapy. In the MENSA trial, 194 participants were treated with mepolizumab 100 mg SC for 32 weeks and in the SIRIUS trial, 69 participants were treated with mepolizumab 100 mg SC for 20 weeks. The greatest concern is that relatively uncommon side effects, such as opportunistic infections, will emerge as a larger group of patients is treated for several years.

It is also worth noting that there was a marked decrease in the annual rate of asthma exacerbations in the placebo group of the MENSA trial. In the year prior to randomization, the rate was 3.6 exacerbations per person and that declined by more than 50% to 1.74 per person during the trial. This marked reduction is greater than the difference in exacerbation rates between the mepolizumab and placebo groups. It could reflect optimization of the standard of care, highlighting the potential benefits of greater attention to maximizing adherence to standard therapy in patients with severe asthma. There may also be a component of regression to the mean.

In addition, there were not enough patients studied who are of African descent or who are younger than 18 to draw any meaningful conclusions about the net health benefits of mepolizumab in these two important subgroups. The FDA is requiring the conduct of two post-marketing studies specifically in children aged 6-11.

Summary

For adult patients with severe eosinophilic asthma, we judge there to be moderate certainty of a comparable or better net benefit for mepolizumab 100 mg SC every four weeks compared with standard of care including high dose ICS, LABA, and additional controller medications. There is moderate certainty because both the MENSA trial, which demonstrated a significant reduction in asthma exacerbations, and the SIRIUS trial, which demonstrated a significant reduction in OCS dosage, were relatively small studies of short duration. There is considerable uncertainty about the long-term durability of the therapy as well as potential harms from modulation of the immune system and hypersensitivity reactions including anaphylaxis. Ongoing post-marketing trials evaluating mepolizumab may demonstrate a wide variety of outcomes, from substantial net health benefit to a more even balance of benefits and harms that would yield a comparable rating. Therefore, we judge the current body of evidence on mepolizumab to be “comparable or better” using the ICER Evidence Rating framework.

5. Other Benefits or Disadvantages

Our reviews seek to provide information on other benefits or disadvantages offered by the intervention to the individual patient, caregivers, the delivery system, other patients, or the public that would not have been considered as part of the evidence on comparative clinical effectiveness. Examples include but are not limited to:

1. Methods of administration that improve or diminish patient acceptability and adherence
2. A public health benefit, e.g., reducing new infections
3. Treatment outcomes that reduce disparities across various patient groups
4. More rapid return to work or other positive effects on productivity (if not considered a benefit as part of comparative clinical effectiveness)
5. New mechanisms of action for treatments of clinical conditions for which the response to currently available treatments varies significantly among patients for unknown reasons (substantial heterogeneity of treatment effect)

A major potential benefit of mepolizumab is a reduction in the long term harms associated with chronic corticosteroid use. The SIRIUS trial was too small and too short in duration to capture these potential benefits.

Mepolizumab is a subcutaneous injection that requires an office visit every four weeks for administration. The burden of travel to a physician's office and the requirement for an injection may decrease long-term patient adherence to therapy. Conversely, the monitoring and opportunity for patient education at these visits may offer additional benefits.

Mepolizumab offers a new mechanism of action to treat a disease (severe asthma) that severely compromises patients' quality of life. No data were reported in clinical trial publications, but mepolizumab may lead to fewer days lost from school and work – two significant burdens borne by patients with severe asthma.

6. Comparative Value

6.1 Overview

To assess the incremental costs per outcomes achieved, we conducted a cost-effectiveness analysis (CEA) using a simulation model of asthma outcomes and costs in a representative population of candidates for mepolizumab therapy. We estimated the incremental cost-effectiveness of mepolizumab using drug cost estimates derived from current prices and estimates of reductions in asthma exacerbations and oral corticosteroid use from relevant clinical trial data.

Outputs from this model were also used to inform a population-based analysis of the one- and five-year budgetary impact of mepolizumab (see section 6.4). Budgetary impact was assessed using assumed levels of uptake over these timeframes and included assessment of drug costs as well as cost savings from averted exacerbations. We also define a "value-based price benchmark" for mepolizumab based on a calculated threshold for policy intervention to manage the costs of a new pharmaceutical.

6.2 Prior Published Evidence on Costs and Cost-Effectiveness of Mepolizumab

We did not identify any published articles or public presentations pertaining to the costs and/or cost-effectiveness of mepolizumab. An online abstract describes a decision-analytic model in a hypothetical cohort of 10,000 US patients followed for a 10-year time horizon.[35] Cost-effectiveness was estimated to be $21,388 per quality-adjusted life-year (QALY) gained over this timeframe. Importantly, however, this analysis was restricted to patients who respond to biologic therapy, a subpopulation that was not studied in either of the clinical trials that assessed mepolizumab in its available form (i.e., subcutaneous injection).

6.3 Incremental Costs per Outcome Achieved

Cost-Effectiveness Model: Methods

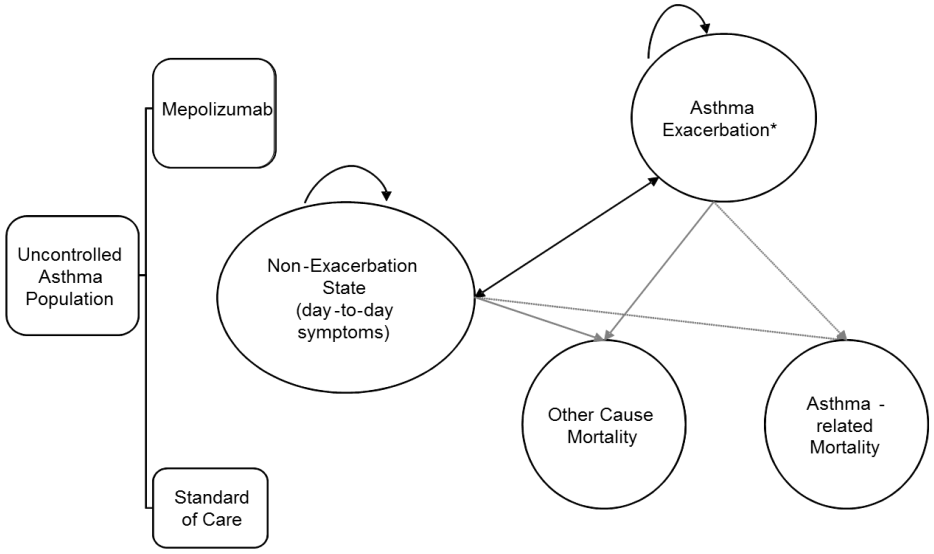
Model Structure

We modeled the population of adult asthma patients using a Markov cohort framework that included three primary health states: asthma non-exacerbation state (i.e., day-to-day asthma

symptoms), an asthma exacerbation state (including three mutually exclusive subcategories: asthma-related event that requires an oral corticosteroid burst, asthma-related ED visit, or asthma-related hospitalization), and death (including asthma-related mortality and other cause mortality) (see Figure 3). The model structure is similar to other published asthma CEA models, including a model of omalizumab, an approved biologic agent also used in severe allergic asthma but with a different phenotype. This model is described in the National Institute for Health and Care Excellence (NICE) appraisal determination from 2013.[17,36-40]

Asthma-related mortality and other cause mortality was modeled for all living health states (non-exacerbation and exacerbation).[40] The definition for exacerbations is somewhat different in trials of mepolizumab and omalizumab, however. Specifically, the mepolizumab model separates exacerbations into three subcategories including a category for asthma-related hospitalization, whereas some omalizumab models do not make this distinction. There is a known increased risk of death linked with asthma-related hospitalizations as described by Watson and colleagues, who analyzed a United Kingdom database including 250,043 asthma-related hospital admissions to determine the mortality rate following these hospitalizations.[41] Therefore, for the asthma-related hospitalization exacerbation subcategory only, we added the relationship of increased death consistent with Watson et al. to the background of asthma-related mortality and other cause mortality (see *Mortality* description for further details).

Figure 3. Markov Model Structure for Mepolizumab CEA



*Note: Exacerbation is defined as one of three subcategories:

1. Asthma related event that requires an oral corticosteroid burst of at least three days (but not ED visit or hospitalization)
2. Asthma related event that requires ED visit (but not a hospitalization)
3. Asthma related event that requires a hospitalization

Model Parameters

We assumed a lifetime horizon in the base-case, consistent with the literature in asthma cost-effectiveness modeling.[40,42,43] Omalizumab treatment in the NICE assessment was limited to 10 years with a lifetime horizon. Given uncertainty around duration of treatment with mepolizumab, and the relatively limited incremental impact of mortality on the costs and outcomes in this population, we also decided to evaluate a lifetime treatment horizon as the base-case and determined the impact of shorter treatment time horizons in sensitivity analyses.

We used a cycle length of two weeks to reflect the average length of time for an asthma exacerbation, and to be consistent with prior omalizumab published cost-effectiveness analyses[17,37] as well as asthma guidelines that suggest exacerbation events should only be considered new after at least a seven-day period.[44] The discount rate for all costs and outcomes was 3% per year. The analysis was conducted from the payer perspective; as such, the model focused attention on direct health care costs only.

Target Population

The population of focus for this analysis included adults with severe, uncontrolled asthma and evidence of eosinophilic inflammation. All individuals were treated with high-dose inhaled corticosteroid therapy and at least one additional controller medication (e.g., long-acting beta agonists, leukotriene agonists, theophylline, oral corticosteroids).

The population characteristics of the modeled cohort are described in Table 3. The model is mostly agnostic to the population characteristics, but they provide a context for describing the model inputs and assumptions. These characteristics mirrored the randomized controlled trial population in the mepolizumab exacerbation trial.[14]

Table 3. Model Cohort Characteristics

High-Dose ICS + Additional Controller(s) Uncontrolled and Eosinophilic Population	Value	Primary Source
Mean age	50	Ortega et al., 2014[14]
Female	57%	Ortega et al., 2014[14]
Caucasian	90% (Black: 4%, other: 6%)	Ortega et al., 2014[14]
Mean FEV_1 % of predicted	61%	Ortega et al., 2014[14]
Mean reversibility	28	Ortega et al., 2014[14]
Mean blood eosinophil count	445	Ortega et al., 2014[14]

Note: Model is agnostic to these characteristics except for age and % female, which impact mortality risk only. Characteristics are provided to aid in communication of the model and its findings.
FEV_1: forced expiratory volume in one second

Treatment Strategies

The intervention of interest was mepolizumab 100 mg by injection once every four weeks, in conjunction with daily inhaled corticosteroid and other controller therapy. The primary comparator of interest was SoC, consisting of daily inhaled corticosteroid and other controller therapy with or without oral corticosteroids (control arms in the mepolizumab trials also received placebo injection).

We assumed a proportion of the SoC alone and the mepolizumab + SoC arms used chronic oral corticosteroids at a level thought to be potentially harmful (>5 mg per day)[13] and therefore linked to adverse event costs and disutility. As evidenced in the SIRIUS trial, the mepolizumab + SoC arm had a smaller proportion at this potentially harmful level in comparison to SoC alone.[13] See *Costs* and *Utilities* sections for further discussion of the impact of chronic oral corticosteroid use.

We initially considered omalizumab as an alternative comparator for those with severe persistent allergic IgE-mediated eosinophilic asthma. However, given the lack of published head-to-head or even single arm evidence within the severe persistent allergic IgE-mediated eosinophilic asthma subpopulation who are naïve to either therapy, we did not formally assess the cost-effectiveness of mepolizumab relative to omalizumab. We note, however, that the average treated patient wholesale acquisition costs of mepolizumab and omalizumab are comparable,[17] as are the reported ranges of treatment effects.[14,45]

Model Inputs

Model inputs are displayed within Tables 4 and 5 as model-wide (i.e., non-treatment-specific) and treatment-specific inputs, respectively. Text discussing specific input values and rationale is included within the subsequent subheadings (costs, clinical events, mortality, utilities).

Table 4. Model-wide Key Inputs

Model-wide Inputs	Value	Sources
Asthma-related mortality per 100 person years	0.4	de Vries et al. 2010[46]
Additional risk of death given asthma hospitalization	2.48%	Watson et al., 2007[41]
Additional risk of death given ED visit	0%	Assumed
Additional risk of death given oral corticosteroid burst	0%	Assumed
Disutility for hospitalization	-0.2	Lloyd et al.[47]
Disutility for ED visit	-0.15	Lloyd et al.[47]
Disutility for oral corticosteroid burst	-0.10	Lloyd et al.[47]
Disutility for chronic oral corticosteroid use	-0.023	NICE omalizumab manufacturer's base-case[40]
Cost for asthma-related hospital stay	$9,960 / stay	Cangelosi et al.[48]
Cost for asthma-related ED visit	$684	Cangelosi et al.[48]
Cost for oral corticosteroid burst exacerbation	$156	Cangelosi et al.[48] & Redbook®[17]
Annual cost for Standard of Care	$5,738	Cangelosi et al.[48] & Redbook®[17]
Annual cost of chronic oral corticosteroid use	$73	Redbook®[17]
Annual cost of adverse events due to chronic oral corticosteroid use	$784	Shah et al.[49]

Table 5. Treatment-Specific Model Inputs

Input	Value	Source
SoC		
Annual exacerbation rate per person year	1.74	Ortega et al., 2014[14]
Proportion of hospitalizations	5.75%	Ortega et al., 2014[14]
Proportion of ED visits	5.75%	Ortega et al., 2014[14]
Proportion of oral corticosteroid bursts	88.51%	Ortega et al., 2014[14]
Discontinuation rate over entire time horizon	6%	Ortega et al., 2014[14]
Utility value for non-exacerbation health state	0.77	Ortega et al., 2014[14]
Percent using chronic oral corticosteroids >5mg per day	68%	Bel et al., 2014[13]
Mepolizumab + SoC (limited to parameters that differ from SoC alone)		
Annual exacerbation rate per person year	0.83	Ortega et al., 2014[14]
Proportion of hospitalizations	3.61%	Ortega et al., 2014[14]
Proportion of ED visits	6.02%	Ortega et al., 2014[14]
Proportion of oral corticosteroid bursts	90.36%	Ortega et al., 2014[14]
Annual cost for mepolizumab	$32,500	Redbook®[17]
Discontinuation rate over entire time horizon	5%	Ortega et al., 2014[14]
Utility value for non-exacerbation health state	0.828	Ortega et al., 2014[14]
Difference in utility value for non-exacerbation health state (compared to SoC alone)	0.059	Ortega et al., 2014[14]
Percent using chronic oral corticosteroids	46%	Bel et al., 2014[13]

Costs

Unit costs for asthma-related hospital stays, ED visits, and office (scheduled or unscheduled) visits were derived from an analysis of private, commercial payer claims data from the Truven® MarketScan™ database for years 2006–2011 and inflated to 2014 US Dollars (USD).[48] All drug prices unless otherwise noted were from Redbook® and were based on current wholesale acquisition costs.[17]

For the oral corticosteroid burst event, we assumed $10 for an oral corticosteroid burst,[17] with 75% of such events requiring an outpatient visit at $195 per visit; visit costs are in 2014 USD.

Treatment-related costs (SoC as well as mepolizumab) were assigned by treatment scenario for all living health states (exacerbation and non-exacerbation states). Annual SoC cost was assumed based on the cost of Advair Diskus® 500/50 twice daily.[50] We used the wholesale acquisition cost (WAC) of $2,500 per vial as the base-case annual cost for mepolizumab as published in Redbook®.[17]

All treatment-related wholesale acquisition costs were reduced based on the percentage of patients observed to have discontinued therapy in the pivotal RCT by Ortega et al.[14] These reductions in treatment cost over the entire lifetime horizon were relatively small (5% for mepolizumab and 6% for SoC).

The chronic use of oral corticosteroids likely results in adverse clinical events and their associated costs. We assumed that doses of daily oral corticosteroids above 5 mg were potentially harmful to the patient in terms of adverse events and could impact day-to-day living. The annual US cost associated with an individual who uses oral corticosteroids chronically above the 5mg dose level was $857,[17,49] including the annual cost of the drug ($73)[17] and the weighted adverse event cost ($784)[49] based on the proportion of chronic oral corticosteroid users who develop the following events: type 2 diabetes, myocardial infarction, glaucoma, cataracts, ulcer, osteoporosis, and stroke.

Clinical Events

Clinical inputs of the model focused on average exacerbation rates (per person year) for each treatment group and were derived from the major exacerbation trial of mepolizumab.[14] Uncertainty in the relative rate reduction of 53% was reported as a 95% confidence interval with lower and upper bounds of 36% and 65%, respectively.[14] The three subcategories of exacerbation events were also reported by treatment arm within this trial and were used as inputs in the Markov model as a proportion of exacerbation events by subcategory for each treatment strategy.[14]

Mortality

There were three possible levels of mortality included within this model: 1) asthma-related mortality, 2) all other cause mortality, and 3) asthma exacerbation-related mortality.

- **Asthma-related mortality** was based on the de Vries et al. study; we assigned an annualized rate of 0.4 per 100 person years to all living health states in the model for those with uncontrolled Treatment Step 4 (i.e., Global Initiative for Asthma Treatment Step 5) level disease.[46] Global Initiative for Asthma Treatment Step 5 is consistent with SoC for the mepolizumab modeled cohort, namely high-dose inhaled corticosteroids plus additional controller medication and eligible for biologic therapy.
- **All other cause mortality** was based on US average life tables (http://www.cdc.gov/nchs/products/nvsr.htm) for all living health states in the model.
- **Asthma exacerbation-related mortality**: As described previously, for the asthma-related hospitalization exacerbation subcategory only, we added the link of increased death consistent with Watson et al. to the background of (1) asthma-related mortality and (2) all other cause mortality.

All-cause mortality rates were adjusted to exclude those deaths pertaining to asthma using a cause elimination approach (consistent with the NICE omalizumab assessment group's model).[40]

Utilities

Utilities were assigned to all health states in the model. For the non-exacerbation health state, the clinical evidence from Ortega et al. reported on the St George's Respiratory Questionnaire (SGRQ) for mepolizumab + SoC versus SoC alone.[14] There is a published mapping between mean total SGRQ scores and the European Quality of Life-5 Dimensions (EQ-5D). The mean total SGRQ score of 38.9 for SoC and 31.9 for mepolizumab plus SoC[14] provided the required inputs for the aggregate mapping algorithm (EQ-5D utility = 0.9617 - 0.0013*SGRQ score - 0.0001*(SGRQ score)^2 + 0.0231* male).[51] Uncertainty in mapped EQ-5D utility was examined based on 95% confidence intervals for SGRQ scores.

Utilities for the exacerbation health states were assumed to be the same across treatment strategies.[47] Given a dearth of data on the utility associated with an asthma-related ED visit, we assumed the mid-point between the values for hospitalization and oral corticosteroid burst events. We assigned the pre-post decrement in utilities observed in Lloyd et al. for exacerbation-related events and applied them to the SoC non-exacerbation baseline value of 0.770. Results of our derivation can be found in Table 5 above.

The disutility of chronic oral corticosteroid use for patients using >5 mg daily (0.023) was assumed to be equivalent to the disability-adjusted life years (DALYs) that were weighted by the proportion of chronic oral corticosteroid users who developed the following adverse events: type 2 diabetes, myocardial infarction, glaucoma, cataracts, ulcer, osteoporosis, and stroke.

Sensitivity Analyses

The model programming allows for flexible and comprehensive sensitivity analyses. One-way sensitivity analyses used the low and high bounds from 95% confidence intervals from clinical evidence where available. In lieu of 95% confidence intervals for inputs, uncertainty in other parameters was based on plausible values from the published asthma model literature.

A scenario analysis was also conducted to determine the price of mepolizumab that would produce cost-effectiveness results at willingness-to-pay thresholds of $50,000/QALY, $100,000/QALY, and $150,000/QALY, respectively. Other scenario analyses investigated the impact of treatment time horizon on the incremental cost per QALY and the impact of assuming no excess risk of death related to asthma hospitalizations.

Cost-Effectiveness Model: Results

Over a lifetime treatment horizon, the model estimated that 23.96 exacerbations would be averted (non-discounted) per patient receiving mepolizumab with SoC versus SoC alone, over 28.89 person-years of treatment. Avoidance of exacerbations and the reduction in chronic oral corticosteroid use resulted in over $18,000 in cost offsets among those receiving mepolizumab, but treatment costs were increased by over $600,000. The resulting incremental cost per exacerbation averted was $24,626 (this estimate discounted costs but not exacerbations averted). Treatment with mepolizumab resulted in a gain of 1.53 QALYs relative to SoC alone, approximately 70% of which was due to quality of life improvement alone (1.1 versus 0.43 for improved survival). This resulted in a cost-effectiveness estimate of $385,546 per QALY gained (see Table 6).

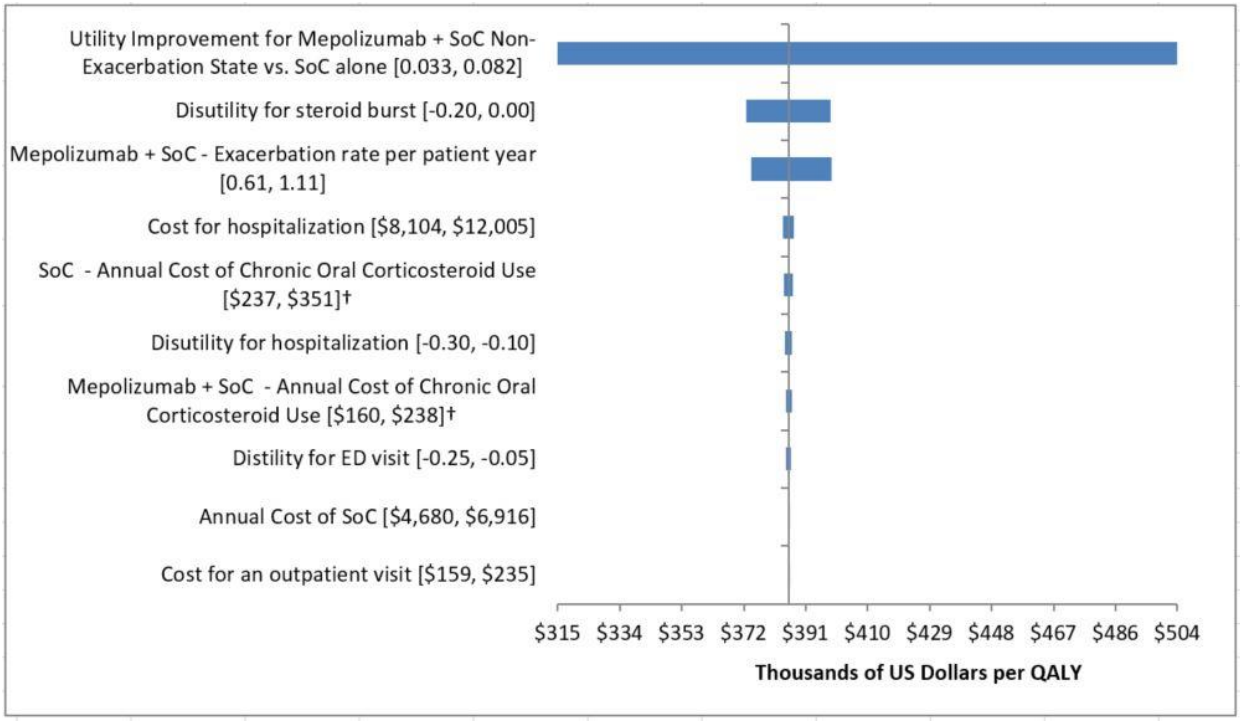
Table 6. Base-Case Clinical and Economic Outcomes from the Payer Perspective: Lifetime Treatment Horizon

	QALYs	Treatment Costs	Non-Treatment Costs	ICER ($/QALY)
Mepolizumab + SoC	15.12	$706,111	$15,465	$385,546/QALY
SoC alone	13.59	$98,083	$33,552	--

Future costs and QALYs are discounted 3% a year. Treatment costs include the cost of Mepolizumab and SoC. Non-treatment costs include the cost of exacerbations and chronic oral corticosteroid use.
ICER: Incremental cost-effectiveness ratio

Findings from our one-way sensitivity analysis can be found in Figure 4. Results were most sensitive to changes in utility benefit with mepolizumab + SoC, the utility of a corticosteroid burst, and the annual exacerbation rate for mepolizumab + SoC. In all situations, however, cost-effectiveness estimates remained well above commonly-cited thresholds (i.e., $50,000, $100,000, or $150,000 per QALY gained).

Figure 4. One-Way Sensitivity Analysis Results: Tornado Diagram

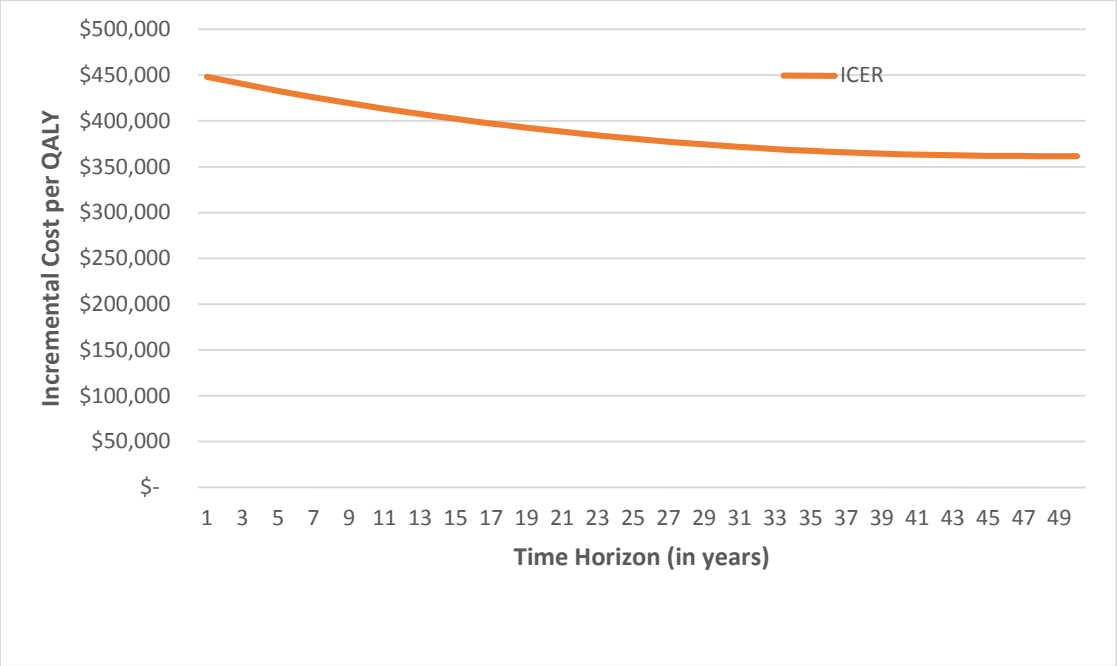


*Lower and upper input values used to produce the one-way sensitivity findings are depicted in the input text. 95% confidence intervals were used to inform the lower and upper values where evidence existed.

† This value is a function of three inputs: 1) annual cost of chronic oral corticosteroid use, 2) annual cost of adverse events due to chronic oral corticosteroid use, and 3) treatment-specific percent of patients using chronic oral corticosteroids >5mg per day.

We also varied the treatment time horizon from 1 to 50 years to examine the impact of this variation on cost-effectiveness findings. Findings are presented in Figure 5. Because model results are driven primarily by outcomes and costs that accrue on a constant basis over time (i.e., exacerbations and drug costs), varying the treatment time horizon had little impact on model outputs. Mepolizumab's cost-effectiveness was approximately $450,000 per QALY gained over a one-year treatment horizon and was approximately $350,000 at 50 years.

Figure 5. ICER by Time Horizon: Payer Perspective



Findings from our sensitivity analysis in which no excess risk of death related to asthma hospitalizations was assumed can be found in Table 7. Life expectancy in both treatment groups was increased in this analysis, and as a result, the number of exacerbations averted also increased slightly (25.69 versus 23.96 in the base-case). Cost offsets from avoided exacerbation events and reductions in chronic oral corticosteroid use totaled over $19,000 for mepolizumab. However, treatment costs were over $610,000 higher for mepolizumab patients, while QALY differences narrowed (from 1.53 in the base-case to 1.22 in this analysis) because no mortality benefit was assumed from averted hospital-based exacerbations. As a result, while the cost per exacerbation averted declined slightly to $23,072, the cost per QALY gained increased to $485,094.

Table 7. Mortality Sensitivity Analysis: Clinical and Economic Outcomes from the Payer Perspective

	QALYs	Treatment Costs	Non-Treatment Costs	ICER ($/QALY)
Mepolizumab + SoC	15.27	$713,298	$15,623	$485,094/QALY
SoC alone	14.05	$101,417	$34,692	--

This sensitivity analysis assumed no additional risk of death related to asthma hospitalizations. Only the de Vries et al. asthma-related mortality and all other-cause mortality apply to all living health states.
Future costs and QALYs are discounted 3% a year. Treatment costs include the cost of Mepolizumab and SoC. Non-treatment costs include the cost of exacerbations and chronic oral corticosteroid use.

Finally, prices for mepolizumab that would achieve cost-effectiveness thresholds of $50,000, $100,000, and $150,000 per QALY gained are presented in Table 8. The costs associated with the

office visits to administer the SC injection are included in the analysis to generate these results but are not included in the prices in this table, which are only for mepolizumab itself. The last row in the table corresponds to the cost-effectiveness ratio and mepolizumab list price from the base-case analysis.

To achieve a cost-effectiveness ratio of $150,000 per QALY gained, the price per mepolizumab vial would need to be $932 ($12,116 annually), a 63% discount from the $2,500 WAC ($32,500 per year). To achieve $100,000 per QALY gained, a price of $599 per vial would be required (a 76% discount). Finally, a discount of 89% would be necessary ($266 per vial) to reach a threshold of $50,000 per QALY gained.

Table 8. Threshold Analysis for Cost of Mepolizumab

ICER	Price per Vial (% of base-case)	Price per Year
$50,000/QALY	$266 (10.6%)	$3,458
$100,000/QALY	$599 (24.0%)	$7,787
$150,000/QALY	$932 (37.3%)	$12,116
$385,546/QALY (base-case)	$2,500	$32,500

6.4 Potential Budget Impact

We also used the cost-effectiveness model to estimate the potential total budgetary impact of mepolizumab based on assumed patterns of product uptake. We then combined consideration of the price range between cost-effectiveness thresholds of $100,000 to $150,000 per QALY with potential budget impact to calculate value-based price benchmarks.

Potential Budget Impact Model: Methods

We used the same model employed for the cost-effectiveness analyses to estimate total potential budgetary impact. Potential budgetary impact was defined as the total incremental cost of the therapy for the treated population, calculated as incremental health care costs (including drug costs) minus any offsets in these costs from averted exacerbations. All costs were undiscounted and estimated over one- and five-year time horizons. The five-year timeframe was of primary interest, given the potential for cost offsets to accrue over time.

The potential budget impact analysis included the entire candidate population for treatment, which was considered to be patients age 12 and older with severe asthma with poorly controlled disease (defined as two or more exacerbations in the past year) and eosinophilic inflammation (150+ cells/µl at treatment initiation). To estimate the size of the potential candidate population for mepolizumab, we first applied the estimated prevalence of asthma in those aged 12-17 years

(10.5%)[52] and 18+ years (8.0%)[53] to the projected 2015 US population. We assumed that 10% of the population with asthma would have severe disease[18,19], and that 19.9% of those with severe asthma have had at least two exacerbations in the past year[54] Finally, we assumed that 72% of patients with severe asthma and two or more exacerbations also had eosinophilic inflammation. [20] This resulted in a candidate population size of approximately 320,000 individuals in the US.

ICER's methods for estimating potential budget impact and calculating value-based benchmark prices are described in detail elsewhere. Briefly, our calculations assume that the utilization of new drugs occurs without any payer, provider group, or pharmacy benefit management controls in place, to provide an estimate of "unmanaged" drug uptake by five years after launch.

In general, we examine six characteristics of the drug or device and the marketplace to estimate "unmanaged" uptake. These characteristics are listed below:

- Magnitude of improvement in clinical safety and/or effectiveness
- Patient-level burden of illness
- Patient preference (ease of administration)
- Proportion of eligible patients currently being treated
- Primary care versus specialty clinician prescribing/use
- Presence or emergence of competing treatments of equal or superior effectiveness

Based on our assessment of these criteria, we assign a new drug or device to one of four categories of unmanaged drug uptake patterns: 1) very high (75% uptake by year 5); 2) high (50% uptake by year 5); 3) intermediate (25% uptake by year 5); and 4) low (10% uptake by year 5). In this analysis, we assumed a low uptake pattern for mepolizumab. Mepolizumab is the first anti-IL-5 treatment for adults and adolescents with severe asthma featuring an eosinophilic phenotype. However, requirements for office-administered injection might dampen enthusiasm among some patients, and clinical evidence suggests that even standard treatments for severe asthma may provide benefit in this phenotype. Finally, another anti-IL-5 agent for eosinophilic asthma is under review by the FDA, with potential approval and market entry as early as March 2016.[21,22]

The resulting population size after five years, assuming an estimated 10% uptake, was 32,035. For consistency, uptake was assumed to occur in equal proportions across the five-year timeframe, and we adjusted net costs to account for this. For example, in this population estimated to have a 10% five-year uptake, 2% of patients would be assumed to initiate therapy each year. Patients initiating therapy in year one would accrue all drug costs and cost offsets over the full five years, but those initiating in other years would only accrue a proportional amount of the five-year costs and cost-offsets.

Using this approach to estimate potential budget impact, we then compared our estimates to a budget impact threshold that represents a potential trigger for policy mechanisms to improve

affordability, such as changes to pricing, payment, or patient eligibility. As described in ICER's methods presentation (http://www.icer-review.org/wp-content/uploads/2014/01/Slides-on-value-framework-for-national-webinar1.pdf), this threshold is based on an underlying assumption that health care costs should not grow much faster than growth in the overall national economy. From this foundational assumption, our potential budget impact threshold is derived using an estimate of growth in US gross domestic product (GDP) +1%, the average number of new drug approvals by the FDA each year, and the contribution of spending on retail and facility-based drugs to total health care spending. Calculations are performed as shown in Table 9.

For 2015-16, therefore, the five-year annualized potential budget impact threshold that should trigger policy actions to manage affordability is calculated to total approximately $904 million per year for new drugs.

Table 9. Calculation of Potential Budget Impact Threshold

Item	Parameter	Estimate	Source
1	Growth in US GDP, 2015-2016 (est.) +1%	3.75%	World Bank, 2015
2	Total health care spending ($)	$3.08 trillion	CMS NHE, 2014
3	Contribution of drug spending to total health care spending (%)	13.3%	CMS National Health Expenditures (NHE), Altarum Institute, 2014
4	Contribution of drug spending to total health care spending ($) (Row 2 x Row 3)	$410 billion	Calculation
5	Annual threshold for net health care cost growth for ALL new drugs (Row 1 x Row 4)	$15.4 billion	Calculation
6	Average annual number of new molecular entity approvals, 2013-2014	34	FDA, 2014
7	Annual threshold for average cost growth per individual new molecular entity (Row 5 ÷ Row 6)	$452 million	Calculation
8	Annual threshold for estimated potential budget impact for each individual new molecular entity (doubling of Row 7)	$904 million	Calculation

Potential Budget Impact and the Value-based Price Benchmark

We combine consideration of the potential budget impact with the threshold prices presented in Section 6.3 above (i.e., prices based on incremental costs per outcomes achieved) to calculate a value-based price benchmark for each new drug or device. This price benchmark begins with the price range to achieve cost-effectiveness ratios of $100,000-$150,000 per QALY for the population being considered, but it has an upper limit determined by the price at which the new drug would exceed the potential budget impact threshold (i.e., $904 million). If the potential budget impact

does not exceed these thresholds, then the value-based price benchmark remains the full price range determined from the analysis of incremental costs per outcomes achieved.

Potential Budget Impact Model: Results

Table 10 below presents the potential budgetary impact of one year and five years of mepolizumab in the candidate population, assuming the uptake patterns previously described. (Undiscounted costs per patient for years 1 through 5 are provided in Appendix Table G4.) Results are presented for both one-year and five-year time horizons.

Results from the potential budget impact model showed that, with the uptake pattern assumptions mentioned above, an estimated 6,407 individuals would receive mepolizumab in the first year. After one year of treatment, with net annual costs of $31,388 per patient, one-year budget impact is estimated to be $201.1 million.

Over the entire five-year time horizon, we estimate that "unmanaged" uptake would lead to approximately 32,000 persons taking mepolizumab. Across the full five-year time horizon, the weighted potential budgetary impact (i.e., adjusted for differing periods of drug utilization and associated cost-offsets) is approximately $93,000 per patient. Total potential budgetary impact over five years is approximately $3 billion, with an average budget impact per year of approximately $596 million. This annualized potential budget impact is 66% of the budget impact threshold of $904 million for a new drug.

Table 10. Estimated Total Potential Budget Impact (BI) of Mepolizumab

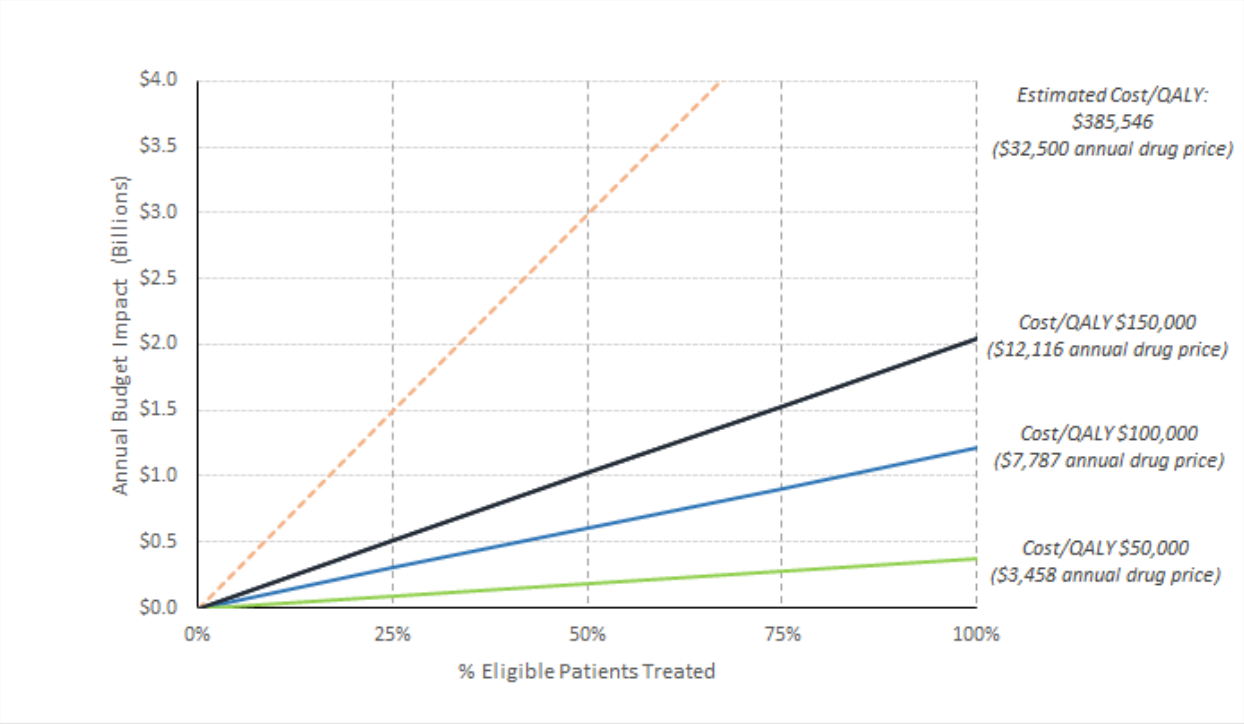
		Analytic Horizon = 1 Year			Analytic Horizon = 5 Years		
	Eligible Population (thousands)	Number Treated (thousands)	Annual BI per Patient ($)*	Total BI (millions)	Number Treated (thousands)	Weighted BI per Patient ($)*	Average BI per year (millions)
Mepolizumab	320	6.4	$31,388	$201.1	32.0	$93,043	$596.1

*Weighted budget impact calculated by subtracting cost offsets from drug costs for one-year horizon. For five-year horizon, drug costs and cost offsets apportioned assuming 20% of patients in uptake target initiate therapy each year. Those initiating in year 1 receive full drug costs and cost offsets, those initiating in year 2 receive 80% of drug costs and cost offsets, etc.

Figure 6 provides findings of multiple analyses that give perspective on the relationship between varying possible drug prices, cost-effectiveness ratios, uptake patterns, and potential budget impact. The vertical axis shows the annualized budget impact, and the horizontal axis represents the percentage of eligible patients treated over a five-year period. The colored lines demonstrate how quickly the annual budget impact increases with increasing percentages of patients treated at four different prices: those at which the cost/QALY = $50,000, $100,000, and $150,000; and the list price used in this analysis (i.e., $32,500 annually for mepolizumab).

As can be seen in Figure 6, the dashed line – representing the potential annual budget impact for mepolizumab at list price – shows that annualized potential budget impact increases from $596 million at our assumed 10% uptake to $1.5 billion at 25% of eligible patients treated, and further up to approximately $6 billion if 100% of eligible patients were treated. In addition, if the annual price for mepolizumab was lowered to $12,116 to meet a cost-effectiveness threshold of $150,000/QALY, just under 50% of all eligible patients could be treated over a five-year time period before the annualized budget impact reaches the $904 million threshold. In the $100,000/QALY scenario (assuming $7,787 annual drug price), approximately 75% of eligible patients could be treated before the annualized budget impact exceeds the threshold; if all eligible patients were treated at this price, the annualized budget impact is approximately $1.2 billion.

Figure 6. Combined Cost-effectiveness and Potential Budget Impact Graph for Mepolizumab



Note: Colored lines represent the annualized budget impact of different uptake patterns (eligible patients treated) at the actual list price of the drug (dashed line), and at drug prices needed to achieve common incremental cost-effectiveness ratios.

6.5 Draft Value-based Benchmark Prices

Our draft value-based benchmark prices for mepolizumab are provided in Table 11. As noted in the ICER methods document, the draft value-based benchmark price for a drug or device is defined as the price range that would achieve cost-effectiveness ratios between $100,000 and $150,000 per QALY gained, without exceeding the $904 million budgetary impact threshold for new drugs.

As shown in Table 11, the price range based on cost-effectiveness thresholds ($7,787 to $12,116/year) is much lower than the actual list price for mepolizumab ($32,500/year), as our analyses indicated a cost/QALY much higher than $150,000 for this intervention at the list price. As noted previously, the budgetary impact of mepolizumab at list price does not exceed our stated $904 million threshold when annualized over a five-year time horizon. The price of mepolizumab that could be charged and not exceed the $904 million benchmark is higher than the price range that would achieve $100,000 to $150,000 per QALY gained. Details of the budget impact threshold price analysis can be found in Appendix Table G5.

Therefore, the draft ICER value-based price benchmark for mepolizumab, with all the assumptions mentioned previously regarding five-year uptake patterns and net costs, is $7,787 to $12,116 per year, which represents a 63-76% discount from the full list price ($32,500 per year).

Table 11. Draft Value-based Price Benchmark for Mepolizumab

Population	Price to Achieve $100K/QALY	Price to Achieve $150K/QALY	Exceeds Potential Budget Impact Threshold?	Draft Value-Based Price Benchmark
Mepolizumab (n=32,035)	**$7,787/year**	**$12,116/year**	**No**	**$7,787 to $12,116/year**

6.6 Summary and Comment

The base-case cost-effectiveness estimate of mepolizumab + SoC versus SoC alone was substantially higher that commonly-cited thresholds of $50,000/QALY, $100,000/QALY, and $150,000/QALY. After varying the most influential parameters, the cost-effectiveness estimates remain unfavorable. Meeting willingness to pay thresholds of $50,000/QALY, $100,000/QALY, and $150,000/QALY requires a significantly reduced price of mepolizumab.

The mepolizumab value findings as compared to the omalizumab value findings from the US payer perspective[17] suggest globally comparable results with some notable differences. The omalizumab US payer value estimates published in 2010 suggested a cost-effectiveness estimate of $287,200/QALY.[17] The average annual price of omalizumab assumed in Campbell and colleagues' 2010 publication was approximately $20,000. Therefore, with the present (2015) annual WAC of mepolizumab at $32,500, we anticipated a higher ratio in this analysis. Further, one of the drivers of cost-effectiveness, the difference in non-exacerbation utility between treatment arms, was found to be comparable but slightly higher in the omalizumab study (0.063) compared to the mepolizumab mapping (0.059). Finally, an analysis of responders to omalizumab yielded a more favorable value estimate of $172,300/QALY; there are no published data of mepolizumab responders, therefore we did not estimate the value for this group.

Limitations to the present study include the following: limited long-term follow-up data; lack of absenteeism data to account for productivity differences from a societal perspective; the assumption that the efficacy trial evidence and corresponding SoC within the trial are appropriate inputs for the model and may translate into long-term costs and outcomes; clinical outcomes (exacerbation rates as well as utility values for health states) are constant through time and benefits observed in the trial continue to occur throughout the time horizon of the model; the wholesale acquisition cost of drugs approximates the true transaction cost of drugs; and beyond discontinuation, the simulated cohorts continue to be adherent to mepolizumab and standard of care. We note, however, that most of these assumptions were tested in sensitivity and threshold analyses.

Additionally, neither responder scenarios with mepolizumab nor any comparisons with omalizumab were conducted. A responder scenario would better approximate the real-world cost-effectiveness of mepolizumab and if similar to the omalizumab value estimates, would show a more favorable incremental cost-effectiveness result. Evidence is needed to define response as well as to link response (or lack thereof) with costs and outcomes. We did not formally assess the cost-effectiveness of mepolizumab relative to omalizumab due to the lack of published head-to-head or even single arm evidence within the severe persistent allergic IgE-mediated eosinophilic asthma subpopulation who are naïve to either therapy.

Furthermore, one-way sensitivity analyses suggested that the non-exacerbation utility difference between mepolizumab plus SoC versus SoC alone was the key driver of value. The utilities for the non-exacerbation state were derived from the SGRQ total scores that were mapped to the EQ-5D. Given alternative approaches in estimating utility scores for the non-exacerbation health state and its corresponding uncertainty, further research may be warranted to explore alternative approaches.

Finally, our assumed levels of mepolizumab uptake in the marketplace by five years were based on reasoned assumptions, but actual uptake may vary from these estimates. We also present potential budget impact across a range of uptake possibilities in sensitivity analyses.

In summary, adding mepolizumab to SoC for adult patients with severe eosinophilic asthma appears to confer clinical benefits in terms of reduced rates of exacerbation and improved quality of life. However, at the current wholesale acquisition cost, the estimated cost-effectiveness of mepolizumab exceeds commonly-cited thresholds. Achieving levels of value more closely aligned with patient benefit would require discounts of two-thirds to three-quarters from the current list price of mepolizumab.

****

This is the first CTAF review of mepolizumab.

References

1. Centers for Disease Control and Prevention. Asthma Facts—CDC's National Asthma Control Program Grantees. 2013.
2. Cisternas MG, Blanc PD, Yen IH, et al. A comprehensive study of the direct and indirect costs of adult asthma. *Journal of Allergy and Clinical Immunology.* 2003;111(6):1212-1218.
3. Expert Panel Report 3 (EPR-3): Guidelines for the Diagnosis and Management of Asthma-Summary Report 2007. *The Journal of allergy and clinical immunology.* 2007;120(5 Suppl):S94-138.
4. National Asthma Education and Prevention Program. Guidelines for the Diagnosis and Management of Asthma. Expert Panel Report 3. Vol 08-4051. Bethesda, MD: National Institutes of Health; 2007: http://www.nhlbi.nih.gov/health-pro/guidelines/current/asthma-guidelines.
5. Buchman AL. Side effects of corticosteroid therapy. *J Clin Gastroenterol.* 2001;33(4):289-294.
6. Chung KF. Defining phenotypes in asthma: a step towards personalized medicine. *Drugs.* 2014;74(7):719-728.
7. Moore WC, Meyers DA, Wenzel SE, et al. Identification of asthma phenotypes using cluster analysis in the Severe Asthma Research Program. *Am J Respir Crit Care Med.* 2010;181(4):315-323.
8. Bousquet J, Chanez P, Lacoste JY, et al. Eosinophilic inflammation in asthma. *New England Journal of Medicine.* 1990;323(15):1033-1039.
9. Wardlaw AJ, Brightling CE, Green R, Woltmann G, Bradding P, Pavord ID. New insights into the relationship between airway inflammation and asthma. *Clinical science (London, England : 1979).* 2002;103(2):201-211.
10. Sehmi R, Wardlaw AJ, Cromwell O, Kurihara K, Waltmann P, Kay AB. Interleukin-5 selectively enhances the chemotactic response of eosinophils obtained from normal but not eosinophilic subjects. *Blood.* 1992;79(11):2952-2959.
11. Chung KF. Targeting the interleukin pathway in the treatment of asthma. *Lancet.* 2015;386(9998):1086-1096.
12. GlaxoSmithKline. Nucala Full Prescribing Information. 2015; https://www.gsksource.com/pharma/content/dam/GlaxoSmithKline/US/en/Prescribing_Information/Nucala/pdf/NUCALA-PI-PIL.PDF. Accessed December 10, 2015.
13. Bel EH, Wenzel SE, Thompson PJ, et al. Oral Glucocorticoid-Sparing Effect of Mepolizumab in Eosinophilic Asthma. *New England Journal of Medicine.* 2014;371(13):1189-1197.
14. Ortega HG, Liu MC, Pavord ID, et al. Mepolizumab Treatment in Patients with Severe Eosinophilic Asthma. *New England Journal of Medicine.* 2014;371(13):1198-1207.
15. Pavord ID, Korn S, Howarth P, et al. Mepolizumab for severe eosinophilic asthma (DREAM): a multicentre, double-blind, placebo-controlled trial. *Lancet.* 2012;380(9842):651-659.
16. Cox L, Platts-Mills TA, Finegold I, Schwartz LB, Simons FE, Wallace DV. American Academy of Allergy, Asthma & Immunology/American College of Allergy, Asthma and Immunology Joint Task Force Report on omalizumab-associated anaphylaxis. *The Journal of allergy and clinical immunology.* 2007;120(6):1373-1377.
17. Campbell JD, Spackman DE, Sullivan SD. The costs and consequences of omalizumab in uncontrolled asthma from a USA payer perspective. *Allergy.* 2010;65(9):1141-1148.
18. Chung KF, Wenzel SE, Brozek JL, et al. International ERS/ATS guidelines on definition, evaluation and treatment of severe asthma. *The European respiratory journal.* 2014;43(2):343-373.

19. Moore WC, Bleecker ER, Curran-Everett D, et al. Characterization of the severe asthma phenotype by the National Heart, Lung, and Blood Institute's Severe Asthma Research Program. *The Journal of allergy and clinical immunology.* 2007;119(2):405-413.
20. California Department of Health Care Services. Contract Drugs List. https://files.medi-cal.ca.gov/pubsdoco/manual/man_query.asp?wSearch=(%23filename+drugscdl*.doc+OR+%23filename+drugscdl*.zip)&wFLogo=Contract+Drugs+List&wFLogoH=52&wFLogoW=516&wAlt=Contract+Drugs+List&wPath=N. Accessed December 13, 2015.
21. Teva Pharmaceuticals. FDA Advisory Committee Recommends Approval of Teva's Asthma Biologic Reslizumab. 2015; http://www.tevapharm.com/news/fda_advisory_committee_recommends_approval_of_teva_s_asthma_biologic_reslizumab_12_15.aspx. Accessed December 15, 2015.
22. US Food and Drug Administration. *BLA 761033: Reslizumab for intravenous injection to reduce exacerbations, relieve symptoms, and improve lung function in adults and adolescents (12 years of age and above) with asthma and elevated blood eosinophils who are inadequately controlled on inhaled corticosteroids.* December 9 2015.
23. Anthem Blue Cross. Mepolizumab (Nucala®). https://www.anthem.com/ca/medicalpolicies/policies/mp_pw_c184800.htm. Accessed December 13, 2015.
24. Humana. Medical and Pharmacy Coverage Policies. http://apps.humana.com/tad/tad_new/home.aspx?type=provider. Accessed December 13, 2015.
25. Aetna. Specialty Pharmacy Clinical Policy Bulletins Aetna Non-Medicare Prescription Drug Plan (Nucala). 2015; http://www.aetna.com/products/rxnonmedicare/data/2015/RESP/Interleukin%20Antagonist.html. Accessed December 17, 2015.
26. Aetna. Formularies & Clinical Policy Bulletins. https://www.aetna.com/health-care-professionals/clinical-policy-bulletins/pharmacy-clinical-policy-bulletins.html. Accessed December 13, 2015.
27. Anthem Blue Cross. Omalizumab (Xolair®). https://www.anthem.com/ca/medicalpolicies/policies/mp_pw_a050293.htm. Accessed December 13, 2015.
28. Anthem Blue Cross. Drug Lists: The prescription drugs your plan covers. https://www.anthem.com/ca/pharmacyinformation/. Accessed December 14, 2015.
29. CIGNA. CIGNA Drug and Biologic Coverage Policy: Omalizumab (Xolair®). https://cignaforhcp.cigna.com/public/content/pdf/coveragePolicies/pharmacy/ph_4026_pharmacycoverageposition_xolair.pdf. Accessed December 13, 2015.
30. UnitedHealthcare. Xolair® (omalizumab). https://www.unitedhealthcareonline.com/ccmcontent/ProviderII/UHC/en-US/Assets/ProviderStaticFiles/ProviderStaticFilesPdf/Tools%20and%20Resources/Policies%20and%20Protocols/Medical%20Policies/Drug%20Policies/Xolair_policy.pdf. Accessed December 13, 2015.
31. Cook DJ, Mulrow CD, Haynes RB. Systematic reviews: synthesis of best evidence for clinical decisions. *Annals of internal medicine.* 1997;126(5):376-380.
32. Moher D, Liberati A, Tetzlaff J, Altman DG. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *Annals of internal medicine.* 2009;151(4):264-269, w264.
33. Agency for Healthcare Research and Quality. *U.S. Preventive Services Task Force Procedure Manual.* 2008.

34. Ollendorf DA, Pearson SD. An integrated evidence rating to frame comparative effectiveness assessments for decision makers. *Medical care.* 2010;48(6 Suppl):S145-152.
35. Bogart M, Roberts A, Wheeler S. Cost-effectiveness of refractory asthma treatment strategies: a decision tree analysis. Paper presented at: ISPOR 20th Annual International Meeting; May 2015, 2015; Philadelphia, PA.
36. Campbell JD, McQueen RB, Briggs A. The "e" in cost-effectiveness analyses. A case study of omalizumab efficacy and effectiveness for cost-effectiveness analysis evidence. *Annals of the American Thoracic Society.* 2014;11 Suppl 2:S105-111.
37. Sullivan SD, Turk F. An evaluation of the cost-effectiveness of omalizumab for the treatment of severe allergic asthma. *Allergy.* 2008;63(6):670-684.
38. Faria R, McKenna C, Palmer S. Optimizing the position and use of omalizumab for severe persistent allergic asthma using cost-effectiveness analysis. *Value in health : the journal of the International Society for Pharmacoeconomics and Outcomes Research.* 2014;17(8):772-782.
39. Norman G, Faria R, Paton F, et al. Omalizumab for the treatment of severe persistent allergic asthma: a systematic review and economic evaluation. *Health technology assessment.* 2013;17(52):1-342.
40. National Institute for Health and Care Excellence. Omalizumab for treating severe persistent allergic asthma. Technology appraisal guidance 278. 2013.
41. Watson L, Turk F, James P, Holgate ST. Factors associated with mortality after an asthma admission: a national United Kingdom database analysis. *Respiratory medicine.* 2007;101(8):1659-1664.
42. Campbell JD, Spackman DE, Sullivan SD. Health economics of asthma: assessing the value of asthma interventions. *Allergy.* 2008;63(12):1581-1592.
43. Einarson TR, Bereza BG, Nielsen TA, Van Laer J, Hemels ME. Systematic review of models used in economic analyses in moderate to severe asthma and COPD. *Journal of medical economics.* 2015:1-92.
44. Reddel HK, Taylor DR, Bateman ED, et al. An official American Thoracic Society/European Respiratory Society statement: asthma control and exacerbations: standardizing endpoints for clinical asthma trials and clinical practice. *Am J Respir Crit Care Med.* 2009;180(1):59-99.
45. Bousquet J, Cabrera P, Berkman N, et al. The effect of treatment with omalizumab, an anti-IgE antibody, on asthma exacerbations and emergency medical visits in patients with severe persistent asthma. *Allergy.* 2005;60(3):302-308.
46. Vries Fd, Setakis E, Zhang B, Staa TPv. Long-acting β2-agonists in adult asthma and the pattern of risk of death and severe asthma outcomes: a study using the GPRD. *European Respiratory Journal.* 2010;36(3):494-502.
47. Lloyd A, Price D, Brown R. The impact of asthma exacerbations on health-related quality of life in moderate to severe asthma patients in the UK. *Primary care respiratory journal : journal of the General Practice Airways Group.* 2007;16(1):22-27.
48. Cangelosi MJ, Ortendahl JD, Meckley LM, et al. Cost-effectiveness of bronchial thermoplasty in commercially-insured patients with poorly controlled, severe, persistent asthma. *Expert Rev Pharmacoecon Outcomes Res.* 2015;15(2):357-364.
49. Shah M, Chaudhari S, McLaughlin TP, et al. Cumulative burden of oral corticosteroid adverse effects and the economic implications of corticosteroid use in patients with systemic lupus erythematosus. *Clinical therapeutics.* 2013;35(4):486-497.
50. National Institute for Health and Care Excellence. *Omalizumab for treating severe persistent allergic asthma. Review of technology appraisal guidance 133 and 201.* 2013 2013.

51. Starkie HJ, Briggs AH, Chambers MG, Jones P. Predicting EQ-5D values using the SGRQ. *Value in health : the journal of the International Society for Pharmacoeconomics and Outcomes Research.* 2011;14(2):354-360.
52. Bloom B, Jones L, Freeman G. *Summary Health Statistics for U.S. Children: National Health Interview Survey, 2012.* 2013.
53. Blackwell D, Lucas J, Clark T. *Summary Health Statistics for U.S. Adults: National Health Interview Survey, 2012.* 2014.
54. GlaxoSmithKline. Data on File. 2015N237794_01. 2015.
55. CIGNA. CIGNA's Prescription Drug Lists. https://cignaforhcp.cigna.com/web/public/resourcesGuest/!ut/p/z1/hY3NDoIwEISfhQNH2SVG5EpMBAyJJBygvZgFK9RAacqP-vbCAxDmNplvZoBDAVzRLGsaZa-oXTzj3uMe-p4bZRiFt_SKcYqX2M2yI_oI-R7Alxg3FKx9voew5eK8fXGCfJbiA9m6ZMQLmI2DHMVgY9VU2kYjhn4yIUhkacj8bNQNmS6ayoTUU6ra0VSLtfymmb6O7s3YitGhARiC7go8sM7_BJb1B9Xhs5w!/dz/d5/L2dBISEvZ0FBIS9nQSEh/p0/IZ7_OG861HS0HGJPF0IP0CI1SS3085=CZ6_OG861HS0HGJPF0IP0CI1SS3080=LA0=Eref!QCPsitesQCPchcpQCPresourceLibraryQCPpharmacyResourcesQCPpharmDrugListsCignaGw.page==/#Z7_OG861HS0HGJPF0IP0CI1SS3085. Accessed December 14, 2015.
56. UnitedHealthcare. 2015 Prescription Drug List. https://www.unitedhealthcareonline.com/ccmcontent/ProviderII/UHC/en-US/Assets/ProviderStaticFiles/ProviderStaticFilesPdf/Tools%20and%20Resources/Pharmacy%20Resources/PDL_Phys_Bk.pdf. Accessed December 13, 2015.
57. Health Net. Xolair® (omalizumab). https://www.healthnet.com/static/general/unprotected/html/national/pa_guidelines/xolair_natl.html. Accessed December 17, 2015.
58. Liu Y, Zhang S, Li DW, Jiang SJ. Efficacy of anti-interleukin-5 therapy with mepolizumab in patients with asthma: a meta-analysis of randomized placebo-controlled trials. *PloS one.* 2013;8(3):e59872.

APPENDICES

Appendix A. Search Strategies and Results

Table A1. PRISMA 2009 Checklist

	#	Checklist item
TITLE		
Title	1	Identify the report as a systematic review, meta-analysis, or both.
ABSTRACT		
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.
INTRODUCTION		
Rationale	3	Describe the rationale for the review in the context of what is already known.
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).
METHODS		
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.

Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.
RESULTS		
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).
DISCUSSION		
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.
FUNDING		
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.

From: Moher D, Liberati A, Tetzlaff J, Altman DG. The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(6): e1000097. doi:10.1371/journal.pmed1000097

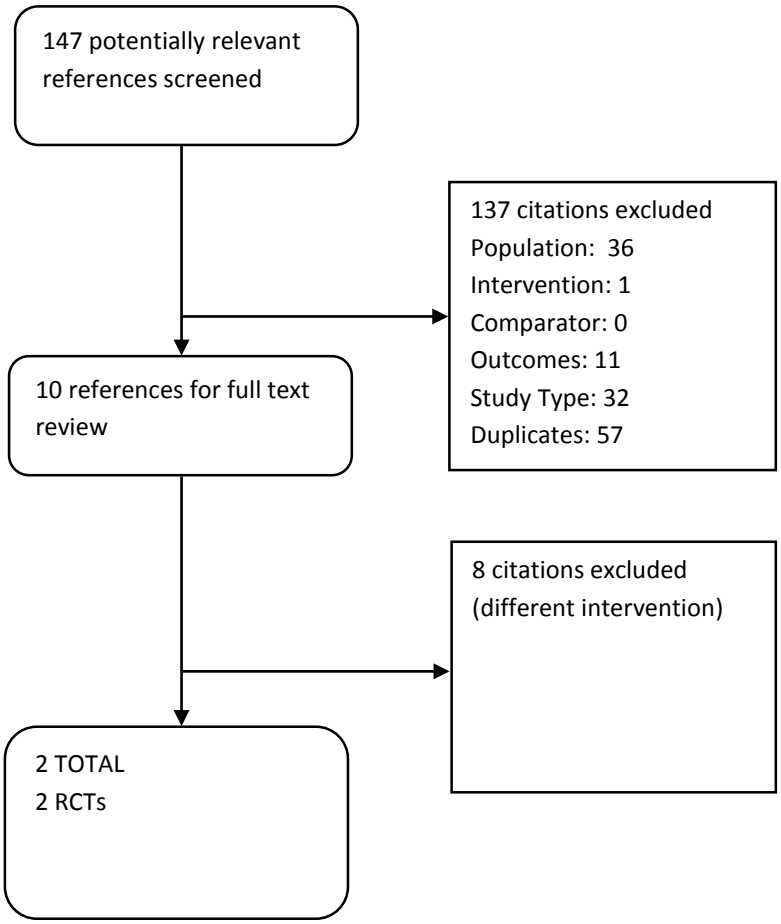
Table A2. Search Strategies for Mepolizumab

PUBMED
Mepolizumab – 197 articles
Limits: Randomized Controlled Trial, Systematic Review, Meta-analyses – 37 articles

EMBASE
mepolizumab AND [randomized controlled trial]/lim
Results: 45

Cochrane
Mepolizumab – 70 articles
Limit to Trials – 65 articles

Figure A1. PRISMA flow Chart Showing Results of Literature Search for Mepolizumab



Appendix B. Clinical Guidelines

National Heart, Lung, and Blood Institute (NHLBI), 2007

http://www.nhlbi.niah.gov/health-pro/guidelines/current/asthma-guidelines

NHLBI considers children over the age of 12 and adults to have severe asthma in the presence of the following components: symptoms throughout the day; nighttime awakenings often on seven nights per week; the use of short-acting beta agonists (SABA) multiple times per day; extremely limited ability to perform normal activity; FEV_1 less than 60% of predicted value or FEV_1/forced vital capacity (FVC) reduced more than 5%; two or more exacerbations requiring the use or oral systemic corticosteroids within the past year. Asthma is considered to be very poorly controlled when a patient experiences symptoms throughout the day; awakens during the night due to asthma more than four times per week; is extremely limited in his or her ability to perform normal daily activity; uses a SABA multiple times per day; has FEV_1 or peak flow below 60% of predicted or personal best; scores 3-4 on the Asthma Therapy Assessment Questionnaire (ATAQ), N/A on the Asthma Control Questionnaire (ACQ), or less than or equal to 15 on the ACT; and experiences two or more exacerbations requiring oral systemic corticosteroids per year.

NHLBI recommends a stepwise approach to pharmacological treatment for patients with persistent asthma, beginning with low-dose inhaled corticosteroids (ICS). Patients with severe asthma should begin treatment with a high-dose ICS in combination with a long-acting beta agonist (LABA), adding an oral corticosteroid in the most severe cases. Omalizumab should be considered for patients who have allergies. All patients should be prescribed an inhaled SABA for the management of acute symptoms, and patients who use a SABA two or more times per week should be tried on more intensive asthma-control regimens.

European Respiratory Society (ERS) / American Thoracic Society (ATS), 2014

http://www.ers-education.org/lrMedia/2014/pdf/236633.pdf

The ERS/ATS guidelines define severe asthma as asthma that requires treatment with high-dose ICS, a second controller, and/or systemic corticosteroids to prevent asthma from becoming uncontrolled or that remains uncontrolled despite the above therapy. Uncontrolled asthma is defined as asthma that meets any of the following criteria: Asthma Control Questionnaire (ACQ) response consistently greater than 1.5 or Asthma Control Test (ACT) below 20; frequent severe exacerbations requiring the use of systemic corticosteroids for more than three days two or more times within the past year; one hospitalization, intensive care unit stay, or mechanical ventilation within the past year; and forced expiratory volume less than 80% after both short- and long-acting bronchodilators are withheld.

The guidelines recommend that treatment for adults with severe asthma be guided by clinical criteria and sputum eosinophil counts performed in experienced centers; children with severe asthma should have their treatment guided by clinical criteria alone. Both adults and children over six years old with severe asthma that is uncontrolled by optimal pharmacological and non-pharmacological management and allergen avoidance should attempt use of omalizumab if their total immunoglobulin E (IgE) serum level is 30-700 IU/ml. The ERA/ATS guidelines note that the recommendation places a higher value on clinical benefit and a lower value on increased resource use. Patients who do not respond to omalizumab within four months should have their treatment with the drug discontinued.

Institute for Clinical Systems Improvement (ICSI), 2012

https://www.icsi.org/_asset/rsjvnd/Asthma.pdf

Asthma in adults and children over the age of 12 should be considered severe in the presence of the following components: symptoms throughout the day, nighttime awakenings often seven nights per week, short-acting beta agonist use several times per day for symptom control, severely limited normal activity, FEV_1 less than 60% or FEV_1/FVC reduced more than 5%, and two or more exacerbations requiring oral systemic corticosteroids per year. A patient in the same age range should be considered to have very poorly-controlled asthma if he or she has symptoms throughout the day; nighttime awakenings four or more times per week; extremely limited ability to perform normal activity; uses beta agonists for symptom control several times each day; FEV_1 or peak flow is less than 60% of predicted or personal best; scores of 3-4 on the Asthma Therapy Assessment Questionnaire (ATAQ), N/A on the ACQ, or less than or equal to 15 on the ACT; and two or more exacerbations requiring oral systemic corticosteroids per year.

ICSI recommends that asthma should be managed with a stepwise approach using escalating doses of ICS with the addition of a LABA and oral corticosteroids for patients who are unable to achieve control with ICS alone. The guidelines recommend that ICS be used preferentially for patients with mild persistent asthma, with leukotriene receptor agonists listed as a non-preferred alternative option.

National Institute for Health and Care Excellence (NICE), 2008 and 2013

ICS: http://www.nice.org.uk/guidance/ta138

Omalizumab: https://www.nice.org.uk/guidance/ta278

The NICE quality standard on asthma recommends that practitioners use the British Thoracic Society (BTS) / Scottish Intercollegiate Guidelines Network (SIGN) guidelines (described in a

separate entry below) to arrive at a judgement on asthma severity and level of control for each patient.

Regarding treatment, NICE recommends a stepwise approach beginning with SABAs for patients with mild intermittent asthma. An ICS should be added for patients who: have had an exacerbation within the past two years, use SABAs three or more times per week, are symptomatic three or more times per week, or wake up at night at least once per week due to asthma. If the addition of an ICS is insufficient to control asthma, additional therapy should be added, beginning with a LABA and potentially including oral leukotriene receptor antagonists, theophyllines, and slow-release beta agonists. A patient who is unable to achieve asthma control with ICS doses of up to 800 micrograms per day of beclomethasone dipropionate in combination with a LABA should intensify control through one of the following: increasing ICS dosage to up to 2,000 micrograms of beclomethasone dipropionate equivalent per day; adding a leukotriene antagonist, a theophylline, or a slow-release beta agonist. Patients with severe asthma unable to achieve control on the aforementioned regimens should add an oral corticosteroid.

Omalizumab should be added to optimized standard therapy for patients over the age of six who have severe persistent allergic IgE-mediated asthma and used oral corticosteroids four or more times in the previous year. NICE further recommends using omalizumab only if the manufacturer provides a discount agreed to in patient access plans. Patients whose asthma does not improve markedly after 16 weeks of therapy with omalizumab should discontinue the use of the drug.

British Thoracic Society (BTS) / Scottish Intercollegiate Guidelines Network (SIGN), 2014

https://www.brit-thoracic.org.uk/document-library/clinical-information/asthma/btssign-asthma-guideline-2014/

The BTS/SIGN guidelines recommend that mild intermittent asthma be treated with a SABA and state that any patient who is prescribed more than one SABA should undergo assessment to determine the level of asthma severity and control. An ICS should be first-line pharmacotherapy for children over the age of 12 and adults who use an inhaled SABA three or more times per week, experience symptoms three or more times per week, wake from sleep due to asthma one time or more per week, or have had an asthma attack requiring oral corticosteroids within the past two years. Several alternatives to ICS therapy are listed including the addition of a LABA to ICS therapy; a leukotriene receptor agonist for patients unable to take ICS; sodium cromoglicate and nedocromil sodium; and theophylline.

Physicians should consider adding a LABA before increasing dosage of beclomethasone or an equivalent drug above 400 micrograms per day. If control is not achieved through the addition of a LABA, physicians should increase ICS dosage to 800 micrograms per day; if increasing ICS dosage does not achieve control, further addition of a leukotriene receptor antagonist, theophylline, or

slow-release beta agonist (for adults only) should be considered. For patients who are still unable to achieve control with 800 micrograms per day of an ICS in combination with a LABA, physicians should consider increasing ICS dosage to 2,000 micrograms per day, or adding a leukotriene receptor antagonist, theophylline, or slow-release beta agonist tablet. Oral corticosteroids should be added for patients still unable to achieve control with the options presented in the previous step. When control is achieved, physicians should reduce the dosage of pharmacological treatments when possible.

Appendix C. Public and Representative Private Insurer Coverage Policies

Given mepolizumab's recent approval (November 2015), coverage policy may still be under development for many payers. We supplemented our search for coverage policy on mepolizumab with summaries of existing policies on omalizumab as a model for office-administered antibody therapy for severe asthma.

National Public Payers

Centers for Medicare & Medicaid Services (CMS)

We were unable to find any National Coverage Decisions or Local Coverage Decisions pertaining to mepolizumab or omalizumab. Medi-Cal, California's Medicaid program, does not include omalizumab in its contract drug list.

National Private Payers

Aetna[25,26]

Aetna covers mepolizumab for patients with severe eosinophilic asthma for patients aged 12 and older who meet several criteria. Patients over the age of 18 must have a FEV_1 less than 80% of predicted values (<90% for patients aged 12 to 17); FEV_1 reversibility of at least 12% and 200 ml after salbutamol administration; two or more exacerbations requiring systemic corticosteroid use in the previous 12 months despite the use of high-dose ICS; two or more exacerbations in the previous 12 months despite ICS and corticosteroid use; and current treatment with another non-ICS controller medication for at least three months or documented unsuccessful treatment with a non-ICS controller medication for at least three out of the past 12 months. Continued authorization is contingent upon a reduction in asthma signs and symptoms, a decrease in use of rescue medication, a decrease in exacerbation frequency, and an increase in predicted FEV_1 from baseline.

Aetna considers omalizumab to be medically necessary for patients ages six or older with severe persistent allergic asthma and a baseline serum IgE level between 30 and 1,500 IU/ml; symptoms that are inadequately controlled with a moderate-dose ICS and LABA or leukotriene inhibitor for at least three months; and daily symptoms and/or exacerbations that affect activity and sleep. Additionally, patients must have poorly-controlled asthma as demonstrated by one of the following: daily SABA use; diurnal variation in peak expiratory flow (PEF) greater than 30%; FEV_1 less than 60% of predicted value; PEF less than 80% of personal best; or three or more hospital admissions, treatments with high-dose injectable or oral corticosteroids, or visits to emergent or urgent care.

***Anthem*[23,27]**

Anthem covers mepolizumab for patients over the age of 12 with severe eosinophilic asthma that is inadequately controlled by one of the following combination therapies: 12 months of an ICS and a LABA, leukotriene receptor agonist, or theophylline; or six months of an ICS with a daily oral glucocorticoid and three months of a LABA, leukotriene receptor agonist, or theophylline. A patient does not have to meet the aforementioned criteria if intolerant or contraindicated to one of the above agents. Patients must also have blood eosinophil counts of least 150 cells per microliter at therapy initiation or 300 cells per microliter in the previous 12 months, FEV_1 less than 80% of predicted volume, and FEV_1 reversibility of at least 12% and 200 ml after the use of albuterol. Reauthorization at 12 months is contingent on clinical improvement as demonstrated by decreased use of rescue medication, decreased frequency of exacerbations, increase in predicted FEV_1 from pretreatment baseline, or reduction in asthma-related symptoms.

Anthem covers omalizumab for patients over the age of 12 with moderate to severe persistent asthma who meet all of the following criteria: symptoms that are inadequately controlled after at least three months of therapy with a medium to high dose ICS and a LABA or leukotriene modifier; positive skin test or in vitro reactivity to a perennial allergen; FEV_1 less than 80% of predicted level; serum IgE of at least 30 IU/ml. Patients who experience clinical improvement (i.e., decreased use of rescue medication, decreased frequency of exacerbations, increase in FEV_1 from baseline, reduction in symptoms) during the first 12 months of treatment with the drug are eligible for continued authorization.

***CIGNA*[29,55]**

Cigna covers omalizumab for patients with moderate to severe persistent allergen-related asthma who have either a history of beneficial response to the drug or meet all of the following criteria: age of at least 12 years; positive skin test or in vitro reactivity to a perennial allergen; asthma inadequately controlled with ICS; and regular use of an ICS in addition to another controller therapy (i.e., LABAs, leukotriene receptor antagonists). Reauthorization after 12 months is contingent on demonstrated clinical benefit.

***Humana*[24]**

Humana covers mepolizumab for patients aged 12 and older with severe eosinophilic asthma who have blood eosinophil levels of at least 300/µL and who have been unable to achieve adequate control while on high-dose ICS therapy in combination with a LABA or leukotriene inhibitor.

Humana covers omalizumab for patients over the age of 12 with moderate to severe persistent asthma; evidence of specific allergy sensitivity demonstrated through positive skin test or blood test for a specific IgE or in vitro reactivity to a perennial allergen; baseline serum IgE of 30 to 700 IU/ml;

and inadequately controlled asthma despite the use of ICS. Therapy may be continued for patients who are stabilized on omalizumab and continue controller therapy with an ICS with or without a LABA.

***UnitedHealthcare*[30,56]**

UnitedHealthcare (UHC) covers omalizumab for patients over the age of 12 who meet the following criteria: positive skin test or in vitro reactivity to a perennial allergen, inadequately controlled asthma despite the use of ICS, and baseline plasma IgE level between 30 and 1,500 IU/ml.

Regional Private Payers

***Health Net*[57]**

Health Net covers omalizumab for patients over the age of 12 with moderate to severe persistent asthma; a positive skin test or in vitro reactivity to a perennial allergen; who are unable to control their asthma with ICS and a second controller agent; who have serum IgE of more than 30 IU/ml; two or more exacerbations requiring oral or systemic corticosteroids within the past 12 months, or one exacerbation that requires intubation. Omalizumab must be prescribed by a pulmonologist or allergist.

We were unable to find any publicly available coverage policies or drug lists from Health Net pertaining to coverage of mepolizumab.

Blue Shield of California

We were unable to find any publicly available coverage policies or drug lists from BSCA pertaining to private of mepolizumab or omalizumab.

Pharmacy Benefit Managers

CVS Caremark

We were unable to find any publicly available policies or drug lists pertaining to mepolizumab or omalizumab from CVS Caremark.

Appendix D. Previous Systematic Reviews and Technology Assessments

We identified one systematic review of mepolizumab:

1. Liu Y, Zhang S, Li DW, Jiang SJ. Efficacy of anti-interleukin-5 therapy with mepolizumab in patients with asthma: A meta-analysis of randomized placebo-controlled trials. *PLoS One.* 2013; 8(3):e59872.

The systematic review identified 7 RCTs (N=1131) of IV mepolizumab for asthma, including the DREAM trial.[58] In their analysis, IV mepolizumab significantly reduced eosinophils in the blood and sputum, but there were no significant differences in lung function as assessed by FEV_1 or peak expiratory flow (PEF). The review found a significant decrease in asthma exacerbations (OR 0.30, 0.13 to 0.67) based on four studies. They also found a significant improvement in scores on the Asthma Quality of Life Questionnaire (AQLQ) based on two studies, but no significant difference in asthma control as assessed by the Asthma Control Questionnaire (ACQ) based on four studies.

Appendix E. Ongoing Studies

Title/ Trial Sponsor	Study Design	Comparators	Patient Population	Primary Outcomes	Estimated Completion Date
Mepolizumab					
Cessation Versus Continuation of Long-term Mepolizumab in Severe Eosinophilic Asthma Patients **NCT02555371**	RCT	Mepolizumab 100 mg SC every 4 weeks Placebo to match	N = 300 3 years treatment with mepolizumab	Time to first asthma exacerbation	November 2018
Efficacy and Safety Study of Mepolizumab Adjunctive Therapy in Participants With Severe Eosinophilic Asthma on Markers of Asthma Control **NCT02281318**	RCT	Mepolizumab 100 mg SC every 4 weeks Placebo to match	N = 544 Age ≥ 12 Men and women Severe eosinophilic asthma ≥ 2 asthma exacerbations in the prior year	Mean change from baseline in St. George's Respiratory Questionnaire (SGRQ) score at Week 24	June 2016

Appendix F. Comparative Clinical Effectiveness Supplemental Information

We performed screening at both the abstract and full-text level. A single investigator screened all abstracts identified through electronic searches according to the inclusion and exclusion criteria described earlier. We did not exclude any study at abstract-level screening due to insufficient information. For example, an abstract that did not report an outcome of interest would be accepted for further review in full text. We retrieved the citations that were accepted during abstract-level screening for full text appraisal. One investigator reviewed full papers and provided justification for exclusion of each excluded study.

We also included FDA documents related to mepolizumab. These included the manufacturer's submission to the agency, internal FDA review documents, and the transcript of Advisory Committee deliberations and discussions. All literature that did not undergo a formal peer review process is described separately.

We used criteria published by the US Preventive Services Task Force (USPSTF) to assess the quality of RCTs and comparative cohort studies, using the categories "good," "fair," or "poor" (see Appendix Table F2)[33] Guidance for quality ratings using these criteria is presented below, as is a description of any modifications we made to these ratings specific to the purposes of this review.

Good: *Meets all criteria: Comparable groups are assembled initially and maintained throughout the study; reliable and valid measurement instruments are used and applied equally to the groups; interventions are spelled out clearly; all important outcomes are considered; and appropriate attention is paid to confounders in analysis. In addition, intention to treat analysis is used for RCTs.*

Fair: *Studies were graded "fair" if any or all of the following problems occur, without the fatal flaws noted in the "poor" category below: Generally comparable groups are assembled initially but some question remains whether some (although not major) differences occurred with follow-up; measurement instruments are acceptable (although not the best) and generally applied equally; some but not all important outcomes are considered; and some but not all potential confounders are addressed. Intention to treat analysis is done for RCTs.*

Poor: *Studies were graded "poor" if any of the following fatal flaws exists: Groups assembled initially are not close to being comparable or maintained throughout the study; unreliable or invalid measurement instruments are used or not applied equally among groups (including not masking outcome assessment); and key confounders are given little or no attention. For RCTs, intention to treat analysis is lacking.*

Note that case series are not considered under this rating system – because of the lack of comparator, these are generally considered to be of poor quality. Nevertheless, we restricted our use of case series to those that met specific criteria, including a minimum of six months follow-up, clearly defined entry criteria, and use of consecutive samples of patients.

Table F1. Overview of Studies

Reference	Study	Phase	N	FU, weeks	Treatment	Control	Population	Age, years	Sex, %F	Asthma duration, years	FEV1, % predicted	Reversibility, %	ACQ score	OCS use, %	Eosinophil count	Exacerbations in prior year
Mepolizumab																
Severe eosinophilic asthma																
Pavord 2012	DREAM	3	616	52	Mepolizumab 75 mg, 250 mg, or 750 mg IV q4 weeks	Placebo	Recurrent exacerbations	49	63	19	60	28	4.2	31	250	3.6
Ortega 2014	MENSA	3	576	32	Mepolizumab 75 mg IV or **100 mg SC** q4 weeks	Placebo	Recurrent exacerbations	50	57	20	61	27	2.3	25	290	3.6
Bel 2014	SIRIUS	3	135	24	Mepolizumab **100 mg SC** q4 weeks	Placebo	Chronic OCS use	50	55	19	59	26	2.2	100	240	3.1

Note: FU=follow-up; q4=every 4 weeks; IV=intravenous SC=subcutaneous; FEV_1=forced expiratory volume in one second; ACQ=Asthma Control Questionnaire; OCS=oral corticosteroids

Table F2. Quality Metrics

Reference	Study	Adequate randomization	Allocation concealment	Patent blinding	Staff blinding	Outcome adjudication blinding	Completeness of follow-up	Intention to treat analysis	Incomplete data addressed	Selective outcome reporting	Industry funding	Free from other bias	Overall quality
Mepolizumab													
Severe eosinophilic asthma													
Pavord 2012	DREAM	Yes	Yes	Yes	Yes	Yes	16% withdrew	Yes	Yes	No	Yes	Yes	Good
Ortega 2014	MENSA	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Good
Bel 2014	SIRIUS	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Good

Table F3. Outcomes

Reference	Study	Intervention	N	Annual rate of exacerbations	Annual Rate ER or hospitalization	Annual rate of hospitalization	Change in FEV1 from baseline pre-bronchodilator	Change in FEV1 from baseline post-bronchodilator	Change in ACG	Change in SGRQ	90-100% reduction in OCS dose	≥50% reduction in OCS dose	No reduction in OCS dose
Mepolizumab													
Severe eosinophilic asthma													
Pavord 2012	DREAM	Mepolizumab 75 mg IV	153	1.24	0.17	0.1			-0.75				
		Mepolizumab 250 mg IV	152	1.46	0.25	0.1			-0.87				
		Mepolizumab 750 mg IV	156	1.15	0.22	0.07			-0.8				
		Placebo	155	2.4	0.43	0.2			-0.59				
Ortega 2014	MENSA	Mepolizumab 75 mg IV	191	0.93	0.14	0.06	186	176	-0.92	-15.4			
		Mepolizumab 100 mg SC	194	0.83	0.08	0.03	183	167	-0.94	-16			
		Placebo	191	1.74	0.2	0.1	68	30	-0.5	-9			
		Diffference SC vs. Placebo		53% (36% to 65%)	61% (17% to 82%)	69% (9% to 89%)			-0.44 (-0.63 to -0.25)	-7 (-10.2 to -3.8)			
Bel 2014	SIRIUS	Mepolizumab 100 mg SC	69	1.44		0					23%	54%	36%
		Placebo	66	2.12							11%	33%	56%
		Difference							-0.52 (-0.87 to -0.17)	-5.8 (-10.1 to -1.0)			
ER	Emergency Room												
FEV1	Forced expiratory volume in 1 second												
ACQ	Asthma Control Questionnaire												
SGRQ	St. George's Respiratory Questionnaire												
OCS	Oral corticosteroid												
IV	Intravenous												
SC	Subcutaneous												

Table F4. Harms

Reference	Study	Intervention	N	Any AE	SAE	Death	Drug related	Discontinue due to AE	Hyper-sensitivity	Injection reaction	Headache	URI	Sinusitis
Mepolizumab													
Severe eosinophilic asthma													
Pavord 2012	DREAM	Mepolizumab 75 mg IV	153		13%	0 (0%)		3%					
		Mepolizumab 250 mg IV	152		16%	2 (1%)		5%					
		Mepolizumab 750 mg IV	156		12%	1 (1%)		6%					
		Placebo	155		16%	0 (0%)		4%					
Ortega 2014	MENSA	Mepolizumab 75 mg IV	191	84%	7%	0 (0%)	17%	0%		3%	24%	12%	6%
		Mepolizumab 100 mg SC	194	78%	8%	0 (0%)	20%	1%		9%	20%	12%	9%
		Placebo	191	83%	14%	1 (1%)	16%	2%		3%	17%	14%	9%
Bel 2014	SIRIUS	Mepolizumab 100 mg SC	69	83%	1%	0 (0%)	30%	5%		6%	20%	4%	10%
		Placebo	66	92%	18%	1 (2%)	18%	4%		3%	21%	8%	9%
From FDA documents													
No anaphylaxis													
Systemic hypersensitivity same as placebo (2%)													
Opportunistic infections 1% versus 0 in placebo													

Note: IV=intravenous SC=subcutaneous; AE=adverse event; SAE=serious adverse event; URI=upper respiratory infection

Appendix G. Comparative Value Supplemental Information

Table G1. Model-wide Key Inputs and Assumptions

Model-wide Inputs	Value	Sources / Assumptions	Notes
Asthma-related mortality per 100 person years	0.4	de Vries et al. 2010[46]	Assumes a general increased risk of asthma-related death given the higher severity of this uncontrolled subpopulation eligible for biologic therapy (Step 4/5).
Additional risk of death given asthma hospitalization	2.48%	Watson et al., 2007[41]	Added risk above that of the general asthma-related mortality
Additional risk of death given ED visit	0%	Assumed to not impact mortality over and above the treatment step 5 asthma-related mortality rate for all living health states in model	
Additional risk of death given oral corticosteroid burst	0%		
Disutility for hospitalization	-0.2	Lloyd et al.[47]	Disutilities are assumed to be for two weeks. Disutility is the same value as assumed in the NICE omalizumab assessment groups' base-case.[40]
Disutility for ED	-0.15	Assumption based on Lloyd et al.[47]	
Disutility for oral corticosteroid burst	-0.10	Lloyd et al.[47]	
Disutility for chronic oral corticosteroid use	-0.023	NICE omalizumab manufacturer's base-case[40]	Disutility assumed the same as disability-adjusted value from DALYs.
Cost for asthma-related hospital stay	$9,960 / stay	Assumed no difference across arms in hospital days, Cangelosi et al.[48] Inflated to 2014 USD	Unit costs for hospital, ED, and office visits were derived from a large-scale US claims analysis of the MarketScan data from years 2006-2011 and inflated to 2014 USD.
Cost for asthma-related ED visit	$684	Cangelosi et al.[48] Inflated to 2014 USD	
Cost for oral corticosteroid burst exacerbation	$156	US national schedule of reference costs (assumes $10 for oral corticosteroid burst[17] and 75% of events require an outpatient visit at $195 per visit;[48] visits are inflated to 2014 USD)	For oral corticosteroid cost, chose maximum cost per unit at approximately $1 per pill.
Annual cost for Standard of Care	$5,738	Assumed Advair 500/50, one inhalation twice daily for each day (2015 Redbook WAC is $407.51 per 30 days[17]) and quarterly office visits (4*$195[48])	These costs do not change for the treatment arms in the model and therefore washout for the incremental results
Annual cost of oral corticosteroid	$73	Redbook®[17]	Market basket of 2015 REDBOOK WAC for 10mg oral Prednisone, once daily is $0.20 per day[17]
Annual cost of adverse events due to chronic oral corticosteroid use	$784	Shah et al.[49]	Cost assigned to the adjusted proportion of each arm that receives a daily oral glucocorticoid dose > 5.

Table G2. Treatment-Specific Model Inputs and Notes

Input	Value	Source/Assumptions	Notes
SoC			
Annual exacerbation rate per person year	1.74	Ortega et al., 2014[14]	
Proportion of hospitalizations	5.75%	Ortega et al., 2014[14]	
Proportion of ED visits	5.75%	Ortega et al., 2014[14]	The rate of exacerbations requiring an ED visit was calculated based on information presented by Ortega et al.[14] We assumed the rate of exacerbations requiring an ED visit was equal to the rate of exacerbations requiring hospitalization or ED visit minus the rate of exacerbations requiring hospitalization.
Proportion of oral corticosteroid bursts	88.51%	Ortega et al., 2014[14]	The rate of exacerbations resulting in an oral corticosteroid burst was calculated based on information presented by Ortega et al.[14] We assumed the rate of exacerbations resulting in an oral corticosteroid burst was the rate of clinically significant exacerbations minus the mean rate of exacerbations requiring a hospitalization or ED visit.
Discontinuation rate over entire time horizon	6%	Ortega et al., 2014[14]	Discontinuation rate only reduces the cost of treatment as clinical impacts already account for discontinuation in the trial.
Utility value for non-exacerbation health state	0.77	Ortega et al., 2014[14]	Used aggregate St. George RQ score mapped to the EQ-5D[51]
Percent using chronic oral corticosteroids >5mg per day	68%	Bel et al., 2014[13]	Proportion based on the adjusted numbers presented by Bel et al. Assumed reduction in daily oral glucocorticoid dose to a level ≤5 mg was not harmful in terms of adverse events or disutility.
Mepolizumab + SoC (limited to parameters that differ from SoC alone)			
Annual exacerbation rate per person year	0.83	Ortega et al., 2014[14]	
Proportion of hospitalizations	3.61%	Ortega et al., 2014[14]	
Proportion of ED visits	6.02%	Ortega et al., 2014[14]	The rate of exacerbations requiring an ED visit was calculated based on information presented by Ortega et al.[14] We assumed the rate of exacerbations requiring an ED visit was equal to the rate of exacerbations requiring hospitalization or ED visit minus the rate of exacerbations requiring hospitalization.
Proportion of oral corticosteroid bursts	90.36%	Ortega et al., 2014[14]	The rate of exacerbations resulting in an oral corticosteroid burst was calculated based on information presented by Ortega et al.[14] We assumed the rate of exacerbations resulting in an oral corticosteroid burst was the rate of clinically significant exacerbations minus the mean rate of exacerbations requiring a hospitalization or ED visit.
Annual cost for mepolizumab	$32,500	Redbook®[17]	
Discontinuation rate over entire time horizon	5%	Ortega et al., 2014[14]	Discontinuation rate only reduces the cost of treatment as clinical impacts already account for discontinuation in the trial.
Utility value for non-exacerbation health state	0.828	Ortega et al., 2014[14]	Used aggregate St. George RQ score mapped to the EQ-5D[51]
Difference in utility value for non-exacerbation health state (compared to SoC alone)	0.059	Ortega et al., 2014[14]	Used aggregate St. George RQ score mapped to the EQ-5D[51] (mepolizumab + SoC minus SoC alone)
Percent using chronic oral corticosteroids	46%	Bel et al., 2014[13]	Assumed reduction in daily oral glucocorticoid dose to a level ≤5 mg was not harmful in terms of adverse events or disutility.

Table G3. Scenario Analysis for Hospitalization Cost

	QALYs gained	Treatment Costs	Non-Treatment Costs	ICER ($/QALY)
Mepolizumab + SoC	15.12	$706,111	$18,860	$380,559/QALY
SoC alone	13.59	$98,083	$44,577	--

Future costs and QALYs are discounted 3% a year. Treatment costs include the cost of Mepolizumab and SoC. Non-treatment costs include the cost of exacerbations and chronic oral corticosteroid use.
ICER: Incremental cost-effectiveness ratio

This scenario analysis assumes a higher cost for hospitalization based on data provided by GlaxoSmithKline. The cost per hospitalization used in this scenario analysis was $16,228, which was the average cost for an asthma-related inpatient stay of any length provided by GlaxoSmithKline.[20] The hospitalization cost assumed in the base-case analysis was $9,960.[48] Using the higher hospitalization cost and over a lifetime treatment horizon, 23.96 exacerbations were averted (non-discounted) per patient receiving mepolizumab with SoC versus SoC alone, and there were 28.89 person-years of treatment. Avoidance of exacerbations and reductions in chronic oral corticosteroid use resulted in over $25,000 of cost offsets for the mepolizumab arm, but treatment costs were increased by over $600,000. The resulting incremental cost per exacerbation averted was $24,307 (this estimate discounted costs but not exacerbations averted). Treatment with mepolizumab resulted in a gain of 1.53 QALYs relative to SoC alone, resulting in a cost-effectiveness estimate of $380,559 per QALY gained (see Table G3 above).

Table G4. Undiscounted Budget Impact Cost per Patient from 1 to 5 Years: Payer Perspective

	Mepolizumab + SoC		SoC	
	Treatment Costs	Non-Treatment Costs	Treatment Costs	Non-Treatment Costs
1 year	$37,761	$827	$5,365	$1,835
2 years	$75,178	$1,647	$10,671	$3,650
3 years	$112,241	$2,458	$15,919	$5,445
4 years	$148,939	$3,262	$21,105	$7,220
5 years	$185,262	$4,058	$26,231	$8,973

Table G5. Budget Impact Threshold Price Calculations

Population	(A) Average Person-Years	(B) Budget Impact/Year	(C) Difference from Threshold $904m – (B)	(D) Difference per Person-Year (C)÷(A)	(E) Base-case Price per Year	(F) Budget Impact Threshold Price (D)+(E)
Taking Mepolizumab (n=32,035)	19,221	$596,131,627	$307,868,373	$16,017	$32,500	$48,517